

PAIRED PULSE  
STIMULATION OF  
THE HEART





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*Proceedings of the Second Conference on  
Paired Pulse Stimulation and  
Postextrasystolic Potentiation in the Heart  
May 12 and 13, 1967*

Paul F. Cranefield and Brian F. Hoffman, *Editors*



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The Second Conference on Paired Pulse Stimulation  
and Postextrasystolic Potentiation in the Heart  
is dedicated to

Louis N. Katz, M.D.

in recognition of his long and distinguished career as a  
physiologist, in recognition of his many contributions to  
our knowledge of cardiac physiology, electrocardiography  
and clinical cardiology, and in particular recognition of  
his role in awakening interest in the subject of paired  
pulse stimulation of the heart.

The Rockefeller University - May 12, 1967

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Francis Hoffmann  
Paul Cranefield  
Joe & Lee  
Eric L. Meyler  
Vla. J. van Krevelen  
J. L. Linn  
Elin Feigl  
Marty L. Fox  
Edmund H. Sonnenblick  
Robert C. Scherf  
Samuel Hirsch  
Richard G. S. S. S. S.  
K. H. H.  
Ferdinand Kaveler  
S. Scherf

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John J. B. B.  
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William M. Chundrick  
Richard L. B. B.  
Dressler  
Ephraim  
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C. P. B. B.  
D. J. B. B.  
L. B. B.  
William W. Sleator  
Arnold M. Katz  
Jean Koch-Weiser  
Kalman Blangman  
Charles E. Korman

## Preface

THE FIRST conference on paired pulse stimulation and postextrasystolic potentiation in the heart was held on January 13, 1965. The great interest which was shown in the subject and the many unsolved problems which remained at the end of the conference led to a second conference being held at The Rockefeller University on May 12 and May 13, 1967. The second conference provided a forum for the reporting of further laboratory studies on the nature of paired pulse stimulation and for the reporting of clinical experience with the use of the technique in the treatment of arrhythmias and cardiac failure. A special session of the conference was devoted to the subject of diastolic compliance of the ventricle. The suggestion made at the first conference that paired pulse stimulation increases ventricular compliance proved to be a remarkably stimulating and controversial one. The renewal of interest in the whole issue of whether diastolic compliance is variable was one of the unexpected benefits of the renewed interest in paired pulse stimulation, and the articles on that subject contained in the present book are of very great importance to both the physiologist and the clinical cardiologist.

A few reports given at the conference are not included in this volume (those by Arthur Grishman, Paul Harris, and Robert C. Schlant, as well as a report read on behalf of George Rodewald) but the articles which appear here represent a full survey of all aspects of the problem. The conference was sponsored by the New York Academy of Medicine, The Rockefeller University, and the New York Heart Association and was supported by grants from the New York Heart Association and the National Heart Institute (Grant 1 R13 HE 09974-01A1 NSS).

PAUL F. CRANFIELD

BRIAN F. HOFFMAN

*The Rockefeller University and  
Columbia University College of  
Physicians and Surgeons*



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# Clinical Investigation of Paired Stimulation and Postextrasystolic Potentiation

D. DURRER, R. M. SCHUILENBURG, and F. L. MEIJLER

From the Department of Cardiology and Clinical Physiology, University of Amsterdam, Wilhelmina Gasthuis, Amsterdam, The Netherlands

## INTRODUCTION

The development of the clinical application of paired stimulation has been very disappointing. One of the factors responsible for the retardation of the clinical application of potentiation is the nonexistence of a commercially available, versatile, reliable, and safe clinical stimulator. After the first conference on paired stimulation it soon turned out that advanced sophisticated clinical studies in this field could not be performed either because of the fact that the stimulators, versatile enough, were not safe, or because the stimulators, safe enough, were not versatile. Even with a stimulator possessing ample safeguards, clinical application of paired stimulation may jeopardize the patient's life because of the tremendous increase in the demand for oxygen by the myocardium while using this method (1, 2).

In this paper some clinical investigations of paired stimulation or of related stimulation patterns applied with the aid of a new specially designed stimulator are discussed. We will not repeat all the possible hazards and difficulties one may encounter using artificial stimulation in man (3). However, we have attempted to repeat standard physiological procedures learned in the laboratory for the evaluation of human myocardial contractile behavior during a number of induced variations in rhythm.

## METHODS

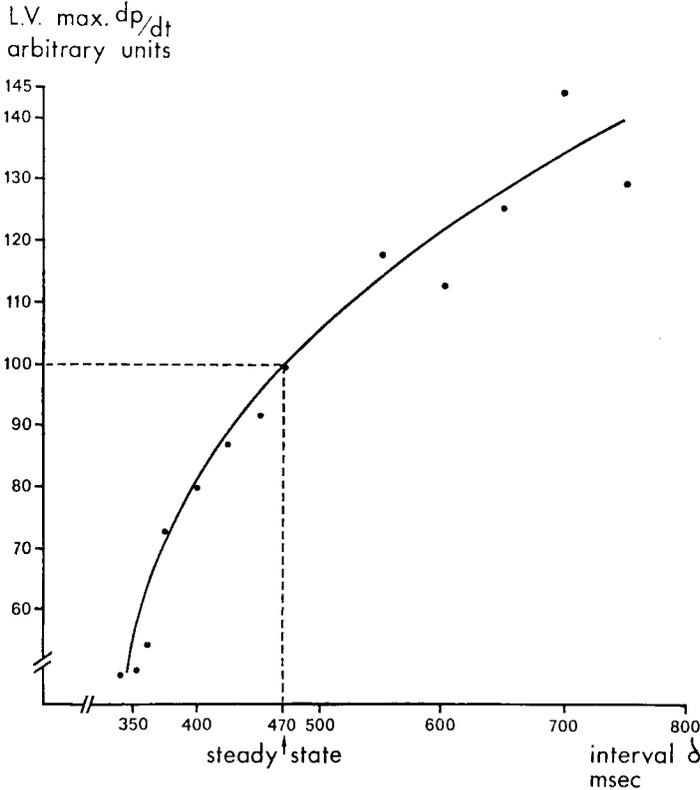
The Laboratory of Medical Physics of the University of Amsterdam has built a versatile and safe stimulator for clinical use. The requirements for programming certain stimulation patterns were learned from laboratory studies with a stimulator specially designed for excitability and interval-contractility studies. The new apparatus is a current-source stimulator with ample safeguards, suitable for either single or paired stimulation, for coupled pacing and delivering premature stimuli after chosen delays and after certain numbers of normal beats. Duration as well as strength of the stimuli can be independently varied. This, for example, may be necessary if the second impulse of a pair of stimuli is approaching the vulnerable period of the preceding cycle.

Clinical observations with paired stimulation or with induced premature beats were made during routinely performed cardiac catheterizations using standard techniques.

## RESULTS

Fig. 1 shows a restitution curve of a 20 year old man with a hypercirculation syndrome. As a measure for myocardial contractility the maximum of the first derivative

of the left ventricular pressure curve has been used. The measurements were made during a routine left and right heart catheterization. Because of a slight increase in the PQ interval found during normal sinus rhythm a study of the conduction system was performed by giving atrial premature beats after a varying delay interposed between eight normally initiated beats. At the same time left intraventricular pressure was



### Restitution curve of intact human heart

FIGURE 1. Restitution curve of intact human heart at a steady-state heart rate slightly over 120 per min. Left ventricular maximum  $dp/dt$  has been used as a measure for the contractile state of the myocardium. LVEDP has remained unchanged throughout the experiment.

recorded. By plotting the varying RR interval vs. the maximum  $dp/dt$  following those RR intervals the restitution curve outlined in Fig. 1 was obtained. A close resemblance exists between this restitution curve and those found in animal experiments (4).

The Brockenbrough phenomenon (5) uses postextrasystolic potentiation as an aid to the diagnosis of subaortic stenosis due to myocardial hypertrophy. The deliberate use of potentiation mechanisms may also aid in differentiating between a muscular and a membranous ventricular septal defect. This can be done by well-positioned premature beats or by poststimulation potentiation (6) occurring directly after cessation of a run

of fast beats. Fig. 2 demonstrates the effect of poststimulation potentiation in a patient with a membranous ventricular septal defect. After cessation of the high frequency stimulation period potentiation occurs, resulting in an increase in loudness and dura-

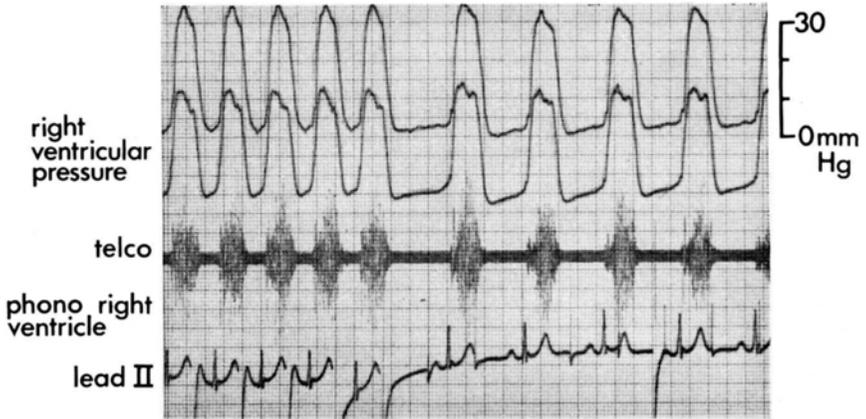


FIGURE 2. Right ventricular pressure records and intraventricular phonocardiogram (phono) made during a sudden decrease of the heart rate in a patient with a membranous ventricular septal defect. The first contraction of the slower rhythm has been potentiated, increasing the intensity and duration of the murmur. On Figs. 2 and 3 "telco" stands for intracardiac catheter-tip pressure recording. *Figure reprinted by permission from Excerpta Medica International Congress Series 137, 1967, 441.*

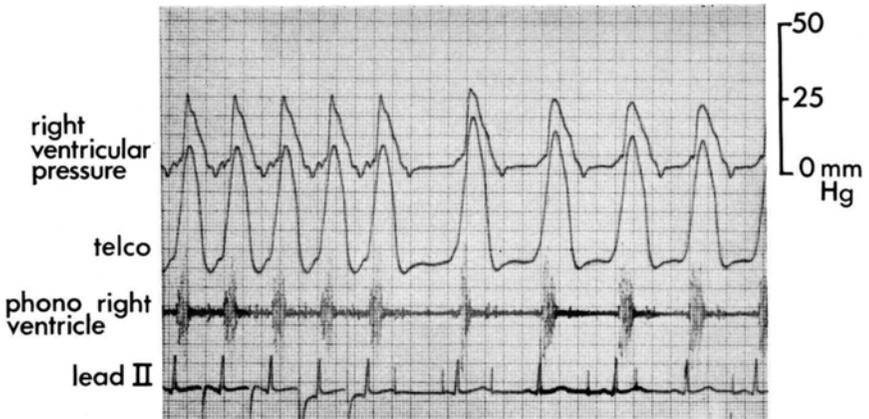


FIGURE 3. Right ventricular pressure records and intraventricular phonocardiogram made during a sudden decrease of the heart rate in a patient with a muscular ventricular septal defect. The first contraction of the slower rhythm has been potentiated, diminishing the duration of the murmur. *Figure reprinted by permission from Excerpta Medica International Congress Series 137, 1967, 441.*

tion of the murmur. The same procedure was carried out in a patient with a muscular ventricular septal defect as shown in Fig. 3. The potentiated beats after the high frequency stimulation period are accompanied by murmurs of diminished duration indicating a closure of the defect during the potentiated contraction. Together with a

phonocardiogram the knowledge of potentiation mechanisms may contribute to cardiac diagnosis.

From physiological studies it is a well-known fact that the amount of postextrasystolic potentiation is inversely related to the delay of the premature beat (7, 8). Thus an early premature beat produces more postextrasystolic potentiation than a premature beat occurring after a longer delay. This phenomenon can also be used for the

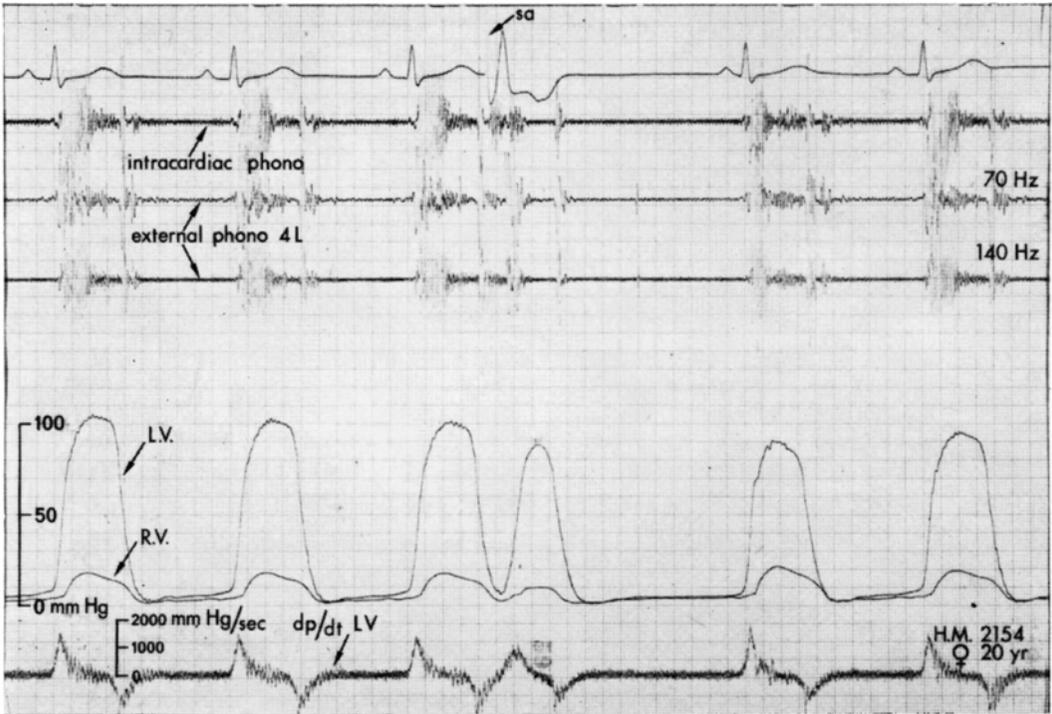


FIGURE 4. Electrocardiogram, phonocardiogram, left and right intraventricular pressure curves, and left ventricular  $dp/dt$  in a patient with a muscular ventricular septal defect. A ventricular premature beat has been applied after a delay of 470 msec. The  $dp/dt$  in the postextrasystolic beat has been enhanced (postextrasystolic potentiation). The systolic murmur in the postextrasystolic beat has been diminished in amplitude and duration.

diagnosis of either a muscular or a membranous ventricular septal defect. The effect of an early and a late premature beat on loudness and duration of the postextrasystolic murmur in a patient with a muscular ventricular septal defect is shown in Figs. 4 and 5. The early premature beat (470 msec) is followed by a more potentiated contraction as indicated by the  $dp/dt$ . This postextrasystolic beat is accompanied by a murmur of clearly shorter duration (Fig. 4). The premature beat occurring later in the cardiac cycle (630 msec) hardly influences the postextrasystolic murmur (Fig. 5). These examples have been given to demonstrate that for diagnostic purposes other ways of potentiation than paired stimulation can be used. In a previous communication (2)

we showed that paired stimulation can be used for the demonstration of papillary muscle dysfunction.

Elevated end-diastolic pressure in the left ventricle is often regarded as an indication of left ventricular failure. In rheumatic heart disease, however, aortic incompetence can elevate LVEDP without necessarily demonstrating diminished functioning of the left ventricular myocardium.

If paired stimulation increases maximum  $dp/dt$  of the left ventricle without raising or while lowering LVEDP, the myocardium of such patients may be regarded as

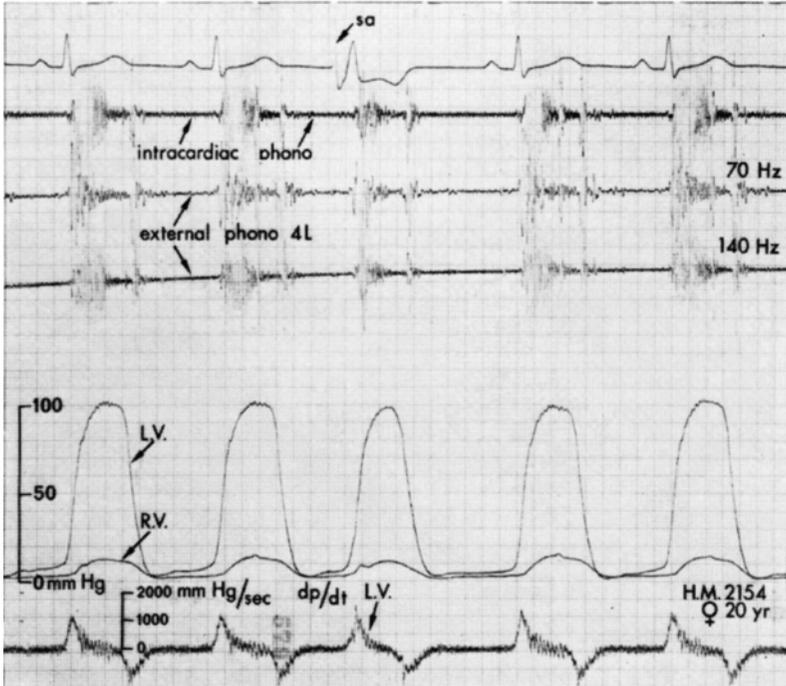


FIGURE 5. For description see Fig. 4. The premature beat has been given after a delay of 630 msec. The potentiating effect in the postextrasystolic beat is less in comparison with that in Fig. 4. There is still a slight effect on the murmur.

being in a reasonable functional state. In Fig. 6 the effect of paired stimulation on right ventricular end-diastolic pressure and maximum  $dp/dt$  of right ventricular pressure is given. The observations were made in a patient with rheumatic heart disease and atrial fibrillation. It can be seen that although paired stimulation gives rise to a more than twofold increase in  $dp/dt$ , at the same time there is an increase in the end-diastolic pressure in the right ventricle. We are fully aware that these types of observation may not lead to definite conclusions, but from experience with animals we know that paired stimulation potentiation in normal hearts always occurs at the same or at a lower end-diastolic pressure. The results demonstrated in Fig. 6 probably indicate that besides the valvular lesions the myocardium is or has been involved in the rheumatic process.

We have also studied the effect of paired stimulation on the hemodynamics of two patients with rheumatic heart disease and atrial fibrillation. For this type of study we prefer patients with atrial fibrillation because the complicated and confusing results obtained are not also open to misjudgment because of the effect of the atrial contractions.

We have tried to compare paired stimulation with single stimulation at the same mechanical heart rate in order to exclude the influence of rate on the measurements. Tables I and II give the results of paired stimulation as compared with single stimulation in two patients. The mechanical heart rate chosen was prescribed by the sponta-

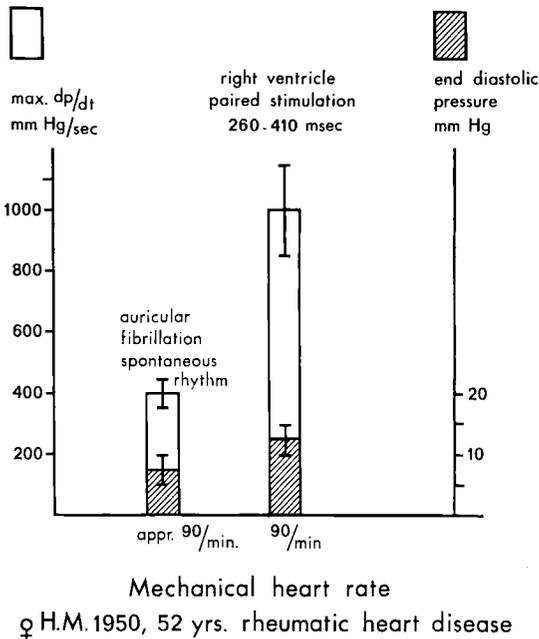


FIGURE 6. Right ventricular maximum dp/dt and end-diastolic pressure during the spontaneous ventricular rhythm in atrial fibrillation (left bar) and paired stimulation with approximately the same mechanical heart rate (right bar). Paired stimulation increases maximum dp/dt. There is also a slight increase in end-diastolic pressure.

neous ventricular rate of the patient under study. It can be seen that in patient HM 641 paired stimulation had a slight effect on cardiac output, stroke volume, and maximum dp/dt. This is accompanied by a slight rise in LVEDP and  $O_2$  consumption. It cannot be excluded that a rise in LVEDP during paired stimulation is not (at least partly) due to incomplete relaxation. Patient HM 2088 shows a much larger increase in hemodynamic parameters at a high cost in oxygen consumption but with a decrease in LVEDP. In this case the reaction of the heart to paired stimulation was considered to be normal.

## DISCUSSION

In our opinion the slow and retarded development of paired stimulation as a clinical discipline is due to:

1. The nonexistence of a versatile and safe stimulator.
2. The fact that for diagnostic purposes other ways of deliberately chosen potentia-

tion, such as postextrasystolic potentiation or poststimulation potentiation, are as valuable as and far less hazardous than paired stimulation. Figs. 2-5 give examples of the application of other potentiation mechanisms for diagnostic purposes.

TABLE I

The effect of paired stimulation compared with that of single stimulation at the same mechanical heart rate on a number of hemodynamic parameters in a patient with rheumatic heart disease and atrial fibrillation. For further details see text.

	Single stimulation 600 msec	Paired stimulation 230-370 msec
Mechanical heart rate	100/min	100/min
Peak LVP, mm Hg	108	112-120
LVEDP, mm Hg	10-11	6.5-7
Maximum dp/dt LV, mm Hg/sec	1000-1100	1300-1400
Peak RVP, mm Hg	45	54
RVEDP, mm Hg	9-10	6-8
O <sub>2</sub> LV, %	94	94
O <sub>2</sub> RV, %	49	44
O <sub>2</sub> consumption, ml/min	272	470
Cardiac output, liters/min	2.8	4.3
Cardiac index	1.6	2.4
Stroke volume, ml	28	43

♂ HM 2088. 53 yr. Rheumatic heart disease, auricular fibrillation.

TABLE II

Same as Table I.

	Single stimulation 800 msec	Paired stimulation 270-530 msec
Mechanical heart rate	75/min	75/min
Peak LVP, mm Hg	140	120
LVEDP, mm Hg	4	6-8
Maximum dp/dt LV, mm Hg/sec	2250	2850
Mean LAP, mm Hg	26	27
Mean PAP, mm Hg	27	40
O <sub>2</sub> LV, %	94	97
O <sub>2</sub> PA, %	64	63
O <sub>2</sub> consumption, ml/min	230	285
Cardiac output, liters/min	4.2	5.5
Cardiac index	2.3	3.0
Stroke volume, ml	56	73

♀ HM 641. 51 yr. Rheumatic heart disease, auricular fibrillation.

3. Paired stimulation is prohibited in all patients with coronary heart disease because of the tremendous increase in O<sub>2</sub> consumption (1, 2). Since a large part of the cardiac patients are suffering from coronary heart disease the potential therapeutic use of paired stimulation has become nil.

4. Paired stimulation has come to the clinic at the moment that DC countershock for the acute treatment of almost any disturbance in rhythm has left the experimental field (9). At the same time the blockers of the  $\beta$ -ganglion have turned out to be a useful supplement to our therapeutic arsenal (10) for slowing heart rate during tachycardia.

In this paper we have described our initial attempts with paired stimulation and other potentiating stimulation patterns. It is almost undeniable that in all instances in which paired stimulation can be useful for diagnosis other ways of potentiation can do as well. For the moment the only indication for the clinical use of paired stimulation seems to be its application for evaluation of the functional state of the myocardium. If during paired stimulation maximum dp/dt and/or other hemodynamic parameters increase while the LVEDP decreases, it can probably be said that the myocardium has reacted as one would expect under physiological conditions (Table II).

If during paired stimulation LVEDP rises, a definite verdict cannot be given because incomplete relaxation may confuse the issue (Table I).

Our results are few and meager and disappointing. However, the paired stimulation boom has focused clinical attention on the interval-contractility relationship of the heart and as such will turn out to have contributed to a better understanding of the mechanical and electrical activity of the heart.

This work was supported by grants from the Netherlands Organization for the Advancement of Pure Research (Z.W.O.), The Hague, The Netherlands.

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# Hemodynamics of Paired Electrical Stimulation in Complete Heart Block in Man

MARTIN L. FOX, ALFRED J. KALTMAN, GEORGE BEAR, and  
CHARLES E. KOSSMANN

From the Department of Medicine, New York University School of Medicine, New York 10016

Numerous studies in the past several years have demonstrated that the mammalian heart responds to paired electrical stimulation by a sustained marked enhancement of its contractile state. Although the potentiation has been shown to be greater than that induced with the usual inotropic drugs cardiac output is not increased unless a state of "failure" is first acutely induced in the heart-lung or intact animal preparation (1-9).

Observations in man have been noteworthy in their demonstration that the improved contractility associated with paired pacing generally has not been associated with improved cardiac output even with heart failure present (8-11).

The following study was undertaken to determine the hemodynamic effects of paired pacing in acquired heart block, an entity in which this intervention has heretofore not been investigated in man. To better define the clinical value of paired pacing in heart block, the effects of this modality were contrasted in each patient to those of acute isoproterenol infusion, as well as to conventional single stimulus pacing at similar rates of contraction.

## METHODS

Nine patients have been studied to date, ranging in age from 51 to 80 yr. None was in clinical congestive failure nor was receiving digitalis or diuretics at the time of study. In none was there any clinical or laboratory evidence of recent or old myocardial infarction, or of valvular or congenital heart disease. Two had systemic hypertension (Table I).

Continuous right ventricular endocardial pacing by means of a bipolar electrode catheter had been performed from 1 to 3 days preceding the study. Right heart catheterization was performed and a brachial artery was cannulated. First derivatives of the brachial artery pressure pulses ( $dp/dt$ ) were obtained by an RC differentiating circuit incorporated in an oscilloscopic photographic multichannel recorder (Electronics for Medicine Model DR-8, manufactured by Electronics for Medicine, Inc., White Plains, N.Y.).

Cardiac output was obtained by the indicator-dilution technique using indocyanine green as the indicator, with 5 mg of dye injected into the pulmonary artery with sampling in the brachial artery. Oxygen content of the pulmonary arterial and brachial arterial blood was determined by the Van Slyke method.

Single and paired electrical stimuli were delivered from a battery-driven pulse generator (Model 5837, manufactured by Medtronic, Inc., Minneapolis, Minn.). The stimulus strength

was kept at limits of twice threshold, and except for brief trials, did not exceed 5 ma. The "delay interval," the shortest period after a stimulus in which a second would result in a depolarization varied from 230 to 370 msec. Although the longer intervals could be shortened somewhat by increasing stimulus strength, the resultant rhythm was unstable in every case attempted because of the inconstancy with which the second depolarization would occur, or because of repetitive firing induced by it.

Isoproterenol hydrochloride was administered intravenously at a rate varying between 4 to 16  $\mu$ g per min in order to obtain ventricular rates similar to those obtained with single electrical stimulations.

The electrical and pharmacological interventions were maintained for 10 to 15 min prior to and during pressure and flow measurements.

TABLE I  
CONTROL DATA, SPONTANEOUS IDIOVENTRICULAR RATE

Patient and age	B.S.A.(M <sup>2</sup> )	Ventricular rate	Brachial artery pressure	Right ventricular pressure	Q-T interval	Delay interval
			<i>mm Hg</i>	<i>mm Hg</i>	<i>sec</i>	<i>msec</i>
L. M., 67	1.80	48	125/45	30/7	0.44	300
G. C., 71	1.67	40	130/70	26/5	0.42	280
F. P., 65	2.17	50	186/68	32/5	0.46	230
S. DeS., 58	1.83	42	170/60	44/7	0.41	250
E. P., 51	1.71	50	260/113	33/7	0.42	260
A. F., 70	1.97	42	250/90	37/6	0.42	280
A. L., 80	1.80	34	168/56	43/7	0.44	360
G. S., 55	1.84	54	184/56	58/6	0.46	350
J. C., 59	1.80	48	120/60	20/6	0.44	370

## RESULTS

### *Spontaneous Idioventricular Rhythm*

In the control state during idioventricular rhythm, five patients had elevations of the right ventricular pressure ranging from 33/7 to 58/6 mm Hg. Arteriovenous oxygen difference varied from 5.1 to 6.3 volumes %, averaging 5.8 volumes %. Cardiac output ranged from 2.0 to 5.8 liters per min with an average of 3.1 liters per min (Tables I and II).

### *Single Stimulus Pacing*

In seven patients both cardiac output and A-V oxygen difference were determined during single stimulus pacing (Table II); in five patients these did not change significantly from those values obtained at the spontaneous idioventricular rate. Arteriovenous oxygen difference was narrowed in only three patients (F. P., A. F., and J. C.), the reduction for these three averaged 1.3 volumes %. Stroke volume, systolic ejection period, and mean systolic ejection rate fell in nearly all patients.

TABLE II  
COMPARISON OF SPONTANEOUS VENTRICULAR RHYTHM TO SINGLE ELECTRICAL STIMULATION

Patient	Spontaneous idioventricular rhythm							Single electrical stimulation						
	Cardiac output liters/min	Arterio-venous oxygen difference vol %	Stroke volume ml	Systolic ejection period msec	Mean systolic ejection rate ml/min	Brachial artery pressure mm Hg	Maximal rate of rise of brachial artery pressure mm Hg/sec	Cardiac output liters/min	Arterio-venous oxygen difference vol %	Stroke volume ml	Systolic ejection period msec	Mean systolic ejection rate ml/min	Brachial artery pressure mm Hg	Maximal rate of rise of brachial artery pressure mm Hg/sec
<b>Group 1</b>														
L. M.	2.1	5.7	64 (33)	360	177	125/45	1467	1.7	5.4	26 (65)	300	87	132/67	1467
G. C.	3.0	5.1	75 (40)	300	250	132/56	2420	2.9	5.6	39 (75)	240	161	118/68	1550
F. P.	3.8	5.9	79 (50)	290	272	186/86	2280	—	4.5	—	250	—	185/77	2140
S. DeS.	5.8	6.1	96 (42)	340	280	168/61	1700	—	—	—	—	—	—	—
E. P.	2.9	5.8	55 (50)	360	161	248/89	3000	2.3	6.1	36 (80)	260	139	260/113	3440
<b>Group 2</b>														
A. F.	3.9	5.6	79 (42)	400	198	258/72	3715	4.4	4.2	55 (75)	300	184	249/94	2255
A. L.	2.0	6.3	59 (34)	260	227	168/56	890	1.8	6.6	22 (80)	230	98	138/65	1200
G. S.	3.0	6.3	56 (54)	260	214	184/56	1608	3.7	6.2	49 (75)	260	190	196/70	2230
J. C.	3.6	5.6	79 (46)	400	197	120/58	944	4.9	4.5	66 (75)	300	220	133/70	1030

Number in parentheses next to stroke volume is heart rate.

TABLE III  
COMPARISON OF PAIRED ELECTRICAL  
STIMULATION TO ISOPROTERENOL INFUSION

Patient	Isoproterenol infusion						Paired electrical stimulation							
	Cardiac output liters/min	Arterio-venous oxygen difference vol %	Stroke volume ml	Systolic ejection period msec	Mean systolic ejection rate ml/min	Brachial artery pressure mm Hg	Maximal rate of rise of brachial artery pressure mm Hg/sec	Cardiac output liters/min	Arterio-venous oxygen difference vol %	Stroke volume ml	Systolic ejection period msec	Mean systolic ejection rate ml/min	Brachial artery pressure mm Hg	Maximal rate of rise of brachial artery pressure mm Hg/sec
Group 1*														
L. M.	2.5	4.1	46 (65)	300	152	173/47	3373	1.7	5.6	26 (65)	240	109	156/64	2053
G. C.	4.2	4.3	63 (67)	220	285	141/58	2860	3.1	5.9	41 (75)	200	207	125/66	2030
F. P.	5.0	5.0	70 (72)	230	305	226/70	3420	6.8	4.8	97 (70)	200	485	207/75	2860
S. DeS.	4.9	5.3	90 (54)	300	300	167/66	1840	6.5	4.8	75 (84)	280	270	173/71	2340
E. P.	3.1	4.3	40 (77)	280	144	232/83	3000	2.3	7.2	29 (78)	230	125	264/95	4300
Group 2†														
A. F.	5.3	4.8	76 (70)	240	317	226/50	4850	3.5	7.1	42	210	200	230/92	3325
A. L.	3.0	4.7	64 (47)	280	228	95/27	1800	1.7	6.7	34 (80)	220	185	132/60	1350
G. S.	6.1	3.5	81 (75)	270	300	200/42	2960	2.7	10.3	36 (75)	190	185	225/67	3415
J. C.	8.3	3.1	106 (78)	290	365	105/46	1377	5.5	6.1	51 (108)	220	232	123/75	1236

\* Technically adequate paired pacing.

† Technically inadequate paired pacing.

*Isoproterenol Stimulation*

Isoproterenol infusion (Table III) raised the cardiac output in six of eight patients. The average output for the group increased to 4.3 liters per min, 39% greater than during the control state. The individual differences ranged from 12 to 100%. Arterio-

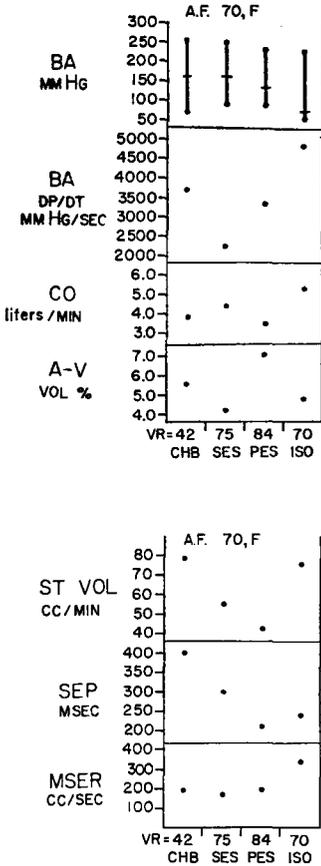


FIGURE 1. 70 yr old female with adverse hemodynamic events associated with paired pacing. Abbreviations: BA, brachial artery pressure; BA dp/dt, first derivative of brachial artery pressure; CO, cardiac output; A-V, arteriovenous oxygen difference; CHB, complete heart block state, spontaneous idioventricular rhythm; SES, single electrical stimulation; PES, paired electrical stimulation; ISO, isoproterenol infusion; ST VOL, stroke volume; SEP, systolic ejection period; MSER, mean systolic ejection rate.

venous oxygen difference decreased in all nine patients to a mean of 4.3 volumes %, or a reduction of 26%. Brachial artery dp/dt increased with isoproterenol in eight of the nine patients and in most instances was maximum for each patient in this phase of the study.

*Paired Pacing*

The effects of paired electrical stimulation on cardiodynamics at rest (Table III) depended upon the technical adequacy of the pairing. When the delay interval could not be reduced below 300 msec the second depolarization always was associated with a discrete mechanical event detected on the downslope of the right ventricular and

brachial artery pressure pulses. In the four patients in which this difficulty was encountered, designated as group 2, the associated effects resembled those of an "excessive" tachycardia. In each instance cardiac output fell to its lowest level and A-V oxygen difference was the greatest observed. This represented, in average values for the group, a decline of 20% from an already low control cardiac output, and a 30% increase in the A-V oxygen difference. One of these patients (A. F.) developed oppressive substernal pain within several minutes after the paired electrical stimulation was instituted and it had to be discontinued (Fig. 1).

In five of the nine patients, designated as group 1, paired electrical stimulation could be performed with technical adequacy, and in none could the second systole be

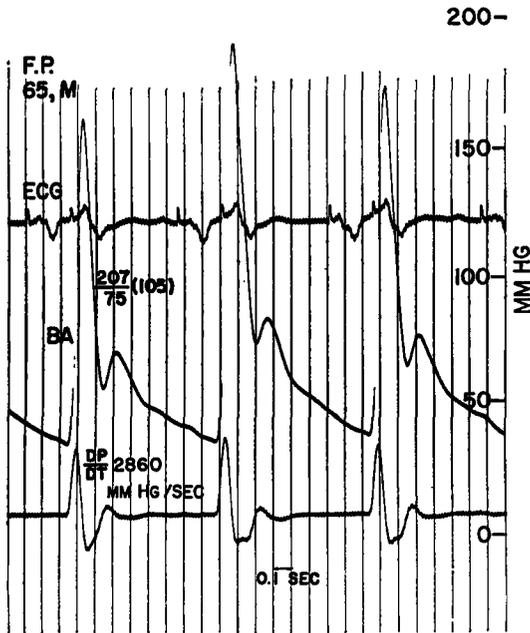


FIGURE 2. Brachial artery pressure pulse during technically adequate paired pacing in a 65 yr old male.

detected in the brachial artery or right ventricular pressure pulse (Fig. 2). Cardiac output was increased in two of these five patients, and more effectively in them than with acute isoproterenol infusion. The increase was 31% in one patient and 81% in the other (Fig. 3). The A-V oxygen difference in these two patients fell by 1.5 volumes % and 1.1 volumes % respectively as compared to values at the idioventricular rate. There were varying increments in A-V oxygen difference for the remaining three patients, so that for the group of five patients the average A-V oxygen difference was unchanged from control levels (Table IV).

The brachial artery  $dp/dt$  was consistently greater with paired electrical stimulation than with single pacing. This occurred whether the stroke volume increased, decreased, or remained unchanged. In three patients  $dp/dt$  was greater with paired pacing than with isoproterenol.

The systolic ejection period tended to decrease with paired pacing as compared to

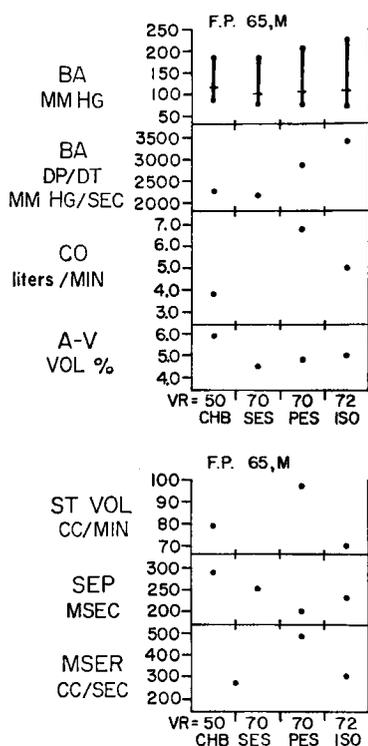


FIGURE 3. Increased cardiac output during technically adequate paired electrical stimulation. Abbreviations as in Fig. 1.

single pacing at the same mechanical rate. Mean systolic ejection rate increased notably only in those two patients whose stroke volume increased with paired as compared to single electrical stimulation.

DISCUSSION

In a previous systematic investigation of the hemodynamic effects of paired pacing in man, cardiac output did not increase with this intervention despite significantly en-

TABLE IV  
AVERAGE VALUES

	CHB	SES	ISO	PES	
				(5) Group 1 (adequate)	(4) Group 2 (inadequate)
C.O., liters/min	(8) 3.1	(6) 2.9	(8) 4.3	4.4	2.6
A-V oxygen difference, vol %	(9) 5.8	(8) 5.4	(9) 4.3	5.7	7.5
B.A., mm Hg	(9) 177/68	176/78	175/54	185/74	178/74
B.A.dp/dt, mm Hg/sec	(9) 2003	(8) 1868	(9) 2831	2709	2332
R.V., mm Hg	(9) 35/6	30/5	39/5	30/2	39/4
Heart rate	43	75	65	74	82

Numbers in parentheses indicate the number of patients involved in each average.

hanced contractility (8). The nine patients constituting that group were younger than those in the present study, and none was in heart failure nor in complete heart block. Comment (9) was made on eight subsequent patients with unexplained cardiomyopathy and congestive failure, who similarly did not show increased output with paired pacing.

Paired pacing in acute heart block has been studied in open chest anesthetized canine preparations (7), where it has been shown to produce increases in LV dp/dt, peak LV pressure, peak aortic flow, and stroke volume. The improvement in these parameters markedly increased when tricuspid valve regurgitation was acutely induced.

The present study demonstrates that when paired electrical stimulation is adequately performed in unanesthetized intact patients with acquired chronic complete heart block, cardiac output generally is not increased above that with single electrical stimulation at similar rates despite evidence of enhanced inotropic state; viz., changes in mean systolic ejection rate, systolic ejection period, and brachial artery dp/dt. A-V oxygen difference tended to widen suggesting that myocardial oxygen consumption was increased by this procedure. This has been noted and commented on by other investigators (3-11).

Isoproterenol infusion was most often associated with the greatest acute improvement in hemodynamic state at similar rates of contraction; i.e., greatest cardiac output, stroke volume, mean systolic ejection rate, brachial artery dp/dt, and smallest A-V oxygen difference. The observed effects of isoproterenol are in agreement with those previously reported (12-14).

Two patients were noted to have achieved greater hemodynamic improvement with paired pacing than with isoproterenol. However, one showed only a slight chronotropic and inotropic isoproterenol effect (S. DeS.). Other than the finding that a very short interstimulus interval could be achieved with these two patients (Table I), nothing else was noted which accounted for their unique response to paired electrical stimulation as distinguishing them from other patients.

In four of the nine patients studied the interstimulus interval could not be sufficiently reduced to eliminate the second mechanical event, even when maximum output of the pulse generator (10 ma) was briefly attempted. The applicability of the technique is thus seriously limited, as the resultant tachycardia in our patients was associated with rapid hemodynamic deterioration. We did not attempt to shorten the absolute refractory period by catecholamine stimulation since this carries the risk of lowering the fibrillatory threshold.

Cardiac output did not vary significantly in our patients from the states of spontaneous idioventricular rate and single pacing at rates of 70-80 beats per min. In this respect the group resembled Sowton's patients with the "flat" rate-resting output curves (15) whose outputs did not vary by more than 15% over a range of 30 beats per min. Half of the 28 patients in his study were in this category. The flat curve is suggestive of the well-functioning heart, which is able to preserve output over a wide range of rates (16, 17).

Although several of our patients appear to have markedly reduced cardiac outputs at rest, their responses to the various modalities of stimulus were considered in their relative rather than absolute sense.

## SUMMARY

Paired electrical stimulation was observed in nine patients with complete heart block by measurements of pressure pulses in the right ventricle, pulmonary artery, brachial artery, maximal rate of rise of pressure in the brachial artery, and cardiac output. The effects were compared to those produced by isoproterenol infusion and by single stimulation at similar ventricular mechanical rates.

In only five of the nine patients could paired electrical stimulation be performed with technical adequacy. All five evidenced an enhanced inotropic state but in only two of them was there an associated increase in cardiac output.

Isoproterenol infusion appeared to be a more effective and more easily applicable method of acutely increasing cardiac output than paired electrical stimulation in the patient with chronic heart block.

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# Experimental Paired Stimulation of the Ventricle and Its Clinical Application

LEON RESNEKOV, EDGAR SOWTON, PETER LORD, and  
JOHN NORMAN

From the Institute of Cardiology, National Heart Hospital, London, W.1., and the Department of Physiology, Royal College of Surgeons of England, London, W.C.1, England. Dr. Resnekov's present address is the Department of Medicine (Cardiology), University of Chicago, Chicago, Illinois 60637

Slowing of the heart may be achieved by electrical stimulation using an impulse of an excessively long duration or when two short stimuli are applied separated by an appropriate time interval (1). When two such stimuli are delivered to the ventricle the technique is called paired pulse stimulation and earlier reports (2-5) confirmed its use in slowing the heart. In contrast "coupled pacing" (6) is achieved by allowing the heart to respond to its own pacemaker and using the normal beat to trigger a stimulus which will provoke a premature response and the normal sequence of atrioventricular excitation is therefore retained; the experimental and clinical application of this technique has been well-documented (6-8).

In paired stimulation of the ventricle, with which this communication is concerned, the first stimulus of the pair drives the ventricle at a fixed rate and causes an effective mechanical systole. The second impulse, which is spaced to occur in the relative refractory period, results in an electrical premature beat without a corresponding mechanical contraction; the refractory period is prolonged and the rate of the heart is slowed. Since a premature electrical depolarization precedes every ventricular contraction, each mechanical beat shows the phenomenon of postextrasystolic potentiation (9).

In order to investigate the circulatory effects of the technique and to assess its usefulness in clinical practice a stimulator (Fig. 1) was designed and built by one of us (J. N.) and has since been modified to provide the additional facility of triple stimulation. In its original form, stimuli, either singly or in pairs, were delivered at rates between 30 and 250 per min with a 1 msec impulse duration at voltages up to 10 v. The strength of each stimulus was independently variable and the delay between the two stimuli could be adjusted to between 35 and 350 msec. The experimental studies were performed on a series of dogs under general anesthesia with sodium pentobarbital during maintained respiration with room air delivered through a cuffed endotracheal tube from a positive pressure pump. The chest was opened by a left thoracotomy and the heart stimulated directly either from the atrium or from the ventricle. Left ventricular pressure was measured through Teflon tubing (T.F. 30) or through gray KIFA tubing introduced into the apex of that chamber by the technique described by Seldinger (10) or passed retrogradely from the external carotid artery across the aortic valve and connected to a Sanborn

pressure transducer and carrier amplifier. The electrocardiogram was recorded from limb leads or more usually via an electrode catheter positioned in the right atrium from the jugular vein. Total blood flow immediately distal to the origin of the left subclavian artery was measured using an electromagnetic flowmeter and probes of appropriate size (Medicon), and all data were recorded on a multichannel oscillographic system (Phillips). Studies were performed during sinus rhythm and during artificially created supraventricular and ventricular tachycardia by driving the atrium or ventricle at rates up to 250 per min using an additional pacemaker. The clinical application of the technique was studied in patients seriously ill as a result of resistant dysrhythmias and also in patients with intractable heart failure to observe whether electroaugmentation (11) would occur and result in clinical improvement.



FIGURE 1. Paired stimulator of the ventricle.

## RESULTS

### A. Dog Experiments

#### 1. HEART RATE

(a) *Sinus Rhythm* Slowing of the heart rate below the sinus rate could always be achieved (Fig. 2). Maximal slowing to about 45% of the initial rate may result, for the first stimulus has to drive the heart. The delay between the two stimuli is critical and requires careful adjustment and readjustment as needed; if too long, a mechanical contraction may be associated with the second impulse but if the delay is too short, the second stimulus will fall in the absolute refractory period of the ventricle and a sinus beat will interpose (Fig. 3).

(b) *Supraventricular Tachycardia* No difficulty was experienced in controlling supraventricular tachycardia created by driving the atrium with a second pacemaker at rates of up to 250 beats per min.

(c) *Ventricular Tachycardia* The ventricle was stimulated by a second pacemaker at a rate of 214 per min (Fig. 4) which caused a profound decrease in aortic flow and left ventricular pressure. While paired stimulation reduced the ventricular rate to 118 per min associated with an improvement in the circulatory state, interference cycles were recorded (Fig. 5) between the paced tachycardia beats and those caused by the paired stimulator. Nevertheless even under these circumstances when

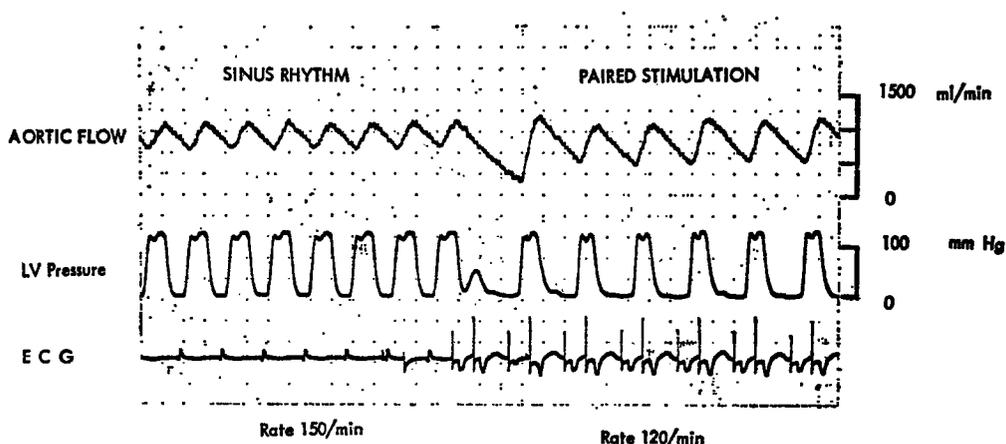


FIGURE 2. Sinus rhythm slowed from 150 to 120 per min with the onset of paired stimulation. From above downwards are recorded flow in the thoracic aorta, pressure in the left ventricle and the electrocardiogram. Only one mechanical beat results from each pair of electrical depolarizations. Notice slurring of the descending limb of the ventricular pressure pulse during paired stimulation. Figs. 2-7 are reproduced with the kind permission of the Editor of the *British Heart Journal*. 1966. 28:622 ff.

the ectopic focus could not be depolarized adequately, the over-all hemodynamic effects of the ventricular tachycardia were still diminished by paired stimulation.

## 2. ELECTROAUGMENTATION

The first derivative of the left ventricular pressure pulse ( $dp/dt$ ) is frequently used as an index of myocardial potentiation but its dependence on heart rate must be allowed

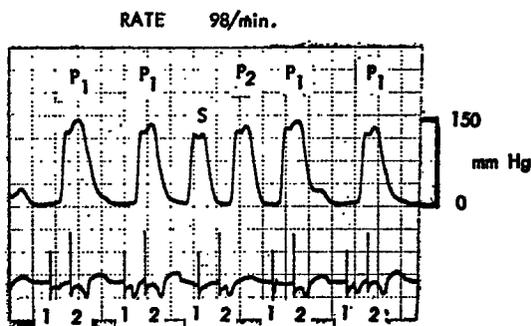


FIGURE 3. Incorrect adjustment of the delay between the first and second stimuli. Pressure in the left ventricle (above) is recorded with the ECG (below) during paired stimulation at an effective heart rate of 98 per min. The driving stimulus is labeled 1 and the paired stimulus 2. The first two left ventricular beats result from the first stimulus of each pair and are labeled  $P_1$ . The delay of the paired stimulus of the second beat is short, occurs when the ventricle is in the absolute refractory period, and has allowed a sinus beat (S) to interpose. The beat following ( $P_2$ ) has resulted from the second (2) of the next pair for the ventricle was refractory to the first (1), but thereafter paired stimulation recurs.

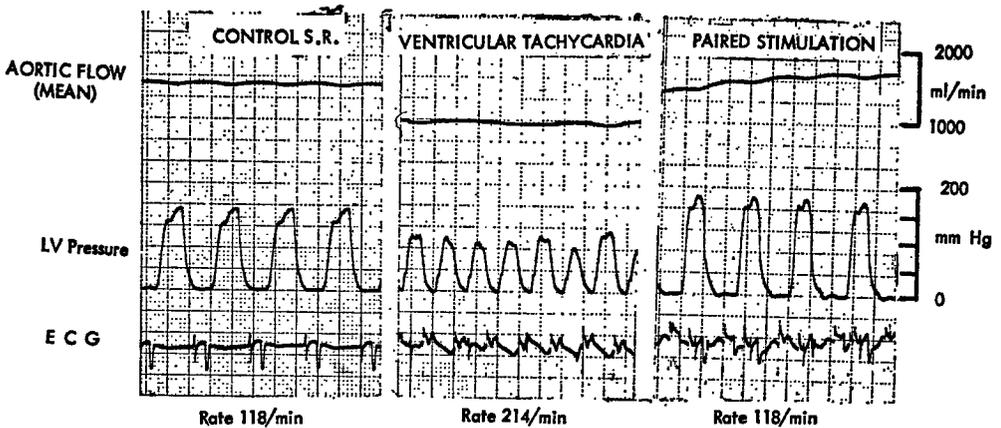


FIGURE 4. Paired stimulation of an artificially created ventricular tachycardia. Mean flow in the thoracic aorta is recorded above simultaneously with pressure in the left ventricle (middle) and a right atrial intracavitary ECG lead (below). Sinus rhythm is recorded on the left. The onset of ventricular tachycardia produced by stimulating the ventricle at a rate of 214 per min is associated with a considerable fall in aortic flow and in pressure in the left ventricle. The ventricular rate is slowed to 118 per min by paired stimulation followed by an increase both in left ventricular pressure and in aortic flow.

for (5). It is important, therefore, that the effect of electroaugmentation during paired stimulation be demonstrated at a rate identical to the control sequence (Fig. 6). A significant increase in both left ventricular pressure and  $dp/dt$  is demonstrated at an equivalent ventricular rate despite the absence of atrial contribution to ventricular filling during paired stimulation since the stimulatory electrodes were attached to the ventricle. Unless cardiac output was reduced during the control period no corresponding increase in aortic flow was recorded during paired stimulation despite the increased contractile force obtained. A sustained increase in flow was always

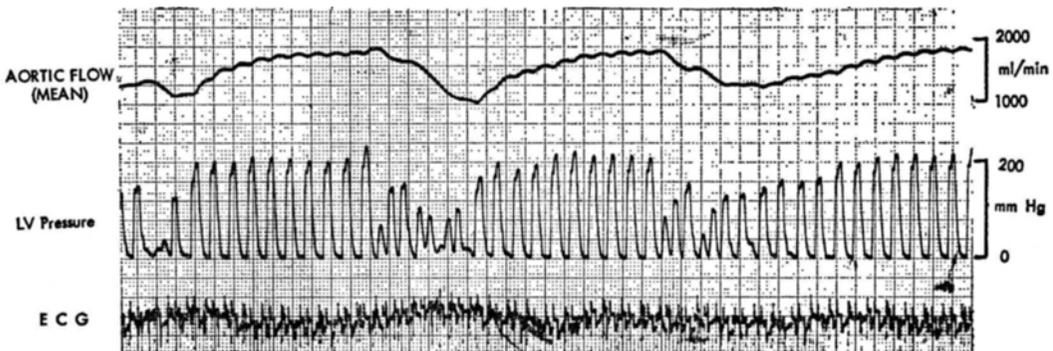


FIGURE 5. Paired stimulation of ventricular tachycardia, interference cycles. The layout is as in Fig. 4. Interference cycles between the driving pacemaker and the paired stimulator result in short runs of ventricular tachycardia associated with a reduction in aortic flow and left ventricular pressure.

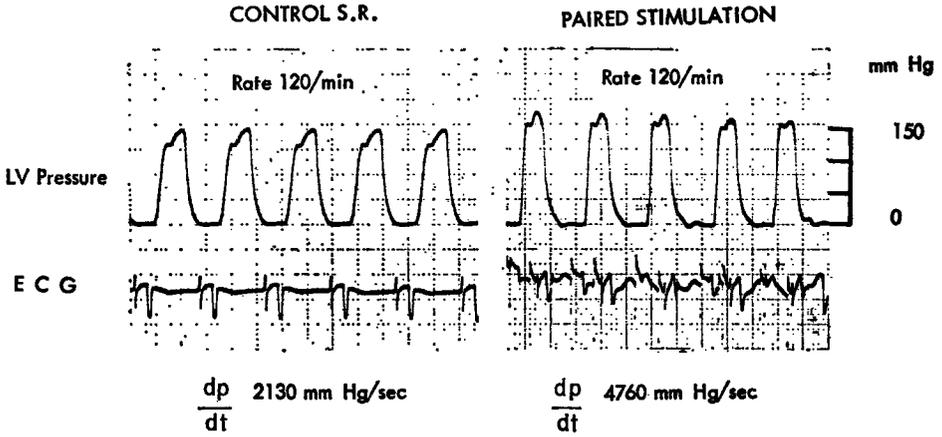


FIGURE 6. Electroaugmentation produced by paired stimulation. Pressure in the left ventricle (above) is recorded simultaneously with a right atrial intracavitary lead (below) first in sinus rhythm and then during paired stimulation, both at a ventricular rate of 120/min. Pressure in the left ventricle has increased by 16% and  $dp/dt$  by 125% during paired stimulation.

recorded, however, when cardiac output was reduced during sinus rhythm or as a result of a rapid dysrhythmia (Fig. 4). The positive inotropic action of paired stimulation could also be demonstrated by the response of the left ventricular end-diastolic pressure; when raised during the control period a fall to normal values often occurred shortly after the onset of paired stimulation (Fig. 7).

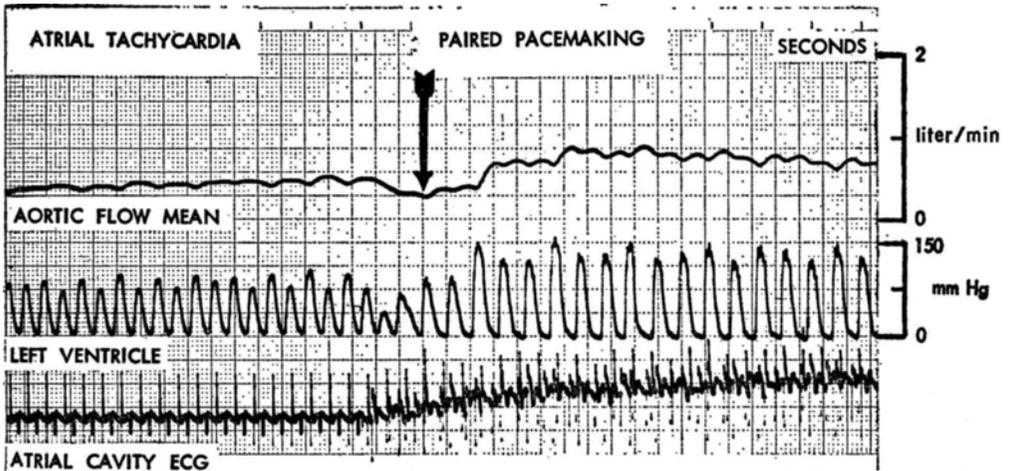


FIGURE 7. Positive inotropic action of paired stimulation. A ventricular rate of 190 per min produced by a paced atrial tachycardia is slowed to 140 per min during paired stimulation. An increase in mean flow in the aorta and a fall in left ventricular end-diastolic pressure are recorded shortly after the onset of paired stimulation.

### *B. Clinical Application*

Paired stimulation has been used in an attempt to control the ventricular rate in resistant dysrhythmias and to improve the circulatory state in intractable heart failure. The following are five illustrative examples.

1. A man of 23 yr developed an atrial tachycardia (ventricular rate 180 per min) in association with the Wolff-Parkinson-White syndrome which proved to be completely resistant to drug therapy and direct current shock. His condition deteriorated rapidly, severe heart failure occurred, and he became semiconscious due to a low cardiac output; extreme peripheral vasoconstriction was present. Paired stimulation was attempted following the positioning of an electrode catheter in the right ventricle; the heart responded to both stimuli and ventricular fibrillation followed immediately thereafter but was converted to normal sinus rhythm by a single unsynchronized direct current shock.

2. A woman of 58 yr developed a ventricular tachycardia at a rate of 170 per min following a recent myocardial infarction which failed to respond to routine medical treatment. Paired stimulation was attempted to the right ventricle via a transvenous electrode catheter. It proved impossible to find a satisfactory delay between the two stimuli which would ensure pairing but would not provoke ventricular dysrhythmias despite maintaining the stimulus strength at just above threshold levels and changing the driving rate. The attempt at paired stimulation was, therefore, abandoned.

3. A man of 50 yr developed supraventricular tachycardia and atrial fibrillation at a mean ventricular rate of 202 per min in the postoperative period following aortic and mitral valve replacement under cardiopulmonary bypass. Drug and electrolyte therapy and DC shock all failed to control the tachycardia. An electrode catheter was passed to the right ventricle, a fine polyethylene catheter (Portex F.G. 3) "floated" to the pulmonary artery, a fine Teflon tube (T.F. 11) passed by the Seldinger technique to the brachial artery, and paired stimulation of the ventricle commenced. The ventricular rate was slowed to 130 per min, the pulmonary arterial saturation rose from 34% to 56%, and the systemic arteriovenous oxygen difference fell from 83–56 ml per liter. Paired stimulation was continued for 48 hr during which time considerable clinical improvement occurred.

4. A man of 64 yr known to have had atrial fibrillation for some years developed a myocardial infarction which was followed by a ruptured ventricular septum and the sudden development of severe congestive and left ventricular failure. Routine treatment failed completely to improve his condition and paired stimulation was undertaken to obtain the benefit of electroaugmentation in an attempt to improve his circulatory state prior to surgical repair of the ventricular septum. The presence of a left to right shunt at ventricular level was confirmed at cardiac catheterization and following the collection of control data, the hemodynamic effects of single and paired stimulation of the right ventricle were noted (Table I). The pulmonary:systemic flow ratio remained at 2:1 throughout, and electroaugmentation as shown by an improvement in  $dp/dt$  did not occur. The systemic arteriovenous oxygen difference did not improve nor were any beneficial changes recorded in the aortic, pulmonary arterial, pulmonary "wedge," or right atrial pressures. Although some improvement in cardiac output and stroke volume was found, these changes were rate-dependent and there was no evidence that they were produced by a positive inotropic effect of paired stimulation. The technique was maintained for 24 hr without objective clinical evidence of benefit.

5. This was a woman 48 yrs old in chronic left and right ventricular failure, secondary to rheumatic mitral stenosis and regurgitation, aortic stenosis and regurgitation, restrictive pulmonary hypertension, tricuspid regurgitation, and atrial fibrillation. The mean ventricular rate was 80 per min and paired stimulation was undertaken in an attempt to improve myocardial function

TABLE I  
HEMODYNAMIC RESULTS, SINGLE AND PAIRED VENTRICULAR STIMULATION IN ACUTE HEART FAILURE—MYOCARDIAL INFARCTION AND RUPTURED VENTRICULAR SEPTUM (CASE 4)

Note: Pressures in mm Hg, with reference to the sternal angle.

Rhythm	VR	RAm	RV			PA			PCm	Aorta				AVDO <sub>2</sub>		Flow		SV		P:Sy
			S	D	dp/dt	S	D	M		S	D	M	dp/dt	P	Sy	P	Sy	P	Sy	
AF	110	19	66	0-18	470	64	18	42	20	115	85	98	900	40	82	5.7	2.8	52	25	2:1
SP	125	19	60	0-18	300	60	13	34	20	115	75	85	960	46	90	5.0	2.5	40	20	2:1
PS	75	19	58	0-18	470	60	13	35	20	115	70	85	900	38	78	6.0	3.0	80	40	2:1

AF, atrial fibrillation  
 SP, single pacemaking  
 PS, paired stimulation  
 VR, ventricular rate per min  
 RAm, mean right atrial pressure  
 RV, right ventricle  
 S, systolic pressure  
 D, diastolic pressure  
 dp/dt, first derivative of pressure pulse, mm Hg per sec

PA, main pulmonary arterial pressure  
 M, mean pressure  
 PCm, mean pulmonary "wedge" pressure  
 AVDO<sub>2</sub>, arteriovenous oxygen difference, ml per liter  
 P, pulmonary  
 Sy, systemic  
 Flow, output in liters per min  
 SV, stroke volume, ml  
 P:Sy, pulmonary:systemic flow ratio

prior to mitral and aortic valvular replacement. Control values in atrial fibrillation confirmed the severity of the lesions but as can be seen (Fig. 8) paired stimulation at a similar ventricular rate produced a marked deterioration with a reduction in cardiac output to even lower levels, an increase in the gradient across the mitral valve, and a fall in the systemic arterial pressure; electroaugmentation failed to occur and paired stimulation had to be abandoned.

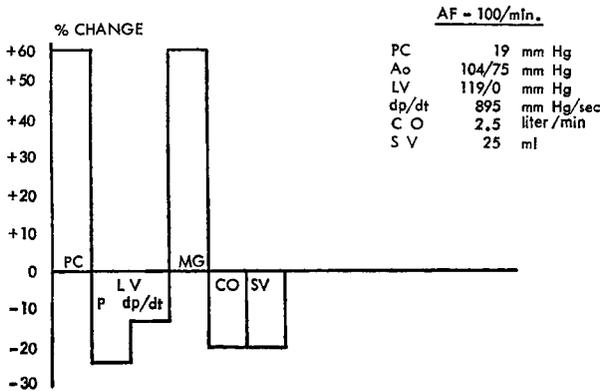


FIGURE 8. Percentage changes recorded when paired stimulation of the ventricle was used in chronic heart failure due to rheumatic heart disease with severe mitral and tricuspid regurgitation (case 5). Control values in atrial fibrillation. AF, atrial fibrillation; Ao, ascending aorta; dp/dt, first derivative of left ventricular pressure pulse; SV, stroke volume; P, pressure; PC, pulmonary "wedge" pressure; LV, left ventricle; CO, cardiac output; MG, diastolic gradient, mitral valve; pressures with reference to the sternal angle.

## DISCUSSION

The principle of paired stimulation (1) is that the first of the pair of electrical stimuli drives the ventricle at a fixed rate while the second is timed to occur in the relative refractory period when electrical depolarization unaccompanied by a mechanical contraction will occur. The sinus node may be suppressed or sinoatrial dissociation occur to prevent the normal pacemaker from driving the heart but it is more likely that the atrioventricular junction is kept unresponsive by concealed retrograde conduction of each electrical impulse; retrograde stimulation of the atria may also be caused. The net result is that the refractory period is prolonged. One mechanical contraction follows each pair of electrical depolarizations and the ventricular rate is slowed. Experimental and clinical reports have confirmed (1-5) the effectiveness of the technique in controlling the rate of the heart.

Since a premature electrical depolarization precedes each mechanical contraction the phenomenon of postextrasystolic potentiation (9) will occur. This effect is an inherent property of heart muscle and, while in the intact heart there is a longer time for filling of the ventricle during the compensatory pause which follows an ectopic beat, a similar potentiating effect follows interpolated extrasystoles (12), or when isolated strips of atrial or ventricular muscle are mounted so that only isometric contraction will occur. The earlier the postextrasystolic beat the greater is its potentiating effect (13) and augmentation will still occur when the extrasystole comes so early in the relative refractory period that no mechanical response is possible (14). The effects of postextrasystolic potentiation may be demonstrated, particularly in a ventricle contracting against a heavy resistive load or in the failed ventricle (15, 16), by an increase in the maximal force of contraction during systole to 64% of the control values at any given ventricular volume (17), by an increase in the rate of development of tension, an increase in the rate of relaxation, and by an increase in the velocity of myocardial fiber shortening (18). A sustained positive inotropic action is seen particularly in myocardial failure by a reduction in the ventricular end-diastolic pressure when raised, an increase in the cardiac output when reduced, and a decrease in the size of the heart. The fall in the raised end-diastolic pressure has been attributed (19) to an increase in diastolic compliance of the heart produced during paired stimulation and while not all workers accept this explanation a similar effect has been demonstrated in isolated muscle preparations. If this is so it follows that the end-diastolic pressure can no longer be accepted as a guide to the end-diastolic volume (16). The fundamental mechanism underlying postextrasystolic potentiation is not known. The effect can always be demonstrated unless calcium levels are markedly elevated (20), and occurs even in hearts treated with reserpine, suggesting that the local release of norepinephrine does not play a significant role (11). Loss of potassium ions may be important (21) and an influx of calcium ions has been shown to be related to the degree of depolarization and to be involved in positive inotropic effects (22).

The observed hemodynamic effects of paired stimulation in acute heart failure in experimental animals are often dramatic and gratifying (Figs. 4 and 7) and have been confirmed by many reports (15, 23-25) sometimes in terms of hyperbole (16). Although slowing of the heart will result in a longer diastolic filling time and a bigger

stroke volume, the cardiac output is not increased unless myocardial function is depressed during the control period (2, 5, and 23); despite an increase in myocardial contractility cardiac output and arterial pressure were both reduced during paired stimulation when myocardial function was normal (18). The positive inotropic action is most marked when myocardial function is more severely affected possibly due (18) to the differing contractility response of the failing and nonfailing heart, the increase in the end-systolic volume in heart failure more easily permitting a positive inotropic effect to result in an increase in stroke volume, and to the failure of reflex mechanisms in heart failure to initiate compensatory phenomena which would maintain a steady cardiac output despite paired stimulation. The effect of paired stimulation is similar to that of digitalis although acetylcholine tends to elevate arterial pressure more than does paired stimulation (18). The increase in ventricular contractility produced by paired stimulation in the intact heart can still

TABLE II  
CLINICAL INDUCTION OF PAIRED STIMULATION  
(PS) OF THE VENTRICLE

An example of the settings to be used when a ventricular rate of 200 per min is to be slowed to 110 per min.

Ventricular rate, tachycardia	200/min
Ventricular rate, PS (55%)	110/min
Mechanical time interval, <i>msec</i>	540
Electrical depolarizations	220/min
Delay between pulses, <i>msec</i>	290

be augmented by an infusion of norepinephrine (17) which is unlike the effect of paired stimulation on isolated cat papillary muscle or on the isovolumic dog ventricle in which a pharmacological intervention fails to provoke any additional inotropic effect.

Despite the considerable literature on the experimental and basic aspects of the technique the indications for its clinical application have not yet been established. This is perhaps regrettable for its action particularly in controlling heart rate is most useful and the technique should be available in every intensive care unit. Nevertheless it is well to remember that it is a demanding technique to be employed only by those trained in its application and that patients being treated by paired stimulation require constant attention and frequent readjustment of the delay between the two stimuli. The five examples presented in the clinical section of this paper were chosen to demonstrate not only the beneficial effects of the technique but also the problems and difficulties that might be encountered. It is important to ensure that the heart will not respond to both electrical stimuli (see case 1) by determining the appropriate driving rate of the first stimulus and the correct delay between the first and the second, before starting to stimulate the heart (Table II); small readjustments may then be made safely to obtain the maximal potentiating effect if desired. We feel that although not essential, a simultaneous record of a ventricular pressure pulse is desirable and helpful in adjusting the delay (Fig. 3); the stimuli should be at

the lowest effective electrical energy by using an impulse of not more than 1 msec width at just above threshold levels to lessen the risk of ventricular fibrillation. We have not met the problems that have been reported (3) when paired stimulation is stopped and our routine is to allow the spontaneous pacemaker to dominate rapidly over several beats by stopping the second impulse and reducing the rate and amplitude of the first. Even when all precautions are observed, however, certain groups of patients may be unsuitable for paired stimulation. Our experience in the use of paired stimulation for the control of dysrhythmias in association with coronary arterial disease (case 2) has been unhappy. Although the second impulse has to be placed close to the vulnerable phase of the ventricle for ventricular fibrillation, this by itself is not likely to be the cause. It has been demonstrated (26) that paired stimulation following acute experimental coronary arterial occlusion results more frequently in ventricular fibrillation than does single pacemaking, and a slower heart rate (27) which results in asynchrony of the recovery of excitability of the ventricles implicated; irregular perfusion of the ventricles (28) will have a similar effect and predispose to the development of postextrasystolic rhythms. Both in coronary arterial disease and in complete atrioventricular dissociation (16) where once more an induced postextrasystolic beat may cause repetitive activation, a relatively high basic heart rate should be chosen if paired stimulation is to be used at all, and the threshold for stimulation kept at no more than twice the diastolic level.

Disturbances in rhythm occurring during the postoperative period following open heart procedures have responded well to paired stimulation (case 3); the heart rate has usually been easily controlled resulting in an improved circulatory state. Paired stimulation should be considered in any patient in whom electroconversion and drug therapy fail to control the heart rate and should be used before serious effects of the tachycardia are allowed to develop.

Its use in acute (case 4) or chronic (case 5) heart failure to improve myocardial function when ventricular rate per se is not the problem, is more debatable. In neither patient did we obtain any improvement in the circulatory state or indeed any hemodynamic evidence that electroaugmentation had occurred. Atrial fibrillation was present in both, so that the loss of atrial systole which accompanies the use of paired stimulation of the ventricle in sinus rhythm could not be the cause. Clinical experience (7, 29) indicates that despite the documented beneficial action of paired stimulation in acute experimental heart failure, the increased myocardial contractility that results is not often accompanied by an increase in cardiac output when used in patients with a reduced myocardial function. Although it has been considered (2) that no mechanical event need follow the early second depolarization, slurring of the descending limit of the ventricular pressure is almost inevitably seen (Fig. 2) and may well impede ventricular filling. Furthermore the pathway of ventricular excitation is now quite abnormal and in addition, closure of the atrioventricular valves is interfered with (30). It may well be that where it is important to preserve atrial systole, coupled rather than paired stimulation should be used as advocated by Frommer (6). Considerable hemodynamic deterioration followed the use of paired stimulation in case 5 (Fig. 8) where the technique presumably increased the regurgitant volume across the mitral and tricuspid valves and it is likely that the technique should be avoided in patients with significant mitral and/or tricuspid valvular regurgitation.

There now seems to be little doubt that the myocardial oxygen consumption is increased during paired stimulation of the ventricle (4, 7, 8) even when the cardiac output remains unchanged. The amount of oxygen needed for electrical activation of the heart is less than 1% of the total myocardial oxygen consumption (31) and can therefore not be responsible for increases which are in the order of 35%, which probably result from the increased speed of contraction (11) during paired stimulation; comparable increases in external work of the ventricle did not occur, however, and the tension-time index (32) was actually reduced presumably due to the fact that this parameter could not reflect energy used to generate the increased rate of contraction. In contrast, however, indirect evidence (33) suggests that myocardial oxygen consumption might even be reduced when the rate of the heart is slowed by paired or coupled stimulation of the atria, an observation that might have considerable clinical significance. An inability to provide the additional myocardial oxygen requirements because of coronary arterial disease or ventricular hypertrophy might well be responsible for the disappointing results observed when paired stimulation of the ventricle is used clinically to improve myocardial function. Triple stimulation of the ventricle, despite the occasional report of its successful use in controlling rhythm disturbances (34), is presumably as limited as paired stimulation in this respect for although the heart may be slowed even further, additional electroaugmentation is not obtained (6). The hope that, during paired stimulation a concomitant increase in coronary arterial flow (35) would compensate for any increased need for oxygen supplies to the heart, is unfortunately not often realized in its clinical use.

#### SUMMARY

The hemodynamic results following the use of paired stimulation of the ventricle in experimental animals are described and the basic principles underlying its action discussed. Its clinical application is described on the basis of selected groups of patients. Although demanding as a technique, paired stimulation of the ventricle should be available in any unit undertaking intensive care, particularly for its action in controlling ventricular rate; dysrhythmias in the postoperative period following heart surgery will respond particularly well. Undue slowing of the heart is undesirable in patients with coronary arterial disease in whom the technique has to be used with caution; similarly patients with atrioventricular dissociation may be unsuitable for paired stimulation. Atrioventricular regurgitation may be increased during paired stimulation of the ventricles and the technique should be used with caution, if at all, in such patients. Although experimentally induced acute heart failure responds well to its positive inotropic action, its clinical use to improve myocardial function when rate disturbance is not present frequently proves disappointing and the reasons for this are discussed with reference to the underlying mechanisms of the technique and to the myocardial oxygen requirements during paired stimulation of the ventricle. Coupled rather than paired stimulation of the ventricle, or coupled or paired stimulation of the atrium in the absence of conduction defects, might be a more appropriate technique in the presence of myocardial dysfunction.

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# The Effect of Atrial Depolarization on the Response to Subthreshold Stimulation of the Ventricles

## *A preliminary report of clinical and experimental observations*

E. R. ARBEL, R. LANGENDORF, A. PICK, and LOUIS N. KATZ

From the Cardiovascular Institute and the Division of Cardiovascular Disease, Department of Medicine, Michael Reese Hospital and Medical Center, Chicago, Illinois 60616

The method of coupled or paired electrical pacing of the heart lends itself to the exploration of the responsiveness of cardiac tissue to stimulation during various portions of the cardiac cycle. Extensive studies of myocardial excitability have shown that the diastolic period is a stable state of excitability. Strength duration and strength interval curves showed the threshold of stimulation to be constant throughout the diastolic period (1).

Subthreshold stimulation via a transvenous right ventricular catheter electrode in patients with complete A-V dissociation due to an advanced A-V block revealed that ventricular responses occurred when stimuli were delivered in a close time relation to spontaneous atrial depolarization. In this preliminary report one example of a clinical and one of an experimental observation in the dog will be presented to illustrate this phenomenon.

Fig. 1 shows three portions, A, B, and C, of a continuous electrocardiogram of a 74 yr old patient with complete A-V dissociation due to advanced A-V block and with a spontaneous supraventricular pacemaker discharging at a rate of 43 per min. In each portion, the upper strip is continuous with the lower one; in panels A and B, the last ventricular complex of the upper is repeated as the first ventricular complex of the lower strip; in panel C the last three ventricular complexes are repeated in this manner. The subthreshold artificial stimuli are indicated by arrows. Each is coupled to the spontaneous R wave at an almost constant interval of 800 msec. Their relationship to the P waves changes periodically due to the presence of a slight sinus arrhythmia (the sinus cycle varies between 820 and 880 msec). Most of the stimuli falling shortly after the beginning of a P wave are effective and yield premature ventricular complexes, marked with large arrows. The other stimuli, mostly preceding a P wave, are ineffective; these are marked with small arrows.

Fig. 2 shows the percentage of effective subthreshold stimuli in relation to their

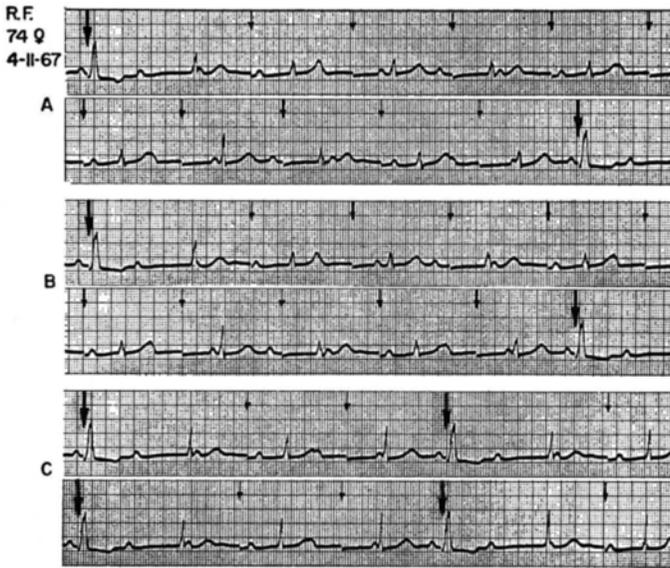


FIGURE 1. Electrocardiogram obtained on a 74 yr old white woman with advanced A-V block. Monopolar cathodal subthreshold ventricular stimulation via catheter electrode, coupled to R waves with Medtronic 5837D pulse generator. Stimulus intensity 3.65 ma. Threshold 3.7 ma. See text for explanation.

distance from the beginning of the P wave (P-S interval). A total of 589 stimuli was administered in the entire record. The peak incidence of about 55% of the effective stimuli occurs at P-S intervals of 100–200 msec. This is followed by a period of 580–680 msec during which the number of effective stimuli was markedly reduced (to

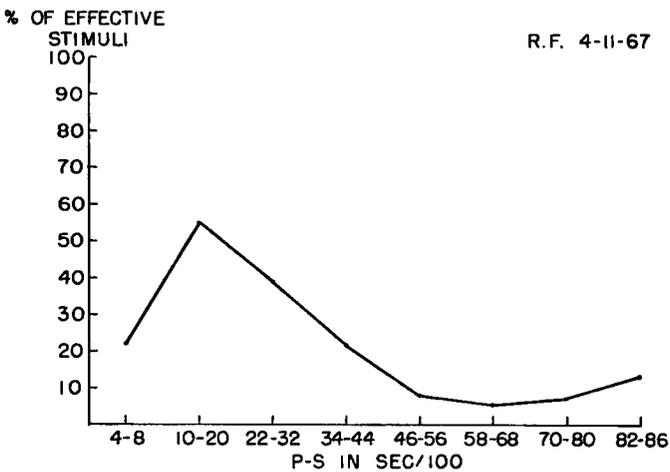


FIGURE 2. Percentage of ventricular responses to subthreshold stimulation in relation to spontaneous atrial depolarization in the entire record illustrated in Fig. 1. See text for explanation.

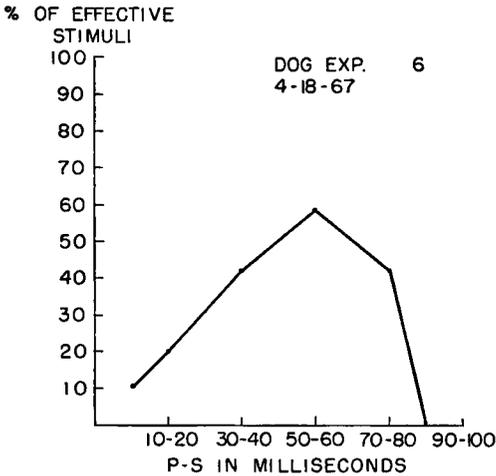


FIGURE 3. Mongrel dog. Monopolar anodal subthreshold ventricular epicardial stimulation coupled to R waves. Percentage of ventricular responses in relation to spontaneous atrial depolarization. Stimulus intensity 0.93 ma. Threshold 1.2 ma. See text for explanation.

4%). At a P-S interval of 860 msec there is a slight rise to an incidence of 13% of effective stimuli.

Such enhancement of response to subthreshold pacing of the ventricles by spontaneous atrial depolarization was investigated experimentally in the anesthetized dog with normal A-V conduction.

Fig. 3 summarizes the experimental results of 227 subthreshold anodal test stimuli of constant strength applied via an epicardial right ventricular electrode in a dog. It shows, as does Fig. 2, the percentage of effective stimuli in relation to their distance from the beginning of atrial depolarization (the P-S interval). The curve starts with

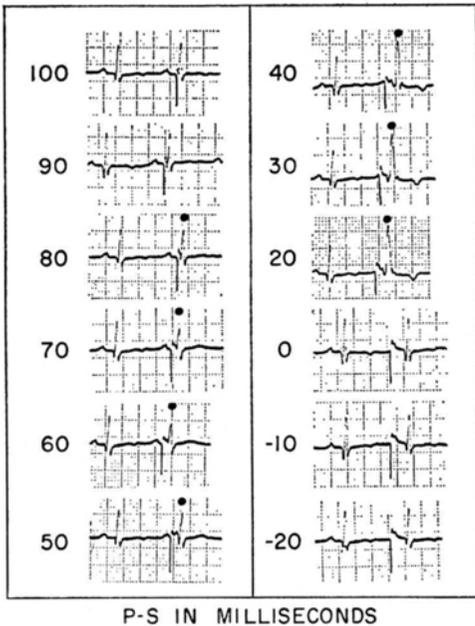


FIGURE 4. Same dog experiment as in Fig. 3. Portions of an electrocardiogram showing ventricular response to subthreshold stimulation dependent on temporal relation between atrial depolarization (P) and artificial ventricular stimulus (S). Effective stimuli are indicated by dots.

12% effective stimuli that just precede sinus P waves, reaches its peak of 60% effectiveness at P-S intervals of 50–60 msec, and falls to zero response at a P-S interval of 80 msec. In the remaining portion of ventricular diastole, during the P-R interval (up to 100 msec), there is a complete failure of response to the same subthreshold stimulus.

The actual records of this experiment are illustrated in Fig. 4 which shows representative portions of a continuous electrocardiogram recorded with double speed (50 mm per sec). Responses to the subthreshold ventricular stimulation are marked with dots. A response does not occur until the P-S interval shortens to about 80 msec. Here, and up to a P-S of 40 msec, the artificial stimulus shares with a conducted sinus impulse in ventricular depolarization, giving rise to a ventricular fusion beat. Thereafter, with a P-S interval of 30–20 msec, the ventricular activation is entirely the result of the artificial stimulus. At P-S intervals shorter than 20 msec the artificial stimuli are ineffective.

The enhancing effect of atrial depolarization on ventricular excitability, although mentioned by Soloff and Fewell (2), apparently has remained unrecognized until Fisch and Knoebel<sup>1</sup> recently observed it in man.

We are pursuing further the present observations on the influence of atrial depolarization on ventricular excitability both in patients with A-V block and in dogs in which A-V conduction has been interrupted. The latter procedure is necessary because of the rapid natural rate of the dog heart which tends to bring the P wave so close to the T wave that it becomes impossible to separate the well-established supernormal phase of excitability in the early phase of the cycle from the lowered threshold of excitability associated with atrial depolarization.

As an extension of the above studies, recent observations in two patients with normal A-V conduction suggest that the enhancing effect of atrial depolarization on ventricular excitability may be a physiological phenomenon not dependent on the presence of A-V conduction block. This was assumed by Fisch and Greenspan (3) in analogy to the nervous impulse producing an increase in excitability beyond a region of block (4, 5). However, we concur with their explanation of ventricular response to subthreshold stimuli late in diastole as the result of summation with the electrotonic spread to the ventricles of the atrial depolarization potentials.

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<sup>1</sup> Fisch, C., and S. B. Knoebel. Unpublished observations.

# Ventricular Coupled Stimulation in Myocardial Infarction with Severe Cardiocirculatory Insufficiency

## *A preliminary report*

RENE GOURGON, PHILIPPE COUMEL, GILBERT MOTTE,  
DANIEL LAURENT, and YVES BOUVRAIN

From the Centre de Soins Intensifs, Service de Cardiologie, Hôpital Lariboisière, Paris, et  
Centre d'Etudes des Techniques Chirurgicales (C.N.R.S.), Hôpital Broussais, Paris, France

This preliminary account reports attempts to apply ventricular coupled pacing (VCP), a method described by Frommer and Braunwald (11), to patients with myocardial infarction. A single delayed stimulus is applied to the ventricle, following each spontaneous depolarization. In the presence of sinus rhythm without retrograde ventriculoauricular conduction the occurrence of the electrically induced ventricular premature systole makes the ventricle refractory to the next auricular excitation. Thus the effective cardiac period becomes twice the sinus period. Such a method is primarily an elective procedure for slowing the heart. Moreover the maintenance of a normal mechanical auriculoventricular sequence favors the maximal reinforcement of the efficient ventricular contraction (10, 13).

At least in pharmacologically depressed hearts, both cardiac output and mean aortic pressure may be markedly increased (13, 21). Furthermore, in comparison with the ventricular paired stimulation, the advantages of the coupled pacing technique appear to be: (a) a greater prolongation of diastole, (b) a lessened probability of causing ventricular fibrillation (5, 10), and (c) at least at high cardiac rates, a lessened myocardial oxygen uptake for the same amount of external cardiac work, resulting in an enhancement of mechanical heart efficiency (19). These features seemed to justify the trial of VCP on patients with acute severe coronary shock and cardiac failure.

## MATERIAL AND METHODS

A No. 6 USCI unipolar catheter was advanced under fluoroscopy into the right ventricle, until it came into contact with the apical endocardium; 2.5 msec rectangular impulses, triggered on the R waves of a suitable ECG lead after an adjustable delay were delivered through an isolation unit. The trigger circuit was provided with an adjustable refractory period<sup>1</sup> so that it was not activated by the induced premature systoles. The voltage of the stimulus was ad-

<sup>1</sup> Manufactured by Serdal, 77-St. Remy les Chevreuse, France.

justable within the 0–20 v range. Only the cathode was used as an active electrode. In each case, by applying the impulses in late diastole after completion of the refractory period, the diastolic excitability threshold was determined; as a rule, this threshold did not exceed 3 v (case 4 was the only exception). Then with the same voltage setting, the R impulse delay was progressively shortened to the minimal value compatible with an efficient stimulation; depending upon the heart rate this value varied from 230 to 400 msec. The ECG was permanently monitored and clinical evaluation was done at regular intervals.

About every 60 min coupled pacing was systematically discontinued for 10–25 min in order to evaluate the possible changes in the clinical state; when pacing was reestablished, voltage and R impulse delay were adjusted if necessary.

### CASE REPORTS

Table I summarizes the clinical results, immediate and late, obtained in eight trials on seven patients with myocardial infarction and cardiogenic shock. The presence of a recent infarction was established by electrocardiographic evidence and enzymatic blood tests, with one exception (case 2, 21 days infarction). All patients were in a critical, desperate state; coupled pacing was only attempted after failure of other therapeutic measures. These patients exhibited a striking decrease in blood pressure (below 80 mm Hg, systolic), except in two cases of long-standing hypertensive cardiovascular disease (cases 3 and 6). Clinical evidence of shock was assessed from signs of severe circulatory impairment such as pallor, cold extremities, profuse sweating, dulled sensorium, and anuria. In four patients pulmonary edema was present. Except for one patient (case 5) neither digitalis nor pressor amines nor diuretics were given during the course of VCP.

#### *Case 1 (Fig. 1)*

J. H., a 55 yr old male patient, an established coronary case for 8 yr, was admitted with electrocardiographic evidence of a recent anteroseptal infarct with auricular fibrillation and pulmonary edema. DC cardioversion was immediately achieved. 10 hr later an attack of pain occurred, and a state of severe shock ensued (systolic BP, 60 mm Hg). Under norepinephrine infusion some increase in BP was observed, but 8 hr later the clinical state was found to have deteriorated as evidenced by extreme coldness and pallor, profuse sweating, persisting anuria, diffuse rales over the chest, and obtundation with episodes of agitation. 20 min after discontinuing the norepinephrine infusion, coupled right ventricular pacing was undertaken. A regular efficient cardiac rate of 61 per min was obtained. Blood pressure rose from 75 mm Hg (systolic) to 120/80 mm Hg and later on was maintained at about 95/65 mm Hg. Almost immediately after starting VCP, the clinical state was drastically transformed: consciousness was regained, sweating and chest rales disappeared and within the first 4 hr 150 ml of urine were passed. 30 hr later, when VCP was stopped all symptoms of shock and pulmonary edema had cleared. BP was stabilized at about 120/80 mm Hg. A good clinical condition persisted during the 17 following days. Unfortunately a new lateral infarct occurred, complicated by runs of ventricular tachycardia. Repeated attempts at ventricular coupling although effective in reducing cardiac rate from 140 to 70 beats per min, failed to improve the clinical state. The patient died from irreversible shock 2 days after his second coronary attack. Autopsy was unobtainable.

In summary, this patient in the early stage of an acute infarction exhibited a picture of severe cardiocirculatory failure with pulmonary edema. Pharmacological agents were unable to improve the clinical state. Sustained ventricular coupled pacing, used

TABLE I  
SUMMARY OF CLINICAL DATA

Case No.	Age, Sex	Age of infarction*	Duration of circulatory pulmonary failure*	Presence of pulmonary edema*	Nature of underlying rhythm*	Heart rate		Duration of VCP	Result	
						spontaneous*	Under VCP †		Immediate	Late
1. J.H.	55 yr, M.	19 hr	10 hr	Yes	Sinus T.	120	61	26 hr	Favorable	New infarction 17 days later
2. G.S.	—	12 hr	12	Yes	Sinus T.	140	70	4 hr	None	Death
3. R.D.	56 yr, M.	21 days	6	No	Sinus T.	110	60	8 hr	Favorable	Recovery
	50 yr, F.	15 hr	15	No	Sinus T.	112	56	40 min	None (technical failure)	Death
4. G.P.	65 yr, F.	22 hr	4	No	Sinus T.	96	48	30 min	None (inexcitability)	Death
5. H.G.	62 yr, M.	60 hr	6	Yes	Ventricular T.	170	86	8 hr	Favorable	Recovery
6. P.L.	76 yr, M.	18 hr	8	Yes	Supraventricular T.	165	84	20 hr	Favorable	Death (apparatus failure)
7. G.R.	71 yr, F.	5 days	6	Yes	Sinus T.	170	—	—	None	Death

VCP, ventricular coupled pacing. T, tachycardia.

\* These data concern the basal state when coupled pacing was started.

† New hemodynamical state reached under ventricular coupling; obviously the spontaneous rate may change during the course of prolonged coupling.

on this patient without other therapy, drastically transformed the clinical situation. The use of this technique for 26 hr was uneventful. 17 days later a new infarct occurred with a severe shock: several attempts at ventricular coupling controlled the tachycardia but were judged inefficient in improving the cardiac function.

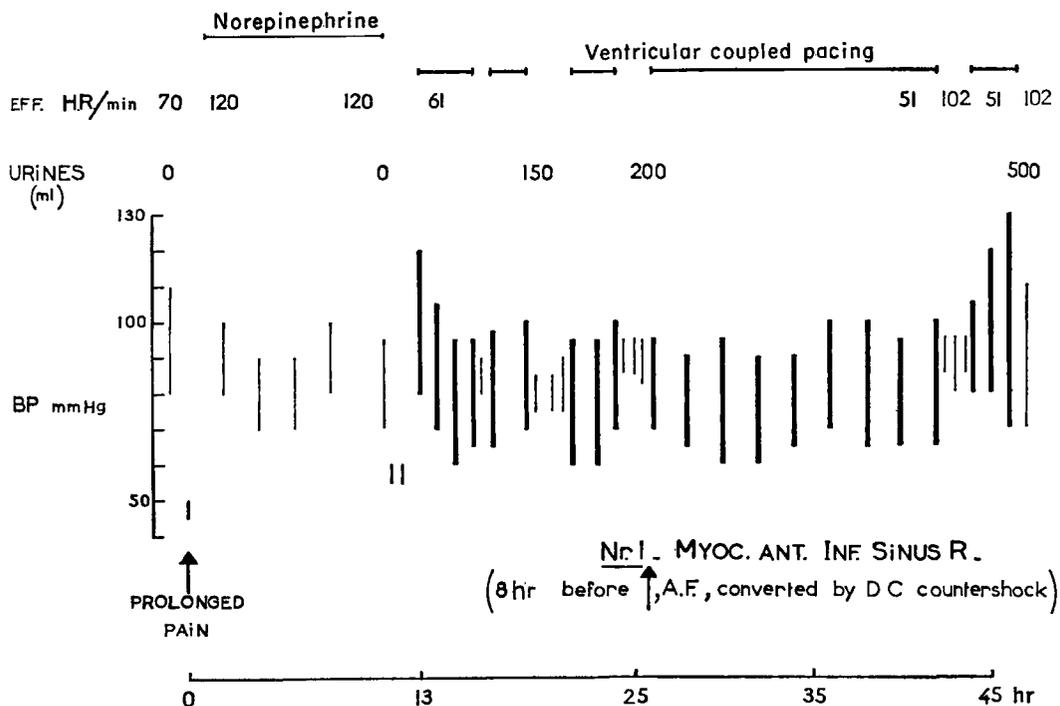


FIGURE 1. Diagram of findings in a patient (case 1) with myocardial anterior infarction under VCP (for details, see text). Heavy bars show BP readings under VCP.

### Case 2

G. S., a 56 years old patient, had experienced a severe chest pain 3 wk before admission, which was considered to be the result of a myocardial infarction, despite inconclusive ECG evidence, due to a rare type of right bundle block. He was taken to the intensive cardiac care unit because of the occurrence of a recent 2/1 flutter, with high ventricular rate (140 per min) and marked hypotension (systolic blood pressure, 75 mm Hg). Successive electrical shocks were given. 2 hr after successful cardioversion, in spite of intravenous treatment with digitalis and norepinephrine infusion, a very pronounced state of shock persisted; obtundation was marked; anuria was persistent for 6 hr. At that time cardiac rate was 110 per min, and arterial pressure was 90/70 mm Hg. As soon as ventricular coupling was started (after cessation of pressor agents), BP immediately rose to 130/90 mm Hg and was maintained at about 100/60 mm Hg a few minutes later. Efficient cardiac rate was 60 per min under stimulation. With only brief interruptions, VCP was used for an 8 hr period without any associated drug. Diuresis started, all symptoms of circulatory failure disappeared, and the patient regained full consciousness. When the sinus frequency, progressively decreasing under ventricular coupling, was 75 per min pacing was discontinued. No further accident ensued; the patient was discharged from the

intensive care unit 2 wk after admission; he was examined 6 months later and was found to be in good condition.

In summary, a patient with coronary shock persisting after electrical conversion of an atrial flutter seemed to be immediately improved by ventricular coupling alone. Sustained VCP caused progressive disappearance of the circulatory failure.

### *Case 3*

R. D., a 50 yr old female hypertensive patient, was admitted for a recent (12 hr) posterior myocardial infarction with severe cardiogenic shock and persisting chest pain. High dosages of vasopressive drugs had previously been given. Sinus rhythm was present (120 per min); BP was 125/100 mm Hg. Because of progressive worsening of the patient's condition during the first hours after admission (anuria, obtundation), it was decided to attempt to undertake ventricular coupled stimulation but during the course of catheterization a brief run of ventricular tachycardia occurred. The electrode was misplaced, in the right infundibulum; it was not possible to reduce the interval to less than 80 msec between the end of the T wave and the beginning of the premature induced systole, at the diastolic excitability threshold. Frequent spontaneous ventricular premature systoles persisted during coupling (of the same type as those spontaneously occurring at the time of catheterization). No objective improvement in the picture of shock was noticeable during VCP except that arterial pressure rose to 135/95 mm Hg. After 40 min, stimulation had to be discontinued due to technical failure whereupon heart rate and arterial pressure returned to their previous values. The patient expired 12 hr later in asystole. Autopsy was not available.

In summary, in a patient with severe diffuse myocardial infarction ventricular coupled pacing failed to exert any beneficial effect. Factors contributing to this failure may have been misplacement of the active electrode (and consequently late extraactivation of the ventricle) and the occurrence of spontaneous premature ventricular systoles.

### *Case 4*

G. P., a 65 yr old female patient, was admitted 24 hr after an acute attack of chest pain, because of the occurrence of shock with anuria and coma; ECG evidence of a recent posterolateral infarct was obtained. Isoproterenol, metaraminol, and hydrocortisone failed to produce any clinical improvement. Due to a relative "inexcitability" of the myocardium, VCP could not be achieved successfully even with a 14 v stimulus; moreover R impulse delay could not be adjusted below 400 msec. The spontaneous cardiac rate was only 96 per min. No favorable effect was obtained and coupling was stopped 30 min later. The patient died 3 hr later in ventricular fibrillation. Autopsy confirmed a massive infarction of the posterolateral region of the left ventricle.

In summary, on an infarcted patient with moderate sinus tachycardia and severe shock, the coupling technique could not be used because of relative myocardial inexcitability.

### *Case 5*

H. G., a 62 yr old male patient, was admitted for a long-lasting chest pain with ECG evidence of posterolateral infarction. 48 hr later he developed severe shock, ventricular tachycardia, and auricular fibrillation; two types of ventricular complexes were irregularly alternating, complexes of supraventricular origin interfering with idioventricular R waves. Neither procain amide

infusion nor repeated DC countershocks (250 J.) could restore a stable sinus rhythm. Since the systolic blood pressure was under 70 mm Hg, catheterization of the right ventricle was done 90 min after the occurrence of ventricular tachycardia. Successive trials of ventricular coupling resulted in reestablishment of the interference phenomenon, which had disappeared; the net result was a chaotic heart action. Lanatoside C (0.12 mg intravenously) depressed auriculo-ventricular conduction and consequently 4 hr later the interference phenomenon disappeared, allowing the application of a regular and efficient VCP. At that time the patient having deteriorated further in spite of metaraminol infusion (systolic BP 58 mm Hg, unceasing nonproductive cough, anuria), a permanent ventricular coupling was undertaken. Spontaneous tachycardia was converted into regular efficient activity, but the patient remained unconscious, restless, tachypneic, moist and cold. Still under VCP, a slow intravenous drip of metaraminol was able to improve strikingly the clinical condition; 90 min later the mean BP was 90-110 mm Hg, 300 ml of urine was passed, and the picture of shock faded away. Nevertheless, 2 hr

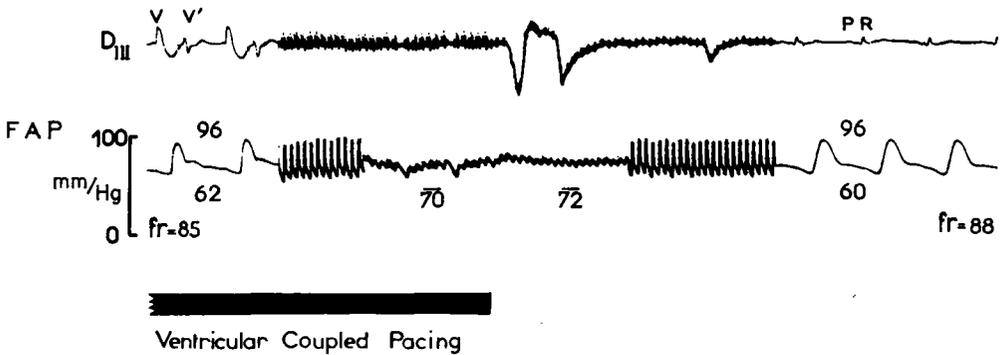


FIGURE 2. Spontaneous reestablishment of sinus rhythm after discontinuation of VCP on a patient with ventricular tachycardia (case 5; for details, see text). FAP, femoral arterial pressure.

after cessation of vasopressive therapy, although still under coupling, the patient's condition deteriorated again. A rapid infusion of low molecular weight dextran (750 ml in 45 min) failed to improve it. A new dosage of metaraminol had to be given concurrently with stimulation; within 2 hr, signs of shock cleared again and the drug could be withdrawn. Ventricular coupled pacing was still pursued for a total duration of 8 hrs. When it was discontinued a spontaneous sinus rhythm was reestablished (88 per min) (Fig. 2). Femoral blood pressure was then 96/60 mm Hg. All unfavorable symptoms had disappeared. A spontaneous sinus rhythm was maintained for 9 hr. Later a sequence of regular ventricular tachycardia occurred, which was easily treated with intravenous ajmaline. The subsequent course was uneventful, except for a new paroxysmal tachycardia, auricular in origin, which necessitated DC countershock. The patient was discharged 1 month later; he was examined 8 months later and was found to be in good condition.

In summary, this patient with an acute myocardial infarction exhibited a severe arrhythmia convertible by neither pharmacodynamical therapy nor successive countershocks. Because of the occurrence of irreversible shock of long duration, ventricular coupled stimulation was attempted and maintained for 8 hr until the spontaneous disappearance of the ventricular tachycardia.

*Case 6*

P. L., a 76 yr old male patient, known to be hypertensive for years, developed a massive septal infarct 24 hr after total gastrectomy for cancer. He was admitted to the intensive care unit in critical condition, unconscious, with acute myocardial insufficiency, peripheral hypocirculation, anuria, and pulmonary edema. A paroxysmal atrial tachycardia with 2/1 A-V ratio and high ventricular rate (165/min) was present. Countershocks and drugs failed to convert the arrhythmia and immediately after induction of coupled ventricular stimulation, the BP rose from 100/85 mm Hg to 130/80 mm Hg (Fig. 3). Within 2 hr of continuous coupled pacing

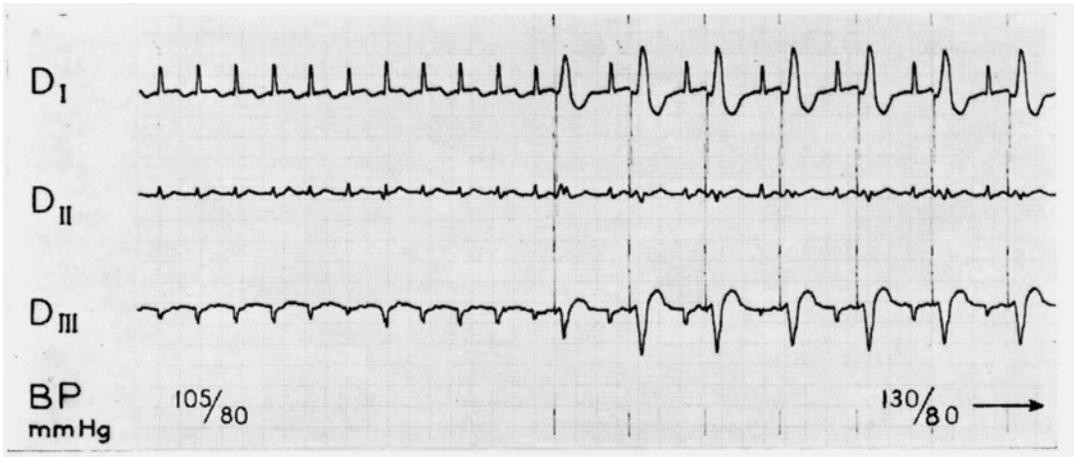


FIGURE 3. Initiation of VCP in a patient (case 6) with supraventricular tachycardia (165 per min). Recent myocardial infarction. Tachycardia resistant to countershock, digitalis, quinidine.

all symptoms and signs of cardiocirculatory insufficiency cleared, consciousness reappeared, and urine was passed. These good results remained unchanged for 12 hr. At that point conversion of the underlying arrhythmia was easily obtained with ajmaline, but the clinical state was found to be deteriorating again so that it was then judged necessary to resume sustained VCP, since the spontaneous ventricular action was not hemodynamically efficient. Under such pacing the blood pressure averaged 100/70 mm Hg. 8 hr later the patient died from ventricular fibrillation caused by failure of the apparatus (unexpected continuous firing at 200 per min). Autopsy showed an extensive posteroseptal infarction and a pulmonary embolism.

In summary, thanks to ventricular coupled pacing a very spectacular improvement of the clinical state was observed on a patient with massive septal infarction complicated by a supraventricular tachycardia. Unfortunately a long-term good result could not be secured due to technical failure.

*Case 7*

G. R., a 71 yr old female patient, exhibited a clear-cut pattern of myocardial infarction associated with sinus tachycardia and heart failure which had been treated daily with digitalis and diuretics. 5 days after the attack, she developed an auricular flutter with 2/1 A-V ratio

and a ventricular rate of 150 per min; heart failure rapidly became more severe, with circulatory collapse and pulmonary edema. Countershock permitted reestablishment of sinus rhythm after a short stage of cardiac arrest.

A permanent sinus tachycardia (160 per min) supervened; blood pressure declined (80 mm Hg, systolic) and shock became more severe with pulmonary edema. All attempts at ventricular coupling encountered severe difficulties, due to the occurrence of runs of ventricular tachy-

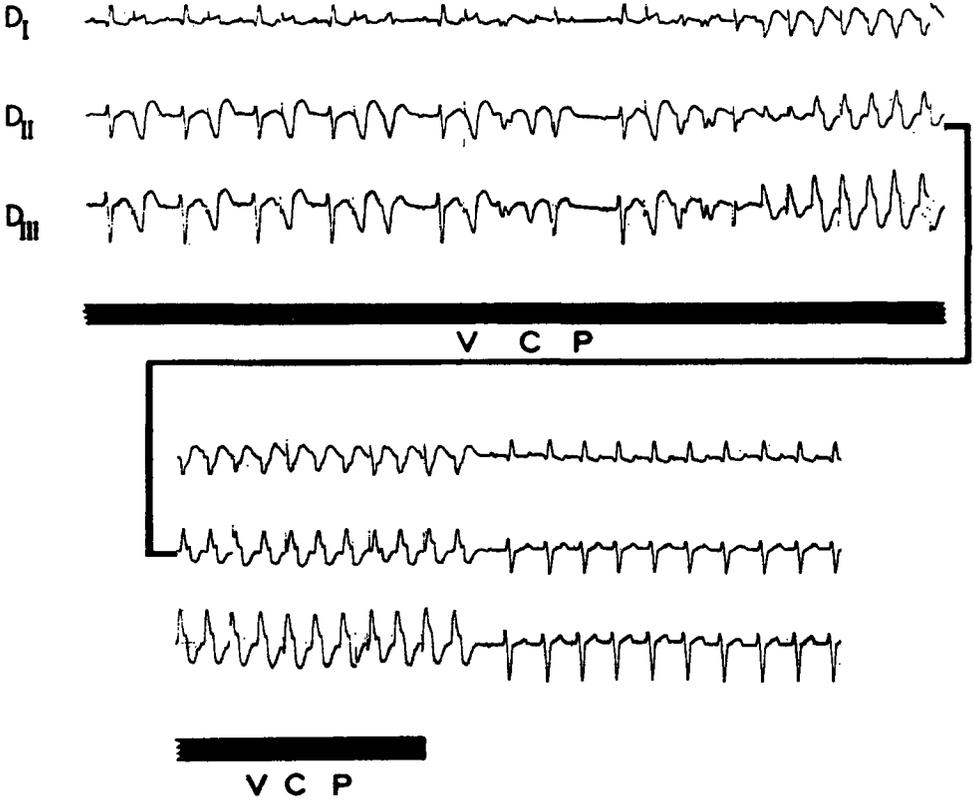


FIGURE 4. Ventricular tachycardia induced by VCP (case 7).

cardia, which spontaneously disappeared when VCP was stopped (Fig. 4). VCP was resumed under ajmaline (i.v. infusion 1 mg per min) but failed to be effective, because of a paroxysmal induced arrhythmia. All other therapeutic agents failed to improve the clinical condition and the patient expired 10 hr later from irreversible ventricular fibrillation. Autopsy showed a massive anterior wall infarction of the left ventricle.

In summary, ventricular coupled pacing had to be abandoned in this case of coronary shock with sinus tachycardia. The induction of runs of ventricular tachycardia made it impossible to continue ventricular coupling.

COMMENTS AND DISCUSSION

As a rule neither side effects nor deleterious consequences seem to have resulted from ventricular coupling except for one case of myocardial hyperexcitability. The most

striking feature under sustained ventricular coupling was, in four instances out of seven apparently intractable cases, a drastic improvement of the cardiac function, leading to clearing of the shock and/or cardiac failure. Surely pure coincidence may not be ruled out. Nevertheless these preliminary results have to be discussed in the light of experimental data on dogs subjected to ventricular coupled pacing.

### *I. Ventricular Coupling and Cardiac Slowing*

The first beneficial effect of VCP is slowing of the heart: as a rule the rate of hemodynamically efficient beats is halved unless retrograde ventriculoauricular conduction is present (as it was in case 2).

An exceedingly fast tachycardia may contribute importantly to the development of an acute heart failure. In such cases slowing of efficient cardiac rate, with concomitant lengthening of the period of ventricular filling, may (as in case 6) improve cardiac pumping per se.

Moreover, myocardial oxygen use ( $M \dot{v}O_2$ ) is strictly related to cardiac rate (20). In the normal dog  $M \dot{v}O_2$  is always greatly increased by application of paired ventricular stimuli since the efficient stimulation frequency equals the spontaneous rate (the number of electrically induced depolarizations being doubled) (2, 22, 24). On the other hand,  $M \dot{v}O_2$  has been reported to decrease when efficient cardiac rate was reduced (6, 16). In anesthetized dogs, with a spontaneous cardiac rate averaging 180 per min, halving of efficient heart rate with ventricular coupled pacing produced a mean decrease of 37 per cent in  $M \dot{v}O_2$ , without any significant change in cardiac output or mean aortic pressure (19). Increase in mechanical cardiac efficiency and maximal lengthening of diastole may have contributed to the favorable results observed in four patients of the reported series (cases 1, 2, 5, and 6).

Thus two possible clinical indications for slowing the heart by VCP may be outlined.

(a) In cases of ectopic tachycardias responsible for acute heart failure, intractable to treatment by pharmacological agents or repeated countershocks, ventricular coupling may double the cardiac period. Such a result, however, is not to be expected in cases of retrograde ventriculoauricular conduction (case 2), or auricular fibrillation, nor in some cases of supraventricular tachycardia. For example, a paroxysmal atrial tachycardia (tachysystole) with a 2/1 A-V ratio is often transformed only to a tachysystole with an irregular 3/1 A-V ratio; either a paired ventricular pacing or an auricular coupled or paired pacing would then be preferred to ventricular coupling (7). The method is also applicable to cases with ventricular tachycardia. In a patient with ventricular tachycardia, less slowing than expected has been observed under VCP, because the induced premature systole favored the appearance of the next spontaneous activation (case 5).

(b) Such a method may be useful for some cases of sinus tachycardia with cardiac failure: both slowing and postextrasystolic potentiation should permit, at least in some circumstances, an increase in the mechanical efficiency of the heart. However, in the presence of myocardial insufficiency, pronounced slowing may exaggerate the failure. It therefore seems necessary to obtain an actual potentiation of the mechanically effective contraction simultaneously with the slowing effect.

## II. Ventricular Coupling and Postextrasystolic Potentiation

Potentiation of contraction is to be expected only if the extraactivations are quite premature. In the normal anesthetized dog slowing of the rate by whatever means (12, 15) does not induce significant changes in cardiac output and/or mean aortic pressure. Under VCP cardiac output is maintained and the slight reduction observed in mean arterial pressure may be due to a vagal effect or to changes in aortic compliance according to the decrease in telediastolic aortic pressure. Nevertheless, these over-all effects may result in part from a cardiac adaptation following Starling's law

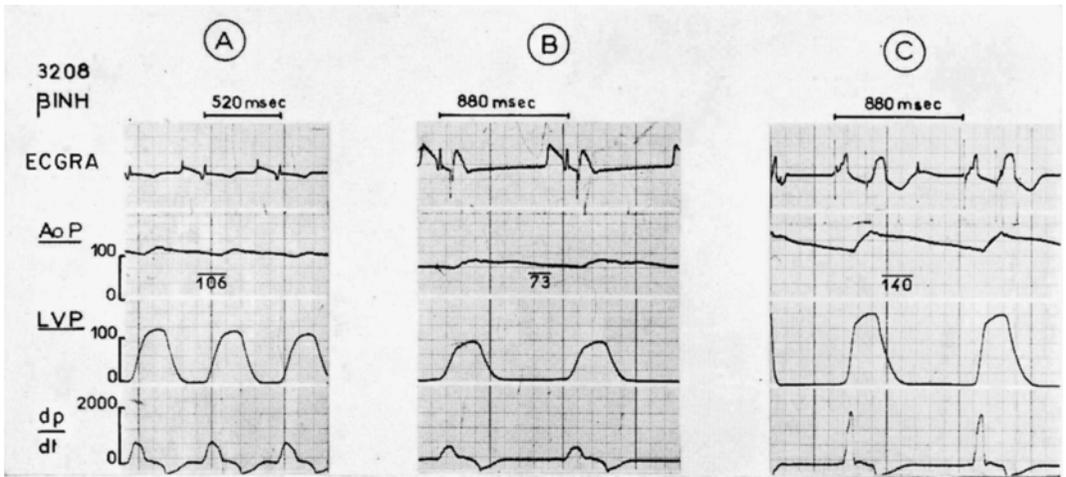
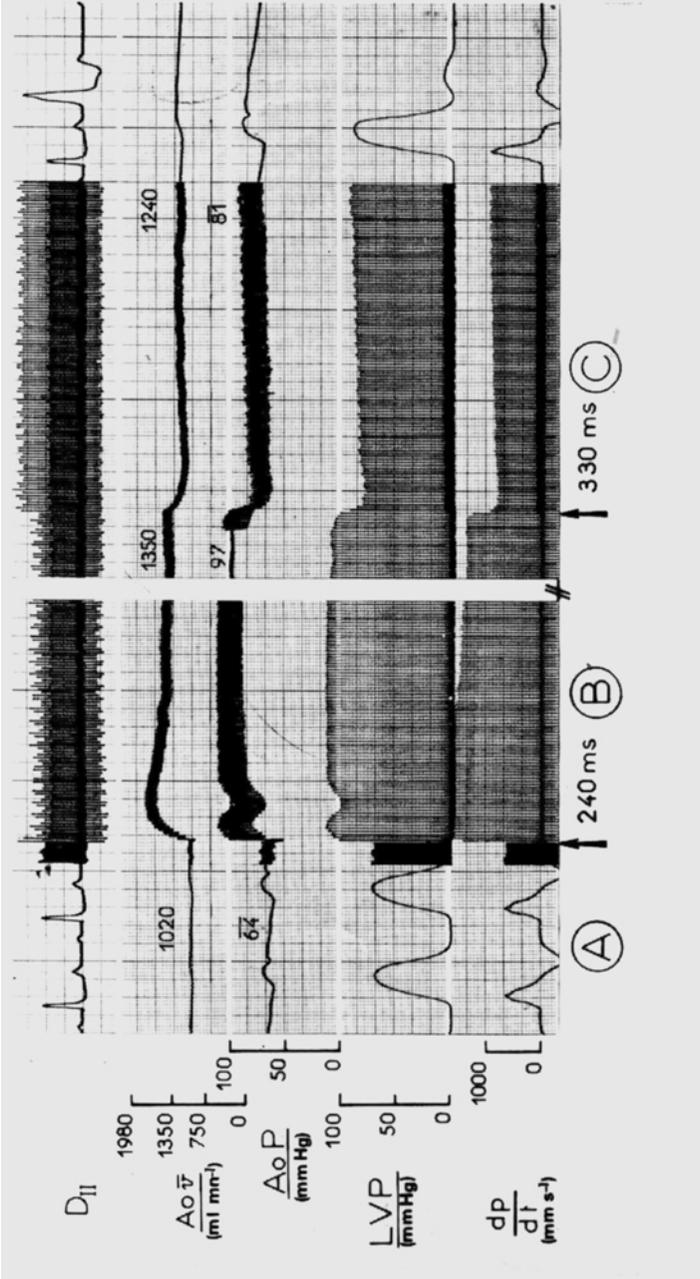


FIGURE 5. Slowing effect, augmentation, and potentiation. Dog pretreated by a  $\beta$ -blocking agent. From left to right: A, control (H.R., 115/min); B, auricular coupled pacing with some degree of A-V block: slowing of electrical and efficient ventricular rate (68/min) and augmentation, without potentiation; C, paired ventricular pacing at the same efficient heart rate (68/min): slowing and potentiation. ECGRA, Right intraauricular electrocardiogram.

(“augmentation”) (13, 18, 19). Previous cardiac “insufficiency” allows separation of the phenomena of augmentation and potentiation (Fig. 5); under these experimental conditions, potentiation of the mechanically efficient ventricular contraction by ventricular coupling was observed as an increase in cardiac output (Fig. 6) in spite of the doubled period between effective contractions (13). Moreover, if the induced frequency of effective contractions is not too low (as a rule 55 or more beats per min), increase of cardiac output and mean arterial pressure is not significantly different under ventricular paired and coupled pacing, even when paired stimulation induces higher cardiac rates. This fact may be due either to a lessened potentiating effect when high cardiac rates are present (14, 17), or to a better mechanical efficiency of normally activated ventricular beats, in which a normal auriculoventricular sequence of excitation is maintained. The tracing of Fig. 7 illustrates this phenomenon which has already been mentioned in studies on single pacing (1, 3, 4, 23).



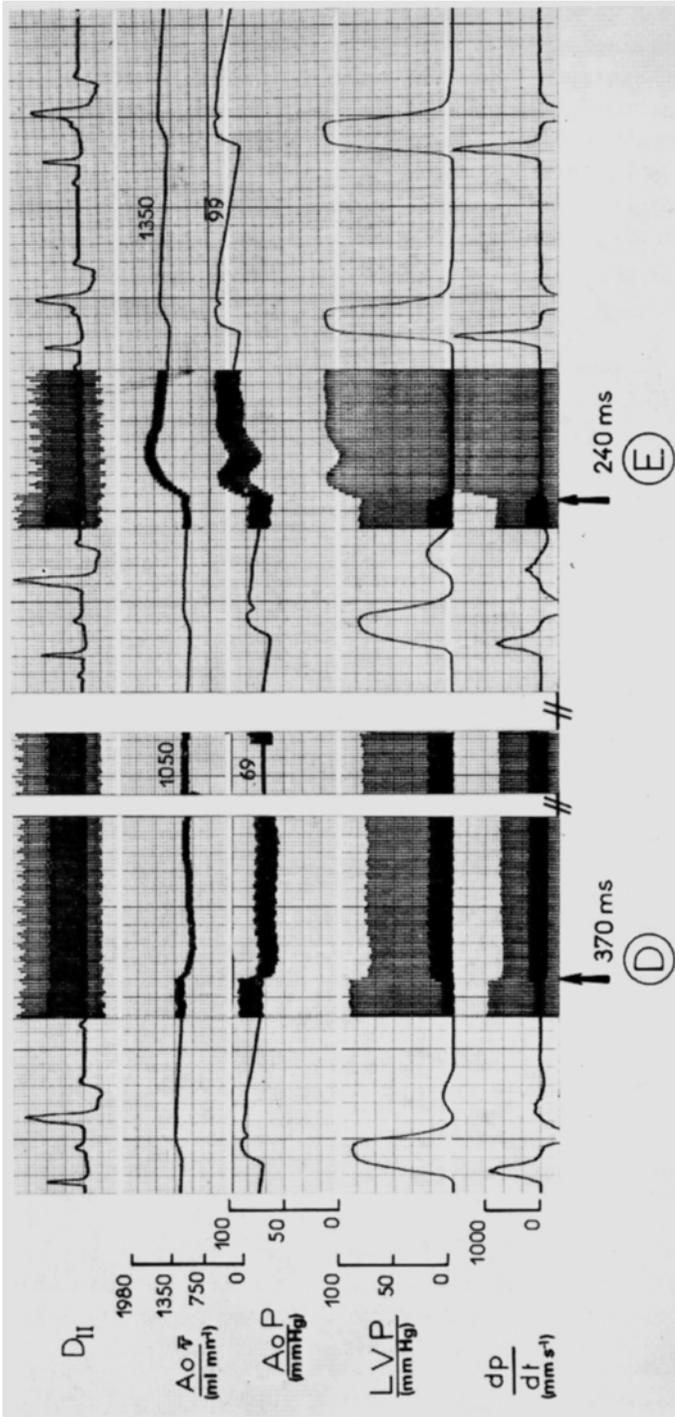


FIGURE 6. Influence of prematurity on cardiac output increase under  $dp/dt$ , first time derivative of LVP.  $\text{D}$ , control period;  $\text{E}$ , VCP. Dog pretreated by a  $\beta$ -blocking agent. Ao $\bar{v}$ , mean ascending successive episodes of VCP at various R stimulus delays. Numbers aortic flow. AoP, aortic pressure. LVP, left ventricular pressure. following arrows correspond to R stimulus intervals.

Although the cardiac output was not measured in the cases reported above, it was presumably at least maintained, if not increased, in two patients with sinus tachycardia (cases 1 and 2), where signs of circulatory impairment cleared under ventricular coupling. In the case of ventricular tachycardia "treated" by ventricular coupling, the arterial pressure was the same as it was when sinus rhythm had been reestablished (case 5, Fig. 2). Favorable clinical results have also been reported in cases of myocardial failure of various types (8, 25), one of which was due to myocardial infarction associated with nodal rhythm.

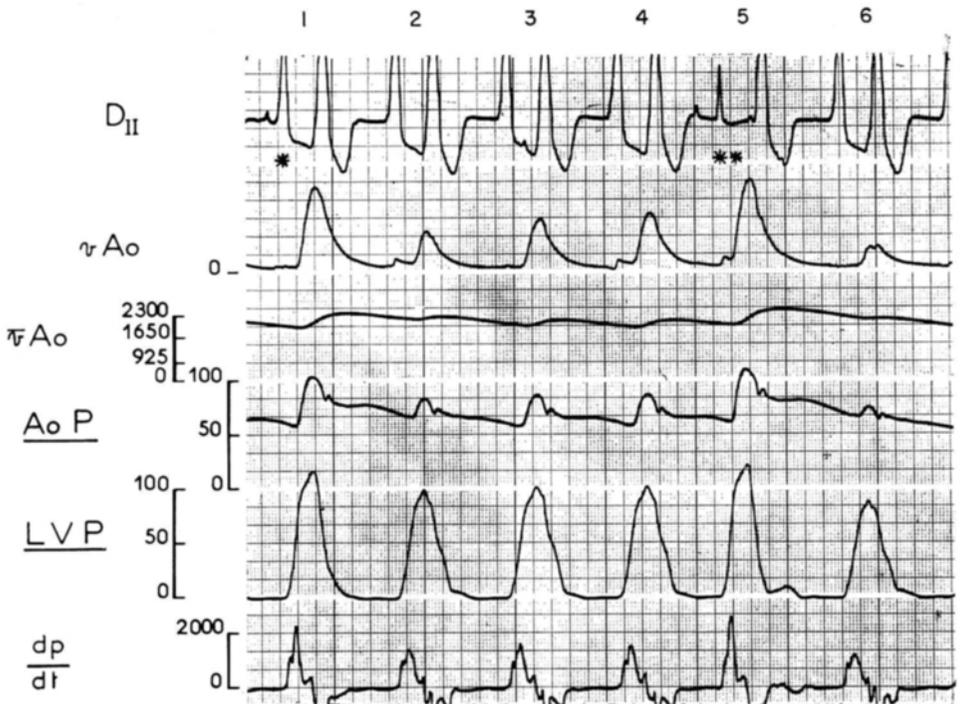


FIGURE 7. Better efficiency of normally activated ventricular beats (asterisks). Paired ventricular pacing on a  $\beta$ -blocked dog with interference phenomenon. Instantaneous ( $\tau A_o$ ) and mean ( $\bar{\tau} A_o$ ) ascending aortic flow.

### III. Hazards of Ventricular Coupling

The obvious major hazard is the occurrence of ventricular fibrillation, but when voltages corresponding to diastolic excitability threshold are used and the cathode is used as the active electrode, VCP does not seem to induce ventricular fibrillation.<sup>2</sup> Conversely, brief attempts at paired stimulation, in two out of three patients of the

<sup>2</sup> The sole instance of ventricular fibrillation under VCP encountered in the present series (case 6) was not due to the method itself, but to a gross technical failure of the stimulator.

present series (cases 1 and 3), using identical voltages to those employed in coupled stimulation, resulted in repetitive ventricular responses, evidencing a striking contrast with the well-tolerated coupled ventricular pacing. In cases of highly sensitive ischemic hearts VCP offers an obvious advantage over ventricular paired stimulation in that there is less risk of ventricular fibrillation. Nevertheless in one instance (case 7), runs of ventricular tachycardia resulted in an obligatory discontinuance of VCP. It is noteworthy that runs of ventricular tachycardia under these conditions could sometimes be suppressed by ajmaline.

Although less striking, the transient, severe poststimulation depression encountered in dogs seems also to be present in human beings. It therefore seems logical to diminish the postextrasystolic potentiation gradually before discontinuation of the coupled pacing (15); that can be achieved by either a progressive increase in the R stimulus delay or an increase in the trigger's refractory period so that the ratio between R waves and induced extrasystoles rises to 2/1.

#### *IV. Causes of Failure of Ventricular Coupling*

As far as the VCP technique is concerned, three major causes could result in failure.

1. A ventricular hyperexcitability (as in patient 7 of this series) may compel abandoning the attempt.

2. If the left ventricular depolarization is not premature enough to be mechanically inefficient, it may be impossible to obtain a successful potentiation. This fact may be due to a relative myocardial inexcitability (as in patient 4) or to a substantial delay of right to left conduction.

In the clinical series reported the mechanical prematurity of the ventricular extra-activation was assessed from auscultatory data (9) but in the present series an apical pseudosplitting of the second sound was often observed. Experimentally the optimal premature interval exceeds the minimal stimulation interval by a significant amount (17).

No attempt at direct left ventricular stimulation was made on these patients. However, when right ventricular pacing was used, it seemed necessary to look for the location permitting the earliest left ventricular depolarization and this was usually the apical region.

3. The spontaneous cardiac rate is the critical factor for success in VCP; no good result is to be expected when there is no tachycardia. Although ventricular coupling does not hinder the physiological control of sinus rate, the minimum efficient rate compatible with maintenance of VCP depends altogether on the state of myocardial contractility and on the degree of potentiation. Such a factor may have contributed to the failure of VCP observed in one patient (case 4) in whom the spontaneous heart rate was 96 per min. In such cases either paired ventricular stimulation or VCP superimposed on an induced supraventricular pacing might have been preferred.

#### CONCLUSIONS

This preliminary report on clinical trials of heart potentiation and slowing using ventricular coupled stimulation does not permit a definitive assessment of the validity of the technique or of its indications. The immediate clinical evidence of a better

tissue perfusion and of improved cardiac performance was obtained in four out of seven desperate cases of myocardial infarction with intractable cardiogenic shock and acute left heart failure, four of which exhibited pulmonary edema. At the very least the increased duration of diastole should have improved the myocardial perfusion. Nevertheless convincing objective proof for true potentiation and increased cardiac efficiency is lacking in these preliminary clinical attempts. In such circumstances repeated proper evaluations of the clinical state are needed; moreover if it is possible to improve the results of the ventricular coupled pacing technique by the use of pharmacological agents, the rationale for their use in such cases should be substantiated by adequate estimates of the cardiac performance.

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# Possible Mechanisms Involved in Potentiation Phenomena

V. KRUTA and P. BRAVENÝ

From Katedra Fysiologie, Universita J. E. Purkyne, Brno, Czechoslovakia

The increase in the strength of myocardial contraction due to paired stimulation is a special case of the variations of contractility first observed almost a hundred years ago and studied since then by many authors. These variations occur during the transition from rest to regular activity or from one frequency to another, or even after a change of a single interval. These phenomena are amazingly regular and reproducible, so that it may be presumed some very precise and rather complicated physiological mechanism is behind them, which reacts to the changes in the interval between successive stimuli. Great efforts have been expended upon the investigation of the nature of these phenomena during the last 10 years and many data have been accumulated. The exact cause of potentiation is not known as yet but review of the known facts may help in understanding the phenomenon.

In contrast to the skeletal muscle in which activity is graded by the recruitment of an increasing number of motor units, heart muscle normally responds with a contraction of all its fibers, which are functionally interconnected. In addition, it cannot increase its contraction strength by temporal summation as in tetanic shortening and thus must have some other means of changing the strength of its contraction. As a matter of fact, two different types of gradation appear to exist in heart muscle.

The variation of strength in response to the degree of initial distension (heterometric gradation) seems to be due to the change in the extent of overlapping of the two systems of elementary filaments in the heart muscle fibers (Sponitz et al., 1966). In this type of gradation there are no transient phenomena (Sarnoff and Mitchell, 1961) and no changes in the duration of contraction as in the second type (Sonnenblick, 1962).

Gradation without change in the initial length (homeometric gradation) occurs in response to variations of the interval between contractions (interval-strength relationship, reviewed by Koch-Weser and Blinks, 1963), to changes in ionic composition of the surrounding medium, changes in temperature, or inotropic drugs (catechol amines, acetylcholine, cardiac glycosides, purines, etc.). The common features of these variations are gradual transient phenomena and, usually, a change in the duration of the contraction.

The manifestations of homeometric gradation are very complex but extremely regular. During the period 1936-39, and again since 1957 (with P. Bravený, J. Hlávková-Stejskalová, and J. Šumbera) we have studied the effects of changes of frequency (interval), effects of temperature and of some drugs and ions. Our main

experimental preparation has been the isolated left atrium of the guinea pig (we have also used the atria of the rabbit, cat, dog, rat, hamster, etc.). We have studied both isotonic and isometric contraction. There are only small differences between the two recording techniques, but there are some marked species differences, as well as differences between the atrial and ventricular tissue or papillary muscle. According to our experience, the guinea pig atrium is a very stable preparation giving regular, consistent, and reproducible results. Changes in strength occur with only small changes in the peak time, which are much smaller than in ventricular or papillary muscles (unpublished observations). It seems to us that this feature makes the interpretation easier and gives more hope of understanding the underlying mechanisms.

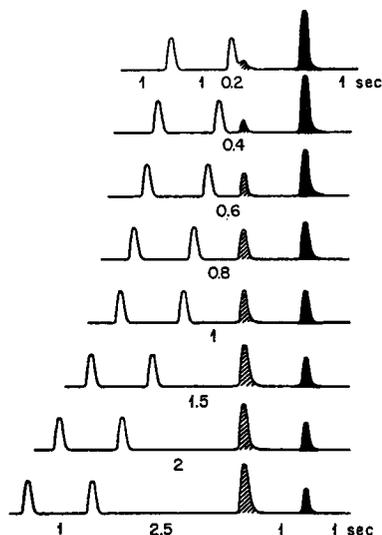


FIGURE 1. The effect of a change of one single interval on the immediate (shaded area) and following (black area) contraction, showing the reciprocal development of contractility of these two neighboring beats in respect to the steady state (unshaded). Redrawn from a representative experiment on guinea pig atrium at 32°C and 60 per min stimulation (isometric recording).

The variations in the strength of contraction of mammalian heart muscle due to changes of frequency are well-known. There is a staircase-like increase during the transition from rest to a steady-state activity elicited by regular rhythmic stimulation. The steady-state strength eventually reached varies with the frequency. In atrial muscle it follows a triphasic (S-shaped) curve. It is high at very low frequencies, declines, and reaches a minimum (pessimal frequency) at about 60–80 per min at 37°C, then increases progressively up to a second critical frequency (optimal frequency), and declines again slowly. The subpessimal rise seen at very slow rates is lacking in ventricular and papillary muscle preparations (Koch-Weser and Blinks, 1962). During regular steady-state activity every irregularity of rhythm causes a disturbance of the mechanical response: premature beats are weaker and delayed beats stronger, followed by stronger and weaker contractions respectively; complete return to the former steady state usually requires a few cycles.

There are several possible ways of analyzing these phenomena. One of them, relating the observed variations to a reference value, the strength of contraction in the rested state which is not influenced by the preceding interval was used by Blinks and Koch-Weser (1961).

We have attempted another approach and analyzed:

1. Variations due to prematurity or delay of a contraction, which makes it possible to trace the curve of restitution, indicating the progressive recovery of the contractility after each beat (Fig. 1).
2. Variations of the immediately following contraction, which is greater (potentiated) after the premature beat and smaller (depressed) after the delayed one.
3. Transitional phenomena between two steady states or after a short disturbance of a steady-state activity connected with a process of increase or decrease of some gradient or gradients which determine the extent of the contraction.

### *Restitution*

Restitution of contractility is a continuous progressive process, which, however, can be followed only in a discrete way, since after each contraction the muscle returns to the initial conditions. Under stable experimental conditions the recorded values of contraction amplitudes follow a smooth curve with only few and insignificant irregularities. This curve has an initial rapid phase and a subsequent slow one, indicating two stages or perhaps two different kinds of processes. It may be of some significance that in the same experiment the course of the restitution process is parallel at different frequencies, so that it looks as if this mechanism operates along the same curve (Kruta and Bravený, 1961), but starts at a different point for each state. Thus each frequency of activity corresponds to a particular section of the same curve.

There is an important characteristic of premature beats during a staircase which is worth recalling. If at any time during the buildup of a staircase a premature beat is interpolated at a given interval (say half-way between the regular beats), the strength of the premature contraction is always the same fraction of the expected value of the contraction at that point in the buildup of the staircase. Thus if the regular contraction has a force  $B$  and the premature beat has a force  $E$ , we find that

$$E/B = \text{constant.}$$

This means that during the staircase the process of restitution is progressively accelerated over its whole course and at a given interval always reaches the same relative portion of its final value. That, of course, could be expected but the interest of this finding lies in its contrast to the behavior of the following potentiated contraction (see below).

### *Potentiation*

The effect of a premature (or delayed) response on the contraction which follows immediately at its regular interval is inverse to the change in the irregular contraction. (Figs. 1 and 2): after a premature beat the contraction is increased (potentiated), after a delayed beat it is decreased (depressed). The two effects obviously occurring at different levels in the chain of processes leading to the mechanical response are in equilibrium during the regular steady-state activity where both curves (Fig. 2) intersect. However, the increase (or decrease) of the subsequent contraction is not a

simple compensation for the first change (deficit or excess) in the contractile strength, and it is to be noted that the "immediate effect" is a particular phenomenon occurring at an upper link, *i.e.*, further from the contractile process, and that it is independent of the actual level of the steady-state value of contractions. It can indeed be shown

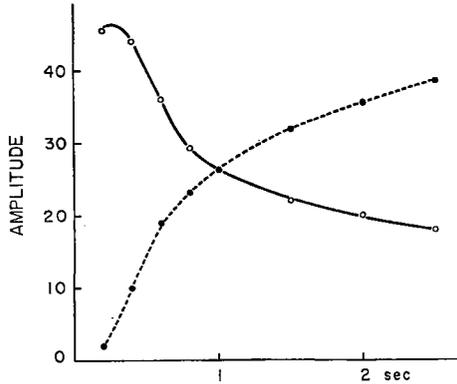


FIGURE 2. The data from Fig. 1. Abscissa, duration of the changed interval. Ordinate, contractile tension in arbitrary units. Dashed line, the amplitudes immediately following the changed interval; solid line, the amplitudes of the subsequent contraction. The former curve depicts the course of restitution, characteristic for the given driving rate, the latter curve shows the gradual decline of potentiation, which appears with a delay of one cycle.

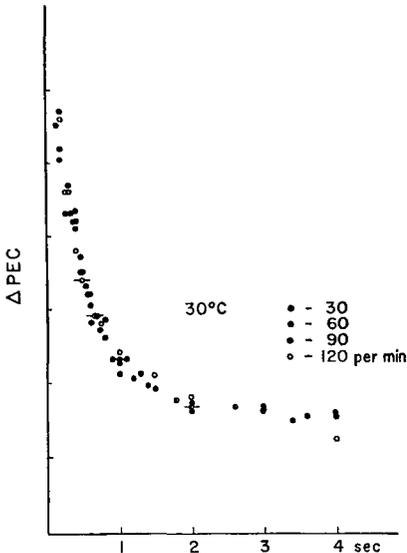


FIGURE 3. The course of potentiation indicated as an increment of contraction above the steady-state amplitude (marked by a short dash across the respective point for each of the frequencies studied, *i.e.*, 30, 60, 90, 120 per min). Abscissa, the duration of the changed interval. The set of experimental values for each rate was shifted along the vertical axis to cancel the cumulative level of contractility. All data show the same course of decay irrespective of the stimulation frequency. Guinea pig atrium, 30°C; isotonic recording. PEC-potentiated (postextrasystolic contraction).

that the curves of potentiation at different steady-state levels (*i.e.* at different frequencies of regular activity) are parallel and if the values are appropriately shifted along the vertical axis, the experimental points range very closely along a single curve (Fig. 3). This suggests that the phenomenon is the same at different steady-state levels

(and rates of activity), and that only the transition between the positive and negative section of each individual curve differs according to the basal interval.

This is in agreement with the observation that for the same interval of premature contraction the increment during the staircase is constant (Fig. 5), i.e. if basal amplitude is called  $B$  and the potentiated beat  $P$ ,

$$P - B = \text{constant} \quad \text{or} \quad \Delta P = \text{constant}.$$

The third piece of evidence for a special position of the immediate effect is

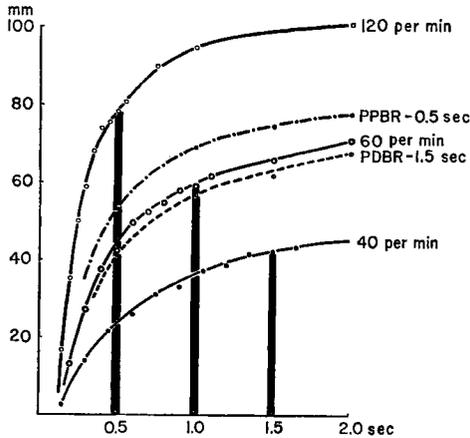


FIGURE 4. Restitution of contractility in guinea pig atrium at  $32.2^{\circ}\text{C}$  and at basal rates of 40, 60, and 120 per min as revealed by the amplitude of shortening of premature and delayed contractions (ordinate). Abscissa, interval preceding the measured contraction. The steady-state amplitude for each of the three frequencies is marked by a black column. PPBR, postpremature beat restitution = accelerated (potentiated) restitution following a premature beat (interval 0.5 sec); PDBR, postdelayed beat restitution = slowed restitution following a single delayed beat (interval 1.5 sec). Differences between the two upper (120 per min and PPBR) and two lower (PDBR and 40 per min) curves indicate the effects due to cumulation (single and repeated intervals of 0.5 and 1.5 respectively). Kruta and Braveny, 1963.

offered in the action of metabolic inhibitors, which clearly depress the steady-state contractility, but produce almost no change in the immediate potentiation (Kruta and Braveny, 1963, Fig. 2). The immediate effect thus seems to be of a different nature from the over-all contractility, to which each individual activation contributes a certain amount.

#### *Cumulative Effects*

The immediate effect corresponds roughly to what is usually called postextrasystolic potentiation, but each premature (or delayed) beat has, as has been shown earlier in this review, not only an immediate effect (potentiating or depressing) on the immediately following contraction, but it also affects the subsequent contractions and con-

tributes to the cumulative phenomenon which, of course, becomes fully apparent only after several cycles of activity (Fig. 4).

In our earlier work it seemed to us that the cumulative effect was due to summation of certain fractions of the individual potentiating effects, the residues of which persisted after each contraction (Kruta, 1937) in a manner similar to the "*addition latente*" (Lapicque, 1925). More recently, however, it appeared that although brought about by the individual cycles of activity, the cumulative effect is a phenomenon of its own, going on in parallel to the immediate effects, so that each activation has simultaneously two effects: (a) triggering the mechanical response; (b) determining the process of gradual setting of contractility at a higher level.

An increase in the strength of a contraction elicited at the same interval as a previous smaller one, means that the rate of the restitution processes has been increased, and thus a steeper course of the restitution curve can be detected between the pessimal and optimal frequency. There is a certain limit to this acceleration of restitution. Beyond optimal frequency its steepness does not increase and further shortening of the intervals between beats leads to a decrease in the strength (amplitude of contraction) because the course of restitution is interrupted by the next activation (cf. Kruta, 1964, Fig. 6).

An important feature of the cumulative effects is their dependence on metabolism. Anoxia or metabolic inhibitors, such as DNP, fluoroacetate, iodoacetate etc., interfere with the cumulative potentiation and eliminate it at an early stage of their action while the immediate potentiation remains unaffected until later stages when the whole complicated physiological mechanism is damaged (Kruta and Bravený, 1963).

### *Temperature*

For more than a century variations of temperature have been known to exert important inotropic effects (cf. Kruta, 1938). These effects are brought about by the action of temperature on the same mechanism which causes the modifications of mechanical response that are associated with the changes in interval and frequency. This can be seen most clearly in studies on the effects of rapid temperature variations (Šumbera, Kruta, and Bravený, 1966; Šumbera, Bravený, and Kruta, 1967).

A rapid variation in temperature (e.g. cooling from 32° to 22°C or warming from 22° to 32°C) causes a change in the strength of contraction which is in many respects similar to that caused by a change in the frequency of stimulation—a staircase-like transition to a new steady state.

A very short exposure to a higher or a lower temperature, limited to the duration of a single contraction, causes a change in the mechanical response similar to that brought about by a variation of a single interval; a short rise in temperature is accompanied by a transitory decrease of strength followed by an increase; lowering of the temperature is accompanied by an increase in the strength of the contractions followed by a gradually vanishing decrease. The principal factor determining this modification of the mechanical response seems to be the change in the duration of depolarization (Wood and Weidmann, unpublished data). The effect depends on the duration of the depolarized state.

All these factors, such as change in interval, variations in frequency, variations in temperature, as well as some cardioactive drugs, etc. which produce inotropic effects

in the heart muscle, are likely to act through their influence on the physiological mechanism involved in excitation-contraction coupling and at the same time they are responsible for the gradation of myocardial contraction.

### *Interpretation*

With regard to the nature of these different phenomena it was thought earlier (Vaughan Williams, 1959; Giotti, 1957; Bravený and Kruta, 1958; Bonnet-Seoane, 1964) that the variations in the contractile strength reflect changes in the transformations of energy from the reserve pool to an available form which could be utilized by the contractile system. But, on the other hand, Furchgott and Lee (1961) found no change in the content of high energy compounds under conditions of increased mechanical response, and concluded rather that there must be a change in the utilization of available energy.

Potentiation, both immediate and cumulative, is brought about by premature stimulation provided that it does not fall in the absolute refractory period of excitation and does elicit an action potential. Potentiation appears even without a detectable contraction (Siebens et al., 1959; Kruta and Bravený, 1961). On the other hand there is no correlation between the strength of the mechanical response and any of the parameters of the action potential (Sleator et al., 1964). Even if the underlying processes are complicated and both electrochemical changes and metabolic energy transformations may be involved, the gradation of myocardial contraction seems essentially to be caused by modifications in the process of excitation-contraction coupling and activation of the contractile system. Since the first findings of Locke and Rosenheim (1907) and Mines (1913) much evidence has been accumulated on the central role of calcium in these processes, both in skeletal and in cardiac muscle (cf. recent reviews by Brady, 1964; Lüttgau, 1964; and Sandow, 1965).

The action of an irregular, premature, or delayed stimulus on the next and the following contractions shows clearly that excitation and associated membrane changes must exert two dissociable effects: triggering that amount of contraction available at that moment (degree of restitution), and at the same time controlling the strength of the following contraction; i.e., a preparatory process. Both effects depend on the interval separating the actual excitation from the preceding one and they necessarily occur on two different levels. In general, the dependence on interval means that some processes going on between the two excitations are stopped and subsequently initiated anew.

On the evidence available from many laboratories it is reasonable to assume that calcium is the activator of the contractile system and that membrane changes associated with excitation set it in motion towards the active sites of the elementary filaments. The influx of external calcium ions through the cell membrane is very small in proportion to the calculated number of myosin molecules (1:500, Winegrad and Shanes, 1962), so that despite the possible initiating role of calcium entry during the action potential, a subsequent calcium release from internal stores must be quantitatively much more important. The restoration of contractions by paired stimulation (Nieuwendijk, 1966) or low temperature (Šumbera, Bravený, and Kruta, 1967)

following a previous electromechanical uncoupling in low calcium media, may be explained most properly by a redistribution of internal calcium.

The complexity of the variation in the contractile strength indicates that the movement of calcium cannot be only a matter of simple penetration through the membrane, followed by an extrusion, nor a liberation from and return to an internal compartment. As we attempt to outline briefly in this review, there must be a more complicated transfer in several stages and through some intermediary compartments or forms—chemical bindings or reversible associations. The evidence for and dis-

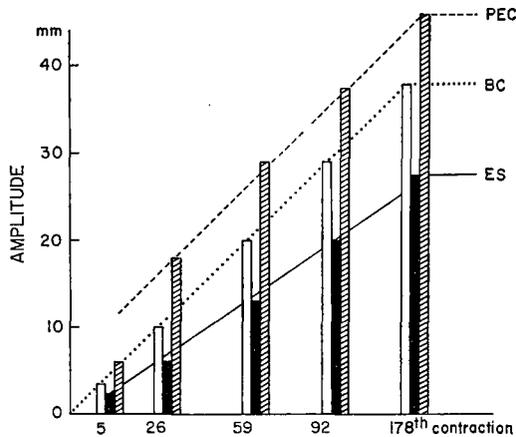


FIGURE 5. Dependence of the extrasystole (black column) and the subsequent potentiated beat (shaded column) on the basal contraction (unshaded column) during the Bowditch staircase (3 min rest, stimulation rate 60 per min, preextrasystolic interval 0.5 sec). Digits indicate the number of the reference BC after the onset of stimulation. Last group corresponds to steady-state conditions. ES remains in an approximately steady proportion to its BC, but the increment of PEC is constant irrespective of the BC (apart from the first intervention). Guinea pig atrium, 32°C. BC = basal contraction, ES = premature contraction (extrasystole).

cussion of the assumed intracellular calcium cycle will be the subject of a separate paper.

The progressive increase in the capacity to contract during the interval following the previous mechanical response leads to an assumption of a terminal compartment to which the activator moves during the interval, and from which it will be released to the active sites by the next activation. There is normally no other outlet from this compartment, and its actual content at the moment of activation is completely discharged. The course of the restitution indicates the progress of this filling, and in general the mechanical response would depend on the content of calcium available for release in this compartment. The evidence for calcium movements through the other compartments is not so direct and is based on more complicated deductions.

The immediate potentiation (or depression) reflects a process going on at the same time at an earlier stage since it appears with only a delay of one cycle. It has an opposite course as though the content of the activator in an upper compartment de-

creased progressively during the interval between the two following excitations (Blinks and Koch-Weser speak of the decay of the “positive inotropic effect of activation”—PIEA). The constancy of the increment corresponding to a given interval (Fig. 5) seems to indicate that each membrane change (action potential) liberates and moves a given amount of calcium to this intermediary compartment, which is added to the residual quantity—greater if the interval is short, smaller if it is long. This would account for the previously mentioned reciprocal relation between the course of restitution and potentiation or depression (Fig. 2).

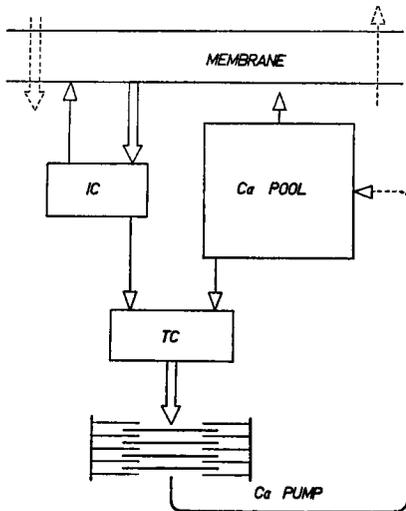


FIGURE 6. Tentative diagram of the postulated compartments of activator involved in its turnover during the activation cycle. For explanation see the text.

If the muscle is excited at regular intervals, both processes come into an equilibrium characteristic for the corresponding steady state, and the course of restitution remains steady. If an interval is shortened the subsequent course of restitution is accelerated, as though less calcium is escaping from the intermediary compartment; if an interval is prolonged the course of restitution is depressed, in keeping with the longer duration of the escape of calcium from the intermediate compartment.

The staircase and the slow transient phenomena point to the existence of another compartment, a kind of calcium pool which would account for the observed inertia in the contractility changes; i.e., for the fact that a rapid step-like change (of frequency or temperature) is followed by a slow staircase-like transition to the new steady state. The concentration gradient between this pool and the terminal compartment would also determine the general level of contractility, which in turn reflects the rapidity of the process of restitution. This pool most probably would be filled by the return of calcium from the active sites of the contractile system.

The supposed cyclic movements of calcium (or, a more general way of speaking, of the activating agent) are summarized in a tentative diagram (Fig. 6). Some of these movements are active, depending on energy supply, others are passive, depending very probably on concentration gradients and on the permeability of the

separating structures. Some of these processes are intermittent, pulsatory, i.e. brief bursts in the system of cyclic transfers, other seem to be continuous flows.

The proposed scheme is, of course, much simplified, and some points which may prove to be quite important, have been left out (e.g. relations of changes in strength to those in peak time and velocity, dealt with in our other papers (Šumbera, Kruta, and Bravený, 1966; Šumbera, Bravený, and Kruta, 1967). The scheme is based largely on indirect evidence, and should be considered as tentative, as a stage in the endeavor towards an understanding of numerous phenomena which we and many other workers have observed and analyzed. Intracellular concentration gradients of electrolytes and calcium in particular, the presence of several forms of calcium, as well as intracellular barriers have been described by several authors (Winegrad and Shanes, 1962; Grossman and Furchgott, 1964; Langer, 1964; Teiger and Farah, 1967). In addition, several structures, the sarcoplasmic reticulum, mitochondria, and the inner face of the cell membrane, are known to have special relations to calcium and its active transport and accumulation. But, on the basis of our interpretation of the mechanical phenomena, it would be premature to identify any of the proposed compartments with some of these structures. Much more experimental work is needed.

Paired stimulation is a special case of sustained postextrasystolic potentiation (Cranefield, 1965; Brutsaert, 1966), which fits well into our scheme. The disparity of the two alternating intervals causes the negative process, a decay of activator in the higher intermediary compartment, to be interrupted earlier by the premature stimulus, which at the same time delivers a new dose of activator. Thus, a surplus amount of activator is added to the next stage, increasing the rate of restitution for the subsequent beat. The positive process of accumulation of activation in the terminal compartment, however, being one stage lower, takes place during the longer interval and therefore can fully develop before the activator is released into the contractile apparatus. The complete effect is established progressively by the cumulative process which maintains the calcium pool at a high level. This means also that it depends on the integrity of metabolic processes and actually requires a greater oxygen supply (Meijler and Durrer, 1965), which would be of importance in the consideration of clinical applications.

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# Physiological Basis of Paired Stimulation Potentiation

F. L. MEIJLER, E. S. NIEUWENDIJK, and D. DURRER

From the Department of Cardiology and Clinical Physiology, University of Amsterdam, Wilhelmina Gasthuis, Amsterdam, The Netherlands

## INTRODUCTION

The meager clinical results obtained with paired stimulation after the initial promising observations (1, 2) may in part be due to the fact that the underlying physiological mechanisms involved are too little understood. The deliberate application of potentiation of contraction induced by certain stimulation patterns requires some knowledge of the relationship between the RR interval and contractile behavior of the myocardium. Although the biochemical basis and/or the factual site on the cellular or molecular level of this relationship is virtually unknown, something can be said about the way the myocardium reacts to changes in duration between depolarizations (R waves).

## METHODS

Isolated rat hearts perfused according to Langendorff were used for these studies. Contractions were recorded by means of a Sanborn 7 DCDT-100 displacement transducer (Sanborn Co., Waltham, Mass.). This is an almost isotonic recording device. Contractility is defined as contraction height (vertical displacement of the apex of the heart). Perfusion and recording techniques have been published in detail previously (3, 4).

Paired stimulation or other stimulation patterns desired were derived from a specially designed current source stimulator.

## RESULTS

Fig. 1 (left) demonstrates the effect of one shorter interval (200 msec) interposed between a train of regular beats. It can be seen that this shortened interval not only gives rise to a small beat directly following that short interval, but also to a number of enlarged contractions coming thereafter. This phenomenon is known as "postextrasystolic potentiation" (4, 5). One interposed short interval has thus potentiated a number of contractions. The effect of one interposed longer (600 msec) interval is shown in Fig. 1 (right). The contractions directly following the interval of longer duration are enhanced ("rest contraction") (6) but the beats coming thereafter are somewhat smaller than the controls. Katz (personal communication) has suggested that we call this phenomenon "depotentiation." It is of importance to note that the increase in contraction height originated by the postextrasystolic potentiation surpasses the decrease in contraction height originated by the postrest depotentiation.

Fig. 1 also demonstrates the effect of a short and a long pause on the beat directly following that pause, A shorter interval is followed by a smaller contraction, a longer interval is followed by a larger contraction. This direct relationship between interval and contraction is called the restitution curve (7, 8) (Fig. 2).

Restitution curves can be explored to describe potentiation of myocardial tissue or hearts. A shift of restitution upward implies potentiation, a shift downward depotential. Fig. 3 demonstrates the effect of different steady-state heart rates on the resti-

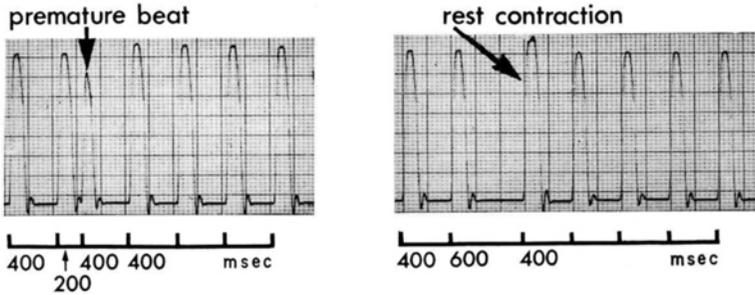


FIGURE 1. Isotonic contractions of an isolated rat heart showing the effect of a premature beat (left) and a delayed beat (right) on the subsequent contractions. It can be seen that the potentiating effect of the premature beat surpasses the depotentiating effect of the rest contraction.

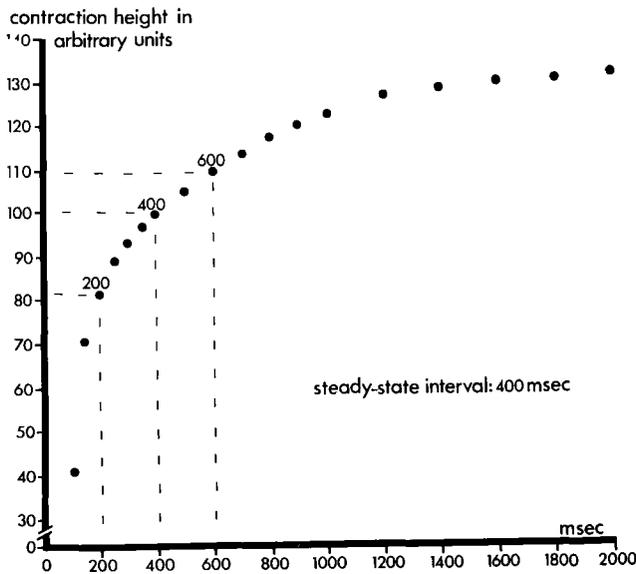


FIGURE 2. Restitution curve of an isolated rat heart. For further details see text.

tution curves derived during those rates. A higher heart rate potentiates in relation to a lower one, and a lower heart rate depotentiates in relation to a higher one.

By the same token the potentiating effect of one or two premature beats can be demonstrated (Fig. 4). The depotentiating effect of a delayed beat expressed by a downward shift in restitution as well as the potentiating effect of a premature beat expressed by an upward shift in restitution is demonstrated in Fig. 5. For this experi-

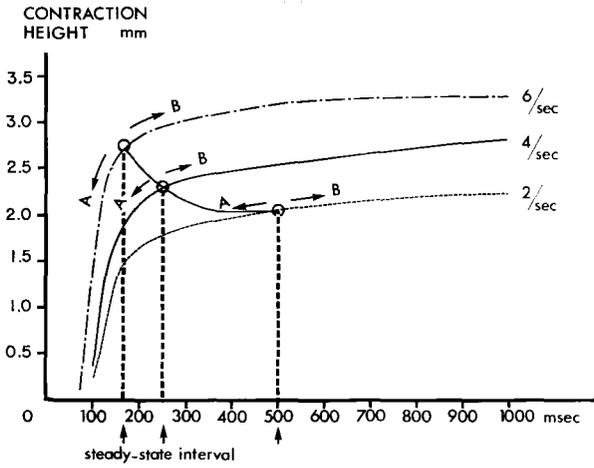


FIGURE 3. Restitution curves of an isolated rat heart at three different steady-state heart rates. The A part of each curve is the "premature beat part," the B part "the rest contraction part" of the curve. The open circle on each curve represents the contraction height at the steady-state frequency. The line connecting these three circles represents the relationship between heart rate and contractility at the steady state.

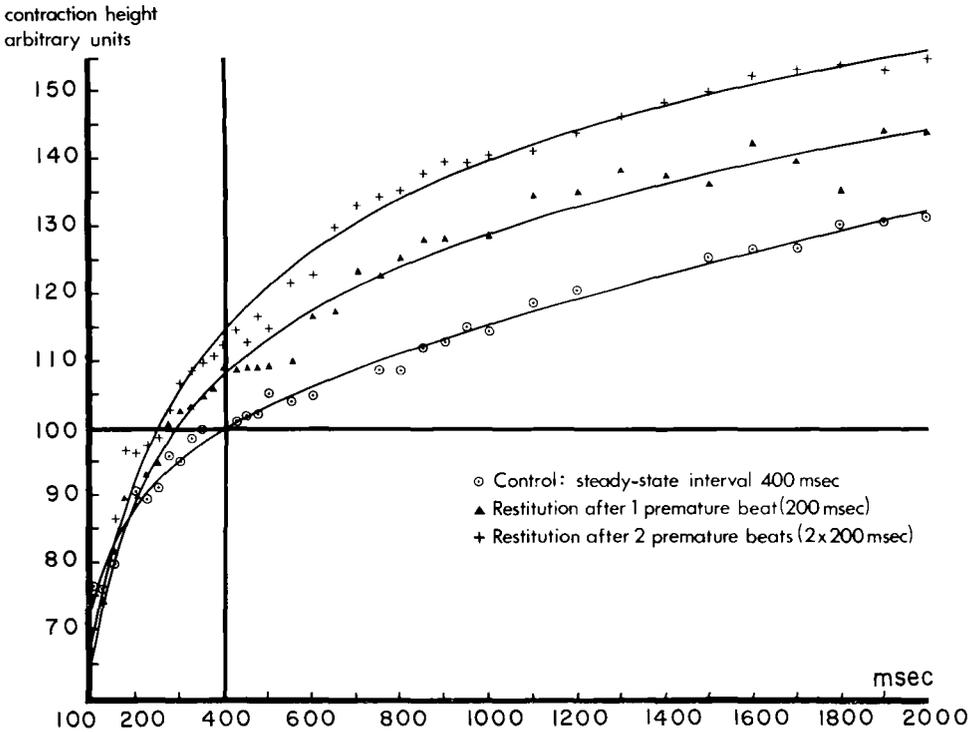


FIGURE 4. Restitution curves of an isolated rat heart. The effect of one and of two premature beats on the restitution is demonstrated.

Contraction height  
Arbitrary units

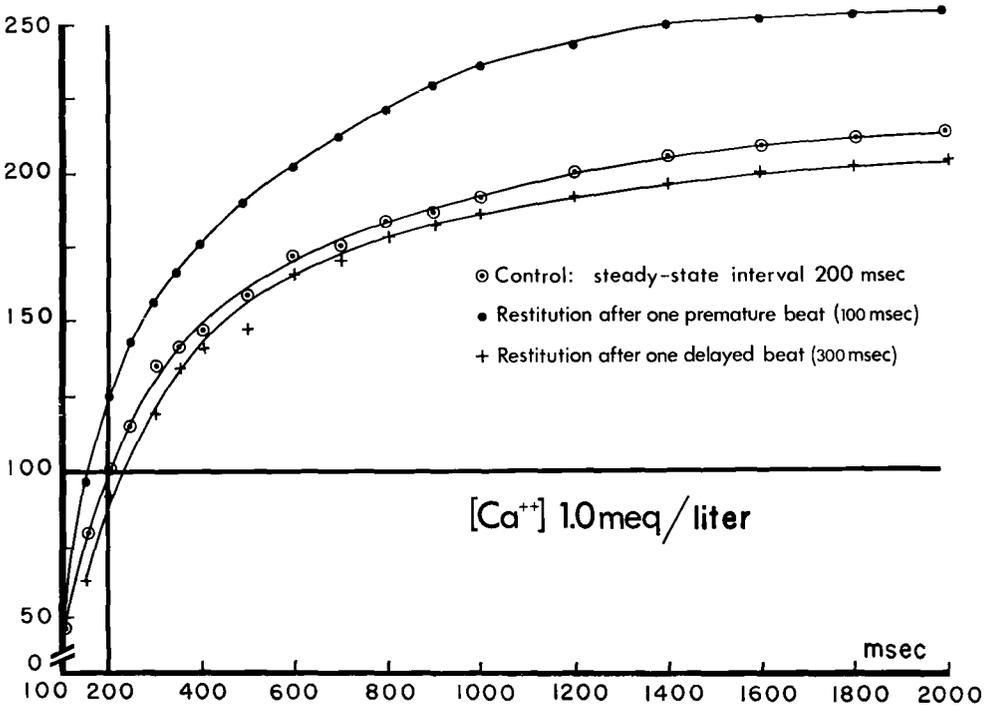


FIGURE 5. Restitution curves of an isolated rat heart at a steady state of 5/sec (200 msec RR interval) and following a premature beat (100 msec) and a delayed beat (300 msec) during low calcium perfusion. For further details see text.

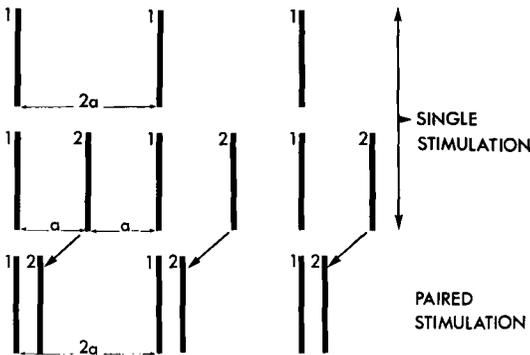


FIGURE 6. Schematic representation of the transformation of single into paired stimulation. Figure reprinted by permission from *Nederlands Tijdschrift voor Geneeskunde*, 1965, 109: 1628.

ment low calcium perfusion and a high steady-state heart rate were used in order to demonstrate the depotentiation by the long interval. In previous work (9, 10) we have demonstrated that perfusion with low calcium enhances relative changes in contraction by interval variation. Fig. 5 also shows that the potentiating effect of the pre-

mature beat is much larger than the depotentiating effect of the corresponding delayed beat.

Paired stimulation can be effected in two ways; *i.e.*, either by adding one extra stimulus after each regular beat and thus doubling the electrical heart rate or by placing each second stimulus closer to the preceding one with the mean electrical heart rate remaining constant. This is schematically demonstrated in Fig. 6.

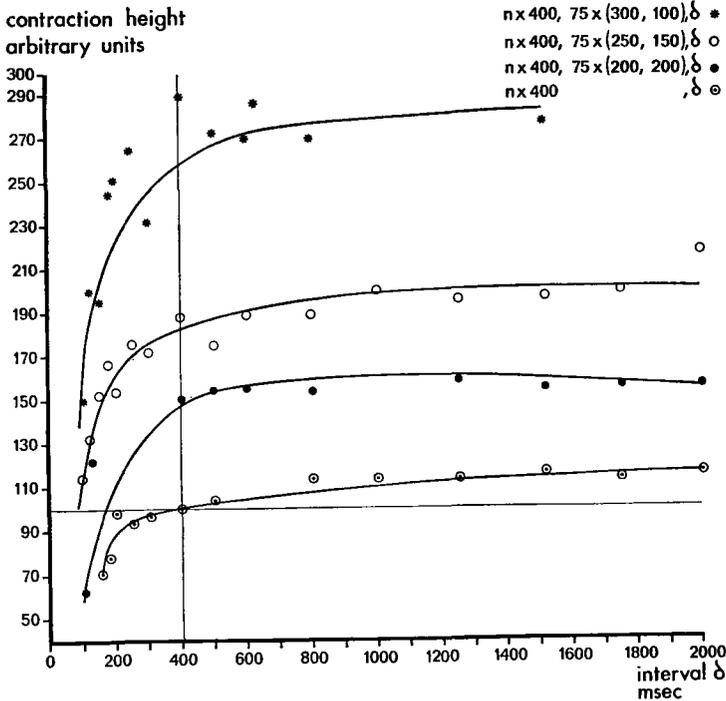


FIGURE 7. Restitution curves of an isolated rat heart. The effect of paired stimulation on the restitution can be derived from the comparison between the top curve and the bottom curve. For further details see text.

In order to study the effect of paired stimulation at the same mechanical heart rate the electrical rate has to be doubled. By means of a family of restitution curves the potentiating effect of paired stimulation can easily and more or less quantitatively be demonstrated. In Fig. 7 restitution curves are shown at the steady-state heart rate of 2.5/sec (RR interval of 400 msec), after doubling the heart rate for 75 periods and after gradually effecting paired stimulation by finally delivering stimuli after 300 and 100 msec, respectively. It should be realized that the mechanical heart rate during the control rhythm (bottom curve) has been the same as during the paired stimulation period (top curve). The tremendous shift of the restitution curve representing the potentiating effect of the paired stimulation should be noted.

## DISCUSSION

In this paper we have attempted to demonstrate and explain the effect of paired stimulation by generally accepted and more or less standard physiological procedures. The contractile state of the heart in relation to its interval history can easily be described by a restitution curve (7, 8). Changes in interval will either shift the restitution curve upward, downward, or leave the original control curve unaltered. Potentiation is said to have taken place if the restitution curve is shifted upward and to the left, while depotentiation is expressed by a restitution curve shifted downward and to the right. There is one restriction in that we only want to speak about potentiation and depotentiation if shifts of restitution curves are originated by changes in RR interval. Of course, an upward shift of the restitution curve will be found if at a fixed heart rate other positive inotropic interventions have been introduced.

By means of restitution curves the potentiating effect of an increase in heart rate (Fig. 3), postextrasystolic potentiation (Fig. 4), doubling heart rate, and paired stimulation (Fig. 7) can be demonstrated. Paired stimulation is no more and no less than the repetitive occurrence of one short interval followed by a long one. The potentiating effect of a short interval surpasses the depotentiating effect of the corresponding long interval. In Fig. 5 this is demonstrated with the aid of restitution curves. This phenomenon is the key to the explanation of the net augmenting effect of paired stimulation also and even if the mean electrical heart rate has not been changed. In another way this has been shown by the fact that the potentiating effect of paired stimulation mainly depends on the duration of the interval between a pair of stimuli. Hence when paired stimulation with alternating intervals of 100 and 900 msec is changed into paired stimulation with alternating intervals of 100 and 400 msec, hardly any change in contractility occurs (10). Thus paired stimulation can easily be explained from one of the intrinsic properties of the myocardium known as the interval-contractility relationship. Knowledge of the physiological basis of the potentiating mechanism may encourage its use for clinical purposes (11).

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# “Contractility” in the Excised and the *In Situ* Papillary Muscle

FREDERIC KAVALER, ANTHONY MARLON, RAMON S. HARRIS,  
and VINCENT J. FISHER

From the Department of Physiology, Downstate Medical Center, State University of New York, Brooklyn, New York 11203, and the Cardiopulmonary Laboratory, Veterans Administration Hospital, New York 10010. Dr. Marlon's present address is the Department of Medicine, Palo Alto-Stanford Hospital Center, Palo Alto, California 94304

In utilizing results of experiments on isolated cardiac tissues in the interpretation of *in situ* myocardial dynamics, it would be useful to obtain a direct measurement of the capacity for linear force development of some sample of the ventricular musculature. There is a closely related question of whether forces recorded from isolated muscle preparations are comparable to those developed by the *in situ* muscle or represent only a small residuum of normal contractile behavior. Derived values for linear force per unit cross-section in the heart are complicated by uncertainties as to distribution of fiber orientation, fiber length, and other influences on contractile behavior which may vary from one myocardial site to another (1). In addition, the assumptions regarding ventricular shape which underlie the calculation of wall tension from cavity pressure have still to be validated (2).

In the papillary muscle excised from the right ventricle of the cat, the variables of afterload and of muscle length can be satisfactorily controlled by isometric recording techniques. Length can be set at a value optimal for force development. The additional variable of inotropic influences which may act on the contractile process can also be set at a near maximal value through the use of calcium-rich (10.8 mM), sodium-poor (110 mM) perfusing solution or by means of maximal postextrasystolic potentiation in normal Tyrode's medium (1.8 mM calcium). As a result of using extremely thin muscle preparations (<0.1 mm<sup>2</sup> cross-section), and of maximizing these three factors, an impressively constant value for force development was obtained in four preparations (3).

Results from our present total of 17 excised cat papillary muscle preparations are reported here. Of these, the seven thinnest muscles (0.1 mm<sup>2</sup> cross-section, or less) again showed a quite constant maximal force development of  $5.9 \pm 0.7$  g per mm<sup>2</sup>. This value is compared directly with that obtained from an *in situ* papillary muscle preparation, contracting isometrically in the right ventricle of the dog. The contractile maximum was attained, in this case, through the use of paired electrical stimulation. Maximal force development by the *in situ* muscle, while more variable, roughly ap-

proximated that found in the excised tissue, having a value in 17 preparations of  $5.2 \pm 1.6$  g per  $\text{mm}^2$ .

## METHODS

Although it would be desirable, for purposes of this comparison, to use the same muscle in both the in situ and the in vitro studies, this is not feasible, since papillary muscles in the right ventricle of the dog are quite thick, being 3.4 mm or more in diameter in these studies. Such diameters are far in excess of presently available estimates (4, 5) of the value critical for diffusion limitation in vitro. Papillary muscles and trabeculae from the right ventricle of the cat were used and these ranged in diameter from 0.18 to 1.00 mm, when stretched to a length optimal for tension development.

TABLE I  
DATA ON *In Situ* PAPILLARY MUSCLES

Optimal length	Heart rate	Muscle weight	Calculated cross-section	"Maximal" developed force
<i>mm</i>	<i>beats/min</i>	<i>mg</i>	<i>mm<sup>2</sup></i>	<i>g/mm<sup>2</sup></i>
10.2	22	139	13.6	4.85
7.3	21	124	17.0	2.64
10.0	35	142	14.2	5.63
9.7	35	142	14.6	6.58
7.1	30	121	17.0	3.12
7.9	30	100	12.6	3.84
7.8	35	101	12.9	4.76
7.6	27	79	10.3	6.79
13.0	35	243	18.6	2.74
11.1	28	125	11.3	7.52
8.1	27	138	17.0	8.18
10.6	27	119	11.2	6.06
7.5	36	71	9.5	6.11
8.1	34	73	9.0	5.78
9.6	44	110	11.5	4.52
11.5	28	207	18.0	3.89
9.5	28	111	11.7	5.64

### *Isolated Cat Papillary Muscle*

In a total of 17 preparations, developed isometric tension was measured by a technique previously described (6). Briefly, this involved clamping the muscle between two Lucite plates, in the upper one of which was a hemicylindrical hole not quite large enough to contain the end of the muscle loosely. Stimulating wires were embedded in the lower plate. The other end of the muscle was snared by a loop of thin nylon ( $20 \mu$  diameter) fiber held tightly in a glass tube, which in turn was attached firmly to the anode pin of an RCA 5734 mechanoelectric transducer tube. The 17 muscles were obtained from about four times as many cats. Only those muscles whose transverse dimensions were quite constant along their lengths, and which could be mounted without major deformation or torsion, were selected for this study. The diameter measurements were made with the ocular micrometer of a dissecting microscope and values obtained at five or more points along the axial extent of each muscle selected were all

within 5% of the mean, when the muscle lay unrestrained in the bath. Uniformity of transverse dimensions was even greater in all but the three thickest muscles (0.8, 6.93, and 1.0 mm diameter) at the length optimal for force development. In addition, shortening was observed, by the same means, to be under  $1\frac{1}{2}\%$  of the total muscle length for all muscles. For further details, see reference 6. All results from the tissues selected in this way are reported here. The muscles were electrically driven at a rate of 15 per min. A calcium-rich (10.8 mM), sodium-poor (110 mM) Tyrode solution was used, at a temperature of 29°C. Muscle length was adjusted to that optimal for contraction, as a result of several lengthening and shortening sequences. Paired electrical stimulation was also used, at a rate of 15 pairs per min and at a pair interval optimal for contraction, in normal Tyrode's medium.

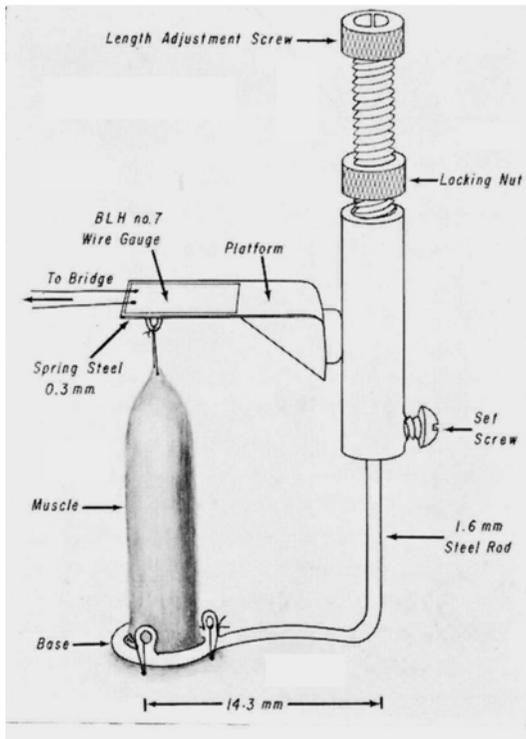


FIGURE 1. *In situ* papillary muscle mounted in force gauge. Gauge has linear calibration (to 2%) over force range, 0–150 g. Frequency response 20 cycles.

### *In Situ Dog Papillary Muscle*

A gauge (Fig. 1) was designed for isometric recording from the anterior papillary muscle of the right ventricle. During cardiopulmonary bypass, at a blood temperature of about 27°C, the right ventricle was opened and the tendinous attachment of the muscle was severed. A close-fitting steel ring was passed around the muscle to lie firmly against the septal endocardium at the muscle's origin. The tendon was tied to the underside of a spring steel platform 0.012 inch thick. To this platform's upper surface was bonded a resistance wire gauge (Baldwin-Lima-Hamilton (C No. 7). Three superficial sutures secured the steel loop to the septal endocardium at the base of the muscle. A screw at the top of the assembly made it possible to move the platform relative to the steel ring in a graded fashion and thus to stretch the muscle by calibrated length increments. In all but the first six experiments the close-fitting ring was not sutured at the base

of the muscle, but was held in place by three prongs projecting downward from the ring. When this device was used, only the upper portion of the length-tension relationship was explored, since it was only at the greater muscle lengths that the ring was held firmly against the septal endocardium. Deformation of the gauge in the long axis of the muscle was under 1% of muscle length when subjected to a force (100 g) slightly more than the greatest one recorded.

At the conclusion of each experiment the heart was stopped in diastole by injection of a 25% solution of KCl into the coronary arteries. The ascending aorta was then ligated around a catheter and 500 ml of a 10% formaldehyde solution was perfused through the coronary arteries at an average pressure of 100–150 mm Hg. This method of fixation was found to increase the water content of heart muscle by an average of 0.3%. Immediately after completion of the

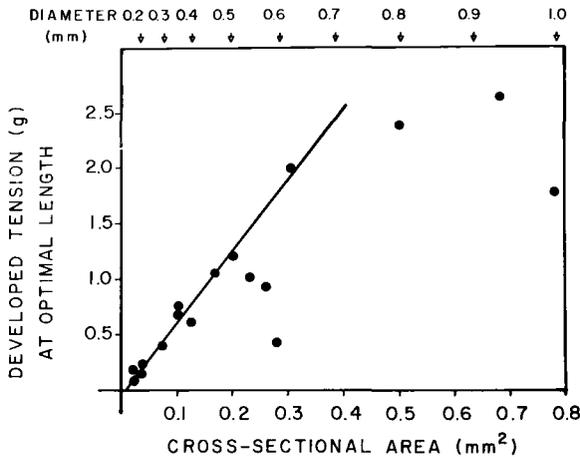


FIGURE 2. Plot of developed force against area of cross-section (at optimal length) in calcium-rich (10.8 mM), sodium-poor (110 mM) Tyrode's medium, for 17 isolated cat papillary muscle preparations.

formaldehyde perfusion the papillary muscle studied was cut free at its septal attachment. The chorda was removed, the muscle blotted dry, and rapidly weighed (within 3 min after excision). After weighing the muscle its length was measured and its cross-sectional area calculated assuming the muscle to be a cylinder and with a specific gravity of 1,000. Most muscles were of fairly uniform transverse dimensions except for tapering at the apical end and tended to be slightly elliptical in cross-section.

### *Isovolumic Left Ventricle of the Dog*

In a few experiments, left ventricular contraction was monitored as pressure exerted on an indwelling polyethylene balloon during total cardiopulmonary bypass. This technique has been described by several authors (see reference 3).

## RESULTS

### *Force Development by the Isolated Cat Papillary Muscle*

The 17 values obtained for developed force, at optimal length and in the calcium-rich, sodium-poor Tyrode medium, are plotted in Fig. 2 as a function of the area of cross-

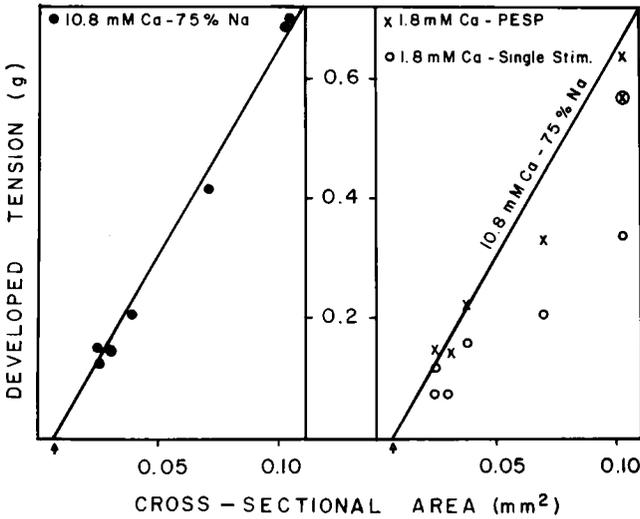


FIGURE 3. Plot as in Fig. 1 for the seven thinnest muscles. Inotropic conditions indicated.

section. This area was derived in each case from the diameter of the optimally stretched muscle. A scale for the corresponding diameters is shown at the top of the illustration. Force has an impressively linear relationship to cross-section for the thin muscles and falls off for the thicker ones, although the data are insufficient for any estimate of a critical diameter for contraction. In order to use a reliably constant force as our yardstick of comparison with the *in situ* preparation, we considered only the

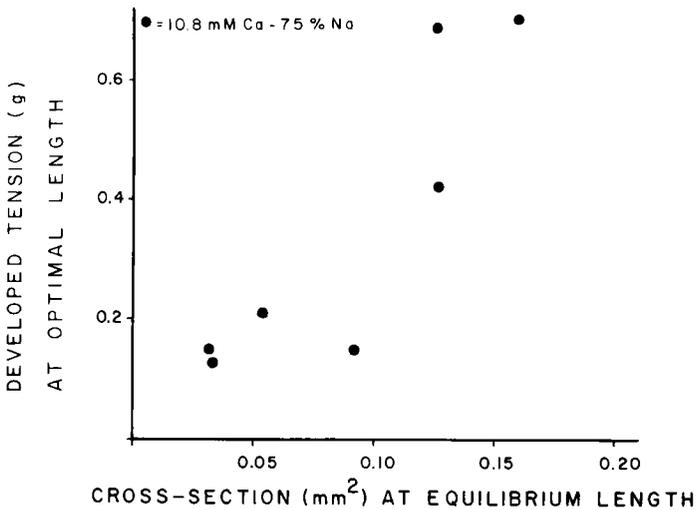


FIGURE 4. Plot of same force values as in Fig. 2 (left panel). Abscissa, however, is *equilibrium* cross-section.

seven thinnest muscles. These values are shown again in Fig. 3 (left panel) where a line of least squares is drawn through the points. This line is redrawn in the right panel, and, by comparison, control contractile forces in normal Tyrode's solution are relatively randomly distributed, while those resulting from paired electrical stimulation in normal Tyrode's medium approximate reasonably well the maximal values. Developed force in the calcium-rich medium is less linearly related to the equilibrium cross-section, measured when the muscle lies unmounted in the bath, than it is to the cross-section at optimal length. This is evident in Fig. 4, where the same force values shown in Fig. 3 (left panel), are replotted against cross-section, derived from measurements of diameter at equilibrium length.

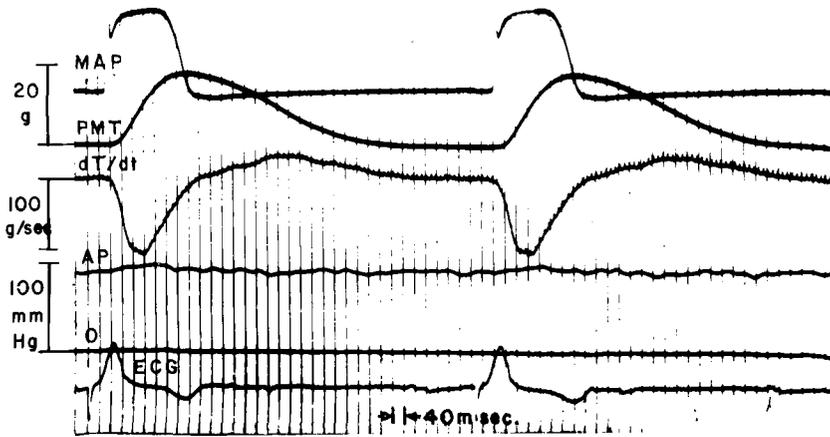


FIGURE 5. Traces, from above down, are, monophasic action potential (suction electrode); papillary myogram (PMT); rate of change of papillary muscle force (positive downward,  $\frac{dT}{dt}$ ); aortic pressure maintained by the bypass pump (AP); zero pressure; ECG.

If force development per unit cross-section in the calcium-rich medium is obtained for each of the seven thinnest muscles, the mean value is  $5.9 (\pm 0.7)$  g per  $\text{mm}^2$ . Rest potentiation, following a 1 min period of quiescence in the calcium-rich, sodium-poor, medium, produced a small (7%) further increase in developed force on two occasions bringing our estimate of maximal contractile force in this preparation to a value of  $6.3$  g per  $\text{mm}^2$ . This is about one-sixth of the highest value reported for a tetanus of a single skeletal muscle fiber (7).

#### *Force Development by the In Situ Dog Papillary Muscle*

Fig. 5 shows a representative trace from an experiment on the *in situ* preparation. The muscle is at optimal length and contraction and relaxation phases of the papillary myogram are well-correlated with the depolarization and repolarization (8) limbs, respectively, of the monophasic action potential recorded by a suction electrode (9) at the base of the muscle. In addition, although the muscle is under considerable pas-

sive tension at this length, the myogram is free of detectable excursions during diastole, indicating that this record of papillary muscle contraction is not influenced by forces transmitted from the rest of the heart, at least during this period. Recordings from the myocardial wall by the Walton-Brodie technique (10) or its Hefner variant (11), in contrast, usually show considerable diastolic excursion.

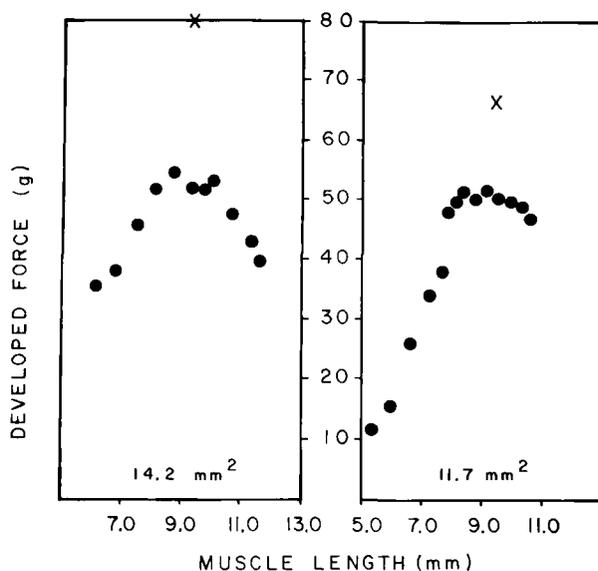


FIGURE 6. Length-tension plots for two *in situ* papillary muscle preparations (filled circles). Also forces developed during paired electrical stimulation at optimal length (X's).

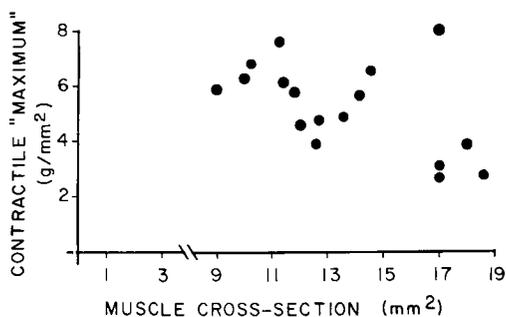


FIGURE 7. Muscle thickness and measured "contractility" of *in situ* papillary muscle preparations.

In Fig. 6 are shown length-tension plots from two representative preparations, as well as the developed tension during paired electrical stimulation at optimal length. Maximal contractile force, estimated in this way, amounts to 5.6 g per  $\text{mm}^2$ , in both cases. These curves are technically less satisfactory than those obtainable from thin isolated muscles (see reference 7, Fig. 3, right panel).

Unselected results from all 17 *in situ* preparations studied are shown in the table. The mean value for developed force at close to optimal length and during paired elec-

trical stimulation is  $5.2 \pm 1.6$  g per  $\text{mm}^2$ , or nine-tenths of that found in the isolated cat papillary muscle. Recorded force development decreases with increasing muscle thickness over the range of cross-sectional areas found for these preparations, and this trend is evident in Fig. 7 in spite of the considerable variability of the data as compared with those obtained from the isolated tissue.

### *Limiting Effect of Heart Rate on Mechanical Potentiation by Paired Electrical Stimulation*

The use of paired electrical stimulation to attain a maximal inotropic effect on ventricular muscle is severely limited by the fact that developed force falls quite sharply

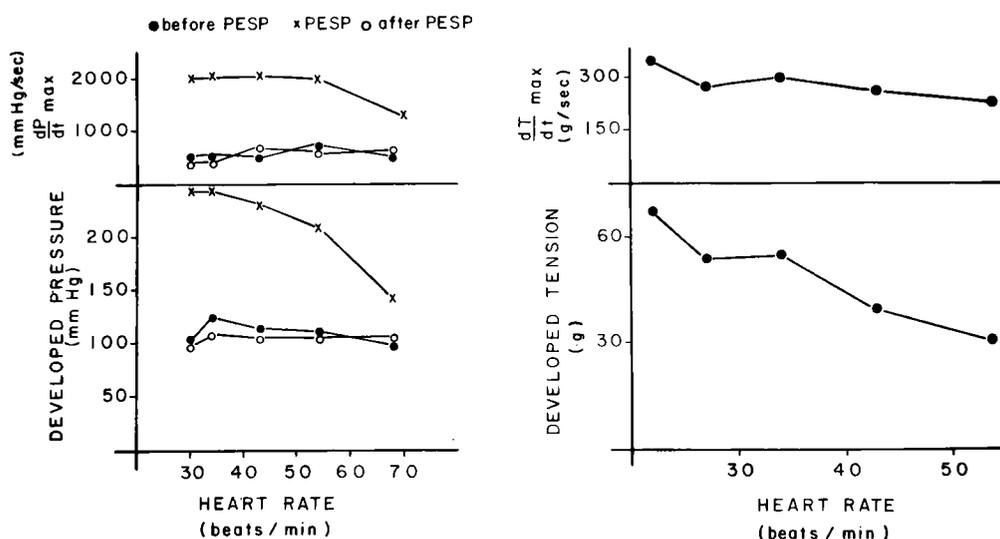


FIGURE 8. Negative force-frequency relationship, characteristic of contraction potentiated by paired electrical stimulation, as determined in the isovolumic left ventricle (left panel) and *in situ* right ventricular papillary muscle (right panel) preparations.

with increasing basal rate (i.e. of the pairs). This "negative staircase" for the effects of paired stimulation has its onset at extremely low rates, as shown by Fig. 8 for the isovolumic left ventricle of the dog (left panel) and for the *in situ* dog papillary muscle (right panel). The same holds true for the differentiated record of force or pressure development, although the rate of onset of this effect is somewhat higher.

### DISCUSSION

Isometric force development, at optimal length and inotropic state, has been found to amount to  $5.9 \pm 0.7$  g per  $\text{mm}^2$  in the excised cat papillary muscle and  $5.2 \pm 1.6$  g per  $\text{mm}^2$  in an *in situ* dog papillary muscle preparation. These values are quite close to one another and may provide a quantitative estimate of the contractile capacity of mammalian ventricular muscle. This possibility is supported by the impressive constancy of developed tension in the very thin excised tissue preparations. For a final evaluation

of such a measure of myocardial contractility, however, additional information of several kinds will be necessary.

The possibility that inotropic effects exist, which are considerably greater than that elicited by the calcium-rich, sodium-poor medium, cannot be dismissed at present. Epinephrine, staircase, and paired electrical stimulation appear to have been excluded in this regard, although rest potentiation does result in a small increment in tension development by the excised muscle. This larger tension, as additionally augmented by an optimal rest period, was not used here as our basis of comparison, since this condition cannot be duplicated *in situ* without additional maneuvers to suppress pacemaker activity (and perhaps also, contraction).

Whether the papillary muscle is, quantitatively, a representative sample of the ventricular myocardium is not known. It is, however, a sample accessible to reasonably adequate isometric recording techniques.

How uniformly the contractile proteins in papillary muscles are oriented parallel to one another and to the recording apparatus is, similarly, a matter of great uncertainty. The impressive linearity of the plot of tension against cross-section, for the very thin excised muscles, suggests that the parallel fiber assumption is a reasonable approximation. Even in these thin muscles, however, the values for developed force at optimal length are more randomly related to equilibrium cross-section (Fig. 3) than they are to cross-section at optimal stretch (Fig. 2, left panel). This suggests that the parallel fiber approximation is indeed a crude one, which gives the best fit under the deformation of stretch. It would also be expected that the parallel fiber assumption would be still less satisfactory for muscles of greater diameter. Whether this effect, or that of diffusion limitation, is the one primarily responsible for the lower force per unit cross-section found in the thicker excised muscles, it is nevertheless clear that quantitative studies of force development are best carried out on thin preparations. An additional problem in evaluating mechanical recordings from cardiac muscle has been noted by Gay and Johnson (12). In their anatomical studies of papillary muscles and trabeculae from the right ventricle of the rabbit, they found marked "buckling" of many sarcomeres at degrees of stretch where the muscle appeared grossly to be straight and taut.

Such problems, arising from a complex disposition and orientation of the force-producing elements, would be expected to be still more serious in the much thicker *in situ* preparations. The trend shown in these data (Fig. 7) is one of larger tension values for smaller muscles, without any indication that a plateau has been reached at the smallest diameters. The *in situ* results may, for this reason, underestimate contractile capacity. An error of overestimation is also inherent in this preparation. In these muscles, which taper at their free ends, the thin end segments may support a force in excess of what their contractile mechanism can generate, by virtue of parallel elastic elements. This would be especially likely to occur at optimal muscle lengths.

Finally, the additional observation that the degree of postextrasystolic potentiation attained *in situ* is rate-dependent indicates that it can be used to elicit the contractile maximum only at slower heart rates than are likely to occur spontaneously.

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# Alterations in the Hemodynamic and Sequential Responses of the Ventricles to Paired Pacing in the Dog

LEROY J. HIRSCH, SALVADOR LLUCH, and A. ELLIS

From the Cardiovascular Institute and the Division of Cardiovascular Disease, Department of Medicine, Michael Reese Hospital and Medical Center, Chicago, Illinois 60616

The site of electrical pacing of the heart has been the subject of much investigation, primarily using single pacing. Thus, Lister et al (1) utilizing a number of sites on both the right and left ventricles have shown that cardiac performance can be altered positively or negatively depending on the sites selected for pacing. They observed that certain pacing sites on the left ventricle were hemodynamically more effective than others and that the better left ventricular sites were more effective than any of the right ventricular sites tested. They recorded differences of over 100% in cardiac outputs when pacemaker sites on both ventricles were compared. Similarly, Gilmore et al. (2) have shown that important differences occur when single stimuli to the atria and ventricles are compared. The most apparent effect was on atrial contribution when ventricular stimulation was placed at such a point in time as to cause the atrium to contract against a closed mitral valve. This reduced the atrial contribution to ventricular filling and with it, cardiac output.

Obviously, single stimulation does not have the potent inotropic effect on ventricular contraction that paired pacing does. We have recently shown (3) in atrial vs. ventricular paired pacing that at high driving frequencies paired ventricular pacing produces a more effective cardiac performance than does atrial pacing at comparable rates. On the other hand, atrial pacing at rates below 120 beats per min is just as effective as ventricular pacing. Therefore, it appears that paired pacing may significantly alter hemodynamic response when the heart is stimulated from different locations.

The present report deals with the ventricular response to paired pacing when the heart is stimulated from several locations on the ventricles.

## METHODS

15 animals were anesthetized with Nembutal (30 mg per kg). The chest was opened at the fourth or fifth intercostal space and the animal placed on positive pressure respiration. Electrodes were sutured to the ventricles at the following locations: (1) right ventricle, midway between base and apex and 15 mm from the interventricular sulcus; (2) left ventricle, midway between base and apex, 15 mm from interventricular sulcus; (3) same as (2), but 35 mm from interventricular sulcus; and (4) apex of the left ventricle.

Pressure catheters were placed in the right ventricle via the external jugular, the left ventricle via the femoral artery, and the aorta via the carotid artery. The catheters were connected

to Statham pressure transducers. The first derivative of the left ventricular pressure pulse ( $dp/dt$ ) was recorded electronically. Lead II of the electrocardiogram was usually recorded.

The cardiac electrodes were connected to a multiplex switch so that the impulses could be instantaneously changed from one location to another. A Grass S4G stimulator was attached to the multiplex switch. The impulses generated were of 2 msec duration, 2-3 v intensity, and the delay between impulses ranged between 100 and 200 msec. The frequency of pairs depended on the heart rate desired.

## RESULTS

The placement of the electrodes in various locations on the ventricles appeared to have its greatest effect on right ventricular pressure development.

Fig. 1 shows the effect of ventricular paired pacing (PS) at three locations with a reduction in heart rate from 150 to 110 beats per min (LV site = 1). It will be seen that PS of the right ventricle produces the greatest increment in pressure in that chamber; LV stimulation reduces the RV pressure development when compared to that when RV is the site of stimulation. Apical stimulation reduces RV pressure even more; however, the peak pressure in the right ventricle remains higher than that observed during the control periods.

The increase in left ventricular pressure amounts to approximately 10 mm Hg in all instances, which is the usual effect when PS was used in normotensive animals (4). LV stimulation produces a somewhat greater LV  $dp/dt$  than the other two sites explored. Cardiac output decreased slightly regardless of the site at which stimulation was employed. Left ventricular end-diastolic pressure (LVEDP) increased slightly in all instances, whereas RVEDP decreased slightly.

When the heart rate is maintained at the normal sinus rate with PS (Fig. 2), little change from Fig. 1 is observed, although the alterations in LVEDP and RVEDP appear to be more marked.

When the site of LV stimulation is moved to a point approximately 35 mm (site 3) from the interventricular sulcus and the heart rate maintained constant (Fig. 3), the effect of LV stimulus on RV pressure is reduced from that observed in Figs. 1 and 2, while it appears that RV and apical stimulation do not alter the RV response. There is a slight decrease in both RVEDP and LVEDP. Left ventricular peak pressure is not much altered from the control pressures.

Fig. 4 shows a similar response with constant rate at faster record speed. A reduction in RVEDP is more obvious in this animal. The effect of PS on RV pressures at the second site on the left ventricle is the same as shown in Fig. 3. When the right ventricle is the site of stimulation there is a marked alteration in the RV pressure wave form as compared to either apical or LV sites of stimulation.

Fig. 5 shows the same animals as in Fig. 4, but with the effective contractions reduced from 150 to 100 beats per min. The response of the right ventricle is qualitatively similar to that seen in Fig. 4, but the pressure development is greater. This may be due to both postextrasystolic potentiation and augmentation due to increased fiber length. Left ventricular pressure development on the other hand is not greatly different from that in the control. There is also a noticeable decrease in RVEDP.

Fig. 6 shows a high-speed recording in which the heart rate was maintained constant and several interesting facts appear. The vertical lines show the onset of either

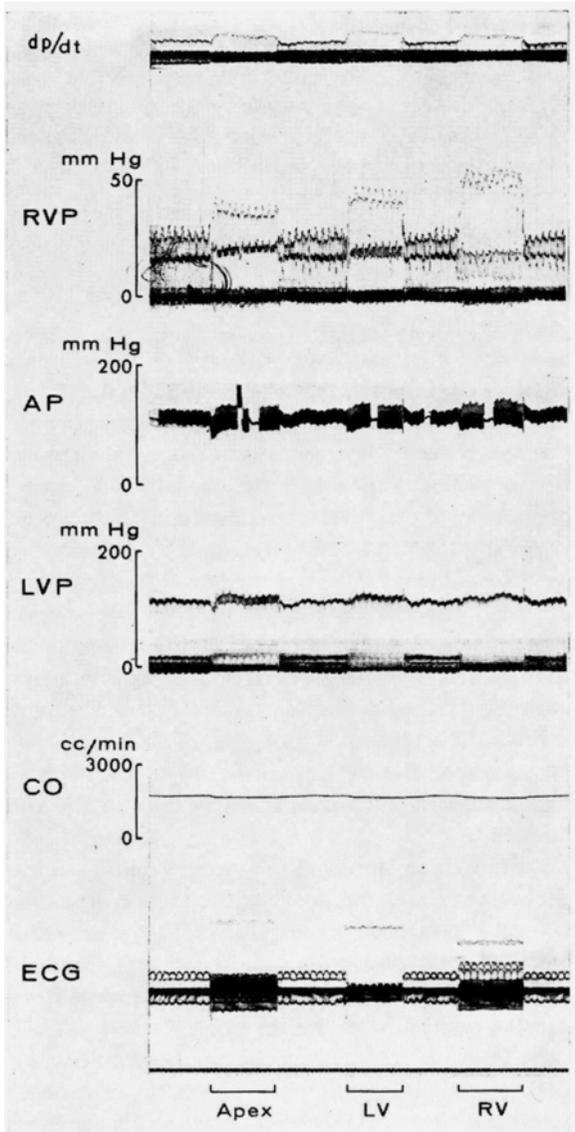


FIGURE 1. Paired pacing effects on right ventricular pressure development. Heart rate reduced from 150 to 110 beats per min. Apex, LV, and RV, sites of ventricular pacing. CO, cardiac output, LVP, left ventricular pressure, AP, aortic pressure, RVP, right ventricular pressure,  $dp/dt$ , first derivative, left ventricular pressure pulse. Discussed in text. Record speed, 0.5 mm/sec.

left ventricular or right ventricular contraction. In the control panel on the left, the contraction sequence of the two ventricles appears to be almost simultaneous. In the second panel, which is apical stimulation, the left ventricle begins its contraction approximately 20 msec prior to the onset of right ventricular contraction. We have observed time differences up to 40 msec between LV and RV sequences at this site of

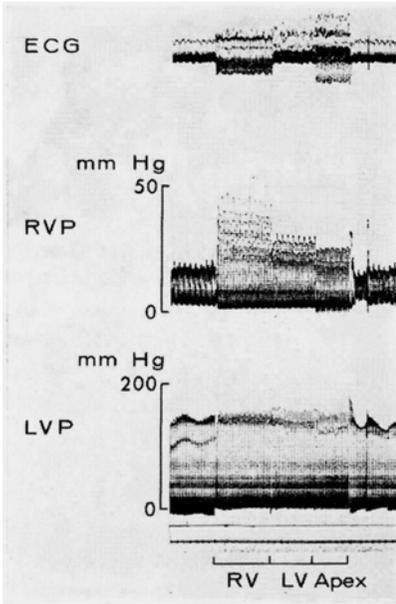


FIGURE 2. Paired pacing in animal without reduction in heart rate. Responses similar to those seen in Fig. 1. Record speed, 1 mm/sec.

stimulation. In the third panel, where the left ventricle is the site of stimulation, the onset of left and right ventricular contraction is similar to that observed in the control panel. When the right ventricle is the site of stimulation, there is a large difference in time of activation with the right ventricle preceding the left by 50 msec.

It is obvious from the recording that both LV and RV dp/dt are increased, systolic

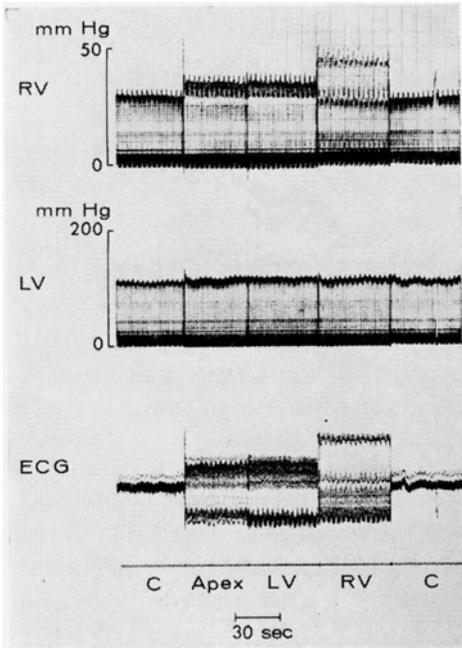


FIGURE 3. Response of a dog in which LV site of stimulation has been moved 35 mm from interventricular sulcus (LV site 3). Right ventricular pressure development from this site lower than that seen in Figs. 1 and 2. No change in heart rate. Discussed in text.

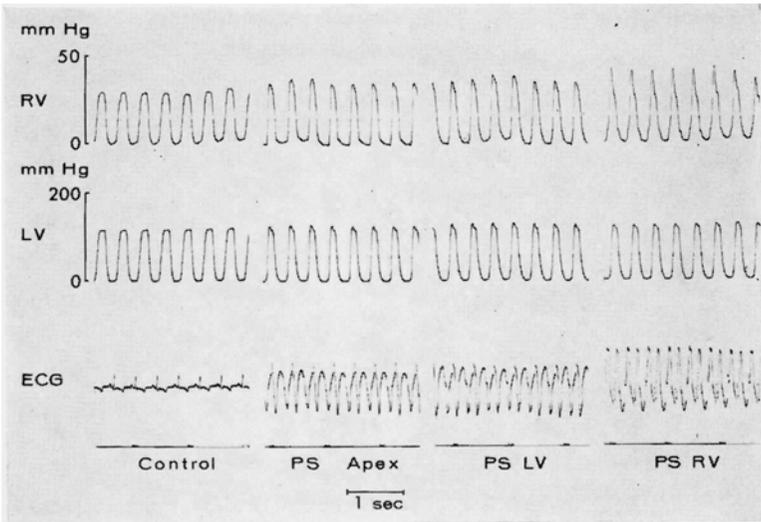


FIGURE 4. Response similar to that seen in Fig. 3. Constant heart rate. Record speed, 25 mm/sec. Discussed in text.

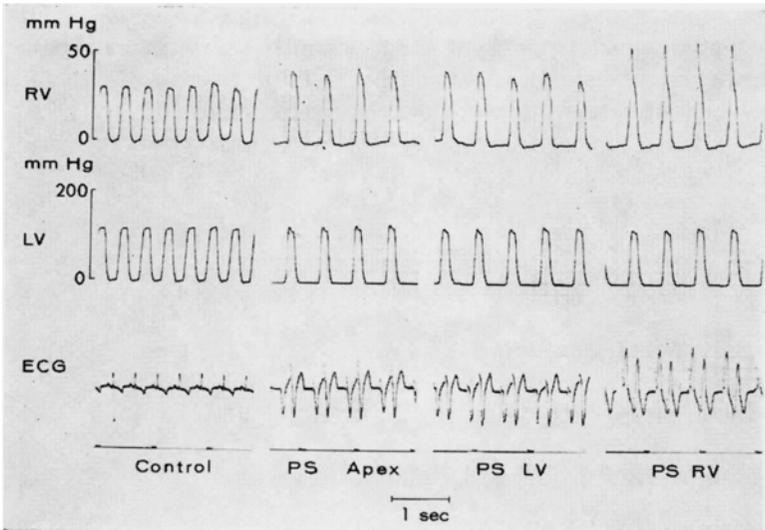


FIGURE 5. Same animal as in Fig. 4 with heart rate reduced from 150 to 100 beats per min. Response is similar but there is greater pressure development in right ventricle. Record speed, 25 mm/sec.

time is reduced, and RVEDP is decreased. Any change in the slope of relaxation is probably obscured by slurring at the foot of the ventricular pressure curves. This in all probability is due to the second impulse producing a minor ventricular contraction which does not show on the recording (5).

DISCUSSION

The two most obvious effects of paired pacing in these series of experiments are the profound effect on right ventricular pressure development while little effect is seen in the left ventricle and the alteration in the sequence of ventricular activation depending upon site of stimulation.

The right ventricle is a low pressure system which under ordinary circumstances is not called upon to develop high pressures. This does not mean, however, that it is unable to increase the force and power of its contraction. In a failing left ventricle, where the contractile force is diminished and pressure reduced, paired stimulation can

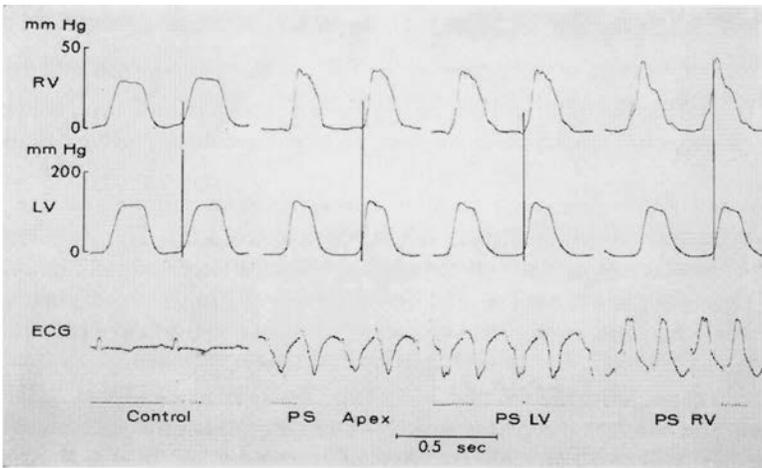


FIGURE 6. Change in sequence of ventricular contraction of left and right ventricles. Perpendicular lines indicate beginning of isovolumic contraction of one or both ventricles.

restore the force of contraction and with it intraventricular and systemic pressures. If this is used as an analogy to what occurs in the right ventricle it might be said that all the right ventricle needs is a potent inotropic agent to increase its force of contraction and elevate the intracavitary pressure. In other words, unlike the left ventricle, under normal circumstances, the right is not performing at its optimum level. Thus, the intervention of a potent inotropic force, such as PS, produces a greater effect in the low pressure system on the right side than it does on the optimally functioning high pressure system on the left.

In all the instances described the development of pressure in the right ventricle is higher than during the control period regardless of the rate or site of stimulation. However, a graded response is seen depending on the point of the stimulus, with RV stimulation producing the greatest effect in that chamber.

The effect of paired stimulation on the sequence of activation of the two ventricles is obviously due to the differences in the spread of excitation from the point of the stimulus on the myocardium. It is interesting to note that the normal sequence of

activation seen when the left ventricle is the site of stimulation corresponds quite closely to the area where Lister's group (1) observed the best hemodynamic effects with single pacing. This brings up a most important point; namely, to what area on the myocardium should paired pacing be directed? It would appear that the right ventricular site produces the greatest increase in right ventricular and pulmonary artery pressure producing a pulmonary hypertension which may have some effect during prolonged pacing. Under the conditions of these experiments, site 3 produces a normal sequence of left and right ventricular contraction with the least alteration in right sided pressure development. With the normal sequence of contraction the full measure of the atrial contribution to cardiac output is obtained, whereas, at the other sites where asynchrony takes place there may be some impingement on this important function of the atria.

#### SUMMARY

The effect of altering the ventricular sites of paired electrical stimulation is to produce important changes in ventricular hemodynamics and synchrony of ventricular contraction.

Paired pacing of the ventricles, regardless of site, increases right ventricular pressure development without much change in left ventricular pressure. There is, however, a graded response in the right ventricle depending upon the site of stimulation. Stimulation of the right ventricle produces the largest increment in right ventricular pressure development. Other sites on the left ventricle and apex cause a lesser response in the right ventricle.

Paired stimulation of the left ventricle midway between base and apex maintains a normal sequence of left and right ventricular contraction. Right ventricular stimulation on the one hand activates right ventricular contraction up to 50 msec prior to left ventricular contraction, while apical stimulation, on the other hand, activates the left ventricle faster than the right.

The site of stimulation may play an important role in maintaining normal hemodynamics in long-term paired pacing.

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# Effects of the Driving Frequency of Paired Stimulation at Different End-Diastolic Pressures upon Left Ventricular Performance

SALVADOR LLUCH, LEROY J. HIRSCH, and LOUIS N. KATZ

From the Cardiovascular Institute and the Division of Cardiovascular Disease, Department of Medicine, Michael Reese Hospital and Medical Center, Chicago, Illinois 60616

## INTRODUCTION

In numerous studies of the effects of paired stimulation on cardiac performance in both the experimental animal and in man the inconstant effects of paired stimulation on cardiac output have been demonstrated (1-10). This has been investigated by us in the present study. Recent evidence from this laboratory indicates that the site of stimulation influences the hemodynamic response to paired stimulation (11, 12). However, to our knowledge, no systematic study has been done relating the driving frequency of paired stimulation to the hemodynamic response of the heart and, in consequence, how the sinus rate would influence this response. In the present study, the effects of paired stimulation of the right ventricle at different driving frequencies upon left ventricular end-diastolic pressure, aortic pressure, cardiac output, and left ventricular minute work were examined over a wide range of left ventricular filling pressures, established by varying blood volume.

## METHODS

26 mongrel dogs of both sexes, ranging in weight from 15 to 20 kg, anesthetized with sodium pentobarbital (30 mg per kg), were used in these experiments. After starting positive pressure breathing, the heart was exposed through a left lateral thoracotomy. Systemic blood flow (cardiac output minus coronary flow) was measured with an electromagnetic flow probe placed around the ascending aorta and connected to a Medicon electromagnetic flowmeter (Model M-4001). The flow probe was calibrated as previously described (13). The aortic pressure was obtained via polyethylene tubing introduced through the left carotid artery and left ventricular end-diastolic pressure via a short metallic cannula inserted through the apex of the left ventricle. The Statham pressure transducers used (P 23AA) were zeroed to the level of the mitral valve. Aortic and left ventricular pressure, as well as systemic aortic flow and lead II of the electrocardiogram, was recorded simultaneously on a Sanborn multichannel polygraph.

After pericardiectomy, wire electrodes were sutured to the right ventricle and paired stimulation was applied with a Grass impulse generator. Stimuli of 2-4 v and 2-2.5 msec in duration were delivered. The interval between each impulse of a pair was set between 150 and 250 msec,

depending on the driving frequency. That interval was selected which gave an apparent single mechanical response of the left ventricular pressure curve and two QRS responses.

Cardiac function curves (14) were obtained by infusing the animals with Ringer's solution from an elevated reservoir via a large catheter in the left jugular vein. For each filling pressure, comparisons were made between left ventricular dynamics during sinus rhythm and that occurring at three different frequencies of paired stimulation (approximately 50, 75, and 100% of the sinus rate).

In the experiments done before infusion the hemodynamic response to paired stimulation appeared to be a function of the original sinus rate. The 26 dogs were divided into two groups. In group I (20 in number) were those with sinus rates ranging between 136 and 165 beats per

TABLE I  
EFFECTS OF PAIRED STIMULATION AT A DRIVING  
FREQUENCY EQUAL TO THE NATURAL RHYTHM

	Group I		Group II	
	Control	Paired stimulation	Control	Paired stimulation
HR	149	147	101	102
MAoEP	106	102	97	102
LVEDP	4.1	4.3	3.5	2.9
CO	1844	1608*	1313	1254
Minute work	2586	2143*	1465	1462
Stroke work	17.5	14.5*	15.7	15.8

The data are expressed as the mean values from 20 dogs of group I and 6 dogs of group II. HR, heart rate; MAoEP, mean aortic ejection pressure in millimeters of Hg; LVEDP, left ventricular end-diastolic pressure in millimeters of Hg; CO, minute cardiac output in cubic centimeters per minute; minute work, external minute work of left ventricle in gram-meters per minute; stroke work in gram-meters per stroke.

\* Significant ( $p < 0.05$ ).

min (mean, 149). In group II (six in number) were those with sinus rates ranging from 95 to 111 beats per min (mean, 100). Three of the animals in group II had the S-A node crushed; the other three had spontaneously slow sinus rates.

## RESULTS

*Effects of Paired Stimulation at a Driving Frequency Equal to the Natural Rhythm at the Control Filling Pressures* Table I shows the results of applying paired stimulation at the same driving frequency as the dog's own rate in the two groups of experiments. In both groups the data are expressed as mean values based on at least three observations in each animal. Paired stimulation in group I produced a drop in mean ejection pressure and an increase in left ventricular end-diastolic pressure although the changes were not significant. Cardiac output and left ventricular minute work decreased significantly as did stroke work. This is seen clearly in Fig. 1, a recording from one of these animals. In contradistinction to group I, the experiments in group II showed no change in mean aortic ejection pressure and only an insignificant decrease in left

ventricular end-diastolic pressure. Cardiac output, left ventricular minute work, and stroke work showed no significant change. Fig. 2 illustrates the findings recorded from one of the dogs of group II.

*Effects of Driving Frequency of Paired Stimulation at Different End-Diastolic Pressures*

The effects of stepwise increases in left ventricular end-diastolic pressures were compared during periods of paired stimulation at different driving frequencies (expressed as a percentage of the natural rate) and during normal sinus rate. Fig. 3 shows the

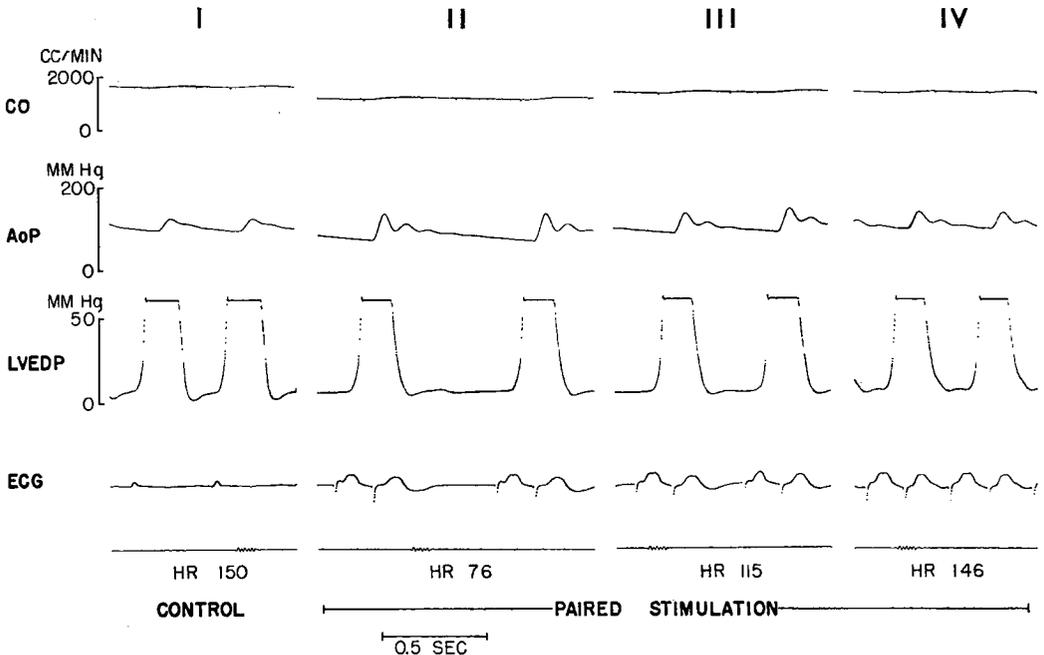


FIGURE 1. Hemodynamic effects of paired stimulation of the right ventricle at three different driving frequencies compared to those with normal sinus rhythm in a dog from group I. CO, mean systemic aortic flow; AoP, aortic pressure; LVEDP, left ventricular end-diastolic pressure; ECG, electrocardiogram; HR, heart rate. Discussed in text.

regression lines for all 20 animals of group I and represents the results of 30 experiments. Cardiac output, stroke volume, left ventricular minute work, and stroke work are plotted against left ventricular end-diastolic pressure. The several regression lines indicate the observations at the natural rate compared with paired stimulation at 50, 75, and 100 % of each dog's natural rate. As seen in Fig. 3, paired stimulation at approximately 50 % of the natural rate produced higher stroke volume and left stroke work at any given left ventricular end-diastolic pressure despite the consistent drop in cardiac output and left ventricular minute work. This resulted in a shift of the lines of stroke volume and stroke work upward and to the left. Paired stimulation at 75 % also shifted these lines upward and to the left, but not as much as with 50 %; cardiac output and left ventricular minute work although lower than that which occurred with-

out pacing, were higher than those obtained at 50%. Paired stimulation at the same rate as the natural rate altered the relation between end-diastolic pressure, on the one hand, and stroke volume and stroke work on the other; the curves were shifted downward and to the right. The relation of end-diastolic pressure to cardiac output and left ventricular minute work was found to be shifted to somewhere between the lines obtained at 75% and 50% of the natural rate.

Fig. 4 shows the same type of analysis for group II and represents a total of 10 experiments on the 6 animals. Paired stimulation at the three different driving frequencies (approximately 50, 75, and 100% of the natural heart rate) produced higher

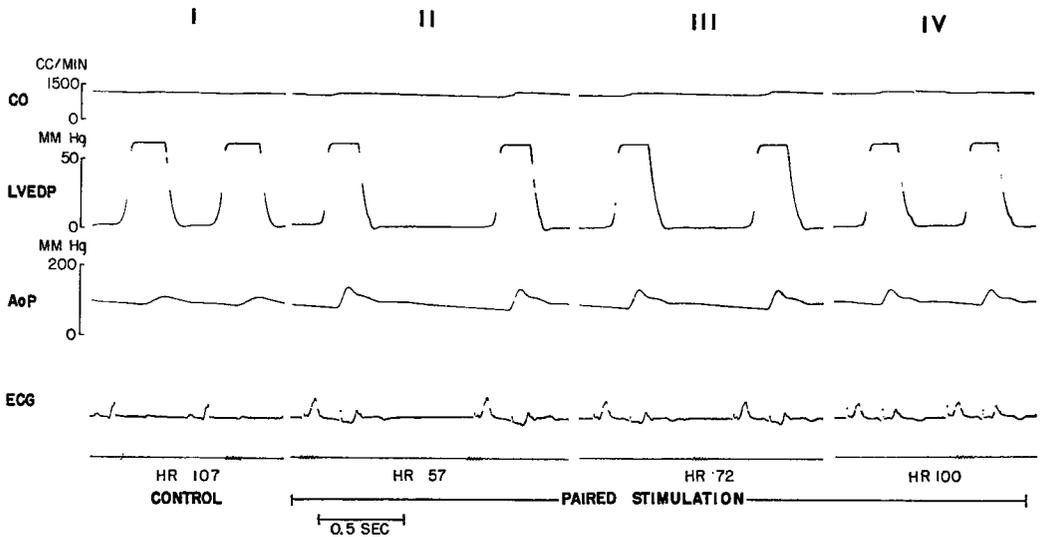


FIGURE 2. Hemodynamic effects of paired stimulation of the right ventricle at three different driving frequencies compared to those with normal sinus rhythm in a dog from group II. Symbols as in Fig. 1. Discussed in text.

stroke volume and stroke work for any given end-diastolic pressure (except at very low filling pressures). The relationship between end-diastolic pressure and cardiac output and minute work did not change significantly when paired stimulation was compared to the control at low filling pressures. However, when the end-diastolic pressure was raised, the lines representing paired stimulation showed higher cardiac output and left ventricular minute work than did the control.

Fig. 5 is an example of the actual recordings in a dog from group I with a high end-diastolic pressure obtained by infusion. Panel I shows the control curves and panels II, III, and IV those during paired stimulation at approximately 50, 75, and 100% of the normal sinus rhythm. The significant changes in end-diastolic pressure and cardiac output in this animal contrast sharply with those obtained in a control animal in group I with a low end-diastolic pressure as in Fig. 1.

Fig. 6 is a recording from a dog of group II with a high end-diastolic pressure in which paired stimulation was applied as in Fig. 5. The significant changes in cardiac

output and left ventricular end-diastolic pressure can be seen when this figure is compared with Fig. 2 from a dog of group II with a low end-diastolic pressure.

DISCUSSION

These experiments suggest that the spontaneous initial heart rate of the dog with intact circulation is one of the chief factors determining the type of hemodynamic re-

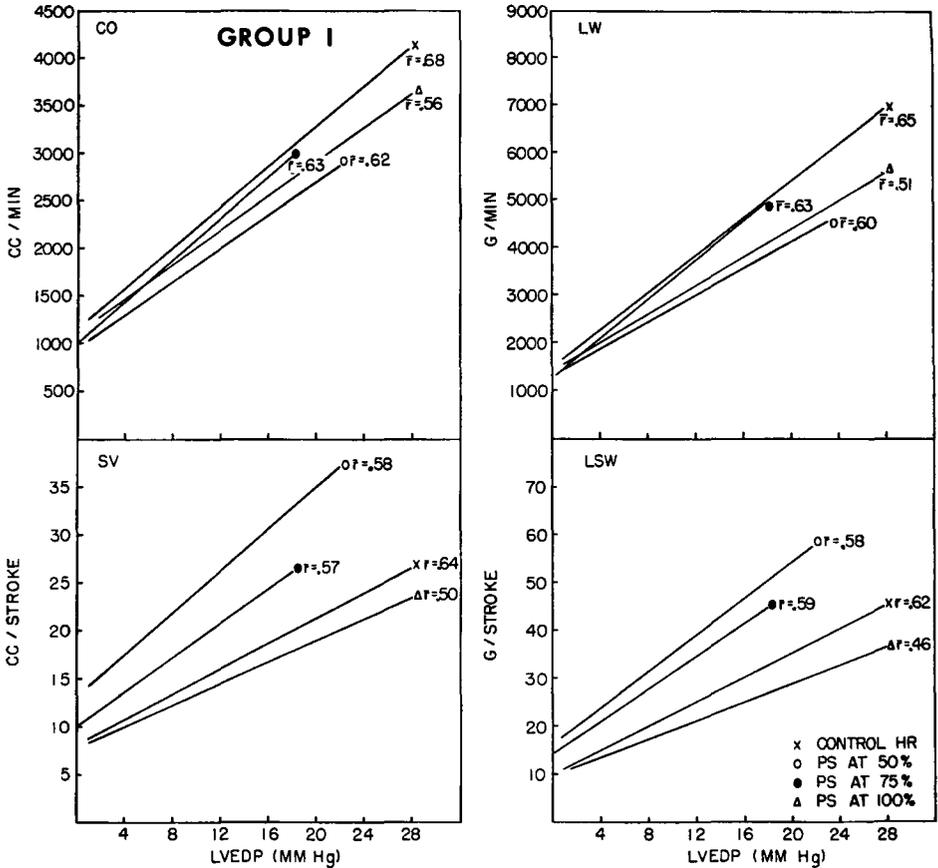


FIGURE 3. The regression lines represent the data obtained with sinus rhythm and with paired stimulation at approximately 50, 75, and 100% of each dog's natural rate for all 20 animals of group I (30 experiments). SV, stroke volume; LW, left ventricular minute work; PS, paired stimulation. Other symbols as in Fig. 1. Discussed in text.

sponse obtained when paired stimulation is applied. Table I shows clearly the difference between the group of animals in which the control sinus rate was considered to be "high" (mean, 149 beats per min) and the group in which it was "low" (mean, 101 beats per min). The major differences found when paired stimulation was applied at the same rate as in the control group were in the minute and stroke output and in left ventricular minute and stroke work. Thus, in the group with higher heart rate, the

cardiac output decreased 12.8% while in the group with lower heart rate the drop was only 5%. Left minute work and stroke work dropped 17% in the group with higher heart rate, but there was no change in the group with lower heart rate. This difference in the effect of paired stimulation, which is dependent on the initial heart rate, would be one factor which needs to be considered in explaining the discrepancy in the results in cardiac performance following paired stimulation found by others

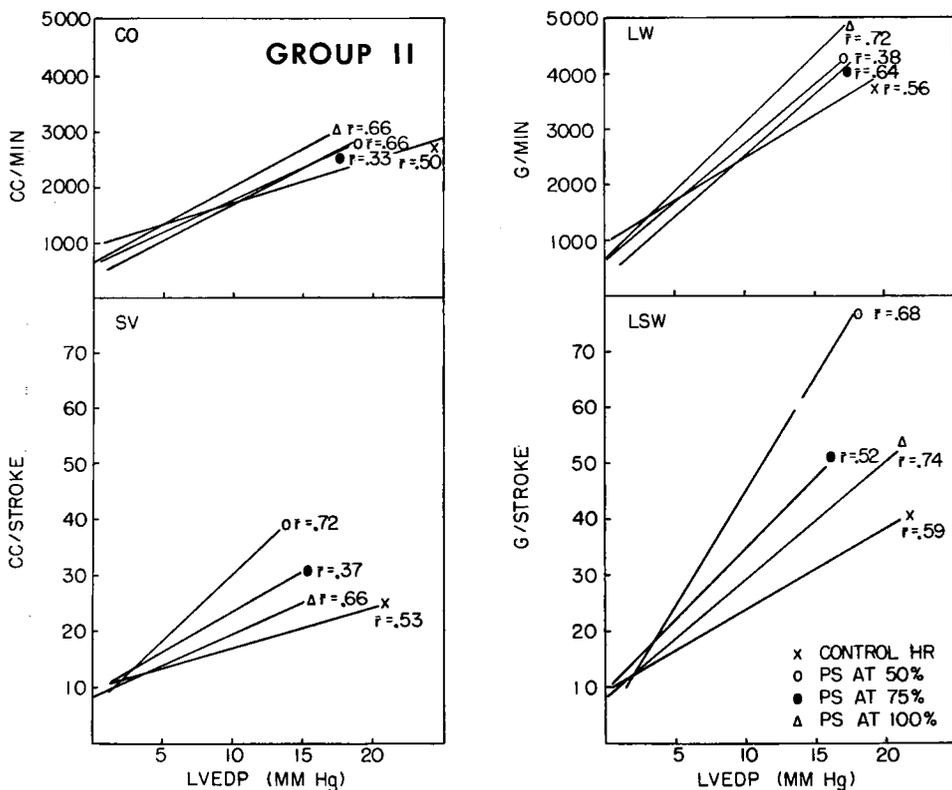


FIGURE 4. Same type of regression line analysis as in Fig. 3 for the means of 6 animals of group II (10 experiments). Discussed in text.

(1-10). The detrimental effect of paired stimulation as compared to sinus rhythm when the sinus and driving frequencies are relatively high probably is due to the fact that the increase in the amount of oxygen required by the myocardium is greater for equal increments of rate change as the heart speeds up. Even though the number of effective ventricular beats (about 150 per min) is the same during paired stimulation as when the heart is controlled by its natural pacemaker, paired stimulation actually causes both the ventricular depolarizations and the number of ventricular contractions to be doubled (to 300) as demonstrated with a strain gauge (15). As with single stimulation the increase in driving frequency of paired pacing, while it increases the energy requirement (16), is not necessarily accompanied by an increase in cardiac

output, aortic blood pressure, or left ventricular end-diastolic pressure. In fact, above a *critical driving rate* these parameters actually begin to reveal a decrease in ventricular performance (17-20). One example of this is seen in Fig. 7 in which the driving frequency of paired stimulation was increased in a stepwise fashion; it was found that cardiac output and left ventricular minute work did not begin to drop until a rate above 135 beats per min (270 ventricular depolarizations) was reached. Another im-

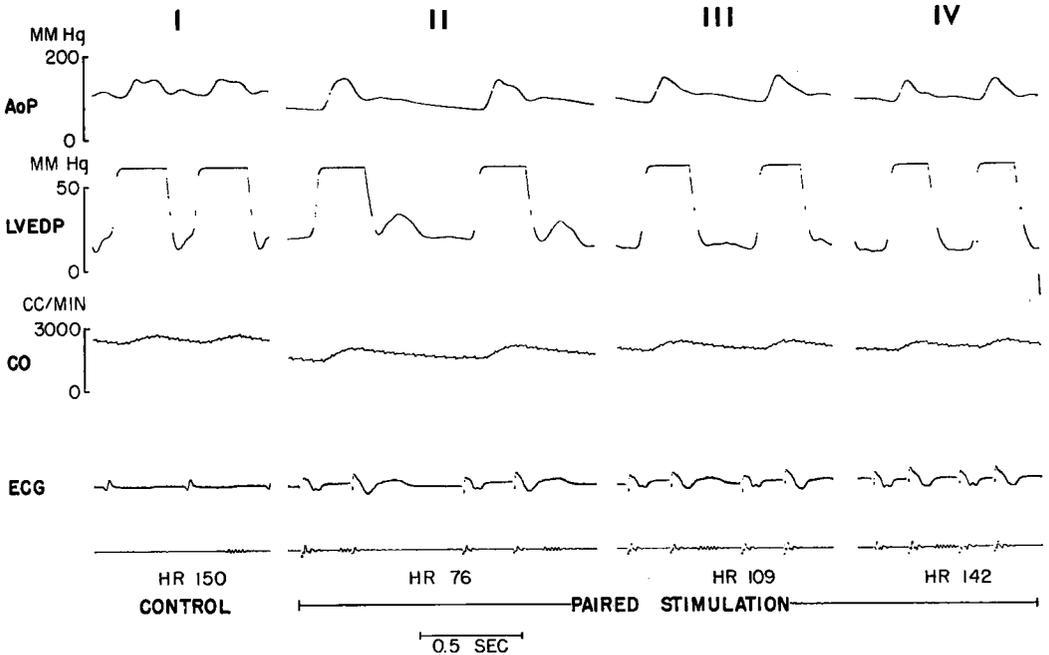


FIGURE 5. Recordings in a dog from group I with a high left ventricular end-diastolic pressure obtained by infusion. Panel I shows the control curves at normal sinus rate. Panels II, III, and IV indicate data obtained during paired stimulation at approximately 50, 75, and 100% of the normal sinus rhythm. Notice in panel II the small ventricular contraction in the left ventricular pressure curve associated with the second depolarization of each pair. Symbols as in Fig. 1. Discussed in text.

portant factor controlling the effect of paired stimulation is the level of the end-diastolic pressure of the left ventricle. In the group with high initial heart rate (Figs. 3 and 5) the left ventricular stroke work for any given end-diastolic pressure is related to the driving frequency of the paired stimulation. As expected a greater left ventricular stroke work corresponds to a slower driving rate. The difference between the sinus rhythm and paired pacing at different heart rates is clearly revealed by the divergence of the lines relating them to the filling pressure. This effect is due mainly to the drop in end-diastolic pressure as seen in Fig. 5. Paired stimulation will not greatly modify the end-diastolic pressure when it is low or normal (Table I and Fig. 1); but when the end-diastolic pressure is elevated, paired pacing will tend to restore it towards normal as part of its potentiating effect.

In the group of experiments in which the initial heart rate was low (Fig. 4) there is a similar significant difference in the slope of the lines relating cardiac performance to end-diastolic pressure depending upon the driving frequency of paired stimulation. But when paired stimulation is at the same rate as the natural rhythm, a higher left ventricular stroke work at any given end-diastolic pressure is produced. The improvement in this group with slow natural rhythm is manifested not only in left ventricular stroke work and in stroke volume but also in minute cardiac output and minute left

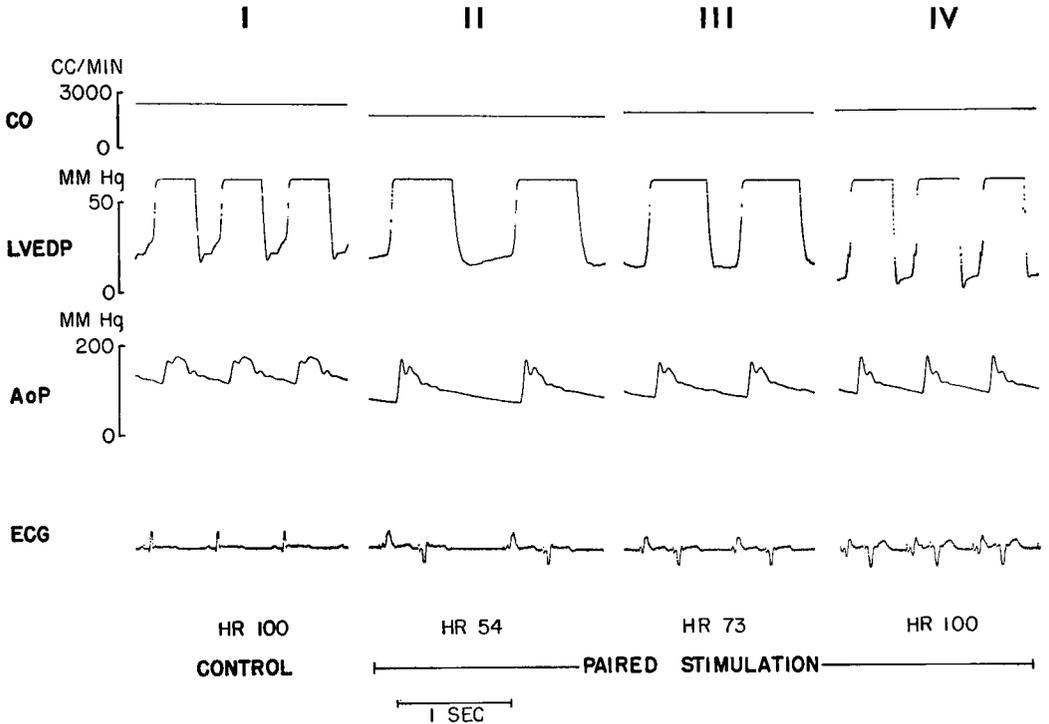


FIGURE 6. Recordings in a dog from group II with a high left ventricular end-diastolic pressure obtained by intravenous infusion. Symbols as in Fig. 1. Discussed in text.

ventricular work, provided the values are compared at the same end-diastolic pressure. If the change in end-diastolic pressure produced by paired pacing at a driving frequency equal to the initial control rate is ignored, the minute cardiac output and minute left ventricular work show a decline as do stroke output and stroke work. The decline, however, is attributable to the drop in end-diastolic pressure which the paired stimulation induces as part of the effect of potentiation. When these parameters are compared using the same end-diastolic pressure, the increase in ventricular performance following paired pacing becomes apparent. This improvement disappears when the natural rate and driving frequency of paired pacing are both increased above a critical value. This may be due to the excessively rapid frequency with which the heart has to beat to give rise to a frequency of effective beats equal to the sinus rate.

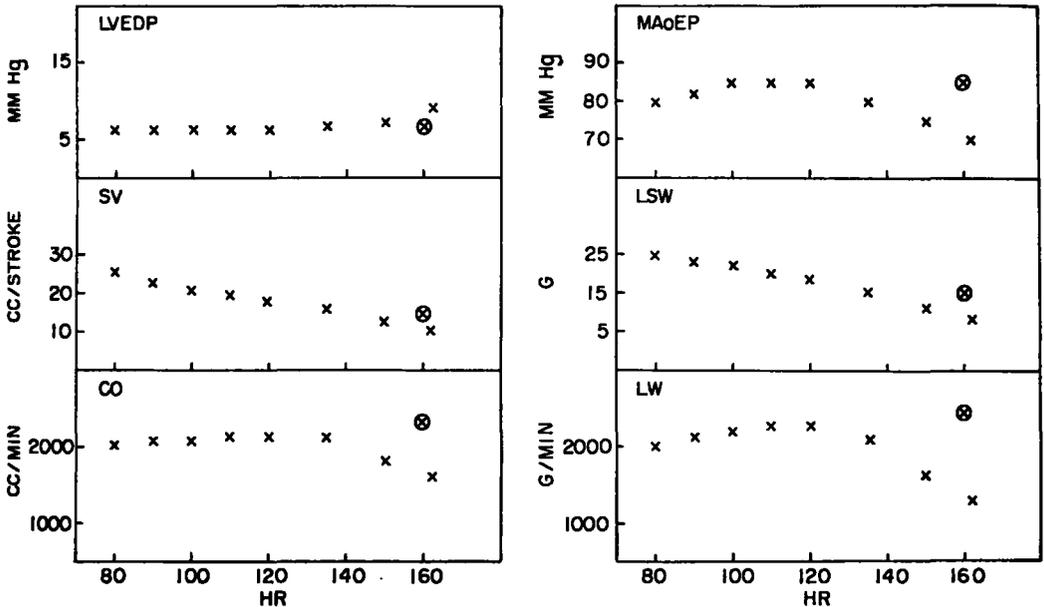


FIGURE 7. Experiment in which the driving frequency of paired stimulation was increased in a stepwise fashion. Notice that cardiac output did not begin to drop until the rate rose above 135 beats per min (270 ventricular depolarizations). Circled x, control measurements before paired stimulation was applied. MAoEP, mean aortic pressure during ejection. Other symbols as in Fig. 3. Discussed in text.

Since the heart with paired pacing is beating at twice its sinus rhythm (300 per min), there is a striking increase in cardiac oxygen demand (21), decreasing its capacity for performance.

#### SUMMARY

The role of various hemodynamic factors (initial natural rate, left ventricular end-diastolic pressure, and driving frequency of stimulation) which might influence the ventricular response to paired stimulation has been analyzed in anesthetized dogs. In a group of experiments (group I) in which the sinus rate was considered to be high (149 beats per min), paired stimulation at the same rate produced a decrease in cardiac output, left ventricular minute work, and left stroke work. In another group of dogs (group II) with a low natural rate (101 beats per min), paired stimulation did not change the control parameters significantly. Cardiac function curves at the natural heart rate were compared with those obtained at different frequencies of paired stimulation (50, 75, and 100% of the natural rate) in both groups of experiments. In group I, left ventricular stroke work was greater with paired stimulation at 50 and 75% of the sinus rate for any given left ventricular end-diastolic pressure, despite the drop in cardiac output; however, paired stimulation at the same rapid frequency as the sinus rate decreased left ventricular performance. In group II, paired stimulation at the same frequency as the natural rhythm increased ventricular performance.

The difference in the effects of paired stimulation depending on the relationship of driving frequency to natural frequency and on the level of left ventricular end-diastolic pressure is a factor which could explain the discrepancy in previous reports following paired stimulation.

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# Postextrasystolic Potentiation in Experimentally Induced Myocardial Ischemia

WILLIAM J. KERTH, J. J. KELLY, JR., M. NASSAR, and  
P. SANCHEZ

From the Departments of Cardiovascular Surgery and Medicine, Institute of Medical Sciences,  
and the Presbyterian Hospital, San Francisco, California 94115

At the first conference on Paired Pulse Stimulation and Postextrasystolic Potentiation of the Heart, we and others (1-3) presented data to demonstrate that postextrasystolic potentiation (PESP) could relieve or improve experimentally induced heart failure in the dog. Considerable discussion occurred on that occasion concerning the metabolic cost of PESP (4,5). Views were presented that the metabolic cost would not be tolerable for human beings with coronary artery disease although no data were available to support this contention directly. Contrary views were also voiced. Because of this, we have attempted to determine whether animals with reduced coronary vascular capacity could tolerate paired pacing and prolonged application of post-extrasystolic potentiation.

## METHODS

A total of 18 adult mongrel dogs was used in these experiments. In six of these animals the anterior descending coronary artery was ligated just distal to the septal branch. Four of these six animals developed ventricular fibrillation and succumbed. The two survivors developed an acute myocardial infarction which was documented electrocardiographically and finally by postmortem examination. These two survivors were studied 1 wk and 11 days after ligation of the coronary artery. In six dogs, coronary insufficiency and myocardial infarction were produced by an Ameroid (American Plastics Division of the Tenneco Chemicals, Inc., New York, N.Y.) constriction around the left anterior descending coronary artery. The hydrophilic material of the Ameroid slowly swells, producing gradual occlusion of the coronary artery. Fig. 1 demonstrates the method of insertion of an Ameroid about a coronary artery. The effectiveness of the Ameroids in occluding coronary arteries is seen in Fig. 2. In all instances myocardial infarction was proven by postmortem examination of the heart at the conclusion of the experiments. These latter animals were studied between the 3rd and 4th wk after the implantation of the Ameroid. The dogs were all studied in open chest experiments in which ventilation was maintained by intermittent positive pressure provided by a Palmer pump. The animals were anesthetized with intravenous Nembutal and were given supplements as needed. The right chest was opened in the fourth interspace and the pericardium incised. Rigid catheters were placed in the right atrium, the left ventricle, and the ascending aorta. Pressures were sensed by Statham strain gauges and recorded on an Electronics for Medicine multi-channel oscilloscope (Electronics for Medicine, Inc., White Plains, N.Y.). Aortic flows were measured by a calibrated electromagnetic flowmeter<sup>1</sup> and integrated with time. A small

<sup>1</sup> Carolina Medical Electronics, Inc., Winston-Salem, N. C.

catheter was placed in the coronary sinus and secured in place with a circumferential suture to allow direct measurement of coronary sinus flow and sampling. Coronary blood flows were obtained by collecting the coronary sinus blood for short timed periods. Myocardial oxygen consumption was determined by multiplying the coronary sinus flow by the aortic-coronary sinus oxygen difference. The oxygen content of the blood was measured by the Van Slyke technique. All blood losses were measured and were replaced by transfusion. Frequent determinations of the arterial pH,  $p\text{CO}_2$ ,  $p\text{O}_2$ , and standard bicarbonate were made. Corrections of these parameters were made as needed in an attempt to keep a constant experimental preparation. The electrical stimuli were delivered by two Teflon-coated wires sutured into the right



FIGURE 1. An Ameroid placed on a coronary artery. The hydrophilic material is between the metal case and the coronary artery. The Ameroid imbibes water, and gradually occludes the coronary artery.

ventricle. The stimuli were delivered by a Medtronic stimulator (model 5837). The stimuli were usually 2 msec in duration and twice diastolic threshold in intensity.

14 dogs were studied in a similar manner. These animals were six controls with no coronary insufficiency, two survivors of the ligation of the anterior descending coronary artery, and six dogs with myocardial infarction resulting from the ameroid occlusion of a coronary artery.

These animals were studied during sinus rhythm as a control, then for a period of 1 hr during synchronized pacing. This was followed by another control period of 20 min and then a period of paired pacing for 1 hr. A final control period concluded the studies. In synchronized pacing the R wave of the electrocardiogram is detected by the stimulator and the stimulus is delivered at the end of the refractory period. With synchronized pacing atrial contraction preceded ventricular contraction.

The left ventricular mass of the left ventricle of the hearts was determined by dissecting the left ventricle free from the remainder of the heart.

## RESULTS

Dogs which survive an acute myocardial infarction tolerate paired pacing and synchronized pacing as well as dogs which are apparently normal when studied from 1-4 wk following the myocardial infarction. One episode of ventricular fibrillation oc-

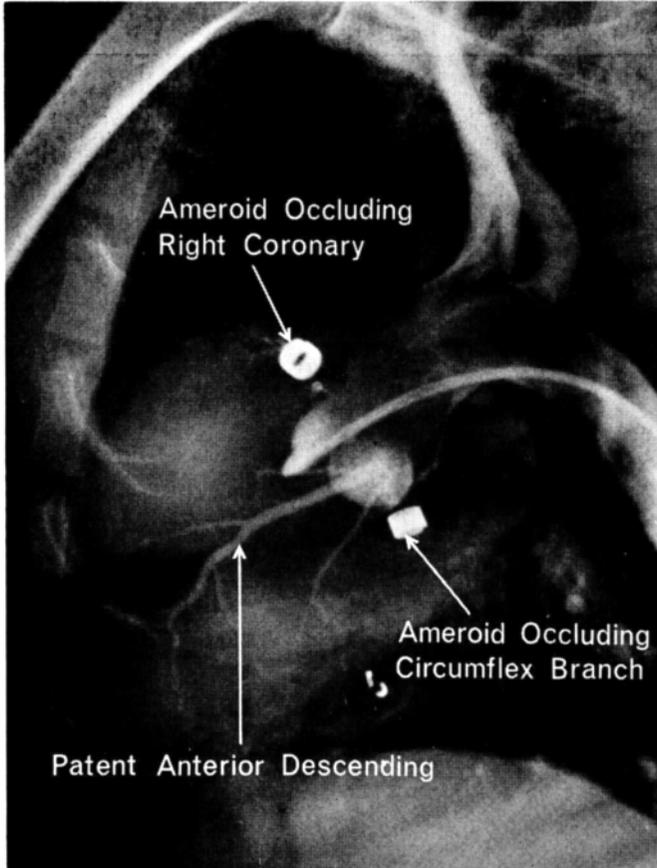


FIGURE 2. Aortogram of a dog demonstrating Ameroid occlusion of the right coronary artery and the circumflex branch of the left coronary artery. The anterior descending branch of the left coronary artery is patent.

curred with paired pacing both in a control animal and in one of the ameroid group. Both dogs were successfully restored to sinus rhythm. No instances of ventricular fibrillation occurred with synchronized pacing in either group of animals. Although the data are too few to be certain, this suggests that synchronized pacing is safer than paired pacing.

Furthermore no significant difference could be found in either group of animals in

their toleration of paired or synchronized pacing over a period of 1 hr. Both groups of animals showed similar responses of aortic flow. In neither group did deterioration of cardiac output occur.

Of the 14 animals subjected to paired pacing and synchronized pacing no evidence of heart failure was found in 12; that is, the left ventricular end-diastolic pressure did not exceed 12 mm Hg. Two animals with myocardial infarction resulting from ameroid constriction of a coronary artery were in heart failure by this definition. In the 12 animals without heart failure no significant change occurred in aortic flow when either paired pacing or synchronized pacing was used. A 13% variation occurred in the aortic flow in these animals. In the two dogs with heart failure significant increase in cardiac output occurred with both synchronized and paired pacing.

TABLE I

	Sinus rhythm	Paired pacing
Heart rate, <i>min</i>	165	112
Cardiac output, <i>liters/min</i>	2.4	2.3
Stroke volume, <i>cc</i>	15	21
Coronary flow, <i>cc/min</i>	78	74
Myocardial oxygen consumption, <i>cc/min</i>	12.1	10.4
Myocardial oxygen consumption per liter of cardiac output, <i>cc/liter</i>	5.0	4.5

In one animal the aortic flow rose from 1080 cc per min in the control period to 1900 cc per min during 1 hr of synchronized pacing to fall in the following control period to 1300 cc per min. Paired pacing was then well-tolerated with an aortic flow of 1700 cc per min at the end of 1 hr of paired pacing. In the second animal aortic flow rose from a control of 1000 cc per min to 2200 cc per min with an hour of synchronized pacing. The aortic flow of the control period following the hour of synchronized pacing was now 1520 cc per min. Another hour of paired pacing resulted in no significant change with an aortic flow of 1600 cc per min. In both these instances the left ventricular end-diastolic pressure dropped to normal with the initial application of PESP and remained within normal limits afterwards.

These were the only striking changes that occurred in 72 determinations of aortic flow in this study. Again data are few but one is tempted to conclude that post-extrasystolic potentiation was responsible for the amelioration of heart failure in both these instances. Also it is suggestive that synchronized pacing is more effective than paired pacing. As expected from the technique the heart rates of the animals with paired pacing were just slightly greater than one-half of the sinus rate. This was found to be true also with synchronized pacing. The control heart rate was 161 beats per min during sinus rhythm and 95 per min during synchronized pacing.

In the healthy control dogs, it was readily demonstrated that paired pacing resulted in increased coronary sinus flow and myocardial oxygen consumption particularly if the mechanical pulse rates were similar. However, if the heart rate were significantly reduced with paired pacing, then the differences in myocardial oxygen consumption were not striking. Such data from a dog without myocardial infarction are presented

in Table I. In this instance the cardiac output was the same during sinus rhythm with a rate of 165 per min and during paired pacing at 112 per min. The myocardial oxygen consumption was reduced with paired pacing as a result of the slowing of the heart rate. Therefore, when assessing the metabolic cost of postextrasystolic potentiation, relationship of myocardial oxygen consumption should be made to cardiac output or work.

Myocardial oxygen consumption was measured in these experiments and was related to aortic flow. A total of 72 such determinations was made on the healthy dogs and on the dogs with coronary occlusion. Measurements were made during sinus rhythm and during the application of PESP, both by paired pacing and synchronized pacing. The results show marked variability both under control conditions and during PESP. However, no significant difference in the myocardial oxygen consumption per liter of cardiac output could be demonstrated between animals during PESP and under control conditions. A  $-2\%$  change in myocardial oxygen consumption per 100 g of left ventricle per liter of aortic flow occurred during PESP. A variation up to 50% occurred in the same animals during control studies at different times.

#### DISCUSSION

The observations collected in this study confirm and extend those of Singer and his associates (6) who found that dogs surviving an acute myocardial infarction produced by ligation of a coronary artery tolerate paired pacing as well as control dogs. Ventricular fibrillation is not an appreciable hazard in dogs subjected to PESP days following an acute myocardial infarction. The frequency of ventricular fibrillation immediately following acute occlusion of a major coronary artery is so high that we were not able to assess the further hazard of PESP.

It has also been demonstrated that prolonged application of PESP in dogs with coronary insufficiency does not result in a deterioration of cardiac performance. No fall in aortic flow was seen with prolonged application of PESP.

During the first conference on paired pacing, Hoffman pointed out that toleration by animals of prolonged periods of PESP would indicate that the metabolic cost of PESP would not limit its usefulness. Other experience supports this view. We found no significant change in myocardial oxygen consumption during control periods and periods of PESP when oxygen consumption was related to cardiac output. Although the animal model used in these experiments possesses reduced coronary arterial bed, it does not represent the conditions found in human beings with coronary arteriosclerosis where diffuse involvement of the coronary arteries is the rule. Because of this one should hesitate before application of these results to the human condition. It is apparent that another model with diffuse obstruction of the coronary arteries should be developed.

Our experience with the application of PESP to human beings is meager. We have used paired pacing in a total of 10 human beings, on two of whom paired pacing was used prior to going on cardiopulmonary bypass, and on two others in the cardiac catheterization laboratory in whom malfunctioning pacemakers were replaced. None of these subjects was in heart failure. All tolerated the paired pacing for short periods without difficulty. No change in cardiac output occurred when measured in two subjects although they were not in heart failure. One of these subjects complained of

angina during the rapid heart rate phase which occurred while there was a one to one relationship of a QRS complex to the mechanical pulse. The angina disappeared when the second stimulus of the paired pacing provoked a QRS but no mechanical response. Two subjects, both moribund from a myocardial infarction, were subjected to paired pacing. In one we were not able to use paired pacing; in the other patient, however, this method was used with very transient improvement in blood pressure, but the patient soon died. Both subjects had massive myocardial infarctions on post-mortem examination.

In three other patients, all with severe intractible heart failure, an attempt was made to use paired pacing with a cardiac catheter in the right ventricle. Ventricular tachycardia occurred repeatedly when an attempt was made to capture control of the rhythm with paired pacing. All these patients had severe coronary artery disease.

This experience points to some of the difficulties encountered when an attempt is made to use paired pacing on individuals with coronary disease and heart failure. This failure has dampened our enthusiasm for paired pacing. In another patient with severe intractible heart failure due to repeated myocardial infarction, synchronized pacing was accomplished without difficulty. A period of synchronized pacing was maintained for 45 min without the patient experiencing any angina. The cardiac output was unchanged but the stroke output doubled. Unfortunately, the pulse rate was halved by the synchronized pacing.

This experience with synchronized pacing is encouraging. Myocardial contractility was improved. Because the second stimulus moves from the R wave out to the T wave, there is less risk of a tachycardia with its harmful consequences. Certainly synchronized pacing deserves a critical trial in subjects in shock or with intractible congestive heart failure.

#### SUMMARY

Dogs that have survived a recent myocardial infarction produced by either ligation of a coronary artery or by Ameroid constriction of a coronary artery, tolerate paired pacing and synchronized pacing as well as do dogs without coronary insufficiency. Ventricular fibrillation is no appreciable hazard a week after a myocardial infarction. No appreciable deterioration of cardiac output occurred during 1 hr periods of paired or synchronized pacing. The metabolic cost of PESP is easily tolerated in these animals. The myocardial oxygen consumption per liter of cardiac output is not changed by either paired or synchronized pacing.

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# Spontaneous Paired Pacing in Human Atrial Muscle

WILLIAM SLEATOR and TAISIJA DE GUBAREFF

From the Department of Physiology and Biophysics, Washington University School of Medicine, St. Louis, Missouri 63110

For several years we have been studying the mechanical and electrical properties of human atrial muscle *in vitro*. Under a wide range of conditions this tissue shows a kind of behavior which might appropriately be called "spontaneous paired pacing." When stimulated with single pulses at regular intervals, the muscle usually responds with an action potential consisting of two spikes (the second arising from a low plateau) and a mechanical response, sometimes double, which varies in strength depending on the nature of the preceding action potentials.

Although there are differences between this behavior and that of other kinds of cardiac muscle subjected to paired pulse pacing by external stimulators, there are many fundamental similarities, and it is likely that something can be learned about both processes from a comparison of these two phenomena. Therefore it is appropriate to include a consideration of some of our experiments with human atrial tissue at this symposium on paired pulse stimulation.

## BEHAVIOR OF HUMAN ATRIAL TISSUE UNDER STANDARD CONDITIONS

Atrial muscle from cardiac patients undergoing open heart surgery was set up in a conventional muscle bath containing Krebs-Henseleit bicarbonate solution oxygenated with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. (Further details of methods will be found in reference 1.) When this tissue was stimulated at regular intervals, most of the time it did not approach a steady state of constant contraction, but instead alternated periodically between two phases having markedly different strengths of contraction. Examples of this can be seen in Fig. 1 (taken from reference 1) which shows isotonic contraction patterns characteristic of atrial muscle from three different patients. (All such patterns were nearly the same whether the recording was isometric or isotonic.)

Such regular variations in strength occurred in most of the specimens and will be referred to hereafter as "cycling." The duration of these cycles varied from about 1 min to 4 min at 30°C. In the two bottom rows (C) of Fig. 1 it is clear that each of the large contractions has two components which are more separated at the end of the high phase part of the cycle. At the beginning of the high phase, contractions are also separate and one can see that the maximum strength is attained after about seven double contractions have occurred.

The nature of these double contractions became clear when records with intra-

cellular electrodes were obtained from this tissue. An example of such a record is shown in Fig. 2. (Details of the experiment are given in the legend.) Here, as in all such records, when the tissue goes into high phase the action potential acquires a second spike which arises spontaneously from the plateau. At the beginning of high phase the second spike starts at the end of the plateau, and with each beat moves closer to the first until about the middle of the phase. It then begins to move away

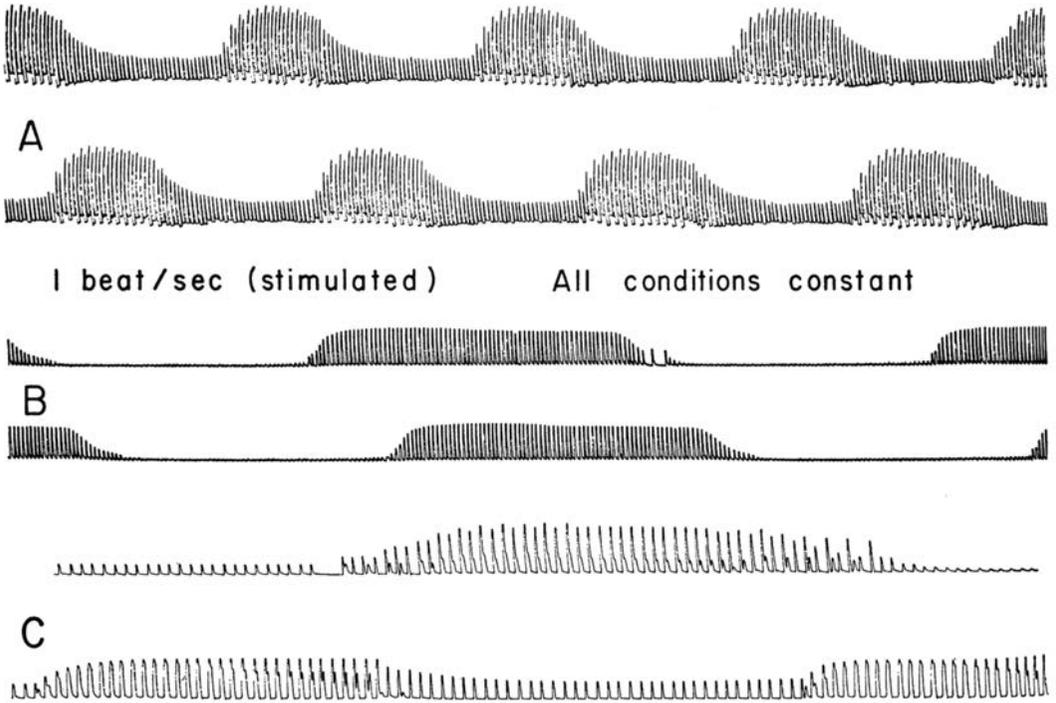


FIGURE 1. Cycling at room temperature: "steady-state" isotonic contractions of right atrial muscle from three different patients all stimulated electrically with near threshold shock at a frequency of 1 per sec. A. Patient 9 yr old; interatrial septal defect (called IASD hereafter); operated on under hypothermia without heart lung machine. B. Patient 8 yr old; pulmonary valvular stenosis and interventricular septal defect (IVSD). C. Patient 24 yr old; IASD (frequency 1 per sec; recording speed higher than A and B). *Figs. 1 to 3 reprinted by permission from American Journal of Physiology, 1964, 206:1000.*

from the first, and by the end of the high phase the separation is sufficient to make the mechanical responses distinct. Finally, the second spike drops out entirely and the tissue enters low phase.

The variations in contraction strength occurring during these cycles can be clearly seen in Figs. 2 and 3. Note that the second spike of an action potential does not contribute anything to the peak tension of the contraction triggered by that action potential. The effect of the second spike appears in the first component of the following contraction: its strength is increased by the presence of the previous second spike.

This effect is cumulative through 5 to 10 action potentials so that the full contraction strength is not attained until at least five beats after high phase starts. Similarly, the effect persists in about the same way at the end of high phase and contraction strength does not reach the steady low phase level until more than five action potentials without second spikes have occurred. Thus, we must infer that an intracellular process is going on which can accumulate some effect of the second spike over a period in which the tissue is active and can put it to use in subsequent contractions. In this respect the process is similar to that in paired pulse stimulation where comparable delays occur between the start of the double stimuli and the peak contraction strength attained.

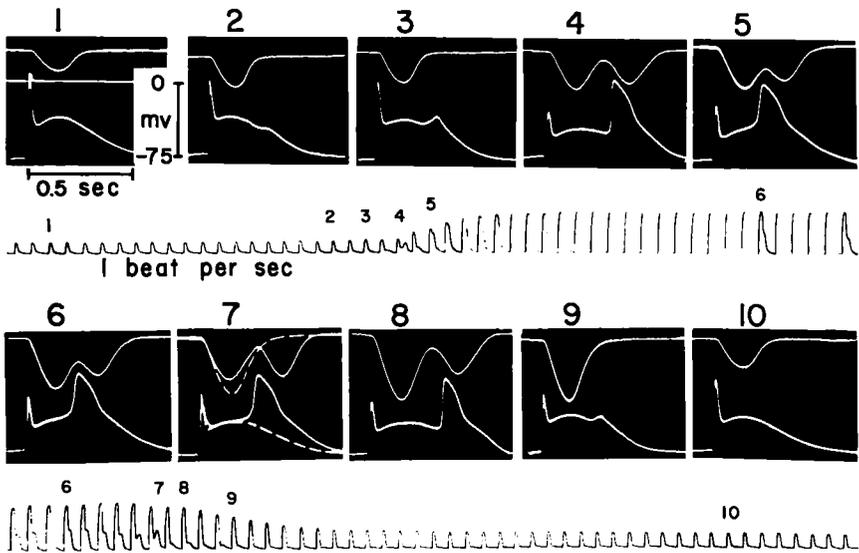


FIGURE 2. Correlation of electrical and mechanical events during a single cycle. First and third rows, oscillograph records of isometric contractions and intracellular AP's of muscle strip stimulated at 1 per sec under standard conditions (right atrium of 9 yr old patient with IVSD). Second and fourth rows, isotonic contractions during high and low phases (complete cycle) under standard conditions. The numbers above certain contractions refer to the oscillograph record which most nearly corresponds to that contraction (right atrium of 5 yr old with IASD and pulmonary valve atresia).

Another unusual feature of this tissue is the manner in which its properties change with temperature. The effects described and illustrated so far can usually be seen only at temperatures below 33°C. At 37°C the action potentials have a more conventional shape; i.e., the plateaus are shorter in duration, and at a higher (less negative) voltage. These relations can be seen in Fig. 4. As the temperature falls below 37°C, the plateau not only becomes longer in duration, but also shifts to a lower (more negative) voltage; at 24°C (top row) it is nearer to resting potential than to zero. This behavior is quite different from that of other kinds of cardiac muscle we have studied. In general, when temperature is lowered, the plateau simply becomes longer in duration, but its mean voltage stays the same. It is precisely the property of human atrial cell membranes which produces this fall in plateau voltage with temperature

that is responsible for the unique behavior of human and chimpanzee tissue. With a long duration plateau at a low enough voltage, reactivation of sodium conductance can occur, and if the potential is near threshold at this time, another spike will be triggered. One can view this process as similar in effect to holding the membrane near threshold voltage with a polarizing current; in many excitable tissues this induces

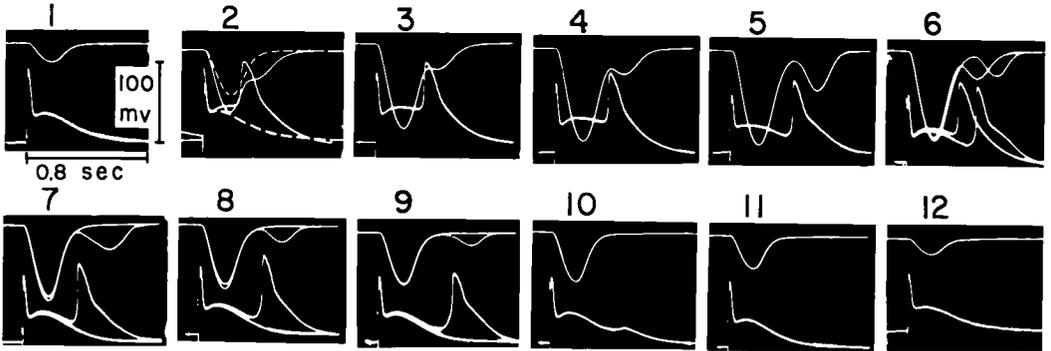


FIGURE 3. Isometric contractions and transmembrane AP's throughout a cycle of which the high phase started after a 10 sec rest interval. Total duration of high phase (frames 2 through 11) about 30 sec. Electrode in same cell from frames 2 through 12 (right atrium of 12 yr old with aortic stenosis).

Frame 1, control, low phase steady state before interval. Frame 2, the second response (broken lines) and the third response (solid lines) after the interval. (The first response, not shown, had an AP similar to that of the third, but a contraction smaller than the second.) Frames 3 to 5, records every 2 or 3 sec; every response double; the second spike of the AP gradually moves out (away from the first) along the plateau, while the two components of the contraction become more separate, and the first component increases in strength. Frame 6, superposition of two consecutive beats; second spike alternates between two positions near end of plateau; strength of contraction (first component) remains near maximum. Frames 7 to 9, superposition of consecutive beats; alternation between single and double responses with second spike becoming later; decrease in strength of both components of contraction. Frame 10 (2 sec after frame 9), second spike replaced by a "hump" with barely perceptible contractile response. First component of contraction same as frame 9. Frame 11 (4 sec after frame 10), second spike completely gone throughout preparation; contraction still above low phase level. Frame 12 (10 sec after frame 11), AP and contraction complete return to low phase steady state. (Compare with frame 1.)

multiple firing. Second spikes rarely occur above 33°C presumably because the voltage is not low enough nor the time long enough for sodium conductance to recover.

Some information about the state of the membrane during the plateau can be gained from experiments with acetylcholine (ACh). It has been established for many kinds of heart muscle that ACh increases the potassium conductance of the cell membrane. The plateau represents a period when  $g_K$ , the potassium conductance of the membrane, has a value lower than that for the "resting" membrane (3). Thus the

ability of ACh to shorten or abolish the plateau in these species can be explained on the basis of its augmentation of  $g_K$ . The results of applying ACh in low concentrations to human atrial muscle can be seen in Fig. 5 (some details of the experiment are given in the legend). It seems probable that in frames 7 and 8 changes in  $g_K$  have been effectively eliminated from the action potential, and that what we see here is purely the time course of the  $g_{Na}$  changes. Similar experiments have been done with adenosine (2) which also increases  $g_K$  in some kinds of cardiac muscle. Like ACh, adenosine

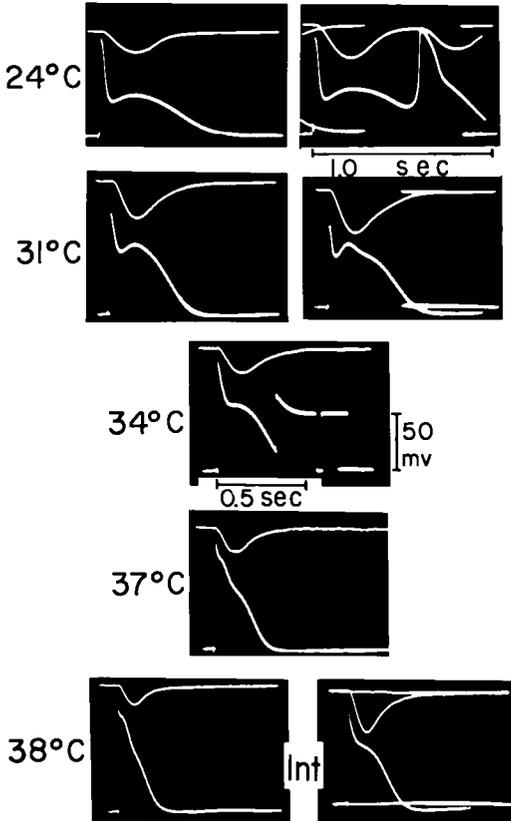


FIGURE 4. Effects of temperature changes on action potentials and isometric contractions. Right atrial muscle from 5 yr old with IVSD. Temperature increased from 24° to 38°C. 24°C. Typical low and high phase AP's and contractions. 31°C. Rest interval, preceding frame 2. 38°C. Rest interval, 20 sec, between frames. Changes form of AP.

can completely abolish the plateau in human atrial muscle, and the AP "spike" which remains is indistinguishable from that seen in the presence of ACh. Taken together, these results provide persuasive evidence that the plateau in human atrial muscle is due to a period in which the membrane has a low potassium conductance.

#### STUDIES OF CHIMPANZEE ATRIAL MUSCLE

One finding of great interest is that atrial muscle from chimpanzees manifests the same complex pattern of behavior as that of human beings. Although no intensive systematic study of heart muscle from chimpanzees has yet been carried out, we have worked with atria from four different chimpanzees and have confirmed in detail that

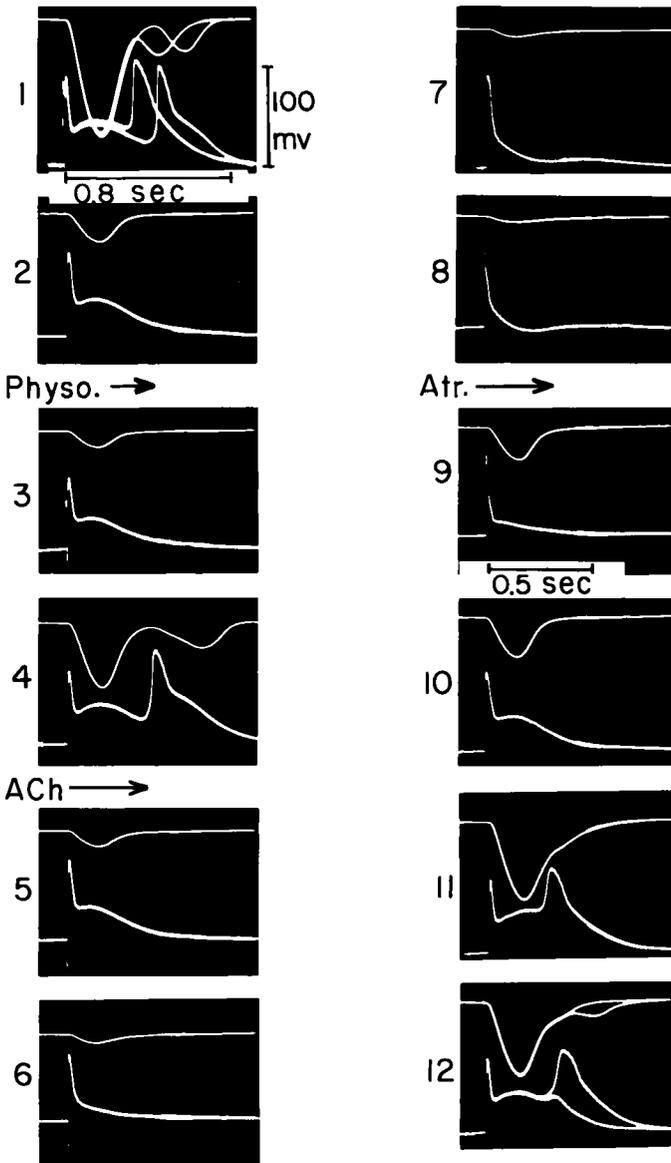


FIGURE 5. Effects of acetylcholine on action potentials and contractions under standard conditions (right atrium of 12 yr old patient with aortic stenosis). Frame 1, superposition of two responses near end of high phase of control cycle. Frame 2, low phase control. Physostigmine salicylate,  $2.5 \times 10^{-6}$  moles per liter, added between frames 2 and 3. Frames 3 and 4, AP's same as controls. Acetylcholine,  $4 \times 10^{-8}$  moles per liter, added between frames 4 and 5. Frame 5, 10 sec after ACh. Frame 6, 2 min after ACh. Frame 7, 5 min after ACh. Frame 8, 15 min later; full ACh effect on AP's and contractions. Atropine sulfate,  $5 \times 10^{-6}$ , added between frames 8 and 9. Frame 9, 1 min after atropine: record of contraction in low phase. Frames 10 to 12, 5 to 35 min after atropine: recovery of low and high phase AP's.

this muscle is almost identical in physiological properties to human tissue. This applies both to the ability of the cell membranes to generate second spikes, and also to the tendency to alternate regularly (to cycle) between "high phase" periods when action potentials have double spikes, and "low phase" periods when AP's are single and contractions relatively small. (A number of attempts to induce double spiked action potentials and/or cycling in a variety of the more ordinary laboratory species, including several kinds of monkeys, have been uniformly unsuccessful.)

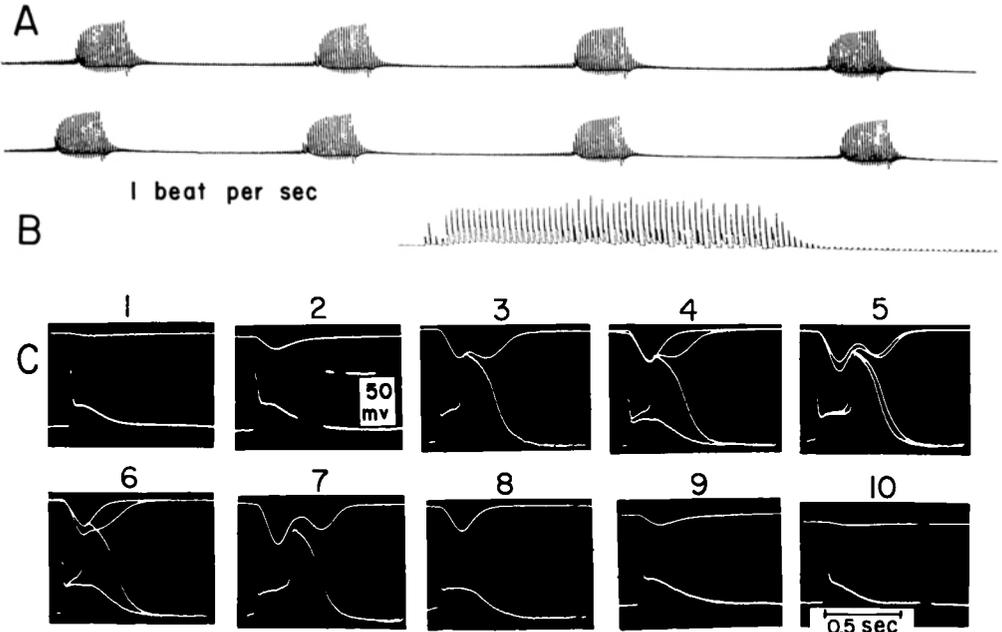


FIGURE 6. Behavior of right atrial muscle from chimpanzee (stimulation at 1 per sec in oxygenated Krebs' solution at 30°C.). Row A, cycling pattern similar to that seen in human atrium. Row B, one cycle from a different preparation showing alternation between single and "double" contractions at end of high phase. Row C, isometric contractions (upper trace) and transmembrane action potentials (from the same preparation as row B). Frame 1, low phase. Frame 2, single AP at start of high phase. Frame 3, early in high phase. Frames 4 and 6, alternation of single and double spikes in last half of high phase. Frames 8 to 10, return to low phase; note decreases in duration and height of plateau.

A series of records taken from one of the chimpanzee experiments is shown in Fig. 6. (Experimental conditions were the same as those normally used with human atrium: temperature 30°C) Though all the chimpanzees showed both double spiked AP's and some capacity to cycle, there appeared to be considerably more variation from one individual to another than in human beings. The results shown in Fig. 6 are from the chimpanzee experiment in which the muscle behaved most nearly like human tissue.

In row A, isotonic contractions were recorded during a period of very regular cycling having a pattern which has been seen occasionally in human tissue. The

over-all period is about 100 sec; 25 sec in high phase, the rest in low. (The two phases are usually about equal in human beings.) The transitions to and from high phase both take five or six beats which is quite typical. In row B, another preparation from the same animal was recorded at higher paper speed. From the middle of the high phase, here lasting about 60 sec, there is irregular alternation between single and double AP's. As expected, the single contractions are generally larger since they are preceded by AP's with double spikes. Again the transitions last about five beats, indicating that the effect of a double AP persists about this long in a regularly beating muscle.

Row C shows isometric contractions (upper trace, tension increase downward), and transmembrane action potentials recorded during transitions into and out of high phase. The variations in time between first and second spikes are clearly shown (frames 4 and 5, or 6 and 7) as well as the frequent alternation between single and double spiked AP's (frames 4, 5, and 6 are each superpositions of two successive sweeps).

The over-all picture presented by these results could easily be mistaken for that of human tissue, even by one familiar with several hundred records from the latter. However, one feature of this record is unusual among human specimens, i.e. the duration of the second spike, here about 200 msec or more than eight times the duration of the first spike. Such long second spikes have only showed up in human records once or twice among 200 different specimens and then are only probable when the subject is young. (The chimpanzee of Fig. 6 was about 10 yr old, which is fully mature.) Since we don't yet know the ionic mechanism of the second spike the possible significance of this difference is not clear. However, if the hypothesis outlined below is valid, the second spike represents a period of high  $g_{Na}$  (sodium conductance) and is not dependent on a concomitant fall in  $g_K$ . Thus when the second spike is longer, more  $Na^+$  comes in, and the number of beats during which a cell can remain in high phase before saturation with sodium (or exhaustion) is more limited. This effect could account for the shorter duration of high phase characteristic of chimpanzee muscle.

#### THE LONG DURATION OF THE SECOND SPIKE

One of the most striking features of these action potentials, as recorded above from both human and chimpanzee atria, is the long duration of the second spike. On the average this is about five times that of the first spike (125 msec at 27°C compared to 25 msec) and it may last more than 200 msec (see Fig. 6 above and reference 1, p. 1005). It was also shown in reference 1 that the duration of a second spike is the same whether it arises spontaneously from the plateau, or is triggered by an external stimulus (when the preparation is in low phase) at a corresponding interval after the first spike.

The question now arises as to what is the nature of the second spike that could cause such a long duration relative to the first; i.e., is a different ionic mechanism involved? We are here adopting the plausible view, well-supported by indirect evidence such as that given in the first section above, that the first spike represents almost exclusively the very rapid changes in sodium conductance and that the plateau is a long-lasting period of reduced potassium conductance. On this basis, we have in the human atrium a situation in which the two major conductance changes involved in the action potential are naturally almost completely separated, so that their de-

pendence on various agents and conditions (e.g. temperature) can be separately observed.

Several attempts were made to measure cell membrane resistance directly in human atrium with the method of current pulses described by Fozzard and Sleator (3). However, insufficient reliable data were obtained to draw conclusions, due mainly to the difficulty of placing the current electrode close enough to the voltage electrode in the irregular pieces, containing much connective tissue, with which we usually had to work.

We therefore undertook to study the nature of the second spike by a different method. In most mammalian atria, acetylcholine reduces the action potential duration

## CONTROL

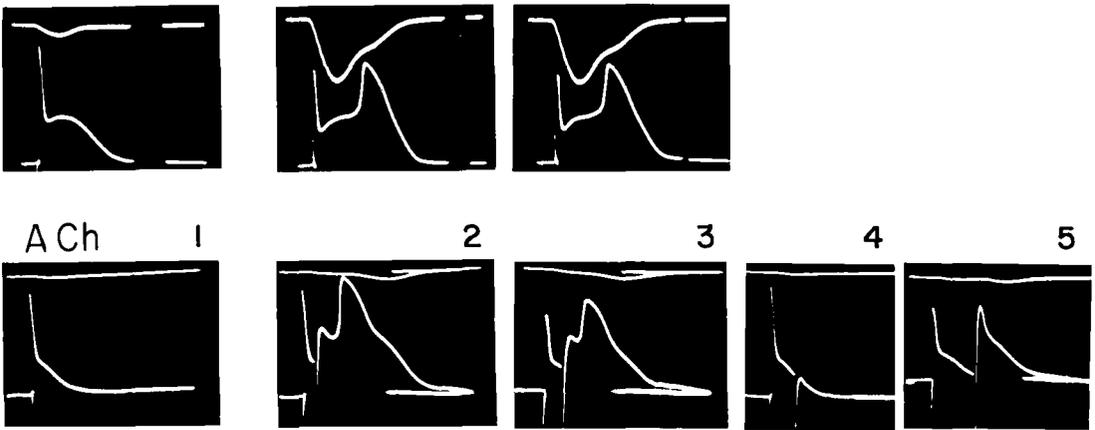


FIGURE 7. Human atrial strip. Top row, control records showing low and high phase potentials with spontaneous second spikes. Bottom row, after full effect of  $10^{-7}$  mole/liter acetylcholine. Frame 1, control. Frame 2, second stimulus applied 70 msec after first; resulting in a second spike of same shape and duration as in absence of ACh. Frame 3, second stimulus at 96 msec. Frame 4, at 130 msec. Frame 5, at 215 msec; spike shape approaching normal, but duration still prolonged.

by shortening or eliminating the plateau. This results from its action on  $g_K$ : it increases resting  $g_K$ , and blocks or reduces the decrease in  $g_K$  (normally following depolarization) which slows repolarization thus producing the plateau. Support for this view of the mechanism of acetylcholine action on guinea pig atria is provided by the membrane resistance measurements reported in reference 3. In human and chimpanzee atrium, ACh has no visible effect on the first spike, but it shortens or eliminates the long plateau (Fig. 5). Adenosine, another agent which increases  $g_K$  and shortens atrial action potentials in other mammals, also eliminates the plateau in human atrial muscle (2). These facts make it almost certain that the effect of ACh on human atrial tissue is to increase  $g_K$  and reduce or prevent the fall in  $g_K$  normally associated with the plateau.

As one might expect, eliminating the plateau in human and chimpanzee atrium also

eliminates the spontaneous second spikes. However, it is possible with a second stimulus to produce second spikes in the presence of ACh, at the times they would have occurred spontaneously. Records from an experiment in which this was done are shown in Fig. 7. After control records were taken (top row) ACh was applied at such a concentration ( $10^{-7}$  M) as to nearly abolish the plateau (bottom row, frame 1). All action potentials were alike (no spontaneous second spikes) until double stimuli were applied (frames 2–5). At intervals of 70 and 96 msec the second stimuli (which were about four times threshold voltage) resulted in second spikes. These had the same long duration (120 msec) as spontaneous ones occurring at similar intervals after the first spike in the absence of ACh. The fact that a saturating dose of ACh does not alter the duration of the spike is strong evidence that a decrease in  $g_K$  is not involved in it.

What possibilities then remain to explain the long duration of the second spike? The most plausible way is to postulate that the mechanism is the same as that of the first spike; i.e., an opening and closing of sodium channels only, with a delay four to eight times longer between activation and inactivation. Other possible mechanisms for a long duration spike would involve fluxes of chloride or of calcium. Chloride was ruled out by replacing it with acetyl glycine and finding no significant change in behavior. The possibility that calcium is involved was studied by increasing its concentration in the medium. The results (described in the next section) combined with some rough calculations indicate that Ca is not carrying a significant part of the current. (Niedergerke and Orkand (4) reached the same conclusion concerning calcium in frog heart.)

This leaves us with the mechanism involving sodium conductance alone; it implies that the sodium channels open up again and remain open for the duration of the second spike (the order of 100 msec) and that their closing is coincident with, and indicated by, the falling limb of the spike. Thus the basic time constants controlling sodium conductance are dependent on the interval between spikes. At short intervals something must strongly delay sodium inactivation. Evidence that calcium, or lack of it, may be involved in this delay is presented below.

Such a process would result in a much greater influx of sodium during the second spike than during the first (roughly proportional to the area under the spikes). Thus, during a period of high phase there should be a net increase in intracellular sodium, which would have to be pumped out during the subsequent low phase. Cycling would therefore be associated with variations in intracellular sodium concentration. This provides an attractive explanation for the cycling phenomenon, if we add the plausible assumption that high internal sodium changes the threshold for firing a second spike, or the time for reactivation of sodium conductance after the first spike. Further experiments, including measurement of intracellular sodium during the two phases, should enable us to apply the critical tests to these hypotheses.

#### THE EFFECTS OF HIGH CALCIUM AND REST INTERVALS

Some time ago we noticed that high calcium in the external medium had an effect on the spikes as well as on the plateau (in contrast to ACh which changes only the plateau). This question has now been studied systematically; one of the relevant experiments is shown in Fig. 8. Here the top row shows control records with 2.5 mM

$\text{Ca}^{++}$  in the medium. A rest interval is introduced between frames 1 and 2 to induce a second spike. Note that frame 3 (in all rows) was taken at a high sweep speed to show first spike durations. The second row shows the effects on the same preparation of 5 mM calcium in the medium. The plateau is not shortened much, and again a rest interval induces a second spike; however, this one has less than half the duration of that in the control records. In frame 3 note that the first spike is also markedly shortened.

In the bottom row, the same tissue had reached a steady state in 7.5 mM  $\text{Ca}^{++}$

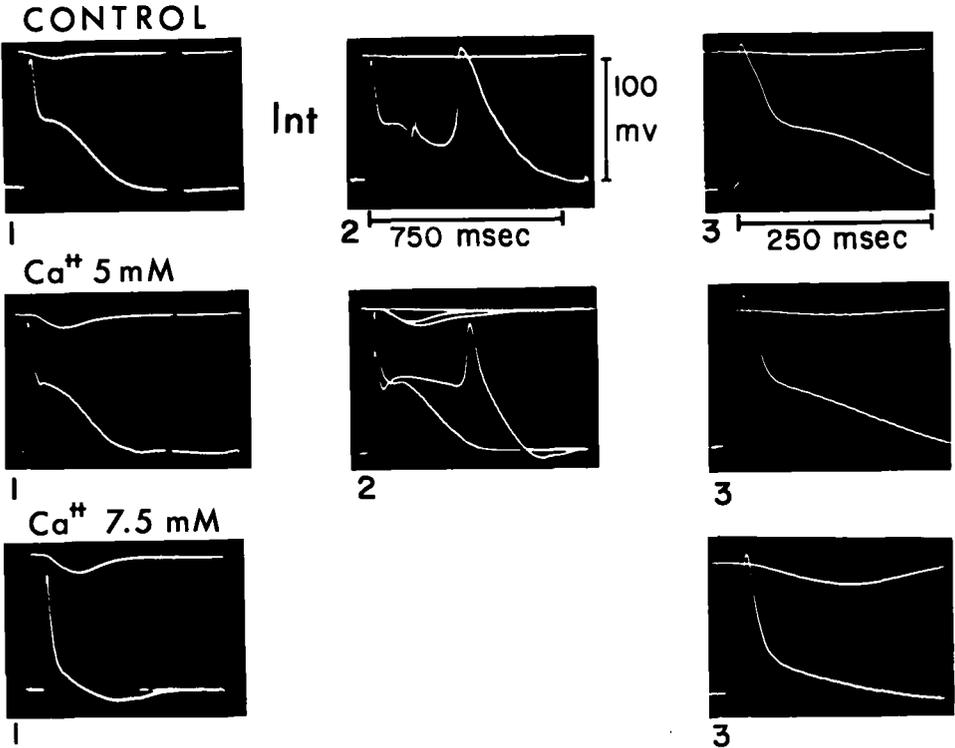


FIGURE 8. Effect of high calcium on first and second spikes. Top row, control record of high and low phase (note that last frame in each row is taken at high sweep speed) Middle row, effects of 5 mM calcium (twice normal). Bottom row, calcium at 7.5 mM Note shortening of first spike in last frame (taken with 250 msec sweep).

Here the plateau has been nearly eliminated, and it was not possible to obtain a second spike even by stimulation. In the last frame, however, it can be seen that the first spike is considerably shorter than in either of the records above. (In spite of the absence of a plateau here the contraction strength was greater than previously.)

What is the possible bearing of these results on the question of the difference in duration between first and second spikes observed in the normal medium? On the basis of these and many other experiments (including those on guinea pig) we will propose the following hypothesis: (1) Assume that normally the spike duration, i.e. the time that  $\text{Na}^+$  channels remain open, is determined by the amount of  $\text{Ca}^{++}$  bound to a

particular site on the cell membrane (call it the  $\text{Ca}^{++}$  M site). More M site  $\text{Ca}^{++}$  produces quicker closure of the sodium channels and leads to short-duration spikes, and less M site  $\text{Ca}^{++}$  produces long-duration spikes. (2) When the cell is depolarized this calcium is released and diffuses away (some of it enters the sarcoplasm and plays a role in contraction). (3) It takes considerable time (the order of 1 sec, i.e. longer than the normal plateau duration) to restore the M site  $\text{Ca}^{++}$  with normal calcium concentrations in the medium. Thus, when the membrane is fired early, there is a deficit of M site  $\text{Ca}^{++}$ , sodium channels remain open, and the spike has a long duration. With higher  $\text{Ca}^{++}$  concentrations in the medium, the M sites are filled faster, and spike duration is shorter at all intervals.

The question now arises whether, with normal calcium in the medium, the M sites

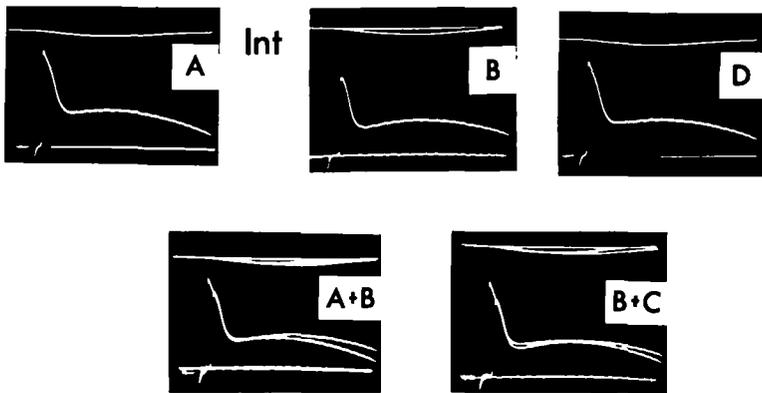


FIGURE 9. Effect of rest interval on configuration of action potential. Human atrial muscle, standard laboratory conditions. Frame A, control. Frame B, first AP and contraction after 10 sec rest interval. Frame D, third after rest interval. Second row, superposition of A and B, and of B and C (second AP after interval). Time axes coincide at moment of stimulation. Note that in B height of spike and its rate of rise are lower than in A or C, and conduction is slower (stimulus-response latency greater). Also, in B, the plateau is of longer duration.

are saturated during the 1 sec interval between stimulated beats under standard conditions. Results on human atrium relevant to this question can be seen in Fig. 9. Here we introduced a 10 sec rest interval into a low phase steady state, and examined the shape of first spikes at high sweep speed. The superpositions in the bottom row show that the first spike after the rest interval (frame B) is both lower and shorter in duration than those in the 1 per sec steady state. Also the rate of rise is slower, and the conduction time is longer, indicating lower conduction velocity. These effects are just what would be predicted by the above hypothesis if the time required to saturate the M sites with calcium were greater than the 1 sec interval between beats. Other experiments, such as that of Fig. 8, show that when calcium concentration is high, rest intervals do not alter the form of the first spike. (A very similar effect of rest intervals on action potential configuration also occurs in guinea pig atrium (5), and it seems likely that the same explanation applies there.)

By means of the mechanism outlined above, the results on human atrium shown in Figs. 7 to 9 can be quite well accounted for. A great number of other experimental results, on other mammalian atria as well as on human and chimpanzee atria, can be brought into a unified harmonious picture by means of some expansions and slight modifications of the ideas underlying the above hypothesis. The problem before us now is to find and apply more direct methods to the determination of what is actually happening at the molecular level in the cell membranes.

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# Observations on Several Mechanical Characteristics of Isolated Mammalian Myocardium

ARTHUR L. BASSETT, BRIAN F. HOFFMAN, and  
HERBERT J. BARTELSTONE

From the Department of Pharmacology, College of Physicians and Surgeons, Columbia University, New York 10032

The existence of tonus changes in cardiac muscle has been considered for more than forty years (1, 2). However, the introduction of the ventricular function curve as an index of ventricular contractility (3) led to the assumption that there was a constant relationship between end-diastolic pressure and fiber length. This concept was supported by reports which failed to show any effect of stimulation of the vagus nerve or stellate ganglia on ventricular extensibility (4). In contrast, other studies, employing several different experimental procedures, have shown that the mechanical characteristics of mammalian myocardium can vary during the diastolic interval (5-9). Such variability would influence the diastolic pressure-volume relationship for the mammalian ventricle and affect both the performance of the heart as well as any quantification of performance.

Several years ago, we found that the diastolic pressure-volume relationship, as well as systolic force in the *in situ* dog heart, was modified by paired electrical stimulation (PS) (10). We used the term variable diastolic compliance to describe such induced changes in the tension-length relationship during diastole and distinguished them from changes in the pressure-volume relationship which are caused by alterations in the configuration of the ventricular cavity. However, Sonnenblick (11) found no changes in diastolic compliance during paired stimulation in isometrically contracting papillary muscle. Because of the disagreement between his results and our previous data (10), we extended our studies to the isolated muscle preparation. We confirmed our previous findings since *in vitro*, as well as *in vivo* PS caused an increase in diastolic compliance (12). Furthermore, the change in compliance was not necessarily dependent on the force developed by the preceding contraction (12). Additional studies by ourselves (13) and others (14) have shown that diastolic compliance is also affected by other inotropic agents including cardiac glycosides and catecholamines.

Recently, Sonnenblick has again reported on experiments with isolated papillary muscles (15). He now shows that diastolic compliance can indeed vary as a result of PS, the actions of catecholamines, and other experimental interventions. The existence of variable diastolic compliance as a property of mammalian cardiac muscle can no longer be questioned. However, there is disagreement about the mechanisms re-

sponsible for the observed changes in compliance. Sonnenblick has found that in his experiments changes in compliance are visible only if systolic force is allowed to vary; no changes in diastolic length or tension with various interventions were noted during isotonic or afterloaded contractions of cat papillary muscles. Sonnenblick suggests that the increase in systolic force (noted under the appropriate recording procedures) causes an elongation of a viscous element in series with the contractile components of cardiac muscle and that this elongation results in the observed changes in diastolic compliance (15).

Our interpretation of the mechanism responsible for changes in diastolic compliance (12, 13) differs from that of Sonnenblick (15). In addition, because some of his experimental findings are in disagreement with ours, we have undertaken further studies of this problem. We have advanced the hypothesis that changes in diastolic compliance and systolic force may be explained, at least in part, by interactions in the contractile components of cardiac muscle (12, 13). Others have presented evidence that part of the resting tension in cardiac muscle is borne by the contractile components (16).

In the present communication, the results of experimental studies on isometric and afterloaded contractions of isolated cat papillary muscle and trabeculae carneae are considered in relation to possible models for the system which generates and transmits force in cardiac muscle. Our findings indicate that a force-dependent series viscous element cannot wholly explain the observed changes in diastolic compliance and the associated changes in systolic force.

## METHODS

Papillary muscles and trabeculae carneae were dissected from the right ventricle of cats anesthetized with pentobarbital sodium, 25–30 mg per kg. For studies on atrial muscle, thin strips were removed from the right atrial appendage of dogs anesthetized with pentobarbital sodium, 30 mg per kg. For the muscles used, the maximal diameter under a load of 1 g was 0.35–1.0 mm. Muscle length was between 4 and 8 mm for ventricular tissue and 8 and 15 mm for atrial trabeculae. The muscles were mounted in a Lucite tissue chamber and were perfused with a Tyrode solution containing, in mM per liter: NaCl, 137; NaHCO<sub>3</sub>, 12; NaH<sub>2</sub>PO<sub>4</sub>, 1.8; CaCl<sub>2</sub>, 2.7; KCl, 2.7 or 5.4; MgCl<sub>2</sub>, 0.5, and glucose, 5.5. A mixture of 95% O<sub>2</sub> and 5% CO<sub>2</sub> was used to gas the tissue chamber and reservoir solutions. Temperature within the chamber was maintained at the desired level by means of a heat exchanger or a proportional temperature control unit (17); flow rate through the chamber was 6 ml per min.

One end of each muscle was directly tied with 6.0 silk thread to a hook which extended through a rubber diaphragm in the bottom of the tissue chamber. The hook was affixed to a Statham bidirectional transducer (model UC-2). The other end of the muscle was tied to a fine gold chain which was attached to a light isotonic lever (18). The lever system was originally designed for studies on skeletal muscle; for the present experiments the lever arm was made of magnesium and reduced in length and mass. The use of mechanical stops allowed us to study contractions under isometric or isotonic conditions or under constant afterload.

Stimuli were delivered through large platinum plates extending along the entire length of the muscle; stimulus duration was 5–10 msec and stimulus strength was always suprathreshold. The stimulator has been described previously (19); output stimulus frequency and mode were programmed by an American Electronics Laboratory stimulator (American Electronic Laboratories, Inc., Colmar, Pa.).

Measurements of contraction were made at constant length or during programmed cyclic

increases and decreases in length (17). Isometric force, recorded at high and low sensitivity, diastolic length, changes in length, time of stimulation, and rate of change of systolic force or length were recorded on an eight-channel Electronics for Medicine (Electronics for Medicine, White Plains, N. Y.) recorder. Measurements of diastolic tension were made at sensitivities up to 25 mg per cm chart; measurements of changes in diastolic length were accurate to within  $2 \mu$ . Compliance of the recording system, in the absence of a muscle, was  $<15 \mu$  per g. (One end of the gold chain was tied directly to the hook in the force transducer and the other end of the chain was tied to the isotonic lever; dry, 6-0 silk thread was used. Compliance was measured as the change in length per gram load between 0-2 g.)

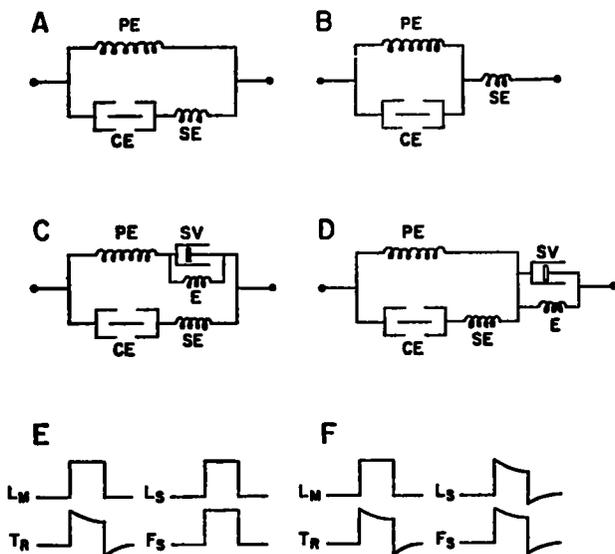


FIGURE 1. Diagrams of possible mechanical analogues of cardiac muscle. For A-D, PE, parallel elastic element; CE, contractile element; SE, series elastic element; SV, series viscous element; E, elastic element in parallel with SV. Note that in A, SE is in series only with CE; while in B, SE is in series with both CE and PE. In C, a viscous element has been added in series with PE, while in D the viscous element is in series with both PE and CE. In E and F are shown the effects of elongation of the series viscous element in C and D, respectively, on muscle length ( $L_M$ ), sarcomere length ( $L_S$ ), resting tension ( $T_R$ ), and systolic force ( $F_S$ ). Note that only for the model shown in D would an elongation of SV result in the changes in resting tension and systolic force which are shown in Fig. 3. See text for discussion.

Most experiments were conducted at temperatures between  $30^{\circ}$ - $37^{\circ}$ C and a stimulation rate between 20-60 per min. Exceptions are noted in the results.

## RESULTS

### I. Studies on Stress-Relaxation

Analysis of the mechanical behavior of striated muscle customarily has employed an analogue consisting of an elastic element in series with the contractile element and a second elastic element in parallel with both the contractile and series elastic elements

(20). In descriptions of the force-velocity relationships for cardiac muscle and in characterization of its contractile and elastic properties (21-23) these three elements usually have been arranged in the manner shown in Fig. 1 A. However, it also is possible that a more appropriate analogue might be formed if the three elements were arranged in the manner shown in Fig. 1 B (24-26) and several recent studies of cardiac muscle have suggested that, under appropriate conditions either or both might best represent certain of the properties of cardiac tissue (27, 28). Because of this uncertainty and because results of experiments employing the technique of quick release have

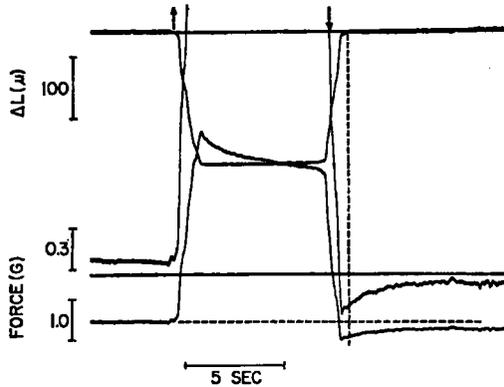


FIGURE 2. Records of length and high and low sensitivity records of force recorded from quiescent cat papillary muscle. The top trace is a superimposition of the record of length and a reference line; increase in length is indicated by a downward deflection. The next trace from the top is a high sensitivity force trace, the next is a reference line, and the bottom a low sensitivity force trace. At the first arrow ( $\uparrow$ ) length was increased by slightly more than  $200 \mu$ ; at the second arrow ( $\downarrow$ ) length was returned to the control value. During elongation the high sensitivity force trace was driven off the recording. Note that, when the muscle was held at a constant increased length, force decreased first rapidly and then slowly. Also, after returning to the control length force fell below the control value and increased only slowly. The interrupted vertical line indicates the moment when length reached the control value,  $\pm 2 \mu$ ; the horizontal interrupted line indicates the level of force recorded at low sensitivity prior to elongation. Temperature,  $35^{\circ}\text{C}$ . (Slight variations in length and force result from the fact that length was changed manually.)

shown a preference for the earlier analogue (25, 28) or have failed to demonstrate that it is inappropriate (27), we have elected to use the model shown in Fig. 1 A as a basis for discussion. The conclusions which we reach would be qualitatively similar for either model.

The utility of the model depends upon two assumptions: first, when the muscle is at rest, the contractile element offers no resistance to elongation; second, the parallel elastic element does not act as a compression spring. In terms of the model, therefore, when the muscle is at rest the length of the contractile element (i.e., sarcomere length) will bear a linear and predictable relationship to total muscle length, at least over the greater part of the tension-length curve (29). Thus, the contractile element will

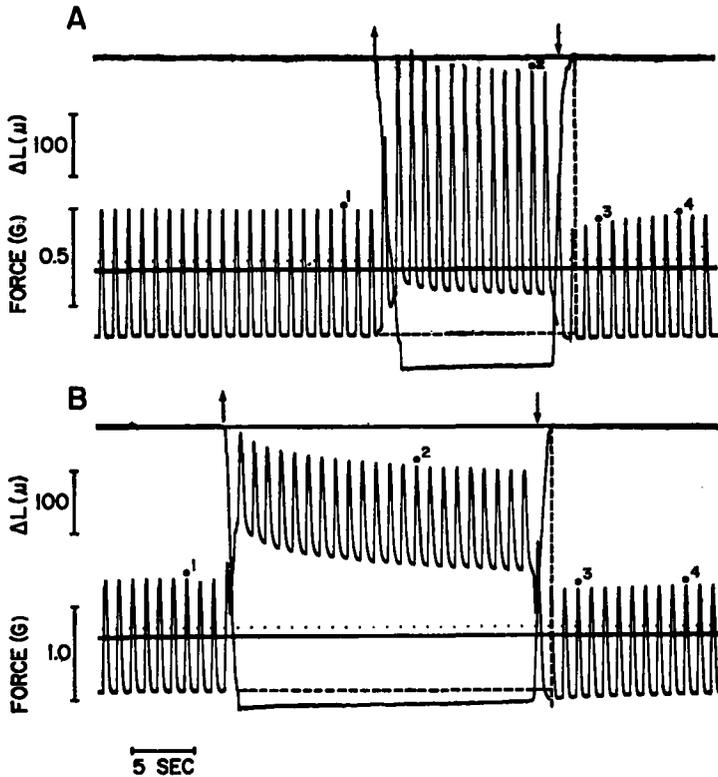


FIGURE 3. Effects of increases and decreases in length on diastolic and peak isometric systolic force of cat papillary muscle as a function of initial muscle length. A and B, rate, 60 per min; temperature, 35°C. From above down the traces show the record of muscle length (increase downward), superimposed on a reference line, stimulus artifacts on a second reference line, and a record of isometric force. Horizontal interrupted line shows level of diastolic tension prior to stretch, and vertical interrupted line the moment when length returns to the control value. In A, prior to stretch the length of the muscle was less than  $L_0$ ; i.e., the muscle was on the ascending limb of the length-tension curve. After elongation, there was an increase in diastolic and systolic force and, at constant length a small progressive decrease in both. After returning to the control length, diastolic and systolic force fall below control values and then increase slowly. For Fig. 3 A, the values of developed (systolic) force at points 1, 2, 3, and 4 are 0.64, 1.14, 0.51, and 0.62 g respectively. In B, the control muscle length is near  $L_0$ . Note decreased sensitivity on force trace. After elongation systolic force is slightly reduced and, although there is marked stress-relaxation, after the muscle is returned to control length in spite of a lower diastolic tension systolic force is approximately equal to the control value. For Fig. 3 B, the values of systolic force at points 1, 2, 3, and 4 are 1.15, 1.02, 1.12, and 1.13 g respectively.

have no effect on the tension-length relationship of quiescent muscle and the force developed during contraction will depend on the length of the muscle prior to excitation.

In terms of the model, if a suitable preparation of cardiac muscle were brought

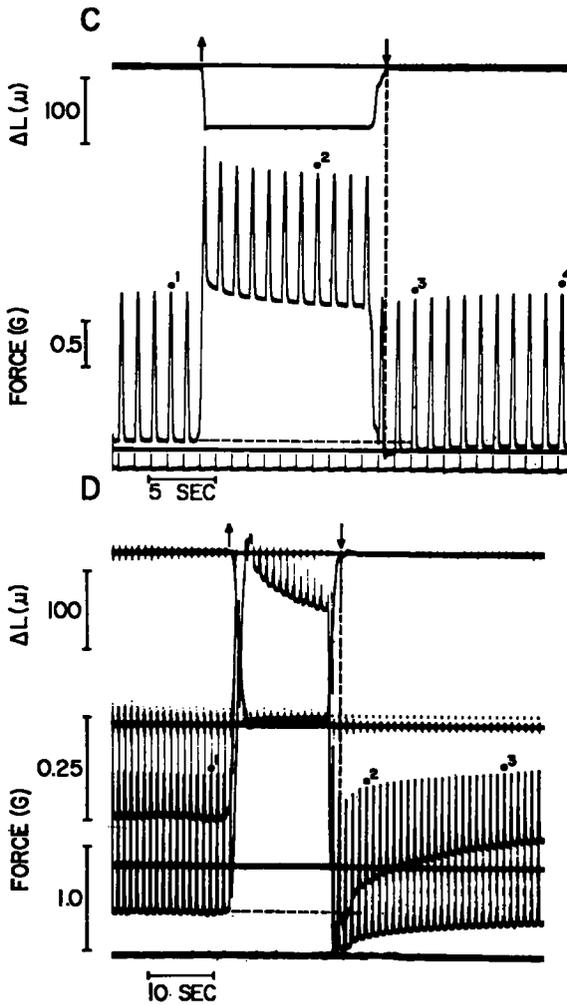


FIGURE 3 *concluded*

C, records from a different preparation. Rate, 45 per min; temperature, 36°C. Stimulus artifacts at bottom of record. Prior to stretch the muscle length is slightly greater than  $L_0$ , and on elongation systolic force is decreased. After returning to control length there is the usual decrease in diastolic tension but a slight, persistent increase in systolic force. For Fig. 3 C, the values of systolic force at points 1, 2, 3, and 4 are 1.51, 1.32, 1.54, and 1.58 g respectively. D, experiment on another muscle. Temperature, 35°C; rate, 60 per min. Force recorded at both high and low sensitivity. Prior to elongation the muscle has been brought to a point on the descending limb of the length-tension curve; i.e., to a length  $> L_0$ . During elongation only the bottom of the low sensitivity force trace is seen. Stress-relaxation is marked. After returning to control length diastolic tension is markedly reduced and systolic force considerably increased. For Fig. 3 D, the values of systolic force at points 1, 2, and 3 are 1.30, 1.43, and 1.43 g respectively.

rather slowly from one length to a greater length the diastolic tension would be expected to change from its initial value to a new value and then remain constant. Also, force developed during systole would be proportional to the new muscle (and sarcomere) length and would not change as a function of time. A number of studies have shown that this is not the case for cardiac muscle (30–33) and that there may be stress-relaxation or “creep” after elongation. The records shown in Fig. 2 demonstrate this phenomenon for quiescent cat papillary muscle. When length is increased rather abruptly, diastolic tension increases. Then, although the muscle is kept at the same length, diastolic tension decreases first rapidly and then progressively more slowly. Also, when muscle length is returned to the control value, tension falls below that recorded for the same length prior to elongation and then slowly increases. These time-dependent changes in tension would not result from the behavior of the undamped elastic elements in the model in Fig. 1. A and are not due to properties of the recording apparatus. To explain them it is necessary to assume that there is in cardiac muscle another element which has viscous properties. Such a viscous element might have several locations in an analogue. In terms of the model in Fig. 1 A, the results obtained from studies of quiescent muscle would not differentiate between Fig. 1 C, where the viscous element is in series only with the parallel elastic element, and Fig. 1 D, where the viscous element is in series with both the parallel and series elastic elements. In either case it is necessary to assume that there is an additional elastic element in parallel with the viscous element so that, when force on the system is decreased, the viscous element will return to control length. A choice between these two possibilities for locating the viscous element (Figs. 1 C and D) can be made if the length of the muscle is varied, as in the experiment shown in Fig. 2, during regular contractions of the muscle and if the experiment is repeated with the initial muscle length set first on the ascending limb, then at the peak, and finally on the descending limb of the tension-length curve. The results of such an experiment are shown in Fig. 3. In Fig. 3 A the muscle length was changed between two values on the ascending limb of the tension-length curve; after elongation there was, as expected, an increase in developed isometric systolic force and a progressive decrease in diastolic tension as the muscle was maintained at the new length. When length was returned to the initial value and diastolic tension fell below the control it is clear that systolic force was reduced with respect to the control value obtained at the same length. Force then increased slowly as diastolic tension increased towards the control value. The records in Fig. 3 B were obtained when the muscle length was varied between two points near the peak of the tension-length curve and those in Figs. 3 C and D when length varied between two points on the descending limb of the curve. In Fig. 3 B the changes in length have little if any effect on the active systolic force even though there are time-dependent changes in diastolic tension after both elongation and shortening. However, in Fig. 3 C it is evident that force developed during systole was decreased after the muscle had been elongated. This is to be expected since the muscle was on the descending limb of the tension-length curve. The significant observation (Figs. 3 C and D) is that when muscle length was returned to the control value, force developed during systole was greater than that recorded prior to elongation. With the passage of time, as diastolic tension increased there was a decrease in the developed systolic force.

For the models in both Figs. 1 C and 1 D an imposed change in muscle length would result in a change in the length of the contractile element. As a result there would be a change in developed systolic force appropriate to the position of the muscle on the tension-length curve. Thus a change in systolic force would be expected to follow immediately on lengthening or shortening. Also, in terms of either model, an increase in length would be expected to result in a gradual, force-dependent elongation of the viscous element. However, in the case of the model shown in Fig. 1 C, after the initial imposed elongation the redistribution of length changes would be restricted to the parallel elastic and viscous element; there thus would be no changes in the length of the contractile element. Therefore the model in Fig. 1 C could not account for either the slow changes in developed systolic force which were seen after the imposed elongation or shortening or the fact that, when the muscle had been returned to control length, developed systolic force was not the same as that recorded prior to elongation.

The results of the experiment shown in Fig. 3 thus suggest that the viscous element behaves as though it has the location shown in Fig. 1 D, in series with both the parallel and series elastic elements, and thus in series with the contractile element as well. Changes in length of such a series viscous element would permit the length of the contractile element to vary and thus cause the changes in systolic force shown in Fig. 3. After elongation of the muscle, a gradual increase in length of the series viscous element would permit shortening of the contractile element. After the muscle had been returned to control length, because of the elongated series viscous element, the contractile element would be somewhat shorter than expected on the basis of muscle length. By equating contractile element length and sarcomere length it is reasonable to expect that, at points on the ascending limb of the tension-length curve elongation of a series viscous element would cause a reduction in the isometric force developed during contraction; while at points on the descending limb of the curve, elongation of the series viscous element would permit the sarcomere to shorten and the shorter sarcomere would develop more force during systole. Although there has been some disagreement between results of previous experiments in terms of the change in active tension after stress relaxation (32, 33), the results shown in Fig. 3 are characteristic for isolated preparations of mammalian cardiac muscle. Although they do not exclude other possible causes for changes in diastolic and active tension during stress relaxation (see Fig. 9), they are compatible with a model similar to that shown in Fig. 1 D. More important, selection of this model permits certain predictions about the behavior of cardiac muscle which are subject to test and have direct bearing on the nature of changes in diastolic compliance.

## *II. Changes in Diastolic Compliance after Paired Stimulation*

If there is in cardiac muscle an element which has at least the properties of the series viscous element in Fig. 1 D, the following prediction seems reasonable: Within the limits imposed by the extensibility of the series viscous element, any change in the force developed during contraction would result in a change in the length of this element. Such changes in length of the series viscous element would have a variety of effects on active force development and on the diastolic compliance of the muscle.

We propose to consider only the latter at this time. The records in Fig. 4 show isometric contractions of cat papillary muscle during a control period and after initiation of paired stimulation. It is evident that the paired stimuli cause, in addition to postextrasystolic potentiation of contraction, a decrease in diastolic tension. We have described this decrease in diastolic tension which occurs at constant muscle length as an increase in diastolic compliance (12) and have suggested that it might result from variations in residual interaction between the contractile elements (12, 13). Sonnenblick (15) has studied the same phenomenon and has found that, although there was an increase in diastolic compliance when paired stimulation caused an increase in

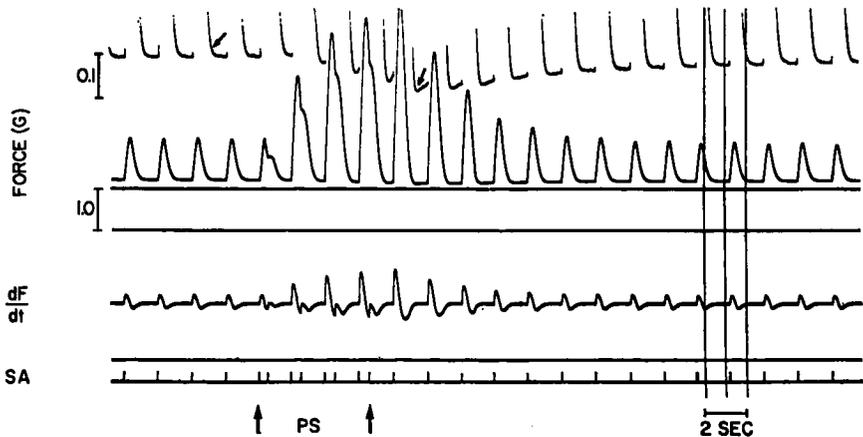


FIGURE 4. Records of isometric contractions of cat papillary muscle during regular stimulation and paired stimulation (PS). From above down the traces show high sensitivity and low sensitivity recordings of force, the first time derivative of the force change ( $dF/dt$ ), temperature ( $31^{\circ}\text{C}$ ), and a stimulus artifact. Stimulus rate, 37 per min; paired stimuli separated by 395 msec. Note that during application of PS, indicated by the vertical arrow at the bottom of the figure, there is an increase in systolic force, a decrease in diastolic tension, and an increase in the rate of change of force during both contraction and relaxation. The arrows pointing to the high sensitivity record of force contrast the terminal rate of relaxation during regular stimulation and paired stimulation; note that PS increases the rate of relaxation even at tensions less than the control end-diastolic value.

systolic force (i.e., under isometric conditions), if the muscle contracted isotonicly or against an afterload of constant magnitude the diastolic length or tension did not vary during or after application of paired stimuli. These results led him to conclude that the change in compliance caused by PS resulted from force-dependent changes in length of a series viscous element similar to that shown in Fig. 1 D.

We have made similar studies of changes in diastolic tension at constant diastolic length under isometric and afterloaded conditions and of changes in diastolic length under isotonic conditions. Most of the results are described elsewhere (34); however, some have direct bearing on the models proposed in Fig. 1 and on an analysis of the proposition that all changes in diastolic compliance are a result of force-dependent hysteresis. The records in Fig. 5 show afterloaded contractions of isolated cat papillary

muscle during regular stimulation and after initiation of paired stimulation and the resulting sustained postextrasystolic potentiation. It can be seen that during the period of paired stimulation the magnitude of the afterload is constant. However, the pattern of paired stimulation causes a fairly marked second contraction. As a result,

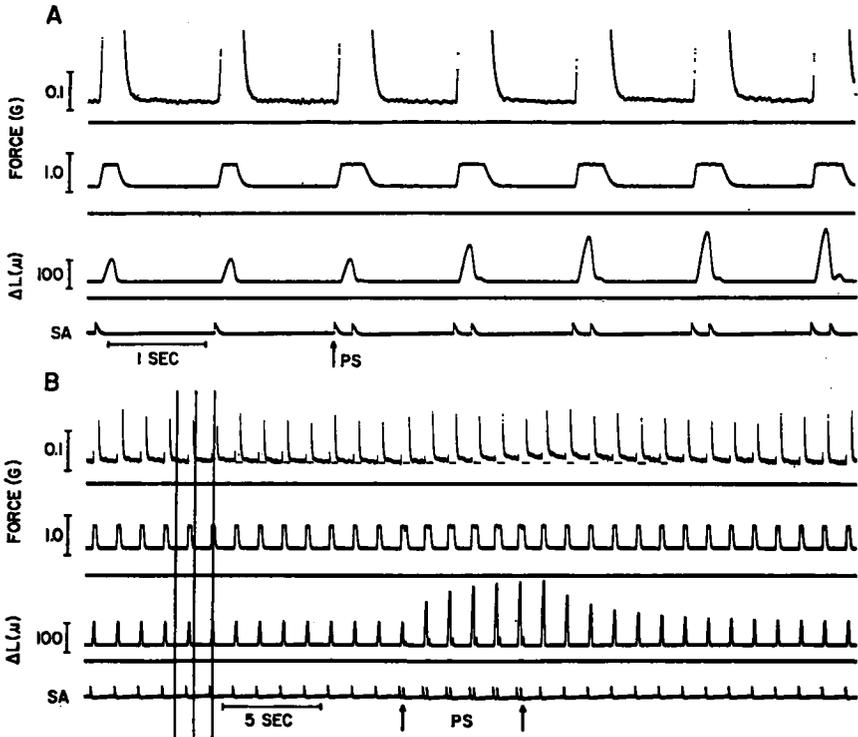


FIGURE 5. Records of force and shortening of afterloaded cat papillary muscle. A, from above down the records show force recorded at high sensitivity and at low sensitivity, length, and a stimulus artifact. Temperature, 37°C; rate, 45 per min; PS, paired stimulation. Note that with the onset of paired stimulation there is an increase in shortening and an increase in the time during which the muscle bears the afterload. B, records from the same preparation obtained at a lower paper speed and with a smaller preload. Note that after initiation of PS shortening increases more markedly and there is in the top trace a change in both the terminal rate of relaxation and the end-diastolic tension. The interrupted line permits the decrease in diastolic compliance (increase in diastolic tension) to be measured.

the muscle bears the entire afterload for a greater fraction of each cycle during paired stimulation than under control conditions (Fig. 5 A). In terms of the model shown in Fig. 1 D each of the potentiated contractions caused by the paired stimulation would be expected to increase the length of the series viscous element. This is so because under these conditions, even though the magnitude of the afterload is constant, the time during which the afterload acts on the series viscous element is increased. One thus would expect that, by increasing the time during which the muscle supported the

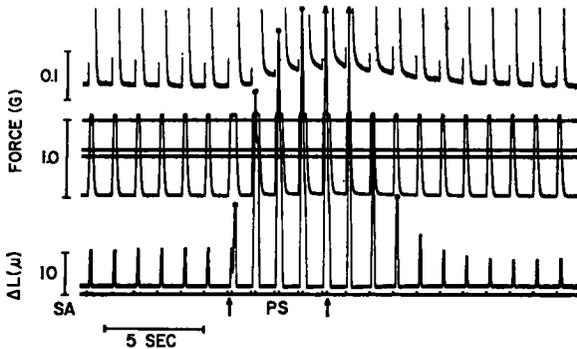


FIGURE 6. Records of afterloaded contractions of a cat trabeculum during regular and paired (PS) stimulation. Records, from above down, show force recorded at high and low sensitivity, length, and a stimulus artifact. Temperature, 37°C; rate 50 per min. Note that on initiation of PS there is a marked increase in shortening and a progressive decrease in both the terminal rate of relaxation and the end-diastolic tension. The peaks of some records of length change have been marked with dots; the small arrows show that the length trace has been deflected off the record. See text for discussion.

afterload, paired stimulation would have caused a decrease in diastolic tension (increased diastolic compliance). In fact, in most of our experiments the records show either no change (Fig. 5 A) or a progressive decrease (Figs. 5 B and 6) in diastolic compliance instead of the expected increase; in the latter, after each of the potentiated contractions diastolic tension is higher than during the preceding diastole. We have

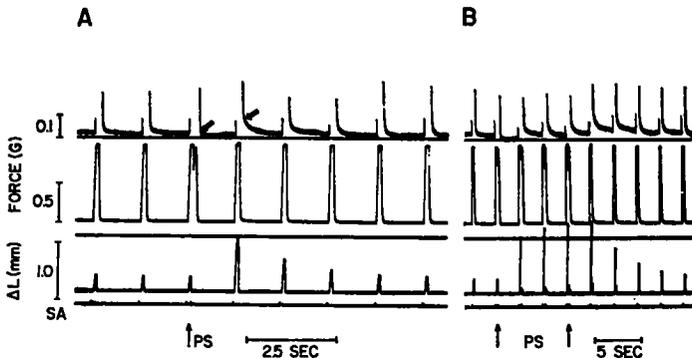


FIGURE 7. Records of afterloaded contractions of cat papillary muscle. Temperature, 36°C; rate, 25 per min. Traces from above down show force at high and low sensitivity, length, and a stimulus artifact. A, a single pair of stimuli (PS) cause an increase in terminal relaxation rate (top trace, solid arrow); the subsequent, potentiated contraction results in greater shortening and a decrease in the terminal rate of relaxation (top trace, unfilled arrow). B, maintained PS causes more rapid relaxation and increased compliance after the first premature contraction and then, as shortening increases, a decrease in the terminal rate of relaxation and a decrease in compliance. These changes persist for several cycles after the end of PS, when the duration of contraction has returned to the control value.

recorded an increase in compliance of extremely small magnitude, and only rarely under these experimental conditions. The fact that neither our experiments nor those of others (15) have demonstrated a consistent increase in diastolic compliance under these conditions may not be used to support the argument that all changes in diastolic compliance are force-dependent. An increase in compliance would be expected if

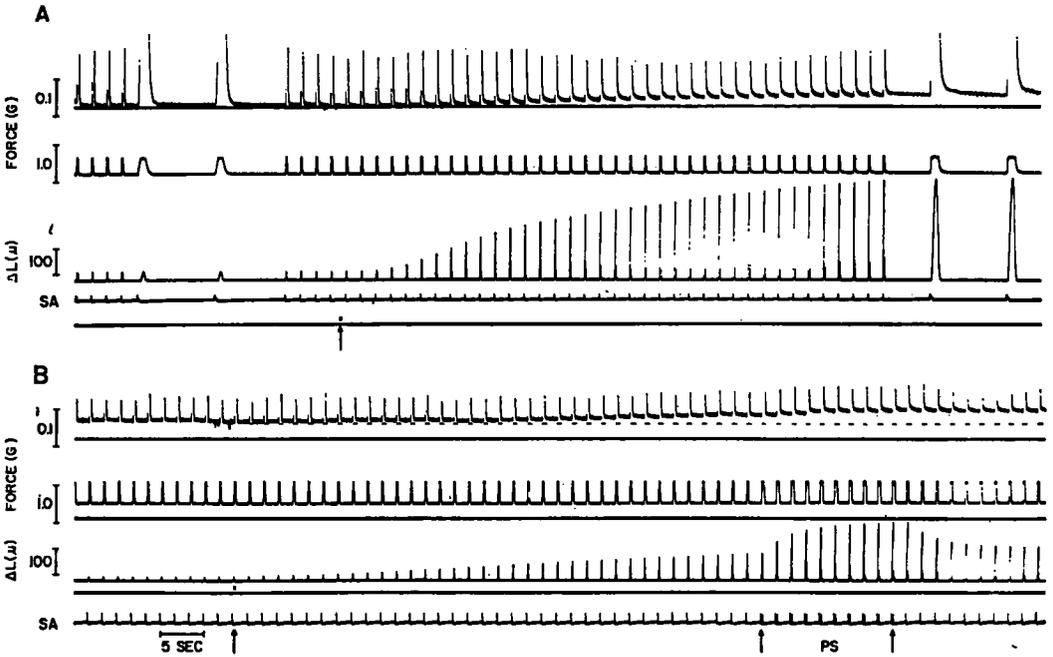


FIGURE 8. Records of afterloaded contractions of cat papillary muscle. Temperature, 36°C; rate, 45 per min. Traces from above down show force at high and low sensitivity, length, a stimulus artifact, and a marker. Paper speed varied to show duration of contraction. A, at the mark (arrow), isoproterenol was added to the bath to give a final concentration of  $1.5 \times 10^{-7}$  M. Note that as shortening increases, terminal relaxation is delayed and end-diastolic tension increases. B, the preload has been increased slightly to diminish shortening and the afterload increased. Isoproterenol in a final concentration of  $5 \times 10^{-8}$  M added at the mark (first arrow). The top trace shows a movement artifact. Isoproterenol causes a slight increase in shortening and a small decrease in diastolic compliance. Initiation of PS causes a further increase in shortening and a more marked decrease in compliance. The dashed line has been drawn for reference to show the decrease in compliance.

changes in this property resulted solely from a series viscous element. Indeed, the experimental results suggest that something other than a series viscous element is important in determining the diastolic compliance of cardiac muscle. The records show one possible mechanism. When under conditions of constant afterload paired stimulation was initiated, the resulting postextrasystolic potentiation caused the expected increase in the velocity and extent of shortening, in addition to the effect on

the duration of afterload mentioned above. Concomitant with the increase in shortening, and apparently in proportion to the increment in shortening, there is a progressive increase in tension during each diastole. If one compares the records in Figs. 5 A and B and Fig. 6, it is clear that the change in end-diastolic tension, or compliance, varies from negligible to marked. Also, the change in shortening caused by PS is small when there is little change in compliance (Fig. 5 B) and large when there is a marked decrease in compliance (Fig. 6). The records suggest that changes in compliance resulted from a decrease in the terminal rate of relaxation and that, although diastolic muscle length was constant, at each instant during diastole during paired stimulation sarcomere length was less than at the same instant during the preceding cycle.

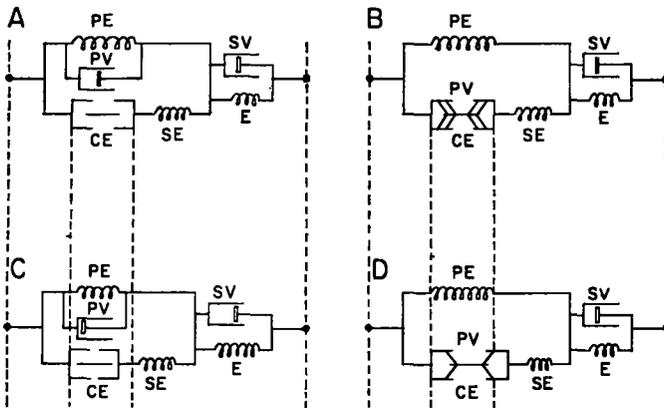


FIGURE 9. A and B show diagrammatic representations of two possible sites for a viscous element (*PV*) which would dampen the length changes of the contractile element (*CE*). Other abbreviations as in Fig. 1. In A the *PV* is represented as a passive element in parallel with the parallel elastic element, *PE*. In B the viscosity (*PV*) is represented as a property of the contractile element of each sarcomere, and is shown diagrammatically as cross-links. In each model the length of *CE* is intended to represent sarcomere length. The diagram in C shows the changes in length of *CE* which would occur if an increase in compliance were to result only from the action of increased force on *SV*, the series viscous element causing it to elongate. That in D shows the changes in length of *CE* that would result if a similar increase in compliance were caused by a change in the compliance of *CE* itself. See text for discussion.

Additional evidence bearing on the relationship between the extent of shortening during contraction and the rate and extent of relaxation is presented elsewhere (34). Only a few points need be made at this time. First, although PS causes an increase in the duration of contraction (by adding a second mechanical event), under isometric conditions the terminal rate of relaxation either is increased or unchanged (Fig. 4). Second, the changes in diastolic tension shown in Figs. 5 and 6 do not appear to result solely from the abbreviation of the diastolic interval. Fig. 7 shows records from a different preparation maintained at a temperature of 36°C and stimulated at a rate of only 25 per min. In Fig. 7 A a single pair of stimuli is introduced. During the cycle containing the premature contraction the muscle bears the afterload for an increased time and the terminal rate of relaxation is increased. During the next cycle, the

potentiated contraction is not increased in duration but shortening is augmented. The terminal rate of relaxation is decreased markedly (compare with Fig. 4). The same changes are shown in Fig. 7 B during sustained PS. After the first pair of stimuli relaxation is accelerated and end-diastolic tension reduced. During subsequent cycles with increased shortening the terminal rate of relaxation is reduced and end-diastolic tension rises. The most marked changes in diastolic compliance are seen after the end of PS, when the duration of contraction returns to normal but shortening still is greater than under control conditions. Further, a similar progressive beat-to-beat increase in the diastolic tension of the afterloaded muscle is observed if a catecholamine is used to cause an increase in shortening (Fig. 8 A). This is so even though catecholamines typically increase the rate of both contraction and relaxation, and thus at constant frequency of contraction under isometric conditions increase the duration of diastole relative to that of systole. With low concentrations of catecholamine, an additional decrease in compliance results from PS (Fig. 8 B).

Although we have not proven here a causal relationship between extent of shortening and diastolic compliance, it is of some interest to examine the possibility that changes in extent of shortening are the immediate cause of the demonstrated alteration in diastolic tension-length relationship in the afterloaded muscle (Figs. 5-7) and to refer again to the muscle models which we have considered. The model shown in Fig. 1 D is not sufficient to explain this relationship. However, (Fig. 9 A) addition of an additional viscous element in parallel with the contractile element (and the parallel elastic element) would change the properties of the model so that under afterloaded conditions the rate of elongation might depend on the extent of shortening. With greater shortening and perhaps with a greater duration of the period of shortening, the viscous element might assume a shorter length than under control conditions and this would retard relaxation.

### III. *The Compliance of the Contractile Element*

As in the case of the postulated series viscous element, a viscous element in parallel with the contractile element would modify several of the characteristics of the model. However, again we will limit our consideration to argument bearing on the nature of changes in diastolic compliance. A parallel viscous element might be passive, in the sense that the traditional elastic elements and our postulated series viscous elements are passive, or it might be active. By active we mean that it might represent a variable degree of persistent interaction in the contractile elements. We have conducted one group of experiments which have some bearing on this question. Two models are shown in Fig. 9. In Fig. 9 A there is one passive viscous element in parallel with the contractile element and another passive viscous element in the location suggested by the experiments on stress-relaxation (see Fig. 1 D). In Fig. 9 B we have attempted to indicate that the contractile element itself may contribute to the diastolic compliance of the muscle because of variable residual interaction. For the model in Fig. 9 A under ideal isometric conditions a change in diastolic compliance would result from force-dependent changes in the length of the series viscous element or from changes in the rate of relaxation which might be caused by slight differences in the extent of internal shortening of the contractile element. In the case of an observed increase in diastolic compliance, we must assume that the series viscous element has been elongated. A

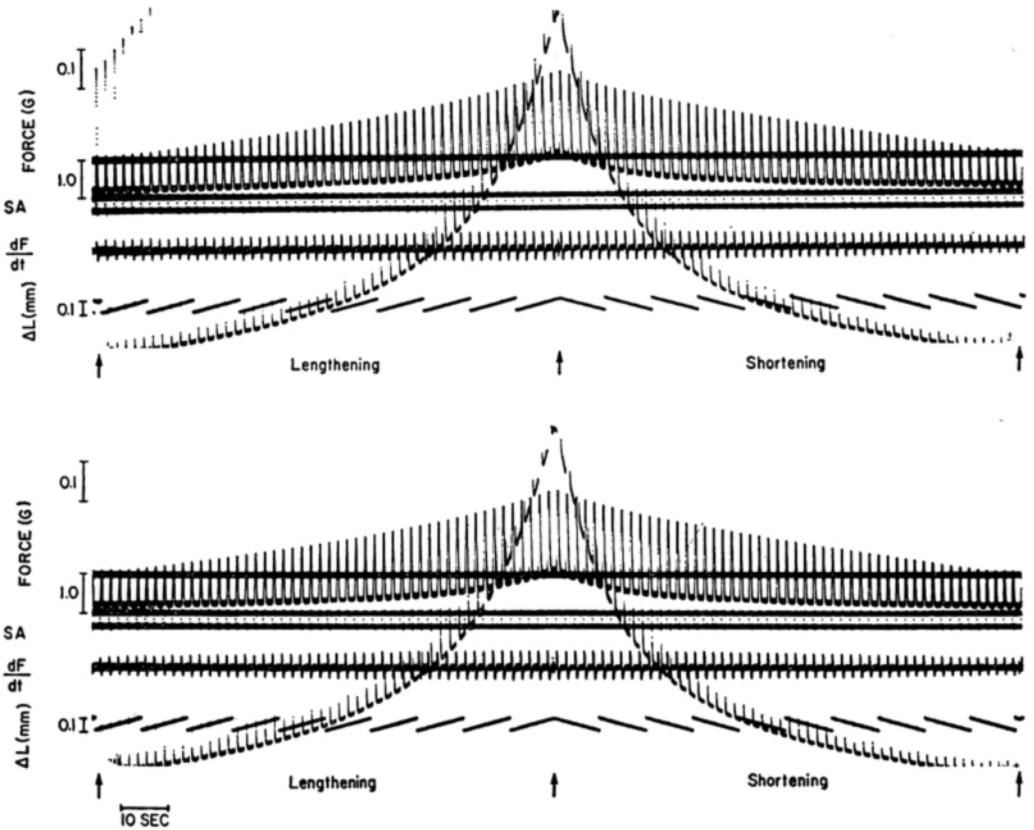


FIGURE 10. Records of two complete lengthening-shortening cycles of cat papillary muscle. Temperature, 30.5°C; rate, 35 per min. Traces show force at high and low sensitivity, marker, and stimulus artifact. Also included is an uncalibrated record of the rate of development of force ( $dF/dt$ ). The sawtooth trace denotes the direction and magnitude of change in length; each sawtooth denotes a length change of 0.1 mm. In this experiment, muscle length was varied at a rate of 0.1 mm per 10 sec. Between the first and second arrows, the muscle is lengthened; at the second arrow, a shortening sequence begins and ends with the muscle at its original length. Then a new cycle of lengthening and shortening begins. Note the change in developed force during lengthening and shortening. On the high sensitivity force record the peaks of the contractions are off the record but diastolic tension is clearly visible. Also, note the hysteresis; developed force is greater and diastolic tension is less during shortening when compared to those values obtaining at the same length during a lengthening cycle. Note the comparability of developed force and diastolic tension during each of the two complete cycles of lengthening and shortening.

necessary consequence of such elongation of the series viscous element is that for any muscle length sarcomere length will be less than that obtaining prior to the increase in compliance (Fig. 9 C).

Conversely, if one assumes that variability of diastolic compliance may result from

changes in the compliance of the contractile element itself (Fig. 9 B), an increase in diastolic compliance would result in a longer sarcomere at any muscle length, than prior to the change in diastolic compliance (Fig. 9 D). In terms of the two models, then, an increase in diastolic compliance would have opposite effects on the relationship between muscle length and sarcomere length and thus on the isometric force developed during contraction at any muscle length. This difference is difficult to quantitate when the muscle is kept at a fixed length since the means we have used to alter diastolic compliance (paired stimulation, catecholamines, etc.) also have direct effects on contractility. However, regardless of the direct positive inotropic actions of the measures used to increase diastolic compliance, each of the mechanisms considered as possible causes of the change (Figs. 9 C and D) would have different effects on the relationship between maximum active tension and muscle length. An increase in compliance due solely to force-dependent elongation of the series viscous element would be expected to shift the tension-length curve so that maximum active systolic force appeared at a muscle length greater than that demonstrated under control conditions since, for any muscle length, the sarcomere length would be less (Fig. 9 C). An increase in compliance caused by a change in the compliance of the contractile element would have the opposite effect: peak active isometric force would appear at a muscle length less than that obtained under control conditions since sarcomere length would now be greater for any muscle length (Fig. 9 D). We have attempted to test these two possibilities by varying muscle length in a controlled manner and recording length as well as systolic and diastolic tension over the greater part of the tension-length curve. The technique employed has been described in detail (13, 17) but some comments should be made here in relation to the experiments to be considered.

The records in Fig. 10 show isometric contractions and changes in length during two of a series of programmed increases and decreases in length. It is clear from the record that during lengthening the muscle has not been carried over the peak of the tension-length curve. If the rate of elongation and shortening is not excessive, consistent results can be obtained from a large number of such cyclic changes in length (17), even if the muscle is stretched over the peak of the curve. The tension-length curves plotted from the results of a series of such determinations, prior to and after experimental intervention, permit one to assign some significance to even rather small changes in the relationship between muscle length and maximum active isometric force. This technique has been used to determine the effect of changes in diastolic compliance on the muscle length at which peak active force is recorded. Fig. 11 and Table I show the results of a number of such experiments.

In all experiments which compared the tension-length curves inscribed during regular stimulation and paired stimulation (Table I) the paired stimuli increased developed systolic force and increased diastolic compliance over the entire curve. Also, PS shifted the peak developed force to a shorter muscle length (Figs. 11 A and B). This suggests that the increase in compliance permitted the sarcomere length to become greater for any muscle length over the entire ascending limb of the curve. In other studies, isoproterenol, norepinephrine, and calcium were used to increase diastolic compliance. These agents have a strong, positive inotropic effect. This

complicates the experiment since a marked increase in systolic force is expected to act on the series viscous element and shift the peak of the tension-length curve to the right; i.e., to greater muscle lengths. In contrast, were these same agents to increase compliance by diminishing residual interaction in the contractile element, they would shift the peak of the tension-length curve to shorter muscle lengths. Depending on the concentration of the agent employed, the two opposing effects might cancel each other

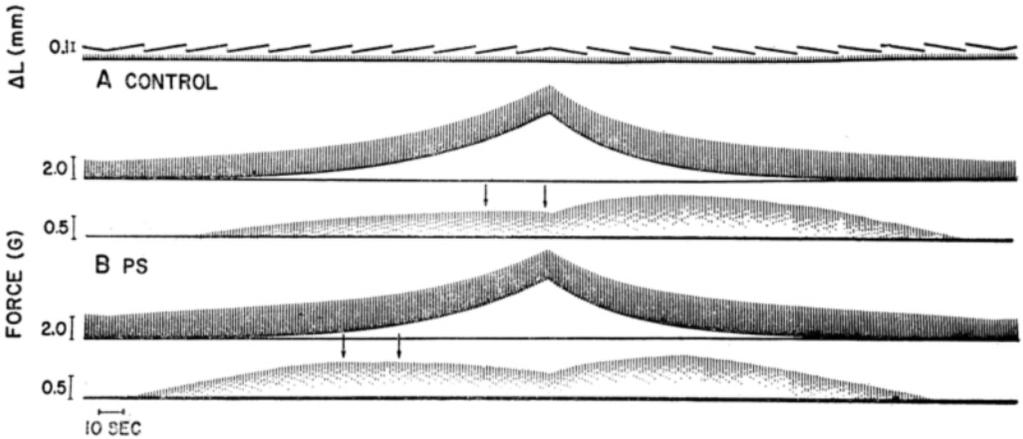


FIGURE 11. A, record of cat papillary muscle contractions during a lengthening-shortening cycle and repetitive single stimulation. Temperature,  $36.5^{\circ}\text{C}$ ; rate, 45 per min; muscle length, 8 mm. Traces from above down show rate of change in length (0.1 mm per sawtooth), stimulus artifact, and force at low and high sensitivity. On the high sensitivity trace of force, only the peaks of the contractions are displayed. The high sensitivity force trace was obtained by capacitor coupling the output from the strain gauge channel before amplification. Thus, a steady diastolic base line was maintained and the display of the peaks of the contractions led to immediate visualization of the apex of the length-tension curve. Note that the apex of the length-tension curve is shown between the arrows just above the high sensitivity force trace. B, record of contractions of the same muscle during a subsequent lengthening-shortening cycle using repetitive paired stimulation. Calibrations and displays same as for Fig. 11 A. Note the marked shift in the apex of the length-tension curve to the left during paired stimulation. The apex of the curve is again shown between the arrows just above the high sensitivity force trace. Thus the muscle developed maximum force at a shorter length during the lengthening portion of the cycle as a result of PS. The increase in diastolic compliance at the maximum length is 900 mg. Note the decrease in hysteresis during lengthening.

or one or the other might predominate. In Figs. 11 C and D, norepinephrine ( $1.2 \times 10^{-7} \text{ M}$ ) has shifted the peak of the curve to a shorter muscle length.

In fact, we found that when contractile force was not maximally increased (Table I), isoproterenol, norepinephrine, and calcium caused an increase in diastolic compliance over the entire curve and shifted the peak active isometric force to a shorter muscle length. Higher concentrations of the same agents, which produced a maximal increase in contractility, either failed to shift the peak of the curve or displaced it to the right. This was true particularly when the preparation was maintained at low

temperatures. Under these conditions both isoproterenol and calcium consistently shifted the curve to the right. These results are those which would be expected if the model in Fig. 9 B is an accurate analogue and if a change in diastolic compliance can indeed result either from effects on a force-dependent series viscous element or from changes in compliance of the contractile element due to alterations in residual interaction. The fact that an increase in compliance, even if it is accompanied by a simultaneous increase in the developed systolic force, may shift the peak of the tension-length curve to shorter muscle lengths convinces us that the compliance of the contractile element must be variable. The fact that a marked increase in de-

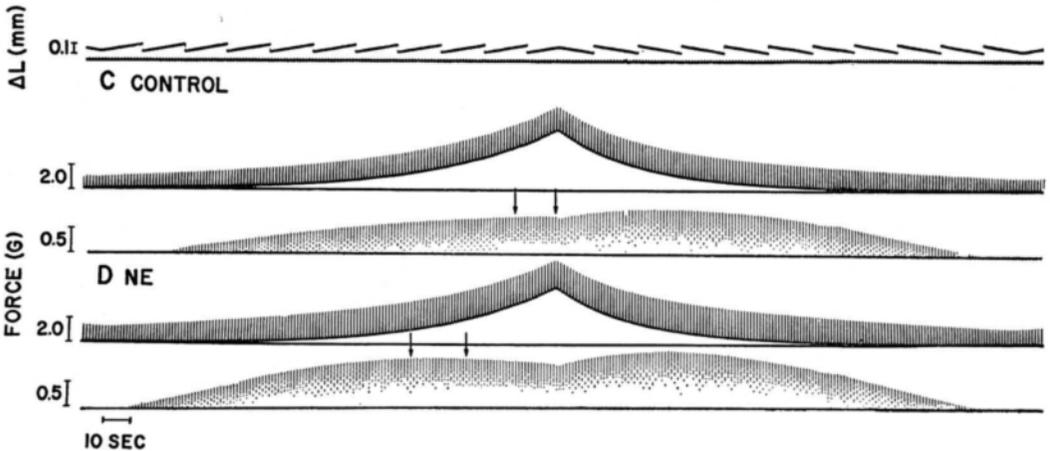


FIGURE 11 *concluded*

C, another control record from the same cat papillary muscle during another lengthening-shortening cycle and single stimulation. All calibrations and displays are the same as in Figs. 11 A and B. Again note that the apex of the length-tension relationship is indicated between the two arrows just above the high sensitivity trace of force. D, shows the same muscle during infusion of norepinephrine ( $1.2 \times 10^{-7}$  M). Note again the marked shift in the apex of the length-tension curve to the left during norepinephrine infusion. Thus, the muscle developed greater force at a shorter muscle length during catecholamine infusion. The increase in compliance (as shown by the decreased diastolic tension) at maximum length is 300 mg.

veloped systolic force shifts the curve in the opposite direction is expected (Fig. 1 D) and does not negate or modify the first conclusion.

Several other characteristics of the records shown in Figs. 10 and 11 appear to support the idea that the compliance of the contractile element may vary. During the shortening half of each cycle end-diastolic tension was less and developed systolic force greater at any muscle length than during lengthening. If one assumes that the increase in compliance, demonstrated by the reduced diastolic tension at each length, has resulted from elongation of a series viscous element, one would expect sarcomere length to be less at each point on the abscissa during shortening than had been the case during lengthening. Obviously, on this basis one would expect developed systolic force to be reduced. Over a wide range of rates of elongation and shortening, we have

found the opposite result. We are forced to conclude that sarcomere length is greater when compliance is greater during the shortening half of the cycle and that therefore the change in compliance cannot be a result solely of elongation of the series viscous element. Further support is provided by experiments in which curves were obtained under control conditions and after exposure of the preparation to agents such as isoproterenol, which increase both diastolic compliance and contractility. The data shown in Fig. 12 were obtained from such an experiment. They clearly show that

TABLE I

Condition		Muscle	Temperature	Rate per min	Peak tension	$L_o - L_R$	Change, diastolic tension †
		mm	°C		g	mm	mg
Control	Ca <sup>++</sup> 2.7 mM	5×0.7	37	60	1.4	0.85	100
Test	Ca <sup>++</sup> 5.4 mM				2.0	0.80	
Control	Ca <sup>++</sup> 2.7 mM	5.2×0.6	36	60	1.2	0.55	80
Test	Ca <sup>++</sup> 5.4 mM				2.2	0.50	
Control		6.5×0.9	30	30	2.6	0.65	250
Test	Isoproterenol (10 <sup>-8</sup> M)				3.8	0.75	
Control	Ca <sup>++</sup> 2.7 mM	7.5×1.0	30	30	0.8	0.90	400
Test	Ca <sup>++</sup> 8.1 mM				1.3	1.00	
Control	Single stimulation	8×0.8	36.5	45	2.3	1.00	900
Test	Paired stimulation				2.6	0.65	
Control		8×0.8	36.5	45	1.8	1.05	300
Test	Norepinephrine (1.2×10 <sup>-7</sup> M)				2.2	0.75	
Control		8×0.8	36.5	45	1.6	1.10	75
Test	Acetylcholine (8×10 <sup>-6</sup> M)				1.85	0.65	
Control	Single stimulation	7.5×1.0	36	45	1.8	0.75	225
Test	Paired stimulation				2.1	0.65	
Control		7.5×1.0	36	45	1.3	0.75	150
Test	Norepinephrine (1.2×10 <sup>-7</sup> M)				1.9	0.64	

\*  $L_o$ , length for maximum force,  $L_R$ , initial length. Data show change in length required to attain peak of length-tension curve (i.e.,  $L_o$ ).

† Change in diastolic tension at maximum length studied.

under the influence of isoproterenol the hysteresis during the shortening half of the cycle is markedly reduced for any muscle length; i.e., end-diastolic tensions are more nearly the same during both lengthening and shortening. Also, developed systolic tension at a given muscle length is nearly the same on both sides of the curve. In terms of the model, these results suggest that isoproterenol directly increases the compliance of the contractile element and for this reason sarcomere length bears a more nearly constant relationship to total muscle length during both elongation and shortening.

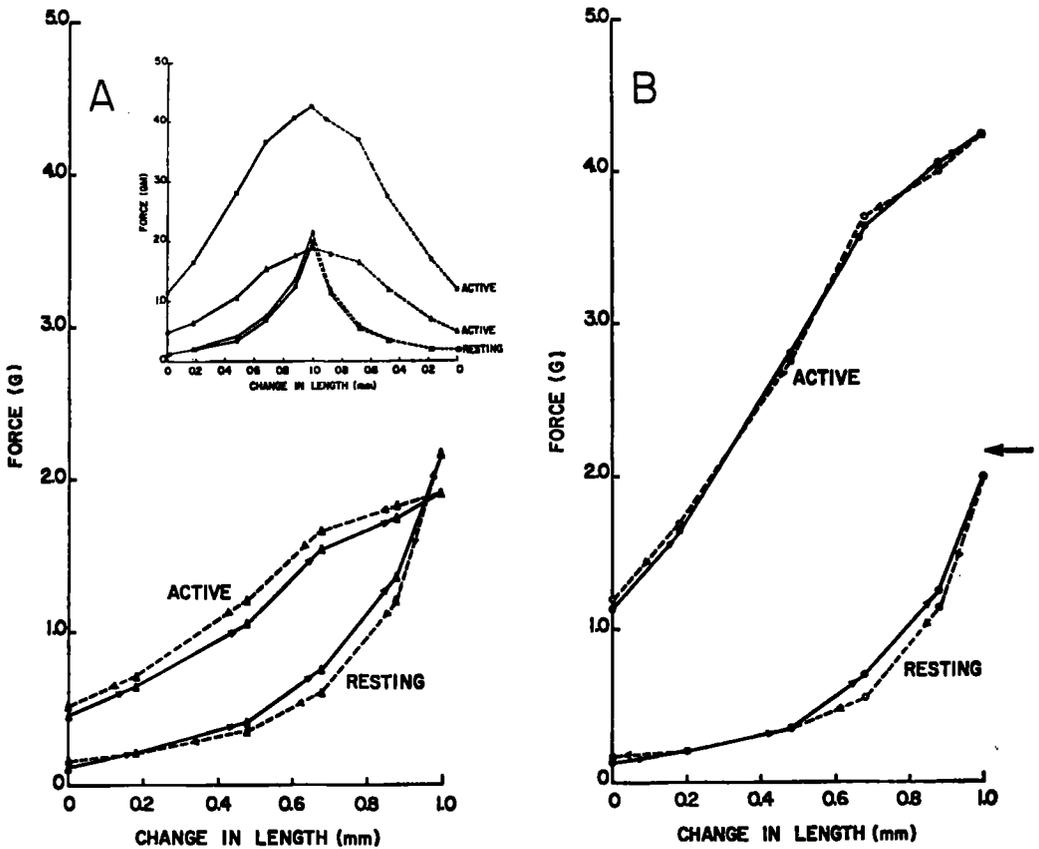


FIGURE 12. A, graph of the changes in active and resting force of a cat papillary muscle during elongation and shortening at a rate of 0.6 mm per min. Filled triangles and solid lines show data obtained during lengthening, open triangles and dashed lines show data obtained during shortening. Arrows on the curves indicate direction of change in length for each curve. Note that during lengthening for any chosen length resting tension is less and active tension is higher over the greater part of the curve. Stimulus rate, 60 per min; temperature, 36°C. Insert shows same data plotted in a manner similar to the records in Fig. 10.

B, similar data obtained from the same muscle during exposure to isoproterenol,  $3 \times 10^{-6}$  M. Filled circles show data obtained during lengthening, open circles show data during shortening. Note that differences between the active tension developed during lengthening and shortening almost have disappeared and that resting tension during shortening still is less than during lengthening. The horizontal arrow shows the resting tension at maximum length in A under control conditions to permit some appreciation of the increase in compliance caused by isoproterenol.

#### DISCUSSION

Grimm and Whitehorn have shown that proteolytic enzymes cause a reduction in both resting and active tension in rat papillary muscle (16). Their finding suggests that some contractile element may be responsible at least partially for resting tension.

Since as much as 30% of total cardiac tension is due to resting tension at the peak of the tension-length curve (21, 35), moderate changes in diastolic compliance are potentially of great significance in the performance of the *in situ* heart. Such changes in the mechanical characteristics of the myocardium during diastole may directly influence ventricular filling, contractility, and cardiac output. In our experiments on isolated cardiac muscles undergoing programmed cyclic length changes, we have shown that inotropic interventions cause very marked reductions in diastolic tension (increased diastolic compliance) when tension-length curves from control and experimental sequences are compared. Of perhaps greater significance is the fact that during interventions which increase diastolic compliance and simultaneously shift the peak of the tension curve to shorter muscle lengths, resting tension, measured at the peak of the curve, may be decreased by as much as 3–4 g. It is of interest to extrapolate this finding for isolated muscle to *in situ*, diseased, "stiff," or failing hearts where such decreases in end-diastolic pressure or tension would profoundly affect ventricular performance.

We have examined the mechanical characteristics of isolated cardiac muscle during diastole in several other papers as well as in this communication (12, 13). We conclude that diastolic compliance (compliance meaning the extent of linear deformation resulting from an applied force acting on the muscle) is variable. Our conclusion is supported by a recent study of Sonnenblick (15) who suggests, however, that changes in diastolic compliance occur as a result of changes in some series viscosity. Our own hypothesis is that changes in diastolic compliance also might result from different degrees of residual interaction in the contractile component of cardiac muscle which would also affect developed force. Such residual interaction might be due to incomplete relaxation from a preceding contraction, from the redevelopment of interaction as seen in aftercontractions (36), or from differing degrees of steady interaction as seen in partial contracture. This residual interaction may be length-dependent; a length-dependent oscillation (changes in tension) in insect fibrillar muscle which is activated by extension and deactivated by shortening has been recently described (37). One may speculate that the large amount of resting tension in cardiac muscle at the peak of the tension-length curve in contrast to skeletal muscle (38), might be due in part to a length-activated interaction in the contractile elements.

The question which we have attempted to answer in this report is whether changes in diastolic compliance result solely from changes in a series viscous element, as postulated by Sonnenblick (15), or whether they also may result from variations in the diastolic compliance of the contractile elements. We have evaluated observed changes in diastolic characteristics in terms of muscle models which contain, in addition to the usual contractile component and parallel and series elastic components, series and parallel viscous components. The results permit certain general conclusions about cardiac muscle which appear to eliminate certain possibilities in the muscle analogues. Elsewhere, we have described experiments utilizing a somewhat different approach to the problems of the basis for variable diastolic compliance (34).

First, our results from experiments on stress-relaxation show that cardiac muscle cannot be described in terms of the three element models. Moreover, they show that there is a viscous element in series with both the parallel elastic and contractile elements. On this basis it is inevitable that there will be at least under some condi-

tions, force-dependent changes in compliance. However, results from experiments on muscles contracting under constant afterload show that the avoidance of change in either resting or active tension may not be sufficient to permit a conclusion concerning the presence or absence of other causes for the variability of diastolic compliance. This is so because relaxation under the same conditions of loading may be changed by the extent of shortening during contraction (34). This finding can be accounted for by placing a second viscous element in parallel with the contractile element. Such an element might be "passive" or might represent a degree of interaction in the contractile element. Our own results indicate that the viscous element in parallel with the contractile element does indeed represent an active property of the contractile element. After an increase in diastolic compliance during gradual elongation of the muscle, maximum active systolic force is developed at a shorter muscle length than prior to the change in compliance. This shift in the peak of the tension-length curve on the length axis is assumed to reflect a change in the relationship between sarcomere length and muscle length; the direction of the shift is opposite to that which would result from the action of increased systolic force on the series viscous element. It is obvious that an increase in diastolic compliance will decrease force exerted on the series viscous element during diastole at any length; however, the means we have employed to increase compliance also cause a sufficient increase in systolic force to more than outweigh this effect. Moreover, with greater increases in contractility the peak of the tension-length curve shifted in the opposite direction, showing that elongation of the series viscous element does have the expected effect.

The means used to increase diastolic compliance also changed the hysteresis observed when muscles were stretched and then allowed to shorten at varying rates. The fact that during shortening diastolic tension was less and active systolic force greater than the values recorded at the same length during extension is not what our model would predict if the change were due to the effect of increased diastolic and peak tension on a series viscous element. Rather, the observation suggests that gradual elongation of the muscle increased the compliance of the contractile element so that during shortening the sarcomeres were longer at any muscle length than had been the case during elongation. One might assume here that, as the muscle was stretched, internal shortening during the isometric contractions was reduced and thus relaxation was more complete. Since agents which increased diastolic compliance diminished this hysteresis, it is tempting to assume that they changed the compliance of the contractile element and thus permitted a better correlation between muscle length and sarcomere length during elongation.

Some comment on the adequacy of the preparation is appropriate. Some years ago (39) it was shown that at temperatures similar to those we have employed, oxygenation of quiescent cat papillary muscle was adequate only if the diameter of the muscle was considerably less than 1.0 mm. The same studies suggested that the maximal permissible diameter for muscle contracting at a rate of 30–60 per min was less than 0.5 mm. More recently studies relating maximal isometric force to cross-sectional area (40) have suggested a similar maximal diameter. Many of the muscles we have used have exceeded these limits; the actual range of diameters has been 0.35 to 1.0 mm. These figures are somewhat misleading since most trabeculae and many papillary muscles are ovoid in cross-section. Nevertheless, it may be true that for some muscles

under some of the test conditions, the core was anoxic and not adequately perfused. Thus, some of the changes in compliance we have observed may reflect such conditions. Indeed, it is intriguing to speculate on possible relationships between changes in the heart produced by ischemia, hypoxia, drugs or disease, and changes in diastolic compliance. Regardless of the conditions primarily responsible for the changes in diastolic compliance, we believe that such changes are real and, moreover, that they do not result only from alterations in forces acting on purely passive elements.

Finally, comment seems indicated on the experiments designed to test whether or not changes in compliance were associated with a shift in the relationship between muscle length and peak active force. The experiments in which PS was used to change compliance gave results which were quite consistent; however, we recognize that they may not be perfectly reliable since the increase in contractility caused by PS might have changed during the period of elongation. It is clear that a decrease in contractility during maintained PS would cause a spurious shift in the peak of the active tension curve. However, when an increase in calcium ion concentration or a catecholamine was used to change contractility and compliance this problem did not arise since the positive inotropic effect of either was constant for a period much longer than the time required to inscribe the curve relating active tension to length. The results obtained with positive inotropic interventions other than PS strongly suggest that the results obtained during PS were not due to the artifact mentioned above.

#### SUMMARY

Isolated preparations of mammalian myocardium have been used to study possible mechanisms responsible for changes in diastolic compliance. Muscles have been studied at rest and during isometric and afterloaded contractions, at fixed initial length and during programmed cyclic changes in length, and under the influence of paired stimulation, catecholamines, and elevated extracellular calcium concentrations. The results obtained indicate that, although there is a series viscous element in cardiac muscle, which accounts for stress-relaxation, some changes in compliance apparently result from alterations in the extensibility of the contractile element. This conclusion is based primarily on experiments showing shifts in the apex of the length-tension curve produced by action of inotropic agents which alter diastolic compliance and on experiments showing that the rate and extent of relaxation of afterloaded contractions depend on the extent of shortening during contraction.

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# Effect of Systolic Activity on Diastolic Compliance of Isolated Myocardium

JAN KOCH-WESER

From the Department of Pharmacology, Harvard Medical School, Boston, Massachusetts 02115

Changes in diastolic length-tension or pressure-volume relationships of heart muscle have been demonstrated by many workers under manifold experimental conditions. It is not their occurrence that is now being debated but their significance and underlying mechanisms. Some hold the view that none of the changes in diastolic compliance so far observed force us to abandon the concept that the contractile element of heart muscle is freely extensible in the resting state (1-4). In the other view the findings suggest a variable "diastolic contractile tone" (5, 6) or raise the possibility that resting tension is not born by the passive elastic, viscous, and plastic elements alone (7, 8). The essential question thus becomes whether all observed changes in diastolic compliance can be explained without recourse to the theory of resting interaction of the contractile filaments.

Diastolic compliance of heart muscle may be altered in a number of ways secondary to events during systole. These changes simply demonstrate that following a contraction return of the myocardium to its true resting state is gradual and may not be fully accomplished during the entire diastolic phase. While such systole-induced changes in diastolic compliance are quite real and may be physiologically important, they must be distinguished from true changes in resting compliance and have very different implications for the question of "diastolic tone" of heart muscle. Some systole-related changes in diastolic compliance are not physiologic and are encountered only under certain experimental conditions. Others result from the fundamental mechanical properties of heart muscle and are therefore universal. A tentative classification of changes in diastolic compliance or extensibility of heart muscle is proposed in Table I.

Spurious changes in diastolic compliance may be due to a number of factors. In the intact heart changes in the geometry of the cardiac chambers can alter the relation of diastolic pressure to any cardiac dimension measured (1). Such alterations need not reflect real changes in myocardial resting extensibility. Numerous experimental artifacts such as inertia of recording levers, compliance and drift of recording systems, slippage of attachments to isolated heart muscle, and leakage or transudation from cardiac chambers can simulate changes in diastolic extensibility (1). The scrupulous avoidance or taking into account of such artifacts is all the more important because actual changes in diastolic compliance are invariably small in comparison to resting length or tension. In fact, most changes in diastolic extensibility are certainly smaller than the methodological error of some techniques used in their study, particularly those employing intact cardiac chambers.

When isolated heart muscle is used in the study of the resting length-tension relationship, changes in diastolic compliance are commonly due to one or two unphysiologic developments: hypoxic rigor or aftercontractions. In the preparations most commonly studied oxygen and metabolic substrates must diffuse into the muscle from its surface (1, 9). If the diffusion distance to the central fibers is excessive, these become depleted of high energy phosphate compounds, their contractility declines, and their extensibility decreases, i.e. rigor (contracture) appears (1). Development of rigor in any load-bearing part of the preparation must invariably change compliance of the entire muscle. If the preparation is so thick that its central fibers are hypoxic at rest, compliance tends to decrease progressively and no meaningful resting length-tension relationship can be obtained. Even if adequate oxygenation of all fibers is achieved at rest, the increased oxygen consumption which accompanies most positive inotropic interventions can lead to central hypoxia and partial rigor of the preparation. A positive inotropic response of the whole preparation by no means rules out increasing

TABLE I  
CHANGES IN MYOCARDIAL DIASTOLIC COMPLIANCE

- 
- A. Spurious changes
    - 1. Distortion of cardiac chambers
    - 2. Experimental artefacts
  - B. Changes related to systolic activity
    - 1. Unphysiological
      - a. rigor (contracture)
      - b. aftercontractions
    - 2. Physiological
      - a. fusion of contractions
      - b. stress relaxation
        - (1) magnitude of systolic tension
        - (2) duration of systolic tension
  - C. Changes in resting compliance
- 

hypoxia, decreasing contractility, and decreasing diastolic extensibility of the innermost fibers (10). In this way increases in magnitude or duration of systolic tension development or shortening can cause decreases in diastolic compliance which are entirely dependent on systolic activity. Correspondingly, decreases in contraction frequency or other factors which decrease systolic activity and oxygen consumption of the preparation can increase diastolic extensibility by decreasing hypoxic rigor of the inner fibers. Many reports of changes in the resting length-tension relationship of heart muscle have been based on findings in excessively thick preparations of isolated myocardium. Following various inotropic interventions we have frequently observed rigor-mediated changes of diastolic compliance in isolated heart muscle which was either too thick or perfused by solutions of reduced oxygen tension. No such oxygen consumption-dependent changes were ever seen in well-oxygenated thin muscles (less than 0.4 mm<sup>2</sup> cross-sectional area) stimulated at low frequencies of contraction.

Aftercontractions, small and slow contractions which follow normal contractions and do not result from propagated action potentials, have so far been clearly observed only in isolated myocardium (3, 11, 12). However, their occurrence in such preparations is so predictable that they may well reflect a fundamental property of heart

muscle. It would not be surprising if sufficiently sensitive techniques could demonstrate aftercontractions in the intact heart. In isolated heart muscle we have found the appearance and amplitude of aftercontractions to be favored by hypothermia, by high frequencies of contraction (frequency potentiation), by paired stimulation (prematurity potentiation), by increased calcium concentrations, by lowered sodium concentrations, by moderate increases in osmotic pressure, by cardiac glycosides, by sympathomimetic amines with beta-adrenergic activity, by xanthines, by angiotensin, and particularly by combinations of the above. In short, it appears that practically any factor which increases myocardial contractility may also elicit the appearance of aftercontractions. Aftercontractions may last as long as 10 sec at physiologic temperatures and considerably longer under hypothermic conditions. The great importance of aftercontractions in studies of diastolic compliance in isolated heart muscle has recently been emphasized (3). It is obvious that the appearance of aftercontractions or an increase in their amplitude can decrease myocardial extensibility during all or part of diastole. Decreases of aftercontraction amplitude will have the opposite effect. Furthermore, compliance during diastole may change simply because of variations in the timing of normal contraction and aftercontraction. Aftercontractions can be avoided in studies of true resting compliance by maintaining preparations at normothermia and by choosing low frequencies of contraction. Under such conditions only the most intense positive inotropic interventions ever cause aftercontractions.

Two other changes in diastolic compliance which are related to systolic activity are seen in intact hearts as well as in isolated heart muscle: fusion of contractions and stress relaxation. Relaxation of heart muscle normally proceeds too slowly to become complete at high heart rates (10, 13). According to the usual usage of the term, diastole still occurs under such circumstances, but true resting compliance is never achieved. In the cat papillary muscle at 38°C relaxation becomes incomplete at about 180 beats per min (10). After sudden increases in the frequency of contraction transient systolic fusion occurs at much lower frequencies. As the temperature of the muscle is lowered fusion begins at progressively lower frequencies of contraction (1). Whenever the frequency of contraction is too high to allow complete diastolic relaxation, any intervention which merely alters heart rate or duration of contraction (i.e. which has purely systolic effects) will change compliance during the entire diastolic period. Depending on their direction such changes in systolic activity may either increase or decrease the greatest compliance achieved between systoles. If the change in duration of contraction is large, it may influence maximum diastolic compliance at surprisingly low frequencies of contraction. Clearly, such changes have no bearing on true resting compliance of heart muscle and should be avoided in studies of this problem.

The final type of change in diastolic extensibility which is related to systolic activity is stress relaxation (1-3, 7). This is not seen in isotonic or isobarically contracting muscle but is often quantitatively very prominent after isometric or isochoric contractions. Stress relaxation is undoubtedly important in the function of the normal heart. It may also contribute to ventricular dilatation secondary to chronically increased resistance to ventricular emptying. It may even play a role in the gradual, secondary decline in left ventricular end-diastolic pressure seen after sudden increases in the resistance to the ventricular ejection, the "Anrep effect" (1, 14).

We have studied changes in diastolic compliance due to stress relaxation in iso-

metrically contracting kitten papillary muscles. Experimental details have been previously described (15). Only right ventricular papillary muscles less than 0.4 mm<sup>2</sup> in cross-sectional area were used and were maintained at 38°C. They were stimulated with rectangular constant current pulses of amplitude no more than 10% above threshold at frequencies of 12–60 per min. Muscle length was set by a vernier micrometer device accurate to 10  $\mu$ . Resting and active tensions were measured by force transducers. Similar experiments with identical results were also performed with isochorically contracting sac preparations of kitten atria (16).

The properties of resting heart muscle suggest that it contains not only prominent parallel and series elastic elements but also viscous and plastic elements (1, 7, 17). If the load on a preparation of heart muscle is suddenly increased, the muscle lengthens immediately, then extends more gradually for several minutes. This slow yielding is

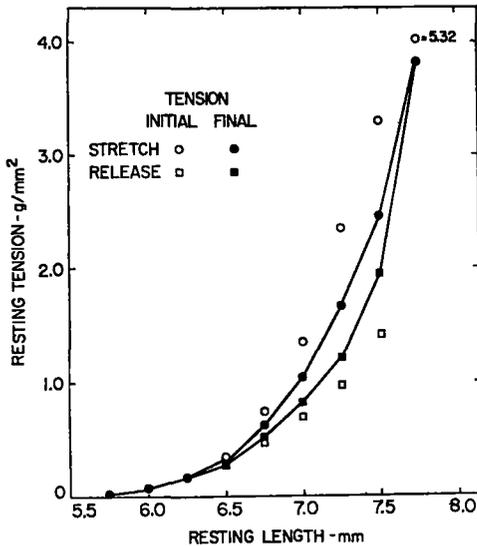


FIGURE 1. Stress relaxation (poststretch relaxation and postrelease tightening) in resting kitten papillary muscle. Resting tension was determined immediately after lengthening or shortening of the muscle and after tension had become stable.

called "creep." Correspondingly, when the muscle is suddenly extended to a fixed length, tension rises abruptly, then decays gradually to a level considerably below the maximum tension achieved immediately after the stretch. While usually labeled "stress relaxation" this phenomenon could be more accurately described as "poststretch relaxation." The opposite effect is seen when a stretched muscle is suddenly partially released. Tension drops abruptly, then gradually rises to a level appreciably higher than that found right after the release. This might be described as "postrelease tightening." These changes are of considerable magnitude (Fig. 1) and may amount to almost 50% of the final tension. Poststretch relaxation is always more prominent than postrelease tightening. At high resting tensions such slow changes in resting length or tension may be detectable for up to 10 min, but their half-time is a matter of a few seconds.

Fig. 1 also shows that even if sufficient time is allowed for the slow changes to run their full course, tension at a given length is greater if the length is approached by

stretching rather than by releasing. In other words, the resting length-tension relationship of heart muscle shows hysteresis. If high resting lengths are avoided, hysteresis is reversible. Resting lengths considerably in excess of those associated with maximum tension development produce irreversible plastic changes in the length-tension relationship of papillary muscles, in the direction of less tension at a given length. Some of these plastic changes may not occur in the muscle proper but rather in its tendon or in its connections with the recording devices.

Stress relaxation is also seen after active tension development and is perhaps quantitatively the most important mechanism by which systolic activity can alter subsequent diastolic compliance of heart muscle. Development of sufficient active tension during isometric or isochoric contractions invariably produces transient increases in diastolic extensibility. This implies that the viscous or damped elastic

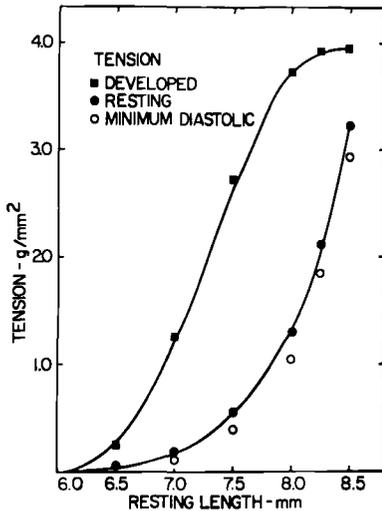


FIGURE 2. Stress relaxation (difference between resting and minimum diastolic tension) due to systolic tension development at seven resting lengths. Kitten papillary muscle, contraction frequency 60 per min.

elements responsible for this type of stress relaxation are in series with the contractile element. Fig. 2 shows such postsystolic stretch relaxation in an isometrically contracting cat papillary muscle. It is clear that the magnitude of the decrease in diastolic tension at a given length is directly proportional to the amount of tension developed during the preceding systoles.

After the onset of active systolic tension development maximum diastolic compliance increases gradually after each of the first 5 to 10 systoles. Once a steady state has been reached the magnitude of stress relaxation due to active tension development is always less than that following a similar degree of sustained passive stretch (Figs. 1 and 2). Upon cessation of contractions diastolic extensibility decreases gradually in an asymptotic fashion toward the resting level. The time required to reestablish the resting length-tension relationship increases with the magnitude of the preceding stress relaxation (and therefore with the intensity of systolic tension development). Even so, we have never found reversal of postsystolic stretch relaxation to require more than 1 min. Reversal of stress relaxation (postrelease tightening) after active systolic tension

development thus appears to proceed more rapidly than after release of a passive stretch.

In heart muscle contracting vigorously and isometrically at usual frequencies some decrease of diastolic compliance toward the resting level occurs during each diastole. However, only at very low frequencies of contraction is the interval between periods of active tension development long enough to allow end-diastolic extensibility to drop

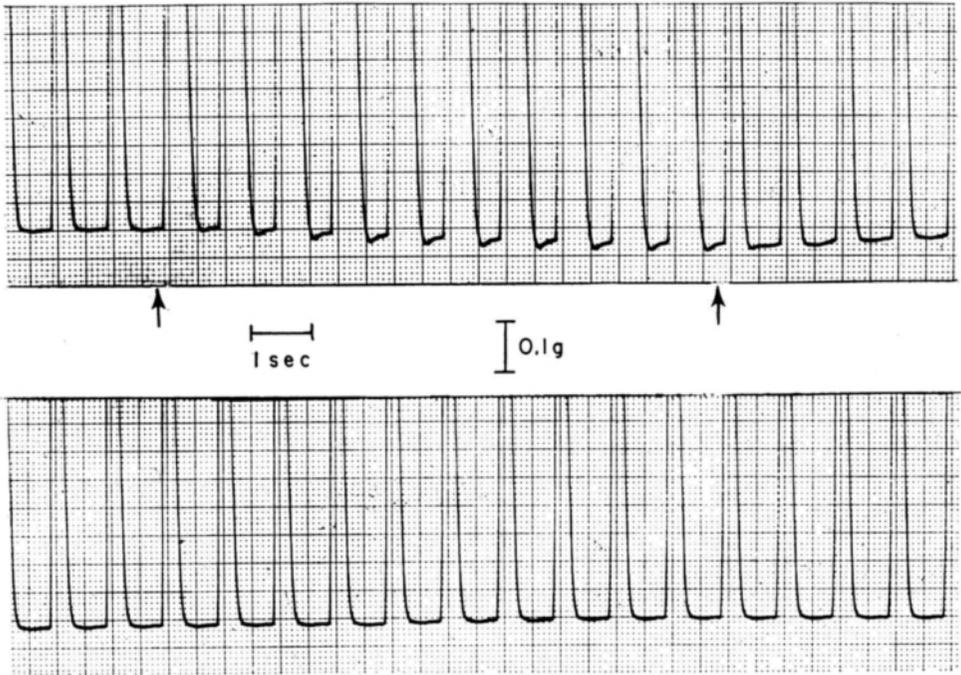


FIGURE 3. Decrease in diastolic tension at fixed length during paired stimulation. Continuous record, only lowest third of isometric mechanogram shown. Basal frequency 60 beats per min, between arrows an extra stimulus was placed 250 msec after each regular contraction. This resulted in a 140% increase in tension developed during regular contractions. Resting tension 300 mg. Note considerably greater decrease in proto-diastolic than in end-diastolic tension during paired stimulation.

to the level of true resting extensibility. A very clear distinction must be made between diastolic and resting compliance. Diastolic extensibility approaches resting extensibility throughout diastole but often does not fully reach it. The failure of heart muscle to reach a true resting state unless diastole is quite long is firmly established for other myocardial functions. The strength of systole becomes independent of previous contractions only after intervals far longer than usual diastoles (13).

Several workers have stressed increases in diastolic compliance of isometrically contracting heart muscle during paired stimulation (2, 8, 15, 18) (Fig. 3). Since such stimulation leads to increased systolic tension development, it would be expected to augment stress relaxation. However, slight decreases in diastolic tension at fixed mus-

cle length have been observed even before the first potentiated contraction (14, 18). In our experience this is seen only after isometric beats when summation of tension development or significant prolongation of contraction occurs with the first premature activation. Thus, this phenomenon may also be due to stress relaxation. Increases in the diastolic compliance of isometrically contracting myocardium during paired stimulation are quite prominent because high systolic tensions are developed even at low frequencies of contraction and because the duration of tension development is

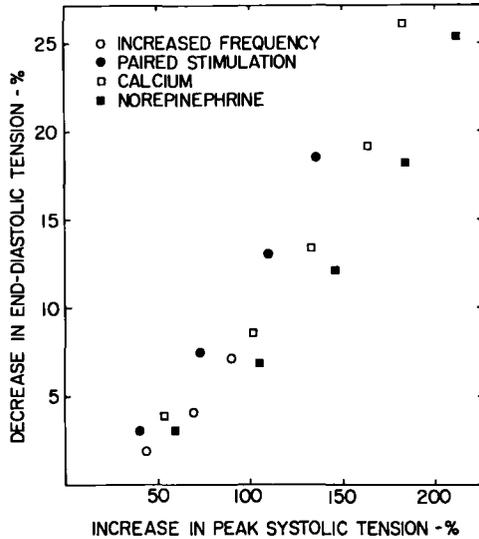


FIGURE 4. Relationship between increases in active tension produced by four inotropic interventions and increases in end-diastolic compliance. Abscissa, increase in peak developed tension over control; ordinate, decrease from control of steady-state end-diastolic tension at fixed length. Each symbol represents mean of values from 6 to 11 kitten papillary muscles. Mean muscle length, 5.4 mm; mean control resting tension, 0.63 g per  $\text{mm}^2$ ; mean control developed tension, 1.4 g  $\text{mm}^2$ .

increased as well. Nevertheless, such compliance changes do not appear to be qualitatively different from stress relaxation which occurs when systolic activity is increased by other positive inotropic influences.

As shown in Fig. 2, stress relaxation increases with active systolic tension development even in the absence of a change in myocardial contractility. Furthermore, after positive inotropic interventions the increase in diastolic compliance due to stress relaxation is proportional to the increase in systolic tension development but largely independent of the nature of the inotropic influence (Fig. 4). A given increase in systolic tension development leads to approximately the same decrease in end-diastolic tension at fixed length regardless of whether the inotropic influence is paired stimulation, an increase in external calcium concentration, or norepinephrine. Increases of diastolic compliance during frequency potentiation are relatively small and more difficult to observe because at the rapid frequencies of contraction required to obtain high systolic tensions some degree of systolic fusion usually occurs.

The increase in end-diastolic compliance after addition of norepinephrine appears to be slightly less than during paired stimulation or during exposure to increased calcium concentrations which raise systolic tension development to the same extent (Fig. 4). This may well be due to the abbreviation of tension development by norepinephrine (19, 20) and to its prolongation during paired stimulation (15). At any given peak systolic tension the total area under the developed tension curve will be smallest under the influence of norepinephrine, greater after addition of calcium, and greatest during paired stimulation. Comparison of the changes in end-diastolic compliance after these interventions thus offers further evidence that both the peak developed tension and the duration of tension development determine the degree of stress relaxation. In contrast to end-diastolic compliance, maximum diastolic compliance which occurs immediately after systole is greater during norepinephrine inotropism than during the same degree of calcium inotropism. Immediately following a systole potentiated and abbreviated by norepinephrine, epinephrine, or isoproterenol there is a distinct dip in diastolic tension at fixed length. This again may result from the more rapid relaxation of the contractile element under the influence of norepinephrine. Accelerated decay of systolic tension shortens the time available during relaxation for postrelease tightening of the damped elastic element.

It is apparent that events during systole can alter diastolic compliance throughout diastole by several mechanisms. Intervals of a minute or more between contractions may be required to dissipate the influence of preceding systolic activity on diastolic extensibility. Only at such low frequencies does end-diastolic extensibility become synonymous with true resting extensibility. Demonstrable changes in diastolic compliance can be accepted as changes in resting compliance only if any role of systole-dependent factors such as rigor, aftercontractions, fusion of contractions, and stress relaxation can be ruled out. In fact, it seems reasonable to require that true changes in resting compliance should be demonstrable in resting heart muscle. Only compliance changes unrelated to systolic activity require the postulation of interaction between contractile filaments in the resting state. We have so far been able to detect such changes only during exposure of heart muscle to contracture-producing concentrations of calcium, cardiac glycosides, and veratrum alkaloids.

#### SUMMARY

Changes in diastolic compliance are frequently observed in isolated heart muscle preparations and can be demonstrated in the intact heart. Most or all such changes are secondary consequences of variations in systolic activity. Hypoxic rigor, aftercontractions, incomplete diastolic relaxation, and stress relaxation are modified by inotropic interventions and in turn alter diastolic compliance. Stress relaxation appreciably alters diastolic compliance after any contraction during which significant active tension is developed. The degree of change in diastolic extensibility due to stress relaxation following an inotropic intervention is directly proportional to the amount of inotropism (change in magnitude and duration of active tension development) but is independent of the nature of the intervention.

The length-tension relation of heart muscle becomes stable during diastole only at

low frequencies of contraction. Diastolic compliance and true resting compliance must be clearly distinguished. Changes in diastolic compliance which are secondary to changes in systolic activity are not changes in resting extensibility.

Genuine changes in the resting length-tension relationship are not dependent on events during preceding systoles. They should be detectable in isometrically and isotonicly contracting and in resting heart muscle. No such changes have appeared in our experiments with isolated heart muscle except during drug-induced contractions.

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## DISCUSSION

After listening to today's presentations it seems to me that there is substantial agreement among most speakers. Apparently all of us have now observed changes in the extensibility of heart muscle during diastole under varied experimental conditions. Of the two major areas of persistent disagreement one seems largely semantic, the other is substantive.

Terminology in the area of myocardial compliance has become increasingly confused. Changes in compliance of inactive heart muscle are described as diastolic, resting, real, apparent, unreal, false, physiologic, or unphysiologic. Some of us describe alterations in compliance during the intersystolic periods due to aftercontractions or stress relaxation as changes in diastolic compliance. Others are unwilling to dignify such phenomena with this title or at least stress that they are only "apparent" changes and not "real." It would seem logical to describe any change in compliance which occurs during diastole as a change in diastolic compliance. If known, its mechanism can then be further specified. If a change in compliance occurs, it is real regardless of its mechanism.

Diastole is not a clearly demarcated period, its end and particularly its beginning are difficult to establish precisely except in hemodynamic, valvular terms. Nevertheless, during what clearly is diastole the compliance of heart muscle is frequently not stable because its course is significantly influenced by events during preceding systoles. Heart muscle during diastole is not necessarily in a true resting state. This is fully recognized for other myocardial functions as in the influence of preceding activations on the strength of systolic contraction. The term "resting compliance" should refer specifically to the length-tension relationship of heart muscle which is not under the influence of preceding systoles. Agreement on such use of the terms diastolic compliance and resting compliance would remove present disagreements in this area which are merely semantic.

The second area of debate is important and factual. Most of us have been unable to observe changes in diastolic length-tension or pressure-volume relationships which could not be explained on the basis of variations in aftercontractions, stress relaxation, fusion of systoles, or anoxia of parts of the preparations. The Columbia group, on the other hand, is able to observe such changes with great regularity under the influence of many factors. They are even proceeding to the classification of such changes. No ready explanation for these opposing experimental results presents itself. It seems highly unlikely that these differences can be explained simply by differences in the sensitivity of recording equipment. One question of considerable interest would be whether Dr. Hoffman's group can observe changes in compliance of resting heart muscle. Demonstration of changes in the myocardial length-tension relationship due to inotropic agents in the absence of contractions would go far to convince those who cling to the concept of free extensibility of the resting contractile element. We have observed marked decreases in compliance of heart muscle exposed to cardiac glycosides or to calcium during periods of complete inactivity. Such changes represent only the well-known phenomenon of drug-induced contracture.

# Effects of Paired Stimulation on Cardiac Muscle during Diastole

ERIC O. FEIGL

From the Department of Physiology, The School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104

A primary determinant of cardiac function is ventricular filling. Since the ventricle is filled during diastole a knowledge of diastolic events is important to the understanding of cardiac function. When the action of the atria and cardiac valves is excluded, the important variables for ventricular filling are the filling pressure, the duration of diastole, ventricular geometry, and the mechanical properties of the diastolic ventricle. The effects of paired electrical stimulation on the mechanical properties of resting cardiac muscle were examined in this study. It was found that aftercontractions were elicited by paired electrical stimulation.

Aftercontractions are spontaneous contractions of cardiac muscle which occur without a propagated action potential (1-3). Aftercontractions are most pronounced at reduced temperatures, in the presence of high calcium, and when the beat frequency is rapid (1-4). Typically aftercontractions follow regular driven beats resulting from a propagated action potential. In the absence of regular driven beats, spontaneous aftercontractions are not maintained. To date aftercontractions have been observed only in isolated cardiac muscle in a bath of physiological salt solution, usually at temperatures below 37°C.

In the present study, the length-tension relationship of diastolic muscle was altered by aftercontractions elicited by paired stimulation at 22°C. In the absence of aftercontractions at 37°C, paired stimulation did not alter the diastolic myocardium except to lengthen the systolic period and thus shorten the diastolic period at a constant beat frequency.

## METHODS

The methods have been described in detail elsewhere (5). Briefly, cats and kittens were anesthetized with pentobarbital 25 mg/kg intraperitoneally. Papillary muscles were quickly excised from the right ventricle and placed in physiological salt solution. Experiments were done at 22° and 37°C. The muscle was stimulated through the bath with platinum electrodes that ran the length of the muscle but did not touch it. The muscle was so arranged that muscle force and shortening could be measured simultaneously. The lower end of the muscle was held in a special spring clamp which was part of the force transducer. The upper end of the muscle was attached to an isotonic lever with a length of straightened stainless steel wire. With this arrangement the muscle could be studied under true isotonic, isotonic afterloaded, and isometric conditions by simply adjusting the load and a moveable lever stop. An operational amplifier

(Philbrick) was used to obtain shortening velocity from the length signal. Recording was on an oscillograph (Brush 1707, Brush Instruments, Cleveland, Ohio).

## RESULTS

At 22°C, with a bath  $\text{Ca}^{++}$  of 2.5 mM/liter, and slow stimulation rates, many papillary muscles do not exhibit aftercontractions. If paired stimulation is begun under these conditions, aftercontractions during diastole will often be elicited by the paired stimulation. In a constantly loaded isotonic preparation this will result in a shortening of the diastolic length. This effect as well as systolic potentiation is illustrated in the experiment shown in Fig. 1. Directly after the first paired electrical stimulation an after-

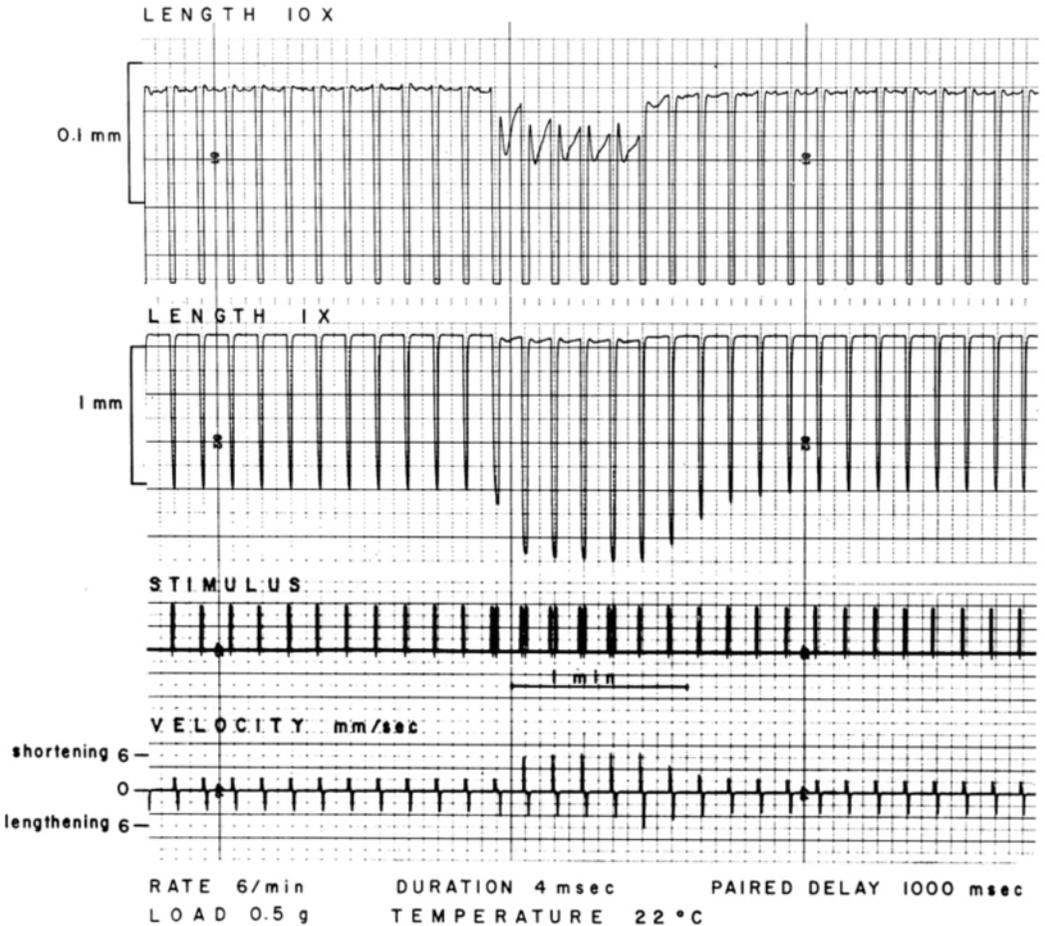


FIGURE 1. Isotonic contractions, shortening downward. Length shown at two recording gains. The high gain record shows the diastolic portion of the record. Paired stimulation (see stimulus record) resulted in potentiation of the systolic (stimulated) beat and the appearance of spontaneous aftercontractions in the diastolic period.

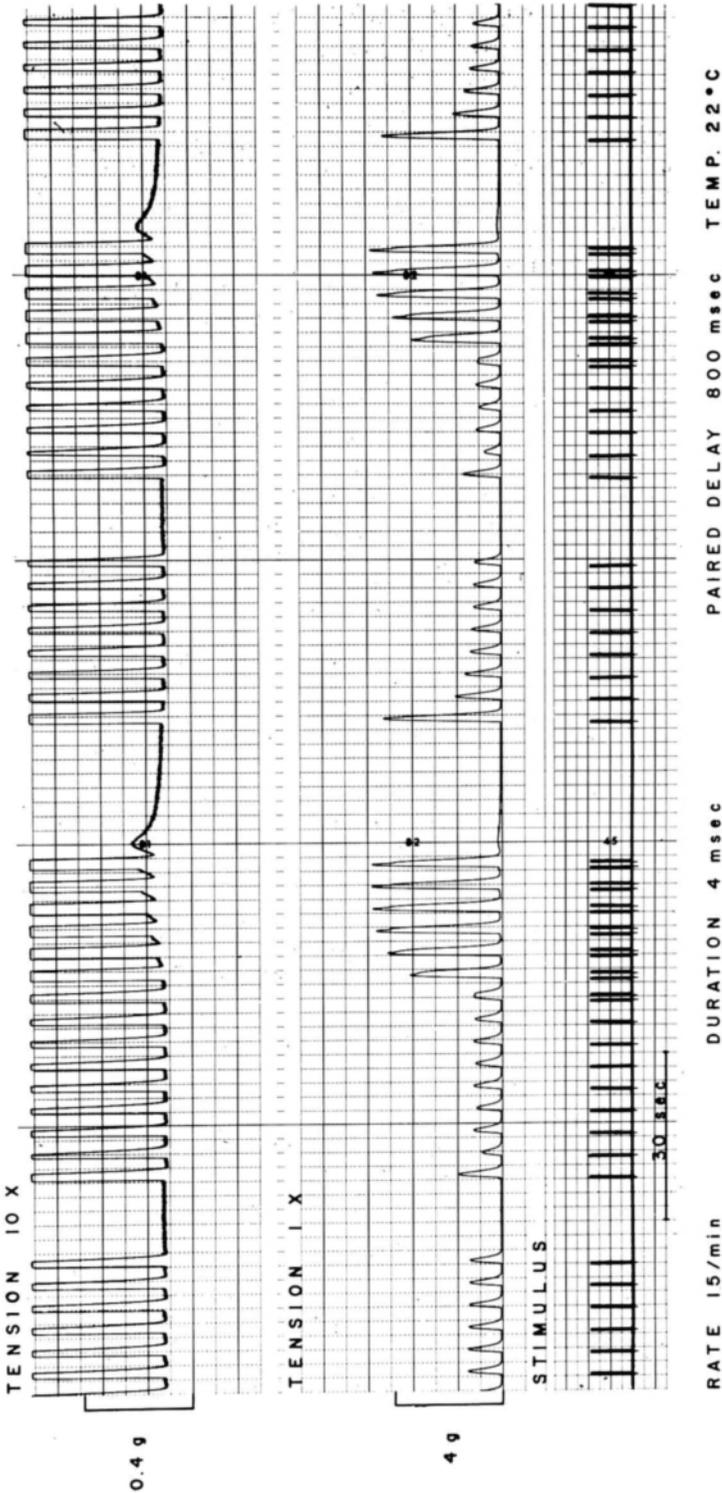


FIGURE 2. Isometric contractions shown at two recording gains, increasing tension upward. From left to right regular (single) stimulation is interrupted—no aftercontractions were observed. Paired stimulation resulted in potentiation and an increase in diastolic tension. The increased diastolic tension was shown to be due to after-

contractions which were evident only when paired stimulation was interrupted. The third interruption is after single stimulation and the fourth after paired stimulation. Without the interruptions the diastolic changes accompanying paired stimulation could not have been recognized as aftercontractions.

contraction was observed during the diastolic period. Such diastolic shortening means that the subsequent beat begins from a shorter length.

The same effect was also observed under isometric conditions at 22°C and is illustrated in Fig. 2. Under regular stimulation at slow rates, aftercontractions were not present. When a train of regular single stimuli was interrupted a steady level of diastolic isometric tension was observed. When paired stimulation was initiated the diastolic tension increased. This increased diastolic tension was due to aftercontrac-

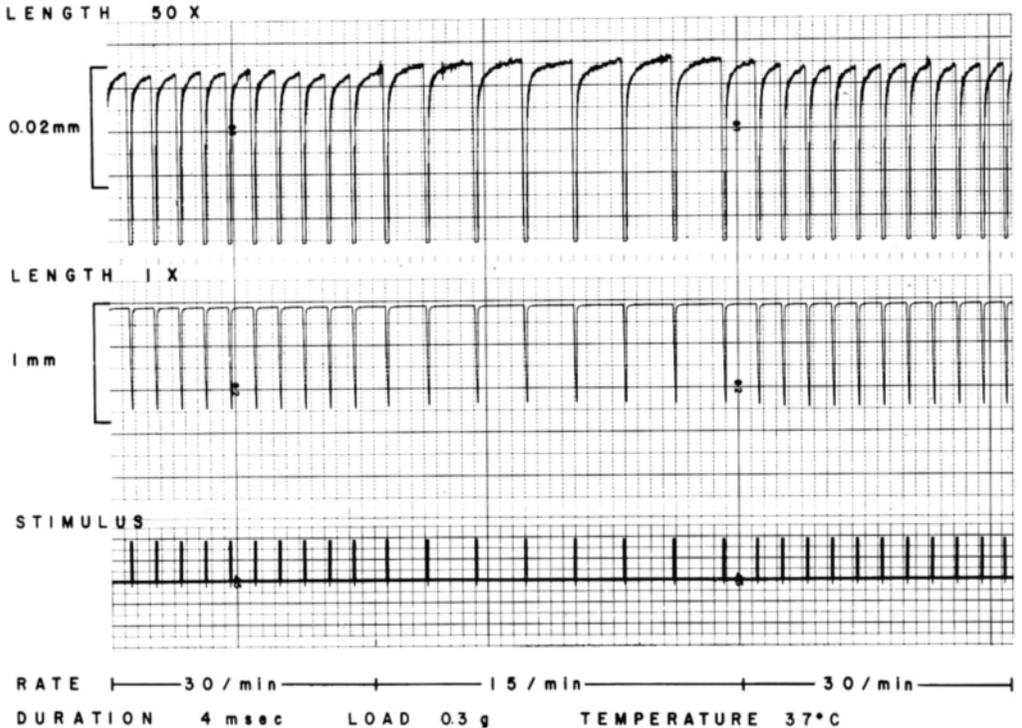


FIGURE 3. True isotonic contractions (no muscle stop, no afterload), shortening downward. When diastole was prolonged by decreasing the stimulation frequency from 30 per min to 15 per min, end-diastolic length increased because of viscoelastic creep.

tions. The aftercontraction was clearly demonstrated by turning off the stimulator as shown in Fig. 2. Note how difficult it would be to recognize the change in diastolic tension as an aftercontraction if the stimulator had not been turned off.

Muscles studied at 37°C with a bath  $\text{Ca}^{++}$  of 2.5 mM/liter did not exhibit aftercontractions. Under true isotonic conditions (no preload stop—no additional afterload) end-diastolic muscle length was dependent on the duration of diastole. This is illustrated in Fig. 3. Muscle is viscoelastic, and under constant load creeps to a longer length with time. The longer the diastolic period, the longer was end-diastolic length.

Paired stimulation at 37°C with 2.5 mM/liter  $\text{Ca}^{++}$  did not elicit aftercontractions. When paired stimulation was added without altering the previous beat frequency,

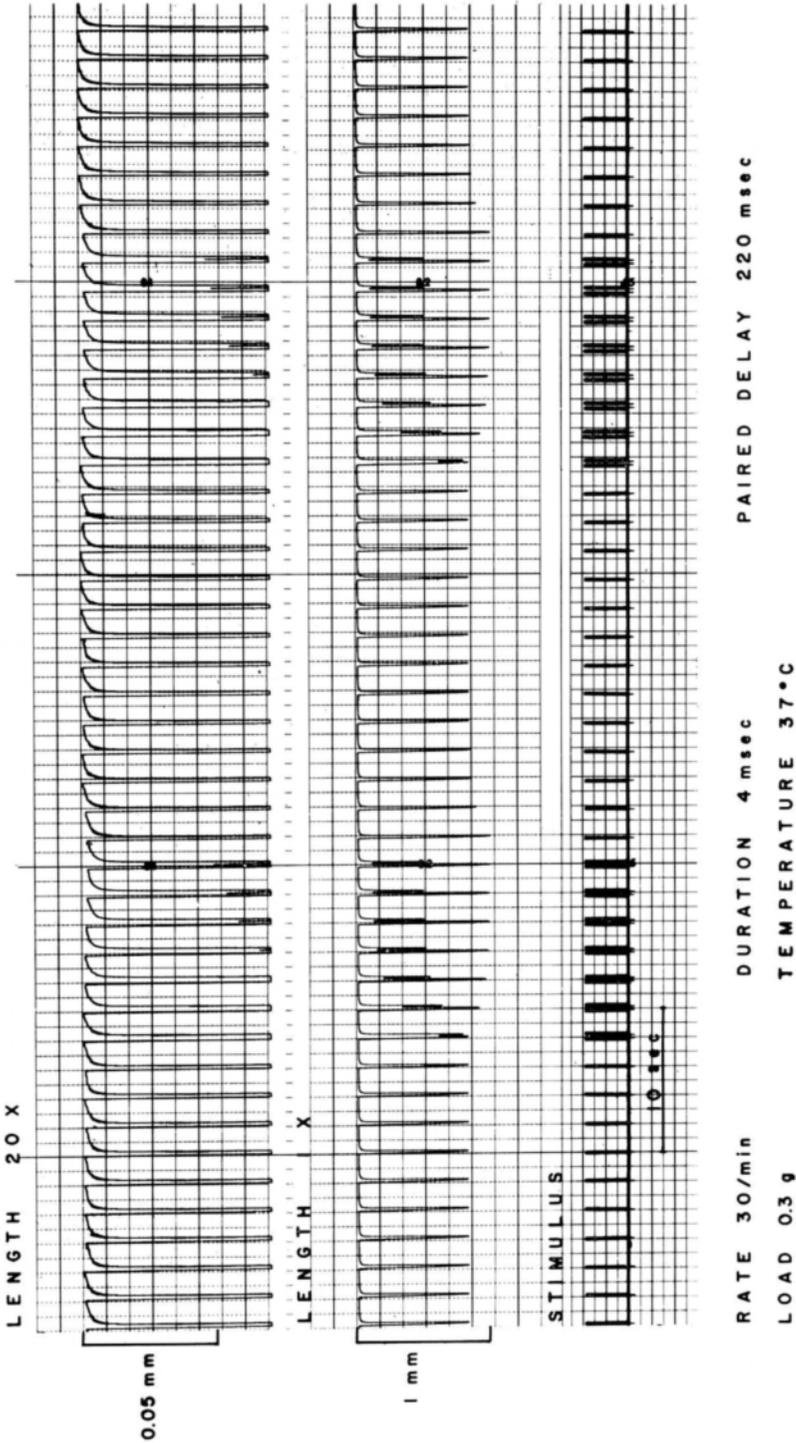


FIGURE 4. Isotonic contractions recorded at high and low gain, slightly shortened because of the prolonged systole with paired stimulation. Two periods of paired stimulation (see stimulus record) showed systolic potentiation. The diastolic period was observed except the abbreviated diastolic period.

the diastolic interval was shortened since paired stimulation prolonged systole. Under true isotonic conditions paired stimulation resulted in a slightly shortened end-diastolic length because the diastolic period was shorter. This effect is illustrated in Fig. 4 where two series of paired stimulations are shown. No evidence was found to support the view that paired stimulation has a direct effect on diastolic extensibility.

## DISCUSSION

Koch-Weser (6), Sonnenblick et al. (7), and Gilmore et al. (8) have used the term compliance to describe viscoelastic behavior in resting cardiac muscle. Since compliance has been used by these authors to include the effects of stress relaxation, it is practical to continue to use the term in this manner. It should be emphasized that stress relaxation and creep occur without a change in the viscosity or elasticity of the tissue. If a viscoelastic material creeps out to a longer length under a constant load, it manifests a different load vs. length relationship because of the effects of time—not because of a change in the material. A change in compliance due to stress relaxation or creep may be considered a “secondary” change in compliance. A “primary” change in compliance would be a direct effect on the extensibility or viscosity of the tissue. That is if the values of the pure elastic or viscous elements of a model representing the tissue are altered this would be considered a change in extensibility or viscosity, and thus a primary change in compliance. A secondary change in compliance in the viscoelastic material would be when the length vs. load relationship was altered because of stress relaxation, creep, or hysteresis, without a primary change in the elastic and viscous elements per se. It is important to retain some terms which specifically pertain to viscosity and elasticity independent of stress relaxation and creep. It would seem practical to keep the terms viscosity, elasticity, and extensibility for this purpose.

It should be noted that many tissues manifest a nonlinear elastic diagram. With increasing stretch, the slope of the stress vs. strain plot increases. If the elastic modulus is taken as the slope of the elastic diagram at a point or if an incremental elastic modulus is calculated from some segment of the line, these moduli will increase with increasing strain. Such changes in calculated moduli are usually not ascribed to a change in the elastic property of the tissue but interpreted in terms of the nonlinearity. A change in the elastic property of such a tissue implies a shift of the entire stress vs. strain curve.

Compliance is used above to describe a *passive* mechanical property of tissue. The distinction between the active and passive state in muscle physiology is a very important one. Compliance is a term which is used to describe the passive properties of tendon, connective tissue, and lung, which are not considered capable of “active” changes. It is probably prudent to reserve compliance to describe passive phenomena in resting muscle. A number of terms are available to characterize various active changes: contraction, contracture, rigor, aftercontraction, and tonus. The elastic properties of active muscle are much more difficult to define, and are not a part of the present discussion.

The current study demonstrates that paired stimulation under in vitro conditions with reduced temperature can alter the diastolic behavior of cardiac muscle by eliciting aftercontractions. After contractions have been observed in cardiac tissue

from several species (9). Aftercontractions have been reported only with in vitro preparations, usually in the presence of high  $\text{Ca}^{++}$  concentration or with other inotropic agents such as epinephrine, digitalis, or high stimulation rates. Aftercontractions are more pronounced at temperatures below  $37^{\circ}\text{C}$  and a reduced temperature of  $22^{\circ}\text{C}$  was used in this investigation to study them.

Aftercontractions elicited by paired stimulation can be considered a primary change in the myocardium and are clearly a change in the activity of the muscle and not in its passive properties. Aftercontractions are active contractions which develop tension and relax under isometric conditions, and also shorten and relax under isotonic conditions as shown in Figs. 1 and 2.

Braveny et al. (4) have examined the effects of aftercontractions on subsequent regular beats. They found that if a regular beat were superposed on an aftercontraction, the regular beat was smaller. They related this to the Frank-Starling mechanism where the aftercontraction caused the muscle to shorten so that the regular beat began from a shorter muscle length and was less vigorous.

Bartelstone et al. (10) and Scherlag et al. (11) have proposed that paired electrical stimulation results in a primary effect on diastolic compliance. In this study, muscles studied at  $37^{\circ}\text{C}$  without aftercontractions did not show a primary effect of paired stimulation on diastolic extensibility. A secondary effect of the prolonged systolic duration which results from paired stimulation was observed. At constant beat frequency, prolonging systole shortened diastole, and the muscle crept out less far under isotonic conditions because of the abbreviated diastole. These observations do not support the hypothesis that paired stimulation exerts a primary effect on the passive diastolic extensibility of resting cardiac muscle.

#### SUMMARY

A number of terms used in describing diastolic mechanical properties are discussed. The distinction between active and passive phenomena is emphasized. It is noted that the compliance (passive length vs. load relationship) of resting diastolic muscle can be altered by secondary effects such as stress relaxation and creep, or by direct primary effects altering the elasticity or extensibility.

The effect of paired electrical stimulation on the diastolic properties of in vitro cat papillary muscle was studied. Under suitable conditions of reduced temperature ( $22^{\circ}\text{C}$ ) paired electrical stimulation elicited diastolic aftercontractions. These aftercontractions were distinct active contractions, and did not represent a change in the passive extensibility of resting muscle. Paired electrical stimulation at a bath temperature of  $37^{\circ}\text{C}$  with normal  $\text{Ca}^{++}$  did not result in aftercontractions. Under these conditions, paired stimulation produced potentiation and prolongation of systole with a corresponding abbreviation of diastole at constant beat frequency. No evidence was found for a direct primary effect of paired electrical stimulation on passive resting diastolic extensibility.

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## DISCUSSION

My understanding of the original hypothesis presented by Bartelstone et al. (10) and by Scherlag et al. (11) is that paired electrical stimulation not only potentiates cardiac contraction but it also has a direct primary effect on passive resting diastolic extensibility. That is, paired stimulation in itself makes resting cardiac muscle more extensible. Subsequently, Sonnenblick et al. (7) and Gilmore et al. (8) demonstrated that compliance changes observed in isometric and isochoric preparations could be explained by the secondary effects of stress relaxation. The alteration of timing between driven beats and spontaneous aftercontractions which occurs with paired stimulation has been presented in a previous paper (5). This effect can explain the rapid change in isometric diastolic tension which followed the first paired stimulation reported by Scherlag et al. (11). The rapid change was unlikely to be caused by stress relaxation.

At this meeting the group from Columbia University has spoken about residual contractile activity during diastole. This possibility has been termed tonus in the older literature (12). It is not clear to me whether the original hypothesis (as I understand it) of paired stimulation causing a primary change in the *passive* elastic properties of cardiac muscle is still being proposed or if it has been modified with continued work to a hypothesis concerning active tonus. The discussion at this conference has pointed up several factors which are important if a primary change in passive extensibility of resting muscle is to be demonstrated. These are:

1. Slow heart rates should be used so that the effects of relaxation or partial fusion of beats are completely ruled out by all observers.

2. An isotonic preparation should be used since an isometric preparation is always subject to stress relaxation.
3. If pressure vs. volume records are obtained from intact ventricles, shape changes should be ruled out. An isolated papillary muscle avoids this difficulty.
4. Aftercontractions present after each beat or elicited by paired stimulation should be ruled out.
5. Contracture of in vitro preparations which may be diffusion-limited or which may become so with the positive inotropism of paired stimulation should be avoided by using thin muscles.

Using these criteria a critical experiment to demonstrate a primary effect of paired stimulation on cardiac diastolic extensibility was suggested during the discussion:

1. A thin papillary muscle less than 0.5 mm in diameter at 37°C with a  $\text{Ca}^{++}$  concentration of 2.5 mM per liter or less.
2. A true isotonic preparation not afterloaded with a stop, since when the lever is against the stop the muscle is isometric and still subject to a slight amount of stress relaxation.
3. A slow basic stimulation rate of 15 per min or less with long control periods before and after the period of paired stimulation.
4. If diastolic changes are observed, the stimulation should be interrupted during regular stimulation and during paired stimulation to rule out aftercontractions.

Sonnenblick et al. (7) and Feigl (5) have reported experiments which were very close to the critical experiment outlined above and failed to observe primary changes in diastolic extensibility with paired stimulation.

Dr. John Blinks pointed out that the above experimental design does not exclude the possibility of viscous creep of the parallel elastic element and that an inotropic intervention which changes the amplitude of shortening would alter the starting point for creep between beats. This effect would result in a secondary (apparent) decrease in resting compliance accompanying a positive inotropic effect. The effect of a damped parallel elastic element can be lessened by using very slow heart rates so that the period of diastole is long compared to the "time constant" of the parallel viscoelastic element.

If the Columbia University group's working hypothesis now is that there is some sort of active tonus during diastole, the first question is whether it is fundamentally different from aftercontractions that others have described (1, 4). If the tonus phenomenon is related to aftercontractions, then the most direct approach would appear to be an intensive study of aftercontractions under conditions where they are clearly present. Currently, aftercontractions are a pharmacological curiosity. They may provide a key to a better understanding of the physiology of cardiac muscle, but there is no evidence yet, that they have physiological significance.

# Ventricular Compliance and Myocardial Potassium Balance during Paired Stimulation of the Heart

J. P. GILMORE, EELCO GERLINGS, and DAVID MILLER

From the Department of Physiology, University of Virginia School of Medicine, Charlottesville, Virginia 22903

At the first conference on paired pulse stimulation data were presented describing in detail the influence of paired stimulation on myocardial performance and oxygen consumption as well as some preliminary data describing the influence of this intervention on myocardial potassium balance (1). It is the purpose of this report to describe in detail the influence of paired stimulation on myocardial compliance and to present more complete data describing the influence of paired stimulation on myocardial potassium balance. This report will consist to some extent of the presentation of data which have been published previously. However, more recent data will also be described which appear to demonstrate quite conclusively that the effect of paired stimulation on myocardial compliance is an indirect rather than a direct one. Also, recent data which substantiate the fact that paired pulse stimulation is indeed associated with a net loss of myocardial potassium will be discussed.

## METHODS

Four preparations were employed in these studies. There were (a) the metabolically isolated supported heart with constant left coronary artery perfusion pressure (2), (b) the left heart lung preparation in which cardiac inflow is controlled by a variable speed pump and aortic pressure controlled by graded constriction of the descending aorta, (c) the Langendorff blood-perfused dog heart with a balloon in the left ventricle, (d) the Tyrode-perfused Langendorff rabbit heart also containing an intraventricular balloon. In this latter preparation coronary outflow was collected via a cannula inserted into the main left pulmonary artery.

Left ventricular circumference was recorded using a mercury in rubber gauge (3). In some experiments left ventricular segment length changes were recorded with the gauge sutured to the epicardium in the base to apex orientation. All potassium analyses were done using automated flame photometry.

Paired stimulation was done through electrodes sewn to the right atrium and ventricle. A Grass stimulator was used with a setting of from 5–7 v and an impulse duration of 2–3 msec. An interstimulus interval was used that gave a maximal response; it varied with heart rate and the experimental preparation. Compliance is said to have changed if a change in ventricular end-diastolic pressure occurred at a constant ventricular end-diastolic volume.

## RESULTS

Fig. 1 shows the influence of coupled pacing on arterial pressure (AP), left ventricular pressure (LVP), left ventricular diastolic pressure (LVDP), left ventricular circum-

ference (LVC), and the first derivative of left ventricular pressure ( $dp/dt$ ), obtained from an experiment using the metabolically isolated supported heart (4). With the onset of coupled pacing (CP) at an interstimulus interval of 230 msec, there occurred a substantial decrease in left ventricular end-diastolic pressure at a time when aortic pressure, stroke volume, and heart rate were maintained essentially constant. The

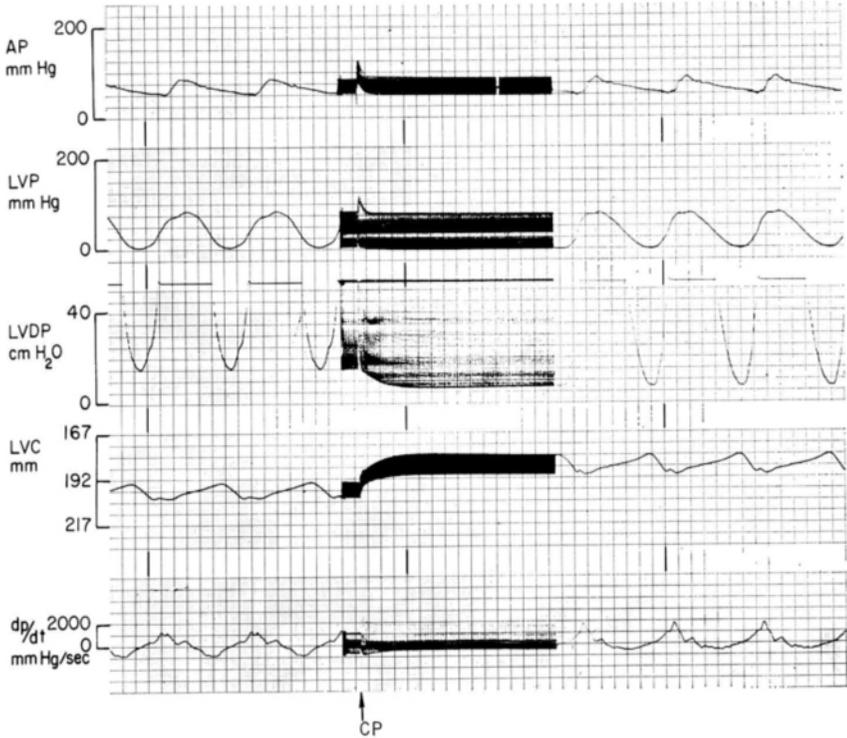


FIGURE 1. The influence of paired stimulation on certain aspects of myocardial performance. AP, aortic pressure, LVP, left ventricular pressure, LVDP, left ventricular diastolic pressure, LVC, left ventricular circumference, and  $dp/dt$ , the first derivative of left ventricular pressure. Heart rate, 172 per min. Cardiac input remained relatively constant throughout. Paired stimulation (CP) initiated at time indicated by vertical arrow. The high speed tracings (left and right of figure) were obtained at 100 mm per sec: slow speed tracings (middle of figure) obtained at 0.5 mm per sec. *Figure reprinted by permission from American Journal of Physiology, 1966. 211:376.*

decline in left ventricular end-diastolic pressure was associated with a substantial decline in left ventricular circumference. Thus, since both left ventricular end-diastolic pressure and left ventricular circumference decreased during coupled pacing, it is apparent that the decline in end-diastolic pressure could not be due solely to a change in ventricular compliance.

A high speed tracing showing the influence of paired stimulation on some aspects of ventricular performance is shown in Fig. 2 (5). The control panel (left) was ob-

tained during simultaneous A-V pace. Between the two panels paired stimulation was initiated and cardiac input increased so as to maintain left ventricular end-diastolic pressure (LVDP) essentially constant. At the same time aortic resistance was decreased to maintain mean aortic pressure essentially constant. The new steady state which obtained is shown in the right panel. Although coupled pacing was associated with a very substantial increase in myocardial contractility as indicated by the increase

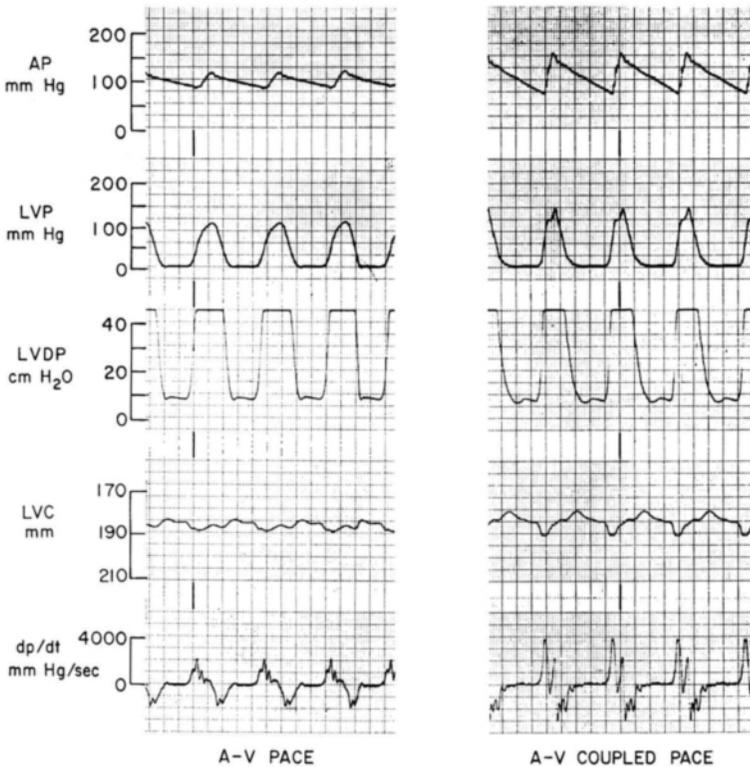


FIGURE 2. The influence of simultaneous atrioventricular coupled pacing on the relation between left ventricular diastolic pressure (LVDP) and circumference (LVC). Heart rate, 132 per min. Other abbreviations same as in Fig. 1. Experiment was obtained from a modified heart lung preparation. For a further description of figure see text. *Figure reprinted by permission from American Journal of Physiology, 1966, 211:1227.*

in  $dp/dt$  at a constant end-diastolic pressure, there was no change in the relation between left ventricular end-diastolic pressure and left ventricular circumference. Fig. 3 shows the influence of atrial pace, simultaneous atrioventricular pace (A-V pace), and coupled pace (A-V coupled pace) on the relation between left ventricular end-diastolic pressure (LVEDP) and circumference (LVC) in the same heart (5). In this experiment aortic pressure was maintained essentially constant throughout and heart size varied by varying cardiac inflow. Although some scatter obtains for the points at the larger heart sizes a single line would describe the points on the lower half of the plot.

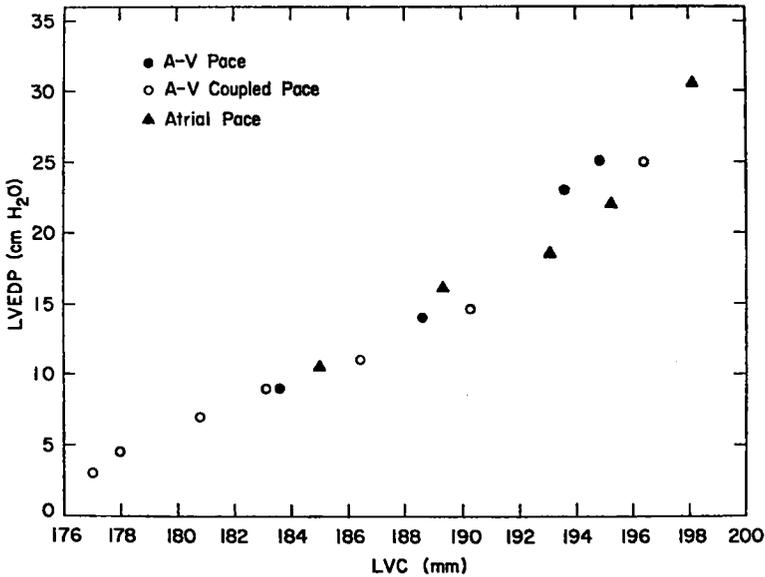


FIGURE 3. The relation between left ventricular end-diastolic pressure (LVEDP) and circumference (LVC) during atrial pace, simultaneous atrial ventricular pace (A-V), and coupled pace (A-V coupled pace). Circumference was increased by increasing cardiac inflow. Heart rate was maintained at 132 per min and mean aortic pressure at approximately 95 mm of mercury. Experiment was obtained from a modified heart lung preparation. *Figure reprinted by permission from American Journal of Physiology, 1967, 211:1227.*

The experiments presented above therefore show no consistent influence of paired stimulation on the relation between left ventricular end-diastolic pressure and left ventricular end-diastolic circumference. These results however, were obtained from

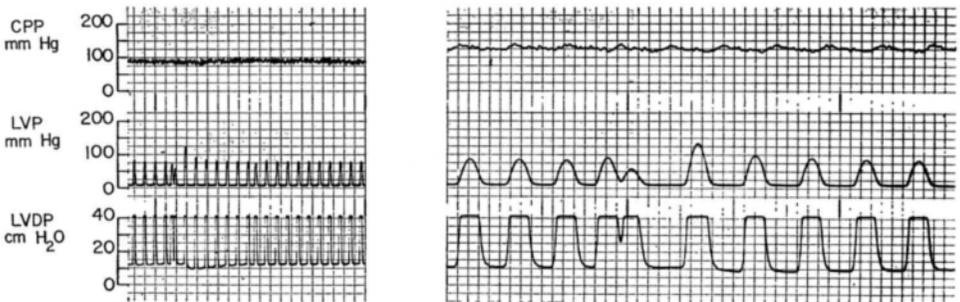


FIGURE 4. Influence of a spontaneous extrasystole on left ventricular compliance. CPP, coronary perfusion pressure, LVP, left ventricular pressure, LVDP, left ventricular diastolic pressure. Panel on left obtained at a paper speed of 5.0 mm per sec, panel on right obtained at a paper speed of 50 mm per sec. The tracing shows two different instances of the phenomenon. Experiment was obtained from a Langendorff blood-perfused dog heart.

working hearts in which any large changes in developed tension were precluded by maintaining essentially constant aortic pressure.

After the completion of the studies presented above, we had the occasion to observe the influence of extra systoles on the dynamics of the isovolumic blood-perfused dog heart. An example of this is shown in Fig. 4. The ventricle of this heart contained a saline-filled balloon at constant volume. The panel on the left is a slow tracing of an extra systole, while the panel on the right shows a higher speed tracing of the phenomenon. The extra systole was associated with a substantial increase in the pressure



FIGURE 5. The influence of coupled pacing on compliance of the isovolumic dog left ventricle. Abbreviations the same as in previous figure. Heart rate was 100 per min. Figure reprinted by permission from *American Journal of Physiology*, 1966, 211:1227.

developed by the ventricle and a decline in ventricular diastolic pressure. It will be noted, however, that the decline in diastolic pressure did not occur until after the potentiated beat. Also, the change in diastolic pressure paralleled the rise and fall of developed pressure. In view of this observation, continuing postextrasystolic potentiation or paired stimulation was used in this preparation. An example of the results of one such experiment is shown in Fig. 5 (5). With the initiation of paired stimulation (A-V coupled pace) there occurred an increase in left ventricular systolic pressure (LVP); this was associated with a decline in left ventricular diastolic pressure (LVDP). Again, the decline in ventricular diastolic pressure did not occur until after the first potentiated beat; also, the decline in diastolic pressure paralleled the increase in left ventricular developed pressure. That this effect is reversible is shown by the

postcontrol tracing to the right of this figure. It will be noted that during the time of potentiation and change in diastolic compliance in both Figs. 4 and 5, the coronary perfusion pressure was essentially constant.

The influence of increasing tension by increasing heart rate on diastolic compliance of the isovolumic dog ventricle is shown in Fig. 6. When heart rate was increased from 60 to 125 per min left ventricular developed pressure increased. This was associated with a progressive decline in left ventricular diastolic pressure, that is, an increase in left ventricular compliance. It is to be noted again that left ventricular diastolic pressure did not begin to decline until the increase in left ventricular developed pressure occurred.

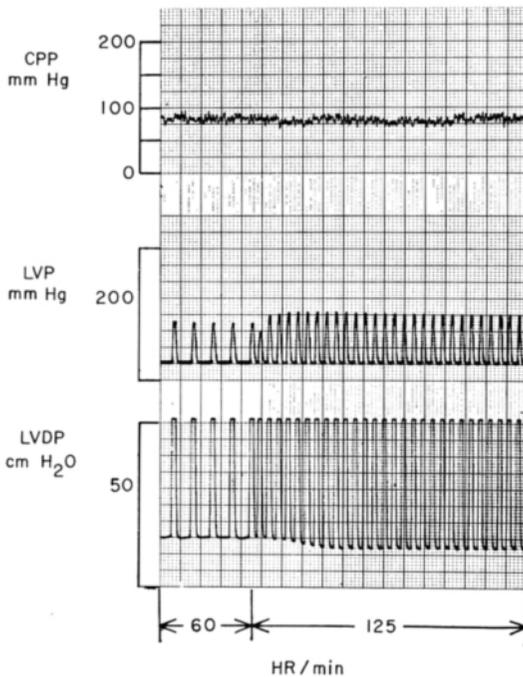


FIGURE 6. The influence of heart rate on the diastolic compliance of the Langendorff blood-perfused dog ventricle. Abbreviations same as in Fig. 5. See text for description of figure.

In order to determine the relation between developed tension and diastolic compliance over a wide range of experimental conditions, studies were done in which the influence of calcium and preload on diastolic compliance was studied in the Langendorff blood-perfused dog heart at constant heart rate. The left ventricle contained a saline-filled balloon which was maintained at a constant volume. Fig. 7 shows the influence of an intracoronary infusion of calcium chloride (36 mg per min) on left ventricular developed pressure (LVP), left ventricular end-diastolic pressure (LVDP), total coronary flow (TCF), and the first derivative of left ventricular pressure ( $dp/dt$ ). With the onset of the calcium infusion, ventricular developed pressure increased; concomitantly, ventricular end-diastolic pressure declined. Since the volume of the intraventricular balloon was constant during the experiment it follows that the compliance of the ventricle increased during the calcium infusion. It will be noted that

the decline in ventricular diastolic pressure correlated in time with the increase in developed pressure. Following cessation of the calcium infusion both the ventricular developed pressure and diastolic pressure returned to approximately the preinfusion level.

Fig. 8 shows the influence of increasing the preload on the performance of the isovolumic dog ventricle. At the time indicated by the vertical arrow the volume of the balloon was rapidly increased by 10 ml. This was associated with an initial rise in both left ventricular developed pressure and left ventricular end-diastolic pressure.

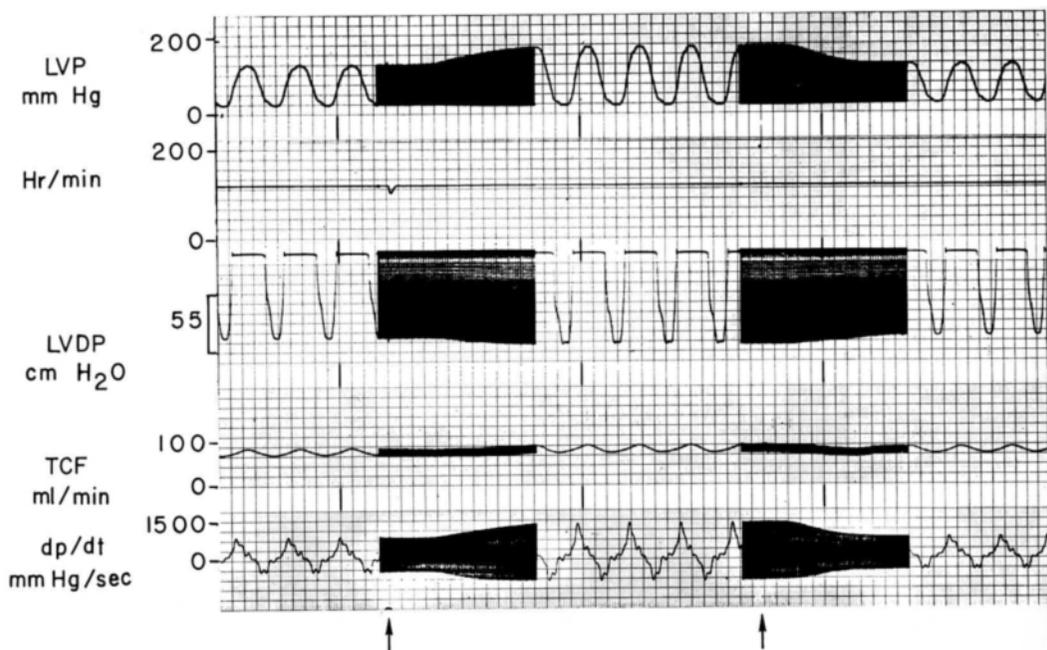


FIGURE 7. The influence of calcium on the diastolic compliance of the isolated blood-perfused dog left ventricle. LVP, left ventricular pressure, HR, heart rate, LVDP, left ventricular diastolic pressure, TCF, coronary blood flow,  $dp/dt$ , the first derivative of left ventricular pressure. Vertical arrows indicate the beginning and end of an intra-coronary infusion of calcium chloride (36 mg per min).

Shortly thereafter however, left ventricular diastolic pressure declined by approximately 4 mm of mercury at which time left ventricular developed pressure increased by approximately 10 mm of mercury. These changes were associated with only a modest increase in total coronary blood flow. Of further interest however, is the observation that while left ventricular developed pressure was increasing and while left ventricular diastolic pressure was decreasing there occurred a significant increase in the first derivative of left ventricular pressure ( $dp/dt$ ). Therefore, an increase in the developed tension of the isovolumic left ventricle by an intervention which can be presumed to be noninotropic can be associated with an increase in left ventricular diastolic compliance.

The data presented above, obtained from the isovolumic ventricle in which the developed tension is not controlled, indicate that when developed tension is increased there can occur an increase in left ventricular compliance. Thus, any influence which coupled pacing may have on the compliance of the ventricle can be attributed to an indirect effect.

What is the cause of the increase in compliance of cardiac muscle when developed tension increases? Is it due to an elongation of the contractile element itself or is it due to an elongation of a noncontractile part of the muscle? If it is due to the former,

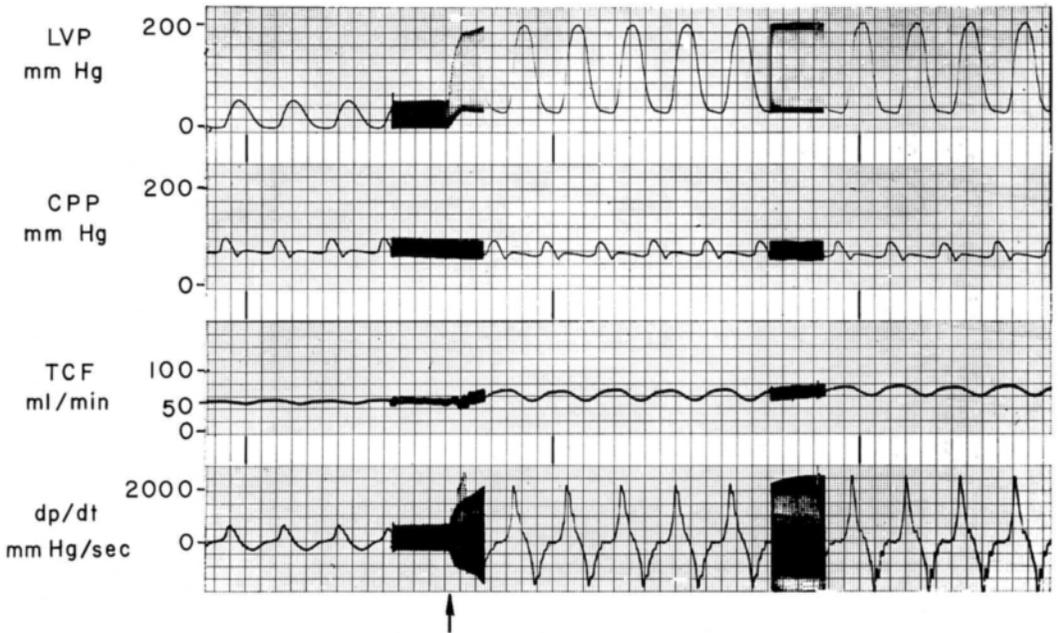


FIGURE 8. The influence of increasing end-diastolic volume on the performance of the isovolumic blood-perfused dog ventricle. LVP, left ventricular pressure, CPP, coronary perfusion pressure, TCF, total coronary flow,  $dp/dt$ , the first derivative of left ventricular pressure. 10 ml of saline were injected at the time indicated by the vertical arrow. See text for further description of figure.

this elongation of the contractile element would contribute to the potentiation of contraction observed. In contrast, if it was due to an elongation of a noncontractile component of the muscle there would then occur, if anything, a shortening of the contractile element itself. Information which bears on this problem is presented in Fig. 8. Subsequent to the inflation of the balloon in this experiment there occurred a progressive decline in left ventricular end-diastolic pressure and a concomitant increase in left ventricular developed pressure ( $dp/dt$ ). Assuming that increasing preload does not increase the contractility of the heart, it is possible that the increase in developed tension in this experiment was a result of elongation of the contractile element as reflected by the decline in left ventricular end-diastolic pressure. If this

change in compliance was a result of an elongation of a noncontractile component of the muscle there is no reason to expect that developed pressure would increase; in fact one might possibly expect under these conditions a parallel decrease in developed tension. Although it is possible that the increase in developed pressure was related to the small associated increase in total coronary blood flow in this experiment, we have seen the same phenomenon in experiments in which little change in coronary blood

Heart rate, min	144	144
Ventricular developed pressure, mm Hg	55	175
Coronary flow, ml/min	64	81
Coronary pressure, mm Hg	95	85
dp/dt, mm Hg/sec	750	2250

ARTERIAL  $\circ$ - - - $\circ$   
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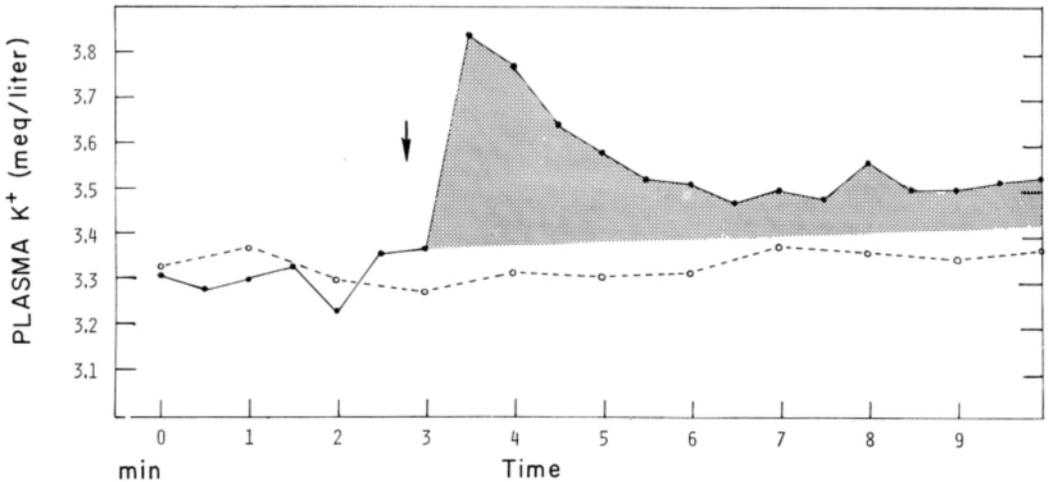


FIGURE 9. The influence of continuous postextrasystolic potentiation (coupled pacing) on potassium balance of the Langendorff blood-perfused dog heart. Coronary pressure, coronary perfusion pressure, coronary flow, total coronary venous flow. The values to the left above the panel equal those which obtained in the control state; those to the right were obtained during coupled pacing which was initiated at the time indicated by the vertical arrow.

flow occurred. Thus, this type of experiment supports the position that the change in compliance which results from an increase in ventricular developed tension is the result, at least in part, of an elongation of some contractile component of the muscle.

#### *Myocardial Potassium Balance during Paired Stimulation*

The increase in contractility and myocardial oxygen consumption associated with coupled pacing has been documented by several investigators. However, there does

not appear to be a consensus that this phenomenon is associated with a net loss of myocardial potassium. Fig. 9 shows the results of an experiment done on an isovolumic blood-perfused dog heart in which the influence of paired stimulation on myocardial potassium balance was determined (6). The hemodynamic values during the control state are shown to the left above the potassium plot, while those which obtained during paired stimulation are shown to the right. During paired stimulation a substantial elevation of coronary venous plasma potassium concentration occurred at a time when arterial plasma concentration remained essentially constant. Thus, paired stimulation

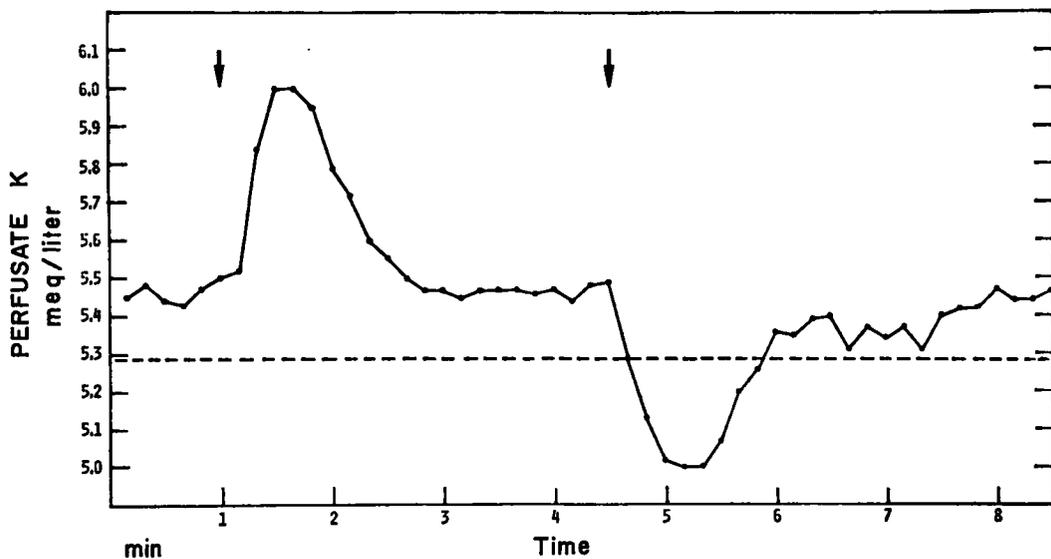


FIGURE 10. The influence of coupled pacing on the potassium balance of the isovolumic Tyrode-perfused rabbit heart. The solid lines represent the coronary effluent potassium concentration; the dashed line equals the coronary arterial perfusate potassium concentration. Coupled pacing was initiated at the time indicated by the first vertical arrow and stopped at the time indicated by the second vertical arrow. Heart rate was maintained constant throughout in this experiment.

of this heart produced a substantial loss of potassium. Fig 10 shows an experiment which was done employing an isovolumic Tyrode-perfused rabbit heart. This particular experiment is shown for two reasons: first, to demonstrate that in the Tyrode-perfused rabbit heart paired stimulation is associated with loss of myocardial potassium; second, since this heart was bathed with high calcium only a minimal change in contractility occurred during paired stimulation.

In a recent study Grupp and associates reported that although they could demonstrate a loss of potassium from the heart when heart rate was increased no such loss obtained during paired stimulation (7). Their explanation for the discrepancy between their experiments and those of Sarnoff and associates (1, 4), was that the preparations employed by the two groups differed in many ways. However, this would not appear to be a likely explanation. We have found consistently during coupled pacing

a net loss of potassium from the isolated working dog heart, from the blood-perfused isovolumic dog heart, and from the Tyrode-perfused rabbit heart. Also, Mansfield and McDonald reported a consistent loss of myocardial potassium from the isolated perfused cat heart during paired stimulation (8). It appears therefore, that the failure of Grupp and his associates to demonstrate a net loss of potassium from the heart during coupled pacing is not due to differences in the preparations employed. More likely is the possibility that their analytical method is such that small changes in plasma potassium concentration cannot be discerned.

Much attention has been given to the possibility that the inotropic influence of coupled pacing is related in some way to the calcium ion. Although it is certainly possible that changes in intracellular calcium are contributing to the inotropic effects produced by paired stimulation, the fact nevertheless remains that no data are available which demonstrate net myocardial calcium changes during paired stimulation. Further, no data are available to indicate that although a net change in myocardial calcium does not occur during paired stimulation, there is an intracellular redistribution of this cation. The only ion for which such information is available is potassium; our experiments in which net changes in potassium were investigated, as shown above, appear to demonstrate conclusively that during paired stimulation there is a net loss of myocardial potassium. Whether or not this net loss of myocardial potassium is the cause of, or contributes to, the associated hemodynamic changes must await elucidation.

The data presented above may be summarized as follows: (a) Coupled pacing has been shown to have an influence on ventricular compliance only under experimental conditions in which developed tension or pressure is not controlled. (b) When coupled pacing is initiated under experimental conditions in which developed tension changes are minimized, no compliance change is observed. (c) Increasing ventricular developed pressure by various interventions causes an increase in ventricular diastolic compliance. (d) The increase in ventricular diastolic compliance associated with increasing developed tension may be related to an elongation of the contractile element. (e) Coupled pacing has been found to be associated consistently with a net loss of myocardial potassium.

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# The Relation between Viscous Elements and Compliance in Heart Muscle

EDMUND H. SONNENBLICK, JOHN ROSS, JR., JAMES W.  
COVELL, and EUGENE BRAUNWALD

From the Cardiology Branch, National Heart Institute, Bethesda, Maryland 20014. Dr. Sonnenblick's present address is the Cardiovascular Unit, Peter Bent Brigham Hospital, Harvard Medical School, Boston, Massachusetts 02115

In the over-all study of muscular activity, attention has been directed to both the mechanical activity of contractile elements and the distensibility of the elastic elements with which they are coupled. Although phenomena related to stress relaxation have been recognized for several years, the question of whether or not inotropic interventions can alter the distensibility of the nonactivated muscle has again become a matter of controversy. While the greater weight of evidence is against such an influence if full relaxation of the muscle has occurred (1-8), and such nonphysiological phenomena as rigor, contracture, or aftercontractions (9) have been excluded, it has recently been suggested that such changes in compliance can be observed following sustained post-extrasystolic potentiation (10). Were a change in distensibility to result from a direct effect of inotropic interventions, one would have to infer either a significant residual interaction between contractile sites in the quiescent muscle and/or an effect of the intervention on passive elastic structures. Except where partial contracture, aftercontractions or incomplete relaxation is evident, as may occur with a muscle bathed in very high, nonphysiological concentrations of calcium or at low temperatures (9, 11), the former possibility has little support. Further there is little to suggest that inotropic interventions exert their effect on passive elastic structures (2, 12).

Since in most experimental preparations inotropic interventions such as catecholamines or sustained postextrasystolic potentiation are associated with substantial increments in the force of contraction, it occurred to us that changes in compliance might occur through increases in systolic force per se rather than through a direct effect of the inotropic stimulus on the muscle (13). Our approach has been based on the following line of reasoning: If increases in the diastolic compliance of heart muscle following inotropic interventions were due to alterations in the contractile system itself, as proposed recently (10), they should be apparent whether a muscle is contracting isotonicly or isometrically. On the other hand, if changes in systolic force were sufficient to explain these findings, then no change in myocardial compliance should be observed when the inotropic stimulus acts on a muscle contracting isotonicly; these changes in compliance should occur, however, whenever systolic force is increased, regardless of whether or not an inotropic influence is introduced.

Our studies were performed with the cat papillary muscle preparation and the isovolumically contracting dog ventricle, and the effects of sustained postextrasys-

toxic potentiation produced by paired stimulation (PS), norepinephrine (NE), and calcium ( $\text{Ca}^{++}$ ) on resting length-tension relations were analyzed. In freely isotonic or afterloaded papillary muscles, when force remained constant, PS, NE, or increased  $\text{Ca}^{++}$  resulted in substantial increments in muscle shortening but produced no change in diastolic compliance (Figs. 1 and 2). However, under isometric conditions, when force of contraction increased following the inotropic interventions,

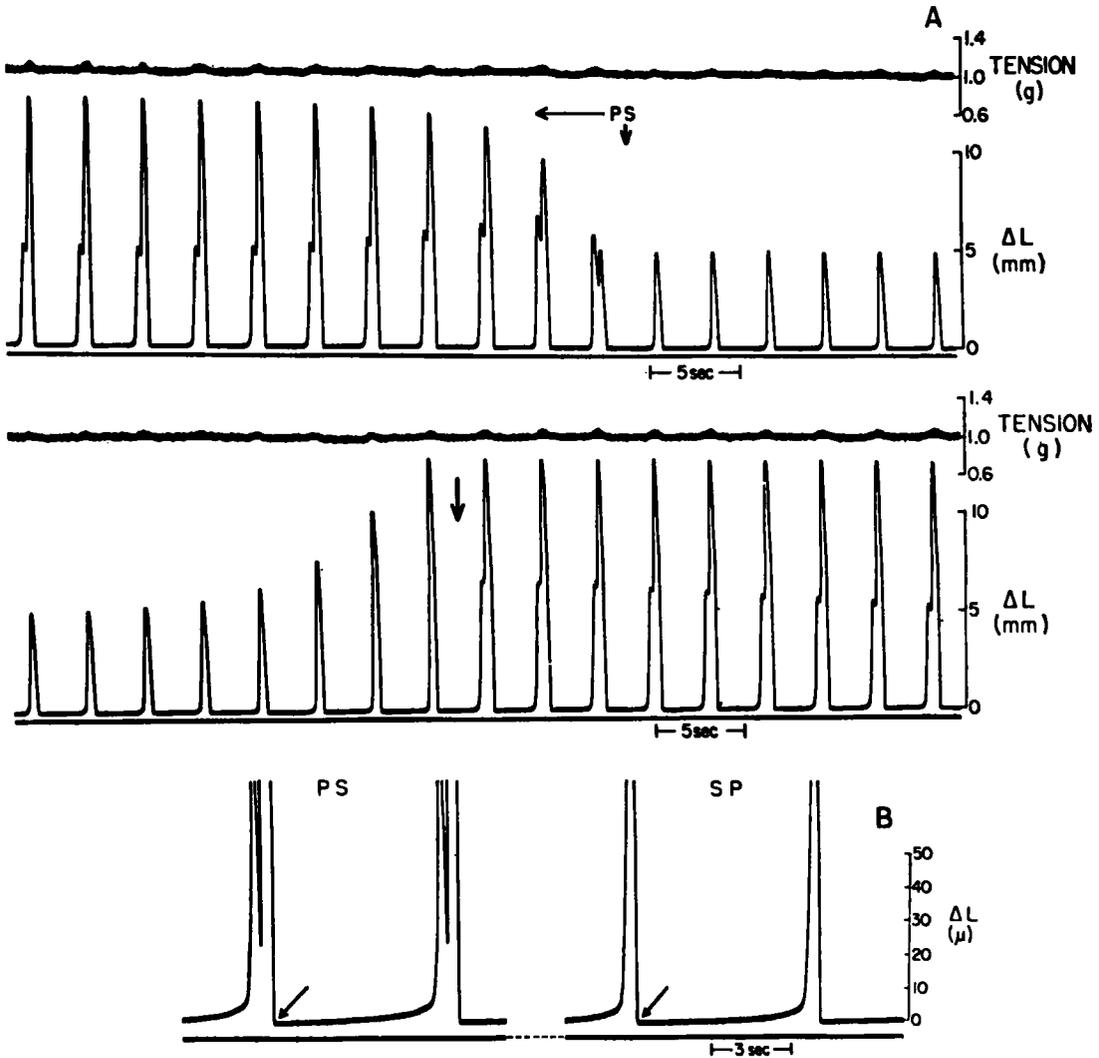


FIGURE 1. Effects of the induction of paired electrical stimulation (PS) during isotonic contractions. Records read from right to left. SP, single pulse.  $\Delta L$ , shortening. In A, with the initiation of PS (vertical arrows), there is a substantial increase in  $\Delta L$ , while tensions remain constant. No changes in diastolic length occur. In B, diastolic muscle length is seen at very high gain. Again, no change in diastolic length is noted during PS. The arrows in the lower panel (B) denote the diastolic length prior to contraction.

PS, NE, and  $\text{Ca}^{++}$  all induced a small increase in resting compliance, but only if systolic force rose (Figs. 2 and 3). Indeed, when PS was imposed on a muscle whose contraction was already augmented by increased  $\text{Ca}^{++}$ , an extrasystolic contraction was clearly evident but systolic force did not increase further and no change in compliance was observed (Fig. 4). Further, decrements in resting tension at a constant muscle length, which reflect increments in compliance, were also observed when systolic force was increased without changing the fundamental contractile state of the muscle; this was the case with changing from isotonic to isometric contractions (Fig. 5) or when increasing afterload at a constant initial muscle length. The same conclusions were reached in the isovolumically contracting left ventricle of the dog (13).

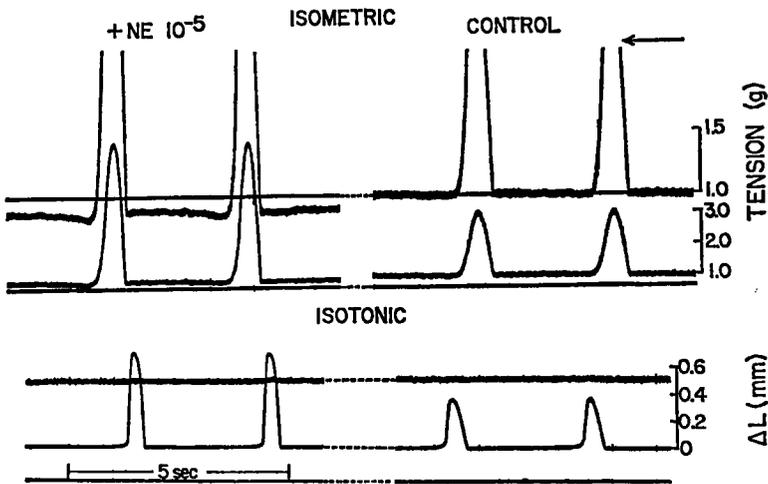


FIGURE 2. Effects of norepinephrine (NE) on isometric and isotonic contractions. Records are from right to left. Tension at high and low gain, and shortening ( $\Delta L$ ) are shown. Under isometric conditions addition of NE results in an increase in developed tension accompanied by a small decline in resting tension. In contrast, under isotonic conditions, NE substantially increases the extent of shortening without changing resting muscle length.

These general findings may be explained by certain modifications of the model for muscle proposed by Hill (14) and they help to explain a certain number of the discrepancies in the vast literature related to myocardial compliance. In the Hill model (Fig. 6 A), muscle has three components: (a) a contractile element (CE) which is freely extensible at rest but shortens and develops force following activation; (b) an elastic component arranged in series with the contractile element, the series elastic element (SE), which at rest is entirely passive and bears negligible tension but is stretched following activation and contraction of the contractile element; and (c) an elastic component that is parallel with the contractile element, the parallel elastic element (PE), which bears essentially all the resting tension. With activation, the CE shortens and stretches the SE, thereby delivering force to the external attachments of the muscle. The findings in our studies cannot be completely explained by this model

but suggest that a viscous component also exists in series with the SE and CE (Fig. 6 B). A spring in parallel with this viscous component would provide a restoring force. It is proposed that elongation of this series viscous component, which occurs whenever force of contraction is augmented, is responsible for the lower resting tension at any

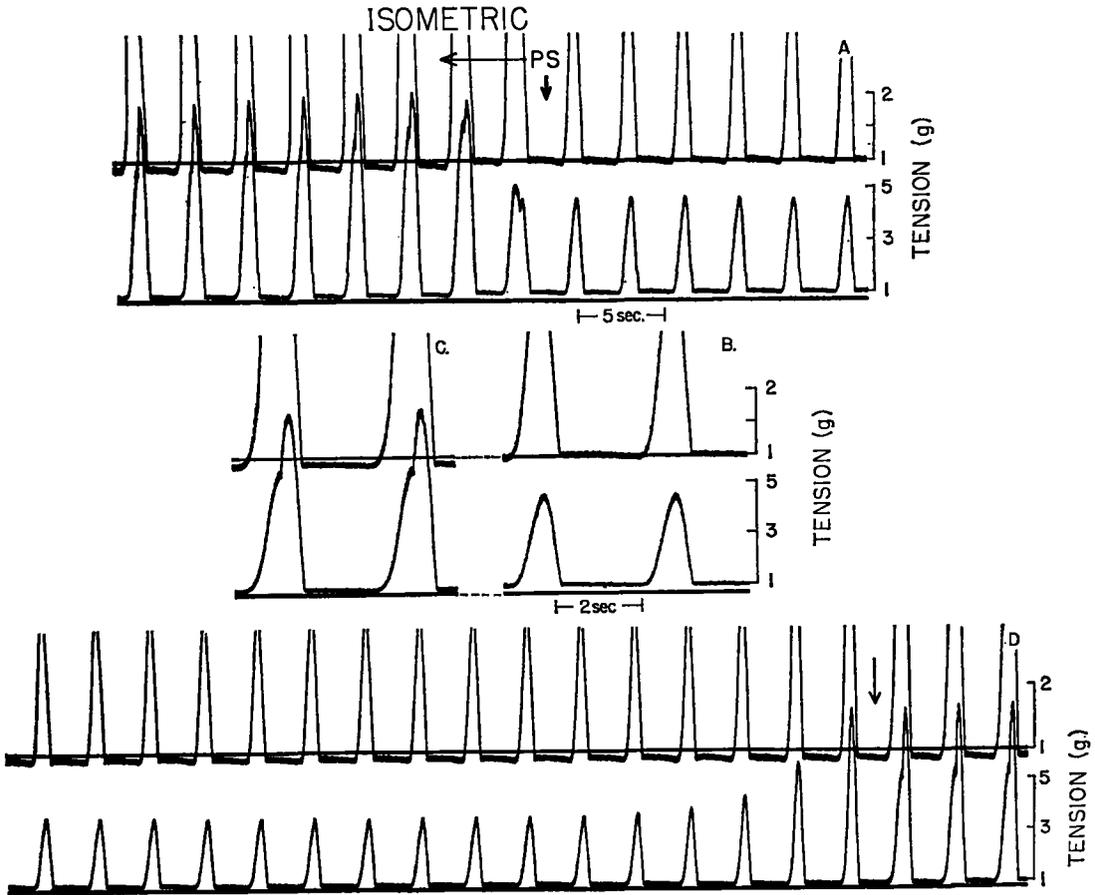


FIGURE 3. Effects of PS during isometric contractions. Records from right to left. Tension is shown at high (upper trace) and low (lower) sensitivities. Rapid recordings are shown in B and C to contrast the two modes of contraction. Onset and cessation of PS at vertical arrows. Note the small fall in resting tension occurring with the increase in developed tension resulting from PS (A) and the small rise in resting tension when PS is discontinued (D).

given initial muscle length, and thus causes a change in compliance. The precise location and nature of this series viscous component have yet to be defined. While viscosity in the tendinous end of the muscle and its myographic attachments, or in a damaged portion of the papillary muscle, could partially explain the findings in the isolated muscle, the demonstration of the same phenomenon in the intact heart

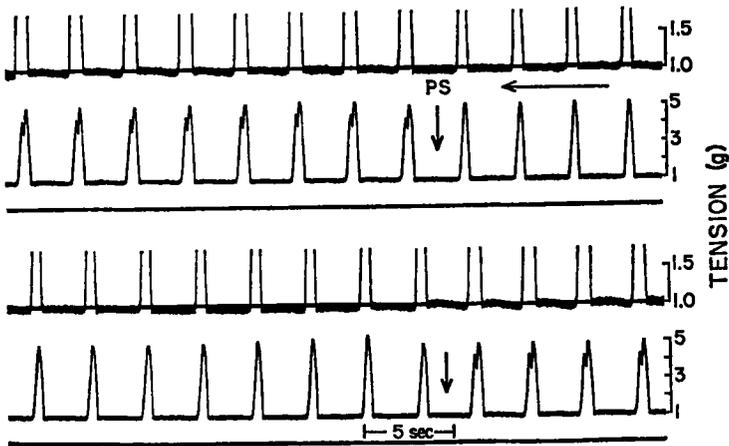


FIGURE 4. Effects of PS on isometric contraction. Records are from right to left. The force of contraction in the control state has been augmented by increasing the  $\text{Ca}^{++}$  in the bath from 2.5 to 5.5 mM. With the initiation of PS at the arrow, an extrasystole is seen, but with the previously augmented contractile state, no further increment in developed tension is noted, in contrast to Fig. 2. Further, in the absence of an increase in developed tension, no fall in diastolic tension occurs.

suggests that these factors cannot account entirely for the extension of this proposed series viscous component.

The present findings bear mostly on a viscous element arranged in series with the

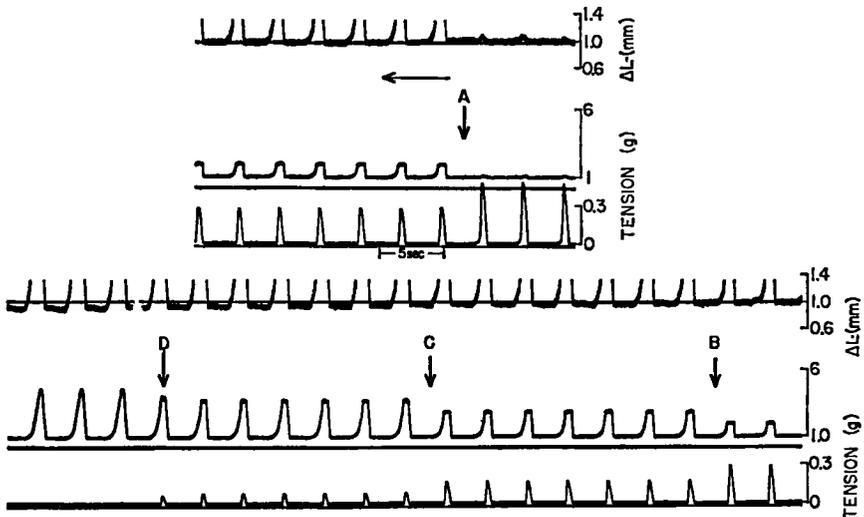


FIGURE 5. Effects on the resting tension of progressively increasing afterload at a constant preload. Records are from right to left and are continuous. High and low sensitivity tracings of tension are shown. Starting at A, afterload was progressively increased. As shown by the tension tracing at high sensitivity, the diastolic tension falls progressively as the afterload is increased.

SE and PE, since over-all muscle length remains constant. However, it is common knowledge that stress relaxation also occurs after the length of the resting muscle is altered. Since preliminary observations suggest that this response to changes in resting muscle length may differ in magnitude from that associated with increments in systolic force alone at one muscle length (Covell, Parmley, Ross, and Sonnenblick, unpublished observations), it is probable that there are at least two viscous elements, one associated with the SE and one associated with the PE (Fig. 6 B).

In summary, the effects of sustained postextrasystolic potentiation and NE on resting length-tension relations of heart muscle have been studied in the cat papillary muscle and in the intact canine heart. When muscles were freely isotonic, or afterloaded, and force remained constant, no change in diastolic compliance was found. However, under isometric conditions, both PS and NE induced an increase in systolic

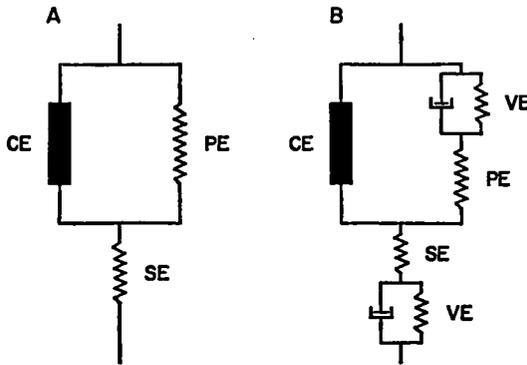


FIGURE 6. Three component models for muscle. CE contractile element, SE, series elastic component, and PE, parallel elastic component. A, model after Hill (14), as shown to be appropriate for heart muscle, B, model for muscle with viscous elements (VE) in series with the SE and PE.

force and a concurrent small reduction in resting tension at a given muscle length. Similar decrements in diastolic tension were observed when contractile force was augmented simply by increasing afterload from a constant initial muscle length. Therefore, inotropic interventions such as PS, or  $\text{Ca}^{++}$  do not per se induce changes in the compliance of heart muscle. However, resting tension at a given initial muscle length does decrease slightly secondary to augmentation of force. These findings explain the apparent changes in compliance which have been reported to occur with inotropic interventions and serve to support the view that there is a series viscous component in heart muscle in addition to viscous components arranged in parallel.

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# Variable Diastolic Compliance in Isotonic, Afterloaded, and Isometric Preparations

HERBERT J. BARTELSTONE, BRIAN F. HOFFMAN,  
and ARTHUR L. BASSETT

From the Department of Pharmacology, College of Physicians and Surgeons,  
Columbia University, New York, New York 10032

In previous publications (1-3) we have attempted to demonstrate that diastolic compliance of mammalian cardiac muscle varies significantly. Initially we showed that, in the case of the isovolumic canine right ventricle, isolated from the circulatory system except for the coronary arteries, paired stimulation (PS) produced a significant reduction in diastolic pressure under conditions which prevented any translation of blood (1). In addition, it was shown that this decrease in end-diastolic pressure was not dependent on the increase in systolic force caused by PS since, under appropriate conditions, the decrease in diastolic pressure was demonstrated during the diastolic interval which followed the first pair of stimuli and which thus preceded the first potentiated contraction. In other experiments ventricular segment length was measured by means of a mercury gauge; in these experiments it was shown that PS caused an increase in diastolic segment length at the same transmural pressure (1).

These findings on the variability of diastolic compliance were in disagreement with results reported by others (4), although supporting evidence was presented in the data of Rushmer (5) and Hefner et al. (6). To clarify the basis for disagreement, the question of variability of diastolic compliance was studied *in vitro* using cat papillary muscles or atrial or ventricular trabeculae from cat or dog. It had been claimed that PS failed to change the diastolic tension of the isolated papillary muscle under isometric conditions (7); we conducted similar experiments and showed that diastolic compliance was increased (diastolic tension decreased) by either PS, suitable concentrations of catecholamines, or digitalis glycosides (2, 3). Also, it was possible to show that the decrease in diastolic tension was not dependent solely on the increase in systolic force (8). It was also shown that the direction of change in diastolic compliance caused by either PS or catecholamines could be reversed by prior exposure to high concentrations of acetylcholine (3).

Koch-Weser (9) has confirmed some of our findings for isometric contractions and Feigl (10) has published results in agreement with our demonstration for the isometric muscle that PS may increase compliance prior to the first potentiated contraction. Sonnenblick (11) has conducted further studies on both the isolated papillary muscle and the *in situ* heart. Although his results now are in agreement with ours (2,

3) for the muscle studied under isometric conditions, since he shows that an increase in diastolic compliance results from PS, catecholamines, and other positive inotropic interventions, he has failed to record any changes in compliance under isotonic or afterloaded conditions. He has suggested that the changes in compliance which he has observed under isometric conditions result from force-dependent hysteresis in viscous elements which reacted to the increased force caused by the positive inotropic intervention.

We believe that changes in diastolic compliance are caused, at least in part, by changes in residual interaction between the contractile elements (2, 3). Since there is evidence for the existence of a viscous element in series with the contractile elements of cardiac muscle (8, 12, 13), other causes for changes in diastolic compliance can be demonstrated only by showing that compliance varies under conditions of constant load, as well as under isometric conditions when the force acting on the viscous element may vary. It is the purpose of this paper to present our data on the marked variability of diastolic compliance under a variety of conditions, emphasizing the changes demonstrated for isotonic and afterloaded preparations. It will be shown that as a result of a variety of pharmacological and physiological interventions, compliance may vary under isometric, afterloaded, and isotonic conditions. Depending on the state of the muscle and its environment, diastolic tension at constant muscle length and diastolic length at constant tension may vary both in terms of the magnitude and direction of the change. Data also will be presented which demonstrate drug-induced alterations in muscle length under constant load in unstimulated cardiac muscle. We believe these results suggest that the heart may relax to varying degrees during diastole and that variations in contractile element interaction can influence significantly the acceptance of blood by the heart as well as the character of the ensuing contraction. Furthermore, we believe that the responsiveness of myocardial tissue can no longer be described in terms of contraction only but must also include consideration of compliance changes during diastole.

## METHODS

Cats and dogs were anesthetized with pentobarbital sodium, 30 mg per kg. The hearts were rapidly removed and dissected at room temperature in Tyrode's solution gassed with 95% O<sub>2</sub>-5% CO<sub>2</sub>. For studies on atrial muscle, thin trabeculae were removed from the right atrium of the cat or dog heart. For studies on ventricular muscle, papillary muscles and trabeculae carneae were obtained from the right ventricle of the cat heart. The maximum transverse dimension of the muscles used in the study, under a load of 1 g, was 0.35-1.5 mm. Muscle length was between 8 and 15 mm for atrial trabeculae and 4 and 8 mm for the ventricular tissues. The muscles were mounted in an appropriate Lucite muscle bath and were perfused with a modified Tyrode solution containing, in mm per liter; NaCl, 137; NaHCO<sub>3</sub>, 12; NaH<sub>2</sub>PO<sub>4</sub>, 1.8; CaCl<sub>2</sub>, 2.7; KCl, 2.7; MgCl<sub>2</sub>, 0.5; and glucose, 5.5 A mixture of 95% O<sub>2</sub> and 5% CO<sub>2</sub> was used to gas both the solutions in the muscle chamber and the reservoir.

Two Lucite muscle baths were used; one had a capacity of 50 ml and the other had a capacity of 8 ml. The larger bath was heated by nichrome wire wrapped around its external surface and connected to a proportional heating device (14). The smaller bath had a thick wall of Lucite; a flow rate of 6 ml per min of warmed Tyrode's solution allowed adequate temperature control ( $\pm 0.2^{\circ}\text{C}$ ). The bottoms of both baths were fitted with a rubber diaphragm through which a

stainless steel rod passed. One end of the rod was attached to a Statham bidirectional transducer (UC-2) which was mounted under the bath. The other end of the rod ended in a small hook. One end of each muscle was directly tied with 6-0 silk suture to this hook. The other end of each muscle preparation was tied to a fine gold chain which was affixed to a light magnesium isotonic lever (15) mounted on a mechanical movement above the bath. For isometric contractions, a mechanical stop was placed and locked under the lever arm to prevent its movement. Another mechanical stop allowed us to vary muscle length. A stainless steel bucket suspended in oil for critical damping was filled with known amounts of mercury to vary the preload and afterload. Stimuli were delivered to the muscle from large platinum plates extending along the entire length of the muscle; stimulus duration was 5 or 10 msec and stimulus strength was always suprathreshold. The stimulator has been described previously (16).

Isometric force, recorded at high and low sensitivity, diastolic length, changes in length, time of stimulation, and rate of change of systolic force or length were photographed on an eight channel Electronics for Medicine recorder. Measurements of diastolic tension were made at sensitivities up to 25 mg per cm chart; measurements of changes in diastolic length were accurate to within 2  $\mu$ . Compliance of the recording system, in the absence of a muscle, was less than 15  $\mu$  per g.

The following drugs were used in this study: acetylcholine, epinephrine, norepinephrine, and acetylstrophanthidin. Drugs and other solutions were added either to the muscle chamber (after warming) or to the reservoir bottles containing Tyrode's solution.

Experiments were conducted at temperatures between 30° and 37°C and at stimulation rates of 20-60 per min.

## RESULTS

In other publications we have shown that, for preparations contracting isometrically, an increase in systolic tension (force) caused by PS is accompanied by an increase in diastolic compliance. These results are illustrated again by the experiment shown in Fig. 1 which shows an increase in systolic force and decreased diastolic force upon initiation of PS. This is a clear increase in compliance associated with PS under conditions in which there are no aftercontractions. This point is emphasized because it has been claimed (10) that changes in diastolic tension at constant length result from the development or disappearance of aftercontractions. A compliance change similar to that shown in Fig. 1 has been recorded at temperatures from 25° to 38°C and when PS were introduced at rates between 20 and 100 per min. Similar results have been obtained for cat papillary muscles and ventricular trabeculae and atrial trabeculae from cat and dog and from human papillary muscles.

We do not subscribe to the concept that force-dependent hysteresis need be the sole or even the primary mechanism responsible for the increase in compliance shown in Fig. 1 or for the increases in compliance caused by other positive inotropic interventions. Experiments designed to develop our concept of residual interaction between contractile elements as a basis for changes in diastolic compliance have been presented elsewhere (8). However, evidence presented in the subsequent sections strongly suggests that active processes, as well as force-dependent hysteresis, produce compliance changes.

In order to demonstrate compliance changes when peak systolic force cannot change and diastolic length is fixed, the afterloaded preparation was employed. The nature of the afterloaded preparation is such that during contraction the maximum

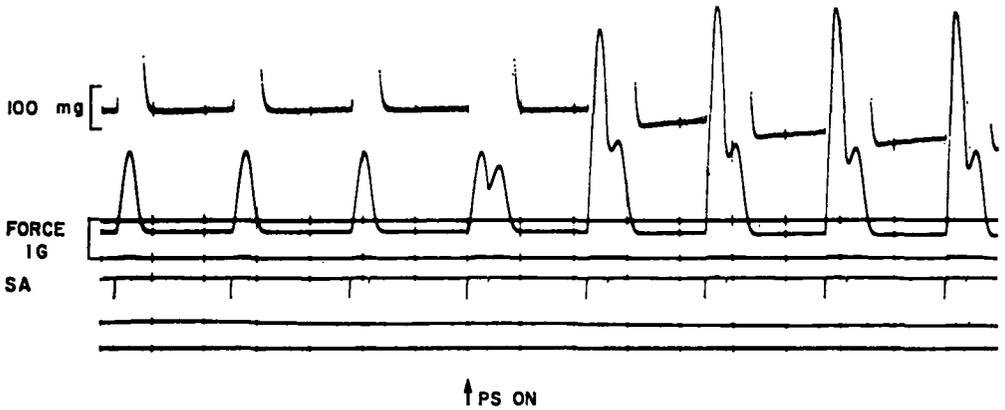


FIGURE 1. Isometric contractions of cat papillary muscle. Top trace is a high sensitivity record of force, only the bottom portion of the contraction is shown; third trace down shows low sensitivity force; SA, stimulus artifact trace. Stimulation frequency, 28 per min; temperature, 37°C. Note increase in systolic force and decrease in diastolic force (increased compliance) when paired stimulation (PS) is substituted for single stimulation. There is no evidence of aftercontraction in these records.

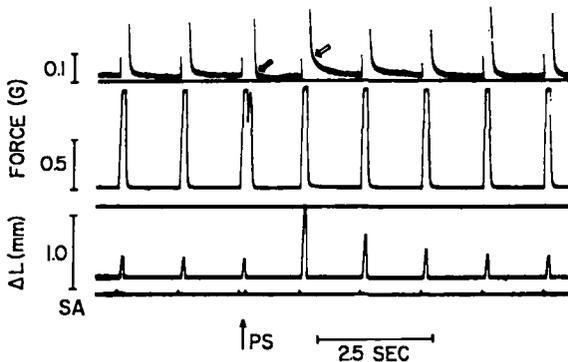


FIGURE 2. Record from cat papillary muscle contracting under afterloaded conditions. Top trace shows high sensitivity force; middle trace is a low sensitivity record of force, bottom trace shows change in length. Stimulation frequency, 25 per min; temperature, 36°C. Induction of one paired stimulus causes a fall in diastolic force (increased compliance) prior to the first potentiated contraction. The postextrasystolic beat shows potentiation (increased extent of shortening) while the subsequent diastolic interval shows that diastolic force is increased (decreased compliance).

force developed cannot vary so long as the contraction achieves enough force to lift the lever. Records from such a preparation are illustrated in Fig. 2. Note that the extrasystole is followed by a diastolic interval in which diastolic tension has decreased; this occurs prior to the first potentiated contraction. Note the increased rate of relaxation following the extrasystole (filled arrow). The diastolic tension following the potentiated contraction is increased concomitant with a decreased rate of relaxation

(open arrow) (8). An increase or decrease in diastolic tension at a fixed muscle length during diastole suggests that changes in the contractile elements induced by the experimental intervention are responsible for the changes in diastolic tension seen here. It is of interest that alterations in extent of shortening during systole may influence the direction and magnitude of the observed changes in diastolic tension in the afterloaded muscle preparation. In Fig. 3, PS is exhibited in a muscle under a greater afterload. Until the positive inotropic action of the PS increases contractile force

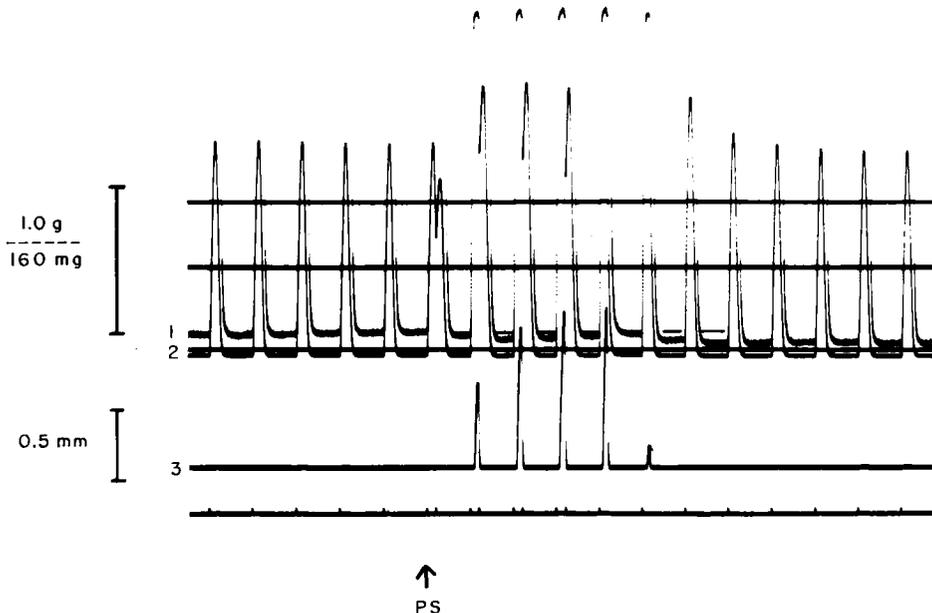


FIGURE 3. Record from cat papillary muscle contracting under afterloaded conditions. Trace 1, high sensitivity record of force, trace 2, low sensitivity record of force, trace 3, record of change in length, bottom trace shows stimulus artifact. Stimulation frequency, 30 per min; temperature, 36°C. Note that before the initiation of paired stimulation (PS), the muscle was contracting isometrically. PS increased systolic force so that the muscle developed enough force to lift the lever off the stop. The first three postextrasystolic diastolic intervals show an increased diastolic compliance (decreased diastolic force, use horizontal bars for reference). As the paired stimulation is continued, the extent of shortening is further increased and diastolic force then increases toward the control value (decreased compliance). See text.

sufficiently to lift the lever, the muscle contracts isometrically. As we have shown previously, there is a small but definite increase in compliance in the diastolic interval following the first extrasystole. The next contraction is potentiated enough so that the muscle lifts the lever off the stop, shortens, and then returns to the same diastolic length as in the preceding contractions; diastolic length remains constant because of the stop. Note that with diastolic length unchanged, compliance is further increased. However, as the paired stimulation is continued and extent of shortening is increased, diastolic tension rises (decreased compliance) again indicating that extent of shorten-

ing must be considered as having an influence on the character and magnitude of tension during diastole. This is also apparent from the records of the contractions immediately following cessation of PS, for with extent of shortening still increasing, diastolic tension rises. The next contraction is still potentiated and lifts the lever but extent of shortening is decreased. Here compliance has increased again with no change in peak systolic force or diastolic length. As potentiation wanes still more in the next contraction, peak systolic force decreases, the muscle does not shorten and, at its same diastolic length, compliance continues to increase.

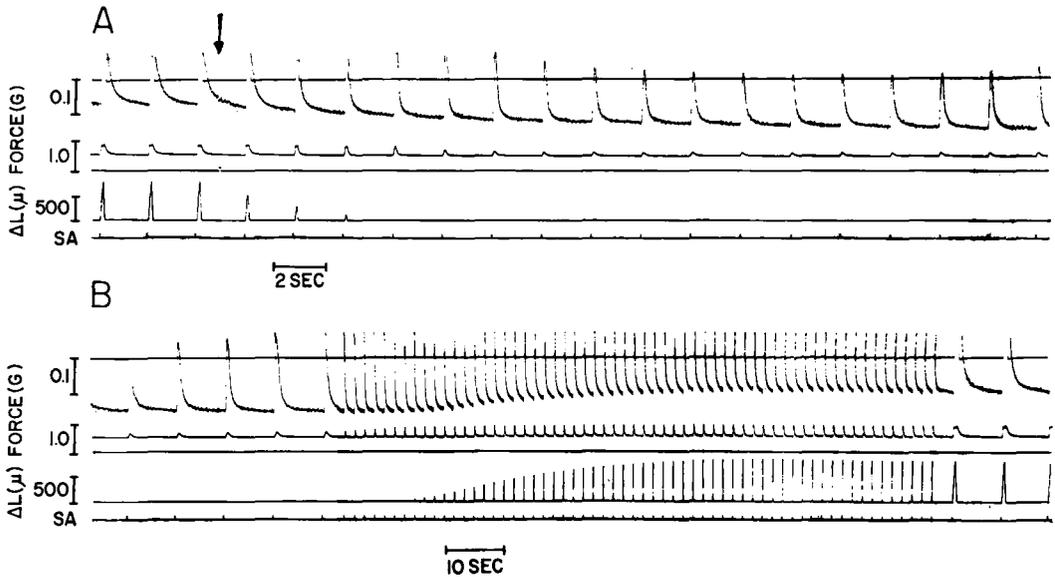


FIGURE 4. Afterloaded contractions recorded from a dog atrial trabeculum. In both A and B, the top calibration refers to the trace of high sensitivity force; the next is a trace of low sensitivity force. Below the marker trace is a trace of change in length ( $\Delta L$ ); bottom trace shows stimulus artifacts. Stimulation frequency, 30 per min; temperature, 37°C. Note that in A, the injection (arrow) of ACh (1  $\mu$ g per ml bath) causes a negative inotropy (decreased shortening), a fall in diastolic force (increased compliance), and an increased rate of relaxation. As the action of ACh continued, the muscle failed to lift the lever off the stop and the muscle contracted isometrically with decreasing peak systolic force and increasing compliance. As the ACh is washed out of the bath the responses of the muscle return to control values (Fig. 4 B).

A positive inotropic intervention has been shown to increase compliance in isometric (Fig. 1) and afterloaded (Figs. 2 and 3) muscles except when extent of shortening is increased. To answer the question as to what a negative inotropic agent would do to compliance in the afterloaded preparation, acetylcholine (ACh) was injected into the tissue bath containing a dog atrial trabeculum during the perfusion with Tyrode's solution (Fig. 4). The ACh produced an immediate decrease in diastolic tension in the diastolic interval during which it was injected (compliance increased). Then for the three subsequent beats, with peak systolic force and diastolic length un-

changed, extent of shortening is decreased and compliance increases from beat to beat. Note that in the first three contractions following the ACh injection the interval during which the muscle develops enough force to lift the lever is shortened. In addition, as the action of the ACh intensifies the muscle fails to develop enough force to lift the lever off the stop. During this period of decreased duration of force development and decreasing peak systolic force, compliance continues to increase. When enough of the ACh has been washed out of the bath (Fig. 4 B), the muscle shows recovery toward control values in all the recorded parameters. These data operate against passive force-dependent hysteresis either of the muscle or the suspension system as being a significant factor in the diastolic compliance changes seen with ACh. Fig. 5 illustrates the response of an afterloaded dog atrial trabeculum to an injection of a smaller dose of ACh ( $0.25 \mu\text{g}/\text{ml}$  bath). Again, there is a definite and reversible change (fall and rise) in diastolic tension at constant muscle length. To produce this increase in dia-

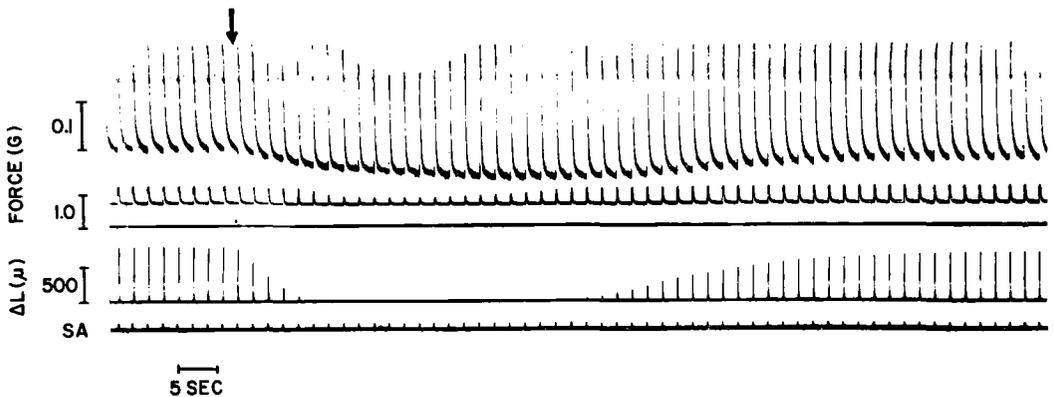


FIGURE 5. Afterloaded contractions recorded from a dog atrial trabeculum. Traces are described in Fig. 4. Note increased diastolic compliance and decreased shortening upon injection (arrow) of ACh ( $0.25 \mu\text{g}$  per ml bath). The changes in diastolic tension occur in spite of the maintenance of fixed external muscle length during diastole.

stolic compliance the length of the contractile apparatus itself must have increased while external muscle length remained fixed in diastole. Thus, under certain conditions, the external length of the muscle does not accurately reflect the dimensional state of the sarcomeres in diastole. Figs. 6 and 7 illustrate the effect of norepinephrine on cat papillary muscle and dog atrial trabeculum contracting under afterloaded conditions. In both instances diastolic tension increased in spite of the maintenance of fixed external muscle length during diastole. This was concomitant with the expected catecholamine-induced positive inotropy (increased extent of shortening). We have seen similar responses to catecholamine with human papillary muscle and Fig. 8 illustrates the response of this muscle to epinephrine injected directly into the bath. This particular muscle was placed in the bath 24 hr prior to the experiment and represents a muscle in failure. The epinephrine induced a change in the contractile apparatus such that the muscle would in diastole bear more and more of the load with no alteration in diastolic length (Fig. 8 B and C). However, as the action of the

epinephrine increases and the sarcomeres lengthen still less during diastole, the muscle fails to lengthen enough to allow the lever to reach the stop (Fig. 8 D). This record clearly establishes the sequence of changes which may underlie the response of cardiac muscle to catecholamine under these extreme conditions. The heretofore unrecognized alteration in sarcomere dimensions during diastole is followed by the gross representation of these changes as manifested in a reduction in diastolic length of the whole muscle (Fig. 8 D).

When acetylcholinesterase is added to the reservoir of fluid perfusing an afterloaded papillary muscle preparation, the response is as illustrated in Fig. 9. There is

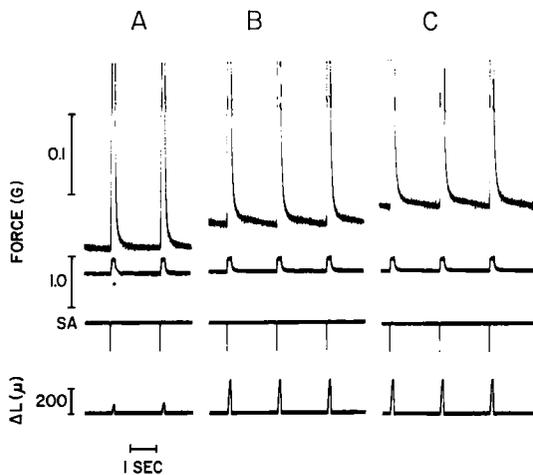


FIGURE 6. Afterloaded contractions recorded from cat papillary muscle. Top trace shows high sensitivity force, second trace shows low sensitivity force, third trace, stimulus artifact (SA); bottom trace shows change in length. Stimulation frequency, 30 per min, temperature, 37°C. Panel A, control record. Panel B shows the effects of norepinephrine ( $1 \mu\text{g}$  per ml bath) 20 beats following administration: Note increased extent of shortening, decreased diastolic compliance (increased diastolic force), and the altered rate of relaxation between A and B. Panel C shows additional decrease in compliance and a slight increase in extent of shortening, 40 beats following the record in panel B.

an increase in extent of shortening, an increase in the duration of maximum peak tension, and a decrease in diastolic compliance at a fixed diastolic muscle length.

After it had been established for the afterloaded preparation, that ACh increases compliance while a cardiac glycoside can decrease compliance, it appeared that ACh could be used to antagonize the response to acetylcholinesterase. Fig. 10 illustrates the results of such an experiment using an afterloaded dog atrial trabeculum. The glycoside was infused at a concentration and rate ( $1 \mu\text{g}$  per ml, 6 ml per min) which would produce an increase in diastolic tension and an indication of aftercontraction. Then while continuing the glycoside administration, ACh was injected into the bath. There was an immediate and marked decrease in diastolic tension at fixed diastolic muscle length. Aftercontractions disappeared and except for one contraction the

extent of shortening decreased. The muscle remained afterloaded during the whole run. Note that in spite of the negative inotropic action of ACh, the first contraction following the abrupt increase in compliance is potentiated (increased shortening). This could occur if the sudden compliance increase elicited by the ACh resulted from an abrupt decrease in residual cross-links in the contractile apparatus so that the next contraction could utilize more cross-links and the extent of shortening could therefore

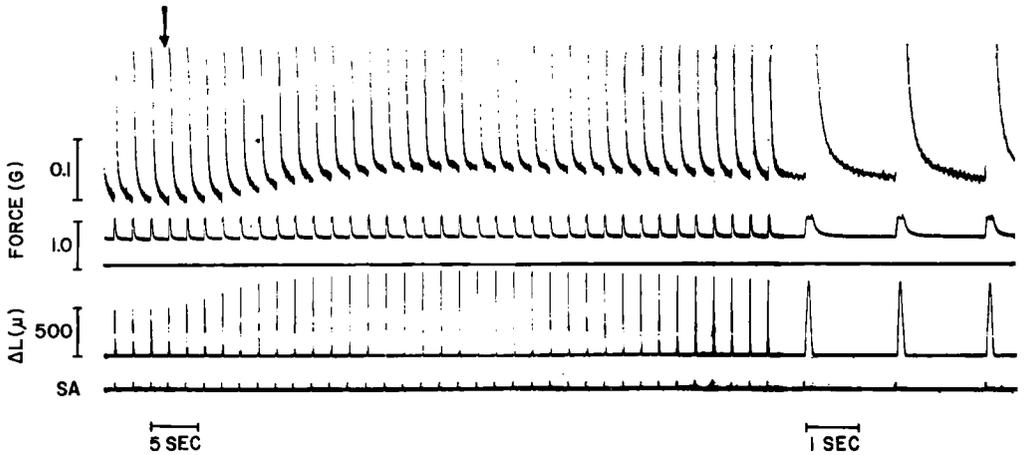


FIGURE 7. Afterloaded contractions recorded from a dog atrial trabeculum. Top trace shows high sensitivity force. Next trace shows low sensitivity force. Below the marker trace is the record of change in length, bottom trace shows stimulus artifacts (SA). Stimulus frequency, 30 per min; temperature, 37°C. The injection (arrow) of norepinephrine (1  $\mu\text{g}$  per ml bath) is followed by a marked increase in shortening and a marked decrease in diastolic compliance. Note that the pattern of relaxation changed early in the response to norepinephrine as aftercontractions appeared. However, aftercontractions were not present later on during the action of the norepinephrine (right side of record) and compliance was still decreased.

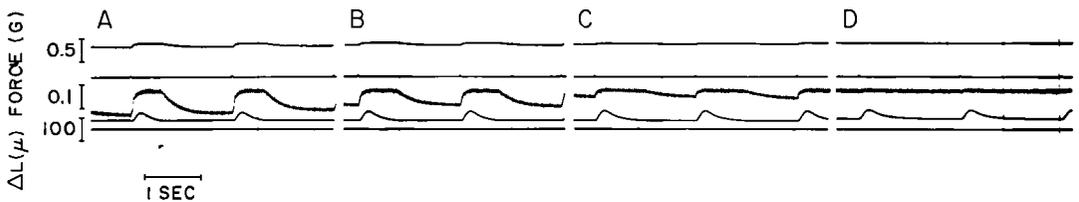


FIGURE 8. Afterloaded contractions recorded from a human papillary muscle. Top trace shows low sensitivity force; next trace down is a record of stimulus artifacts. Third trace down shows high sensitivity force; bottom trace shows change in length. Rate 35 per min; temperature, 33°C. Panel A, control record. Panel B shows the positive inotropic effect of epinephrine (1  $\mu\text{g}$  per ml bath) 30 beats after its injection as reflected in an increased extent of shortening. Note the decreased compliance (increased diastolic tension) concomitant with a change in the rate of relaxation. This decrease in compliance is accentuated 60 and 120 beats after the drug was given (panels C and D).

be increased. This also suggests that ACh may at the same time act to decrease quantitatively the magnitude of the contractile event by one action and in addition exert an effect on those mechanisms involved in the actual termination of one contraction and readying the muscle for the next, so that during diastole sarcomeres become longer without a change in external muscle length.

The following section deals with the results of experiments conducted on atrial and ventricular muscle under isotonic conditions. Our preliminary *in vivo* data (1) indicated that for the isolated dog right ventricle conditions could be altered so that at constant tension diastolic length increased. Since isotonic systems only approach

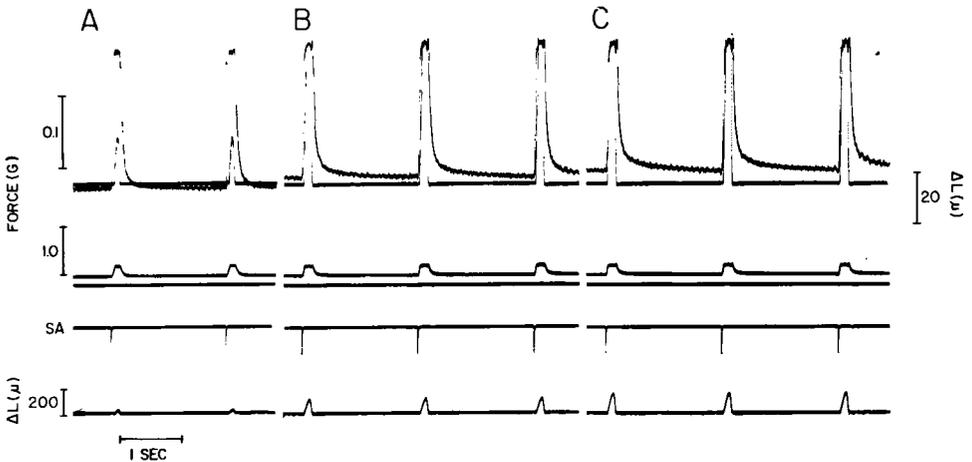


FIGURE 9. Afterloaded contractions recorded from a cat papillary muscle. Top trace shows high sensitivity force. Next trace down shows high sensitivity change in length; third trace shows low sensitivity force. Below the trace showing stimulus artifacts (SA) is the low sensitivity trace of change in length. Panel A is the control record. Panels B and C show the effects of acetylcholine 60 and 120 beats respectively after the addition of the drug to the perfusion fluid ( $1 \mu\text{g}$  per ml, 6 ml per min). Note the increased shortening and decreased diastolic compliance during acetylcholine administration concomitant with a decrease in the rate of relaxation.

isotonicity we feel that it is important initially to present results of experiments in which the changes in diastolic length could not be due to the imposition of artifacts produced by small varying forces imparted to the muscle due to acceleration of a system with finite mass. Fig. 11 illustrates a short control period of an isotonic recording preceding the injection of ACh into the bath. The ACh, when injected, results in the almost immediate onset of increased compliance and a decrease in extent of shortening. This response demonstrates an increase in diastolic length under constant load, decreased duration of the period of contraction, and decreased extent of shortening. The potential for the presence of any lever artifacts of significance is reduced here since under conditions of decreased extent of shortening these artifacts would be expected to act to affect a reduction and not an increase in diastolic length when compared with the control responses. Under the influence of the ACh, and while diastolic

compliance continued to increase, PS was applied to the muscle. With each successive paired contraction diastolic length decreases as extent of shortening increases. The extent of shortening of the last potentiated but unpaired contraction is equal to that of the control period but, because the action of ACh still persists, diastolic length is still increased over the control length even though there has been no change in load

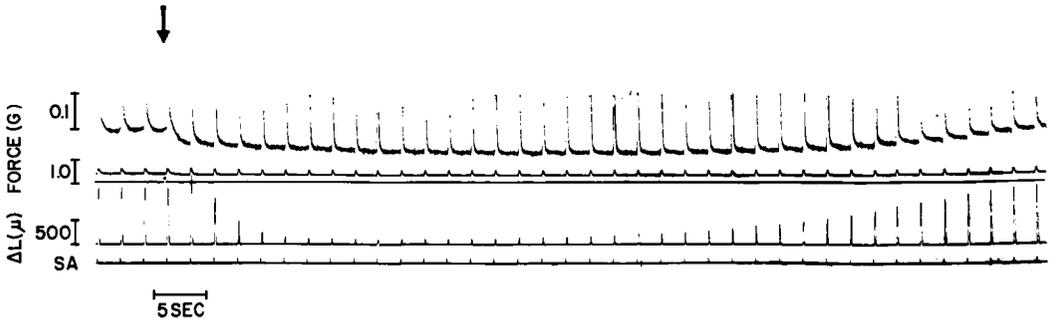


FIGURE 10. Afterloaded contractions recorded from a dog atrial trabeculum. Top trace shows high sensitivity force. Next trace shows low sensitivity force. Below a marker trace is the record of change in length and bottom trace shows stimulus artifacts. Stimulation frequency, 32 per min; temperature, 37°C. This tissue was maintained on a continuous perfusion of acetylcholine (1  $\mu\text{g}$  per ml, 6 ml per min) which induced aftercontractions and decreased diastolic compliance. At the arrow, acetylcholine (0.25  $\mu\text{g}$  per ml bath) was introduced. Note the marked fall in diastolic tension (increased compliance) after the dose of ACh. See text.

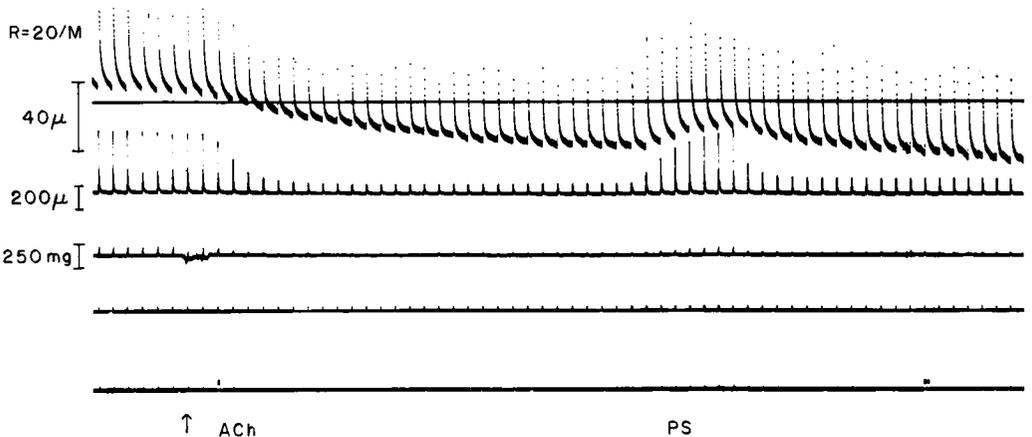


FIGURE 11. Isotonic recording from a dog atrial trabeculum. Top trace shows high sensitivity recording of change in length. Middle trace shows low sensitivity recording of length change. Also on the record is the force trace and stimulus artifact. Stimulation frequency, 20 per min; temperature, 34°C. Note increased compliance (increased diastolic length) and negative inotropy (decreased extent of shortening) following administration of acetylcholine (20  $\mu\text{g}$  per ml bath) and the alterations induced by PS.

on the muscle. While the effect of PS on diastolic length is to decrease it while the extent of shortening is increased, the factors involved in compliance change appear to be partially independent of alterations in extent of shortening. Paired stimulation produced a decrease in diastolic length, increased extent of shortening, and an increase in  $dl/dt$  all of which provides another illustration of the relative lack of significance of lever artifacts here since lever artifacts would have tended to lengthen the muscle under the conditions imposed by paired stimulation. At this point advantage was taken of the fact that ACh induces negative inotropic changes in atrial muscle and positive inotropy in ventricular muscle. The question to be answered was whether the action of ACh on phenomena of the diastolic interval might be the same regardless of

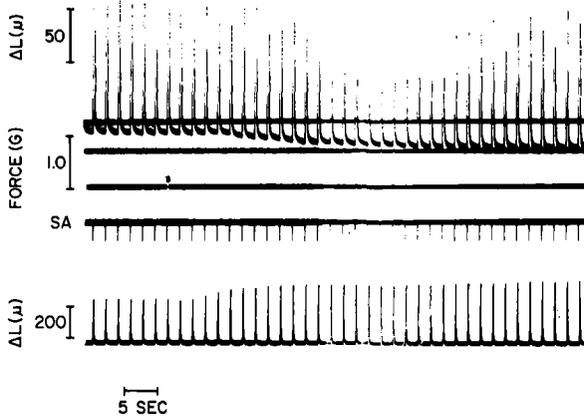


FIGURE 12. Isotonic recording from cat papillary muscle. Top trace shows high sensitivity change in length. Next trace down is the record from the force transducer. Below the marker trace is the record of stimulus artifacts. Bottom trace is a low sensitivity record of length change. Stimulation frequency, 60 per min; temperature, 37°C. Note that the administration of acetylcholine (marker) caused a marked increase in diastolic length and an increase in extent of shortening. Compare these results with those in Fig. 11 and note an increase in compliance with ACh in both experiments.

the direction of the inotropic change. Accordingly, ACh was injected into the bath containing an isotonic preparation of a cat ventricular trabeculum (Fig. 12). Note that accompanying the increase in extent of shortening there is a definite increase in diastolic muscle length at a constant load. Thus ACh can increase diastolic compliance in cardiac muscle while affecting the magnitude of systole in either direction. Not only does this type of data motivate us strongly in our search for the mechanisms which might influence the degree of residual interaction between contractile elements during diastole but it should serve to eliminate concern over variable diastolic compliance as a phenomenon born of artifact.

We have already shown in the afterloaded preparation that ACh can increase compliance in the presence of a concentration of acetylcholinesterase which decreased compliance (see Fig. 10). When acetylcholinesterase is infused in a relatively high dose (1  $\mu\text{g}$  per ml) at 6 ml per min over a prolonged period into a dog atrial prepara-

tion contracting isotonically, the extent of shortening gradually decreases while diastolic length decreases (compliance decreases) (Fig. 13). The first nine contractions of Fig. 13 show a gradually decreasing diastolic length and the presence of aftercontractions. At the first arrow ACh was injected into the bath and an abrupt increase in diastolic compliance (increase in diastolic length) is seen to have occurred. Compliance continues to increase until the ACh concentration is sufficiently reduced by the diluting effect of Tyrode's solution containing the glycoside. At that point, compliance again decreases. When another dose of ACh is injected (Fig. 13, second arrow), the increase in diastolic length is seen to occur again. In this experiment the changes in extent of shortening seen in the low sensitivity trace are also of real interest. With the onset of the increase in diastolic length caused by the ACh, the extent of shortening is seen to increase greatly. ACh usually has a negative inotropic action on

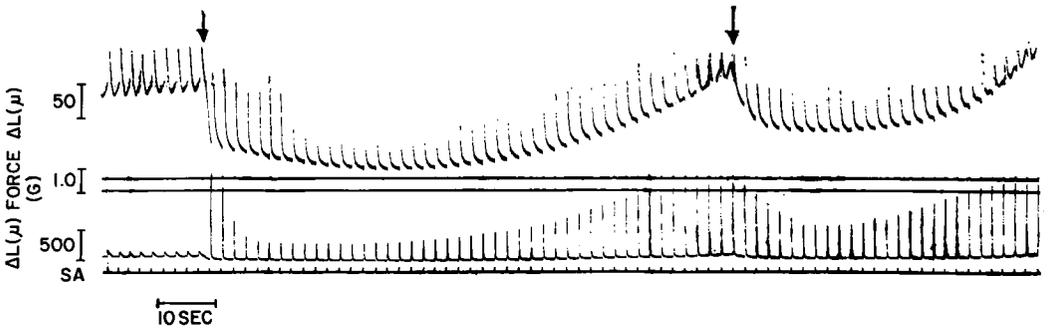


FIGURE 13. Isotonic recording from a dog atrial trabeculum. Top trace shows high sensitivity change in length. Next trace down is a record from the force transducer, after the marker trace is the low sensitivity record of change in length. Bottom trace shows stimulus artifacts. Stimulation frequency, 30 per min; temperature, 37°C. The tissue was maintained on an infusion of acetylthioanthidin ( $1 \mu\text{g}$  per ml, 6 ml per min) which induced aftercontractions and a decreased diastolic length. At the first arrow, acetylcholine ( $0.25 \mu\text{g}$  per ml bath) was added. Note the marked increase in diastolic length, increased shortening, and abolition of the aftercontractions. Acetylcholine was added once again at the second arrow with similar effect. See text.

dog atrium. However, when compliance has been decreased by the glycoside and is then abruptly increased sufficiently by the ACh, the ensuing contractions are greatly increased in magnitude. It may be assumed that the glycoside had so reduced compliance that during diastole the number of residual contractile element cross-links had increased to the point where too few free connections were available between the contractile elements at end-diastole to permit optimum systole. ACh increased compliance and thus reduced, as we believe, the number of residual cross-links in diastole. The ensuing contractions showed a much greater extent of shortening because more connections could be made between the actin and myosin filaments. That the change in length caused by ACh can be related to alterations in sarcomere length is supported by the results of similar experiments under similar conditions but using the afterloaded preparation (Fig. 10). The negative inotropic action of ACh acts partially to

antagonize the positive inotropic effect of increasing diastolic compliance. This is seen by following the compliance increase to its maximum as the ACh action manifests itself fully and noting that its usual negative inotropic action on the contractile phase of contraction partially overcomes the effect of the ACh action on relaxation phenomena and their role in contraction magnitude.

If as we believe, compliance changes reflect an alteration of the contractile elements during diastole, then condition-dependent changes in muscle length should be demonstrable in the unstimulated muscle. Fig. 14 represents the results of such an experiment. A dog atrial trabeculum, contracting isotonically, was perfused with Tyrode's solution containing acetylcholinesterase inhibitor (1  $\mu\text{g}$  per ml, 6 ml per min) until evidence of a compliance decrease (decreased diastolic length) occurred. Then when

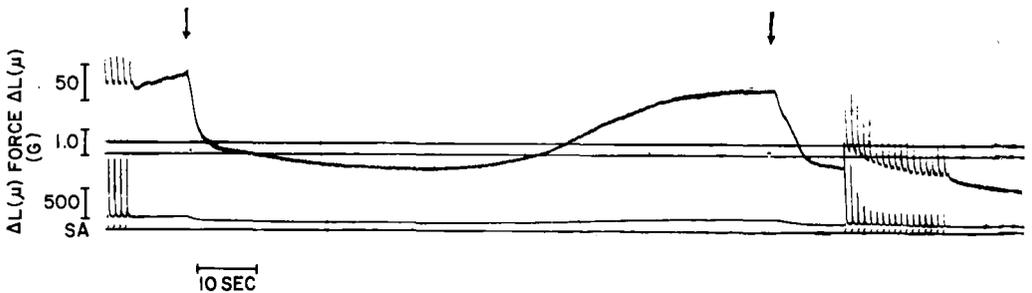


FIGURE 14. Isotonic recording from a dog atrial trabeculum. Stimulation frequency, 60 per min; temperature, 37°C. Traces are as described in Fig. 13. The muscle was maintained on acetylcholinesterase inhibitor (1  $\mu\text{g}$  per ml, 6 ml per min) which caused after-contractions and a decrease in diastolic length under constant load. Note the decrease in diastolic length upon cessation of stimulation. Upon addition of acetylcholine (first arrow) (0.1  $\mu\text{g}$  per ml bath) to the unstimulated muscle there was a marked increase in diastolic length. The same dose of acetylcholine was added once more (second arrow) with a similar result. See text.

the stimulus was stopped, muscle length decreased during the period of quiescence. This decrease in muscle length at constant load is in itself convincing evidence of an active change in the state of the contractile apparatus since the usual trace of unstimulated muscle is quite flat after a few seconds. However, when a small dose of ACh (0.25  $\mu\text{g}$  per ml bath) is injected (first arrow, Fig. 14), there is a remarkable increase in length which occurs just as the small volume (0.05 ml) containing the ACh is injected into the 8 ml bath. Muscle length continues to increase and then as ACh is washed out muscle length decreases again. The ACh was injected again (second arrow) and the unstimulated muscle once again abruptly lengthened. During the action of this second dose of ACh when the muscle was stimulated again, it contracted from a much longer diastolic length than before the first ACh dose. This is similar to the compliance increase seen in Fig. 13. After 17 contractions, the stimulator was turned off again and during the unstimulated period, diastolic length increased. This should be compared with the decrease in diastolic length seen at the beginning of this record (before ACh was injected). In summary, this experiment demonstrates that

during a period free from stimulation (an extended diastole) one drug may cause muscle length to shorten and another drug cause it to increase while the load borne by the muscle remains constant in both instances.

## DISCUSSION

The results of the experiments presented here lend support to our contention (2, 3, 8) that variable diastolic compliance must be considered as part of the process of contraction of cardiac muscle. Diastolic length at constant load and diastolic tension at constant external muscle length do vary depending on experimentally established conditions. We believe that the results cannot be explained on the basis of either force-dependent hysteresis or on equipment-dependent artifacts. These points have been discussed in detail.

Changes in diastolic compliance appear to result from mechanisms which are separable under some conditions from the effects of systole on compliance because unstimulated muscle shows condition-dependent compliance changes. Furthermore, in a number of instances, compliance increased in a stimulated muscle not only when it exhibited an increase in systolic force or decrease in extent of shortening but also when systolic force decreased or extent of shortening increased due to altered experimental conditions.

If the changes in compliance are not due to passive factors, then the responses noted must represent varying degrees of residual interaction between contractile elements during diastole. Conditions which increase compliance would decrease the degree of this interaction and enhance the potential for an increase in magnitude of the ensuing contraction. Whether or not the contraction magnitude does increase is dependent upon other conditions which affect contraction in addition to the influence of the factors involved in increased compliance. This point is supported by the results of those experiments which show that the negative inotropic action of ACh is momentarily overwhelmed by the effects of the increase in compliance it causes. Along similar lines, catecholamines increase contractility in spite of either a decrease in muscle length at constant load or an increase in diastolic tension when the muscle is afterloaded. Here the influence of the decreased compliance is not great enough to decrease the positive inotropy. The experiments with acetylcholinesterase inhibitors are interesting in that, with time, the magnitude of the positive inotropy decreases when compared to the control contractions and finally changes sign as the action of a "toxic" dose begins to manifest itself while compliance continues to decrease throughout this period. Under these conditions, the addition of a negative inotropic agent (ACh) resulted in a positive inotropy possibly because ACh abruptly increased compliance. Thus the potential for the glycoside to improve contractility appears to persist when high concentrations are used but this action is manifested only when the other action of the glycoside, namely to decrease compliance, is antagonized by ACh. Since compliance is variable, mechanisms which can alter diastolic length at constant load either from beat to beat or during unstimulated periods must be considered as part of the active processes involved in cardiac contraction.

It is important to note that drug-induced aftercontractions and contracture in the stimulated preparation are both relieved by ACh. Objections might be raised regard-

ing the value of data obtained during cardiac glycoside-induced aftercontractions or varying degrees of contracture, but the decrease in length seen during unstimulated periods does demonstrate the existence of active processes involving the contractile apparatus during diastole. The glycoside produces compliance changes which are either reversible upon removal of the drug or, more significantly, can be antagonized abruptly by ACh. These results suggest that contracture in these experiments is an example of a marked, sustained, drug-induced reversible increase in the degree of residual interaction of the contractile elements.

It appears from our experiments that the meaning of diastole must be modified to include the potential for dynamic variations in the rate and degree of relaxation, considered either in terms of tension or length. In addition, the results of the experiments using afterloaded preparations make it apparent that the dimensions of the contractile elements can change while external muscle length remains fixed. This may be most significant when considering the phenomenon of failure. We suggest that in failure dissociation may exist between changes in external length and the dimensions of the contractile apparatus and that this may underlie the measurable alterations in performance concomitant with decompensation. In a number of instances we have pointed out the fact that the experimental intervention altered the rate of relaxation. If rate of relaxation is delayed in an afterloaded preparation with diastolic muscle length unchanged, then we may assume that what delayed relaxation indicates is an altered rate of dissociation of actin and myosin filaments of the contractile apparatus during diastole. Thus, it is appropriate to suggest here that alterations in the condition of a muscle during the diastolic interval, which are variously termed aftercontraction, contracture, and altered rate of relaxation, are in fact special instances of the compliance changes which a cardiac muscle can exhibit.

Variable diastolic compliance is a phenomenon exhibited by atrial and ventricular muscle from the cat, dog, and man. The results of our previous studies (2, 3, 8) and those presented here allow us to conclude that changes in diastolic compliance can influence cardiac function by modifying cardiac acceptance of blood during diastole and can modify systole by influencing the degree of residual interaction between elements of the contractile apparatus.

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# The Present Status of Paired Pulse Stimulation of the Heart

PAUL F. CRANEFIELD

From The Rockefeller University, New York 10021

## CLINICAL STUDIES

The use of the techniques of paired and coupled stimulation of the heart in clinical situations has made reasonable progress since the first conference was held in 1965.<sup>1</sup> Before turning to some of the specific investigations it might be noted that most investigators now feel that the equipment initially available was not entirely suitable. This is reflected in the fact that a number of the more detailed studies reported at the second conference were made with equipment especially designed and built for the study in question. It seems likely that a sophisticated combination of physiological stimulators adequately isolated from the patient to prevent 60 cycle leakage can be used for nearly any form of paired pacing. Similarly, stimulators can be built for the purpose in any competent medical electronics shop. The commercially available stimulators can probably be used too, but they may lack the flexibility which is desired for investigative purposes, and in any event cannot be used successfully and safely without a full knowledge of their limits and potential. Those most likely to have such knowledge are also likely to prefer to design their own equipment, especially at this stage.

It should also be noted that although caution continues to be expressed about the hazards of ventricular fibrillation and about the dangers of increasing the oxygen utilization of the myocardium, a rather large number of studies have been carried out without adverse effects and, as we shall see, with beneficial results.

*Diagnostic Studies* Even at the first conference the use of the technique for clarifying certain difficult diagnoses was reported; such studies have been reported in greater detail at the second conference, most comprehensively by the laboratory of Professor Durrer. The use of paired or coupled stimulation for diagnosis is now felt by Durrer to be a valuable but on the whole supplementary procedure, which gives results which can usually be obtained by more conventional means. On the other hand it is possible that time will show that there are particular situations in which potentiation can give answers to specific questions of importance for therapeutic decisions, answers obtainable in no other way. It is, of course, very clear that the use

<sup>1</sup> Copies of the proceedings of the first conference are still available. They may be obtained by writing to The Stechert-Hafner Service Agency, 31 East 10th Street, New York, New York 10003, and requesting *The Bulletin of The New York Academy of Medicine* for May and June 1965. The cost of the two issues together is \$4.00.

of potentiation for diagnosis of that kind requires a profound familiarity not only with the technique but also with the physiology of the normal and diseased heart. It can thus be used only investigatively, and only in laboratories which, like that of Durrer, have active programs of physiological study as well as active clinical programs.

*Arrhythmias* From the first it has been apparent that the presence of two complete cycles of electrical activity accompanied by only one effective contraction might be a useful way of slowing the rate of effective contractions in tachycardias irrespective of their underlying cause. We originally assumed that the protective effect of paired or coupled pacing resided chiefly in the presence of two complete refractory periods in quick succession, a phenomenon which prolongs the period in which a spontaneous abnormal beat cannot propagate. It has since become obvious that in paired or coupled pacing there is an additional effect which tends to suppress arrhythmias, which is the presence in each cycle of two complete waves of propagated excitation, each of which invades, excites, and thus suppresses latent pacemakers. Paired or coupled pacing thus replaces a rapid and/or irregular rhythm with a regular one in which there are two electrical events for each effective mechanical event, and in which there are two sorts of suppression of spontaneous rhythm.

At the present conference Durrer's group remarked that the use of paired or coupled pacing has lost favor in the control of arrhythmias because of the introduction of the use of  $\beta$ -blockade and DC countershock in the treatment of arrhythmias. Dr. Resenkov, however, emphasized the belief that in patients who have had open heart surgery "Paired stimulation should be considered in any patient in whom electroconversion and drug therapy fail to control the heart rate and should be used before serious effects of the tachycardia are allowed to develop." Dr. Gourgon and his colleagues report a series of successes in controlling serious complications of myocardial infarction accompanied by tachycardia; that group has used coupled rather than paired pacing, following and validating a suggestion advanced by Peter Frommer at the first conference. There are surely tachycardias, clinically serious, which do not respond to either drug treatment or DC countershock, and there seems to be adequate reason to continue to regard paired or coupled pacing as a technique to be employed (at least investigatively) in such situations. Indeed, when one hears of countershock repeated over and over with increasingly higher strengths of current, one feels that serious damage might result to the patient in a situation in which coupled pacing might be simpler, quicker, and safer, as well as being effective. As with all potential clinical applications of the technique only long and systematic control studies can give the final answer, but the method seems to have justified, both in terms of safety and usefulness, a continuing and thorough study. In this connection we might note in Dr. Resenkov's summary the belief held by himself and his colleagues at The National Heart Hospital (London) that "Although demanding as a technique, paired stimulation of the ventricle should be available in any unit undertaking intensive care, particularly for its action in controlling ventricular rate; dysrhythmias in the post-operative period following heart surgery will respond particularly well."

*Potentiation in Cardiac Failure* The postextrasystolic potentiation which accompanies paired or coupled pacing has not, from the beginning, seemed to work par-

ticularly well in the heart in established chronic failure, while it has shown dramatic effects in acute experimental failure. Such clinical studies as have been conducted have tended to confirm the relative lack of effectiveness in chronic failure, although one must admit that established chronic failure is a pathological state of the whole organism which probably cannot be reversed, at least not at all rapidly, by an increase in the functional capacity of the heart without extensive attention to the systemic aspects of chronic failure.

The area of maximum controversy continues to be that of the usefulness of paired or coupled pacing and postextrasystolic potentiation in the relatively acute failure which may follow open heart surgery or may supervene in myocardial infarction with shock. I have summarized elsewhere (1) a series of six cases in which profoundly moribund patients were brought into good clinical condition by the use of the technique; since that time two or three similar cases have come to my attention. At the second conference comparatively little was reported which bears on this problem. Dr. Resnekov's successful cases as well as those of Dr. Gourgon were in the main cases in which myocardial infarction, if present, was accompanied by tachycardia. The control of the tachycardia may have been the principal cause of the beneficial effects in those cases. Most of what was said at the conference about the use of potentiation in patients in whom myocardial infarction and shock had brought about a near-terminal state, but in whom the picture was not dominated by tachycardia, was pessimistic. A closer analysis of the material presented revealed that there have been few, if any, sustained and systematic investigations of the use of the technique in that condition. At a given institution trials have been made in a few or perhaps a dozen patients, various difficulties have been encountered, various complications have been noted, and no single decisive success has been achieved, whereupon the technique has been put aside. In the same period myocardial infarction with profound shock has continued to be most refractory to treatment and quite likely to lead to the death of the patient. For that reason there still seems to be every reason to explore the possible benefits of the technique. There is, however, no justification for any further more or less casual use of the technique. It clearly will not work easily or simply, it clearly will not work always, and perhaps not even often, and it clearly cannot be used except by persons deeply familiar with the method who are willing and able to spend a long time at the bedside, giving constant attention to the patient and the stimulators. Yet, as I have said before, if the technique can, properly applied, save the lives of even 10% of patients with myocardial infarction and profound shock, it could save quite a few lives. Now that intensive and highly instrumented care of patients with myocardial infarction is generally accepted and widely available, there ought to be one or two institutions in which a carefully planned and executed, and *sustained* study of this technique is used. A series of perhaps a hundred consecutive cases, treated by persons expert in the technique, might give us some answers. Otherwise we will have to continue to wonder whether we may be neglecting a technique which could be life-saving. I believe that there is a good chance that one or two such well-planned and conducted studies may be initiated soon; they should certainly be worthwhile and will probably result in the accumulation of a great deal of scientifically valuable information no matter what decision may finally be reached about the clinical value of the technique in myocardial infarction with profound shock.

## GENERAL LABORATORY STUDIES

In my summary of the first conference (2) I pointed out a number of interesting and important questions which had been raised and which could be resolved by laboratory study. It is interesting to note that many of those questions remain uninvestigated. We have not, as yet, ascertained whether paired pulse stimulation raises the oxygen consumption of strands of cardiac muscle *in vitro*, provided that the total external work is unchanged. I do not believe that anyone has ascertained the effect of paired pulse stimulation on the contractility of Purkinje fibers. Nor has there been a systematic study of function curves of the ventricle under paired or coupled stimulation. On the other hand many of the questions raised at the first conference have been investigated, as have some questions not raised at the conference. The articles presented in the present volume speak for themselves and are not readily summarized since they range over a wide area, but some points may be made here.

The first conference was organized at very short notice and therefore did not have the opportunity to hear from Drs. Kruta and Bravený. At the second conference Dr. Kruta was able to present his general theory of the effect of rate and rhythm on the contractility of the heart and to place the potentiating effects of paired and coupled stimulation in a broad and extremely interesting framework. Dr. Meijler was able to present certain material of a similar nature, in part reflecting earlier work done by him in collaboration with Dr. Bravený. These articles, as well as that from the laboratory of Dr. Kavalier, again draw our attention to the probable importance of shifts in the distribution of  $Ca^{++}$  in the genesis of potentiation, but the exact details of this remain to be worked out. Dr. Hirsch reports an investigation of the effect of the location of the ventricular electrode on the efficiency of paired pacing: his findings may well prove of particular importance to those investigating the clinical usefulness of paired or coupled pacing as a means of potentiation in cardiac failure. The same is true of the effects studied in the same laboratory, and reported by Dr. Lluch, on the effect of the driving frequency on the efficiency of paired stimulation.

Studies on paired and coupled pacing in the presence of myocardial infarction in dogs, as reported by Dr. Kelly, suggest that the technique is nowhere near as likely to produce ventricular fibrillation as some had feared, and that the metabolic cost of the potentiation can be well-tolerated. These conclusions are subject, however, to the reservation that the condition of the coronary arterial tree in the experimental animals used is not comparable to that of the human being suffering from a spontaneous infarction. The extremely interesting studies reported by Dr. Sleator bring some very curious phenomena to our attention as well as again emphasizing the possible importance of  $Ca^{++}$  in potentiation. Dr. Bassett's report of investigations related to the mechanics of contraction of papillary muscle touches more nearly on the question of diastolic compliance, which is discussed below.

It is evident that the introduction of paired and coupled stimulation has amply justified the prediction made at the first conference that if it did nothing else it would provoke research of both practical and theoretical importance. My general impression is that it continues to do so but that paired pulse stimulation is no longer an object of primary study. It has, instead, been added to the list of techniques which can be used by the experimenter to aid him in the analysis of a variety of problems. The exact

nature and cause of potentiation probably will not be understood until we understand the nature of contraction in cardiac muscle, but the use of paired pulse stimulation as an investigative technique may bring that understanding closer.

#### DIASTOLIC COMPLIANCE

The most unexpected and interesting finding which grew out of the early studies of paired and coupled pacing was the observation that diastolic compliance appears to be variable and that the introduction of a premature electrical event is immediately followed by an increase in diastolic compliance which can be detected even before the next contraction. This claim was naturally very stimulating and provocative because it appeared to challenge the long-held view that the diastolic compliance of the ventricle is not in fact variable. These claims, based on research reported from the laboratory of Brian Hoffman, did not meet with general acceptance. They did, however, stimulate investigation of the problem in several other laboratories and one session of the conference was therefore devoted to a discussion of such studies. That session was followed by a long and provocative discussion period which unfortunately failed to register on the tape recorder. Two of the participants did add their contributions to the discussion as appendices to their articles but the bulk of it was lost.

The articles in this section are only five in number and are all clearly written so that neither summary nor interpretation is needed. In addition, as the reader will see, agreement has not been reached on this important question (contrary to the impression given in the introduction to Dr. Koch-Weser's excellent summary of the problem). It is, I think, fair to say that some investigators who had not previously noted changes in diastolic compliance or who had denied the existence of such changes now note the presence of changes similar to those reported by Hoffman (although some investigators do not). What remains at issue is the interpretation of the observations. The questions as yet unresolved (in the sense that there is no consensus as to their answer) appear to be these:

1. Is diastolic compliance a variable in "normal" heart muscle?
2. If so, is it a variable in fully "resting" heart muscle?
3. If diastolic compliance can vary in fully resting and normal heart muscle, does its apparent variability reflect a variation in the interaction of the contractile elements of the resting fiber?

With respect to the first question, I would like to endorse Dr. Koch-Weser's suggestion that we consider any change in diastolic compliance of any kind to be just that: a change in diastolic compliance. If we do this we can move on, as he suggests, to sort out those various types of changes which may be the result of aftercontractions, incomplete relaxation, stress relaxation, and the like, admitting that whatever their cause they do represent a change in the distensibility of the myocardium. This will then permit the discussion to move in two distinct directions. One will be: what is the significance of changes in diastolic compliance, of whatever kind or cause, for the functional state of the ventricle? The other will be, is there a "fundamental" kind of change in diastolic compliance, based upon a change in the degree of interaction of the contractile filaments and, if so, what is the possible significance of such a change for the function of the ventricle?

The whole problem is under active investigation in several laboratories. It seems likely to give rise to insights of great importance for an understanding of the basic mechanisms of cardiac contraction, insights which may well be the most important consequence of the renewed interest in paired and coupled pacing.

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