Hæmodynamic and Clinical Effects of Paired Stimulation of the Heart

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In 1963, Lopez, Edelist, and Katz demonstrated that electrical stimulation could be used for slowing the heart below its spontaneous rate. These workers noted when pacing the heart of a dog that sudden slowing could consistently be produced when the impulse persisted for about 150 m.sec. They were able to show that this effect was due to stimulation at the "make" and the "break" of the impulse, and that it could also be produced by two short electrical impulses separated by about 150 m.sec. This method has been extensively investigated at several centres in the United States (Char-dack, Gage, and Dean, 1964; Braunwald *et al.*, 1964; Ross *et al.*, 1965). In this communication we present the results of hæmodynamic studies in dogs using the technique of paired stimulation of the heart and describe our early experience in the clinical application of the method in four patients.

SUBJECTS AND METHODS

These studies were performed on 14 dogs under general anaesthesia 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 left thoracotomy and the heart stimulated directly, either from the atrium or from the ventricle, by bipolar intramural electrodes connected to a stimulator designed and built by one of us (J.N.) (Fig. 1). Stimuli, either singly or in pairs, were delivered at a rate of between 30 and 250 beats a minute, with a 2 m.sec. impulse duration at voltages of up to 10 volts. The strength of each stimulus was independently variable and the delay between the two stimuli could be adjusted to between 35 and 350 m.sec. Left ventricular pressure was recorded either through teflon tubing (TF 30), or through Grey KIFA tubing, introduced by the technique described by Seldinger (1953) into the apex of the

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left ventricle and connected to a Sanborn transducer, Sanborn carrier amplifier, and direct writing pen recorder (Phillips 3 channel). The electrocardiogram was recorded from limb leads or more usually via an electrode catheter placed in the right atrium from the jugular vein. An electromagnetic flowmeter (Medicon) recorded total flow from the thoracic aorta immediately distal to the origin of the left subclavian artery. Left ventricular pressure, heart rate, and aortic flow were monitored during sinus rhythm and during paired stimulation of the heart. Supraventricular tachycardias were produced by driving the atrium with a second pacemaker at rates of up to 250 beats a minute and the hæmodynamic changes were observed. The effects of paired stimulation of the ventricle were noted and the hæmodynamic changes followed. Attempts were made to undertake paired stimulation of an artificially created ventricular tachycardia by driving the ventricle directly, using an intramural electrode, and the hæmodynamic changes were followed before and after this manoeuvre.

The effect of "electroaugmentation" (Ross *et al.*, 1965) was observed by analysing the first derivative of the ventricular pressure pulse (dP/dt) from a tangent to the steepest portion of the upstroke of the left ventricular pressure trace during sinus rhythm, and at various heart rates with or without paired stimulation of the heart.

The effects of paired stimulation of the heart were observed in 4 seriously ill patients with tachycardia or intractable heart failure, in 2 of whom it was possible to undertake hæmodynamic measurements before and during paired pulse stimulation.

RESULTS

Hæmodynamic Findings; Dog Experiments. Our results are presented in two groups, those due to an alteration in heart rate and those due to electroaugmentation.

(a) *Heart Rate.* Slowing of the heart rate below that of spontaneous sinus rhythm was achieved on all occasions, and the take-over from sinus rhythm

FIG. 1.—Paired pulsemaking unit (*above*) used in conjunction with Devices external pacemaker unit (*below*).

to controlled paired stimulation is shown in Fig. 2. The maximal slowing achieved was in the order of 45 per cent.

Slowing of a sinus tachycardia was easily achieved with two impulses separated by a delay of between 150 and 250 m.sec. It was frequently necessary to alter the delay between the two stimuli; a small hump appearing on the down slope of the left ventricular pressure curve indicated that the delay was too long (Fig. 2). The hump disappeared as the interval was shortened. When the delay was shortened even further, however, the second stimulus of the pair moved into the absolute refractory period so that the effect of paired stimulation was lost, allowing a sinus beat to interpose (Fig. 3).

An artificially created supraventricular tachycardia produced by driving the atrium with a

second pacemaker at rates of up to 250 beats a minute was consistently slowed by paired stimulation as can be seen in Fig. 4, in which an effective ventricular rate of 120 beats a minute is shown, despite an atrial rate of 216 beats a minute.

Ventricular tachycardia was artificially induced at 214 beats a minute by stimulating the ventricle directly, using an intramural electrode from a second pacemaker, and this was associated with a considerable fall in aortic flow (Fig. 5). Although paired stimulation of the ventricle was effective in reducing the ventricular contraction rate to 118 a minute, and the aortic flow rose to slightly above control levels, the ventricular ectopic focus producing the tachycardia could obviously not be depolarized, since the second driving pacemaker continued to function, and interference cycles

FIG. 2.—Sinus rhythm slowed from 150 a minute to 120 a minute, with the onset of paired stimulation. From above downwards are recorded flow in the thoracic aorta via an electromagnetic flowmeter, the pressure pulse in the left ventricle, and the electrocardiogram. Sinus rhythm present at the beginning of the record at a rate of 150 a minute is slowed to 120 a minute with the onset of paired stimulation. Each pacing stimulus is followed by electrical depolarization but only one mechanical beat results from each pair of stimuli. Notice the small hump on the downslope of the left ventricular pressure pulse just after the onset of paired stimulation (see text).

FIG. 3.—Pressure in the left ventricle (*above*) is recorded with the cardiogram (*below*) during paired stimulation at an effective heart rate of 98 a minute. The driving stimulus is labelled 1 and the paired stimulus 2. The first two left ventricular beats result from the first stimulus of each pair and are labelled P_1 . The delay of the paired stimulus (2) of the second beat is too short, and occurs in the absolute refractory period of the ventricle so that a sinus beat (S) has interposed and the effect of pairing is temporarily lost. The beat following (P_2) has resulted from the second (2) of the next pair of stimuli, the ventricle being refractory to the first, but thereafter paired pacing occurs once more.

between this pacemaker and the paired stimulator were obtained. This effect is shown in Fig. 6 in which the break-through appeared when impulses from the driving pacemaker produced short runs of ventricular tachycardia associated with a fall in aortic flow. Nevertheless there was considerable over-all improvement and the ventricular rate on average was considerably slowed. Even under the

worst possible conditions, therefore, when the ectopic focus cannot be depolarized the effects of a ventricular tachycardia were still diminished by this technique.

(b) *Electroaugmentation*. Although dP/dt may be used as an index of potentiation, the importance of its dependence on rate must be allowed for. The

FIG. 4.—Paired stimulation of a paced supraventricular tachycardia. Mean flow in the thoracic aorta (*above*) is recorded simultaneously with pressure in the left ventricle (*middle*) and a right atrial intracavitary lead (*below*).

A supraventricular tachycardia has been created by pacing the left atrium at 216 a minute. Paired stimulation slows the ventricular rate to 120 a minute. Note the increased pressure in the left ventricle with the onset of paired stimulation and the associated increase in aortic flow shortly thereafter.

FIG. 5.—Paired stimulation of a paced ventricular tachycardia. The three tracings show mean flow in the thoracic aorta (*above*), recorded simultaneously with the pressure pulse in the left ventricle (*middle*), and a right atrial intracavitary lead (*below*). Sinus rhythm is present at the left. Considerable fall in aortic flow and pressure in the left ventricle follow the onset of a ventricular tachycardia produced by stimulating the ventricle at 214 a minute. Paired stimulation has slowed the ventricular rate to 118 a minute, and this is associated with a dramatic increase in aortic flow and in pressure in the left ventricle.

alteration of this index with ventricular rate is demonstrated in the heart of a dog driven by a conventional pacemaker from atrial electrodes (Fig. 7). It is essential, therefore, that the effect of electroaugmentation during paired stimulation be demonstrated at an identical ventricular rate to the control sequence. This is shown in Fig. 8, where

the heart rate is kept constant at 120 beats a minute both in sinus rhythm and during paired stimulation. During paired stimulation the ventricular pressure was 16 per cent higher and dP/dt had increased by 125 per cent above the control value. These changes occurred despite the fact that during paired stimulation the atrial contribution to ventricular filling was

FIG. 6.—Paired stimulation of a paced ventricular tachycardia. The lay-out is as in Fig. 5. Note interference cycles between the driving pacemaker and the paired stimulator resulting in short runs of ventricular tachycardia associated with a fall in the aortic flow (see text).

FIG. 7.—The effect of ventricular rate on the first derivative of the pressure pulse of the left ventricle. dP/dt was obtained at varying heart rates by driving the heart of a dog by a conventional pacemaker from atrial electrodes. Note that dP/dt begins to fall off when the rate exceeds 200 a minute.

lost since the stimulating electrodes were attached to the ventricle.

Despite this demonstration of the inotropic action of paired stimulation on the heart, no corresponding increase in the aortic flow was obtained which remained at normal control values throughout. However, where the aortic flow was already reduced in sinus rhythm or as a result of a rapid arrhythmia paired stimulation always caused a dramatic increase as shown in Fig. 5 and 9.

The inotropic action of paired stimulation was also

demonstrated by the response of the end-diastolic pressure in the left ventricle. When abnormally raised during the control period a fall to normal levels often occurred shortly after the onset of paired stimulation (Fig. 9).

Clinical Application. Up to the present time we have attempted the use of paired stimulation in 4 seriously ill patients.

Case 1. A man of 23 years who had the Wolff-Parkinson-White syndrome was prone to recurrent

FIG. 8.—Electroaugmentation effect of 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. The ventricular rate is 120 a minute during both recordings. During paired stimulation pressure in the left ventricle has increased by 16 per cent and dP/dt by 125 per cent.

FIG. 9.—Inotropic action of paired stimulation. The lay-out is as before. An atrial tachycardia has been produced by pacing the left atrium at 190 a minute. With the onset of paired stimulation a ventricular rate of 140 a minute results. Mean aortic flow is increased and the end-diastolic pressure falls to zero shortly after the onset of paired stimulation.

attacks of paroxysmal atrial tachycardia which had necessitated frequent admissions to hospital over the last year. During his last admission a tachycardia associated with a ventricular rate of 180 beats a minute was present, and was resistant to drug therapy and direct current shock; his condition deteriorated until he became semi-conscious. A right ventricular electrode catheter was positioned under fluoroscopic control, and paired stimulation was attempted, but his heart immediately responded to both electrical stimuli which resulted in the rapid development of ventricular fibrillation. A direct current shock of 400 joules converted him to sinus rhythm but on a subsequent occasion he again developed atrial tachycardia with a very rapid ventricular rate

which proved resistant to all routine forms of treatment, and he died without a further attempt being made at paired stimulation.

Case 2. A woman of 58 years developed bouts of ventricular tachycardia with a heart rate of 170 beats a minute following a recent myocardial infarct. The tachycardia proved completely resistant to routine medical treatment. A right ventricular electrode catheter was inserted and an attempt made at paired stimulation. It proved impossible to find a satisfactory delay between the two stimuli, and each attempt at paired stimulation provoked a run of ventricular tachycardia, despite the fact that the stimulus strength was reduced to just above

TABLE
HÆMODYNAMIC RESULTS OBTAINED IN CASE 4

Rhythm	Rate/ min.	Right ventricle		Pulm. art. (mm.Hg)	Right atrium mean (mm.Hg)	Pulm. cap. mean (mm.Hg)	Aorta		A _{VO} 2 diff. (ml.)		Flow (l./min.)		Stroke vol. (ml.)	
		Pressure (mm. Hg)	dP/dt (mm. Hg/sec.)				Pressure (mm. Hg)	dP/dt (mm. Hg/sec.)			Pulm.	Syst.	Pulm.	Syst.
Spontan- eous atrial fibrillation Single pacing Paired pacing	110	66/0-18	470	64/18 mean 42	19	20	115/85 mean 98	900	40	82	5.7	2.8	52	25
	125	60/0-18	300	60/13 mean 34	19	20	115/75 mean 85	960	46	90	5.0	2.5	40	20
	75	58/0-18	470	60/13 mean 35	19	20	115/70 mean 85	900	38	78	6.0	3.0	80	40

threshold levels. The technique was therefore abandoned.

Case 3. A man of 50 years developed ventricular and supraventricular tachycardia following a reconstructive operation upon his aortic valve under cardio-pulmonary bypass. The arrhythmia was complicated by periods of sinus tachycardia and of atrial fibrillation and the ventricular rate varied from 140 to 220 a minute. Drug therapy to maximal tolerance did not control the ventricular rate. Paired stimulation was undertaken for a period of 48 hours by attaching the pacemaker wires which had been left *in situ* at the time of his cardiac operation and the ventricular rate was slowed by over 30 per cent. During paired stimulation an increase in the pulmonary arterial saturation from 34 to 56 per cent was obtained while the arterio-venous oxygen difference fell from 83 ml./l. to 56 ml./l., and this was associated with considerable clinical improvement.

Case 4. A man of 64 years who had diabetes mellitus developed atrial fibrillation. The ventricular rate was initially controlled with digoxin, but left ventricular and congestive cardiac failure subsequently occurred and were completely resistant to treatment with bed-rest, diuretics, and salt-restriction. Despite the absence of cardiac pain, the electrocardiogram now demonstrated an extensive anterior myocardial infarct, and persistent elevation of the ST segments suggested an additional left ventricular aneurysm. Clinical examination indicated that resistant heart failure was due to a ruptured ventricular septum in association with an anterior myocardial infarct. Because of the complete failure of routine treatment and a rising blood urea, it was decided to undertake paired pacing to obtain the benefit of electroaugmentation, in an attempt to improve myocardial function. The presence of a ventricular septal defect was demonstrated at cardiac catheterization, and the pulmonary: systemic flow ratio was found to be 2:1. Paired pacing was begun, using two stimuli separated by 300 m.sec. delivered to the body of the right ventricle via a bipolar electrocatheter, as a result of which the ventricular rate was slowed from 110 a minute in atrial fibrillation to 75 a minute. Cardiac output, arterio-venous oxygen differences, pressures in the right ventricle, pulmonary artery, and central aorta were monitored during

paired pacing, single pacing, and atrial fibrillation; dP/dt was subsequently measured from the right ventricular record. The results are summarized in the Table.

The hæmodynamic studies indicated that the degree of left-to-right shunt was unaltered during paired pacing at a ventricular rate of 75 a minute and that electro-augmentation as deduced from dP/dt did not occur. Similarly there were no beneficial effects on the systemic arterio-venous oxygen difference nor on the pulmonary arterial and aortic pressures. During single pacing, however, at a rate of 125 a minute considerable hæmodynamic worsening occurred (Table). The beneficial changes in cardiac output and stroke volume during paired pacing were rate-dependent and not due to a positive inotropic action of the technique. An interesting finding was a change in the pansystolic murmur during atrial fibrillation to a mid and late systolic murmur during paired pacing (Fig. 10), presumably due to asynchrony of contraction of the two ventricles, the right ventricle now preceding the left. When the delay between the two stimuli was not critically adjusted a second softer systolic murmur could be heard and was presumably due to a second ventricular contraction corresponding to the second electrical depolarization.

Paired pacing was maintained for 24 hours without objective clinical evidence of benefit.

DISCUSSION

The principle of the technique of paired stimulation as determined by Lopez *et al.* (1963) is that the first of the pair of electrical stimuli drives the ventricle at a fixed rate while the second stimulus of each pair arrives at the heart too soon to cause a mechanical contraction, but late enough in the relative refractory period to cause electrical depolarization. This results in an electrical premature beat with subsequent prolongation of the refractory period, without a corresponding mechanical contraction. In essence, therefore, there are two electrical events for each mechanical contraction and the rate of the heart is thereby slowed. It is apparent that the delay between the two stimuli of

FIG. 10.—High frequency phonocardiogram (Case 4) recorded with the electrocardiogram from the left sternal edge (a) in atrial fibrillation, and (b) during paired stimulation. A pansystolic minimum is recorded in atrial fibrillation. During paired stimulation (P_1P_2), however, a late systolic murmur is recorded (see text).

each pair must be adjusted fairly critically, and throughout this study the adjustment was carried out by monitoring the ventricular pressure until the small pressure event caused by the second stimulus disappeared (Fig. 2). Since electrical depolarization precedes every effective ventricular contraction each mechanical beat shows the phenomenon of post-ectopic potentiation (Hoffman, Bindler, and Suckling, 1956).

The findings in the present series confirm those of earlier workers (Lopez *et al.* 1963; Chardack *et al.*, 1964; Braunwald *et al.*, 1964; Ross *et al.*, 1965) and demonstrate that paired stimulation may be used to control tachycardias of sinus, supraventricular, or ventricular origin. Although slowing of the effective ventricular rate resulted in a longer diastolic filling time and a bigger stroke volume, the aortic flow during paired stimulation was frequently identical to that during the control phase, and this has consistently been noted by other workers (Chardack *et al.*, 1964; Lopez and Petkovich, 1965). If the tachycardia resulted in a subnormal flow during the control phase, a dramatic improvement was always obtained during paired stimulation. Similarly, these studies have shown

that in dogs that were not in heart failure the potentiation effect of paired stimulation was unaccompanied by other evidence of hæmodynamic improvement. It is unlikely, therefore, that there will be any clinical value from electroaugmentation in patients unless cardiac failure is present. This view is supported by the investigations of Ross *et al.* (1965) and Chardack, Gage, and Dean (1965), who both reported that paired stimulation at the control rate increased the myocardial oxygen consumption in excess of the increase in coronary blood flow. Cranefield *et al.* (1964) demonstrated that in the acutely failing dog heart a dramatic improvement occurred with the onset of paired stimulation, resulting in a decrease in heart size, an increase in right and left ventricular systolic pressure, a fall in diastolic pressures, and an increase in flow. These findings are similar to those reported by Lopez and Petkovich (1965).

The clinical application of this technique in man is still in the early stages. The second stimulus of the pair needs to be applied at, or very near to, the vulnerable period, so that there must be a considerable risk of provoking a ventricular arrhythmia in patients in whom the threshold for fibrillation is

unduly low, as occurred in our first patient (the development of ventricular fibrillation in a patient in whom paired stimulation was undertaken is also reported by Katz in 1965). This experience serves to emphasize the warning of Braunwald *et al.* (1964) that the technique is potentially hazardous. The clinical indications for paired stimulation have not yet been defined in man, but 17 patients were studied by Braunwald *et al.* (1965), in whom paired stimulation was undertaken for up to 6 hours; though electroaugmentation was clearly shown, little clinical improvement was demonstrated and this is supported by our experience in Case 4.

The positive inotropic action of paired pacemaking requires an increased myocardial oxygen consumption, so that it would be expected that beneficial clinical results would be more evident in patients without limitations in the delivery of oxygen to the myocardium. It is apparent therefore that much further work is needed before the indications for the technique are established in man.

SUMMARY

The technique of paired stimulation of the heart is described and the haemodynamic results demonstrated in acute experiments conducted on 14 dogs. Paired stimulation was undertaken in 4 seriously ill patients, in 3 of whom a dangerous tachycardia was present; heart failure resistant to conventional therapy was present in the fourth.

Paired stimulation of the heart can be used successfully to slow arrhythmias of sinus, supraventricular, or ventricular origin, both in dogs and in man. Electroaugmentation was demonstrated by an increase in the first derivative of the ventricular pressure pulse (dP/dt), an increase in left ventricular systolic pressure, and a decrease in the end-diastolic pressure of the left ventricle during paired stimulation at heart rates identical to the control values.

Despite the evidence of potentiation a haemodynamic improvement could only be demonstrated when the cardiac output was considerably reduced during the control period.

Paired stimulation is potentially dangerous as the second stimulus has to be applied close to the

vulnerable phase of the ventricle and serious ventricular arrhythmias may be precipitated. Although capable of producing a profound positive inotropic action, this is at the expense of a corresponding increase in the oxygen consumption of the myocardium. The indications for the technique in the clinical management of resistant arrhythmias and intractable heart failure have not yet been determined.

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