Effect of changes in ventricular activation on cardiac haemodynamics in man

Comparison of right ventricular, left ventricular, and simultaneous pacing of both ventricles

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To investigate the influence of changes in activation on left ventricular ejection, the effects of right ventricular, left ventricular, and simultaneous pacing of both ventricles were studied in 6 patients immediately after replacement of the aortic valve with a Starr-Edwards prosthesis. Variation in pacing site caused little or no change in systemic arterial pressure or cardiac output. However, the rate of movement of the ball of the prosthesis at the onset of left ventricular ejection was consistently greater during biventricular pacing than during pacing of the right ventricle alone, with intermediate values during left ventricular pacing. This provides evidence for the development of an increased force by the left ventricle at the onset of systole during biventricular pacing, resulting from a more synchronous contraction, and shows that such changes may occur in the absence of any alteration in the external work done by the left ventricle.

Cardiac performance during ventricular pacing may be impaired in comparison with normal sinus rhythm both by loss of an appropriately timed atrial contraction, and by asynchronous ventricular contraction resulting from abnormal activation. The importance of the former has been documented in man by an increase in cardiac output and systemic arterial pressure during sequential atrio-ventricular pacing compared to that during ventricular pacing in patients with complete heart block due to myocardial infarction (Chamberlain *et al.*, 1970). In order to assess the effects of changes in ventricular activation on left ventricular ejection, we have compared the effects of right ventricular, left ventricular, and simultaneous pacing of both ventricles in patients immediately after replacement of the aortic valve with a Starr-Edwards prosthesis. In these patients it was possible to study not only changes in aortic pressure and flow but also the initial force generated by the left ventricle as reflected in the rate of movement of the ball of the prosthesis at the start of left ventricular systole,

using a phonocardiographic method (Gibson, Broder, and Sowton, 1970).

Methods

Six patients were studied in the recovery ward immediately after replacement of the aortic valve with a Starr-Edwards prosthesis. Clinical details are given in Table 1. Throughout the period of study, all the patients were ventilated with intermittent positive pressure respiration using a Radcliffe Mark II respirator. All had been treated with digoxin, diuretics, and potassium supplements before operation, but these had not been administered since, and in none of the patients were catecholamines being infused.

Haemodynamic measurements Systemic arterial pressure was measured through a radial artery cannula, using Statham P23Gb strain gauge transducers and a Devices direct-writing recorder, operating at paper speeds of 5, 25, and 100 mm/sec. Mean pressures were derived by electrical integration. In 5 patients, cardiac output was measured by the indicator dilution technique. Two ml indocyanine green were injected into the superior vena cava, and arterial blood was withdrawn from the radial artery cannula using a constant rate withdrawal pump at a speed of 2 ml/sec. After the inscription of each dye curve, blood was returned to the patient by reversal of the pump. Calibration was by the dynamic method (Shinebourne, Fleming, and Hamer, 1967) using 2 μ l dye.

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Phonocardiographic measurements The phonocardiogram was recorded from the lower left sternal edge using a Sanborn microphone and a high-frequency filter (cut-off frequency 100 Hz). The indirect carotid pulse was recorded with a Phillips differential transformer. Phonocardiogram, indirect carotid pulse, and electrocardiogram were recorded simultaneously using a photographic recorder at a paper speed of 100 mm/sec. Ejection time was measured from the carotid pulse, A1A2 interval from the opening sound (A1) to the closing sound (A2) of the prosthesis, and QA2 interval from the pacing artefact to A2. Pre-ejection period was derived from QA2 interval less ventricular ejection time (Weissler, Harris, and Schoenfeld, 1968) and ball travel time from ejection time less A1A2 interval (Gibson *et al.*, 1970). The values given in Table 2 are the mean of 10 consecutive beats.

The output of a Devices pacemaker in the demand mode was connected, through a selector switch (Fig. 1) to electrodes placed at the time of operation on the right atrium, the right ventricle, approximately 1.5 cm to the right of the inter-ventricular groove, and on the lateral wall of the left ventricle. It was therefore possible to stimulate either ventricle singly or both simultaneously, using the right atrial lead as indifferent electrode, and to make changes without interruption of pacing.

When arterial pressure, central venous pressure, blood gases, and heart rate were stable on return from the operating theatre, right ventricular pacing was established at a rate of 90/min, or 10 beats/min higher than the minimum rate at which capture occurred, whichever was the greater, and the threshold noted. Right ventricular pacing was confirmed by the presence of a positive deflection in lead I of the electrocardiograms. The threshold for left ventricular pacing was established in a similar way, and electrode placement confirmed by a negative deflection in lead I. In no case was there a difference of more than 1 volt between the thresholds of the two ventricles to pacing. Finally, simultaneous pacing of both ventricles was established (biventricular pacing), using a pacemaker output 1 volt higher than that for either ventricle separately.

When the threshold and position of the electrodes had been checked left ventricular pacing was established, and after 3 minutes, measurements of arterial pressure and cardiac output were made. Biventricular pacing was then instituted, and measurements were repeated within 30 seconds of the change and again after 3 minutes of stable pacing. Similar observations were made during the change from biventricular to right ventricular pacing. The heart rate remained constant throughout. Phonocardiographic observations, which were not made simultaneously with those of arterial pressure and cardiac output, were taken during stable right, left, and biventricular pacing.

Statistical analysis This was by an analysis of variance. The significance of differences between

variance estimates was investigated using Snedecor's 'F' test. The standard error of mean values was derived from the appropriate residual variance, and from this the significance of differences between means was evaluated by the use of Student's 't' test.

Results (Tables 2 and 3)

QRS complex The mean duration of the QRS complex in lead I during right ventricular pacing was 161 msec, and during left ventricular pacing was 154 msec. During biventricular pacing, this was reduced to 136 msec, which was significantly less than during pacing of either right ventricle ($P < 0.01$) or left ventricle ($P < 0.05$).

Haemodynamic measurements Arterial pressure and cardiac output were not significantly different during pacing of either ven-

TABLE 1 Clinical details

Case No.	Age (yr)	Sex	Body surface area (m ²)	Rhythm	Prosthetic valve size (mm)	Other conditions or operative procedures
1	61	F	1.23	SR	9	Hypertrophic cardiomyopathy
2	58	F	1.3	SR	9	—
3	58	F	1.6	AF	10	Mitral valve replacement
4	58	M	1.55	SR	9	—
5	20	M	1.90	SR	10	—
6	56	F	1.68	SR	13	Aneurysmal ascending aorta

SR, sinus rhythm; AF, atrial fibrillation.

TABLE 2 Individual data

Case No.	Pacing mode	Mean arterial pressure (mmHg)	Cardiac output (l./min)	QRS duration (msec)	Ball travel time (msec)	Pre-ejection period (msec)	LV ejection time (msec)
1	R	100	2.1	160	20	—	161
	L	77	2.1	130	20	133	181
	Bi	87	2.0	93	15	130	179
2	R	70	3.6	170	31	—	211
	L	66	3.3	140	26	165	208
	Bi	68	3.4	131	21	166	209
3	R	65	1.6	177	25	—	154
	L	70	1.7	147	24	189	161
	Bi	67	1.7	124	19	190	163
4	R	100	2.8	160	20	—	167
	L	100	2.8	150	19	141	171
	Bi	102	2.9	125	15	145	167
5	R	100	—	170	22	—	207
	L	95	—	136	18	200	207
	Bi	97	—	128	15	200	206
6	R	96	4.0	170	29	—	190
	L	98	4.0	170	24	230	186
	Bi	98	4.0	150	22	234	184
Mean values	R	88.5	2.8	161	25	—	188
	L	85.0	2.8	154	22	175	189
	Bi	87.3	2.8	136	18	175	185

R, right ventricular pacing; L, left ventricular pacing; Bi, biventricular pacing.

FIG. 1 Diagram of selector switch used for single or biventricular pacing.

tricle separately or during biventricular pacing, though small changes occurred in individual patients (Fig. 2).

Systolic time intervals Left ventricular ejection time and pre-ejection period were not significantly altered by a change in pacing site. Pre-ejection period was not measured during right ventricular pacing because the onset of left ventricular activation was delayed by an unknown amount with respect to the onset of the QRS complex.

Ball travel time The mean ball travel time was 25 msec during right ventricular pacing, 22 msec during left ventricular pacing, and 18 msec during biventricular pacing. All 3 values were significantly different at the 1 per cent level (Table 3).

Between patient variance Between patient variance ratios were significant for all quantities measured except QRS duration. They were not investigated further.

Discussion

When left ventricular activation is initiated from epicardial electrodes rather than through the normal conducting system, the resulting pattern of contraction is abnormal. This was first recognized by Wiggers (1925) who showed reduced peak pressure and rate of rise of pressure, while Gilmore *et al.* (1963) subsequently noted that the external work done by the ventricle at any given end-diastolic pressure was lower, and that pressure was developed less rapidly in the early stages of left ventricular contraction. These changes were the result of asynchronous ventricular contraction rather than a negative inotropic effect or loss of an appropriately timed atrial contraction.

In the present study, ventricular activation was much prolonged with respect to normally conducted beats during epicardial pacing. During simultaneous pacing of both ventricles

FIG. 2 The effect of changing from biventricular to right ventricular pacing in Case 4. This is associated with a slight reduction in arterial pressure. In addition, there has been a change in the configuration of the QRS complex as described in the text.

it was consistently shorter than when the impulse originated from either ventricle separately, suggesting that true fusion beats occurred. These changes were associated with evidence of an increase in the initial force generated by the left ventricle. Movement of the ball of an aortic Starr-Edwards prosthesis at the onset of ventricular systole is the result of the force generated by the left ventricle

TABLE 3 Analysis of variance

Variable	Source of variance	Degrees of freedom	Variance estimate	F
Cardiac output	Activation	2	0.0046	347
	Patients	4	2.72	
	Residuals	8	0.0078	
Arterial pressure	Activation	2	26.17	1.05
	Patients	5	675.83	
	Residuals	10	24.9	
Ball travel time	Activation	2	67.56	40.0*
	Patients	5	39.66	
	Residuals	10	1.69	
QRS complex duration	Activation	2	2584.9	20.2*
	Patients	5	391.7	
	Residuals	10	128.3	
Ejection time	Activation	2	57.56	1.37
	Patients	5	1058.90	
	Residuals	10	42.03	
Pre-ejection period	Activation	1	14.08	155.0
	Patients	5	2462.15	
	Residuals	3	15.80	

* 'F' value significant at 1% level.

Significance of differences between means

QRS complex = RV > BiVP < 0.01 LV > BiVP < 0.05

RV and LV not significantly different.

Ball travel time = RV > LV P < 0.01 LV > BiVP < 0.01.

opposed by that due to the diastolic pressure in the aorta. There was no significant change in aortic diastolic pressure in any of the patients, and so the reduction in ball travel time occurring with the change from single to biventricular pacing was due to a consistent alteration in left ventricular performance. Furthermore, pacing from an epicardial site on the lateral wall of the left ventricle was associated with a shorter ball travel time than pacing from a right ventricular site. Similar differences between epicardial pacing from the two sites have been shown in the dog, where left ventricular pacing caused consistently higher values of developed pressure, wall tension, and rate of development of wall tension than did pacing from the right ventricle (Finney, 1965; Millar, Eich, and Abildskov, 1966).

In contrast to changes in the pattern of left ventricular contraction, there is general agreement that the pacing site has little effect on cardiac output, arterial pressure, left ventricular work or ejection time in either dog (Finney, 1965; Fletcher *et al.*, 1963; William-Olsson and Andersen, 1963) or man (Benchimol and Liggett, 1966), with or without heart disease. These results were extended in the present study, where the change not only from right to left, but also from single to biventricular pacing was associated with no consistent alteration in either arterial pressure or cardiac output. It appears, therefore, that a change in the pattern of left ventricular contraction does not necessarily alter the external work done by the heart on the circulation even in the presence of left ventricular disease and a low resting cardiac output. In the present study, simultaneous pacing from only two arbitrarily chosen sites was employed, and it is possible that more conspicuous changes could be obtained by variation in the numbers, position, or sequence of activation of ventricular electrodes. Tyers (1970) has shown a substantial increase in cardiac output in the intact dog during pacing from multiple left ventricular sites compared with that from a single site.

The similarity between the effects of changes in ventricular activation and an alteration in the contractile state of the myocardium was first pointed out by Wiggers (1925). More synchronous contraction has the same effect on left ventricular ejection as a positive inotropic stimulus, but it causes no change in the contractile process itself and therefore no increase in the oxygen uptake of the myocardium (Graham *et al.*, 1968). It is possible therefore that pacing from multiple sites might be preferable to single site ventricular pacing

when cardiac function is critically impaired and myocardial oxygen supply limited, but further investigation is needed to define more closely the value and limitations of the technique.

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