Monophasic action potential recordings during acute changes in ventricular loading induced by the Valsalva manoeuvre

Peter Taggart, Peter Sutton, Roy John, Max Lab, Howard Swanton

Abstract

***Objective*—The strong association between ventricular arrhythmia and ventricular dysfunction is unexplained. This study was designed to investigate a mechanism by which a change in ventricular loading could alter the time course of repolarisation and hence refractoriness. A possible mechanism may be a direct effect of an altered pattern of contraction on ventricular repolarisation and hence refractoriness. This relation has been termed contraction-excitation feedback or mechano-electric feedback.**

***Methods*—Monophasic action potentials were recorded from the left ventricular endocardium as a measure of the time course of local repolarisation. The Valsalva manoeuvre was used to change ventricular loading by increasing the intrathoracic pressure and impeding venous return, and hence reducing ventricular pressure and volume (ventricular unloading).**

***Patients*—23 patients undergoing routine cardiac catheterisation procedures: seven with no angiographic evidence of abnormal wall motion or history of myocardial infarction (normal), five with a history of myocardial infarction but with normal wall motion, and 10 with angiographic evidence of abnormal wall motion—with or without previous infarction. One patient was a transplant recipient and was analysed separately.**

***Setting*—Tertiary referral centre for cardiology.**

***Results*—In patients with normal ventricles during the unloading phase of the Valsalva manoeuvre (mean (SD)) monophasic action potential duration shortened from 311 (47) ms to 295 (47) ms ($p < 0.001$). After release of the forced expiration as venous return was restored the monophasic action potential duration lengthened from 285 (44) ms to 304 (44) ms ($p < 0.0001$). In the group with evidence of abnormal wall motion the direction of change of action potential duration during the strain phase was normal in 7/21 observations, abnormal in 6/21, and showed no clear change in 8/21. During the release phase 11/20 observations were normal, five abnormal, and four showed no clear change. In those with myocardial infarction four out of five patients had changes that resembled those with normal ventricles but the changes were less pronounced. There were no differences in any of the three groups between the changes in monophasic action potential duration in patients taking β blockers and those who were not. The changes in monophasic action potential duration in the transplanted heart resembled those in the group with normal ventricles. Inflections on the repolarisation phase of the monophasic action potential consistent with early afterdepolarisations were seen in three of the patients with abnormal wall motion and in none of those with normal wall motion.**

***Conclusions*—These results are further evidence that changes in ventricular loading influence repolarisation. When wall motion was abnormal the effects on regional endocardial repolarisation were often opposite in direction to those when it was normal. Thus regional differences in wall motion could generate local electrophysiological inhomogeneity which may be relevant to the association of arrhythmia with impaired left ventricular function.**

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There is a strong association between sudden cardiac death and abnormal ventricular wall motion in patients with coronary artery disease.[1,2] The severity of impairment of left ventricular function is a major predictor of mortality after myocardial infarction[3,4] and patients developing an aneurysm within 48 hours are at particular risk.[5] Death is generally considered to be due to arrhythmia and there is a strong correlation in these patients between abnormal wall motion and ventricular arrhythmia.[6-8] Patients with volume or pressure overload such as aortic valve disease[9-11] or dilated cardiomyopathy[12] commonly have ventricular arrhythmia. Though in some patients with congestive cardiac failure death is due to electromechanical uncoupling, sudden death in these patients is also partly due to the increased incidence of ventricular arrhythmias.[13-15] The explanation for the association between abnormality of

ventricular wall motion and serious arrhythmia, however, is unclear.

One possible mechanism may be a direct effect of ventricular loading on the time course of repolarisation and hence refractoriness. This mechanism is known as contraction-excitation feedback[16] (or mechano-electric feedback).

A change in the normal time sequence of repolarisation alters local electrical gradients and is potentially arrhythmogenic.[17] It is known that areas of myocardium where wall motion is abnormal contract differently from normal areas.[18 19] It would be expected therefore that the effect on repolarisation time in abnormally contracting and normally contracting areas of myocardium would be different. In the presence of abnormal wall motion local electrical gradients may be generated which might play a part in the initiation of arrhythmias in these circumstances.

Several studies have examined contraction-excitation feedback in some detail and such feedback has been shown in isolated tissues,[20] isolated hearts,[21-23] and whole animals.[21 24 25] In general these studies have shown that increasing myocardial stretch/strain or increasing loading conditions result in shortening of action potential duration (ie repolarisation time)[16 21] altered refractoriness[22 24 26 27] and arrhythmia formation.[23 25 28 29] Until recently[30-32] there has been no evidence for the existence of this phenomenon in humans. In the present study we used the Valsalva manoeuvre to change ventricular loading within the physiological range in patients undergoing routine cardiac catheterisation for chest pain.[33-35] We recorded monophasic action potentials from the left ventricular endocardium as a measure of repolarisation[36 37] in patients with angiographic evidence of wall motion abnormality and in those without.

The aims of this study were (*a*) to see whether pressure/volume changes influence the timing of regional ventricular endocardial repolarisation and to seek evidence that changes in ventricular loading influence the timing of repolarisation; (*b*) to see whether patients with abnormal wall motion and those with normal wall motion respond differently; (*c*) to see whether there are any electrophysiological changes that would be in keeping with those required for arrhythmia generation.

Patients and methods

We recorded the left ventricular monophasic action potential, arterial pressure, and the routine electrocardiogram in patients undergoing routine cardiac catheterisation for chest pain or, in one patient, routine left ventricular biopsy after heart transplantation.

PATIENTS

Twenty three patients (table 1) were selected at random from the waiting list including one (patient 23) admitted for routine biopsy after a heart transplant. The patients were divided into three groups:

Group 1—Those with no demonstrable angiographic abnormality—that is, normal (n = 7).

Group 2—Those with normal wall motion but a history of myocardial infarction and therefore possible abnormality of left ventricular wall motion not detectable by the methods used in this study (n = 5).

Group 3—Those with angiographic evidence of abnormal left ventricular wall motion either with or without previous history of myocardial infarction (n = 10).

The transplant patient was analysed separately. The study was approved by the hospital ethics committee and informed consent obtained.

METHOD OF EVALUATION OF LEFT VENTRICULAR WALL MOTION FROM LEFT VENTRICULAR CINEANGIOGRAMS

Ventricular synergy was assessed by single plane left ventriculography in the 30° right anterior oblique projection.[38 39] A long axis of the left ventricular endocardial silhouette was drawn between the midpoint of the aortic valve and the left ventricular apex for both end diastolic and end systolic frames. The long axes of the two frames were then aligned and the silhouettes superimposed at the midpoint of the long axis. The long axis was further subdivided to give six segments: anteroapical, inferoapical, anteromedial, inferomedial, anterobasal, and inferobasal. The systolic change in length for each of the above reference segments was normalised for end diastolic length and expressed as percentage shortening (or lengthening in the case of dyskinesis). The inferobasal segment was excluded from analysis of regional contractility because of its large individual variability.[40]

ENDOCARDIAL MONOPHASIC ACTION POTENTIALS

Left ventricular monophasic action potentials were recorded by a purpose built (Cordis) bipolar pressure contact silver/silver chloride catheter electrode (size 7 French). The contact electrode was positioned at the tip with the indifferent electrode 5 mm proximally, flush with the side wall of the catheter. Gentle pressure of the tip electrode against the endocardium gave a signal of between 20 and 40 mV.

ARTERIAL PRESSURE

The routine arterial pressure signal obtained via the catheter sheath was recorded on a Gould Instruments electrostatic chart recorder (model ES1000) at a paper speed of 10 mm/s and used for systolic pressure measurement.

SIGNAL PROCESSING

The monophasic action potential signals were fed into a Gould isolated preamplifier (model 11-5407-58) and then into a DC Gould universal amplifier (model 13-4615-58). The amplifier was set to give an output of 1V for 40 mV input with a frequency response to 300 Hz. The signal was displayed on a Simonsen and Weel monitor (model MTS 102). A Gould Instruments 4 channel RS 3400

Table 1 Details on the 23 patients in the study

Patient	Age	Sex	AP	Previous MI	LV failure	β blockade	Calcium antagonists	EF	No of segments showing abnormal wall motion	Coronary arteries: LAD	Cx	RCA	Group	CABG
1	53	M	+	–	–	–	–	60	0	Severe	Severe	Severe	1	
2	72	M	+	–	–	Atenolol 50 twice a day	Nifedipine 20 twice a day	82	0	Severe	Severe	Severe	1	
3	46	M	–	–	–	–	–	79	0	Mild	Normal	Normal	1	
4	73	M	–	Large anterior	+	–	Diltiazem 60 three times a day	15	3 (2P)	Severe	Severe	Severe	3	
5	48	M	+	Inferior (×2)	–	Metoprolol 50 twice a day	Nifedipine 20 twice a day	66	2	Normal	Severe graft open	Occluded	3	RCA Cx
6	61	M	–	Inferior	–	Atenolol alternate days	–	63	0	Normal	Moderate	Normal	2	
7	52	M	+	–	–	Propranolol 160 once a day	Nifedipine 20 twice a day	80	0	Normal	Normal	Mild	1	
8	52	M	+	–	–	Atenolol 100 once a day	Diltiazem 60 twice a day	79	0	Occluded OM	Normal	Severe	1	
9	61	M	*	–	–	–	–	83	0	Normal	Normal	Normal	1	
10	51	M	+	Lateral	–	Atenolol 50 twice a day	Nifedipine 10 twice a day	84	0	Moderate	Moderate	Moderate	2	
11	56	M	+	Lateral	–	Atenolol 50 once a day	–	46	1	Mild	Normal	Severe	3	
12	53	M	–	Inferior	–	Atenolol 50 once a day	–	54	2	Mild	Moderate	Mild	3	
13	57	M	+	Inferior apex lateral	+	–	Nifedipine 10 three times a day	59	2 (1P)	Moderate	Normal	Moderate	3	
14	49	F	*	–	–	–	–	68	0	Normal	Normal	Normal	1	
15	59	M	+	+	–	Atenolol 50 once a day	–	75	0	Normal	Normal	Normal	2	
16	58	M	+	+	–	–	Nifedipine 20 twice a day	64	1	Occluded	Normal	Ectatic	3	
17	48	M	+	+	–	Metoprolol 50 twice a day	Diltiazem 60 three times a day	80	1	Occluded graft open	Occluded graft open	Moderate	3	Cx LAD
18	59	F	+	+	–	–	Nifedipine 20 three times a day	25	4	Severe	Severe	Tight mid	3	
19	65	M	+	+	+	Atenolol 100 once a day	Nifedipine 20 three times a day	32	2	Occluded graft open	Occluded graft open	Occluded graft open	3	Cx LAD RCA
20	49	M	+	+	–	Atenolol 50 once a day	Nifedipine 20 twice a day	76	0	Moderate	Moderate	Moderate	2	
21	52	F	+	Anteroseptal	–	Propranolol 160 one a day	Diltiazem 60 three times a day	58	2	Mild	Normal	Severe	3	
22	33	M	–	+	–	–	–	78	0	Severe	Normal	Moderate	2†	
23	52	M	–	–	–	–	Nifedipine 20 twice a day							

*Non-specific chest pain; †cardiac transplant.
AP, angina pectoris; MI, myocardial infarction; LV, left ventricle; EF, ejection fraction; LAD, left anterior descending; Cx, circumflex; RCA, right coronary artery; CABG, coronary artery bypass graft; P, paradoxical motion; OM, obtuse marginal.

chart recorder (model 30-V8404-10) was used for hard copy recordings at a paper speed of 125 mm/s. Hard copy recordings of the routine blood pressure were also recorded in order to synchronise the blood pressure measurements with the monophasic action potentials on a beat to beat basis. The routine electrocardiogram monitored at the time was also recorded. The monophasic action potential recording was calibrated with a direct current millivolt source (Time Electronics model 4045). The blood pressure was calibrated against known pressures of 0 and 100 mm Hg.

PROCEDURE

Routine coronary angiography, via the right femoral artery by the Judkins technique, was performed on all patients (except patient number 23). Left ventricular angiography was performed in the right anterior oblique position. Patient 23 had a left ventricular biopsy only (no coronary angiography or left ventricular angiography).

On completion of the routine procedure the angiography catheter (or biopsy catheter) was replaced with the monophasic action potential catheter which was positioned against the left ventricular wall. Right atrial pacing was established via the right femoral vein at a rate of approximately 15% above the patient's resting heart rate. Two patients (2 and 3) were unpaced but were included because the heart rate from control to phase IIA and from phase III to IVA did not change by more than 1%.

VALSALVA MANOEUVRE

The apparatus used for the Valsalva manoeuvre consisted of a 20 ml syringe for a mouthpiece (plunger removed) attached via rubber tubing to a sphygmomanometer. The size of the syringe ensured a tight seal between the patient's lips and the barrel of the syringe. The patient was asked to blow hard and maintain the mercury column at 40 mm Hg for 15 seconds.

A run-in period of atrial pacing for two minutes established a steady state after which continuous recordings were made during the Valsalva manoeuvre. When feasible the procedure was repeated for up to three times. There was a rest period of three minutes between procedures during which atrial pacing was maintained.

ANALYSIS OF DATA

Monophasic action potential duration was measured at 90% and 70% repolarisation. The terminal portion of the action potential was defined by drawing a tangent to the fastest part of the downstroke to the baseline.[41 42] This

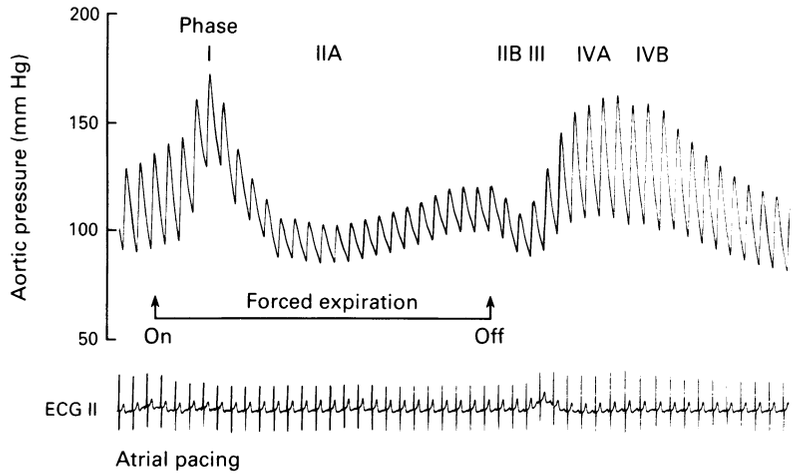

Figure 1 Typical recording of aortic blood pressure during the Valsalva manoeuvre together with the routine electrocardiogram. The four phases of the Valsalva manoeuvre and duration of the forced expiration are shown. Cycle length = 670 ms.

method eliminated the possibility of including afterdepolarisations in the measurements which would have produced long duration action potentials. In addition this technique of measurement also overcomes possible difficulties in measuring action potentials exhibiting a continuous decline of phase IV. Mean values with standard deviations are presented. The data were assessed by a repeated measures analysis of variance and planned comparison of means (Anova).

Results

Figure 1 shows a typical blood pressure response to the Valsalva manoeuvre we obtain in our catheter laboratory. The patient takes a deep breath in and then blows hard against a calibrated resistance of 40 mm Hg. This increases the intrathoracic and intraabdominal pressures thereby impeding venous return, reducing ventricular filling, and reducing left ventricular systolic pressure and volume. Four phases are described. The initial increase in blood pressure seen in phase I lasts for a few beats only and is due to a direct effect of the increased intrathoracic pressure, possibly together with an increased preload caused by a shift of blood from the pulmonary bed into the left ventricle. During phase II there is an initial fall in blood pressure (phase IIA) because venous return is impeded. This results in a reflex increase in peripheral resistance and inotropic state of the myocardium curtailing the fall in blood pressure and resulting in a plateau and even a small subsequent rise (phase IIB). After release of the forced expiration intrathoracic pressure returns to normal and refilling of the pulmonary vascular bed results in a transient further fall in blood pressure caused by a further reduction in ventricular filling for about 2–3 beats (phase III). As the venous return is restored and ventricular filling increases the blood pressure rises (phase IV). Reflex autonomic effects may cause an "overshoot" above control levels of blood pressure (phase IVB).

During the Valsalva manoeuvre there were considerable changes in the time course of repolarisation in the recordings of endocardial monophasic action potential coincident with the changes in blood pressure.

Figure 2 shows the changes typical of monophasic action potential in a patient with no angiographic evidence of abnormal wall motion (group 1). During the strain phase (B) the monophasic action potential duration shortened and subsequently increased after release (C). Action potential duration was measured at 90% repolarisation.

In group 3 (those with regional wall abnormalities) there were 21 observations during the strain phase and 20 during the release phase. During the strain phase the direction of change

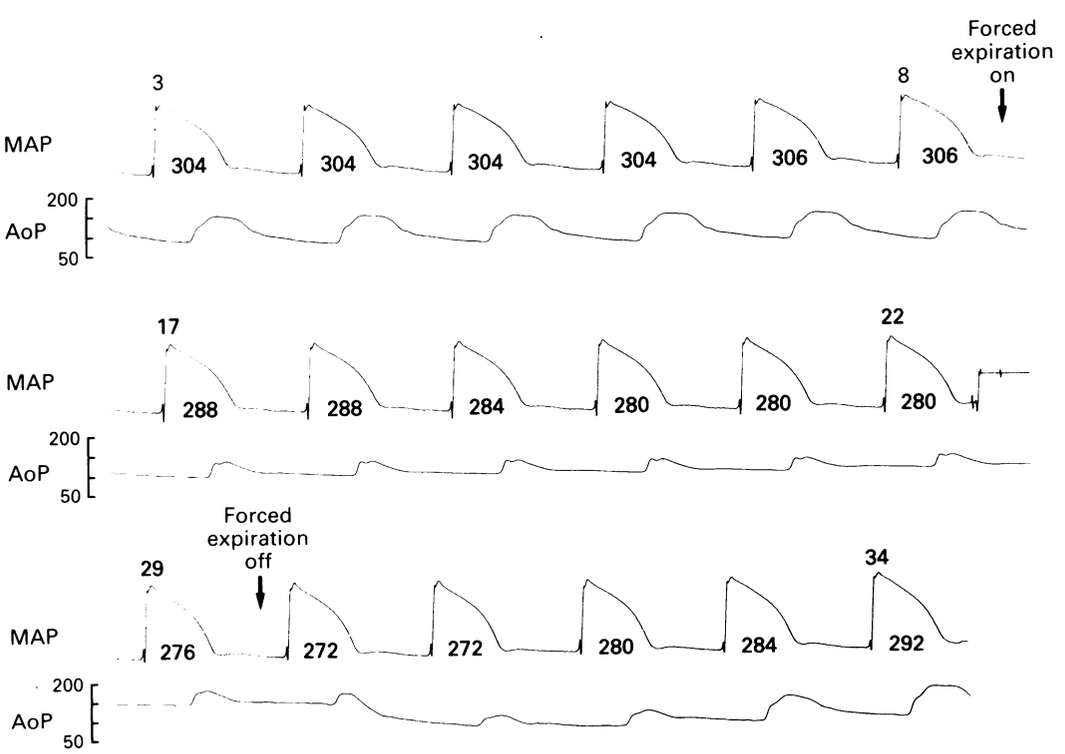

Figure 2 Tracing of monophasic action potentials and aortic pressure before the Valsalva manoeuvre (beats 3–8) during the strain phase (phase II; beats 17–22), and from the release of forced expiration (phase III) (after beat 29 to beat 34). Zero calibration for the monophasic action potentials is shown at the end of the second panel. Cycle length = 584 ms. (Group 1 patient)

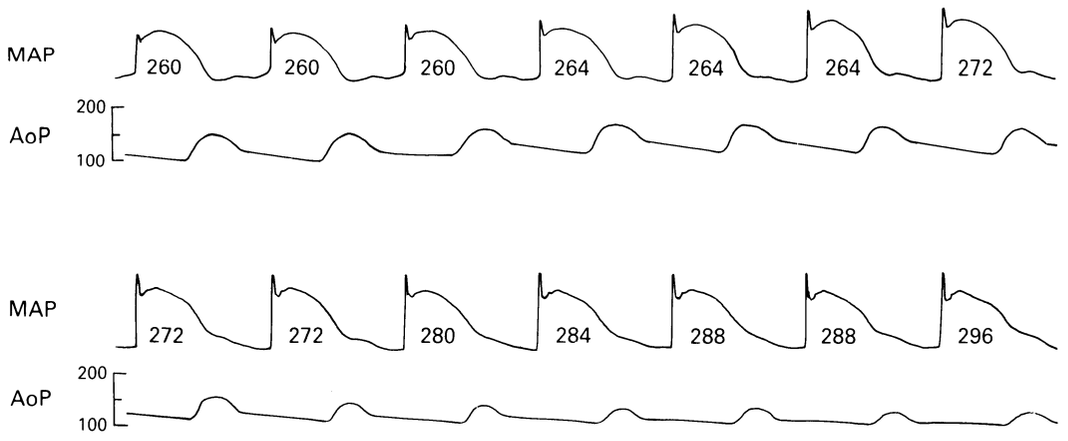

Figure 3 Continuous recording of monophasic action potential and aortic pressure during the strain phase of the Valsalva manoeuvre in a patient with abnormal wall motion and a history of myocardial infarction (group 3). Monophasic action potential duration (at 90% repolarisation) increased progressively from 260 ms to 296 ms as peak systolic pressure fell. The fast phase of repolarisation became progressively delayed possibly representing early afterdepolarisations. Cycle length = 496 ms.

of action potential duration was normal in seven observations, abnormal in six, and showed no clear change in eight. During the release phase 11 were normal, five abnormal, and four showed no clear change. Figure 3 shows an example of changes in monophasic action potential duration which were opposite in direction. Action potential duration increased as systolic pressure fell during the strain phase. In addition the late phase of repolarisation became progressively delayed; this may have represented an afterdepolarisation.

Figure 4 shows the changes in monophasic action potential duration for the first nine beats of the strain phase and the release phase for each patient. Each patient performed up to three Valsalva manoeuvres. The vertical bars indicate the change in monophasic action potential duration with respect to the action potential duration at the start of each phase. As indicated by the scale a bar below the baseline represents a shortening whereas a bar above represents a lengthening. In group 1 there was uniform shortening in the strain phase and uniform lengthening during the release phase. In group 3 this symmetry was no longer apparent with many patients showing changes in the opposite directions to those in group 1. Changes in the opposite direction in at least one

Table 2 Monophasic action potential duration (ms) (mean (SD)) at 90% repolarisation at 70% repolarisation and peak systolic pressure (mmHg) at phases I, IIA, III, IVA and IVB of the Valsalva manoeuvre for patients with no abnormal wall motion and no history of previous myocardial infarction (group 1), those with previous history of myocardial infarction but normal wall motion (group 2), patients with abnormal wall motion (group 3), and for all three groups.

	Strain phase			*Release phase*	
	I	*IIA*	*III*	*IVA*	*IVB*
			At 90% repolarisation		
Group 1	311 (47) $\xrightarrow[n=14]{0.001}$	295 (47)	285 (44) $\xrightarrow[n=14]{0.0001}$	304 (44) / 305 (50) $\xrightarrow[n=11]{0.001}$	293 (48)
Group 2	274 (29) $\xrightarrow[n=9]{NS}$	269 (27)	265 (27) $\xrightarrow[n=8]{NS}$	271 (29) / 270 (30) $\xrightarrow[n=7]{0.005}$	277 (31)
Group 3	285 (33) $\xrightarrow[n=21]{NS}$	287 (28)	279 (30) $\xrightarrow[n=20]{NS}$	285 (35) / 280 (35) $\xrightarrow[n=15]{NS}$	278 (34)
Groups 1, 2 and 3	291 (39) $\xrightarrow[n=44]{0.02}$	286 (36)	279 (35) $\xrightarrow[n=42]{0.001}$	289 (38) / 286 (41) $\xrightarrow[n=33]{NS}$	283 (38)
			At 70% repolarisation		
Group 1	282 (47) $\xrightarrow[n=14]{0.001}$	268 (48)	259 (46) $\xrightarrow[n=14]{0.0001}$	271 (43) / 271 (49) $\xrightarrow[n=11]{0.015}$	262 (47)
Group 2	249 (30) $\xrightarrow[n=9]{0.002}$	239 (29)	234 (28) $\xrightarrow[n=8]{0.05}$	242 (27) / 241 (29) $\xrightarrow[n=7]{0.009}$	250 (31)
Group 3	257 (32) $\xrightarrow[n=21]{NS}$	256 (26)	249 (21) $\xrightarrow[n=20]{0.015}$	257 (37) / 247 (29) $\xrightarrow[n=15]{NS}$	246 (29)
Groups 1, 2 and 3	263 (39) $\xrightarrow[n=44]{0.0001}$	256 (36)	249 (34) $\xrightarrow[n=42]{0.0001}$	250 (36) / 254 (38) $\xrightarrow[n=33]{NS}$	252 (36)
			Peak systolic pressure (mm Hg)		
Group 1	138 (31) $\xrightarrow[n=14]{0.02}$	97 (37)	66 (26) $\xrightarrow[n=14]{0.0001}$	109 (32) / 108 (36) $\xrightarrow[n=11]{0.001}$	145 (33)
Group 2	167 (23) $\xrightarrow[n=9]{0.039}$	110 (19)	86 (15) $\xrightarrow[n=8]{0.0001}$	134 (18) / 138 (15) $\xrightarrow[n=7]{0.001}$	174 (22)
Group 3	160 (17) $\xrightarrow[n=21]{0.0001}$	127 (25)	107 (32) $\xrightarrow[n=20]{0.0001}$	135 (35) / 130 (23) $\xrightarrow[n=14]{0.0001}$	170 (27)
Groups 1, 2 and 3	155 (25) $\xrightarrow[n=44]{0.0001}$	114 (31)	89 (33) $\xrightarrow[n=42]{0.001}$	126 (29) / 124 (29) $\xrightarrow[n=32]{0.0001}$	162 (30)

The significance of any change and the number of observations in each group are shown. NS = not significant at the 95% level.

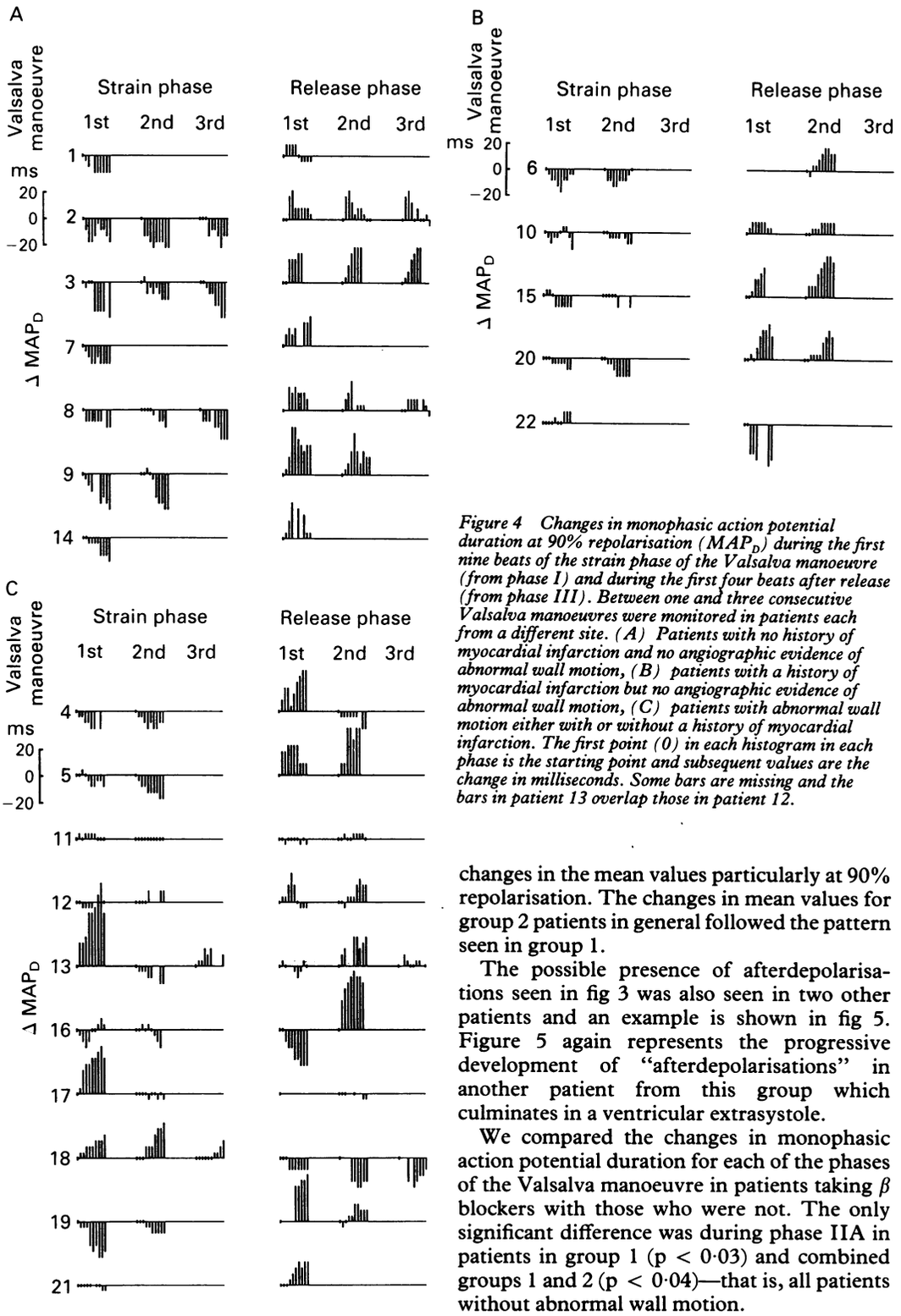

Figure 4 Changes in monophasic action potential duration at 90% repolarisation (MAP_D) during the first nine beats of the strain phase of the Valsalva manoeuvre (from phase I) and during the first four beats after release (from phase III). Between one and three consecutive Valsalva manoeuvres were monitored in patients each from a different site. (A) Patients with no history of myocardial infarction and no angiographic evidence of abnormal wall motion, (B) patients with a history of myocardial infarction but no angiographic evidence of abnormal wall motion, (C) patients with abnormal wall motion either with or without a history of myocardial infarction. The first point (0) in each histogram in each phase is the starting point and subsequent values are the change in milliseconds. Some bars are missing and the bars in patient 13 overlap those in patient 12.

of the manoeuvres was seen in six of the patients. In particular, some patients (for example, case 16) occasionally showed changes in the opposite direction during consecutive Valsalva manoeuvres with the recording electrode positioned at adjacent sites. In group 2 patients in general the changes resembled those in group 1 but were not always as clear cut.

Table 2 shows the mean values. Group 1 patients showed highly significant changes in action potential duration in both phases, reflecting the uniform direction of change in all patients. The lack of uniformity seen in group 3 patients is reflected in the seemingly smaller changes in the mean values particularly at 90% repolarisation. The changes in mean values for group 2 patients in general followed the pattern seen in group 1.

The possible presence of afterdepolarisations seen in fig 3 was also seen in two other patients and an example is shown in fig 5. Figure 5 again represents the progressive development of "afterdepolarisations" in another patient from this group which culminates in a ventricular extrasystole.

We compared the changes in monophasic action potential duration for each of the phases of the Valsalva manoeuvre in patients taking β blockers with those who were not. The only significant difference was during phase IIA in patients in group 1 ($p < 0{\cdot}03$) and combined groups 1 and 2 ($p < 0{\cdot}04$)—that is, all patients without abnormal wall motion.

We studied one additional patient who had received a donor heart six months previously. The changes in monophasic action potential duration in this patient were not included in the statistical analysis. However, monophasic action potential duration changed in a manner similar to those in group 1. Two Valsalva manoeuvres were recorded. The aortic pressure record was almost identical for both runs. In figure 6 the aortic pressure tracing is shown together with beat by beat changes in monophasic action potential duration at 90% and 70% repolarisation for the strain phase (from run one) and the release phase (from run two). Figure 7 shows the monophasic action

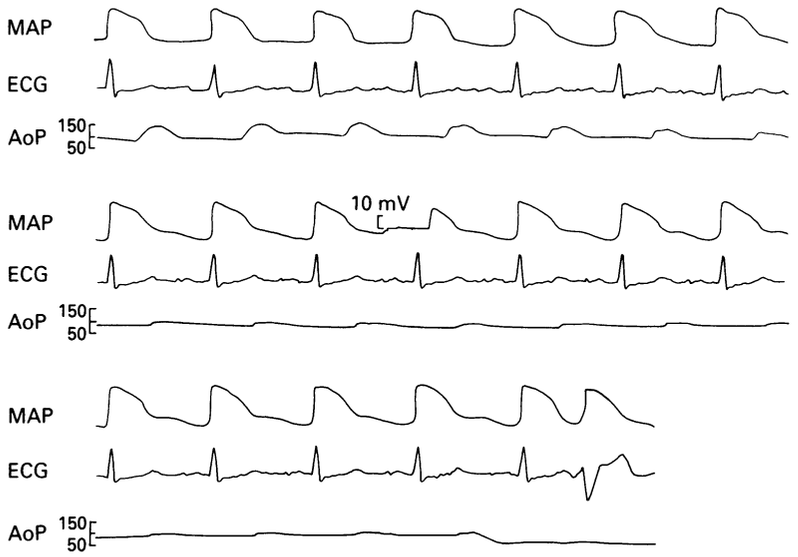

Figure 5 Continuous tracings of monophasic action potential, aortic pressure recording, and electrocardiogram (lead II) during phase II of the Valsalva manoeuvre in a patient with abnormal wall motion and a history of myocardial infarction. The fast phase of repolarisation became progressively delayed culminating in a ventricular extrasystole (arrow). Zero calibration for the monophasic action potential is included between the third and fourth beats in the middle panel. Cycle length = 664 ms.

potentials during the early strain phase. During this strain phase the monophasic action potential duration shortened progressively as aortic pressure fell.

Discussion

Abnormal left ventricular wall motion is a major predictor of sudden cardiac death[1 2] that is often considered to be the result of arrhythmia.[6-8] The mechanism for this relation remains undefined. We examined the effect of acute ventricular pressure/volume changes on ventricular repolarisation in patients with normal and with abnormal wall motion to see whether there were any electrophysiological changes that would be in keeping with those required for arrhythmia formation. A convenient means of altering ventricular pressure/volume is the Valsalva manoeuvre in which a forced expiration impedes venous return, causing a reduction of left ventricular pressure/volume.[33-35] We recorded monophasic action potentials from the left ventricular endocardium as a measure of the time course of repolarisation. We found significant changes in the timing of regional ventricular repolarisation during the Valsalva manoeuvre. In some patients with abnormal wall motion the effects on ventricular repolarisation were opposite in direction to those found in patients with normal wall motion. In both groups of patients the change in the duration of repolarisation in response to changes in ventricular loading suggests that the mechanical effects of the loading may play a part in these changes. It may be argued that the autonomic influences associated with the Valsalva manoeuvre[33-35] may also contribute to our findings because increased sympathetic activity may influence the timing of repolarisation[43-45] (that is, action potential duration). We consider that this contribution is minimal because we confirmed our observations on ventricular unloading to the first few beats—before significant autonomic effects occur.[46] Our observations during ventricular loading were confined to a four beat train during which time changes in autonomic tone would be small. In addition the changes in action potential duration in the transplanted heart, which is devoid of innervation, were comparable in direction to those in our normal patients (group 1). Finally there was no difference in the response in patients receiving β blockade compared with those who were not.

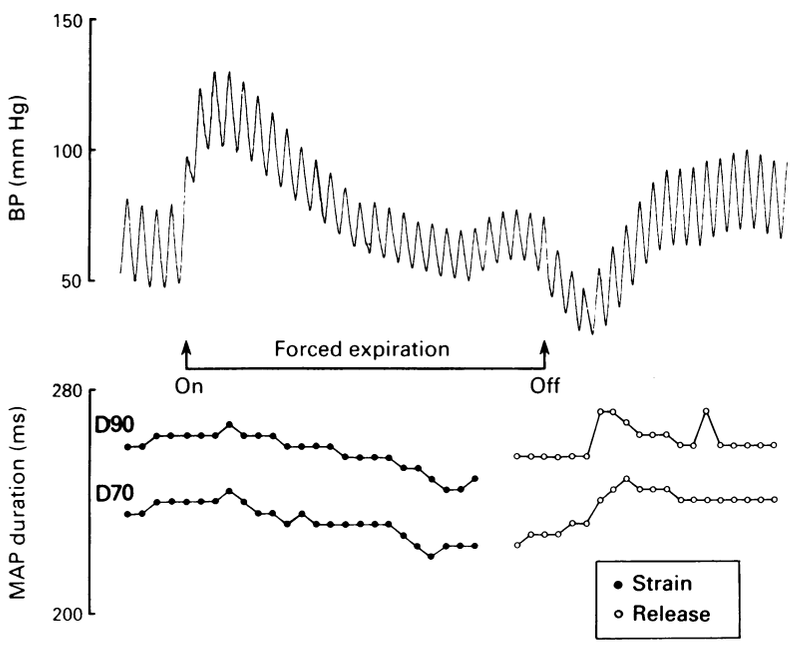

Figure 6 Aortic pressure tracing during the Valsalva manoeuvre in an orthotopic transplanted heart six months after the operation. Beat by beat plot of action potential duration at 90% repolarisation is shown below. Action potential duration during the ventricular loading phase was obtained from a repeat Valsalva manoeuvre in this patient which produced an identical blood pressure profile. During ventricular unloading the action potential duration shortened and subsequently lengthened during the subsequent loading phase.

If we accept that the effects that we have seen are mechanical—in that the changes in ventricular loading directly influence the timing of repolarisation—then our results would be consistent with contraction-excitation feedback. Such a mechanism has been demonstrated experimentally in isolated tissues and in animals. In general, it has been shown that increasing the length of cardiac muscle shortens the action potential duration and decreasing the length of the muscle lengthens the action potential duration.[16] Our patients with normal wall motion (group 1), however, showed opposite effects. A reduction left ventricular volume and peak systolic pressure shortened the monophasic action potential duration and an increase in left ventricular volume and peak systolic pressure lengthened it.

It is probable that several mechanisms are involved—such as stretch and fibre excursion. It has been shown that there is a relation between the extent to which a muscle is allowed to shorten and the duration of the action potential. For example when a contracting muscle is prevented from shortening (that is, isometric contraction) the action potential duration is abbreviated. In the unloading phase

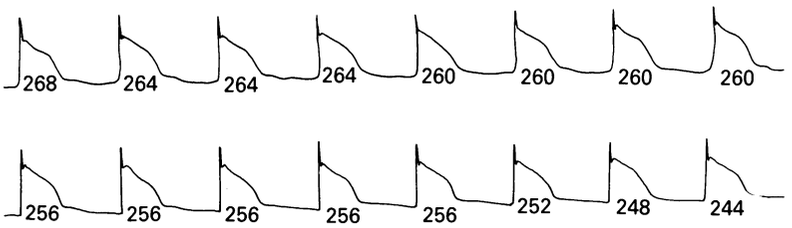

Figure 7 A continuous recording of monophasic action potentials during the strain phase in the patient in figure 7. Monophasic action potential duration is shown at 90% repolarisation and shortened progressively from 268 ms to 244 ms. Cycle length = 584 ms.

of the Valsalva manoeuvre the ventricular cavity size and stroke volume decrease and fibre excursion between end systolic and end diastolic phases is reduced. This would accord with the fibre excursion mechanism being predominant. It is to be expected that fibre excursion would be different in areas of normal and abnormal wall motion. Paradoxical movement (that is, systolic bulging) is common during the early phase of ischaemia when type 1A arrhythmias are common.[47] Local differences in repolarisation and excitability induced by a mechanism such as we describe would facilitate arrhythmia by re-entry mechanisms.

Another mechanism for arrhythmia formation may be the result of early afterdepolarisations[48] that reach threshold for the initiation of a subsequent action potential. An early afterdepolarisation is an inflection on the downstroke of the action potential and can appear in the electrocardiogram as the U wave. Early afterdepolarisations in monophasic action potential recordings could be a mechanical artefact rather than a real electrophysiological phenomenon. Artefacts cannot entirely be ruled out but several studies support the possibility that these are real afterdepolarisations.[25] One preliminary study suggests that mechanically induced early afterdepolarisations in the monophasic action potential show a rate dependence analogous to that of afterdepolarisations recorded with microelectrodes.[49] It may be important that in our study they were accompanied by extrasystoles. These could be attributed to local irritation by the stiff catheter, but extrasystoles have also been seen by various recording techniques in several experimental preparations.[16 20 21 25] We saw some considerable early afterdepolarisations (figs 3 and 5) which were particularly obvious in patients with abnormal wall motion. In the example shown in fig 5 the progressive increase in afterdepolarisations culminated in an extrasystole. In some instances we saw a continuous decline in phase IV even after the termination of the possible afterpotential was seen. We cannot say whether these were artefacts or real phenomena.

There was a wide variability in the size of the effect on action potential duration, which varied from 20 ms to 40 ms in some patients (fig 4). This is greater than the dispersion necessary to facilitate reentrant arrhythmias[50 51] and not dissimilar to action potential durations induced by antiarrhythmic drugs with class III action.[52] In our experience only slight changes in action potential duration were caused by spontaneous variability. Prematurity shortens action potential duration, which depends on the rate and preceding cycle length. For example, during a steady state heart rate of 80/minute (cycle length 750 ms) an early beat of 350 ms shortened the action potential by about 11 ms.[53]

Arrhythmia in patients with coronary heart disease and congestive heart failure is probably multifactorial,[15] with deaths in some instances being due to electromechanical dissociation. In addition to contraction-excitation feedback (or mechano-electric coupling) other important factors may be myocardial fibrosis and hypertrophy[54] activation of the sympathetic nervous system or hypokalaemia induced by a renin angiotensin system[55] diuretic,[56] together with the arrhythmogenic effect of drug treatment such as digoxin and some antiarrhythmic agents. Studies of an animal model of doxorubicin induced heart failure suggest an inherent mechanism not related to mechanical or any of the above effects.[57] Our results, however, support the possibility that mechanically induced electrophysiological changes could play a part in these clinical situations.[58]

Our study confirms that potentially arrhythmogenic changes in action potential duration and excitability in humans may be produced by load changes that are within physiological ranges[59] and that changes in ventricular loading change the time course of repolarisation. An important finding was that such changes could be in opposite directions in patients with normal wall motion and patients with abnormal wall motion. These data suggest that the presence of abnormal wall motion may induce electrophysiological changes by contraction-excitation feedback and this may provide a link between the unexplained association between arrhythmia and impaired left ventricular function.

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