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Sequence of epicardial repolarisation and configuration of the T wave

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SUMMARY Epicardial activation and repolarisation sequences were investigated in patients with upright or inverted T waves in left ventricular leads of the surface electrocardiogram. Fifteen patients were studied: 10 were undergoing coronary artery bypass grafting (upright T waves) and five aortic valve replacement (four patients with T inversion). Monophasic action potentials were recorded intraoperatively from eight to 10 left ventricular sites in each patient. In patients with upright T waves there was an inverse relation between the duration of the monophasic action potential and the activation time (mean slope −1·44). As a consequence, activation and repolarisation proceeded in opposite directions. Dispersion of repolarisation time (14 ms) was less than dispersion of activation time (23 ms). In patients with T wave inversion caused by aortic stenosis there was no relation between the duration of action potential and activation time; the repolarisation sequence resembled the activation sequence, and the dispersion of repolarisation time was greater than the dispersion of activation time (31 and 26 ms respectively).

These results show that there are epicardial repolarisation gradients in man and that these are related to the configuration of the T wave. In patients with upright T waves an inverse relation between the duration of the action potential and the activation time reduces the dispersion of the repolarisation time. When the T wave was inverted this relation was no longer found and the dispersion of repolarisation increased.

The human ventricular activation sequence has been extensively studied. Knowledge of the normal activation sequence[1,2] has contributed to our understanding of the role of abnormalities of activation in arrhythmogenesis.[3] In contrast, little is known of the repolarisation sequence in health or disease. As a consequence the role of repolarisation abnormalities in arrhythmogenesis remains uncertain. Animal studies have shown that increased dispersion of repolarisation is arrhythmogenic,[4–6] but it has been difficult to assess dispersion of repolarisation in man. The contribution of regional differences in repolarisation to the genesis of the T wave of the surface electrocardiogram is similarly unclear.[7]

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Repolarisation times can be accurately determined from monophasic action potentials.[8,9] The recent development of intraoperative techniques for recording monophasic potentials from the epicardium[10–12] offers the opportunity to undertake detailed repolarisation mapping in man. This study reports the sequence of epicardial repolarisation over the left ventricle of patients with upright T waves and patients with inverted T waves in the left ventricular leads of the surface electrocardiogram.

Patients and methods

PATIENTS

We studied 15 patients: 10 undergoing routine coronary artery bypass grafting and five undergoing aortic valve replacement. Patients undergoing bypass grafting had upright T waves in left ventricular leads of their surface electrocardiogram (leads I, aVL, and V3–V6) before operation. Patients undergoing

replacement of the aortic valve had dominant aortic stenosis (catheter or Doppler gradients ranging from 60 to 110 mm Hg) and evidence of left ventricular hypertrophy but no or minimal aortic regurgitation. There was T wave inversion in the left ventricular leads of the preoperative electrocardiogram in four of the five patients with aortic stenosis. In all four patients, leads I, aVL, V5, and V6 showed an inverted T wave. T wave configuration in leads V3 and V4 was either biphasic or inverted (V3 three patients biphasic, one inverted; V4 two patients biphasic, two inverted). In the fifth patient T waves were upright in the left ventricular leads. Four of the five patients with aortic stenosis underwent coronary angiography and none had clinically significant coronary disease.

All patients were in sinus rhythm and none had bundle branch block. No patient had a history of arrhythmias or myocardial infarction and none was being treated with digoxin. Eight of the 10 patients undergoing coronary artery bypass grafting were taking β blockers.

All patients gave informed consent for mapping. The study was approved by the ethics committee of the hospital.

EPICARDIAL MONOPHASIC ACTION POTENTIAL RECORDING

We recorded monophasic action potentials intraoperatively from the epicardium using a hand held probe.[12] The probe was an electrode assembly mounted on a flexible spatula. The electrode assembly was made from two silver-silver chloride electrodes—a central blunted spike electrode, which protruded by 1 mm, surrounded by a flush mounted ring electrode (diameter 7 mm). Potentials were recorded through a purpose built amplifier (bandpass 0·007 to 100 Hz). The signals were displayed on a monitor, which was visible to the surgeon, and recorded on paper (Mingograf) and on magnetic tape (Racal Store 7). For ethical reasons, recordings were confined to the epicardium and the transmural signals were not investigated.

ELECTROCARDIOGRAPHIC MONITORING

Lead I of the surface electrocardiogram was monitored continuously. In three patients the amplitude of the T wave decreased after thoracotomy, but the T wave polarity remained constant. Because mapping required cardiac manipulation and changing the orientation of the heart, the surface electrocardiogram varied during mapping. At intervals during mapping and on its completion the surface electrocardiogram was recorded with the heart in its normal position: T wave configuration was unchanged.

EPICARDIAL MAPPING

The heart rate was maintained constant by right atrial pacing at a fixed rate 10–20 beats/min above the spontaneous rate. Mapping was undertaken on cardiopulmonary bypass to facilitate epicardial access and to minimise the haemodynamic consequences of cardiac manipulation. The patients' temperature was maintained within the range 36–37°C, as indicated by an oesophageal thermistor probe. Mapping was started after six minutes of bypass to avoid the transient changes in the duration of the action potential that occur in the first few minutes of bypass.[12]

Potentials were recorded from 10 sites over the left ventricle (fig 1). These sites covered most of the epicardium of the left ventricle. We did not attempt to map the most apical portion of the ventricle, because mapping this area did not give satisfactory results.[12]

We recorded from the 10 sites on four occasions, starting at a different site on each occasion to ensure that any time dependent changes would influence each site to the same extent. Mapping took approximately eight minutes.

DEFINITIONS AND MEASUREMENTS

Monophasic action potentials were acceptable if they showed an amplitude at least 4 mV, a smooth repolarisation phase, freedom from baseline artefact, and constancy of configuration over at least two consecutive cycles. Potentials were timed with respect to a fixed left ventricular reference electrode (bandpass 30 to 300 Hz) (fig 2).

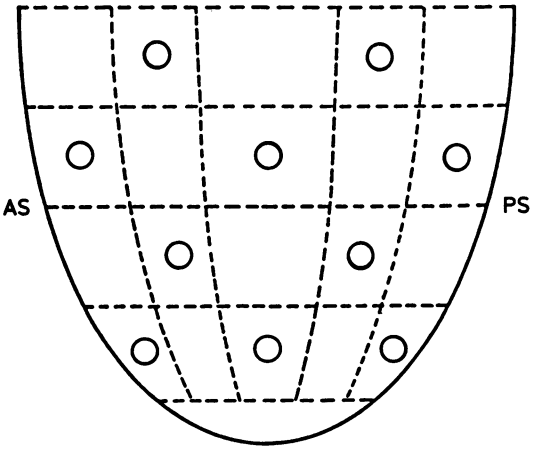

Fig 1 *Epicardial mapping sites. The left ventricle was considered as a grid. The ten sites indicated were mapped. AS, anterior septum; PS, posterior septum.*

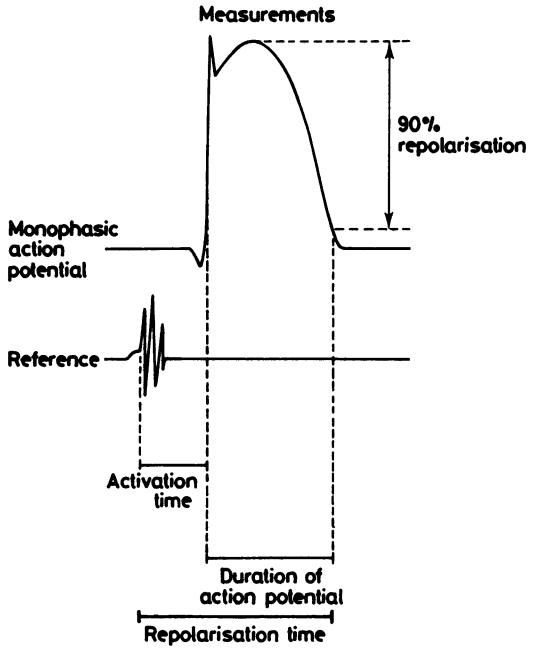

Fig 2 *Monophasic action potentials were timed in relation to a fixed ventricular reference electrode. Repolarisation time at any site is determined by the sum of activation time and action potential duration.*

The activation time was defined as the interval between reference and the visually determined time of maximum velocity of the upstroke of the monophasic action potential.

The action potential duration was defined as the interval between the time of maximum upstroke velocity and the time of 90% repolarisation from maximum plateau amplitude to baseline.

The repolarisation time was defined as the interval between reference and the time of 90% repolarisation—that is, the sum of the activation time and the action potential duration.

For each epicardial site we measured the activation time, action potential duration, and repolarisation time as the mean of the four individual probe applications at that site.

The dispersion of each variable was defined as the difference between the maximum and minimum values of the site means within each patient.

MEASUREMENT OF EPICARDIAL TEMPERATURE

We studied the variation in epicardial temperature in four of the patients undergoing bypass grafting by applying a small thermocouple probe directly to the epicardium. Temperature was recorded at each of the 10 sites used for mapping. The effects of cooling on the duration of the action potential were studied in three of the four patients. Monophasic potentials and temperature were recorded simultaneously during cooling and before cardioplegia. The probe was applied repeatedly at the same site and the heart rate was kept constant by atrial pacing.

STATISTICAL ANALYSIS

The duration of the action potential and the activation time at different epicardial sites were plotted and the regression line was calculated for each patient. Ninety five per cent confidence limits and the statistical significance of the slope of the regression lines were calculated.

Before comparison, values in different patients were normalised to eliminate differences caused by reference placement, the duration of action potential, and heart rate. For each patient, the results of all left ventricular sites were pooled to provide a mean activation time, action potential duration, and repolarisation time. The deviation of each site from the mean was then determined, thereby providing a normalised estimate of the relative timings of different sites. The normalised values for sites were pooled to determine a mean activation and repolarisation sequence for the study group.

Results

ACTIVATION AND REPOLARISATION SEQUENCES FOR UPRIGHT T WAVES

The activation time, action potential duration, and repolarisation time were studied in 10 patients with upright T waves. An inverse relation was seen between the duration of the action potential and the activation time (fig 3). The slope of the regression line for the duration of the action potential against the activation time was negative in all 10 patients (table 1). The 95% confidence limits for the slope varied in different individuals, achieving statistical significance in seven patients and borderline significance in two others.

Because the repolarisation time is determined by the sum of the activation time and the action potential duration, this inverse relation resulted in a relative uniformity of repolarisation times—in eight of the 10 patients dispersion of repolarisation time was less than dispersion of action potential duration (table 2). As a further consequence, the repolarisation time in individual patients was in general found to be independent of the activation time (fig 4a). The exception, patient 10, showed a significant inverse relation between repolarisation time and activation time (slope $-1{\cdot}09$, $p < 0{\cdot}025$), reflecting a particularly steep inverse relation between the activation time and the action potential duration (slope $-2{\cdot}09$).

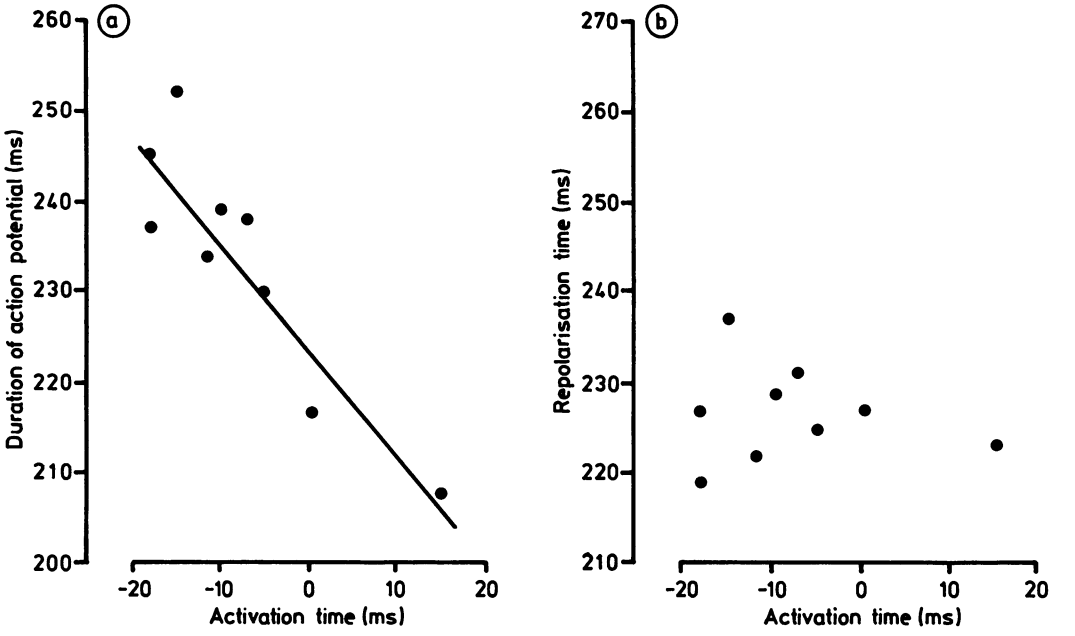

Fig 3 *Relation between the duration of the action potential and the activation time in a patient with upright T waves. The relation between the duration of the monophasic action potential and the activation time for left ventricular sites in one patient (patient 4, table 1) is given on the left. The line for the regression of the duration of the action potential on the activation time is shown (slope −1·17). The resulting distribution of repolarisation times and activation times is shown on the right.*

In view of the variation in the slopes of the regression lines in individual patients, a mean activation time, duration of action potential, and repolarisation time were derived for each site by pooling the standardised data from all 10 patients. Figure 5 shows the relation between the activation time and the duration of the action potential for these standardised site means. There was a close inverse relation between the activation time and the duration of the action potential (slope −1·44, 95% confidence limits of slope −1·15 to −1·73, p < 0·001). In contrast with the data for individual patients, a statistically significant inverse relation between repolarisation time and activation time was evident in the pooled data, indicating earlier repolarisation at sites of later activation (slope −0·44, 95% confidence limits of slope −0·15 to −0·73, p < 0·001). The fact that a statistically significant inverse relation was demonstrated in only one of the 10 patients, when considered individually, reflects the scatter of results

Table 1 *Regression of action potential duration on the activation time in patients with upright T waves*

Case No	*Correlation coefficient*	*Slope*	*95% confidence limits of slope*	*Probability*
1	−0·67	−0·97	−0·10 to −1·84	p < 0·05
2	−0·66	−1·01	+0·04 to −2·05	p < 0·10, NS
3	−0·73	−0·89	−0·06 to −1·72	p < 0·05
4	−0·89	−1·17	−0·67 to −1·67	p < 0·001
5	−0·08	−0·10	+1·01 to −1·21	p > 0·10, NS
6	−0·64	−0·90	+0·06 to −1·86	p < 0·10, NS
7	−0·73	−0·71	−0·12 to −1·30	p < 0·025
8	−0·95	−1·30	−0·93 to −1·67	p < 0·001
9	−0·67	−1·04	−0·02 to −2·06	p < 0·05
10	−0·94	−2·09	−1·35 to −2·83	p < 0·001

Table 2 *Dispersion of activation time, action potential duration, and repolarisation time in patients with upright T waves*

Case No	*No of sites measured*	*Dispersion (ms)*		
		Activation	*Action potential duration*	*Repolarisation*
1	10	28	36	31
2	9	23	48	32
3	8	34	41	22
4	9	33	44	20
5	9	19	25	28
6	9	16	21	15
7	9	31	30	20
8	10	33	37	18
9	9	20	26	26
10	8	34	89	55

The number of sites giving acceptable potentials varied between eight and 10 in different patients. The dispersion of each variable is the difference between the maximum and minimum values of that variable.

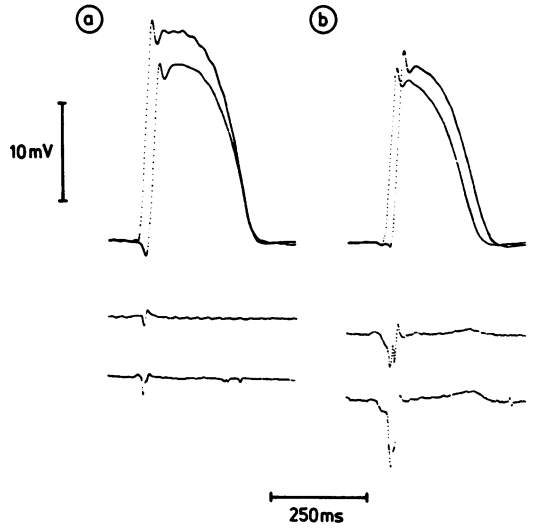

Fig 4 *(a) Monophasic potentials at two epicardial sites in a patient with upright T waves. Potentials were aligned using the reference signals (bipolar recordings, lower traces). Despite differing activation times, repolarisation time at the two sites was almost synchronous, reflecting a shorter action potential duration at the site with later activation. (b) Monophasic potentials at two epicardial sites in a patient with inverted T waves caused by aortic stenosis. The duration of the action potential was independent of the activation time and hence the site which activated later also repolarised later. For clarity of presentation, the upstrokes of potentials have been retouched.*

within individuals and the relatively flat slope of the regression line relating repolarisation time and activation time.

The activation and repolarisation sequences derived from these individual site means are plotted schematically in fig 6. Activation occurred earliest in the anterior and posterior septum. It then spread in two general directions, from each septal border towards the free wall of the ventricle and from apex to base. Dispersion of the mean activation times over the left ventricular sites was 23 ms. The repolarisation sequence was very different from the activation sequence. Repolarisation occurred earliest in the posterobasal region—the areas of latest activation. The areas over the anterior and posterior septum were the last to repolarise; these areas correspond approximately to the earliest areas of activation. There was therefore an inverse relation between the sequences of activation and repolarisation. The dispersion of the mean repolarisation times over the left ventricle was 14 ms.

AORTIC STENOSIS WITH T WAVE INVERSION

We studied activation time, action potential duration, and repolarisation time in four patients with T wave inversion caused by aortic stenosis. In contrast with patients with upright T waves, the duration of the action potential was independent of the activation time (table 3). As a consequence, the repolarisation time was determined by the activation time (fig 4b.)

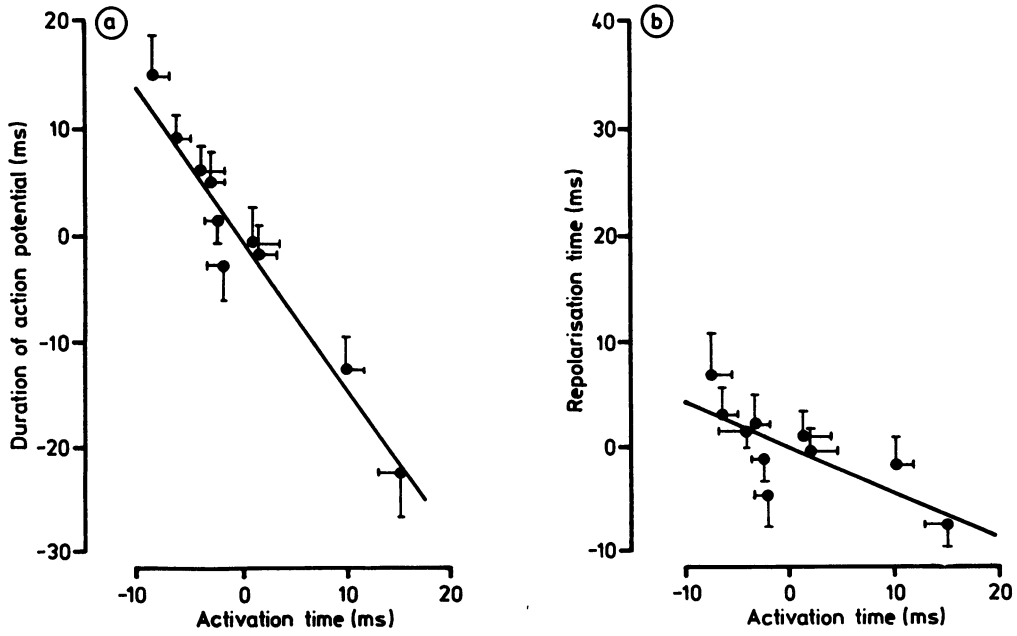

Fig 5 *Mean relation between (a) the duration of the action potential and the activation time for all 10 patients with upright T waves. Normalised data from individuals were pooled to provide a mean activation time and the mean duration of the action potential for each site. (b) The relation between repolarisation time and activation time. Both figures show the SEMs and the regression lines.*

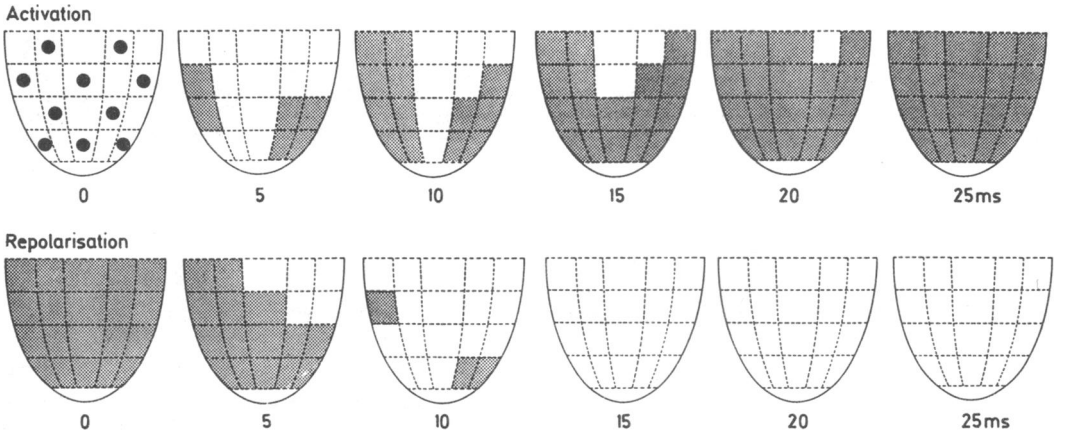

Fig 6 *Representation of left ventricular activation and repolarisation sequences for patients with upright T waves. Diagrams are based on the means of the normalised data for all 10 patients with upright T waves. The 10 mapped sites within the grid are indicated by dots. Estimates of activation time and repolarisation time at unmapped sites were derived as the mean of measurements of all adjacent sites. The shaded areas indicate the extent of depolarised myocardium in successive 5 ms timeframes, timed from the earliest activation or repolarisation. The anterior septum is on the left and the posterior on the right (as in fig 1). The dispersion of activation was 23 ms and the dispersion of repolarisation was 14 ms.*

Table 3 *Regression of action potential duration on activation time in patients with aortic stenosis*

Case No	*Correlation coefficient*	*Slope*	*95% confidence limits of slope*	*Probability*
Inverted T waves:				
1	−0·36	−0·22	+0·30 to −0·84	p > 0·10, NS
2	−0·59	−0·56	+0·04 to −1·16	p < 0·10, NS
3	−0·17	−0·21	+0·76 to −1·18	p > 0·10, NS
4	+0·06	+0·06	+0·84 to −0·72	p > 0·10, NS
Upright T waves:				
5	−0·79	−1·33	−0·48 to +2·18	p < 0·001

In three of the four patients dispersion of repolarisation time was greater than dispersion of action potential duration (table 4).

The mean activation time, action potential duration, and repolarisation time for each site were derived by pooling the standardised data for all four patients (fig 7). There was no significant relation between the action potential duration and activation time. As a result, the repolarisation time was significantly related to the activation time (slope 0·86, 95% confidence limits of slope 0·26 to 1·46, p < 0·01).

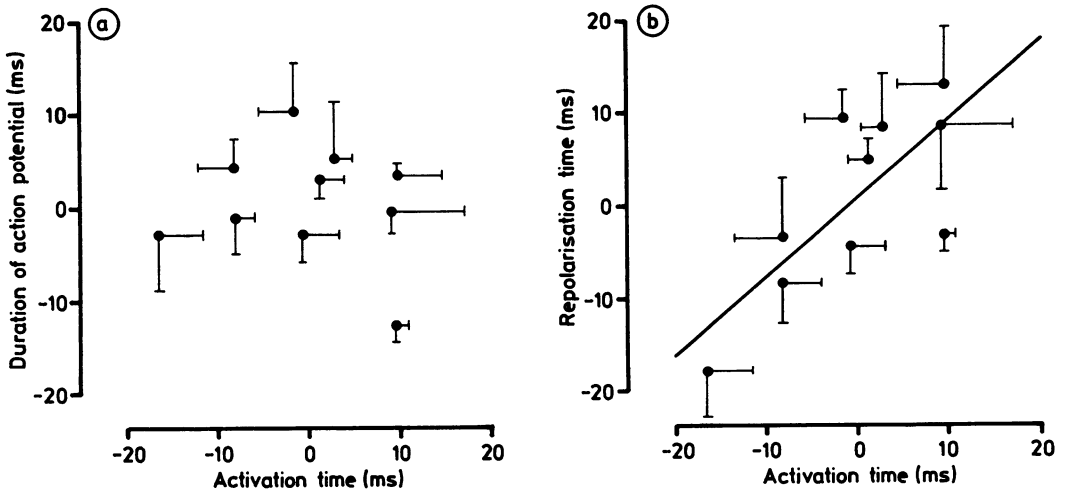

Fig 7 *Mean relation between (a) the duration of the action potential and the activation time for all four patients with T inversion caused by aortic stenosis. (b) The resultant relation between repolarisation time and activation time. Both figures show the SEMs and the regression lines.*

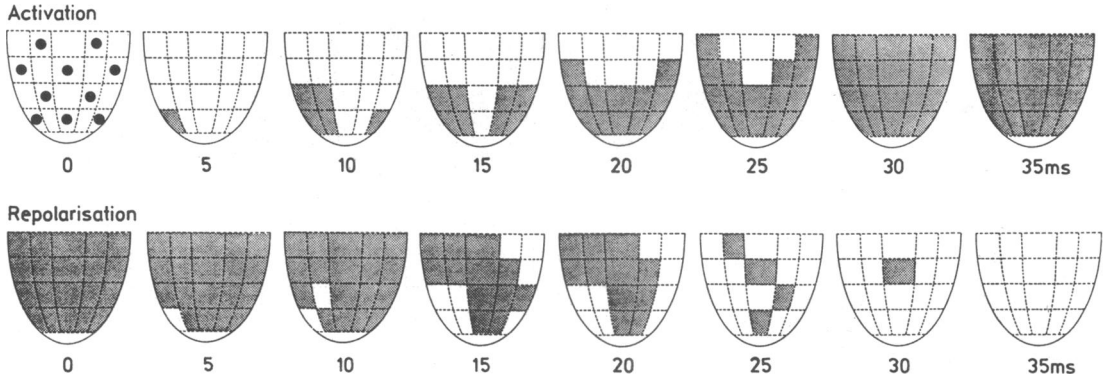

Fig 8 *Representation of left ventricular activation and repolarisation sequences for patients with T inversion caused by aortic stenosis. Diagrams are based on the means of the normalised data of the four patients. The shaded areas indicate the extent of depolarised myocardium in successive 5 ms timeframes. The dispersion of activation was 26 ms and the dispersion of repolarisation was 31 ms.*

Table 4 *Dispersion of activation time, action potential duration, and repolarisation time in patients with aortic stenosis*

Case No	No of sites measured	Dispersion (ms) Activation	Action potential duration	Repolarisation
Inverted T waves:				
1	9	62	37	48
2	10	20	23	17
3	10	24	37	38
4	10	26	25	47
Upright T waves:				
5	10	35	63	39

Figure 8 shows the mean activation and repolarisation sequences. The activation sequence was similar to the sequence in patients with upright T waves. Activation occurred earliest on either side of the septum and proceeded from the septum to the free wall and from the apex to the base. Dispersion of the mean activation times was 26 ms. The repolarisation sequence differed from that in patients with upright T waves; it resembled the activation sequence. Dispersion of the mean repolarisation times (31 ms) was slightly greater than dispersion of activation times.

AORTIC STENOSIS WITH UPRIGHT T WAVES

We studied one patient with aortic stenosis and upright T waves. This patient resembled the other patients with upright T waves in showing a statistically significant inverse relation between action potential duration and activation time (table 3).

VARIATION IN THE EPICARDIAL TEMPERATURE

In the four patients we studied a two way analysis of variance showed no statistically significant difference between epicardial sites. The left ventricle was considered as a series of four coaxial rings from base

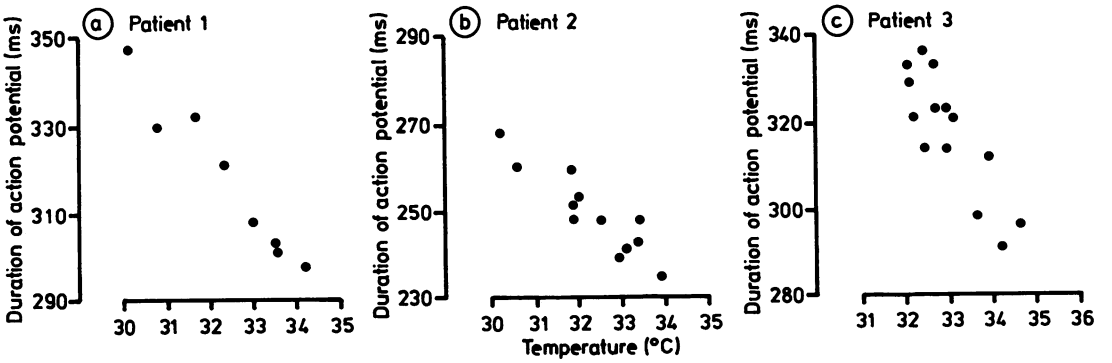

Fig 9 *Relation between the duration of the monophasic action potential and temperature. The effects of cooling on action potential duration in three separate patients are shown.*

to apex. The mean temperature of the four rings from base to apex was 35·1, 35·1, 35·0, and 34·7 °C (differences non-significant).

In three of the four patients the relative magnitude of temperature effects on action potential duration was determined by recording monophasic potentials during cooling. The action potential duration was prolonged (fig 9). The slopes of the regression lines relating action potential duration and temperature varied between 4 and 12 ms prolongation per °C of cooling.

Discussion

This study presents the first maps of the sequence of human epicardial repolarisation. We showed that epicardial repolarisation gradients do exist and that they are related to the configuration of the T wave on the surface electrocardiogram. The relation between activation and repolarisation sequences was different in patients with upright T waves and in those with inverted T waves.

STUDY LIMITATIONS

It is not feasible to record intracellular potentials from the beating whole human heart. The use of monophasic action potentials as a substitute depends on certain assumptions. Monophasic potentials are of much lower amplitude than their intracellular counterparts. Though their overall duration corresponds closely with the intracellular potentials,[8 9] the point of 90% repolarisation is measured in relation to the maximum plateau amplitude and hence may be amplitude dependent. The 90% repolarisation point is only independent of amplitude if the monophasic potential is proportionately reduced from the intracellular potential throughout the whole of repolarisation. Previous studies in isolated rabbit hearts have suggested that this is indeed the case.[9]

There are additional problems in studying repolarisation in vivo. Repolarisation, unlike activation, is a dynamic process, influenced by many factors and capable of rapid change.[7] Consequently, the "normal" or baseline repolarisation state is difficult to establish and to maintain. During open chest surgery differential epicardial cooling or cardiopulmonary bypass may cause changes in repolarisation.

We saw modest evidence of differential apical cooling. Based on the lengthening of the duration of the action potential during cooling, the observed 0·4°C temperature difference between base and apex would be expected to lengthen the action potential duration at the apex by 2–5 ms relative to the base. This effect is small compared with the observed differences in the duration of the action potential.

Cardiopulmonary bypass causes a transient prolongation of the duration of the action potential in the first minutes of bypass.[12] In the present study we started mapping after six minutes of bypass to avoid these transient effects. We adopted a strategy of repeated point mapping to ensure that comparisons between epicardial sites would be independent of any continuing time-dependent influences.

We therefore believe that intraoperative influences on epicardial repolarisation gradients were relatively small.

DISPERSION OF REPOLARISATION

In patients with upright T waves we found an inverse relation between the duration of the action potential and the activation time. The slope of this relation was significantly more negative than -1, reflecting inverse activation and repolarisation sequences. A similar inverse relation between the duration of the action potential and the activation time was reported by Franz *et al*, who recorded endocardial monophasic action potentials in seven patients and epicardial potentials in three patients.[10]

By contrast, in patients with T wave inversion caused by aortic stenosis the duration of the action potential was independent of the activation time (table 3). As a result the repolarisation sequence was largely determined by the activation sequence. Differing relations between the activation and repolarisation sequences of patients with upright and inverted T waves have been reported before.[13]

An important consequence of the observed inverse relation between the duration of the action potential and the activation time is a reduction in the dispersion of repolarisation. In patients with upright T waves, the dispersion of the repolarisation time was less than the dispersion of duration of the action potential. By contrast, in patients with T inversion caused by aortic stenosis, in whom the duration of the action potential was independent of the activation time, dispersion of repolarisation time was greater than that of the duration of the action potential.

Dispersion of repolarisation has been shown to favour the development of arrhythmias,[4-6] so minimising dispersion may be a protective mechanism. The observed inverse relation between the activation time and the duration of the action potential may therefore represent a fundamental intrinsic antiarrhythmic property of the myocardium.

DIFFERENCES IN EPICARDIAL REPOLARISATION AS DETERMINANTS OF T WAVE CONFIGURATION

The concordance of QRS and T waves in the surface electrocardiogram led to the classic hypothesis that activation and repolarisation must proceed in opposite directions.[14] Such an inverse relation might

result from a transmural endocardial-epicardial gradient, from gradients across the epicardial surface, or from both.

There is a consensus, from animal studies, that transmural activation and repolarisation gradients are opposite.[15 16] Whereas activation proceeds from endocardium to epicardium, repolarisation proceeds from epicardium to endocardium. Franz *et al* have provided evidence of a similar transmural gradient in man, based on the finding that endocardial repolarisation occurs later, in relation to the QT interval of the surface electrocardiogram, than epicardial repolarisation.[10]

For gradients across the epicardial surface the situation is less clear. There is some measure of agreement that refractory periods[17] and action potentials[18] are longer at the apex than at the base. Abildskov found that on the epicardium recovery from refractoriness resembled the activation sequence, whereas there was an inverse relation on the endocardium.[19] Toyoshima *et al* found differing relations between activation and repolarisation on the anterior and posterior epicardial surfaces.[20] Spach and Barr found that the apex repolarised later than the base,[15] hence suggesting an inverse relation between activation and repolarisation.

In the present study, we have found that the repolarisation wavefront in individual patients is complex, reflecting differences in repolarisation times between closely adjacent areas of epicardium. A similar complexity of the repolarisation wavefront has been reported in animals.[18 21] Pooling data between patients showed that activation and repolarisation sequences were opposite—activation proceeded from septum to free wall and from apex to base, whereas repolarisation proceeded from base to apex and from free wall to septum. By contrast, in patients with T inversion, the repolarisation sequence broadly resembled the activation sequence. These findings are consistent with classic theories of the genesis of T waves.They suggest that the normal concordance of QRS and T waves is the result of the observed inverse relation between the duration of the action potential and the activation time.

For ethical reasons, our study was confined to the epicardium and simultaneous endocardial recordings were not undertaken. The relative contribution of epicardial and transmural gradients to the T wave remains uncertain. Earlier estimates of dispersion of repolarisation in man, which were based on the variation in QT interval over the body surface, range from 60 to 80 ms in normal subjects.[22 23] These values are considerably greater than the epicardial dispersion we found. This suggests that transmural gradients have a large effect in the overall dispersion of repolarisation.

THE LINK BETWEEN THE DURATION OF THE ACTION POTENTIAL AND THE ACTIVATION TIME

The simplest explanation for the inverse relation between the duration of the potential and the activation time is an indirect association through a third factor, such as site. A posterobasal location, for example, might predetermine both a short action potential duration and a late activation time. The question would then be restated as to how activation time and the duration of the action potential might be jointly predetermined on a regional basis.

Alternatively, there may be a direct causal relation, such that the duration of the action potential adapts directly to the activation sequence. Although the basis for such adaptation is unclear, there is indeed evidence that the duration of the action potential can alter in response to changes in the activation sequence. Alteration in the ventricular activation sequence, whether caused by ventricular pacing,[24 25] intermittent left bundle branch block,[26 27] or intermittent pre-excitation[28] can produce T wave changes that persist after the restoration of normal activation. By inference, the duration of the action potential alters during the period of abnormal activation, resulting in an abnormal repolarisation sequence when normal activation is restored. It can be postulated that an intrinsic property of the myocardium enables the duration of the action potential to adapt to its activation sequence. This would result in a direct link between the duration of the action potential and the activation time and this would provide a possible mechanism for the inverse relation that we found.

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