

## Relation of human cardiac action potential duration to the interval between beats: implications for the validity of rate corrected QT interval (QTc)

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**SUMMARY** Fourteen patients undergoing routine cardiac catheterisation were paced at a steady frequency; after this test, stimuli were introduced with a variable preceding interval (test pulse interval). The QT interval of the electrocardiogram and the duration of the monophasic action potential of the right ventricle were measured. QT interval is a function of action potential duration; the two variables were very closely correlated in this study. Both these variables increased in duration with increasing test pulse interval. A biphasic response, as previously reported, was not seen. An increase in steady state pacing frequency caused QT interval and action potential duration to decrease for any given R-R interval. When frequency of stimulation was suddenly increased and then maintained, there was an immediate action potential shortening followed by a further more gradual shortening occurring over several minutes. These results imply that a simple correction of QT interval for heart rate (QTc) is inadequate.

It is concluded that the relation between action potential duration (or QT interval) and heart rate depends on both the instantaneous interval between beats and the duration of the prevailing heart rate.

When the heart is electrically activated, depolarisation of the myocardium is registered as an upstroke of the action potential and as the QRS complex of the surface electrocardiogram. The period of myocardial depolarisation is indicated by the plateau of the action potential; this is terminated by repolarisation—that is the downstroke of the action potential and the T wave of the electrocardiogram. The interval from the QRS to the T wave of the electrocardiogram (QT interval) thus reflects the duration of the action potential. We have investigated the effect of heart rate on the QT interval using the more direct and accurate measurement of ventricular action potential duration. When an electrical impulse is delivered to the heart immedi-

ately after an action potential, the membrane is refractory and no response is obtained. When the stimulus is delivered a little later, action potentials are obtained which (in most species) are shorter than those in the preceding steady state; they become longer as the interval between beats is increased. When this relation is explored formally by pacing at a given steady state frequency and by introducing a test pulse interval at progressively increasing intervals<sup>1,2</sup> a relation can be defined between action potential duration (or QT interval) and test pulse interval (R-R interval), which is termed the electrical restitution curve.<sup>3-6</sup> There is one study in man that included only five patients, two of whom showed prolongation of the action potential duration over a range of R-R intervals of 300-400 ms.<sup>6</sup> This is unlike the findings in animals of Boyett and Jewell<sup>4</sup> and Elzinga *et al.*<sup>5</sup> The first objective in the present study was to examine electrical restitution in

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a larger group of patients in order to establish the correct restitution curve.

Electrical restitution does not explain all the changes in action potential (and QT interval) that take place when the heart rate is increased. A sustained increase in heart rate causes a slow progressive shortening of QT interval and action potential duration over a period of several minutes. This has been shown for the guinea pig by Attwell *et al*<sup>7</sup> and for intact dog by Drake *et al*.<sup>8</sup> Attwell *et al* also showed that changes in human QT interval (which corresponds to the action potential duration) followed a similar pattern.<sup>7</sup> The second objective of the present study was to examine the longer term response of action potential duration to an increase in heart rate. This is of considerable importance in understanding the relation of QT interval to cardiac frequency.<sup>9-11</sup> Bazett's correction of the QT interval (QTc) was formulated to allow for physiological variation in heart rate, assuming a linear relation. The results of Attwell *et al*<sup>7</sup> strongly suggest that such correction is invalid and we therefore wished to confirm or deny that suggestion with a definitive study.

## Patients and methods

### PATIENTS

Fourteen patients were studied (9 men and 5 women, aged 36-74 years (table 1)). They were patients with ischaemic heart disease who were routinely undergoing cardiac catheterisation for diagnostic purposes. All drugs were stopped 24 hours before the study. No patients had received amiodarone before or during the study. The patients were given 100 mg atenolol orally 4 hours before the study, to avoid the complication of variable adrenergic status, and diazepam 10 mg orally an hour before the study. Measurements were made during

Table 1 Patient data and steady state intervals used in the study

Patient No	Sex	Age	Steady state interval (ms)
1	M	73	800
2	F	72	800
3	M	60	800
4	M	61	800
5	M	49	800
6	M	58	600
7	M	38	500
8	F	74	500 and 800
9	M	36	600
10	F	52	500
11	F	51	500 and 700
12	M	58	450 and 750
13	M	71	800
14	F	57	500 and 800

quiet breathing. The study was approved by the ethics committee of the participating hospitals. Informed consent was obtained from each patient before the study.

### MEASUREMENTS

#### Endocardial action potentials

An action potential catheter as modified by Miller *et al*<sup>12</sup> was used. The catheter was passed from the right femoral vein to the right ventricle and was allowed to touch the endocardial surface. A site on the septum towards the middle of the ventricle was chosen whenever possible to minimise variability between action potential duration and the QT interval. The potential difference between the two silver-silver chloride electrodes of the catheter was measured with a DC amplifier and an oscillographic or electrostatic recorder. Recordings were made simultaneously on to a Racal instrumentation tape recorder. The duration of the action potentials (expressed as time during which the myocardial cells were depolarised by more than 70%) was measured manually from all records at a fast paper speed. A standard electrocardiogram was monitored throughout the procedure. When we analysed the action potential duration we always checked the electrocardiographic signal to ensure that there were no spontaneous beats. QT interval was measured simultaneously from the standard electrocardiogram.

#### Pacing

The heart was stimulated by a right atrial (3 patients) or right ventricular (11 patients) bipolar pacing catheter introduced from the right femoral vein. If the atrioventricular node became refractory during attempted atrial pacing, ventricular pacing was substituted. Stimuli of 2 ms duration and twice threshold strength were produced from an isolated constant current source (Devices 2533) which was triggered by a programmable stimulator.

#### Pacing protocols

To determine the electrical restitution curves, the hearts were paced at a constant base cycle length (see table 1 for details) until action potential duration had reached a steady state. This was usually in 2-3 minutes. In the first five studies we used a basic pacing interval of 800 ms (table 1). This was chosen because it was expected to be comfortably shorter than the spontaneous R-R interval of patients on  $\beta$  adrenergic blockade. We then wished to check the effect of higher basic pacing frequency and used intervals of 500 or 600 ms (patients 6, 7, 9, and 10; table 1). We were also able to study two basic frequencies in individual patients (patients 8, 11, 12,

and 14; table 1). After each period of steady pacing at these intervals a test stimulus was applied after the refractory period of the last regularly paced response via the programmable stimulator. After each test stimulus, regular pacing at the basic cycle length was resumed for at least ten beats to allow recovery of the original steady state. Test pulse intervals were applied with either a progressively longer or shorter interval in sequence, in each patient. Action potential durations were measured at 70% repolarisation and plotted against test cycle length. For pooled data, the duration of the action potential in response to the test beats was expressed as a percentage of that of the steady state beats. When a frequency switch of steady state interval was made (patients 8, 11, 12, and 14) the time taken for the response to reach a new steady state was carefully monitored.

## Results

The monophasic action potential signals recorded with the electrode catheter were of good quality for determination of action potential duration (fig 1). As the interval preceding a test stimulus was extended, the duration of the action potential also increased—see the electrical restitution curve (fig 2a). The results in the three patients in whom the protocol could be carried out by atrial pacing without atrio-ventricular conduction problems were similar to those in the 11 patients studied by right ventricular pacing. We have averaged the data for all those studies in which the steady state interval was 800 ms (fig 2b). This data does not include some patients in

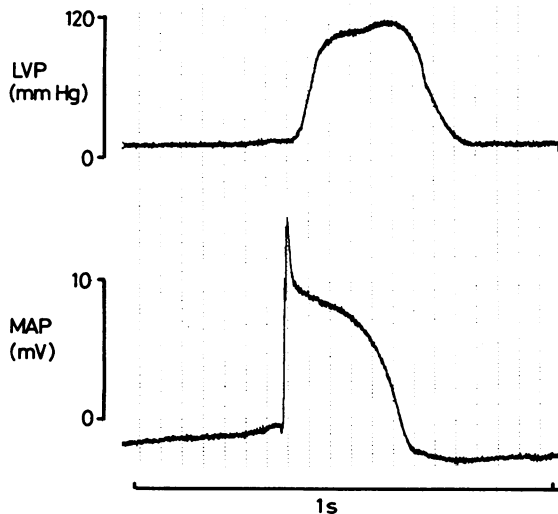


Fig 1 Recordings of typical monophasic action potential signal (MAP) from the human heart and left ventricular pressure (LVP).

whom the spontaneous rate was too high to allow steady pacing at 800 ms intervals. The electrical restitution curves in these patients were similar, however. In every patient there was a smooth increase in action potential duration with interval over the whole range studied. A transient decrease at intermediate intervals, as seen in two patients of Franz *et al*,<sup>6</sup> was not seen in any of the present patients studied.

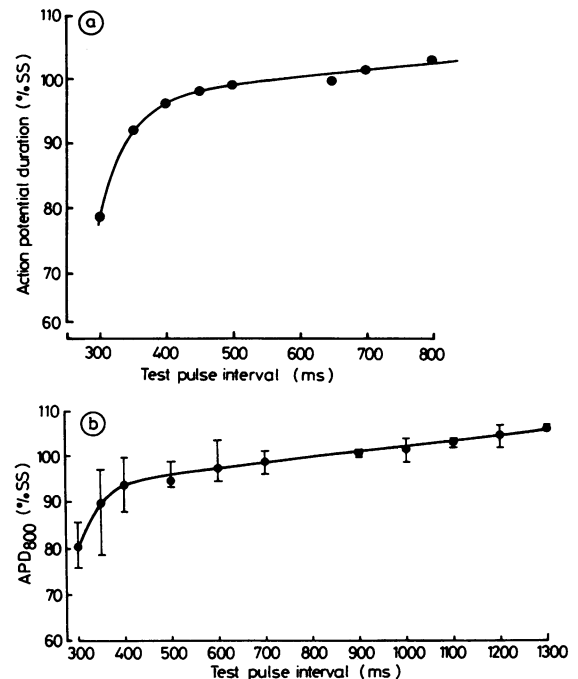


Fig 2 Electrical restitution curves in which action potential duration of the test beats as a percentage of steady state control action potential duration is plotted as a function of test pulse interval. (a) A typical individual example; (b) mean results (range) for all patients in whom the steady state interval was 800 ms.

In four patients we also studied the electrical restitution curve at a higher steady state frequency. This intervention was not possible in some patients because of the occurrence of angina or because it was not advisable to prolong the study. In the cases where results at two frequencies were obtained, the action potentials for all test pulse intervals were shortened at the higher frequency; this resulted in a downward shift of the electrical restitution curve (fig 3). Table 2 summarises the data from all patients.

Figure 4 illustrates the effects of a sudden switch in frequency of stimulation. On the first beat at the high frequency, the action potential was shortened to a degree that was consonant with the electrical restitution curve for the control (low) frequency.

Table 2 Action potential duration measurements for the individual test pulse intervals used in the study

Patient No	Interval																
	300	350	400	450	500	550	600	700	800	900	1000	1100	1200	1300	1400	1500	1600
1	—	235	268	275	280	283	289	280	280	277	284	282	—	—	—	—	—
2	256	287	301	—	292	—	299	300	—	302	312	310	320	—	—	—	—
3	—	—	—	260	255	270	288	297	309	300	308	312	313	318	—	—	—
4	199	246	248	—	242	—	253	265	—	256	259	254	267	—	—	—	—
5	194	—	233	—	237	—	244	252	—	250	250	260	—	—	—	—	—
6	209	242	255	258	259	262	263	266	—	—	—	—	—	—	—	—	—
7	—	—	230	230	—	250	260	260	265	280	280	285	300	300	300	—	—
8a	—	—	203	207	—	216	221	228	232	239	244	248	252	253	254	260	270
b	—	—	—	257	256	260	262	270	275	282	289	290	297	302	302	305	268
9	—	—	—	192	200	202	206	218	222	—	—	—	—	—	—	—	—
10	255	276	276	—	276	—	300	—	—	—	—	—	—	—	—	—	—
11a	206	218	218	222	—	—	210	206	210	—	—	—	—	—	—	—	—
b	213	242	242	254	270	—	—	280	280	280	276	—	—	—	—	—	—
12a	200	203	207	—	213	213	218	217	223	223	228	228	237	—	—	—	—
b	211	234	247	248	—	—	—	257	—	—	270	—	—	—	—	—	—
13	—	265	290	293	305	300	303	310	321	333	325	—	350	—	—	—	—
14a	—	235	237	237	235	—	—	237	250	258	269	295	—	—	—	—	—
b	—	—	—	222	230	—	—	238	244	247	251	249	258	256	—	—	—

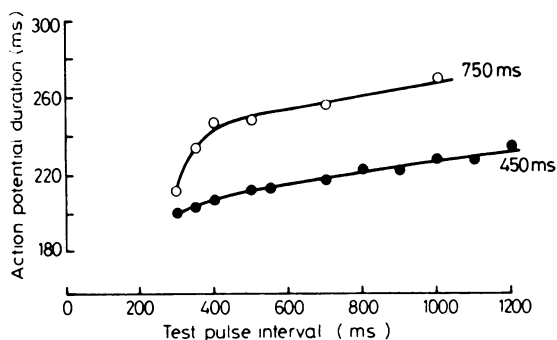


Fig 3 Two electrical restitution curves in one patient recorded at two different steady state intervals.

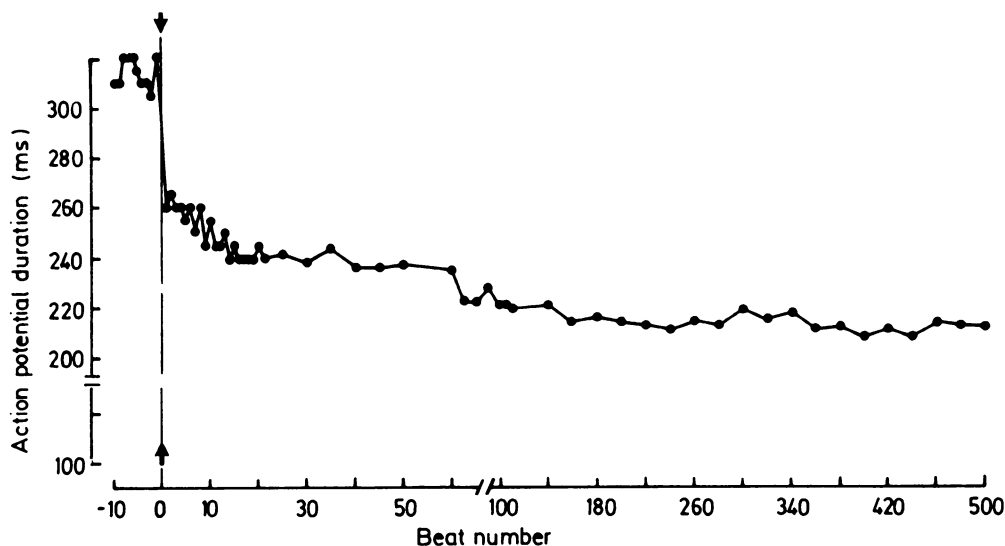


Fig 4 Beat to beat values for action potential duration after a sudden change of interval from 750 to 450 ms.

This was followed by a progressive further shortening for subsequent beats at the new (high) frequency. This shortening continued over several minutes (fig 4); even after three minutes there was still a trend to further action potential shortening with time. In all four cases the changes were qualitatively similar to those described for one patient by Franz *et al.*<sup>13</sup>

In those patients in whom adequate comparison could be made between action potential duration and simultaneous QT interval, the Spearman Rank correlation coefficient ranged from 0.80 to 0.88. Most of the scatter contributing to the comparative analysis was derived from the QT measurements.

## Discussion

Our results confirm that in the intact human heart the relation between action potential duration (and QT interval) and the R-R interval is similar to that of isolated cardiac muscle<sup>3 4 14 15</sup> and intact dog.<sup>5</sup> This relation between action potential duration and test pulse interval is referred to as the electrical restitution curve.<sup>4 5</sup>

A previous report suggests that the electrical restitution curve of man was of a different form, namely a biphasic relation<sup>6</sup> similar to that of the rabbit.<sup>16</sup> There are species differences in the shape of electrical restitution curves. The shapes of the electrical restitution curves reported for two of the five patients by Franz *et al*<sup>6</sup> resemble those of the rabbit, in that action potential duration at intervals of 300–400 ms was prolonged. Action potential duration then declined again at frequencies between 400 and 500 ms, before increasing again with longer intervals. We did not observe such changes in any of our 14 patients. In the study of Franz *et al* the prolonged action potentials at short preceding intervals were accompanied by changes in the shape of the action potential waveform.<sup>6</sup> We are of the opinion that monophasic signals do not give reliable information on action potential shape but only of action potential duration.<sup>17</sup> We would therefore place more reliance on the present measurements in a considerably larger group of patients, and we conclude that the human electrical restitution curve is very similar to that of the cat<sup>4</sup> and of the dog.<sup>5</sup>

The electrical restitution curve determines the action potential duration and QT interval of only the first excitation after the first short R-R interval. If short R-R intervals are maintained by a continuation of pacing at a high frequency there is a further progressive shortening of the action potential duration and QT interval over a period of several minutes. This was reported for the QT interval of man by Attwell *et al*<sup>7</sup> and for the action potential duration of one person.<sup>13</sup> If the electrical restitution curve is redefined after such a period, it is found to show shorter action potential duration at all R-R intervals. This downward shift of the electrical restitution curve when the steady state frequency is higher (fig 3) is very similar to the findings in the dog.<sup>5</sup> The changes in action potential duration with a maintained frequency increase after a sudden switch (fig 4) are also very similar to findings in the dog for both Purkinje fibres<sup>18</sup> and endomyocardial recordings in the intact animal.<sup>8</sup>

It would seem reasonable therefore to assume that the changes we see are due to mechanisms that apply generally in higher animals. The immediate action potential shortening on the first beat is a shift along

the restitution curve for the low steady state frequency. The restitution curve depends on changes in factors affecting recovery of the cell membrane after a depolarisation. This is thought to be due in part to recovery from inactivation of the slow inward calcium channels.<sup>18</sup> There is also decay of outward potassium currents during the polarised period (or electrical diastolic interval)<sup>6</sup> which may be interrupted by shorter intervals. The mechanisms underlying the second, slower phase of further action potential shortening during a period of high frequency pacing (fig 4) were examined in some detail in the intact dog by Drake *et al*.<sup>8</sup> The slow time course of change in action potential duration after an increase in stimulation frequency suggested that these changes are caused by the accumulation of an ion or metabolite, or possibly by changes in activity of the electrogenic Na<sup>+</sup>-K<sup>+</sup> pump<sup>18</sup>; such mechanisms appear to act via an increase in outward background current.<sup>18</sup> Whatever mechanism is responsible for this change, it is clearly maintained for at least 1400 ms.

The results of our study are relevant to arguments concerned with the corrections to be made to QT interval to allow for heart rate.<sup>19–21</sup> Thus from our results and from those using QT intervals<sup>7</sup> it must be concluded that the relation between heart rate and QT interval is not constant. For instantaneous differences in interval between beats, QT interval must be governed by the electrical restitution curve (fig 1). For more prolonged periods, the relation will also be affected by the slower changes in action potential duration, which are time dependent (fig 4). We have confirmed that after one beat at a different interval, it takes up to 10 beats for a steady state to be regained. When there is a switch from one sustained period at a given frequency to a new frequency, it takes at least three minutes for a new steady state to be reached.

Our study does not explore the additional influence of the sympathetic nervous system upon action potential duration and QT interval, because our patients were deliberately subjected to  $\beta$  adrenergic blockade by atenolol. An increase in sympathetic activity in the absence of such blockade causes a further shortening of action potential duration at a given fixed heart rate<sup>22</sup>; this effect is valuable in producing an increase in heart rate with exercise in appropriately programmed pacemakers.<sup>22</sup> Any correction of QT interval for heart rate that ignores changes that might have occurred during the preceding five minutes must therefore be unreliable. Such dubious corrections are sometimes used in human clinical pharmacological studies—for example class III antiarrhythmic agents. From our study we conclude that the use of rate corrected QT

interval is not valid. We suggest that such studies should be carried out at constant heart rate achieved by pacing for at least three minutes.

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