Evaluation of drug-induced changes in myocardial repolarisation using the paced evoked response

R M DONALDSON, A F RICKARDS

From the National Heart Hospital, London

SUMMARY  The use of the paced evoked response system in the assessment of drug-induced changes in myocardial repolarisation is reported. Using a conventional pacing electrode lead for both pacing and sensing, this system records the dominantly local repolarisation which follows a controlled (paced) depolarisation from the same site. Measurements of the latency of the ventricular evoked response at matched heart rates before and after drug administration permit the accurate direct comparison of the effects of drugs with class 3 mode of action on cardiac muscle repolarisation. Using this method we have evaluated the effect on the timing of the evoked T wave of two drugs which are known to prolong phase 2 of the action potential. Intravenous amiodarone (5 mg/kg) prolonged the stimulus-peak evoked T wave interval by an average of 39·4 ms (15% of control values); three hours after oral betanidine (2 mg/kg) this interval increased by an average of 25·8 ms (10% of control values). The effect of therapeutic interventions on the latency of the local paced evoked response provides a simple, accurate assessment of their effect on the cellular action potential duration and constitutes a new tool in electrophysiological investigations.

The modes of action of antiarrhythmic drugs should be studied by their effects on the intracellular action potential, both in vivo and in the intact heart. Drug-induced changes in repolarisation times in man have recently been shown using endocardial suction electrode catheters, but most of the clinical studies have extrapolated the surface QT interval in the assessment of modifications of the action potential by antiarrhythmic drugs. Correction of the surface QT interval to QTc by heart rate assumes a simple relation between rate and QT interval. We and others have recently shown that this assumption is unjustified and does not consider the effects of catecholamines on the QT interval, which are of similar magnitude to rate effects. In the study of drug-induced changes in action potential a pharmacological decision based on a prolonged QTc can be misleading in instances where QT varies at the same heart rate or is invariant as heart rate changes. As many antiarrhythmic drugs induce heart rate and depolarisation changes, a rate independent method using controlled depolarisation would be of value in studying such agents.

We have recently reported the first successful recordings of the endocardial ventricular evoked response after delivery of a pacing stimulus, and have shown that the pacing stimulus to evoked T wave time (St-T latency) can be used as an assessment of physiological demand independent of atrial rate in the context of heart block.

The evoked response system has the advantage of extreme clinical simplicity requiring only a conventional pacing electrode lead. As the same lead is used for pacing and sensing, it is possible to record the T wave which represents dominantly local repolarisation following a controlled pacing-induced depolarisation from the same site at a controlled heart rate.

Measurements of the ventricular evoked response at matched heart rates before and after drug administration should allow direct comparison of drug-induced alterations in the duration of repolarisation and in particular permit assessment of changes in the very slow plateau phase of repolarisation. Such studies are only possible at the present time on a short term basis using endocardial suction catheters. The object of this study was to evaluate this method and to study the effects of two drugs, which are known by different mechanisms to prolong phase 2 of the action potential, on the timing of the evoked T wave.

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Patients and methods

Recordings were performed in 14 patients (10 men, four women, mean age 53 years) studied in the supine post-absorption state. All drugs had been discontinued before the investigation. Eight patients undergoing electrophysiological investigations because of recurrent tachyarrhythmias formed the amiodarone study subgroup; bethanidine was administered orally to another six patients who had temporary pacing catheters inserted for other purposes, mainly for the treatment of heart block. Informed consent and ethical approval was obtained for the drugs administered.

RECORDING EVOKED RESPONSE

The method of sensing and recording the pacing endocardial evoked response has previously been reported by us.3 Using a conventional unipolar pacing catheter, a pacing stimulus at approximately 2-5 mA for 0.5 ms is delivered to the right ventricular endocardium. The input/output circuit of the evoked response pacemaker uses a modified pulse waveform and automatic post-pulse compensation to remove the polarisation and capacitor discharge effects and make possible the recording of the endocardial response which follows the pacing stimulus. Within 5 ms after delivery of the pacing stimulus a true DC recording of the evoked response is possible, with the upper frequency limited by the recording apparatus. Recordings were made using an eight channel ink-jet recorder (Mingograph 82–Siemens-Elema).

![Graph](image)

Fig. 1 Recording of the paced evoked response. The ventricular response is seen as a negative QRS reaching a maximum amplitude approximately 45 ms after the pacing stimulus (St; long arrow). The peak detector has an adjustable sensing window; this detector generates a marker pulse (short arrow) 100 ms after detection of the peak of the evoked T wave (T). This marker is recorded together with St, and the St-T interval measured automatically on a beat to beat basis by the pacing system. The St-T time is corrected by subtracting the 100 ms imposed by the pacing system. Recordings of the scalar leads, the evoked response, and T wave time were made at a paced cycle length of 600 ms and at a paper speed of 100 mm/s. (Recorded with a hot stylus HP 7754B recorder.)

Fig. 1 shows a recording of the evoked response using this system. The ventricular response is shown as negative QRS reaching a maximum amplitude approximately 45 ms after the pacing pulse and is followed by a clearly defined positive T wave. Both QRS and T wave durations are shorter than those observed on a simultaneous surface electrocardiogram, as the evoked response sensed by the pacing electrode reflects a dominance of events local to the depolarising electrode.

Thus, the evoked response pacing system, by using the same electrode for pacing and sensing, is able to record dominantly local repolarisation after a controlled, reproducible, and homogeneous depolarisation.

MEASUREMENTS

Incorporated into the evoked response pacemaker is a peak detector with an adjustable sensing window (Fig. 1). The window position was set up on an oscilloscope to start at the onset of the T wave and terminate at the end of the evoked response. The peak detector generated a marker pulse 100 ms after detection of the peak of the evoked T wave which was recorded together with the pacing stimulus. The stimulus-T time was therefore measured automatically on a beat to beat basis by the pacing system without recourse to eye detection of the T wave of the evoked response. St-T times were taken as the average of 20 consecutive cycles and corrected by subtracting the 100 ms imposed by the pacing system (Fig. 1).

Recordings of the scalar leads I, II, and III, the paced evoked response, and T wave timing were made at a paced cycle length of 600 ms (100 beats per minute) and at paper speeds of 100 and 200 mm/s. Measurements were made before and at five, 10, 15, and 20 minutes after amiodarone infusion, and before and three hours after oral bethanidine.

The effective refractory period of the right atrium, atrioventricular node, and ventricle were recorded during the electrophysiological study before and on average 15 minutes after the amiodarone infusion using the extrastimulus technique. Premature atrial or ventricular extrastimuli (S2) were introduced at progressively shorter coupling intervals after every eight paced basic drive beats (S1-S1) at a cycle length of 600 ms. Measurements of atrial and ventricular refractory periods were taken at the site of stimulation, when the premature impulse failed to propagate through that tissue. Measurements of the atrioventricular nodal refractory record were taken from the His bundle electrogram. Cardiac refractoriness after bethanidine was not assessed.

DRUG ADMINISTRATION

Amiodarone was administered intravenously at a dose of
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5 mg/kg (diluted in 20 ml dextrose) over 10 minutes. Plasma amiodarone levels were measured 10 and 60 minutes after infusion in four patients.

Bethanidine was administered orally at full adrenergic blocking doses (2 mg/kg). This drug is known to be well absorbed after oral administration; plasma levels were not obtained.

SIDE EFFECTS
No significant side effects were noted during these investigations. Patients receiving bethanidine remained supine for eight hours after the administration of the drug to avoid postural hypotension.

Results

AMIODARONE (Tables 1 and 2)
The evoked T lengthened after amiodarone infusion in all patients, and the maximum St-T latency was reached within 10 minutes of termination of the infusion. Mean total increase was 39.4 ms (15% of control values) (Fig. 2). Similar or slightly lower values of St-T were documented at the 15 and 20 minute recordings. The stimulus-T wave interval measured from the scalar electrocardiogram increased by similar values, though in some cases this could not be accurately measured because of the abnormal T wave morphology on the scalar recordings (Fig. 3). Intravenous amiodarone also produced a slight prolongation of the pacing-induced activation, and this was documented only by the paced evoked recordings (Fig. 2, arrows). Plasma amiodarone levels during the infusion reached a mean value of 16.5 mg/l at 10 minutes in the four cases in which this was measured; they then fell fairly steeply reaching mean values of 2 mg/l at 60 minutes. Studies of cardiac refractoriness 15 minutes after amiodarone infusion showed a significant increase in the anterograde and retrograde effective refractory period at the atrioventricular node level in the six patients in whom it could be tested; the average increase was 65 ms (p<0.01); right atrial refractoriness was not significantly altered; the ventricular effective refractory period increased slightly in five patients and was unchanged in three; the overall change at that stage was also not significant.

BETHANIDINE (Table 3)
Bethanidine significantly prolonged the St-T interval at three hours after administration. The total increase was less than that obtained by intravenous amiodarone (average 25.8 ms, 10% of the control St-T). No changes in the pattern of local activation were noted after bethanidine.

Discussion
To study the mechanism of action of antiarrhythmic drugs, their effect on the action potential of myocardial
cells has to be assessed. Most of this information has been obtained by in vitro studies, recording the transmembrane action potential of heart muscle strips using capillary microelectrodes. Knowledge of the electrophysiological effects in the intact beating heart can be obtained from measurement of the refractory periods; interpretation of the course and duration of repolarisation in these conditions has been technically difficult, requiring the use of the intracardiac suction electrode technique, and only recently has this method been applied to the evaluation of drugs in man.

Though recording of these monophasic action potentials bridges the gap between the in vitro studies and the electrophysiological studies performed upon the intact human heart, it is not widely available and has certain technical limitations. Furthermore, intratrial and intraventricular differences in duration of monophasic action potentials preclude long term comparative measurements, and rate induced phenomena cannot be corrected.

In 1981 we showed that after delivery of a pacing stimulus to the ventricular myocardium, it was possible to record the intrinsic evoked response using the same lead for pacing and sensing. The measurement of the paced evoked response, after a controlled depolarisation at matched heart rates before and after drug administration appears to be suitable for the indirect assessment of repolarisation time, in particular the slow initial plateau phase.

The purpose of this study was to evaluate this paced evoked response technique, to document the acute effects of two drugs that are known to lengthen ventricular action potential duration in tissue preparations, and finally to establish the potential clinical applications of this new electrophysiological method.

In the absence of local necrosis, inflammation, or ischaemia, local electrical events reflect accurately the electrical activity of the whole heart. Analysis of a simpler electrophysiological recording, such as the paced surface electrocardiogram which documents the generalised cardiac activation and repolarisation which follows a pacing stimulus, could be expected to provide similar data on the duration of repolarisation to that obtained by the paced evoked response method. In our drug studies, the pacing stimulus–T wave interval measured in the scalar leads lengthened in parallel to the local changes documented by the paced evoked response (Fig. 2); the duration of these intervals was on average 125±30 ms greater than the latency of the locally evoked T wave.

The use of these electrocardiographic recordings has, however, important drawbacks. Chronic myocardial disease, congestive failure, and chronic pacing are usually associated with T wave abnormalities on the electrocardiogram. The inability accurately to localise the peak or trough of the T wave on the surface leads is a source of variability on these scalar recordings, and not all patients in our study had clearly defined T wave morphology even when paced at relatively long cycle lengths (Fig. 3). The T wave morphology becomes more difficult to document at shorter paced cycle lengths which are required for the evaluation of some therapeutic agents. The peak detector incorporated into the evoked pacemaker assures reproducibility of data, as observer bias is eliminated. Furthermore, these local paced evoked recordings from the endocardial electrode are more sensitive than the scalar tracings; the signal to noise ratio of the paced evoked response is tenfold that of the surface electrocardiogram, as average T wave amplitudes documented by this method are 7±3 mV (Fig. 4a). While the paced scalar recordings may permit overall assessment of repolarisation time, they do not visualise activation time and morphology. Changes in local activation induced by drugs (Fig. 2) and ischaemia (Fig. 5) were accurately documented by the paced evoked response method only.

In animal experiments, drug-induced changes in the timing of local repolarisation measured by the paced...
Markers

LV MAP

Paced evoked response

Markers

Scalar

LV ER

FAP

LV MAP

St

St

St

St

St

T

T

T

Evoked response parallel changes in duration of simultaneously recorded paced monophasic action potentials (Fig. 4b and c). Both of these methods appear to be complementary for the indirect assessment of the effects of therapeutic agents on the action potential duration of myocardial cells.

Using intracellular microelectrode techniques, Singh and Vaughan Williams showed that amiodarone lengthened atrial and ventricular repolarisation in tissue preparations by about 30%. This prolongation of the action potential by amiodarone is most probably the result of a decrease in membrane K⁺ conductance, in particular a reduction in the time dependent slow outward K⁺ current (Iₛ). The slower activation of this current, which is responsible for the termination of the action potential, leads to a prolongation of the plateau (phase 2) of repolarisation. Amiodarone-induced changes in the duration of the right atrial monophasic action potentials measured by the suction electrode techniques have been studied in man by Olsson and co-workers. These investigators recorded a 30% increase in atrial monophasic action potentials recordings after chronic oral amiodarone treatment. The effect of intravenous amiodarone on the duration of the action potential has been studied in dogs by these suction electrode catheter techniques. The infusion of this drug prolonged the ventricular monophasic action potentials by 25% but had only slight effect on atrial repolarisation. We are not aware of any publications of ventricular monophasic action potentials recordings in man after the administration of amiodarone intravenously.

After intravenous amiodarone, the latency of the
Fig. 5 Recordings of the paced evoked response from the septal surface of the left ventricle in a patient with severe stenosis of the left anterior descending coronary artery and reversible anteroseptal ischaemia. Control and ischaemic changes shown at a paper speed 200 mm/s and a paced cycle length (CL) of 475 ms. The ST-T interval decreased 40 ms (~17% of control values) during ischaemia. There is elevation of the ST segment in the left ventricular evoked response recording (LVER). Local depolarisation has become delayed and fragmented (non-homogeneous) (arrow). The duration of the stimulus (St)-peak of the T wave interval on the scalar lead II remained unchanged during ischaemia. FAP, femoral artery pressure; T, peak of the evoked T wave. Other abbreviations as in Fig. 1.

paced evoked response was prolonged in all patients in our study by an average 39.4 ms (15.1% of the control St-T) (Table I). Peak prolongation was found between 10 and 15 minutes after infusion, coinciding with peak blood levels; this increased duration of the evoked response persisted in the 20 minutes after infusion recordings. The local pacing-induced activation was also prolonged by the intravenous amiodarone (Fig. 2).

Atrial and ventricular refractoriness were not significantly increased at 15 minutes after infusion; the effective refractory period, however, increased conspicuously at atroventricular node level by about 23%. Amiodarone early activity at atrial and ventricular level thus appears to favour changes in action potential duration as opposed to changes in refractoriness. This effect is predominantly beneficial as evidenced by the effectiveness of this agent in the treatment of cardiac arrhythmias; it may, however, unmask enhanced vulnerability. These paced evoked response and electrophysiological studies in man are similar to the observations obtained after intravenous amiodarone in dogs.

The shortening of phase 2 of the action potential by sympathetic stimulation is mediated mainly by an increase in the K+ current I\textsubscript{K1}. Intracellular studies have shown that ganglion blocking agents prolong the action potential, presumably by decreasing the amplitude of the K+ channels in the membrane. Drugs that depress the function of postganglionic adrenergic nerves have similar effects on myocardial repolarisation. The prolongation in the repolarisation phase of the ventricular action potential by bretylium tosylate has been well shown in vitro, and this drug is effective in the treatment of ventricular arrhythmias. The use of bretylium as an antiarrhythmic agent is largely limited to intravenous use because of poor absorption. Bethanidine, a chemical analogue with identical pharmacological properties, is well absorbed after oral administration, producing adrenergic neuron blockade within two to four hours. In our study, the evoked potential was significantly prolonged three hours after oral administration of bethanidine, values increasing a mean of 25.8 ms (10% of the control values). Because of this increase in the ventricular action potential, this sympathetic antagonist could be useful in the suppression of ventricular tachyarrhythmias. Promising preliminary data using higher doses of bethanidine (16 to 20 mg/kg) have recently been reported.

The effects of drugs on action potentials of various tissue models, together with the clinical electrophysiological data obtained during the investigation of these agents, have contributed to a clearer understanding of specific electropharmaceutical and antiarrhythmic actions and allow comparison with new drugs. Our studies suggest that the effects of class 3 antiarrhythmic agents on local myocardial repolarisation can be assessed accurately by the paced evoked response, and this new method should contribute to overcoming the many difficulties in comparing the results from in vivo experiments with the clinical effects of these drugs in man. Treatment of cardiac arrhythmias, however, is based on complex considerations, including knowledge of their pathophysiology and of the type of cardiac tissue that supports the arrhythmia. Because of this, antiarrhythmic classifications based on the effect of drugs on action potential data have limited value in the treatment of specific arrhythmias and in predicting a specific response to treatment.

We have recently studied the effects of regional ischaemia on the paced endocardial evoked response from the human ventricle. The latency of the local paced evoked response (and indirectly the duration of repolarisation) was shortened by ischaemia and local activation became fragmented and non-homogeneous (Fig. 5). Measurements of the paced evoked response from an electrode positioned in non-ischaemic areas showed no changes. These localised changes preceded overall electrical changes and the stimulus–T wave interval in scalar recordings did not vary during early regional ischaemia (Fig. 5). Measurements of the paced evoked response with intracavity electrodes can thus provide earlier and more sensitive detection of the electrode changes produced by regional ischaemia in man, and
this method should permit the indirect assessment of the effects of therapeutic intervention on the local transmembrane potentials of human myocardial cells. The paced evoked response will thus constitute a new tool for electropharmacological studies in man.

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References


Requests for reprints to Dr A F Rickards, National Heart Hospital, Westmoreland Street, London W1M 8BA.