

Electrophysiological investigation of patients with hypertrophic cardiomyopathy

Evidence that slowed intraventricular conduction is associated with an increased risk of sudden death

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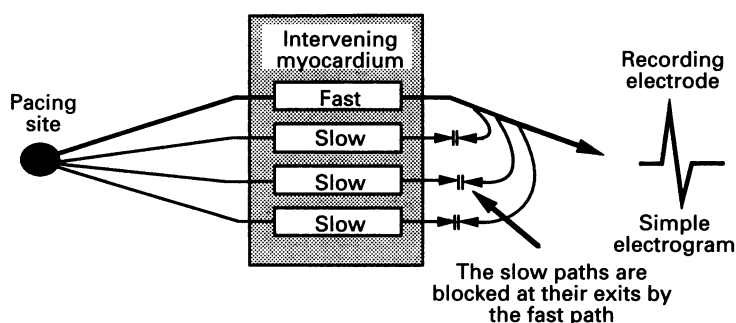
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The elucidation of sudden cardiac death in hypertrophic cardiomyopathy (HCM) is complicated by two difficult electrophysiological problems that stem from the inability of programmed electrical stimulation (PES) to induce the ventricular arrhythmias that have been recorded in individual patients. The first problem is that classic electrophysiological methods of investigating tachycardias, for example observing the initiation and activation sequences, cannot be used because the clinical tachycardias cannot be induced. The second is the major clinical problem of identifying patients who are at risk of arrhythmic sudden death. Such identification depends on interpreting "non-clinical" arrhythmias induced by PES and deciding whether they mimic a potentially lethal clinical arrhythmia and if they are of prognostic importance. I have seen several patients in whom sustained monomorphic ventricular tachycardia (VT)

developed before ventricular fibrillation or non-sustained VT on ambulatory monitoring. However, this type of monomorphic VT has never been induced by PES: polymorphic VT or ventricular fibrillation (VF) was induced instead.

It is likely that, *as a group*, patients with HCM are more likely to develop arrhythmias in response to programmed stimulation than patients with normal ventricles and that high risk patients, *as a group*, are more vulnerable than low risk patients. This does not, however, help to identify individual patients who are at high risk of sudden death. A stimulation protocol that induced arrhythmia in all patients who had survived VF induced an arrhythmia in 30–40% of patients with HCM¹⁻³ but most of these patients will not die suddenly. Though PES will identify a large group of patients who are vulnerable in terms of induction of non-specific arrhythmias, this is unhelpful in the management of patients unless it is acceptable to treat so many with an implantable cardioverter-defibrillator or antiarrhythmic drugs.

Paced beat



Extrastimulus

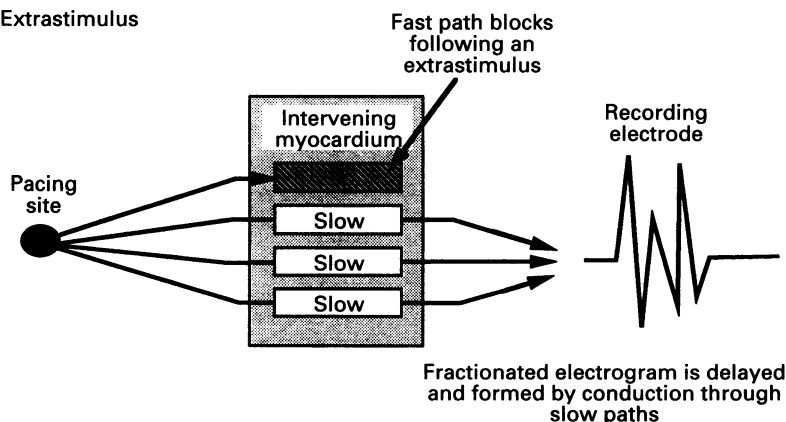


Figure 1 Model of intraventricular conduction that is the basis of the fractionation technique. With premature stimulation fast conducting pathways are refractory and slow conduction pathways are exposed, resulting in electrogram fractionation.

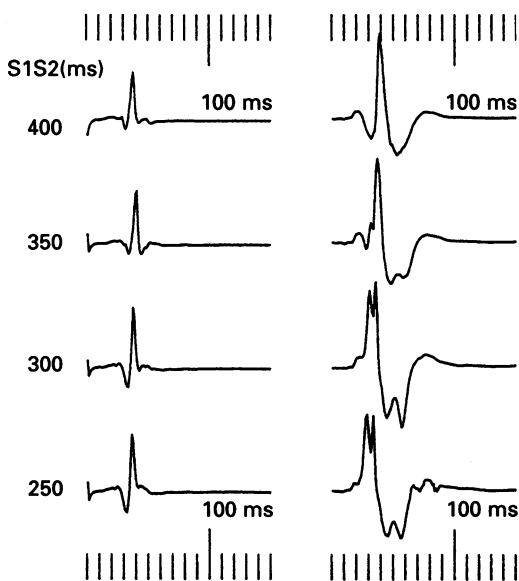
Rationale for new approach

Myocardial disarray in HCM may be expected, on basic principles, to have electrophysiological correlates. First, the distribution of cell diameters is greater than normal.⁴ If the cable theory is applicable in this context, a much wider distribution of conduction velocities and refractory periods than normal would be expected. Second, the abnormal orientation and tortuosity of myofibrils would be expected to create several activation paths throughout the ventricles that could be recruited or blocked depending on local refractoriness. Finally, increased interstitial fibrosis would be expected to increase conduction anisotropy as well as to increase the number of conduction paths within the ventricles.

These ideas lead to the highly speculative hypothesis that disarray would lead to inhomogeneity of intraventricular conduction velocity so creating one component of a re-entrant arrhythmic substrate.⁵ According to this hypothesis, patients who are at high risk of sudden death because of ventricular arrhythmias would have ventricles in which activation spread more slowly than in patients who were at low risk or had normal ventricles.

Figure 1 shows the conceptual model of intraventricular conduction. There are several

Figure 2 Electrograms obtained from a control (left) and from a VF survivor (right). Left hand column shows the S1S2 coupling interval at which they were obtained. Note the increasing fractionation in the VF survivor.



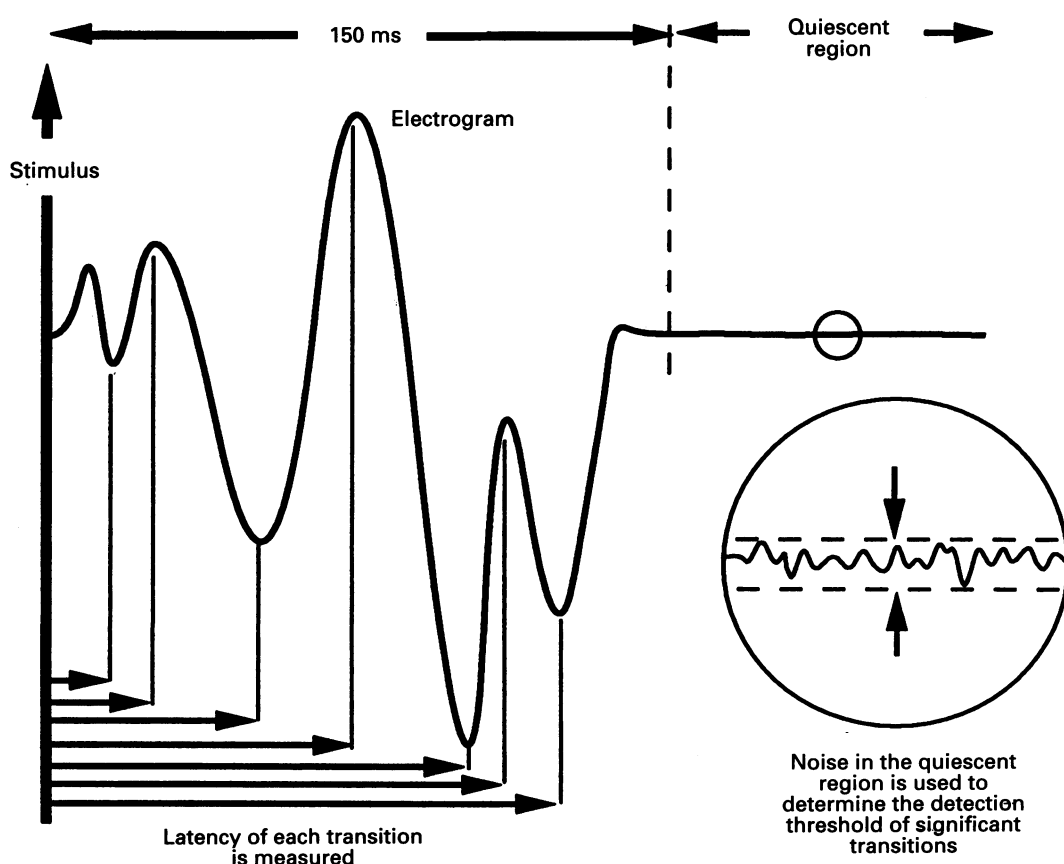
conducting paths. After an extrastimulus the fast paths may be blocked, revealing paths with slower conduction velocities or there may be decrements in the paths themselves resulting in multiple potentials at the recording electrode. This effect is known as fractionation.

Clinical demonstration of slow intra-ventricular conduction

In a clinical study five electrode catheters are placed in the heart. One catheter is placed in the high right atrium (HRA), which is paced simultaneously with the ventricle to avoid fusion beats. The remaining catheters are placed in the right ventricular apex, septum, inferioposterior wall, and outflow tract. A pacing sequence is issued from one right ventricular catheter and electrograms are recorded from the other three electrodes. Once the pacing sequence has been completed an identical pacing sequence is issued from the next catheter and recordings are made from the other catheters. This process is repeated until a pacing sequence has been issued from each of the four catheters and recordings made from the remaining electrodes. A decremental sequence is used with a constant drive chain with a basic cycle length of 480 ms and extrastimuli are inserted every third beat. The extrastimulus coupling (S1S2) interval is reduced from 450 ms in 1 ms steps until it has fallen to 200 ms or a ventricular effective refractory period is encountered.

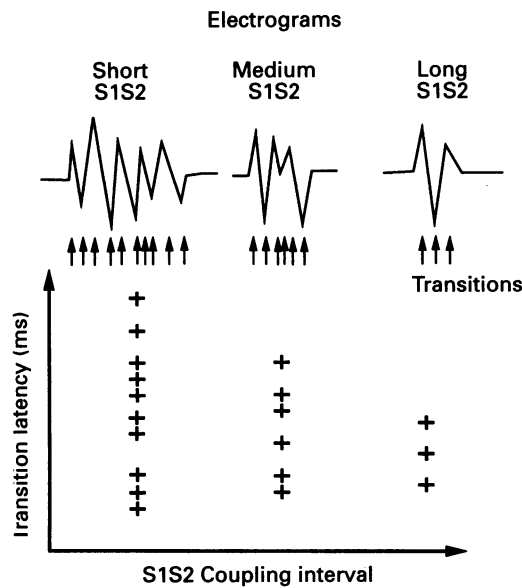
potential conduction paths between a pacing site in the ventricle and a recording site elsewhere within the ventricle. A paced beat would be conducted at different velocities through the intervening myocardium and an electrogram would contain transitions that correspond to the arrival of excitation through different paths. If there was communication between the different paths, the fastest conducting path might block the arrival of slower

Figure 3 Diagram showing how the transitions in a paced electrogram are identified and how their latencies relative to the pacing stimulus are obtained.



Noise in the quiescent region is used to determine the detection threshold of significant transitions

Figure 4 Diagram showing how the latency transitions are plotted against extrastimulus coupling interval to form a conduction curve.



Therefore, at the end of the study there are 12 sets of electrograms each containing 200 to 250 electrograms in response to extrastimuli.

Features of paced ventricular electrograms in HCM

Electrograms recorded in VF survivors show striking fractionation in response to premature stimulation. Figure 2 shows examples of electrograms obtained from a control (left)

and from a VF survivor (right). Electrograms from the control show very little fractionation in response to premature stimulation whereas those from the survivor show fractionation that increases with extrastimulus prematurity. This effect has been recorded in all the VF survivors studied so far: patients who have risk factors for sudden death, a family history of sudden death or VT on ambulatory monitoring, show an intermediate level of fractionation.

Analysis of the paced electrograms and fractionation

After a study four pacing runs will have generated 12 sets of approximately 250 electrograms in response to extrastimuli. The next step is to reduce these data into a manageable and analysable form. At present, the only feature of electrograms that is analysed is the latency of transitions following an extrastimulus. Digital processing emphasises the transitions in the paced electrograms and reduces the contributions of the slow moving components such as the T wave of the preceding beat.

The transitions in the enhanced signals, which are presumably caused by conduction in fibres close to the recording electrode, are then distinguished from those that are caused by noise. The principle of this procedure is to identify a portion of the signal that is pure noise—in other words it has no components that are related to the pacing stimulus. This portion of the signal is used to determine the amplitude of the noise and so set a threshold of transition amplitudes that distinguishes between physiological and random transitions. Once this threshold has been calculated the latency of each physiologically significant transition in the electrogram can be measured (fig 3). Therefore the electrogram in response to an extrastimulus can be described in terms of a set of latencies of each transition.

This process is repeated for the response to every extrastimulus in the pacing run and used to construct a conduction curve of the transition latencies in each extrastimulus plotted against the extrastimulus coupling interval. This is shown in fig 4.

The conduction curve is used to characterise a patient at risk of sudden death. Figure 5 shows a curve from a control. In general, controls and low risk patients have curves that do not show an increase in latency of electrogram transitions until a short S1S2 interval. Patients who have survived a VF arrest show several characteristic features in their curves (fig 6). First there is an increase in electrogram latencies starting at long S1S2 intervals. The second characteristic is that there is a wider electrogram at short coupling intervals, presumably reflecting a decrement in the various conduction processes that generate the electrogram. Finally, many patients with either a family history of sudden death or non-sustained VT on ambulatory monitoring have a pattern that is intermediate between that of VF survivors and that of controls.

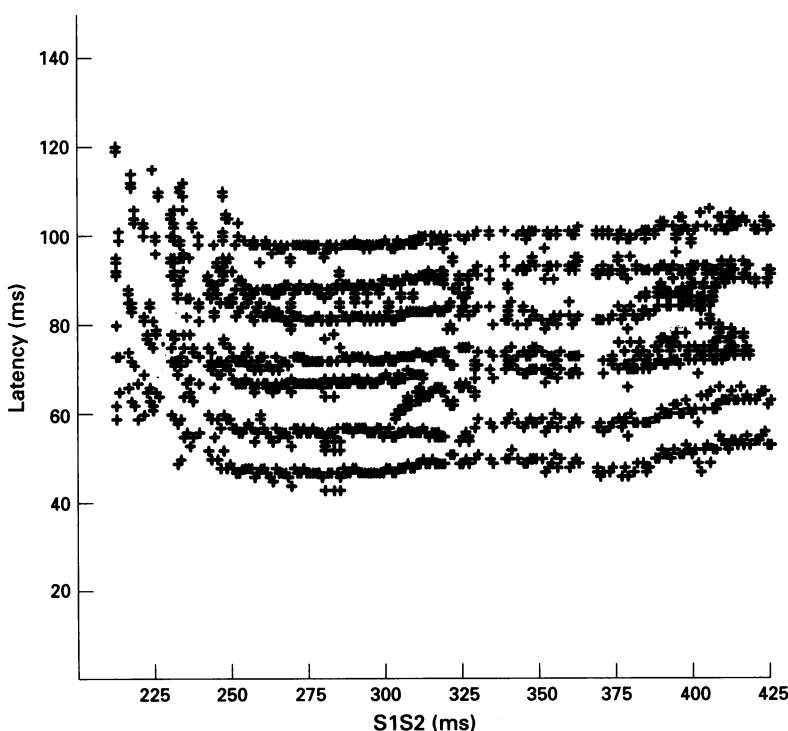


Figure 5 A conduction curve from a control. Note that the curve is relatively constant with extrastimulus prematurity and that the increase in latency only occurs at short S1S2 intervals.

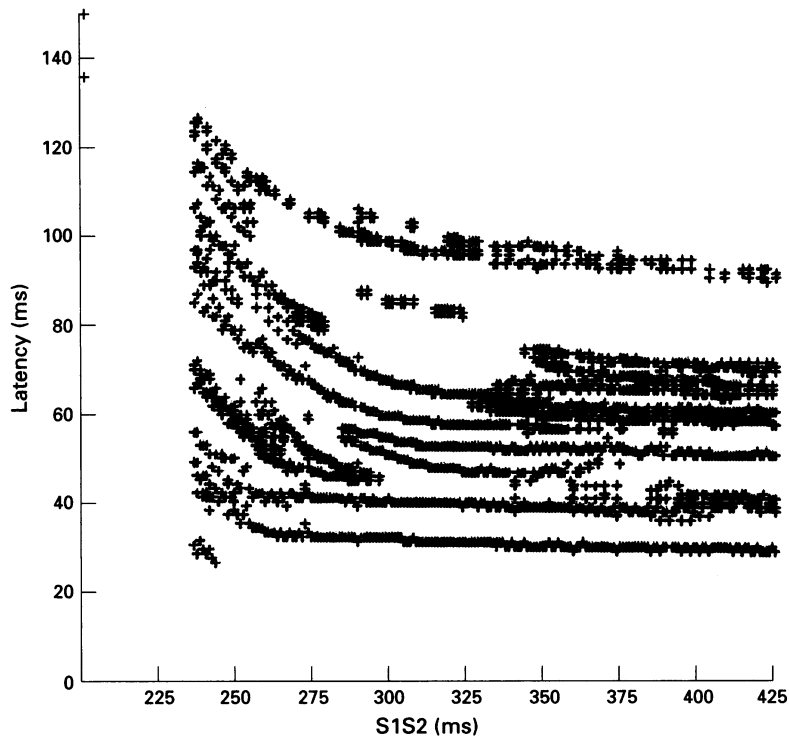


Figure 6 A conduction curve from a VF survivor. There is a characteristic increase in latency and an increasing number of transitions at long S1S2 intervals.

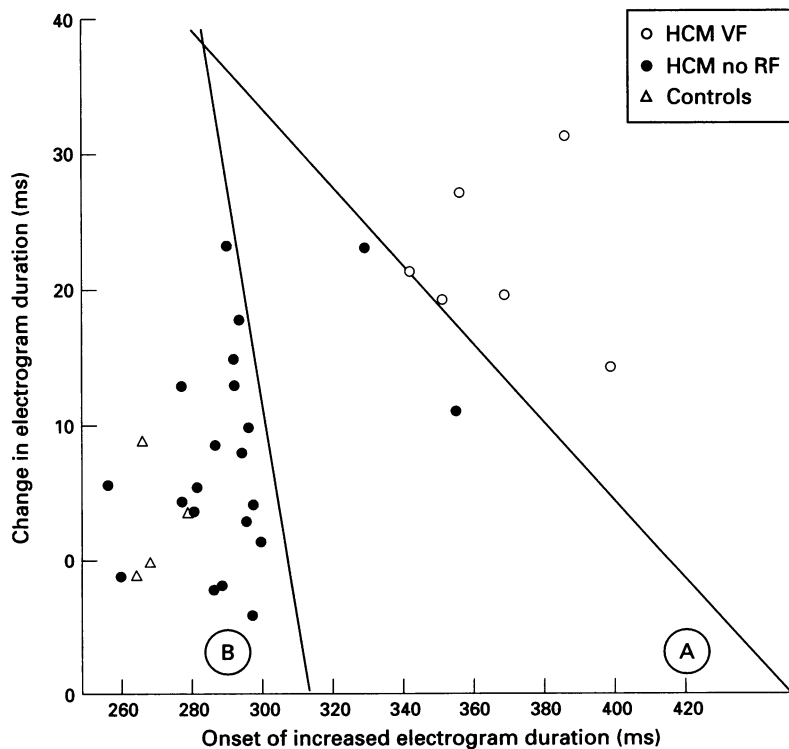


Figure 7 A scattergram of mean point of increased latency against increase in electrogram duration for patients with VF and low risk patients and controls. See text for explanation of lines A and B.

Relation between electrogram fractionation and risk of sudden death

A major problem is to reduce the data in the conduction curves into a manageable form that can be analysed statistically. At present two parameters are extracted from the curves: the point at which latency starts to increase beyond a preset threshold and the increase in electrogram width between a coupling interval of 350 ms and the ventricular refractory period.

These parameters, measured from every curve recorded from an individual patient, are averaged to yield two measurements: the increase in electrogram duration and the S1S2 coupling interval at which latency increases. The advantage of using the mean value of the parameters extracted from 12 curves is that they can be treated statistically as independent observations, whereas the parameters from individual curves in the same individual are often highly correlated.

Figures 7 and 8 show the scatter of results from 35 HCM patients with VF, non-sustained VT on ambulatory monitoring, or no risk factors for sudden death. Six patients with confirmed VF, one of whom was studied before a VF arrest, cluster in a region with increasing latency at the longest S1S2 and large increases in electrogram duration (fig 7). By contrast, low risk patients (those without a family history of sudden death or VT on ambulatory monitoring) and controls show the least increase in electrogram duration and the S1S2 at which it increases is short. Patients with non-sustained VT on ambulatory monitoring (fig 8) have results that range from the sudden death group to the low risk group. This is a potentially important observation because patients who have VT on ambulatory monitoring have a 23% chance of dying suddenly within 3 years⁶ and this spread between the VF and low risk groups may reflect the vulnerability of individual patients to sudden death. Line A is the discriminant line that separates the VF patients from the remaining population whereas line B separates the patients with VF, non-sustained VT, and a family history of sudden death from the low risk patients and controls.

Conclusions

The cardiomyopathies are an important group of diseases that cause sudden death, often in young people. Progress in understanding the pathogenesis of arrhythmias and prediction of sudden arrhythmic death have been hampered by the inability to provoke the arrhythmia so that it can be studied. A new technique, based on a hypothesis relating disarray to the statistics of intraventricular conduction suggests that high risk patients may be identified without induction of arrhythmias. Furthermore, preliminary studies in other diseases (dilated cardiomyopathy, primary VF, and the long QT syndrome) show abnormal intraventricular conduction without myocardial disarray. Therefore abnormal paced electrogram

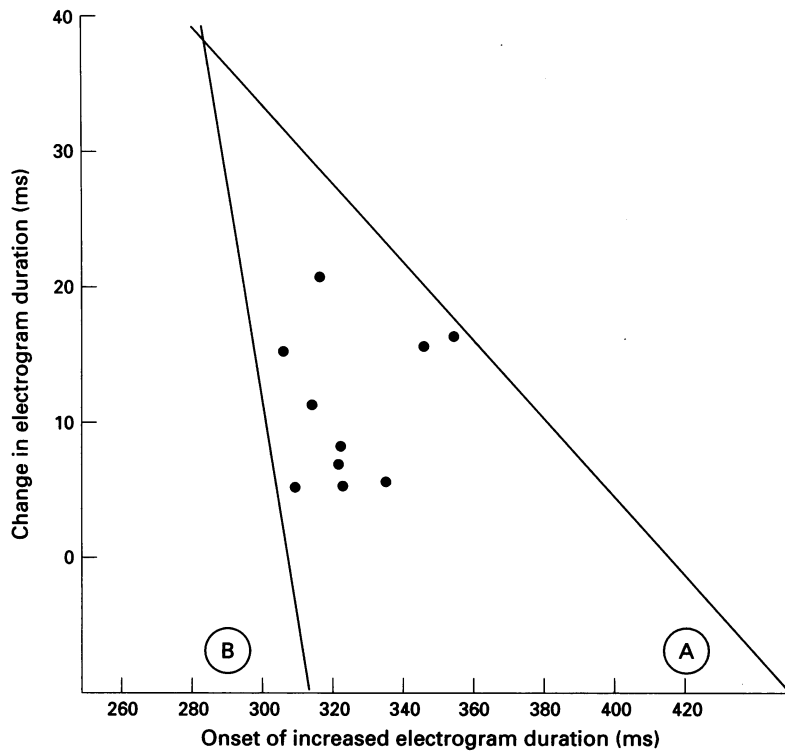


Figure 8 A scattergram showing the mean point of increased latency against increase in electrogram width for patients with non-sustained VT on ambulatory monitoring. The values for these HCM patients range from those typical of VF survivors to those typical of low risk patients.

fractionation may be a general marker of ventricular disease that can be used to investigate a group of patients that is wider than those with HCM.

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