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Review

Paced ventricular electrogram fractionation and sudden death in hypertrophic cardiomyopathy and other non-coronary heart diseases

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1. Introduction

The prediction of sudden arrhythmic death (SCD) in patients with non-coronary heart disease has become increasingly important because of the need to select high risk patients who require prophylactic implantable cardioverter-defibrillators (ICD). Hypertrophic cardiomyopathy (HCM) is an important cause of SCD, and while it is clear that ICDs are effective in aborting SCD due to ventricular fibrillation [1–3], there is no generally accepted method of risk stratification to allow large-scale, selective ICD implantation in such patients [4]. This article reviews the various trials which have been performed to predict SCD in patients with HCM. Then an emerging technique which was initially developed for HCM, paced electrogram fractionation analysis (PEFA), is reviewed. This technique is based on detection of the substrate for VF and has promise in identifying high risk patients with HCM and other non-coronary heart diseases which cause SCD. Finally, preliminary results obtained in man and animal models are compared suggesting that PEFA may be used to interpret electrophysiological data from humans at risk of SCD in the context of animal experiments.

2. Statistical problems in designing HCM trials

A useful 'test' for predicting SCD must have high enough accuracy to persuade physicians to treat their patients either with or without ICDs on the basis of its results. The definition of a good test depends on the perceived risk/benefit ratio of ICDs in HCM and so the minimum required predictive accuracy of the test will vary amongst physicians. As there is no consensus on the criteria for ICD implantation, we hope to achieve a positive predictive accuracy (PPA) of 0.3 so that three out of every ten patients implanted with an ICD would develop VF.

The relatively low SCD rate in HCM causes problems in designing a trial to establish the SCD rate or the PPA of a method of predicting SCD and in the interpretation of published studies. Assume that there are two populations of patients, one with a 4% and the other with 1.5% annual mortality, which are observed for 3 years. Fig. 1 shows the 95% confidence limits of the observed SCD rate as the number of patients are increased and shows that there are large potential errors in measuring the SCD rate with small numbers of patients. Therefore, the SCD rate in HCM is difficult to establish, purely on the basis of sample sizes and this is complicated by selection bias, differing age structures, different phenotypic expression [5–7] and different genotypes which may carry different risks of SCD [8]. The differences in published SCD rates which vary from 7.5 to 0% per annum in small study groups can be explained on the basis of sample size [9–14] while the variability of the estimated SCD is lower in studies with more than 100 patients [15–17].

Trials of intervention to prevent SCD also require estimation of the SCD rates in the treated and control groups with sufficient accuracy that their mean rates can be distinguished. A trial to distinguish between SCD rates of 4 and 1.5% p.a. in the control and treated groups can be seen from Fig. 1 to require about 180 patients in each group as the SCD rate distributions become distinct at this point and some intervention trials have had <30 patients in

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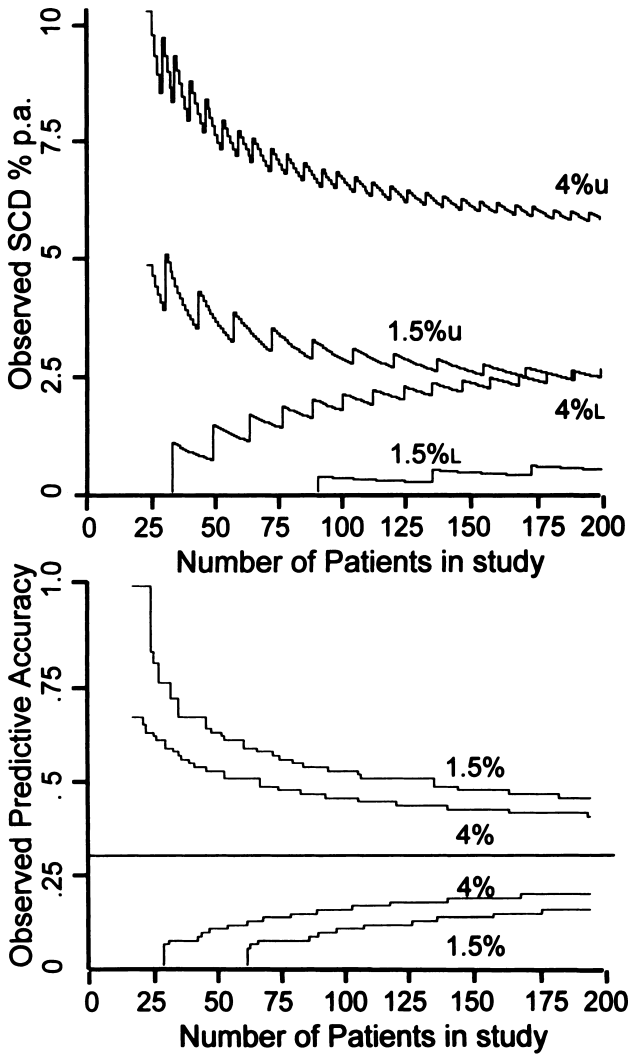

Fig. 1. Upper graph: 95% confidence limits for the observed SCD rate vs. number of patients in observed group. Assumed SCD rates 4.0% per annum and 1.5% per annum followed for 3 years. Note the wide confidence limits when small numbers (<100) patients are studied and that the confidence limits of the 4% and 1.5% death rates diverge when 180 patients are followed in each group. Lower graph shows the approximate confidence limits on the PPA of a test using the same population assuming that the test is 95% sensitive and has a PPA of 0.3 (Monte-Carlo method).

the control and treated groups [13,14] rendering their results open to a range of interpretations.

These arguments apply to estimating the PPA and a large number of patients are needed to establish the PPA reliably as shown in Fig. 1b in which the sensitivity of the test has been calculated so that the PPA of the trial is always 0.3, irrespective of the number of patients in the trial. A trial to establish the PPA of a test must therefore be designed to determine the lower range of the confidence interval of the observed PPA and establish that the true PPA is greater than this limit and therefore of a clinically useful value.

3. Classification of EP methods for prediction of SCD in HCM

Arrhythmic sudden death is thought to occur when a trigger interacts with an abnormality in the myocardium, known as the substrate [18], to produce ventricular fibrillation (VF). The substrate refers to conditions within the myocardium which will allow the re-entrant activation of VF through conduction block and activation delay which may be modified by autonomic activity [18]. The possible triggers of VF include ventricular tachycardia, ischaemia, syncope, exercise, supra-ventricular arrhythmias and hypotension, several of which may co-exist in a patient and may only rarely trigger VF. There are three broad classes of electrophysiological tests based on this concept:

1. Detection of a substrate: (a) late potentials and R wave analysis (b) QT dispersion (c) T wave alternans (d) programmed electrical stimulation (e) paced electrogram fractionation analysis.
2. Detection of a trigger: (a) Non sustained VT on ambulatory ECG (b) atrial fibrillation (?) (c) blood pressure response on exercise (d) ischaemia (e) syncope.
3. Analysis of autonomic activity: (a) heart rate variability.

4. Tests involving detection of an arrhythmogenic substrate

The first tests in these group involve averaging the surface ECG using a number of QRS complexes so that micro-potentials representing slow activation can be distinguished from the noise in the signal and revealed using a variety of processing strategies [signal averaged ECG (SAECG)]. In an early report [19] involving 66 patients with HCM, the retrospective PPA of the SAECG was 0.77 for the detection of either VF or non-sustained VT which were treated as a single group. However two further studies of the ‘spectral turbulence’ of the QRS complex (computation of the power spectrum of short epochs within the QRS complex) showed that in 121 patients of whom nine suffered VF [20] and also in 246 patients of whom 25 developed VF [21] there was no discrimination between the VF and non-VF groups although patients with NSVT were identified. Finally, in a study of wavelet decomposition of the SAECG in 246 patients, there was again, no differences between the VF group (17 patients) and the remainder although patients who died of cardiac failure were identified [22].

The QT interval, corrected for heart rate (QTc), and the QT dispersion (QTd) may reflect regional repolarisation abnormalities and the likelihood of an arrhythmic substrate caused by variable and prolonged refractoriness. Several reports in a small number of patients suggested that the QTc is prolonged in HCM when compared to controls [23]

and that the mean QTc and QTd were increased in patients with arrhythmias. [24,25]. This was not confirmed in a small study with ten HCM VF survivors compared to age- and sex-matched controls [26] and several larger studies of QTc or T wave complexity in patients with risk factors for SCD, but without VF survivors, failed to discriminate between those patients with and without risk factors for SCD [27,28]. Finally, a newer technique, T wave alternans involving 'high risk' patients proposed a concordance between alternans and paced electrogram fractionation analysis (PEFA) in five patients [29].

The most direct conventional way of detecting a substrate for VF is programmed electrical stimulation (PES). A positive result, induction of a clinical monomorphic VT, is important and will determine a therapeutic strategy However, the use of PES in HCM has created the problem of the interpretation of induced arrhythmias because induction of VF, polymorphic VT or a rapid (300 bpm) sawtooth VT in HCM is quite common [30–34] and it is the interpretation of these arrhythmias which are problematic. There are three series of PES in HCM involving more than 50 patients. In one series, using up to two extrastimuli, an arrhythmia was induced in 2/3 VF survivors, 3/8 patients with syncope and 13/43 asymptomatic patients [30]. In the second study, again using two extrastimuli, arrhythmias were induced in 4/6 VF survivors and 10/46 non-VF patients [31]. This failure to identify patients who have suffered spontaneous VF by PES limits its use in risk stratification but as PES has been strongly advocated by one group their studies should be examined in detail. A total of 230 patients were investigated with PES [32–34]. Up to three extrastimuli were delivered initially at the RV apex and if an arrhythmia was not induced, at the right ventricular outflow tract and finally at the left ventricular apex. Thirty-two patients had a prior VF arrest and of these twenty-one (65%) were PES positive and eight of these twenty-one patients went on to die suddenly or have an ICD discharge while of the eleven PES negative patients, two had a further event. This strategy did not identify patients with prior VF arrests who would go on to develop VF a second time ($P>0.05$ Fisher's exact test) and again 35% of VF patients, who presumably had a substrate for VF, were not identified by PES. However, in the 198 patients who had not suffered a prior arrest, 61 were PES positive and 6 of these had a subsequent event while there was only one event in the remaining 137 PES negative patients. This result is significant in testing the null hypothesis that there is no difference between the event rate in the PES positive and negative groups ($\chi^2=10.6$, $P<0.01$). This study illustrates an important error in interpretation as it fails to distinguish between two different hypotheses. The first is that the PES positive patients are different as a group from the remainder and the second is that potential VF patients can be separated from the remainder using PES. The first hypothesis appears to be true but in view of the large number of PES positive patients, it seems unlikely that VF induction identifies a specific substrate for VF. However, the PPA of the technique in identifying high risk patients is only 0.1 (0.06–0.14) and therefore the technique is limited clinically although it may identify patients who are not at risk of VF and need no further intervention.

5. Detection of a trigger for VF

An alternative approach to risk stratification is the detection of triggers of VF in abnormal myocardium which has a substrate for VF. The most consistent marker of an increased risk of SCD is detection of non-sustained VT on ambulatory monitoring. Combining data from two early publications, in a total of 170 patients, 41 had VT on ambulatory monitoring and of the 13 patients who died suddenly, 9 had non-sustained VT while the remaining four SCD patients did not [8,9]. While the absence of NSVT a high negative predictive value in adults, non-sustained asymptomatic VT has a low positive predictive value for SCD [15,16] and NSVT is rarely seen in children and adolescents who are at risk of SCD [35].

A fall in blood pressure (BP) during exercise has an association with a family history of SCD in HCM and suggests that hypotension may lead to reduced coronary flow and triggering of ischaemia-induced arrhythmias and SCD. Abnormal failure to raise BP in response to treadmill exercise [36] and increases in forearm blood flow in supine exercise [37] have been demonstrated in HCM patients with a family history of SCD and these responses are modified by amiodarone [38]. Although the mechanism of exercise hypotension has been considered to be due to abnormal vascular responses, one study [39] has suggested that there was a degree of LV dysfunction contributing to the hypotensive response. Two studies [40,41] have showed an association between SCD and exercise hypotension. The first [40] involved 161 patients with an abnormal BP response in 60 patients with 9 deaths while there were 3 deaths in the remaining 101 patients with a normal BP response yielding a PPA of 0.15 (confidence limits 0.05–0.25). A second study in 126 patients [41] also showed that there was a high negative predictive value for a normal BP response with an odds ratio of risk of SCD in the abnormal BP response group 4.4 times the normal group with a lower 95% confidence limit of 1.1. The lower confidence limits of the PPA in both these studies make the use of exercise hypotension an unreliable indicator of SCD although it is useful clinically in identifying a low risk group for SCD.

Ischaemia in HCM might form a dynamic substrate for VF. The presence of small vessel disease and ischaemia [42,43], possibly modified by verapamil [44], is recognised in HCM but its role in creating VF is unclear. A group of 15 young patients were reported [45] to have ST depression and positive thallium scintigraphy associated with VF

implying a causal role of ischaemia in SCD while a further small study [46] of young patients with HCM identified an association between left anterior descending artery banding and sudden cardiac death. However, the assumed relationship between ST depression on ambulatory monitoring and ischaemia demonstrated by thallium scintigraphy in HCM has been shown to be spurious on the basis of a larger study in 94 patients [47] and a companion study which showed that chest pain induced by dipyridamole was associated with a fall in coronary sinus pH but was unrelated to ST depression [48].

Syncope is a common feature of HCM which is not associated with an abnormal BP response during exercise [36,40]. Using multivariate analysis syncope has been shown to be associated with SCD in a study of 230 predominantly adult patients [33] and a further study of 37 children [49]. Again, while there is an association between syncope and SCD, syncope is only weakly predictive of SCD when treated as a single variable.

6. Changes in autonomic activity

The first large study of heart rate variability (HRV) in 104 patients with HCM showed that HRV was reduced, particularly in patients with a family history of SCD. In this study, 10 patients subsequently suffered SCD or aborted SCD and were not identifiable by HRV [50] A further study of 31 patients showed that HRV was reduced in HCM when compared to 31 age and gender matched controls and that the reduction in HRV is associated with a reduced LV systolic volume and left atrial volume but not with LV wall thickness [51]. However, the results from the 14 of these patients who had suffered SCD or aborted SCD were indistinguishable from 10 age- and gender-matched controls.

The conclusion to be drawn from these studies is that neither analysis of the surface ECG nor conventional programmed electrical stimulation are particularly useful in the prediction of SCD. In HCM these failures have led to a different method of SCD prediction which detects a substrate for VF by measuring discontinuous conduction through the myocardium.

7. Development of paced electrogram fractionation analysis

Conduction delay is one component of a re-entrant substrate and it seemed possible that this could be demonstrated in the ventricles of patients at high risk of SCD. PEFA was originally developed for use in HCM where it was thought that fibre disarray with fibrotic infiltration might cause areas of activation block and circuitous activation through surviving strands of myocardium [52,53], possibly aggravated by gap junction abnormalities [54]. The action potential in HCM [55] is prolonged probably reflecting the alterations in the expression of cardiac ion channels in hypertrophied cells [56,57] and these changes could modify the pattern of activation due to transient conduction block, particularly if the myocardium was partially refractory following premature stimulation or a ventricular extrasystole. Abnormal, anisotropic activation with regional block, which may form a potentially re-entrant pattern, is associated with delayed, fractionated electrograms [58,59]. It was therefore thought the delays in activation of ventricular paced extra-stimuli could be measured clinically and that patients at high risk of SCD might have slowed conduction with a wider distribution of delayed individual potentials, possibly following an extra-stimulus, than those patients at lower risk. However, it is important to realise that the development of PEFA has not tested the hypothesis that disarray in HCM causes slowed conduction, but has tested the hypothesis that slowed conduction is present in the myocardium of patients at risk of SCD and therefore may have a potential application beyond HCM.

8. Clinical technique

In clinical studies four 1-cm bipolar catheters are positioned in the right ventricle (apex, septum, inferior wall and outflow tract). One catheter was paced with a decremental sequence and electrograms were recorded from the remaining sites. The sequence chosen was a compromise between getting accurate data on how activation changes with premature stimulation and a reasonably short (30–40 min) and well-tolerated study. Therefore the sequence was a drive train of two beats with an extra-stimulus inserted every third beat which started with an S1S2 interval of 450 ms that was reduced in 1-ms steps to VERP or to 220 ms depending on which came first. Approximately 230 sets of bipolar electrograms could be collected during a pacing run and since the sequence was delivered from each of the four electrodes, 920 sets of electrograms were usually collected per study.

It was apparent from early studies [60] that patients who had been resuscitated from VF had marked electrogram fractionation with multiple new potentials and electrogram prolongation which appeared with premature stimulation. Fig. 2 shows typical changes in electrograms recorded from a 51-year-old woman with HCM who had been resuscitated several weeks earlier from VF which developed during exercise. This figure shows an increase in the number of potentials and electrogram duration recorded at the septum while there is less change in both the apical pacing catheter and the RVOT when the S1S2 is diminished. This illustrates the concept on which the PEFA technique is based: there is evidence of delayed activation at one site in heart which does not occur to such an extent at other sites, representing dispersion of activation and a

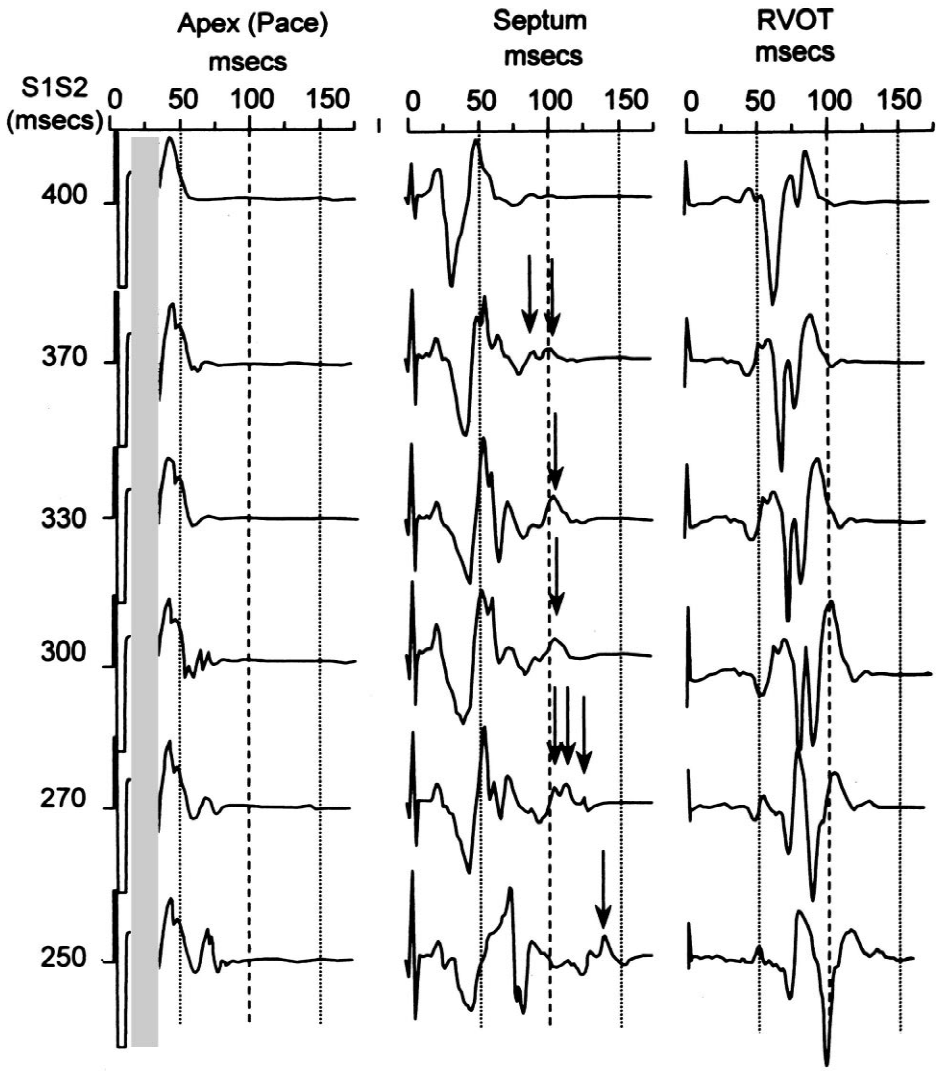

Fig. 2. Electrograms obtained from the RV apex, intra-ventricular septum and RV outflow tract while pacing the apex, in HCM VF survivor at decreasing S1S2 intervals showing systematic increases in electrogram duration and number of potentials. Note that there are delayed potentials at the septum which are not present at the apex, suggesting a tissue conductive effect rather than a stimulus to tissue latency effect. (The grey bar is the time interval over which no electrogram can be measured in the pacing channel).

potential substrate. Whether fractionation is determined at the pacing site or at the recording site or between the two is unresolved. Some studies show identical delays in each recording channel, presumably due to stimulus-to-tissue latencies, while others show completely different patterns between channels suggesting that activation traverses myocardium with patchy disease.

9. Analysis of electrograms

The data obtained from a pacing run are used to construct an intra-ventricular conduction curves [31,60,61]. These are generated by high-pass filtering the electrogram obtained in response to an extrastimulus with a single-pole, zero-phase, digital filter with an f_0 of 150 Hz. This reduces the generally large intrinsic deflection of the signal — so emphasising the smaller high frequency potentials while preserving an acceptable signal-to-noise ratio. The noise is detected in a quiescent portion of the electrogram and potentials with at least three times the amplitude of the noise are identified. The delay in each detected potential in the electrogram following the stimulus is plotted against the S1S2 at which it was obtained to yield curves that demonstrate the overall conduction of the myocardium between the stimulating and recording electrodes. In early studies, the signal between 150 and 200 ms following the stimulus was thought to be random and could be used to estimate noise. However, in some later recordings the electrogram signal persisted into this region and therefore the noise was overestimated in figures leading to loss of detection of later components of the electrogram. The results have been recalculated to allow for this effect which has made a small difference to the shape of some

curves and a slight change in position of the results when plotted on a scattergram (see Figs. 4 and 5) without changing the overall structure of the results.

Fig. 3 shows a curve obtained from a control (lower curve) and from an LQTS (upper) and HCM (middle) VF patient which illustrate the typical differences between low and high risk patients. There is little change in electrogram duration in controls with decreasing S1S2 interval and the number of recorded potentials remains roughly the same and there is an increase in delay, usually without an increase in electrogram duration, at short S1S2 intervals. By contrast, the curves typically seen in patients who have suffered a VF arrest are characterised by an increase in electrogram duration at long S1S2 intervals with additional fractionated potentials as the S1S2 interval is reduced.

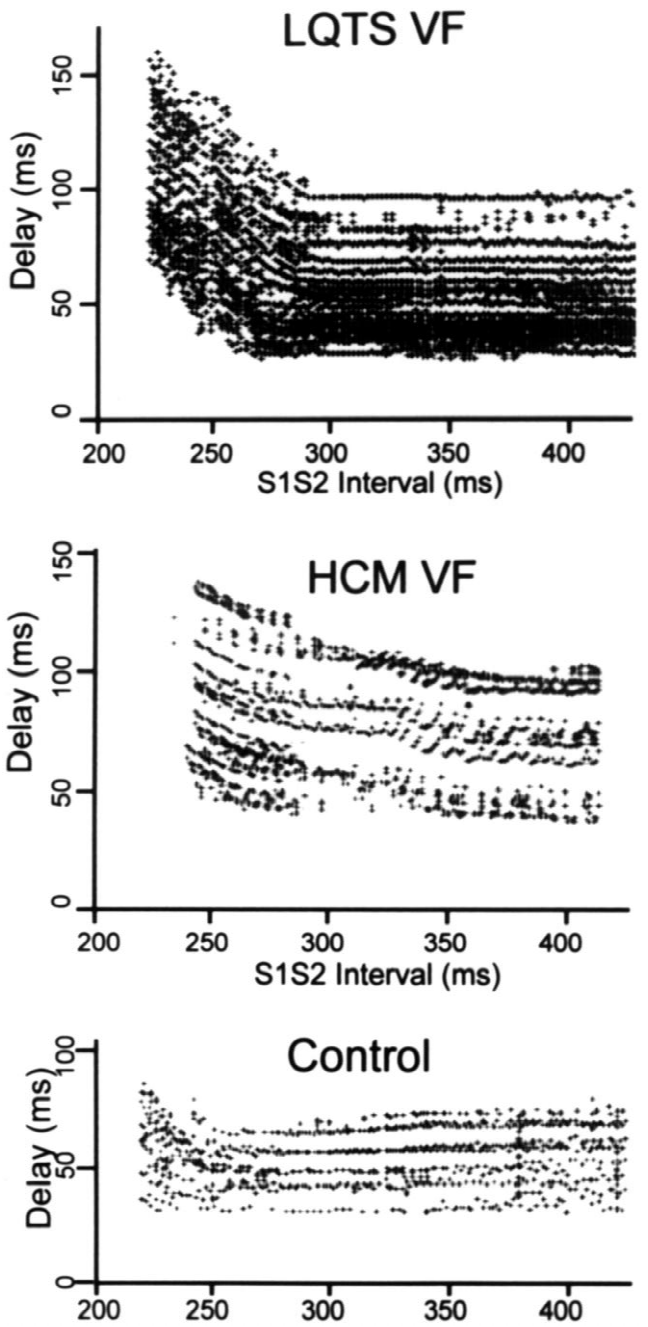

Fig. 3. Conduction curves obtained from a 22-year-old LQTS patient after resuscitation (upper), a 26-year-old HCM patient made 3 months prior to an ECG documented VF arrest (middle) and a control (lower). Note that there is increasing delay at longer S1S2 intervals in the VF patients and that the electrograms at short S1S2 intervals are longer with more potentials in the VF patients.

10. Analysis of conduction curves

The conduction curves have been analysed by an empirical method which was based on the following premises. The first was that the increase in electrogram duration would reflect the ability of the myocardium to generate a substrate with dispersed and delayed activation and therefore prolonged stimulated electrograms might indicate the risk of SCD. Second, if this delayed conduction happened at long, rather than short, S1S2 intervals, the patient may be more vulnerable to triggers, for example a ventricular premature beat, that would create the substrate for VF by generating conduction delay dynamically. In each pacing run the increase in electrogram duration and the S1S2 interval at which it started to prolong were determined. The mean of these values was taken reducing the results of an electrogram fractionation study in an individual patient to a single, statistically independent, observation. This method of analysis was developed using 37 patients with HCM [31] and was then tested prospectively in a further group of 64 patients [60]. The results for a total of 170 HCM patients are shown in Fig. 4 one hundred of which have been published [31,60], and 70 of which form a new cohort of patients recruited for a prospective trial of the technique (see below). Each point represents a patient and the S1S2 interval at which electrograms start to prolong is on the abscissa and the increase in electrogram duration between an S1S2 interval of 350 ms and 5 ms before VERP or at 220 ms (whichever is shorter) is plotted on the ordinate. The hypothetically highest risk category, with maximum fractionation, is in the top right hand corner and the lowest risk category is in the bottom left hand corner. The 25 HCM patients who suffered a VF arrest or died suddenly at an interval after their study have the highest degree of fractionation when compared to the remaining patients. Those patients with either NSVT ($n=57$) on ambulatory ECG monitoring or a family history of sudden death ($n=48$) show a range of results which span the range from controls to those with VF. Thus there is a continuum of EP disturbance, which possibly reflects the risk of SCD, such that the area to the right of the discriminant line in Fig. 5 contains 92% of the VF patients and 23% of the patients who have not yet suffered VF.

This association which shows that HCM VF and non-VF patients form different groups raises the hypothesis that

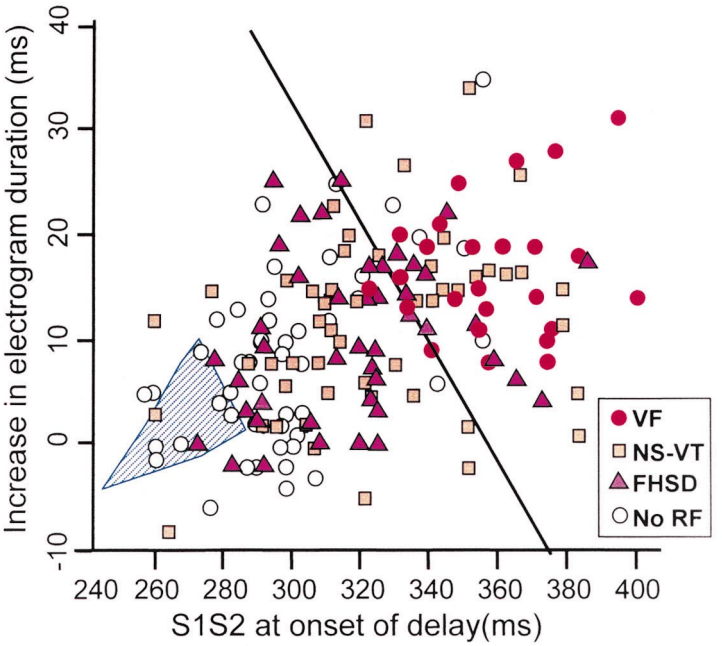

Fig. 4. Scatter diagram of increase in electrogram duration against. S1S2 at which delay increases for HCM patients with VF, non-sustained VT, positive family history of SCD and those with no other recognised risk factors. The discriminant line separates 92% of the VF patients from the remainder and may identify high risk patients who have not suffered VF. The shaded area in the lower left corner is the range of results for controls (n=11) (some data have already been published in Refs. [31,60]).

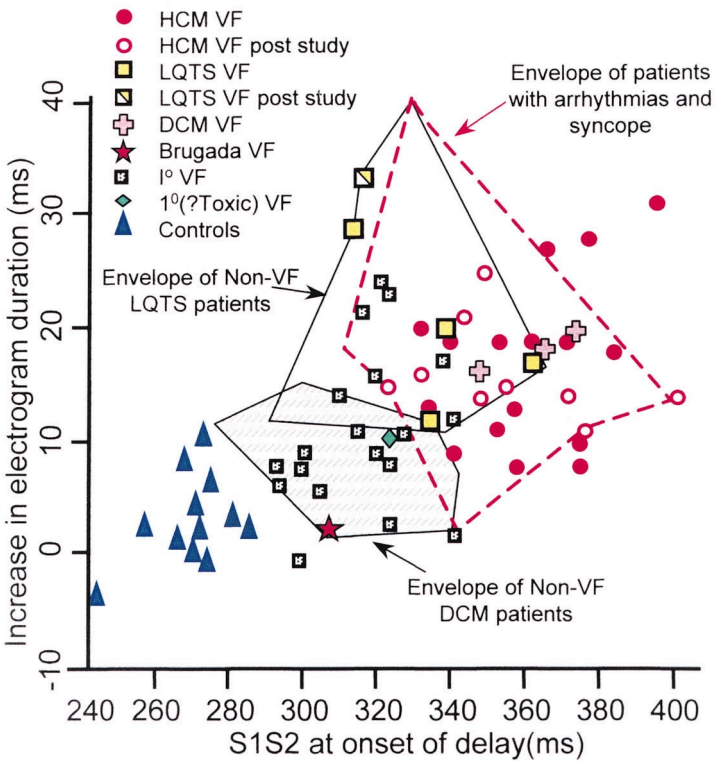

Fig. 5. Scatter diagram of all VF patients studied. Some data have already been published in Refs. [31,60,61]. The region bounded by the broken red line contains all the patients with syncope in the presence of an ECG proven arrhythmia (DCM=3, LQTS=3) and 9 out of 25 patients with HCM who either died or had an ICD discharge after a study. The clustering with the HCM, DCM and LQTS post VF patients suggests that 'fractionation' is not caused by VF arrest and subsequent resuscitation. The region surrounded by the black line contains all the LQTS patients (n=11). The grey area contains the non-VF DCM patients studied to date (n=26).

non-VF patients to the right of the line in Fig. 4 are at higher risk of SCD and that PEFA may have a role in clinical risk stratification. Using the prospective data obtained from 100 patients, the discriminant line in Fig. 4 was constructed to separate the VF and non-VF patients. Seven patients died suddenly or had an ICD discharge after the discriminant line was constructed and the PPA of the technique using this data is 0.29 ± 0.17.

A prospective multicentre trial of the technique has been undertaken to test this hypothesis. Special purpose EP systems have been designed and built to perform the complex pacing protocols and analysis and these are installed in 14 European centres. The trial is designed to recruit and study HCM patients whose progress will be observed. ICD implantation will be undertaken at the decision of the physician managing the patient but use of anti-arrhythmic drugs will cause the patient to drop out. Sequential calculation of the PPA will be undertaken after each event (i.e. death or ICD discharge) and the trial will be terminated when the lower 95% confidence limit of the observed PPA is 0.2. Between 200 and 240 patients will be recruited and a result is expected in 3–4 years.

11. Application in other diseases which cause VF

Fig. 5 shows a scattergram of the 54 patients who have been studied either after a VF arrest or in the case of 10 patients, prior to SCD or a documented VF arrest. HCM, DCM and LQTS patients show the most fractionation while, interestingly, primary VF patients are in an intermediate range between HCM VF and controls [61]. One interpretation of these results is that diseases with a high rate of SCD have well-developed substrates for VF. Therefore HCM, with a high incidence of SCD, and probably DCM and LQTS, may have a well developed substrate. This may render these patients susceptible to triggers, including exercise, psychological factors and diurnal autonomic influences [62,63] which would not cause VF in the presence of a less well-developed substrate. Patients with the LQTS, who do not have abnormal fibrosis, show marked fractionation, strengthening the idea that PEFA measures slowed conduction due to several effects, including prolonged repolarisation due to ion channel mutations, that contribute to an arrhythmic substrate. Finally, the primary VF patients cluster with the non-VF HCM patients and therefore have a less well-developed substrate in histologically myocardium which may be the consequence of abnormal ion channel function. In this case they may require more powerful triggers for VF including coronary artery spasm [64]. These data suggest that the presence of fractionated potentials is a marker of risk of SCD in non-coronary disease, irrespective of the pathology, and has a more general application than simply in HCM for which it was initially developed.

12. Comparison of the technique with surface ECG methods of SCD prediction

When a patient develops VF, an unusual train of events has occurred to match an arrhythmogenic trigger and the potential substrate in the heart to initiate VF. In the normal state, these conditions clearly do not occur and the ECG reflects the electrophysiology of the heart when it is normal or, at least, not in a state that will precipitate arrhythmias. The results from PEFA suggest that in patients who are prone to VF, changes in conduction velocity occur dynamically and the width of electrograms measured in sinus rhythm are the same in VF and non-VF groups. Thus the set of circumstances which give rise to VF are unlikely to be detected in sinus rhythm. Therefore, the difference between ECG measurements in sinus rhythm and PEFA is that the latter measures dynamic changes in intra-myocardial conduction. PEFA presumably measures local refractoriness with changes provoked by a variety of different extrastimulus coupling intervals and so may reveal some of the changes when a substrate develops dynamically during the initiation of an arrhythmia.

13. Problems and limitations of the clinical technique

No obvious relation between PEFA results and individual HCM genotype has yet emerged. Five pairs of affected siblings have been studied, where one sibling had been resuscitated from VF while the other had not had arrhythmias. There were large differences in results between the members of each sibling pair suggesting a wide potential variation of EP phenotype within the context of the same mutation. Furthermore, there is no obvious relationship between the measured fractionation patterns in affected family members emphasising the potential importance of individual electrophysiological assessment.

The induced VF rate during PEFA is about 12%, which is less than with PES, and there is no relationship between VF induction and clinical presentation. Some patients show intense fractionation when VF is induced [31] and the electrogram during the first beats of VT/VF have a similar morphology to paced beats. Others show no fractionation at all preceding VF and the morphology of the first few beats of the arrhythmia is different to paced beats. These differences may be due to VF induction either close to the stimulating electrode in the former case, or at a distance from it in the latter.

One criticism of this work is that electrogram fractionation is created by cardiac arrest and subsequent resuscitation. In the 25 HCM VF patients, there is a subgroup of nine patients who were studied before SCD or an ICD discharge. These data are plotted in Fig. 5 together with five LQTS patients who had suffered VF. The red line encloses the three LQTS patients with syncope in the presence of ECG proven Torsade de Pointes and three

DCM patients who have had syncope with polymorphic VT. The HCM patients, who were studied prior to VF, and the syncopal patients cluster with the HCM, LQTS and DCM patients who were studied after a VF arrest suggesting that cardiac arrest does not create fractionation.

14. Fractionation in the isolated animal heart

The roles of individual mechanisms of fractionation can be studied in animal models (ferret, rabbit, mice) which may be manipulated pharmacologically or genetically to give 'pure' examples of a patho-physiological mechanism. The simplest is the use of dofetilide to model LQT2 [65] as it is a specific I_{Kr} ligand or of antho-pleurin A to model LQT3 [66]. Fig. 6 shows conduction curves obtained between approximately 7 mm spaced, 2-mm bipolar epicardial electrodes in an isolated Langendorff-perfused ferret heart in the control state and during perfusion with 100 nM dofetilide. There is a striking increase in fractionation with dofetilide and these results are comparable to the clinical control and the LQTS VF survivor curve shown in Fig. 3. Using the same analysis shown in Figs. 4 and 5, there is a dose-dependent shift from a low fractionation to high fractionation region with increasing doses of dofetelide (1, 10 and 100 nM) shown in Fig. 7. This shows that the patterns of fractionation seen in the LQTS can be attributed to the inhibition of the currents involved in cardiac repolarisation which can be studied further in transgenic models which have electrophysiological phenotypes [67].

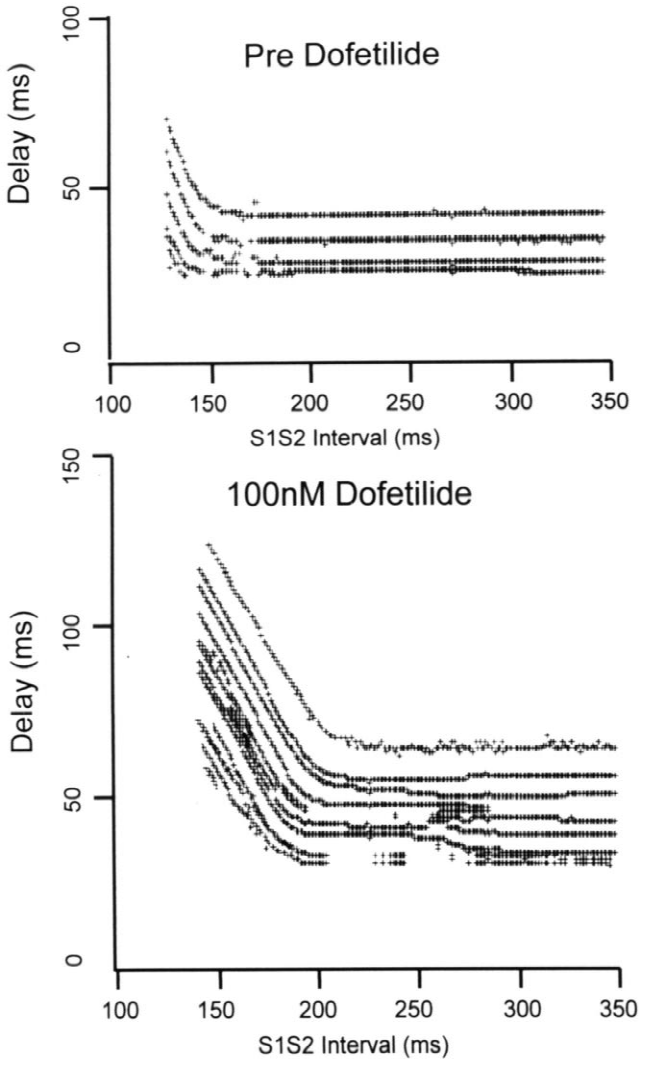

Fig. 6. Conduction curves using 2-mm bipolar epicardial electrodes from a Langendorff perfused Ferret heart in control state and with infusion of 100 nM Dofetilide. Compare these curves with the LQTS and control curves shown in Fig. 3.

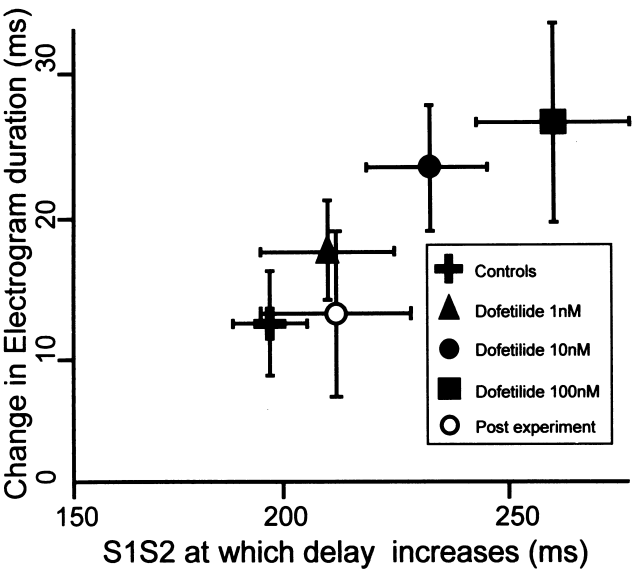

Fig. 7. Scatter diagram of the change in fractionation in the Langendorff perfused ferret heart with in creasing doses of dofetilide. Error bars are ±2 SEM.

15. Conclusion

The identification of HCM or other patients at risk of SCD with sufficient accuracy to guide prophylactic ICD implantation remains a remarkably difficult problem. These difficulties stem not only from the heterogeneous populations of relatively uncommon diseases but also from the lack of understanding of the processes that lead to VF and the difficulties in demonstrating these in individual patients. Paced electrogram fractionation analysis started as a clinical technique to demonstrate an arrhythmic substrate in patients at risk of SCD by measuring some of the assumed effects of the molecular, cellular and architectural abnormalities caused by disease and there is now clinical evidence that there is an association between electrogram fractionation and the risk of SCD in non-coronary disease. Finally, the finding that some results

from human VF patients can be modelled in animal hearts may help to interpret measurements made in patients at risk of lethal arrhythmias in terms of their underlying pathophysiology.

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