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CLINICAL RESEARCH
Heart failure/cardiomyopathy

Paced ventricular electrogram fractionation predicts sudden cardiac death in hypertrophic cardiomyopathy

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Aims Paced electrogram fractionation analysis (PEFA) has been assessed for the prediction of sudden cardiac death (SCD) in a large-scale, prospective study of patients with hypertrophic cardiomyopathy (HCM).

Methods and results We determined the positive predictive value (PPV) of PEFA in relation to other risk factors for SCD and outcomes in 179 patients with HCM and no prior history of cardiac arrest. Patients were followed over a mean 4.3 years (range: 1.1–6.3 years). Thirteen patients had SCD-equivalent events: four of these patients died suddenly, three were resuscitated from ventricular fibrillation (VF), and six had implantable cardioverter-defibrillator (ICD) discharges in response to VF. PEFA identified nine of these patients and another 14 non-VF patients yielding a censored PPV of between 0.19 and 0.59 that was greater than the PPV that was the formal stopping point of the trial (0.18). Eighty per cent of patients were followed for 4 years or more. The PPV for the identification of SCD in this group was 0.38 (0.17–0.59). The use of two or more conventional markers to predict SCD identified five patients with SCD-equivalent events in the 4-year follow-up group and 42 other patients without events yielding a PPV of 0.106 (confidence limits 0.02–0.15).

Conclusion PEFA identifies HCM patients at risk of SCD with greater accuracy than non-invasive techniques and may have an important role in determining indications for ICD prescription.

Keywords Heart arrest • Electrophysiology • Cardiomyopathy • Defibrillation

Introduction

The prediction and prevention of sudden cardiac death (SCD) due to ventricular fibrillation (VF) is the most important challenge in the management of patients with hypertrophic cardiomyopathy (HCM).[1–4] Implantable cardioverter-defibrillators (ICDs) correct potentially lethal arrhythmias in HCM,[5] but the selection of patients for implantation is confounded by current non-invasive risk stratification having low predictive accuracy.[6] Patients deemed to be at low risk following non-invasive assessment might not receive an ICD and die,[2,5] although more usually patients will undergo prophylactic ICD implantation exposing them to

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unnecessary and potentially severe long-term risks.[2,5,7,8] The present study is the first prospective evaluation of the positive predictive value (PPV—the fraction of test positive patients who in fact die) of risk factors for SCD in HCM and demonstrates that a distinct electrophysiological abnormality, paced electrogram fractionation, has greater predictive accuracy for SCD in HCM than conventional criteria.

Re-entrant ventricular arrhythmias, which lead to SCD, arise from a substrate that includes slowly conducting pathways that delay ventricular activation.[9,10] Earlier work[11–13] suggested that the structural disruption and myofibrillar disarray seen in HCM[14] would provide the conditions for unidirectional block and delay, the setting for re-entrant excitation and arrhythmias.[11–13] We suggested that such discrete paths of delayed activation could be inferred from electrograms showing multiple, discrete, and delayed potentials ('fractionation') reflecting disrupted myocardial activation[10–13,15] (*Figures 1* and *2*). These potentials can be provoked by the introduction of paced extra-stimuli (S2) interposed at progressively shortened intervals following successive pacing stimuli (S1) and form the basis for paced electrogram fractionation analysis (PEFA).[13] Increasingly premature S2 extra-stimuli result in slowing or block in some activation paths accentuating slowed conduction and prolonging the electrogram.[10,16,17] The analytical approach of PEFA interprets changes in electrogram morphologies

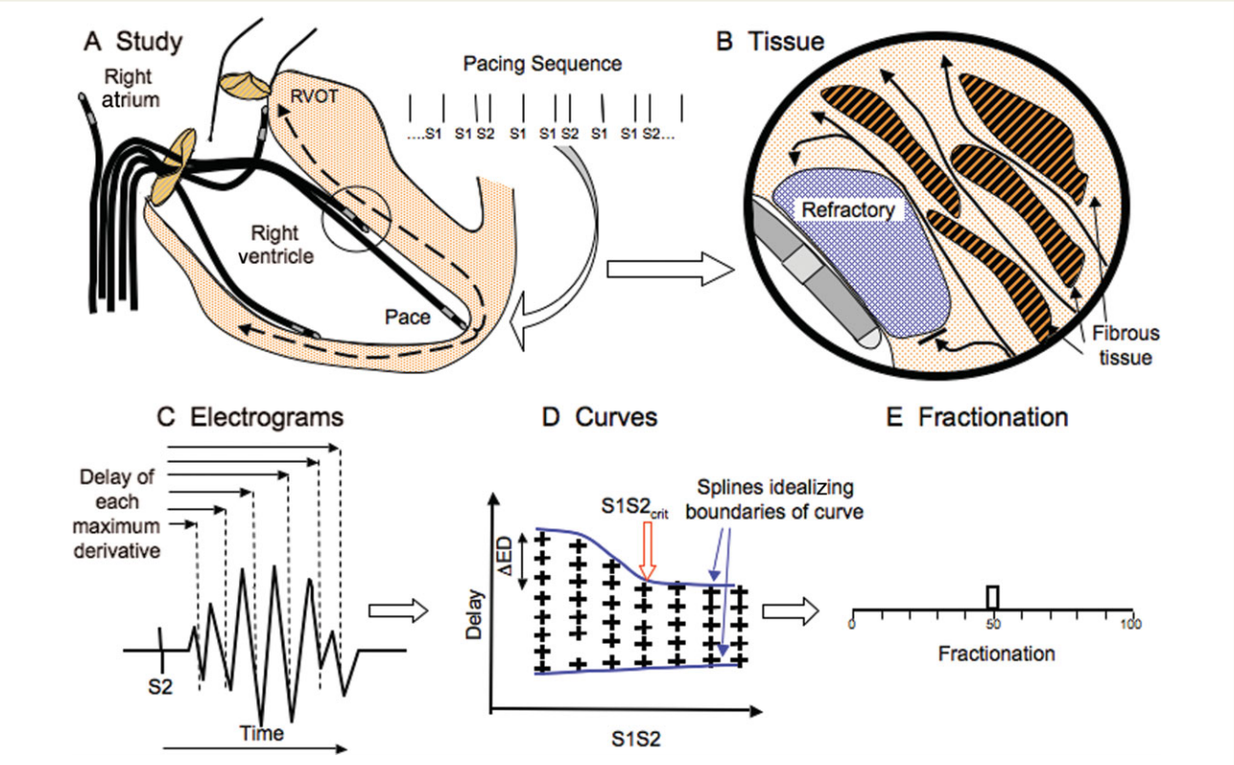

Figure 1 Principles of paced electrogram fractionation analysis. Four electrode catheters are placed in the right ventricle with their arrangement shown in *A* as previously described.[13,16] Each catheter is used to pace and record electrograms. A pacing run is issued from each catheter in turn with recordings of electrograms from the remaining three electrode pairs. Thus, there are four runs per full study with three sets of electrogram recordings each about 5 min in length being obtained in each run. The pacing system is digitally controlled and synchronized with the recording system and consists of a drive train (S1–S1) with an extra-stimulus (S2) delivered every third beat. The extra-stimulus coupling interval is successively reduced from 450 to 220 ms in 1 ms steps resulting in 231 extra-stimulus coupled electrograms in each channel of each pacing run unless limited by ventricular refractoriness. *B* shows how fractionation can occur in diseased areas. Conduction is delayed through areas of diseased and fibrotic tissue near their relative refractory period and blocked by areas of prolonged refractoriness, resulting in the recording of delayed ventricular activation. Note that local block caused by refractory tissue that subsequently repolarizes can be invaded and gives rise to fractionation and potential re-entry. *C and D* summarize the digital processing and analysis of ventricular electrograms. *C* shows an extra-stimulus (S2) followed by a fractionated electrogram (5-pole Bessel Filter −3 dB, 278 Hz) with six points of maximum derivative, which are timed, from the extra-stimulus. The delays in the electrogram shown in *C* are plotted on the ordinate of the graph in *D* against the S1S2 interval at which the electrogram was obtained.[13,16] By performing this for each extra-stimulus, an 'intraventricular conduction' curve is obtained. Cubic splines are fitted to the upper and lower borders of the curve and are used to determine the increase in electrogram duration (ΔED) and the S1S2 ($S1S2_{crit}$) at which electrogram duration starts to increase. The values of the ΔED and $S1S2_{crit}$ for each of the 12 curves are averaged to form a single observation. This observation is projected on to an axis that had been determined from earlier studies to maximize the discrimination between hypertrophic cardiomyopathy ventricular fibrillation (VF) and non-VF patients, thus forming a single ordinal observation describing each patient (*E*).

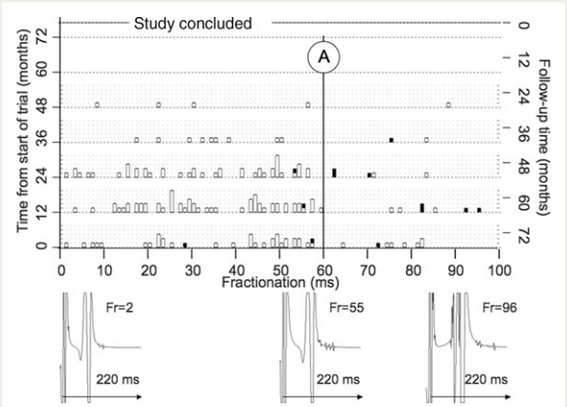

Figure 2 Data summarizing paced electrogram fractionation analysis results for all patients. The abscissa is the degree of fractionation, as represented in *Figure 1E*, with a value of 100 ms indicating a high degree of fractionation and a value of 0 ms, indicating no fractionation at all. The ordinate (left) is divided into blocks of yearly cohorts of time of recruitment and within each cohort the height of each rectangle corresponds to the number of patients recruited during that year. The open rectangles represent patients without an event so far and black rectangles represent patients who have had an event. The right-hand scale shows follow-up time. The distinguishing line, A, is the discriminant between high (test-positive) and low risk (test-negative) groups determined by retrospective data. Representative high-pass filtered (-3 dB = 150–278 Hz) electrograms at an S1S2 of 230 ms are shown for patients with fractionation of 2, 55, and 96 ms.

and is based on these changes providing a quantifiable basis for the substrate for SCD.[11–13] The hypothesis that electrogram fractionation reflects the risk of SCD was based on two retrospective observational studies in HCM[11,12] and other studies of patients at risk of VF[18] including those with LQTS[16] and idiopathic VF.[19] These studies suggested that patients with HCM at risk of VF could be discriminated from other patients not at such risk with a PPV of about 0.4 and established a specific discriminant criterion for patients at high risk of SCD.[12]

The current study tests whether the discriminant criterion genuinely predicts SCD. The PPV was chosen as the primary variable to study because it has immediate and intuitive clinical utility.[13] The study was designed to recruit patients and to follow their progress and when an event, a death or ICD discharge, occurred, the current PPV would be re-calculated and when the lower limit rose above a predetermined threshold, the study would terminate. The threshold chosen was the PPV upper limit for non-invasive tests determined from retrospective data which appeared to be 0.165.[12] Accordingly, a threshold for the lower limit of the PPV was set to 0.18 so that if the two-tailed -2SD lower limit of the PPV was greater than this, the actual PPV must be at least 0.18. This design has important consequences. First, it does not explicitly analyse survival curves. A risk factor may be associated with an increased SCD rate but this does not necessarily imply that this risk factor is a useful discriminant test between high and low risks. Secondly, the patients have been followed up for variable periods ('censored') and the data reflect this. Finally, the test positive group was assumed to be composed of 40% patients with a high SCD rate and the remainder would have a SCD rate of the true negative population and so the PPV would approach some value after these high-risk patients had died, rather than drifting up to 1.0 if all test-positive patients had an equal risk of SCD. The design concluded that if 180 patients were recruited over 5 years and the PPV for events was 0.4, the probability of a positive result was >0.95.

Methods

Patient selection

Each institutional ethics committee approved the protocol and patients gave informed, witnessed, and written consent for the procedure. All patients had been referred to the centres taking part in the trial for overall management of HCM that included risk assessment. Patients recruited had an unequivocal diagnosis of HCM based on electrocardiograms and echocardiographic criteria with a hypertrophied, non-dilated left ventricle in the absence of any other cardiac or systemic disease that could account for hypertrophy.[6] The hypertrophy was nearly always maximal at the septum, 13 patients having apical hypertrophy and 12 concentric hypertrophy. All patients were in sinus rhythm and had no history of atrial fibrillation, sustained ventricular arrhythmia, or of cardiac arrest. Apart from beta-blockers and L-type calcium channel blockers, the use of anti-arrhythmic drugs required withdrawal of a patient from the study. Patients were studied as described in earlier studies[11,18,19] in a drug-free, fasting state with sedation provided with intravenous benzodiazepines or opiates as required. The presence or otherwise of a personal history of syncope, a family history of SCD, or non-sustained VT on ambulatory monitoring were recorded in each patient along with the echocardiographically determined maximum LV thickness and blood pressure response to exercise.[20,21] Identical systems were installed in each centre that controlled the pacing and recording protocols and also required entry of mandated details before a study could begin. The local data collection was transferred to the study centre and added to the main database and when the study concluded each surviving patient was contacted directly with the data further validated.

Electrophysiological testing

Four standard bipolar electrophysiology catheters with 1 cm electrode spacing are introduced to predetermined sites in the right ventricle from the femoral veins.[13,16,18] The pacing sequence is delivered from one ventricular catheter, with the atrium paced 30 ms earlier, and electrograms recorded from the other three electrodes (*Figure 1*). The pacing site is rotated to each catheter a[illegible] same sequence is then delivered. The pacing sequence cons[illegible] a drive train of 2 (S1–S1) beats with an extra-stimulus (S2) every third beat and the extra-stimulus coupling interval reduced in 1 ms steps from 450 to 220 ms or the effective refractory period.[13,16,18] Bipolar electrograms are filtered with 5-pole Bessel anti-aliasing filters (-3 dB = 278 Hz) and digitized during the pacing sequence at 1 kHz. One complete study including catheter placement and the completion of four pacing runs with the collection of three sets of electrograms per run takes ~35–40 min.

Electrogram analysis

After a study, electrograms obtained in response to an extra-stimulus are identified and processed digitally to detect small, delayed potentials

in the presence of noise as previously described in detail[13,16] (*Figures 1* and *2*). The increase in electrogram duration and the S1S2 interval at which the electrogram duration starts to prolong is determined for each channel and pacing run using an automated method and transformed to yield a single observation[13,16] to test the hypothesis that the procedure could separate SCD from non-SCD patients. This axis, which has the units of time, shows the degree of electrogram fractionation, with zero as completely normal and 100 ms as intensely abnormal (*Figure 2*). The hypothesis, i.e. the threshold level proposed to separate SCD and non-SCD patients, had been calculated from retrospective data[12] and is shown at a value of +60 ms. Patients to the right of line A in *Figure 2* are regarded as test-positive and those to the left of it are test-negative. The individual electrograms and their analysis were scrutinized independently (by Professor C.L-H.H., University of Cambridge, UK). The results of individual studies were provided to the physician managing the patient who decided whether to implant an ICD. For those patients who had an ICD discharge, a participating cardiac electrophysiologist (Dr M.J.G.) reviewed blinded ICD disclosures independently of the managing physician.

Statistical analysis

The lower limit (−2SD) of the distribution of the observed PPV was calculated using a two-tailed normal approximation. When the lower limit of the observed, censored, PPV of the fractionation distribution exceeded 0.18, the study was terminated. Eighty per cent of the patients have been followed for 4 years or more. This group contains 11 of the 13 patients who had events but excludes the two patients who died non-suddenly. Subsequent calculations of sensitivity and specificity are performed using this uncensored group.

In view of recent concerns that not all appropriate ICD discharges can be used as a robust surrogate for SCD,[22] the data are reported for two groups of patients. The first group (Group 1) are those who died suddenly or were resuscitated from VF and the second (Group 2) are the patients who had demonstrable appropriate ICD discharge in response to ventricular arrhythmia also considered as an SCD-equivalent event. The comparison of the censored predicted survival curves of the test-negative and test-positive groups of patients was done by the Mantel–Haenszel statistic. The sensitivities and specificities of the electrophysiological data for changing values of fractionation and number of positive non-invasive tests are plotted as receiver-operator characteristic (ROC) curves in *Figure 4*.[23] The sensitivities and specificities were calculated from non-censored 4-year follow-up data. The confidence limits of non-invasive test curves were calculated exactly and checked using Monte-Carlo methods by using observed frequencies of the five non-invasive predictors in patients with only one risk factor. The event rate was calculated assuming that there is a lower event rate in patients with zero risk factors of 0.5% p.a. and the event rate in the one or more risk factor group was 2.2% p.a, so bringing the total event rate to the observed 1.6% p.a.—otherwise the relationship between the presence of non-invasive risk markers and SCD was random.

Results

Characteristics of the patients

One hundred and eighty-five patients (aged 16–63, 105 were male) were recruited in 10 centres over 5.5 years and yielded 179 useful studies. The study protocol did not formally select patients on the basis of risk factors and hence there is a wide range of conventional apparent risk with 31.8% of patients having one risk factor with 22.3% having at least two (*Tables 1* and *2*), which is compatible with other series.[21] Of six unsatisfactory studies, two were abandoned due to recurrent induction of VF and four of the early studies were rejected due to technical problems in data collection. The study terminated at the pre-specified duration with a mean follow-up of 4.3 years ranging from 1.1 to 6.3 years. No significant complications occurred during or following electrophysiology study procedures. During the course of the study, 24 ICDs were implanted for primary prevention programmed to give shocks for VF but not to deliver anti-tachycardia pacing. There were a total of 13 events that were considered to be equivalent to SCD. These were composed of six appropriate ICD discharges (cycle lengths 210, 230, 202, 190–220, 200, 190–235 ms, respectively; Group 2), three patients were resuscitated from VF, two patients could not be resuscitated from VF, one patient who was witnessed to die suddenly during sleep, and one patient was found dead. The seven patients (Group 1) who did not have ICDs were either enrolled early in the study when ICD implantation for primary prevention was not a well-established treatment option or had insufficient risk factors to justify implantation according to the criteria at the time. Two patients in the test-negative group died non-suddenly. There have been five further inappropriate device discharges for atrial arrhythmias.

Predictive accuracy of paced electrogram fractionation analysis

Nine patients who had 'events' (SCD, ICD discharge or resuscitation from VF) were identified prospectively on the basis of PEFA. A further group of 14 patients were also identified as being at risk but had not had an event at the closure of the study. In this group, the censored PPV is 0.39 with a −2SD lower limit of 0.19 that fulfilled the formal stopping criterion of the trial. In the 4-year follow-up group, these observations correspond to a PPV of 0.38 (0.17–0.59) during the period of follow-up. In the test-negative patients during this period, there were three events corresponding to a negative predictive value of 0.95.

Figure 2 shows the distribution of the data plotted against the fractionation coordinate in histograms showing the time at which patients were recruited, emphasizing the censoring of the data. The black rectangles show nine test-positive and four test-negative patients. The open rectangles show the distribution of the patients who have not had an event, 14 of whom are test-positive with the remaining 152 test-negative. *Figure 3* shows Kaplan–Meier survival curves for the total test-positive and test-negative groups. These curves show that there is a higher event rate in patients who are test-positive ($P < 0.001$, Mantel–Haenszel test). The event rate in the low-risk test-negative group is 0.6% p.a. In the high-risk test-positive group, the event rate is about 11% p.a. and the overall mortality was 1.6% p.a.

Predictive accuracy of conventional risk assessment

The value of non-invasive risk factors for SCD was also determined applying established criteria.[5,20] These factors were in summary: a history of syncope, two or more sudden deaths in the same family, non-sustained VT observed on 24–48 h of ambulatory

Table 1 Clinical data on 179 patients with hypertrophic cardiomyopathy evaluated for risk of sudden cardiac death using paced electrogram fractionation analysis and conventional risk assessment algorithms[a]

	Non-SCD, *n* (%)	Events, n (%)	ICD discharge/resuscitated/deaths
Total number (*n*)	166 (92.7)	13 (7.3)	
Number PEFA test positive (*n*)[b]	14 (7.8)	9 (5.0)	
Age, range (years)			
16–20	11 (6.1)	2 (1.1)	
21–40	103 (57.6)	7 (3.9)	
41–60	47 (26.3)	4 (2.2)	
>60	5 (2.8)	0	
Gender (*n*)			
Male/female	96/70 (53/47)	5/8	
Possession of risk factors (*n*)[c]			
Nil	69 (38.5)	–	
Max LV wall thickness ≥ 30 mm	23 (12.9)	5 (2.8)	
Syncope	29 (16.2)	5 (2.8)	
Family history of SCD	22 (12.3)	1 (0.6)	
Non-sustained VT	56 (31.3)	6 (3.35)	
Abnormal BP during exercise	33 (18.4)	6 (3.35)	
Numbers of risk factors (*n*)[c]			
Zero risk factors	67 (37.5)	0	
1 risk factor	50 (27.9)	7 (3.9)	3/2/0
2 risk factors	36 (20.1)	4 (2.2)	2/2/1
3 risk factors	11 (6.1)	1 (0.6)	1/0/1
4 risk factors	2 (1.1)	0	0/0/0
5 risk factors	0	1(0.6)	0/1/0

[a]Data were obtained at the time of admission for PEFA study. The numbers in the table indicate patient characteristics against outcome.
[b]Positive test defined against threshold level of fractionation (+60 ms) based on retrospective studies.[11–13]
[c]Risk factors determined from multiple risk factor algorithm and assessed/measured as previously defined.[20] Percentages shown as component of total population (179). Note that the percentages of risk factors present do not necessarily sum to 100.

Table 2 Numbers of patients, events, and risk factors tabulated by fractionation decile

Fractionation value	*n*	Events	LVH ≥ 30 mm	Syncope	FHSD	Non-sustained VT	Exercise hypotension	Total RFs/*n*
0–9	8		1	2	2	6	5	0.0108
10–19	22		3	4	3	8	4	0.0054
20–29	30		5	2	1	8	5	0.0038
30–39	23	1	5	5	4	10	6	0.007
40–49	30		3	6	3	10	4	0.0047
50–59	43	3	5	6	3	9	7	0.0038
60–69	7	4	2	3	1	3	2	0.0084
70–79	6	3	1	2	2	3	2	0.009
80–89	8		2	3	2	3	2	0.0081
90–100	2	2	1	1	2	2	2	0.0215

This table shows the association between risk factors and fractionation. The total number of risk factors in the decile divided by the number of patients in the decile is shown in the far right-hand column. There are a total of 145 risk factors in the fractionation group 0–59 (156 patients) and 41 risk factors in the group 60–100 (23 patients). $\chi^2 = 14.1$, $P < 0.01$.

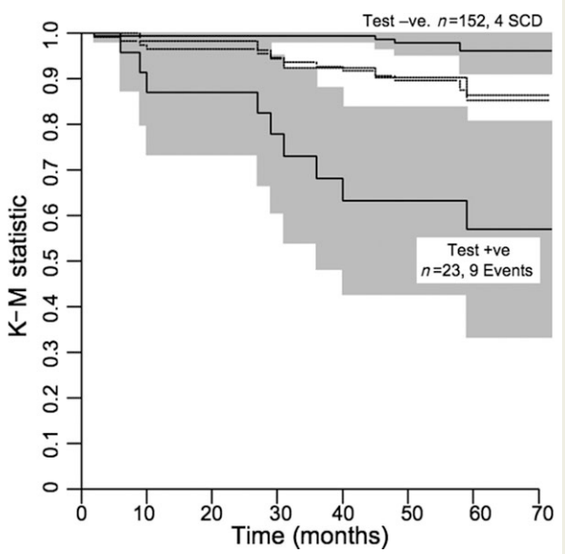

Figure 3 Relationship of paced electrogram fractionation analysis prediction to sudden cardiac death (SCD)-equivalent events and survivorship. Kaplan–Meier survival curves for all patients with, and without, SCD-equivalent events. Patients were categorized as test-positive (fractionation>60 ms) vs. test-negative (fractionation<60 ms) by single ordinal observation. Event rates in test-positive patients exceeded those in test-negative patients ($P < 0.001$, Mantel–Haenszel test). The ± 2 SEM of the test-negative and test-positive groups are shown in grey and the K–M curves for patients with one and two risk factors are shown as dashed lines.

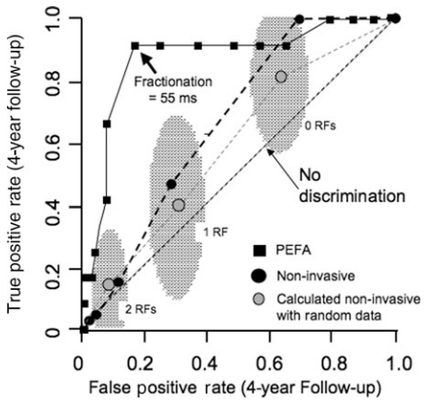

Figure 4 Receiver operating characteristics (ROC) curves for paced electrogram fractionation analysis (PEFA) and non-invasive risk factors. These curves indicate the true and false positive rates for all combinations of the data. The locus of a perfect test would pass through the top left-hand corner of the graph (i.e. ideal true and false positive rates) while a test of no utility will lie on a diagonal line joining the lower left and top right corners (i.e. equal true and false positive rates). The point of the curve, which has the highest derivative, has the best value of sensitivity and specificity and is used to determine the optimum discriminant value. The area under the curve (AUC) is a measure of how the curve lies between a non-discriminant test (AUC = 0.5) and a perfect curve (AUC = 1.0). The two curves representing experimental data are significantly different with the PEFA curve corresponding to a better test than non-invasive risk factors (AUC = 0.88 for the total group of patients vs. 0.71, $P < 0.01$). The points on the PEFA curve correspond to 5 ms steps in fractionation and that which corresponds to the optimum discriminant point is 55 ms. The ROC of a simulation of non-invasive tests under the assumption that there is a reduced SCD rate of 0.05% p.a. in the zero risk factor group, but the distribution of one or two risk factors is random. The presence of zero, one, or two risk factors [0–2 RF(s)] lie within the limits of a random test.

electrocardiography, significant ventricular septal hypertrophy on echocardiography (≥30 mm), and an abnormal blood pressure response during exercise. These results are summarized in *Tables 1* and *2*. Of the prospective VF patients, 0 had zero risk factors, seven patients had one risk factor, four had two risk factors, one had three risk factors, and one had five risk factors.[5] Of the non-VF group, 49 patients had two or more risk factors. In the 4-year follow-up group, the PPV for non-invasive risk factors is 0.106 (0.02–0.15). There is an association between the fractionation value and the total number of non-invasive risk factors in that the test positive group is greater than would be expected, as shown in *Table 2*. However, the individual correlation coefficient between fractionation value and LV wall thickness, which might be expected on physiological grounds, is only 0.11.

In *Figure 4*, the ROC curves are shown for both the PEFA and the conventional risk factor analysis using 4-year follow-up data. The ROC curve is a means of expressing the sensitivity and specificity of all combinations of the data and for comparing tests.[23] A ROC curve for a perfect test should conform to two sides of a rectangle while a test of zero utility follows a diagonal line. It is clear that PEFA conforms more closely to the ideal test than does a conventional non-invasive approach and has superior sensitivity and specificity. The non-invasive ROC curve is distinguishable from one constructed from purely random data because the sensitivity of zero risk factors is 1. However, a modified model in which the risk of an event is 0.5% p.a. and the risk factors are otherwise random includes the observed ROC curve. The area under curve (AUC) for PEFA is 0.88 and for non-invasive tests is 0.71 ($P >$ 0.01). The AUC of the non-invasive curve is significantly different from a purely random test that has an AUC of 0.5.[24] Finally, the point of inflection of the fractionation ROC curve is the point of optimum discrimination of the test and in the case of PEFA is 55 ms which reflects the outcomes of two patients with events whose fractionation values were just below the threshold of 60.

Discussion

This is the first prospective assessment of a large, well-characterized HCM population to determine the risk factors for SCD. The findings demonstrate a clear relationship between electrogram fractionation and SCD, thereby providing evidence that SCD in this disease can be analysed by applying basic

electrophysiological principles.[9,10,25] The lower limit of the censored PPV of electrogram fractionation for events (0.19) over a follow-up period of 4.3 years is higher than that of conventional non-invasive risk factors for SCD (<0.18) whether assessed individually or in aggregate. Since the patients were recruited through nine regional and one national HCM referral centre, they represent a 'truly general HCM population'[5] having an overall risk somewhere between that reported from highly specialized referral centres[5,20] and that reported in community studies[26] and the overall SCD rate of 1.6% per year is in keeping with other large-scale, unselected studies.[27] Retrospective data from specialized centres documents the PPV of all considered non-invasive predictive methods[6,21,27–32] to be lower than that obtained from our direct electrophysiological approach. The triggering mechanism of most episodes of SCD is a ventricular arrhythmia but conventional electrophysiological methods including ventricular provocation studies have been shown to have low accuracy in risk prediction in HCM.[12,33] We suggest that the fractionation technique has a higher predictive accuracy since it reveals components of a re-entrant substrate that may support an arrhythmia.[25] Conversely, the end-point of ventricular provocation is an induced arrhythmia whose interpretation in relation to any future ventricular arrhythmia in an individual patient is problematic.[12]

One of the premises of the design was that an appropriate ICD discharge could be taken as being equivalent to a VF or SCD event[34] but this may not always be the case according to a *post hoc* analysis from the DEFINITE trial.[22] Therefore, we have presented the data for both the patients who did not receive ICDs (Group 1) and those with ICD discharges (Group 2). In Group 1, there were five SCD events in the test-positive group and two in the test-negative group ($P < 0.001$), indicating that in patients without ICDs, PEFA also identifies patients at risk of SCD. If it is assumed on the basis of the DEFINITE study that some of the ICD discharges in Group 2 are associated with SCD, between 1 and 5 of the ICD patients will have had a discharge that genuinely aborted SCD. The results have then been calculated for a range of allowable discharges ranging from 1 to 5. In this event, provided three of the ICD discharges were in response to VF, the PPV would be 0.30 with a lower limit greater than the revised upper limit of the non-invasive PPA (0.12). Therefore, we conclude that PEFA has a higher PPV for SCD than non-invasive methods, despite ongoing uncertainty surrounding interpretation of ICD discharges.[34]

Although the study had the primary objective of assessing the predictive accuracy of PEFA, it is also the first prospective evaluation of non-invasive risk prediction in HCM rather than the usual association of risk factors with SCD through retrospective analysis. Our results show that following the assessment of non-invasive measures of risk, classifying a patient as being at risk due to the possession of at least two out of the five categories[20] prospectively identified 46% of events compared with 70% of events using PEFA. However, on the basis of two or more non-invasive risk factors, 49 non-VF patients are also identified as high risk; in patients with a single risk factor, 117 patients are identified at risk and 13 would have had an event. Accordingly, application of current non-invasive strategies in this highly representative HCM population would lead to substantial ICD over-implantation, increasing the numbers needed to treat to save one life.[2,5,35] The PPV of fractionation is at least 0.19 and although this is admittedly also a modest value, it is an improvement on a PPV of about 0.1. If ICDs were implanted on a purely algorithmic basis, this improvement would halve the number of implantations resulting in considerable clinical benefit.

It is likely that some patients who die will have that characteristic irrespective of whether it is related to an SCD risk. For example, in the 4-year follow-up group, 33% of patients had non-sustained VT on ambulatory monitoring and has a sensitivity (fraction of test positive patients with an event) of 0.45. However, a sensitivity of 0.33 (0.27–0.45) is expected if the events are randomly distributed between patients with, and without, NSVT. The non-invasive ROC curve reflects this effect and is indistinguishable from random data for one and two risk factors, although compatible with an SCD rate of 0.5% p.a. in the zero risk factor group. This suggests that additional use of non-invasive risk factors with PEFA is unlikely to result in increased predictive accuracy. One could conclude that, under current follow-up at least, patients with zero risk factors have a low probability of events and that only patients with at least one risk factor need undergo EP study. However, this assumption may not be correct as larger populations, with longer follow-up, have 6-year risks whose upper confidence limit is 9%.[20] Therefore, long-term, tailored assessments of risk, which may need several invasive assessments, will be required during the lifetime of the individual, the advantage being that ICD therapy with its attendant risks[5,7,8] will be avoided until deemed truly necessary.

This study has a number of limitations. The trial was set up to yield a robust result with the minimum number of patients and an acceptable duration.[13] Therefore, the confidence bands of the PPV are wide and there are different follow-up times so the results may change when all patients have been followed up for a planned 5 years. In addition, a larger group of patients will be required to estimate the PPV with greater accuracy; but to show that the PPV is genuinely above 0.3, assuming that the real value is 0.35, would require about 800 patients. The results are strictly applicable to patients with the same age distribution and recruitment profile of patients in this study and pooling data from a number of centres would be productive in forming a hypothesis relating risk factors to the risk of SCD that could be tested prospectively in a larger, even more diverse group. In addition, since HCM is a progressive disease, the electrophysiological characteristics may change over this period but whether this will, in fact, occur is unknown.

This trial establishes a management strategy for the primary prevention of risk in patients with HCM that is based on the electrophysiological features of the disease. It identifies patients at risk of SCD with higher accuracy than other methods and holds promise for the rational use of ICDs in such patients. Invasive electrophysiological phenotyping of other diseases[16,18] leading to improved risk prediction would also seem possible.[25]

Conflict of interest: none declared.

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CLINICAL VIGNETTE

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Splenic infarction due to multiple left ventricular mobile thrombi in hypereosinophilic endomyocarditis

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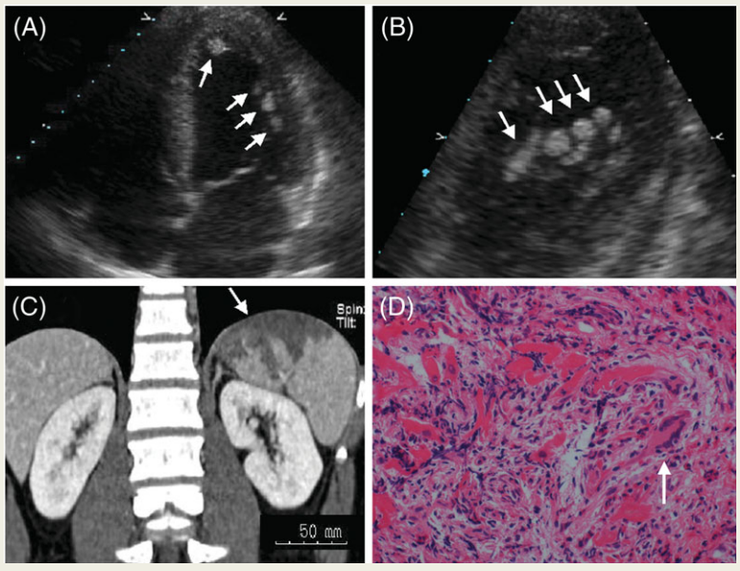

A 30-year-old man was admitted for rapidly developing dyspnoea. He was a basketball player and had not felt chest discomfort until a few days earlier. A chest radiograph showed severe pulmonary congestion and the electrocardiogram revealed sinus tachycardia with ST-segment depression and inverted T waves in inferior leads. Echocardiography demonstrated increased left ventricular (LV) wall thickness and restrictive transmitral flow pattern. We could also observe severe spontaneous echo contrast and multiple mobile thrombi in the LV (Panels A and B). Despite the immediate anticoagulation therapy, these thrombi did not disappear. On day 7, he revealed left upper abdominal pain and computerized tomography scan showed a thrombo-embolic splenic infarction (Panel C). Total blood eosinophil counts incrementally increased and endomyocardial biopsy taken from the right ventricle showed eosinophilic infiltration predominantly in endocardium but also in myocardium, resulting in geographic loss or sporadic damage of myocardial fibres in association with granulation tissue proliferation and fibrosis (Panel D). The clinical and pathological findings suggested the acute necrotic stage of hypereosinophilic endomyocarditis. Steroids therapy provided a dramatical improvement of clinical and echocardiographic findings. However, recurrent inflammation occurred when we reduced the dose of oral predonisolone.

Panels A and B. Echocardiographic images showing spontaneous echo contrast in LV lumen and multiple mobile mural thrombus (arrows).

Panel C. Computerized tomography scan showing a splenic infarction (arrow).

Panel D. High power view of myometrium showing sporadic degeneration of myocytes in association with severe eosinophilic infiltration, fibrosis, and small number of Langhans giant cells (arrow) (haematoxylin and eosin stain, ×400).