

Ventricular Fibrillation in Hypertrophic Cardiomyopathy Is Associated With Increased Fractionation of Paced Right Ventricular Electrograms

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Background. Intraventricular conduction in hypertrophic cardiomyopathy (HCM) has been characterized to test the hypothesis that myofibrillar disarray will cause dispersion of activation throughout the ventricular myocardium.

Methods and Results. Of 37 patients with HCM, four had spontaneous ventricular fibrillation (VF), five had nonsustained ventricular tachycardia (VT), 13 had no risk factors, and 15 had a family history of sudden death. These patients and four controls were studied by pacing one site in the right ventricle and recording electrograms from three other right ventricular sites. These electrograms were high-pass filtered to emphasize small deflections due to activation of small bundles of myocytes close to the electrode. Intraventricular conduction curves were obtained with S_1S_2 coupling intervals decreasing in 1-msec steps from 479 msec to ventricular effective refractory period (VERP). These curves were repeated by pacing each RV site in turn and were characterized by two parameters: the point at which latency increased by 0.75 msec/20 msec reduction of the S_1S_2 coupling interval and an increase in electrogram duration between an S_1S_2 of 350 msec and VERP. Patients with VF, VT, and family history of sudden death had a mean increase in electrogram duration of 12.8 (2.9–32.3) msec versus 4.6 (–4.2 to 14.0) msec in low-risk patients and controls. Electrogram latency increased at an S_1S_2 of 363 msec in the VF group (342–386), 269 msec in the controls (266–279), and 326 msec in the non-VF group (260–399). Discriminant analysis separated VF patients from the remainder ($p < 0.0001$) and VF, VT, and family history of sudden death patients from the low-risk and control groups ($p < 10^{-6}$).

Conclusions. Patients with HCM who are at risk of sudden death have increased dispersion and inhomogeneity of intraventricular conduction, and this may create the conditions for reentry and arrhythmogenesis. (*Circulation* 1992;86:467–474)

KEY WORDS • latency • sudden death • cardiomyopathy, hypertrophic

Hypertrophic cardiomyopathy (HCM) is a common cause of nonaccidental sudden death among persons less than 35 years old,^{1,2} and the identification of patients who are at risk of sudden death and their subsequent management is a major problem. There is evidence that sudden death in HCM involves ventricular arrhythmias. First, a patient who died during ambulatory ECG monitoring developed polymorphic ventricular tachycardia (VT) after a period of nodal rhythm that deteriorated into ventricular fibrillation (VF).³ Second, the presence of nonsustained VT on ambulatory monitoring is a predictor of sudden death in adults,^{4,5} although only about one fourth of

these patients die suddenly within 3 years. Finally, treatment with amiodarone may reduce the likelihood of sudden death in this group of patients.⁶ Despite this suggestive evidence that a ventricular arrhythmia is a component of the mechanism of sudden death in HCM, no specific electrophysiological abnormality has been discovered in patients with the disease.^{7,8} Consequently, evaluation of the risk of sudden death in patients with HCM has been based on induction of polymorphic VT or VF by programmed ventricular stimulation⁹ and detection of nonsustained VT using ambulatory ECG monitoring.^{4,5}

This report describes the development of a test that was designed to detect possible electrophysiological effects of myocardial disarray on intraventricular conduction. The variations in myocyte diameter and length and, hence, cellular volume¹⁰ seen in HCM would be expected, on the basis of cable theory,¹¹ to alter the range of both their conduction velocities and refractory periods. Increased myocyte disarray and interstitial fibrosis may create a number of different potential con-

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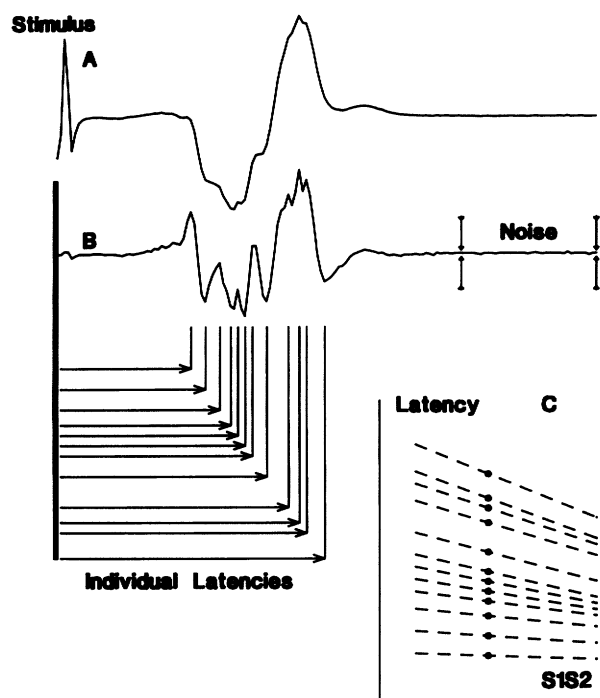


FIGURE 1. Panel A: Diagram showing the method of analysis. The raw electrogram (A) is high-pass filtered to obtain the curve in panel B. The last 50 msec of the curve is used to determine the magnitude of the noise. The last transition in the curve that exceeds this limit is established and taken as the end of the electrogram. All earlier transitions with amplitudes that exceed twice that of the noise are established and the latencies from the stimulus of each transition are extracted. These are plotted as one set of points in a conduction curve (panel C) that relates the latency of all the transitions to extrastimulus coupling interval.

duction paths between a paced and recorded site within the ventricles, and these paths may be recruited or blocked depending on the refractory state of the intervening tissue. If this phenomenon occurs, the dispersion of conduction within the ventricles may form one component of the substrate for reentry and VF.

This idea has led to a test that is based on the analysis of separate components of paced intracardiac electrograms recorded simultaneously at several right ventricular sites that may correspond to activation of individual paths within the myocardium near the recording electrodes. The potential conduction paths between the paced site and the recording electrode may be recruited or blocked by applying pacing stimuli of varying prematurity, and the presence of discrete conduction paths may be inferred by studying the number of components within the evoked ventricular electrograms (Figures 1 and 2).

Methods

Thirty-seven consecutive patients (age, 13–62 years; 22 male) with HCM who were referred to St. George's Hospital for risk stratification or management of out-of-hospital VF were studied. The diagnosis of HCM had been made before the study on the basis of typical clinical, ECG, and echocardiographic features. All patients had left ventricular hypertrophy (LVH) of at least

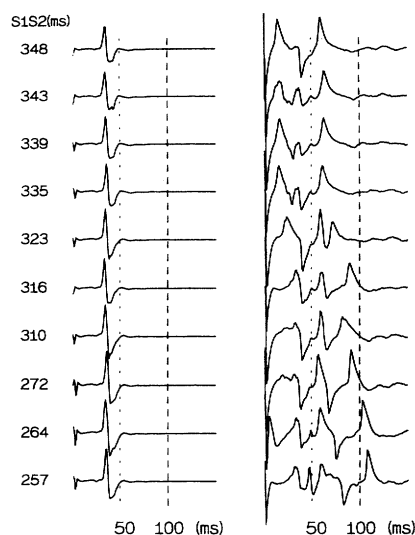


FIGURE 2. Electrograms obtained from the septal channel while pacing the apex. The electrograms in the left-hand column are obtained from a control patient, and those in the right-hand column are obtained from a patient with ventricular fibrillation. Each pair was obtained at the same interstimulus coupling interval during the same protocol. Note the variability of the electrograms in the patient with ventricular fibrillation, which shows a systematic change in the number and latency of the various peaks.

1.5 cm in the absence of systemic disease that could cause LVH. The maximum left ventricular wall thickness was 1.5–3.8 cm (mean, 2.2 cm), and four patients had complete systolic anterior motion of the mitral valve with calculated Doppler left ventricular outflow tract gradient of >30 mm Hg.

Four patients (age, 18–26 years; one male) had suffered a collapse and were found to be in VF when an ECG was recorded either on arrival at the hospital or by paramedical staff during the early phase of their resuscitation. Two of these patients were studied within 14 days of their collapse, one had collapsed 18 months before her study, and the remaining patient collapsed. None had systolic anterior motion of the mitral valve, an outflow tract gradient, or an increased echocardiographic left ventricular mass compared with the remainder of the patients. These patients are assumed to have had a primary out-of-hospital VF arrest. Five patients (age, 31–57 years) had nonsustained VT detected on ambulatory ECG monitoring, 15 (age, 22–58 years) had a family history of sudden death in first-degree relatives, and the remaining 13 had no risk factors. Four control patients (age, 17–54 years) with normal 12-lead ECG and two-dimensional echocardiographic studies who were referred for electrophysiological study in the investigation of syncope or palpitation were studied using the same protocol. Two controls had atrioventricular reentrant tachycardia, and the other two had no electrophysiological abnormality. Informed consent was obtained from all patients, and the experimental protocol was approved by the local (Wandsworth District) ethics committee.

The patients were premedicated with oral lorazepam (0.07 mg/kg) and were sedated as required during the study with intravenous diazepam and diamorphine.

Prochlorperazine (12.5 mg i.v.) was given at the start of the study as an antiemetic. Multielectrode pacing catheters (6F, 1-cm spacing) were introduced via the right femoral vein to the right ventricular apex, His recording position, and the high right atrium to permit a conventional full diagnostic electrophysiological study. At the end of the study, VT stimulation was performed by pacing the right ventricular apex to stage 8 of the protocol described by Wellens et al¹² (pacing cycle length of 420 msec and two extrastimuli). Two additional bipolar catheters were inserted via the right or left femoral vein and were inserted into the right ventricular outflow tract and the right ventricular inferior wall. The His position catheter was advanced so that it lay on the right ventricular septum approximately 2 cm from the apex, and the distal poles were used for recording. Care was taken to place these catheters in a standard position using the standard 1-cm electrode spacing on the catheters to judge their positions relative to each other.

A computer-generated pacing sequence was delivered from one ventricular catheter, and bipolar electrograms were recorded at the other three electrodes. This sequence was repeated by pacing each electrode in turn and recording from the other catheters. The pacing sequence consisted of a 480-msec drive chain with an extrastimulus applied every third beat followed by immediate resumption of the drive chain. The extrastimulus coupling interval was reduced successively by 1 msec on each occasion from 479 msec until the ventricular effective refractory period (VERP) was reached. This sequence allows an intraventricular conduction curve using 1-msec intervals to be built up in a reasonable length of time. The high right atrium was paced synchronously with the ventricular catheter to prevent fusion beats in patients with retrograde block (except in the first two patients, when a 50-msec AV interval was used; both of these patients had AH intervals in excess of 150 msec). Bipolar electrograms were recorded from the nonpaced electrodes over a frequency range of 40–270 Hz (–3 dB) and were digitized at 1 kHz per channel with 12-bit precision. Therefore, in each study, four sets of conduction curves were obtained, each of which contained between 200 and 300 responses to an S₂ stimulus recorded simultaneously from three channels.

During a pacing run, the intracardiac electrograms, with markers showing the position of the pacing spikes, were monitored on the computer display; this allowed the onset of an induced arrhythmia to be detected immediately as the electrogram complexes became dissociated from the pacing spikes.

After the study, the individual electrograms in each run were scrutinized using an interactive computer program. All complexes that showed signs of fusion, were preceded by ectopics, or failed to capture were rejected from the analysis. The remaining electrograms were passed through a high-pass, zero-phase, single-pole digital filter (–3 dB=150 Hz) to accentuate the transitions within the electrogram (Figure 1). The end of the complex was distinguished from noise by assuming that the last 50 msec of a 200-msec poststimulus record was noise alone and calculating the $p = \pm 0.025$ two-tailed limits of its sample distribution. Interpolating polynomials were fitted using the Newton¹³ central difference method to the minima and maxima of the

signal. The earliest point at which both the interpolating polynomials crossed the limits of the noise distribution was taken as the end of the electrogram. All transitions within the electrograms that exceeded twice the amplitude of the noise before this point were treated as representing an activation process within the receptive field of the electrode. Conduction curves of the latency of the individual components of the electrograms for each channel of each run were constructed as a function of interstimulus coupling interval.

Each conduction curve was characterized with an automated method by determining two parameters: the S₁S₂ interval at which latency started to increase and the increase in width of the electrogram between an S₁S₂ of 350 msec and at VERP. The conduction curves were characterized by fitting a cubic spline¹⁴ to the latencies of the first and last components of the electrogram as a function of S₁S₂ interval. The S₁S₂ interval at which the rate of increase of the latency of the last component of the electrogram exceeded 0.75 msec/20 msec were determined from the spline as were the electrogram widths at 350 msec and at VERP. The average latency point and increase in electrogram width were obtained from all channels and pacing sequences in each patient. These data were subjected to linear discriminant analysis¹⁵ to distinguish patients with VF from the remaining patients and the VF, VT, and family history of sudden death patients from the low-risk group and controls.

Results

Two sets of electrograms obtained from the right ventricular apex while the inferior wall was paced are shown in Figure 2. The left-hand set was obtained from a control patient, and the right-hand set was obtained from a patient with VF. The electrograms in each pair were recorded in response to the same stimulus coupling interval during the pacing protocol. This figure illustrates the idea that underlies the test. The electrograms from the patient with VF show that with increasing stimulus prematurity, there is increasing fragmentation in the electrogram with blocking and generation of separate peaks, whereas the control patient does not show this effect. It is also apparent that there are two components to the fragmentation. First, the actual form of the electrogram changes as different peaks appear or are blocked; second, there is an increase in its width with variation in latency of its individual peaks. A conduction curve for the control patient in Figure 2 is shown in Figure 3, and conduction curves from patients who had spontaneous VF are demonstrated in Figures 4 and 5. Curves from patients with VF show several common features. First, there is increasing width of the electrogram with stimulus prematurity. Second, the lines representing the various components in the electrogram change abruptly as different peaks and troughs appear. All of the VF patients showed this effect, which invariably was present when pacing the right ventricular apex. Two had these changes in all curves, one had changes in all curves except during pacing from the right ventricular outflow tract, and one showed the effect in eight of 12 curves. By contrast, Figure 6, taken from an HCM patient without risk factors, shows an increase in electrogram width and increase in latency at a relatively short coupling interval (<262 msec). Figure 7 shows an example of slight facilitation of conduction followed by

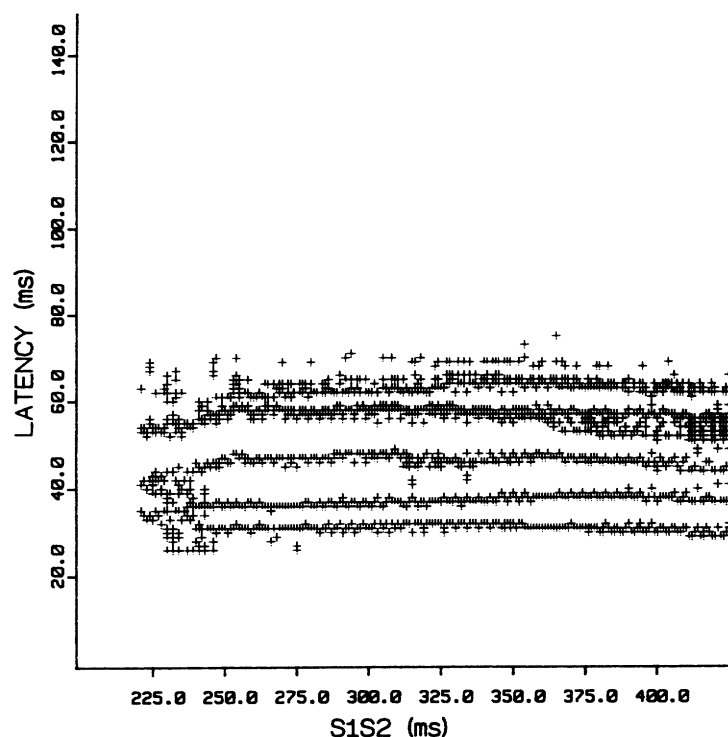


FIGURE 3. Conduction curve from the control shown in Figure 2. The apex was paced, and recordings were made from the septum. (Contrast this with Figures 4 and 5.) It should be noted that this curve is the best example of short duration, nonfractionated electrograms among the control patients.

increasing latency of the response with no increase in the width of the electrogram. Twenty-six patients with HCM and two of four of the controls showed this pattern.

Figure 8 shows a scatter diagram of the change in electrogram width as a function of the S_1S_2 interval at which latency starts to increase. The risk category of each patient is shown, and it is clear that patients with

VF cluster in a group with a marked increase in electrogram width and early increase in latency, whereas the controls and low-risk patients cluster in a group with a late increase in latency and a small increase in electrogram width. Patients with nonsustained VT and family history of sudden death form an intermediate group. Two linear discriminant lines are shown. Line A discriminates between patients with VT

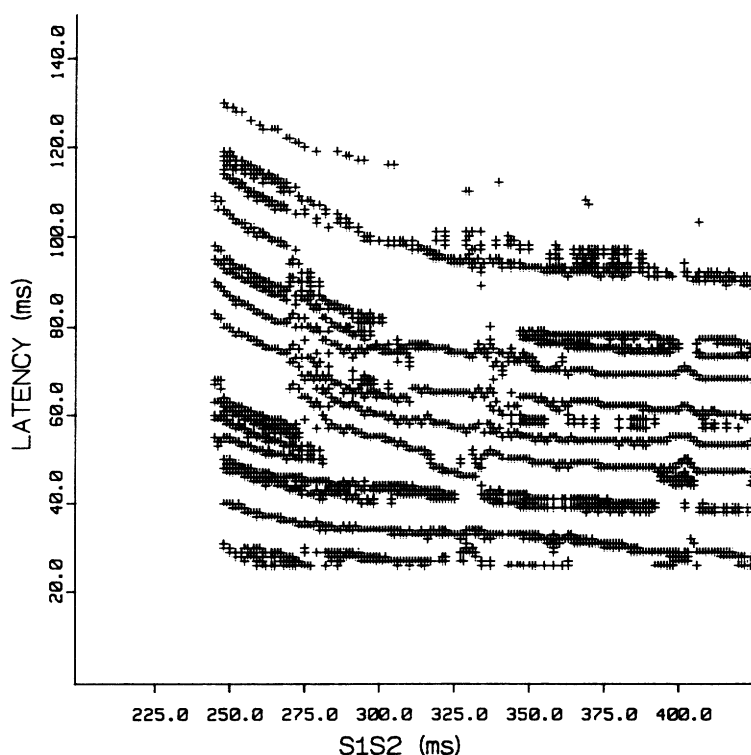


FIGURE 4. Conduction curve from a patient with ventricular fibrillation taken from the inferior right ventricular wall while pacing the septum. Note the changes in number of transitions, increase in electrogram width, and early increase in latency.

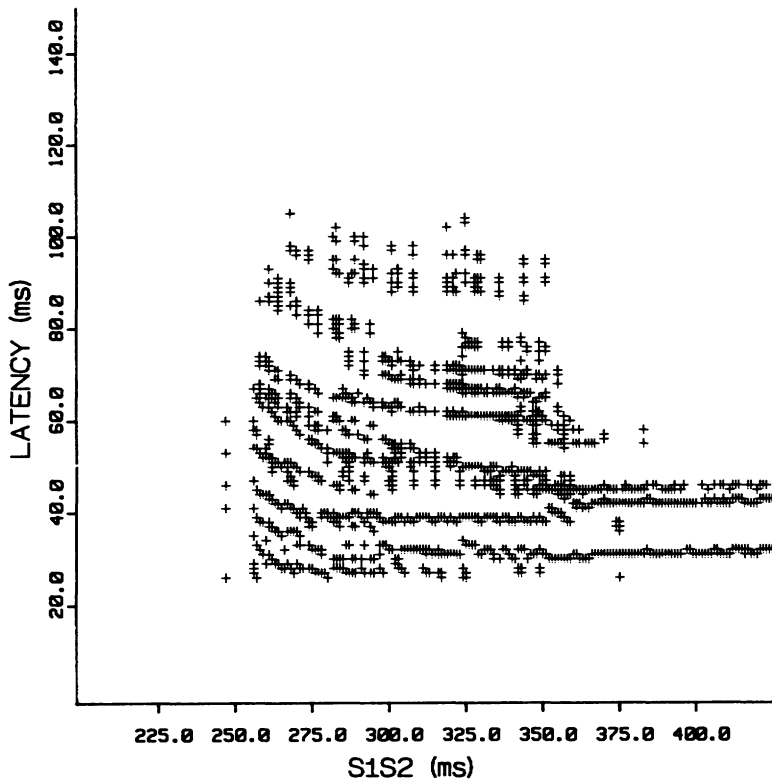


FIGURE 5. Conduction curve from another patient with ventricular fibrillation. The inferior wall is paced, and the recording is from the apex. Note the sudden recruitment of components at an S_1S_2 of 348 msec and the increased width at ventricular effective refractory period.

and the remainder ($p < 0.0001$, Fisher's exact test), and line B discriminates between patients with VF, VT, and family history of sudden death and low-risk patients and controls ($p < 10^{-6}$, Fisher's exact test).

Two patients developed VF during the pacing protocol—one was the patient with family history of sudden

death who clustered in the VF group, and the other had VT on ambulatory monitoring. This occurred at S_1S_2 intervals of 243 and 265 msec. In these patients, there was electrogram widening and fractionation in response to the extrastimulus that preceded initiation of polymorphic VT that degenerated into VF as shown in Figure 9.

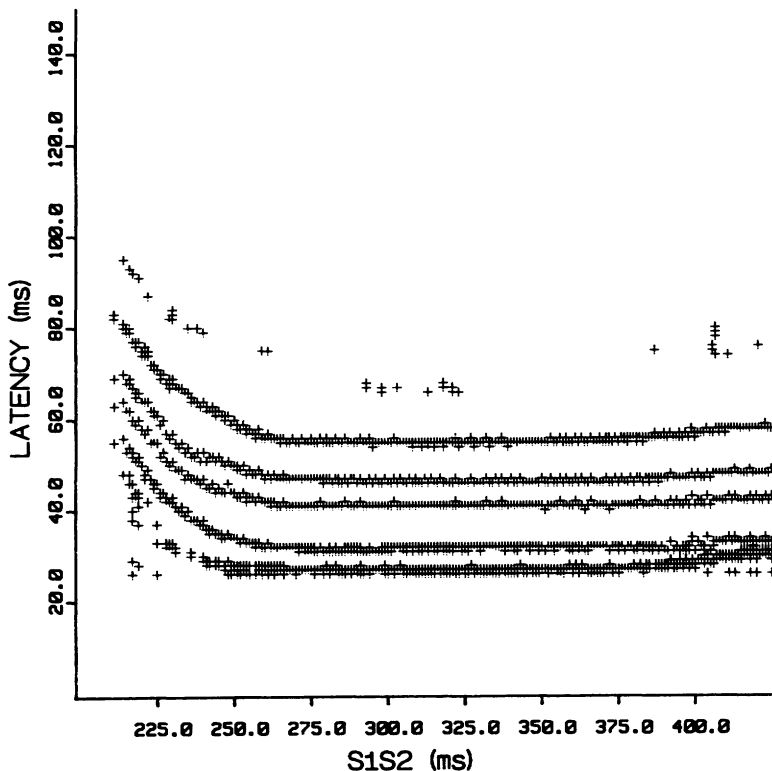


FIGURE 6. Conduction curve (paced septum, recording from apex) from a patient with no ventricular tachycardia on ambulatory monitoring or family history of sudden death. There is a 40-msec increase in electrogram width at ventricular effective refractory period, but the increase in latency does not occur until the S_1S_2 decreases to < 258 msec.

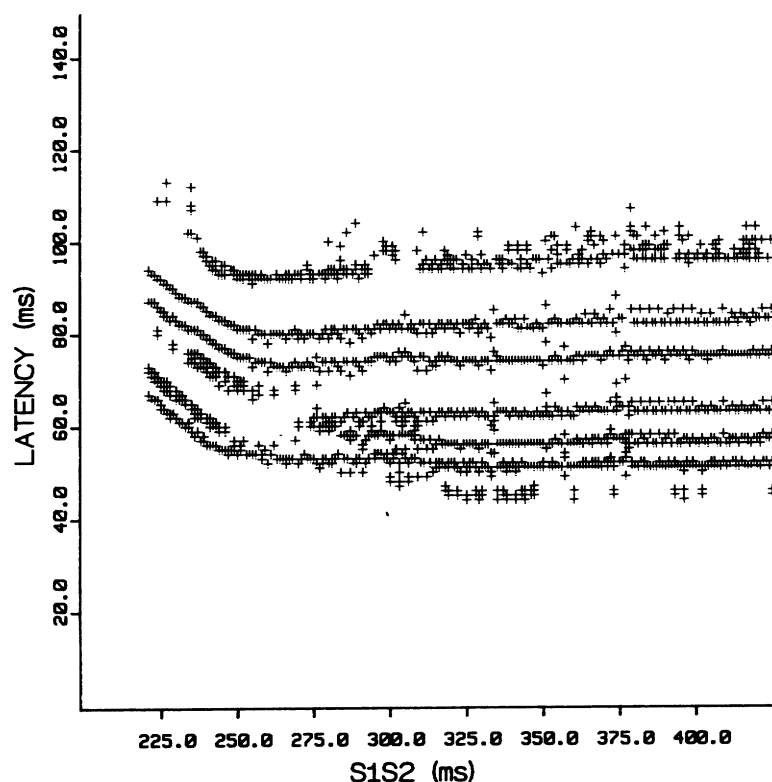


FIGURE 7. Conduction curve from another low-risk patient. There is a slight reduction in electrogram width until the latency increases at an S_1S_2 interval of 260 msec. The electrogram does not increase in width at ventricular effective refractory period. This is a very common pattern.

There was no relation between the presence of VF and QRS duration, electrogram duration, or number of transitions either in sinus rhythm or paced at the basic cycle length, pacing thresholds, or the presence of late potentials. There was no relation between refractory periods at different pacing sites or among different

groups of patients. Twenty-eight patients had retrograde block, and the range of the AH intervals during atrial pacing at 480 msec was 75–230 msec. No patients had accessory pathways. One patient with VF had a “jump” of 220 msec in her antegrade conduction curve, but atrioventricular nodal reentry tachycardia could not

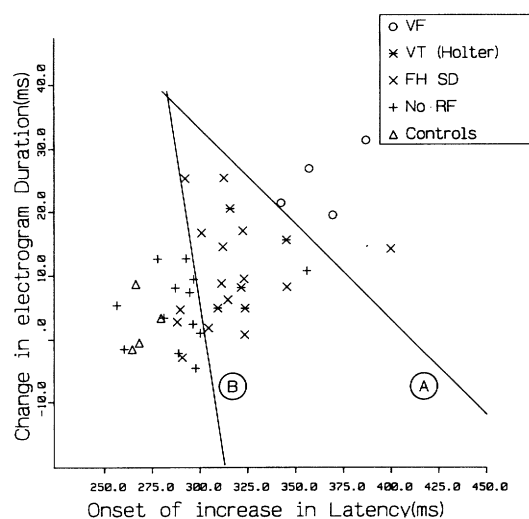


FIGURE 8. Scatterplot of change in electrogram duration against S_1S_2 at which latency starts to increase. Each point is the mean of all the observations in a particular patient. The discriminant line A separates the ventricular fibrillation (VF) patients from the remainder ($p < 0.0001$), and the line B separates the VF, ventricular tachycardia (VT) on Holter monitoring, and family history of sudden death (FH SD) patients from the low-risk patients (no RF [risk factors]) and controls ($p < 10^{-6}$).



FIGURE 9. Electrograms obtained from a patient with family history of sudden death showing induction of polymorphic ventricular tachycardia that degenerated rapidly into ventricular fibrillation at an S_1S_2 coupling interval of 243 msec (apex paced, septum, inferior wall, and right ventricular outflow tract in upper, middle, and lower traces, respectively). The record length is 1 second, and the time scale interval is 50 msec. Note the increased width and fraction of the electrograms after the extrastimulus (arrowhead), which resemble the first beat of ventricular tachycardia (open arrow). Also note the relative timings of the septum and right ventricular outflow tract change compared with those of the inferior wall.

be induced. VT stimulation produced nonsustained (>10 beats) polymorphic VT in one patient with non-sustained VT on ambulatory monitoring, two patients with family history of sudden death, one patient with no risk factors, and one control patient.

Discussion

This study's purpose was to test the hypothesis that patients with HCM would show abnormalities of intra-ventricular conduction that may be the consequence of disarray. Patients with VF, VT, or family history of sudden death show evidence of recruitment of multiple conduction pathways and dispersion of activation at a single site in the ventricle as well as between different ventricular sites. There is a continuous distribution of electrophysiological abnormality, and the magnitude of the disturbance appears to correlate with risk of sudden death. The delays in activating the relatively large amounts of tissue that were studied suggest that there may be diseased regions contained within the myocardium that could act as one of the necessary components of a substrate for reentry. Although no electrograms were recorded from the left ventricle, three electrodes—the apical, septal, and right ventricular outflow tract—recorded activity from the septum that in a pathological study has been shown to have more disorganization in patients with HCM who had died suddenly than in patients who had died of other causes.¹⁶ All of the patients with VF in our study showed the most pronounced fractionation when pacing the apex or the septum, which is compatible with these postmortem observations. However, because HCM does not affect the ventricles uniformly, it is likely that there are areas of diseased myocardium that could act as a substrate but do not lie between the pacing and recording catheters. Also, although the right ventricle is known to show disarray, the quantitative relation between left and right ventricular involvement is unknown. This issue needs investigation through the use of more recording electrodes within the left and right ventricles and pacing from more sites, including the left ventricle, to determine an optimum electrode arrangement.

The statistical analysis of these data presents a number of problems. First, the changes in latency onset and electrogram width were analyzed because they are simple and striking. The means of all the observations in each patient have been used in the analysis because they are independent variables, unlike the observations taken from the individual curves within the same patient. The separation of patients with VF is highly significant even using small numbers of patients, which makes this investigation a potentially useful method for detecting patients at risk of sudden death. A physiological interpretation of this result is that patients with VF have ventricles that have more generalized disease than the remainder and therefore are more likely to contain a substrate for VF within their myocardium. However, because the substrate of VF is unknown, it is equally possible that only one curve in a particular patient may be derived from diseased tissue that contains a potential substrate, and by taking the mean of all of the data from the curves, its presence would be masked. Also, because this study is not prospective, the temporal evolution of conduction disturbance and its relation to the risk of sudden death are unknown. The fact that two VF

patients still showed major conduction disturbances 18 months and 5 years, respectively, after their arrest suggests that the conduction disturbance has been stable with time. These issues can be resolved only by a prospective trial of the technique.

Another statistical issue is distinction between a peak in the electrogram and noise, and this is important when attempting to resolve small deflections by comparing their amplitudes with the amplitude of the noise. A 50-msec period starting 150 msec after the stimulus has been assumed to be noise and to be representative of the noise in the signal. No consistent relations between the noise period and the stimulus could be demonstrated by averaging or by correlation between successive records; therefore, we believe that this approach is justified. Finally, when extracting parameters from the conduction curves, the envelope of the curve was approximated using cubic splines, and the parameters were extracted from the interpolating functions rather than from the data points themselves. The interpolating functions conform to the general shape of the conduction curves, so parameters estimated in this way are relatively insensitive to small short-term transients in the original curves.

In addition to discontinuities, there is decremental intraventricular conduction as the latency of activation of different sites changes smoothly at different rates. Because the drive cycle electrograms remain unaltered during the runs in these patients, it is unlikely that these discontinuities or differential conduction velocities are due to a catheter slipping. Also, there is dispersion of conduction times at VERP in excess of 20 msec between sites in two controls and six HCM patients at S₁S₂ intervals below 230 msec. However, it is not clear what causes this smooth change in latency. One possibility is that myofibrils that form the conduction paths between paced and recorded sites have conduction velocities that are dependent on the degree of stimulus prematurity. A second possibility is the change in anisotropic conduction velocity with premature stimulation.^{17,18} Finally, the change in conduction velocity could be due to gradual blocking of the faster conducting fibers in a distribution of myofibrils with a range of conduction velocities.

An important issue in this analysis is the physiological interpretation of the measured electrograms. Despite the widespread measurement of intracardiac electrograms, their biophysical and mathematical interpretations have attracted remarkably little attention. Because bipolar electrograms were measured and the signals were high-pass filtered, small fractionated features of the electrogram are emphasized and assumed to represent activation of fibers close to the electrode. However, bipolar electrodes are directional, and this may bias the detection of different activation processes. Future research will use unipolar recordings; however, to obtain adequate signal-to-noise ratios to permit this type of analysis, very low noise amplifiers and a 16-bit analog-to-digital converter will have to be used. Furthermore, only the latencies of the various components have been analyzed, and their amplitudes and gradients have been ignored. At present, there is insufficient theory to interpret electrograms in terms of local conduction velocity, conduction direction, volumes of tissue responsible for discrete deflections, and distance from the

electrode of individual fibers. The observations in this study, which show that there are apparently diagnostic differences in the components of electrograms, give an impetus to develop methods of measuring and analyzing electrograms in terms of the physiological processes that generate them.

There were no differences between any patient group in QRS duration, electrogram duration, or morphology during SR or basic rate pacing and signal-averaged ECG. These observations are consistent with the hypothesis that the electrophysiological effects of disarray will be exposed only by altering the distribution of fiber refractoriness and conduction velocity with premature stimuli. This principle may be applicable to other diffuse ventricular diseases, and it is not known if the observations made in this study are specific to HCM or will be seen in other conditions. Because hypertensive left ventricular hypertrophy may show interstitial fibrosis and variations in fiber caliber¹⁹ and is an independent risk factor for sudden death,²⁰ the method may be applicable to this large and important group of patients.

Is there a relation between measurement of abnormal conduction and response to programmed ventricular stimulation? Wellens et al¹² have shown that aggressive programmed ventricular stimulation will induce nonsustained polymorphic VT in 40% of people with normal hearts. Due to the danger of irreversible hemodynamic collapse in HCM, induced polymorphic VT must be defibrillated immediately; therefore, it cannot be established whether it was sustained. The data in Figure 9 show the development of polymorphic VT that degenerated into VF. The electrograms show both widening and fractionation. This behavior is seen in a number of patients with HCM, although they did not develop VF. One control patient also shows electrogram widening and dispersion of 35 msec between channels while pacing the apex, but this occurred at a shorter S₁S₂ interval. Furthermore, this patient developed nonsustained polymorphic VT at stage 8 of the Wellens et al protocol. This suggests that VF and the electrophysiological features of the VF patients may be reproduced in other patients with aggressive stimulation and reflects the small amount of dispersion and fractionation seen in most patients with short extrastimulus coupling intervals. Therefore, it is difficult to establish the level of programmed stimulation that unmasks the pathological substrate of VF in patients with HCM rather than creating a general response that is of no clinical significance. The potential of the test described in this study is that it may reveal the presence of a substrate of VF in a more specific way than programmed stimulation.

This study has demonstrated abnormalities in intraventricular conduction in patients with VF that may act as one part of a substrate for tachycardia initiation. However, the second part of the substrate, changes in refractoriness⁸ and unidirectional block, have not been considered. Characterization of local refractoriness in conjunction with the measurements of conduction delays described in this article will lead to a greater understanding of the mechanisms of sudden death in patients with HCM.

Addendum

During the follow-up period, ranging from 2 months to 2 years, one patient had failed sudden death 8 months after her study. This patient has a malignant family history, and her intraventricular conduction pattern clustered with those of the VF patients (i.e., to the right of line A in Figure 8). During ambulatory monitoring she developed a 100-second run of monomorphic VT, which progressed to polymorphic VT, VF, and finally asystole. She regained sinus rhythm spontaneously with external cardiac massage and ventilation.

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