

Sudden Death in Noncoronary Heart Disease Is Associated With Delayed Paced Ventricular Activation

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Background—Slowed or delayed myocardial activation and dispersed refractoriness predispose to reentrant excitation that may lead to ventricular fibrillation (VF). Increased ventricular electrogram duration (Δ ED) in response to extrastimuli and increased S1S2 coupling intervals at which electrogram duration starts to increase ($S1S2_{\text{delay}}$) are seen both in hypertrophic cardiomyopathy (HCM) in those at risk of VF and in patients with idiopathic VF (IVF).

Methods and Results— Δ ED and $S1S2_{\text{delay}}$ have been measured using paced electrogram fractionation analysis in 266 patients with noncoronary heart disease. Of these, one group of 61 patients had a history of VF and included 21 HCM, 17 IVF, 13 long-QT syndrome (LQTS), 5 dilated cardiomyopathy (DCM), and 5 others. These were compared with 205 patients with similar diseases with no VF history (non-VF group) and a control group ($n=12$) without heart disease. Results from HCM VF patients (Δ ED, 19 ± 3.3 ms; $S1S2_{\text{delay}}$, 350 ± 9.7 ms) differed sharply from observations in HCM non-VF patients (Δ ED, 7.3 ± 1.35 ms; $S1S2_{\text{delay}}$, 312 ± 6.7 ms; $P<0.001$). DCM VF patients had longer delays (Δ ED, 14.3 ± 5.9 ; $S1S2_{\text{delay}}$, 344 ± 11.2) than DCM non-VF patients (Δ ED, 5.8 ± 1.87 ms; $S1S2_{\text{delay}}$, 311 ± 5.7 ms; $P<0.001$), with major differences also seen comparing LQTS VF (Δ ED, 12.4 ± 5.3 ms; $S1S2_{\text{delay}}$, 343 ± 13.8 ms) and LQTS non-VF patients (Δ ED, 11.0 ± 2.7 ms; $S1S2_{\text{delay}}$, 320 ± 5.4 ms; $P<0.001$). IVF patients had both severely abnormal and normal areas of myocardium.

Conclusions—Slowed or delayed myocardial activation is a common feature in patients with noncoronary heart disease with a history of VF, and its assessment may allow the prospective prediction of VF risk in these patients. (*Circulation*. 2003;107:2595-2600.)

Key Words: death, sudden ■ electrophysiology ■ cardiomyopathy ■ long-QT syndrome

Noncoronary heart disease altering myocardial structure or function predisposes to ventricular fibrillation (VF) and sudden cardiac death (SCD).¹⁻³ SCD can be prevented by prophylactic implantable cardioverter-defibrillators (ICDs),⁴ and consequently the identification of patients at high risk of SCD is an important goal of clinical cardiology.^{5,6} Methods for the precise identification of patients at risk of SCD, which might provide a basis for electrophysiological indicators of risk, do not yet exist,^{1,2} a situation that partly arises from our poor understanding of the mechanisms that predispose to VF.⁷

The initiation of reentrant tachyarrhythmias, such as macroreentrant ventricular tachycardia in patients with coronary artery disease, is known to require one or more areas of slowed conduction and activation block.^{8,9} Such anatomical substrates can be demonstrated by following the activation sequence during sustained tachycardia or deduced by observ-

ing the pattern of responses to the delivery of extrastimuli.⁸⁻¹⁰ VF is also thought to be a reentrant tachyarrhythmia⁷; however, it has no specific anatomical basis and so investigations directed to the identification of a functional substrate and the prediction of the risk of VF are likely to require a different electrophysiological approach. The detailed activation mapping of isolated myocardium showed that slowed conduction with activation block results in delayed local electrograms that contain multiple potential deflections corresponding to the individual pathways of myocardial activation.^{11,12} These findings provided the impetus for the development of paced electrogram fractionation analysis (PEFA).¹³⁻¹⁵ The technique was initially introduced to detect the risk of SCD in HCM in which myocyte disarray and fibrosis were suggested to lead to multiple tortuous conduction paths through the myocardium.¹⁶ Results from 101

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patients with HCM¹⁴ demonstrated electrogram fractionation in patients with documented VF or resuscitated SCD consistent with the presence of slowed conduction in patients at risk and thereby suggested a new criterion for discriminating high-risk patients.

This study describes the application of PEFA in comparing a series of patients with different noncoronary heart diseases who have either survived VF or subsequently developed VF with similar patients with no such history and with controls with no demonstrable cardiac abnormality. The results provide powerful evidence that delayed myocardial activation as detected by PEFA is a common feature predisposing to VF in these conditions.

Methods

The protocol was reviewed and accepted by local research ethics committees in participating centers, with all patients giving informed written consent. The clinical technique of PEFA was applied as previously described,^{13–15} with minor modifications in signal processing, as described.¹⁷ In brief, in patients not taking any antiarrhythmic drugs, 4 electrode catheters were positioned at different sites in the right ventricle, and a pacing sequence was applied in turn via each catheter with electrograms recorded at the remaining sites. The sequence consisted of a drive train of pacing stimuli (S1) applied with a 490-ms cycle length with an extrastimulus (S2) inserted every third beat. The coupling interval (S1S2) was successively reduced by 1 ms with each cycle from 450 to either 220 ms or to the ventricular effective refractory period (VERP). The electrograms were used to determine the maximum increase in electrogram duration (Δ ED) after an extrastimulus and the S1S2 interval (S1S2_{delay}) below which the electrogram duration increased.^{14,15,17} The 12 sets of paired measurements (4 pacing runs with 3 recording channels per run) were averaged for each patient and represented as a single, statistically independent point on a plot of Δ ED against S1S2_{delay}.^{15,17}

Statistical Analysis

Line A in Figure 1 is a discriminant line constructed as a hypothesis to separate HCM VF and HCM non-VF patients and is derived from the initial studies^{13,14} revised slightly in the light of modifications in signal processing.¹⁷ The probability of the discriminant line A separating VF and non-VF HCM, LQTS, and DCM patients was calculated using Fisher's exact test. To test the hypothesis that there was a range of abnormalities in patients with IVF, the data from a patient was represented by 2 sets of paired measurements from the 12 collected during a study, the most abnormal with the maximum Δ ED and the greatest S1S2_{delay} and the least abnormal with the minimum changes in Δ ED and S1S2_{delay}. A second discriminant line C (shown in Figures 2A, 2B, and 3) was constructed between the least abnormal results of the initial 9 HCM and 9 IVF patients by linear search (Figure 2A). This hypothesis was tested with subsequent HCM and IVF data for the patient data set shown in Figure 2B using Fisher's exact test.

Results

Experimental Groups

The 266 patients with noncoronary heart disease studied using PEFA fell into the following groups: 61 patients had a range of different pathologies but all had a history of VF. Of these, 21 had HCM, 17 had IVF, 13 had LQTS, 5 had DCM, 1 had idiopathic left ventricular tachycardia that degenerated to VF, 2 had Brugada syndrome, and 2 had arrhythmogenic right ventricular dysplasia (ARVD). Of the 205 without VF used as a comparison group, 126 had HCM, 28 had DCM, 22 had LQTS, 3 had normal heart VT, 3 had mitral valve prolapse, 4 had Brugada syndrome, 2 had ARVD, and the

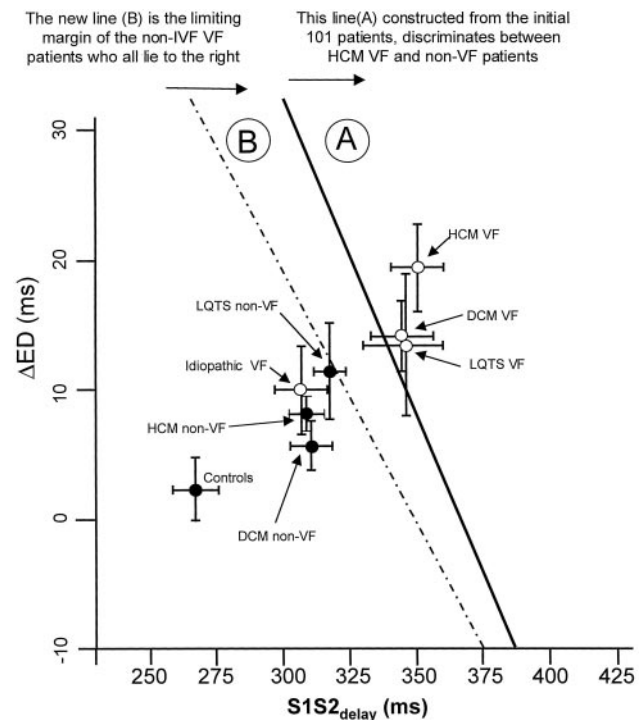


Figure 1. Plots of Δ ED versus S1S2_{delay}. Mean \pm 2 SEM for HCM VF, LQTS VF, and DCM VF and non-VF patients with these conditions. The patients with IVF cluster with the group of non-VF patients with the other conditions. Control patients have the least disturbance. Line A separates the HCM VF and non-VF patients and was constructed from an earlier study.¹⁴ All VF patients lie to the right of line B, which has been constructed as the limiting margin of the non-IVF VF patients.

remainder were investigated for palpitations or a family history of sudden death in the absence of structural heart disease. Finally, 12 individuals, without any evidence of heart disease, were studied using PEFA at the end of a standard diagnostic electrophysiological study.

Figure 1 plots Δ ED against S1S2_{delay} (mean \pm 2 SEM) for all VF and non-VF patients. The means of the HCM VF, LQTS VF, and DCM VF patients are distinct from all patients without VF. By contrast, the IVF patients are similar to the HCM non-VF, LQTS non-VF, and DCM non-VF patients. The discriminant line A was constructed on the basis of the initial 101 HCM patients¹⁴ to discriminate between VF and non-VF patients. The number of HCM VF, LQTS VF, and DCM VF and non-VF patients falling on either side of this line is given in the Table. Line B is constructed so that all HCM, DCM, and LQTS VF patients lie to its right while minimizing the number of non-VF to its right.

Figures 2A and 2B show HCM VF and IVF patients each now represented as a pair of observations. The most abnormal observation is defined as the 1 of the 12 sets of paired measurements obtained during the study from an individual patient that is furthest from the mean value of the 12 normal controls, whereas the least abnormal is that which is closest. The HCM VF and IVF patients are split into 2 groups; those previously published in the initial studies^{14,15} are shown in Figure 2A, which form the hypothesis that there are normal areas in IVF but not in HCM VF, and the results from

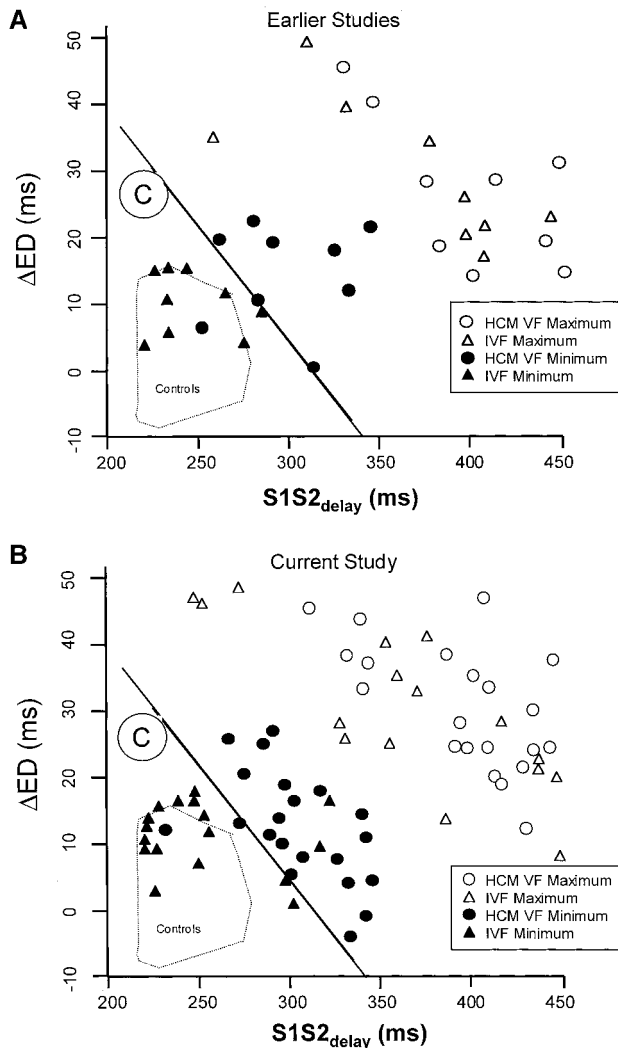


Figure 2. A, Scattergram of most normal and most abnormal values of ΔED and $S1S2_{delay}$ derived from data obtained from patients included in earlier studies.^{14,15} The values have been reanalyzed and are represented by 2 points each for IVF¹⁵ and HCM VF.¹⁴ These patients form the hypothesis that the most and the least severely affected regions of the ventricular myocardium in HCM VF and IVF patients are distinct. Line C is calculated from the patients in the previously published report of HCM VF patients.¹⁴ B, Similar scattergram of data used to test prospectively the hypothesis suggested by panel A. The study group consists of HCM VF ($n=21$) and IVF ($n=17$). Note that the most abnormal results in HCM VF and IVF are indistinguishable, whereas the IVF patients, unlike HCM VF patients, have normal results at 1 or more sites in 15 of 17 patients.

subsequent patients who were used to test this hypothesis are plotted in Figure 2B. In Figure 2A, line C separates the least abnormal measurements of the initial set of 9 IVF and 9 HCM VF patients. The second group shown in Figure 2B consists of the newly reported HCM VF ($n=21$) and IVF ($n=17$) patients and was used to test, prospectively, this hypothesis. There are 2 HCM VF patients to the left of line C with 2 IVF patients to its right ($P<0.001$, Fisher's exact test). Thus, HCM VF and IVF patients are distinct in that, whereas HCM tends to demonstrate anatomically diffuse electrophysiological abnormalities, the IVF patients have some normal regions of myocardium.

Figure 3 shows the results for LQTS VF, DCM VF, ARVD VF, and Brugada VF patients and demonstrates that these patients also have virtually normal areas of myocardium. Nevertheless, all patients no matter what the underlying disease have abnormal regions that are similar to HCM, and, on the basis of this regional electrophysiological analysis, the 4 diseases are indistinguishable. Finally, Figure 4 shows the relative frequency of abnormal sites for VF patients in each disease. Patients with HCM are the most likely to have involvement of all 4 sites (seen in 66%), whereas IVF patients are most likely to have only 1 abnormal site (seen in 58%). Finally, the patients with a family history of SCD without structural disease had a range of results that spanned the range from IVF patients to that seen in controls.

Discussion

This study describes the results obtained at invasive electrophysiological study applying PEFA to cardiac patients with manifest VF and compares their results with those obtained from patients with similar diseases but without such a history. Healthy individuals without demonstrable cardiac disease were used as additional controls. Preliminary evidence¹³ suggested that PEFA may be applicable to the detection of SCD risk in the presence of the anatomically defined substrate of HCM. In such a situation, myocyte disarray,¹⁶ altered action potentials, and dispersed refractoriness could create tortuous activation pathways and intermittent conduction block¹⁷ and suggested a direct mechanism for the observed changes in electrogram dispersion and duration that emerged as a potentially useful prognostic indicator for VF.^{14,17,18} The findings presented here generalize these characteristics of a functional substrate for the initiation of VF to a broader range of diseases and suggest that risk in these conditions is also potentially detectable by a readily applicable clinical technique. The findings are consistent with a common electrophysiological mechanism involving delayed myocardial activation that renders the heart vulnerable to arrhythmogenic triggers.^{9,19–21} The electrophysiological abnormalities detected in DCM presumably have a common basis to those observed in HCM^{13,14} with areas of fibrosis and altered cellular electrophysiology producing activation delay.^{9,22,23}

The mechanisms of the functional activation delay in IVF and LQTS patients are likely to be different from those seen in structurally abnormal hearts and are reflected in the patterns of myocardial conduction. Most strikingly, the averaged delays for the whole myocardium in IVF are less severe than those seen in other diseases and form a distinct group with a different mean to the HCM VF, DCM VF, and LQTS VF patients. This could not be explained in our earlier studies¹⁵ in which we suggested that there was either an implicit assumption in the analysis, which biased the results for IVF, or that the substrate for IVF was only partially revealed by PEFA, because it fundamentally differed from that of HCM.¹⁴ Here we provide clear evidence of anatomical variation of disease in the ventricular myocardium in patients with IVF and other noncoronary heart disease in which some regions are minimally affected or normal. The sites of these normal and abnormal regions were not consistent between patients, and the results cannot therefore be easily explained

Discrimination of DCM VF From DCM Non-VF and LQTS VF From LQTS Non-VF Patients Using Initial HCM Data Set

	HCM		DCM		LQTS	
	Right of Line A	Left of Line A	Right of Line A	Left of Line A	Right of Line A	Left of Line A
VF	17	4	3	2	10	3
Non-VF	30	80	1	27	4	17
<i>P</i> value	<0.0001		<0.005		<0.001	

Numbers of HCM, DCM, and LQTS patients falling to either side of the discriminant line A shown in Figure 1 constructed from the initial 101 HCM patients.¹⁴ The discriminant line separates the VF and non-VF patients not only for HCM but also for DCM and LQTS, suggesting common myocardial phenotypes associated with VF regardless of disease etiology. The *P* value of the discriminant line A separating VF and non-VF HCM, LQTS, and DCM patients was calculated using Fisher's exact test.

purely on anatomical grounds and presumably reflect the underlying heterogeneity of the genetically determined electrophysiological substrate in these conditions.^{24,25} Accordingly, the large number of normal areas in IVF bias the mean results in Figure 1 so that they appear, on the basis of an averaged measurement, to have a less severe disturbance than patients with HCM, confirming the hypothesis that PEFA biases the results in IVF patients.¹⁵ Interestingly, in LQTS, there are abrupt increases in the number of the potentials in the electrogram at a particular S1S2 interval that are coincident with the onset of activation delay¹⁷ and may be the result of heterogeneous channel distribution,²⁶ with regions of myocardium having a differential predisposition to activation delay and local block.²⁰ The advancing activation wavefront could then spread transversely around the refractory region, creating 2 delayed activation fronts, which are detected as delayed potentials in the electrogram.

Risk stratification in HCM, as well as in DCM and LQTS, is difficult, because, although there are markers that are associated with SCD, most techniques have low positive predictive accuracy (PPA) with wide confidence limits.^{2,27}

Invasive risk stratification in HCM using programmed electrical stimulation (PES) has in general been disappointing.^{14,18,27,28} HCM patients in whom VF is induced are, as a group, more likely to suffer SCD than PES-negative patients^{14,28}; however, there are many patients in whom VF is induced by PES who do not die suddenly, lowering the PPA of PES to ≈ 0.1 .^{14,28} Similar problems have been encountered in the examination of patients with LQTS²⁹ and DCM.^{30,31} The potential of PEFA for risk stratification is not only determined by different population means in the VF and non-VF patients (Figure 1) but also the overlap of VF and non-VF distributions that determine the sensitivity and specificity and hence the PPA of these observations.

In this series, 10 of the HCM VF patients were included for prospective evaluation, and, of these, 4 have had appropriate ICD discharges, 1 died on the ICD implantation waiting list, and the remainder either died suddenly some time after their initial electrophysiological study or were resuscitated from VF. Line A (Figure 1) was constructed on the basis of the initial studies^{13,14} but now identifies 83% of the current HCM VF population and excludes 67% of the non-VF patients. This

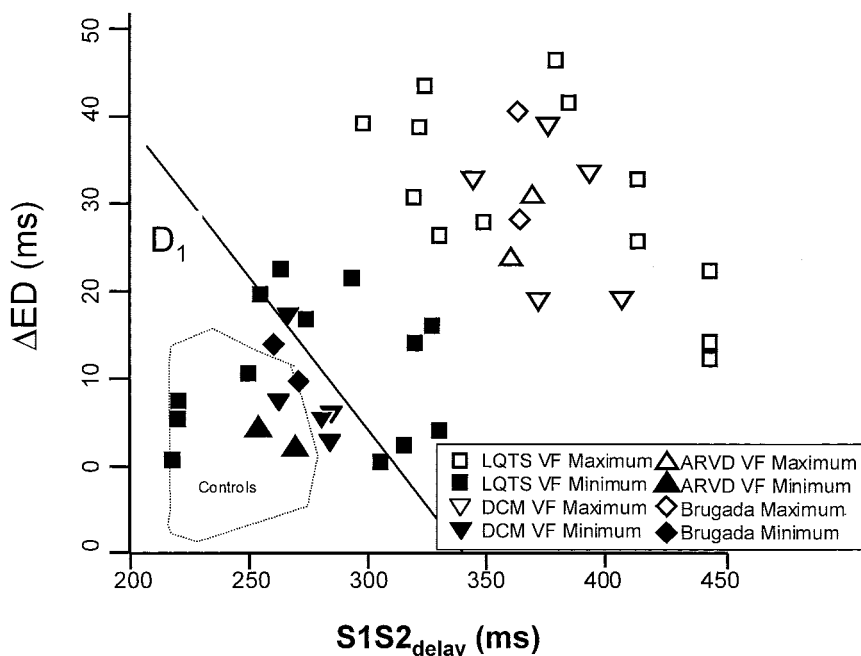


Figure 3. Scattergram of the most normal and most abnormal values of ΔED and $S1S2_{delay}$ represented by 2 points for LQTS VF, DCM VF, ARVD VF, and Brugada VF patients. Again, there is a wide spread of results, although the most abnormal superimpose the most abnormal from the HCM VF and IVF groups (see Figure 2B).

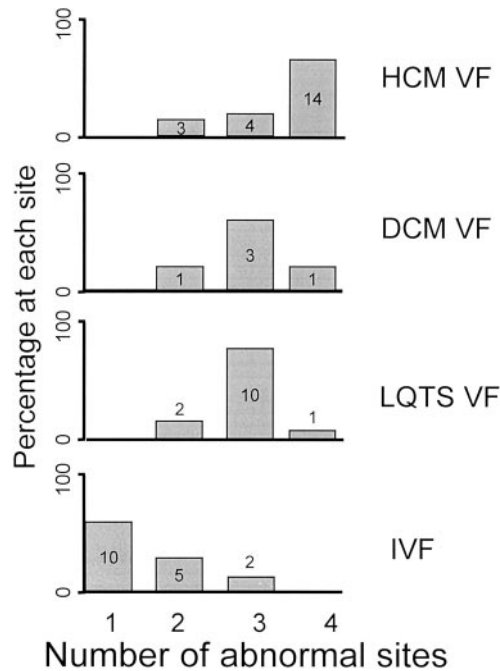


Figure 4. Number of abnormal sites in patients with HCM VF, LQTS VF, DCM VF, and IVF. Abnormal is defined as lying to the right of the line C shown in Figures 2B and 3. There is a diffuse electrophysiological abnormality in HCM VF, variable number of affected sites in DCM, and LQTS and relatively localized abnormalities in IVF. The numbers in each column represent the number of patients.

provides a PPA for VF of 0.36 with a lower confidence limit at 0.22, although we recognize that the definition of the lower limits of the PPA requires more patients. Accordingly, a prospective multicenter evaluation of 200 HCM patients is being conducted with the end point being when the lower limit of the observed PPA reaches a value consistent with a true PPA of greater than 0.3.¹⁷

The striking observation that all patients have at least 1 highly abnormal region that is electrophysiologically indistinguishable from those with HCM VF raises the question as to the minimum volume of diseased myocardium that can act as a VF substrate. Both experimental³² and theoretical⁷ studies suggest that VF can arise from relatively small areas of myocardium, and the data from the IVF, LQTS VF, and DCM VF patients suggest that a single abnormal area may confer a risk of SCD consistent with clinical observations in DCM³³ and Brugada syndrome.³⁴ Having raised this issue in terms of the applicability of PEFA to the broader group of patients with noncoronary heart disease, it is interesting that the LQTS VF and DCM VF and non-VF populations are discriminated by line A in Figure 1, which was constructed for HCM. This shows that the magnitude of the disturbances in VF patients with these diseases is comparable to HCM. Accordingly, the general approach taken for HCM may be useful in these other conditions. This may justify setting up other prospective studies for the prediction of SCD risk, although a more detailed systematic search for abnormal areas may be necessary, possibly modified individually for the condition being studied.

Conclusion

This study demonstrates that an electrophysiological abnormality is readily detected in patients with noncoronary VF that is consistent with the known biological basis of VF induction.⁷ There is substantial anatomical variation of electrophysiological abnormalities, indicating that measurements at multiple sites may be required to characterize a patient at potential risk of SCD. Because the technique exposes a fundamental dynamic electrophysiological component of what is believed to be a substrate for VF, it may have potential for the prediction of the risk of SCD and thereby add additional useful information to guide prophylactic ICD implantation.

Acknowledgments

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