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Altered Dynamics of Action Potential Restitution and Alternans in Humans With Structural Heart Disease

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Background—Restitution kinetics and alternans of ventricular action potential duration (APD) have been shown to be important determinants of cardiac electrical stability. In this study, we tested the hypothesis that APD restitution and alternans properties differ between normal and diseased human ventricular myocardium.

Methods and Results—Monophasic action potentials were recorded from the right ventricular septum in 24 patients with structural heart disease (SHD) and in 12 patients without SHD. Standard and dynamic restitution relations were constructed by plotting APD as a function of the preceding diastolic interval. The dynamic restitution relation of both groups showed a steeply sloped segment at short diastolic intervals that was associated with the occurrence of APD alternans. Patients with SHD had a wider diastolic interval range over which APD alternans was present (mean \pm SEM 68 ± 11 versus 12 ± 2 ms) and showed an earlier onset (168 ± 7 versus 225 ± 4 bpm) and an increased magnitude (20 ± 2 versus 11 ± 2 ms) of APD alternans compared with patients without SHD. The occurrence of APD alternans during induced ventricular tachycardia (6 episodes) and during rapid pacing could be derived from the dynamic restitution function.

Conclusions—There are marked differences in the dynamics of APD restitution and alternans in the ventricular myocardium of patients with SHD compared with patients without SHD. These differences may contribute importantly to cardiac electrical instability in diseased human hearts and may represent a promising target for antiarrhythmic substrate modification. (*Circulation*. 2005;112:1542-1548.)

Key Words: action potentials ■ dynamics ■ electrical stimulation ■ electrophysiology ■ tachyarrhythmias

Sudden cardiac death remains a leading cause of death in the industrialized world despite decades of intense research. The most obvious explanation for the fact that trials of pharmacological prevention of sudden cardiac death have had very disappointing results is our incomplete understanding of the mechanisms underlying the major cause for sudden death, namely, ventricular fibrillation (VF). Recent evidence from computer modeling¹⁻³ and experimental^{4,5} studies suggests that the precipitating event for VF is the breakup and disintegration of reentrant wavefronts. According to the so-called restitution hypothesis, a key determinant of wave break leading to VF is a steeply sloped electrical restitution relation in which small changes in the diastolic interval (DI) can produce large fluctuations in action potential duration (APD) and refractoriness.^{2,6,7} If the slope of the restitution function at short DI, ie, at high heart rates, exceeds unity, alternans of APD occurs, which may lead to functional gradients of repolarization that, in turn, may promote destabilization of reentrant spiral waves.^{8,9} Flattening the slope of the restitution relation and thereby decreasing the magnitude of APD alternans has been shown to have an antifibrillatory effect in vitro.^{6,7}

A shortcoming of the currently available data on electrical restitution and cellular action potential alternans is that experimental studies in both animals¹⁰⁻¹² and humans^{13,14} have been performed almost exclusively in structurally normal myocardium. In the clinical setting, however, VF occurs predominantly in patients with structural heart disease (SHD) such as ischemic or nonischemic cardiomyopathy. We therefore hypothesized that electrical restitution properties and APD alternans dynamics differ between normal and diseased human ventricular myocardium, reflecting an altered arrhythmogenic substrate for the development of VF in patients with SHD. To test this hypothesis, we systematically compared restitution and alternans properties in patients with and without SHD.

Methods

Patient Characteristics

A prospective, single-center study that enrolled 36 patients who underwent an electrophysiological study at the University of Würzburg's Department of Cardiology was conducted. Inclusion and exclusion criteria for the study were defined prospectively, and

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patients fulfilling these criteria were enrolled consecutively. All patients participating in the study received a thorough cardiological examination that included history, physical examination, 12-lead ECG, echocardiogram, treadmill test, and a coronary and left ventricular angiogram where indicated. The patient group without SHD comprised patients (n=12) who were evaluated for supraventricular tachycardia or for syncope of unknown origin. The group with SHD (n=24) consisted of 17 patients with ischemic cardiomyopathy, including 11 patients with an old (>1 month) myocardial infarction and 7 patients with nonischemic cardiomyopathy. Four patients in the SHD group were in New York Heart Association (NYHA) functional class I, 13 in NYHA class II, and 7 in NYHA class III. The primary indication for the electrophysiological study in the SHD group was testing for inducibility of ventricular arrhythmias. Exclusion criteria for the study were current use of Vaughan Williams class I or III antiarrhythmic drugs, patients in NYHA functional class IV, and patients <18 years old. β -Adrenergic receptor blockers and calcium channel blockers were discontinued at least 48 hours before the electrophysiological study. Assessment of left ventricular ejection fraction was performed in all patients either echocardiographically or angiographically. The study protocol was approved by the ethics committee of the University of Würzburg, and all patients gave their written informed consent to participate in the study.

Data Acquisition and Analysis

Monophasic action potentials (MAPs) were recorded from the right ventricular endocardium with either a MAPCATH catheter (7F, Biotronik) or a MAP catheter (7F, EP Technologies). The MAP catheter was introduced through transfemoral access and placed against the right ventricular septum. Additional standard electrophysiology catheters were placed as needed. Right ventricular stimulation was performed through the MAP catheter with rectangular pulses of 2-ms duration at 2 to 3 times the diastolic threshold. Filter settings for the MAP recordings were 0.05 Hz for low pass and 500 Hz for high pass. Analog data were digitized at 1000 Hz with 12-bit resolution and were recorded on a BARD electrophysiology system. Data analysis was performed with custom-written analysis programs in the MATLAB 6.0 language.

The APD restitution relation was determined by plotting APD (measured at 95% repolarization [APD₉₅]) as a function of the preceding DI. To determine the maximum slope of the restitution relation, the data were fitted with overlapping least-squares linear segments. The restitution curves were analyzed in 400ms DI segments in steps of 10 ms commencing from the shortest DI range that contained data points. For example, if the shortest DI range that contained data points was 0 to 40 ms, a linear fit was performed over this DI range. In the next step, a linear fit was performed over a DI range of 10 to 50 ms, then from 20 to 60 ms, 30 to 70 ms, etc. This stepwise linear-fitting method has been described in detail by Taggart et al.¹⁴ No extrapolation of the original data set was performed.

Pacing Protocols

The standard and dynamic restitution protocols used in the present study have been described in detail previously.¹² Briefly, for the standard restitution protocol, a single premature pulse (S2) was delivered after a train of 10 stimuli (S1) at a basic cycle length of 500 ms. The S1-S2 interval was progressively shortened from 500 to 300 ms in steps of 20 ms and from 300 ms to the refractory period in steps of 10 ms. APD₉₅ and the preceding DI were determined for each S2 action potential.

For the dynamic protocol, a drive train of stimuli at a constant cycle length was delivered for 30 seconds, interrupted by a 30-second pause between drive trains. The pacing rate of each drive train was incremented by 10 bpm starting at 100 bpm to a maximum pacing rate of 240 bpm. At pacing rates above 200 bpm, the duration of the drive train was generally reduced to 15 seconds to minimize patient discomfort due to rapid pacing. To generate the dynamic APD restitution curves, APD₉₅ and the preceding DI of the last paced action potential at each cycle length were measured. At high pacing

Comparison of Clinical and Electrophysiological Parameters Between the 2 Study Populations

	SHD (n=24)	No SHD (n=12)	<i>P</i>
Age, y	63.2±1.5	52.7±5.3	...
Male sex, n (%)	19 (79)	4 (33)	...
LVEF, %	48±3	69±2	<0.001
APD ₉₅ at 100 bpm, ms	277±5	270±7	0.39
Dynamic restitution slope	1.05±0.09	0.97±0.16	0.63
S2 restitution slope	0.91±0.06	0.83±0.15	0.57
Alternans onset, bpm	168±7	225±4	<0.001
Alternans magnitude, ms	20±2	11±2	0.03
Alternans DI range, ms	68±11	12±2	0.002

LVEF indicates left ventricular ejection fraction.

Note the statistically significant differences in alternans onset, alternans magnitude, and alternans DI range between the 2 groups.

rates, APD alternans occurred. The onset heart rate for APD alternans was defined as the lowest rate at which APD alternans was detectable by plotting the sequence of APD₉₅ of each single action potential during the drive train. Only sequences that showed stable APD alternans for a minimum of 10 consecutive beats were included in the further analysis. Transient APD alternans that was seen only for a few beats after a sudden rate increase was excluded from further analysis. Alternans magnitude was defined as the maximum difference in APD₉₅ between the long and the short action potential. During alternans, the APD/DI relation of both the long and the short action potential were determined and included in the dynamic restitution relation. To determine the occurrence of APD alternans during ventricular tachycardia (VT), 6 episodes of pacing-induced, monomorphic VT with constant cycle lengths that allowed for stable MAP recordings of each action potential during the VT episode were analyzed.

Statistical Analysis

Data are presented as mean±SEM. A 2-tailed Student *t* test for unpaired data was used for comparison between the 2 patient groups. ANOVA was performed to account for multiple comparisons between groups. In the presence of unequal variances, a Mann-Whitney test was performed. A value of *P*<0.05 was considered statistically significant.

Results

The Table summarizes the clinical and electrophysiological parameters of the 2 patient populations. Patients in the SHD group were predominantly male and were older and had significantly lower left ventricular ejection fraction (48±3%, range 25% to 77%) than patients without SHD (69±2%, range 60% to 80%; *P*<0.001). Steady-state APD₉₅ during constant pacing at 100 bpm was not different between the 2 groups (277±5 ms, range 219 to 324 ms in SHD patients compared with 270±7 ms, range 230 to 318 ms in non-SHD patients; *P*=0.39).

There was no significant difference in the kinetics of the standard S2 restitution curves between the 2 groups (Table). The dynamic restitution curve was a monotonic function and showed a steeply sloped segment at short DI in both SHD patients (maximal mean slope 1.05±0.09) and non-SHD patients (0.97±0.16, *P*=0.63). Figure 1 shows the mean dynamic restitution curves of the 2 patient populations. In

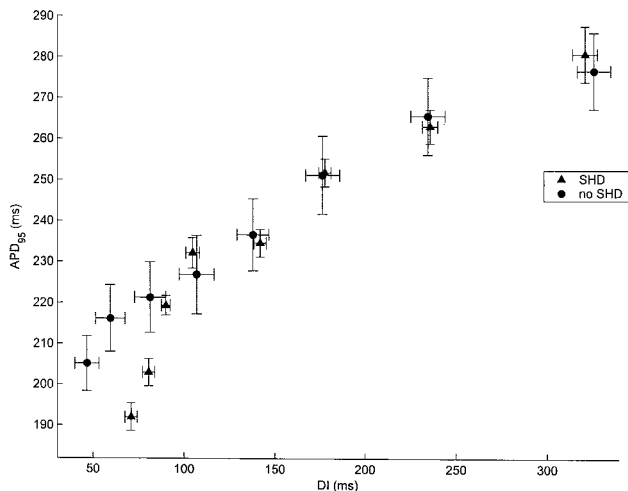


Figure 1. Mean dynamic restitution curves (\pm SEM for DI and APD_{95}) from patients with (\blacktriangle , $n=24$) and without (\bullet , $n=12$) SHD. Note the divergence of the curves at short DI, where the steep portion of the curve is shifted toward longer DI in patients with SHD.

patients with SHD, the steep portion of the curve was shifted toward longer DI than in patients without SHD.

Figure 2 shows representative examples of the dynamic restitution relations from patients with and without SHD. There was a region of slope ≥ 1 at short DI in both restitution relations. In the SHD patient, however, the steep portion of the dynamic restitution function was shifted toward longer DI.

The steep slope of the dynamic restitution relation was associated with the onset of APD alternans at high pacing rates in both groups. In the SHD group, APD alternans had an earlier onset (168 ± 7 versus 225 ± 4 bpm, $P < 0.001$) and a greater magnitude (20 ± 2 versus 11 ± 2 ms, $P = 0.03$) than in the group without SHD. Also, the DI range over which APD

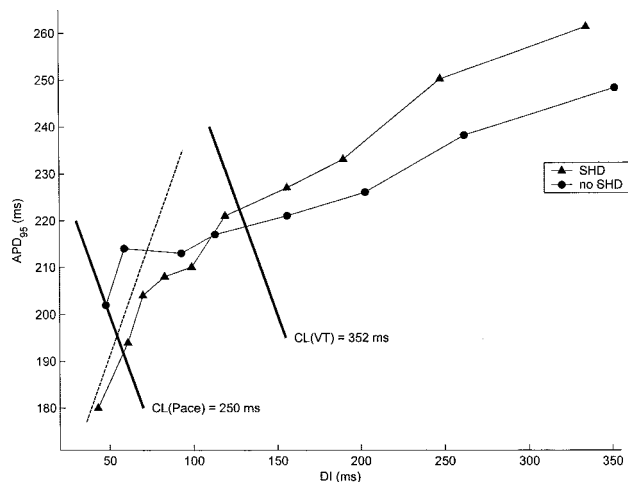


Figure 2. Dynamic restitution curves from a patient with SHD (\blacktriangle) and a patient without SHD (\bullet). Note the steep slope of the restitution curve at short DIs in both patients. In the SHD patient, however, the steep portion of the curve is shifted toward longer DI. Dashed line represents line of identity (slope=1), solid lines represent cycle lengths (CL) of maximal pacing rate ($CL_{Pace}=250$ ms) and of induced monomorphic VT ($CL_{VT}=352$ ms), where $CL=APD+DI$. See text for further explanation.

alternans was present was significantly larger in SHD patients (68 ± 11 ms) than in non-SHD subjects (12 ± 2 ms, $P = 0.002$). Figure 3 demonstrates the differences in onset and magnitude of APD alternans in a patient with SHD compared with a patient without SHD. Figure 4 displays the DI range over which APD alternans was present and the alternans-onset heart rate for each individual patient in the 2 populations.

The occurrence of APD alternans during 6 episodes of VT and during rapid pacing could be derived from the dynamic restitution relation, as shown graphically in Figure 2. The solid lines represent the cycle lengths of an induced episode of monomorphic ventricular tachycardia in a patient with SHD ($CL_{VT}=352$ ms) and the maximum pacing rate during the dynamic restitution protocol in the same patient ($CL_{Pace}=250$ ms), according to $CL=APD+DI$, where CL is cycle length.

The CL_{VT} line intersected the dynamic restitution function of the SHD patient in the flat portion (slope < 1) of the function, where according to the restitution hypothesis, no APD alternans would be expected to occur. Indeed, as demonstrated in Figure 5A, no APD alternans was seen in the MAP recording during this VT episode. In contrast, the CL_{Pace} line intersected the dynamic restitution function in the initial steep portion where the slope was ≥ 1 and APD alternans would be expected to occur. As predicted theoretically, marked APD alternans was seen in the MAP recordings at CL_{Pace} (Figure 5B).

In the 3 VT episodes in which APD alternans was present (CL_{VT} of 246, 274, and 298 ms), the CL_{VT} lines intersected the dynamic restitution function in the steep portion of the curve, whereas in the other 3 VT episodes in which no APD alternans was present (CL_{VT} of 252, 321, and 352 ms), the CL_{VT} line intersected the dynamic restitution curve at a portion of the function where the slope was < 1 . Two VT episodes ($CL_{VT}=352$ and 321 ms) terminated spontaneously, 2 episodes ($CL_{VT}=298$ and 246 ms) were terminated by overdrive pacing, and 2 episodes ($CL_{VT}=274$ and 252 ms) were cardioverted electrically.

Discussion

New Findings

The most important new finding of this study is that the kinetics of electrical restitution and APD alternans differ significantly between patients with and without SHD. We found that a steeply sloped dynamic restitution function in patients with and without SHD was associated with the onset of APD alternans at rapid heart rates. In the SHD group, APD alternans had an earlier onset and an increased magnitude and was present over a wider DI range than in patients without SHD.

Another important finding of the present study is that the restitution function derived from a dynamic pacing protocol represented APD dynamics during rapid ventricular pacing and during VT. At cycle lengths that intersected the dynamic restitution function in the steep portion of the function, where the slope of the curve was ≥ 1 , APD alternans was observed. Conversely, at slower heart rates, where the cycle length intersected the dynamic restitution function at a region with a slope < 1 , no alternans was present. This finding may provide

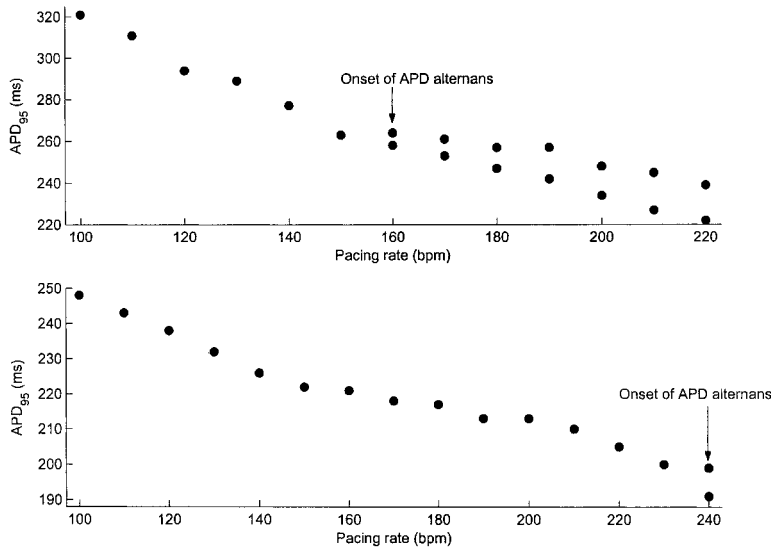


Figure 3. Representative examples of the sequence of APD₉₅ as a function of the pacing rate in a patient with SHD (top) and a patient without SHD (bottom). Note the earlier onset (160 versus 240 bpm), the increased magnitude (18 vs 8 ms), and the wider range of DI (51 vs 7 ms) over which APD alternans occurred in the patient with SHD compared with the patient without SHD.

a mechanistic explanation for the well-recognized clinical observation that VT episodes with short cycle lengths are more likely to degenerate into VF than VT episodes with longer cycle lengths. Rapid VTs may drive the myocardial tissue into a “vulnerable” zone of short DIs associated with a steep slope of APD restitution, thereby promoting the development of APD alternans and increased wave breakup, eventually culminating in VF.

Interestingly, although there was a clear divergence of the dynamic restitution relations at short DI, with a shift of the steep portion toward longer DI in patients with SHD than in patients without SHD, we did not observe a difference in the kinetics of the standard S1-S2 restitution relations between the 2 groups. This finding is in accordance with previous in vitro experiments from our group¹² that showed that a dynamic restitution protocol more closely represents APD dynamics at high heart rates than a standard S1-S2 protocol.

APD Restitution in Humans

Several studies have described APD restitution in humans, although only a few reported the steepness of the restitution

curve. In the study by Taggart et al,¹⁴ the effect of adrenergic stimulation on the standard S1-S2 restitution relation was examined in 18 patients with structurally normal hearts. Under control conditions, the slope of the standard S1-S2 restitution curve determined at a basic cycle length of 500 ms was 0.92 ± 0.06 , which is in good agreement with the value of 0.83 ± 0.15 that we found in the present non-SHD population. Taggart et al reported an increase in the S1-S2 restitution slope after isoprenaline and adrenaline infusion and speculated that fluctuations in autonomic tone and autonomic balance may influence susceptibility to lethal arrhythmias by modulating the APD restitution properties. In a recent trial reported by Pak et al,¹⁵ inducibility of ventricular arrhythmias was found to be correlated with greater spatial dispersion of APD restitution. In accordance with our findings, Pak et al found a steep slope (≥ 1) of the dynamic restitution relation associated with APD alternans in 3 patients; however, no systematic analysis of APD alternans was performed in their study.

To date, the present study is the first to provide a systematic comparison of restitution relations and APD alter-

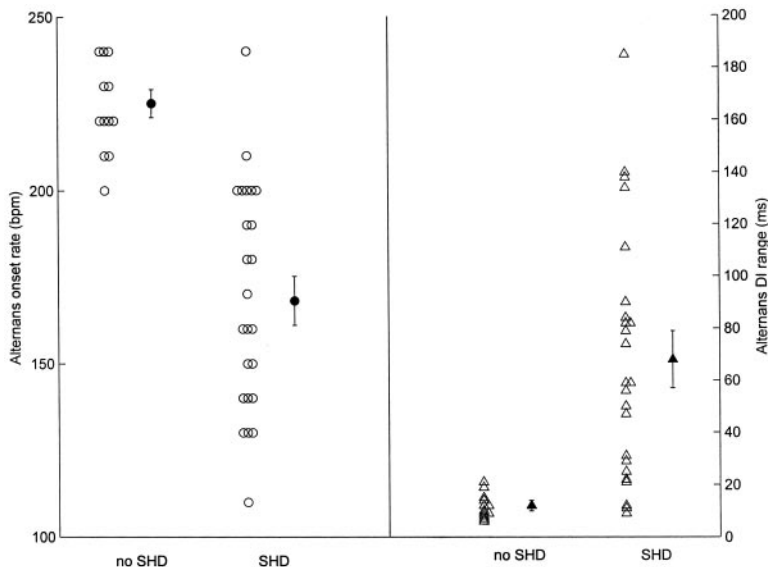


Figure 4. Difference in the alternans onset rate (left) and the DI range over which APD alternans was present (right) between patients with and without SHD. Data are shown for each patient (individual points), as well as the mean \pm SEM.

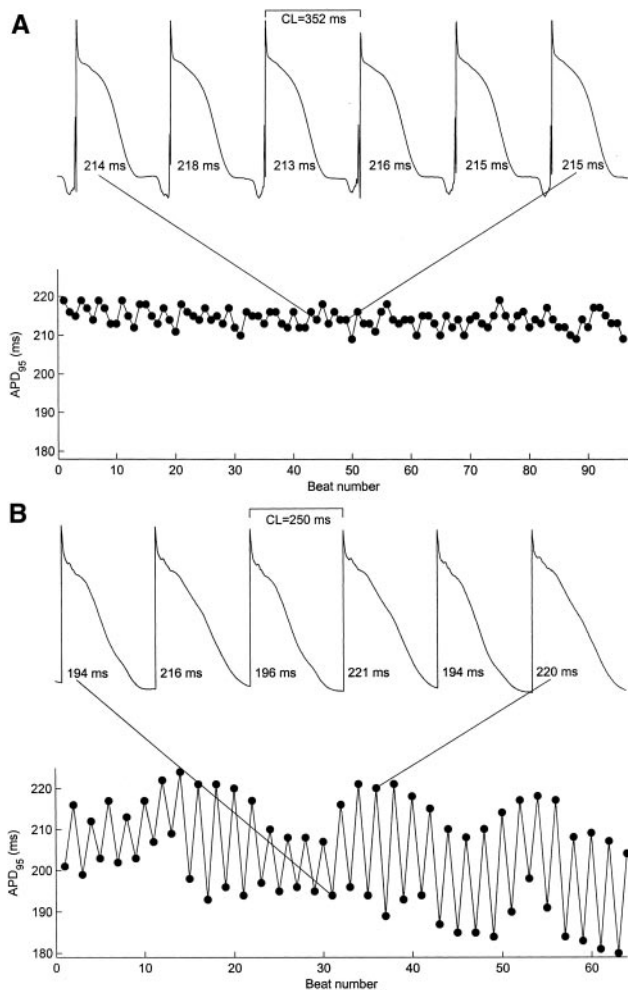


Figure 5. A, Top, Monophasic action potential recording during induced monomorphic VT at a cycle length of 352 ms. Numbers below each action potential indicate APD₉₅ in milliseconds. Data are from same patient as in Figure 2. A, Bottom, Complete sequence of APD₉₅ during the VT episode. Note the absence of APD alternans. Lines indicate section of MAP recording given in the upper panel. B, Top, Monophasic action potential recording during rapid ventricular pacing at a cycle length of 250 ms. Numbers below each action potential indicate APD₉₅ in milliseconds. Data are from same patient as in Figures 2 and 5A. B, Bottom, Sequence of APD₉₅ during rapid pacing at 250 ms. Note the presence of APD alternans. Lines indicate section of MAP recording given in the upper panel.

nans between patients with and without SHD using a dynamic stimulation protocol, which has been demonstrated in vitro to account more closely for APD dynamics at short coupling intervals and during VF.¹² We found significant differences in the kinetics of the dynamic restitution relation between the 2 patient groups, where the steep portion of the function was shifted toward longer DI in patients with SHD. This shift in the restitution relation was associated with the occurrence of APD alternans at lower onset heart rates in SHD patients than in healthy subjects. We found a difference in the kinetics of the dynamic restitution relations, although there was no difference in the standard restitution relations. This observation may explain in part why the predictive value of electrophysiological testing with a standard stimulation protocol is

very low for subsequent VF episodes. It is tempting to speculate that by implementing a dynamic protocol, the predictive value of electrophysiological testing for subsequent VF episodes may be improved. However, this hypothesis remains to be tested.

Reference to T-Wave Alternans

T-wave alternans has been shown to be an important predictor of malignant ventricular tachyarrhythmias and sudden cardiac death in patients with SHD.¹⁶ Studies that used single-site action potential recordings and optical-mapping techniques have suggested that T-wave alternans of the surface ECG arises from alternans of APD that occurs at the level of the single cell.⁹ Our finding that alternans of monophasic APD occurred at a lower heart rate in SHD patients than in non-SHD patients is in keeping with studies showing that T-wave alternans occurs at lower heart rates in SHD patients.^{16–18} Whether this downward shift in the alternans threshold heart rate is caused by disease-induced alterations in the expression of ion currents is unknown.

In 2 recent studies by Tanno et al,^{17,18} microvolt T-wave alternans was induced in humans by right atrial pacing and occurred at onset heart rates between 90 and 120 bpm. In the present study, the onset heart rate for local monophasic APD alternans was 168 ± 7 bpm in SHD patients and 225 ± 4 bpm in patients without SHD. The differences in the onset rate of microvolt T-wave alternans investigated in the studies by Tanno et al compared with local APD alternans investigated in the present study may be accounted for by regional variations in the occurrence of APD alternans and/or alternans of conduction velocity in the AV node or the HIS-Purkinje system. Another possible explanation for this discrepancy is that microvolt T-wave alternans of the surface ECG may be governed by a nonrestitution-dependent process,¹⁹ whereas local APD alternans is primarily a restitution-dependent phenomenon. Further studies are necessary to elucidate these mechanisms.

The SHD group in the present study consisted predominantly of patients with ischemic cardiomyopathy, with a majority of patients in the chronic state after myocardial infarction. It has been well established that after myocardial infarction, the noninfarcted myocardium undergoes significant structural and functional remodeling, including hypertrophy, chamber dilatation,²⁰ and alterations in ion channel expression and kinetics.^{21,22} The functional changes in ion channel kinetics in the remodeled myocardium may explain the altered restitution dynamics in patients with SHD that were found in the present study. Both changes in intracellular calcium cycling¹⁹ and in the rapid component of the delayed rectifier potassium current (I_{Kr})²³ have been shown to play an important role in the genesis of action potential alternans in structurally normal myocardial tissue. It remains to be determined to what extent these ionic events contribute to the earlier onset and the increased magnitude of APD alternans in the remodeled ventricular myocardium.

Modulation of Restitution Properties and Suppression of APD Alternans

Discordant APD alternans creates spatial gradients of repolarization that may lead to reentrant waves of electrical

activity that underlie VF.^{8,24} It has been proposed that flattening the slope of the restitution function and suppression of APD alternans may be antifibrillatory. Drugs that flatten the restitution relation and thereby suppress APD alternans, such as verapamil⁶ and bretylium,⁷ have been shown to have antifibrillatory effects in vitro. Hao et al²⁵ demonstrated recently that β -blockade decreases APD restitution slopes in the porcine heart in vivo, which may be an important mechanism by which β -blockers reduce sudden cardiac death.²⁶

Fixed Versus Dynamic Heterogeneities as a Cause of Wave Break

To what extent structural versus dynamical heterogeneities contribute to wave break as the presumed mechanism for VF currently is unclear. It has been speculated that structural heterogeneities, such as anatomic obstacles or fibrosis, may overwhelm the contribution of dynamic heterogeneity and become the primary determinants for wave break and the development of reentry in patients with SHD. However, Xie et al³ demonstrated in a recent computational study using an anatomically realistic model of the heart that even in the presence of anatomic heterogeneities such as regional differences in fiber orientation, the role of APD restitution in the development of VF remained intact, in that steep restitution was necessary for the disintegration of a single spiral wave into multiple wavelets. In agreement with this computer-modeling study, Ohara et al²⁷ demonstrated in a canine model of chronic myocardial infarction that increased wave break in the epicardial border zone of the infarct is compatible with the APD restitution hypothesis. They found that the dynamic APD restitution curve in the epicardial border zone of the infarct had longer DIs over which the slope was >1 .

The results of the present study suggest that in SHD patients, electrophysiological properties such as APD restitution and APD alternans are altered in a way that may facilitate the development of wave break. It appears likely that a combination of the fixed heterogeneities associated with SHD and the dynamic heterogeneities that arise from altered APD restitution properties may confer a greater risk for the induction of conduction block and wave break than either heterogeneity alone.

Study Limitations

An important limitation of the present study is the fact that local MAPs were recorded from the right ventricular septum only. It would have been desirable to record MAPs from additional right and left ventricular sites to investigate spatial heterogeneity in restitution properties and alternans dynamics. However, we considered the placement of additional catheters not justified for the purpose of this study because of the increased risk of complications associated with placement of additional catheters, particularly on the left side of the heart. Another limitation of the study is that MAP recordings are inherently susceptible to motion artifacts, and we cannot completely exclude the possibility that the action potential alternans observed was influenced by or coincident with mechanical alternans. Also, alternans and restitution dynamics may not have reached steady state at heart rates above 200 bpm owing to the limitation of the pacing duration to 15

seconds, which was necessary to minimize patient discomfort due to rapid stimulation. It is possible that the differences observed in the restitution curves could be explained in part by the age and gender differences in the 2 groups. Finally, the SHD group in the present study was composed predominantly of patients with mild to moderate heart failure. Consequently, extrapolation of the present results to patients with more advanced heart failure who are at greatest risk for sudden cardiac death should be made cautiously until additional data on restitution and alternans properties become available in this patient group.

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