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Global Endocardial Electrical Restitution in Human Right and Left Ventricles Determined by Noncontact Mapping

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OBJECTIVES This study was aimed at evaluating global characteristics of electrical restitution in the human ventricle using noncontact mapping.

BACKGROUND Steep action potential restitution (slope >1) and conduction velocity (CV) restitution have been linked with propensity to ventricular fibrillation, but clinical measurement of global electrical restitution had not been feasible.

METHODS Activation-recovery interval (ARI) and CV restitution curves were simultaneously constructed from 16 regional segments of the left and right ventricles in 8 patients (6 male, 2 female, age 42 ± 17 years) following successful ablation of idiopathic ventricular tachycardia in the absence of structural disease guided by the Ensite 3000 system (Endocardial Solutions Inc., St. Paul, Minnesota). The ARIs were determined from reconstructed unipolar electrograms as validated with monophasic action potential recordings. The ARI restitution slopes were determined using the overlapping least-squares linear segments.

RESULTS Global electrical restitution curves were heterogeneous in shape and distribution. ARI restitution slope was >1 at 25% of 128 sites. The overall mean slope was 0.79 and was greater in the left than the right ventricle (0.93 ± 0.49 vs. 0.65 ± 0.26, $p < 0.001$). Dispersion of ARI restitution slopes increased with decreasing diastolic intervals. The CV restitution operated over a narrower range of diastolic intervals compared with ARI restitution, reaching a plateau (10 ± 6 ms vs. 38 ± 13 ms, $p < 0.001$) after refractoriness. The magnitude of CV restitution was also greater (steeper) than ARI restitution (25 ± 10% vs. 18 ± 9%, $p < 0.001$).

CONCLUSIONS Noncontact mapping can be used to examine global electrical restitution in the human ventricle. The ARI restitution is heterogeneous, with a slope >1 at 25% of all sites. The heterogeneity of ARI and CV restitution may be important in determining myocardial electrical stability. (J Am Coll Cardiol 2005;46:1067–75) © 2005 by the American College of Cardiology Foundation

Spatial and temporal heterogeneity of cardiac repolarization contribute to the occurrence of ventricular arrhythmias (1–5). The action potential duration (APD) restitution curve, which portrays the relationship between local APD and the preceding diastolic interval, has received much interest with its potential role in ventricular fibrillation (VF) (6–8). The "restitution hypothesis" states that a slope of the APD restitution curve >1 may lead to repolarization alternans, wavebreak, and transition from ventricular tachycardia to VF even in a ventricle without pre-existing repolarization heterogeneity (7,9). Conduction velocity (CV) restitution may determine the spatial discordance of repolarization alternans and the genesis of a slower type of VF (10–12). However, clinical data regarding geographic distribution of electrical restitution have been lacking (8,13) because repolarization measurements were limited to sequential acquisition from only one or two sites (3,4,14–17).

We have previously validated the use of activation-recovery intervals (ARIs) reconstructed by noncontact mapping to estimate local APDs in the human ventricle (18). In this study, we used noncontact mapping to construct global electrical restitution curves in the left or right ventricle to determine the characteristics of ARI and CV restitution in patients without structural heart disease.

METHODS

Patients. Eight consecutive patients (6 male, 2 female, age 42 ± 17 years) referred for radiofrequency ablation of idiopathic ventricular tachycardia or unifocal ectopics guided by noncontact mapping were recruited into the study (Table 1). Inclusion criteria were absence of structural heart disease or family history of sudden death, normal twelve-lead surface electrocardiograms, normal echocardiography or magnetic resonance imaging, and absence of significant obstructive stenosis (>50%) on coronary angiography. All antiarrhythmic medications were discontinued for five half-lives. The study was performed in the left ventricle (LV) or right ventricle (RV) in the postabsorptive state after successful ablation of ventricular tachycardia. No patients had inducible ventricular arrhythmias by programmed electrical

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JACC Vol. 46, No. 6, 2005
September 20, 2005:1067–75

Abbreviations and Acronyms

APD = action potential duration
ARI = activation-recovery interval
AT = activation time
CV = conduction velocity
LV = left ventricle
RT = repolarization time
RV = right ventricle
UE = unipolar electrogram
VF = ventricular fibrillation

stimulation following the ablation procedure. All patients had signed written consent before the study. Ethical approval of this study has been granted by the local research ethics committee.

Noncontact mapping. The technique of noncontact mapping using the Ensite 3000 system (Endocardial Solutions, St. Paul, Minnesota) has been described previously (19,20). The system consists of a 64-multielectrode array mounted on a 7.5-ml inflatable balloon on a 9-F catheter, an amplifier system, and a Silicon Graphics workstation. For LV study, the array catheter was introduced under fluoroscopic guidance from the left femoral artery via the retrograde transaortic route into the ventricle. For RV study, the array catheter was introduced from a femoral vein. A 7-F, 4-mm-tip deflectable ablation catheter (Stinger; Bard, Lowell, Massachusetts) was then introduced into the ventricle using the same route as the array catheter. The system calculated the position of the ablation catheter relative to the fixed known positions of the ring electrodes at either end of the multi-electrode array. A three-dimensional geometry of the ventricle was then determined.

Construction of restitution curves. Constant right ventricular pacing (S1) was performed with a bipolar woven catheter (Bard) at the right ventricular apex for 2 min at a baseline cycle lengths of 400 ms using a pulse width of 2 ms duration and stimulus strength of twice the diastolic threshold. After steady state had been established, an extra stimulus (S2) was introduced at every 10-beat cycle. The coupling interval of S1-S2 was decremented by 20 ms every cycle down to 300 ms and by 10 ms every cycle from 300 ms until S1 refractoriness. The APD restitution curves were determined by plotting local ARIs at prespecified sites against preceding diastolic intervals. Conduction velocity restitution curves at the same sites were determined by plotting conduction velocity from the site of earliest activation in the ventricle against diastolic intervals.

Data analysis. Data were analyzed using standard software with the Silicon Graphics workstation (version 4.0, Silicon Graphics Inc., Mountain View, California). Measurements were made manually from electrograms displayed on a color monitor at 200 mm/s resolution. The use of electronic calipers from the workstation allowed timings to be determined to the nearest 1 ms.

LOCAL ARIS. Estimation of repolarization timings from reconstructed unipolar electrograms (UEs) has been validated previously (21). Local activation time (AT) was measured from onset of activation to the time of dV/dt_{min} of the local QRS complex. Activation-recovery interval was defined as the interval between AT and repolarization time (RT). The RT was measured at the dV/dt_{max} for the negative T-wave, the dV/dt_{min} of the positive T-wave, and at the mean time between dV/dt_{max} and dV/dt_{min} for the biphasic T-wave. T waves with an interrupted descending or ascending phase were occasionally seen, which may represent a differential contribution of repolarization from the transmural myocardium (22), resulting in double-peak derivatives. Local RTs at these sites were estimated at the mean time between two peak derivatives. The UEs with flat T waves and ST-segment elevation without discernable T-wave upstroke were excluded from measurement. Diastolic interval was measured from the end of repolarization (RT) from the preceding beat to the AT of the following beat. At very short S1-S2 coupling intervals when the RT of the last S1 beat was not clearly visible owing to encroachment of the S2, the last S1 RT was estimated as the average of three preceding S1 RTs during steady-state pacing.

GLOBAL ARI. A custom-designed template was used to display the paired UE and its first derivative (dV/dt) from three endocardial sites at a time. At each S1-S2 coupling interval, a total of 16 sites were analyzed from each ventricle. Each site was randomly selected from each of 16 predefined segments in the LV or RV geometry (Fig. 1). Sites were

Table 1. Patient Characteristics

Patient	Age (yrs)	Gender	Study Ventricle	Diagnosis	Chamber Diameter (mm)	LVEF (%)	RF Lesions	Location of RF Lesions (Segment No.)
1	37	M	Right	VT	32	57	4	13
2	69	M	Right	VE	31	61	6	13
3	60	F	Right	VE	27	58	6	15
4	61	M	Right	VT	29	66	6	13,16
5	32	M	Left	VT	34	62	3	11
6	20	F	Left	VT	52	58	6	7,12
7	33	M	Left	VT	46	66	10	11,12
8	32	M	Left	VE	47	60	1	1

LVEF = left ventricular ejection fraction; RF = radiofrequency ablation; VE = unifocal ventricular ectopics; VT = sustained monomorphic ventricular tachycardia.

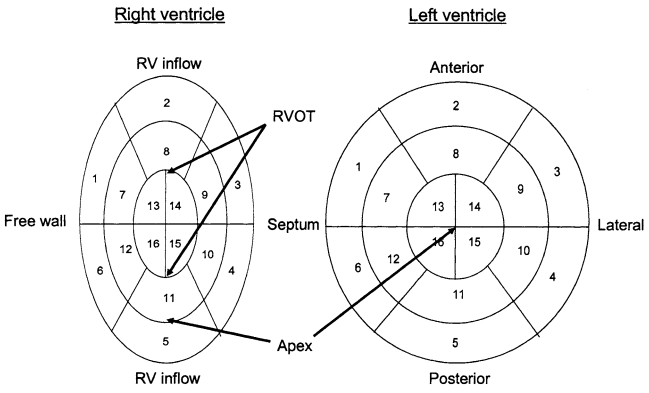

Figure 1. Schematic diagram showing 16 regional segments in both left and right ventricles (RV) from which data were sampled. RVOT = right ventricular outflow tract.

sampled evenly selected from the entire ventricle prior to electrogram analysis. Three reconstructed endocardial UEs from different segments of the geometry were simultaneously displayed on the workstation. Within-segment variability of ARI was calculated in 6 patients (#2 to #7) by the difference in ARI timing between two randomly selected adjacent sites 1 cm apart. Variability measurements were made during constant pacing and at the shortest S1-S2 coupling interval of each restitution curve.

ARI RESTITUTION SLOPES. The maximum slope for each restitution curve was fitted using the overlapping least-squares linear segments (16). Restitution slopes were analyzed from 40-ms diastolic interval segments in steps of 10 ms with the maximum slope used for comparison with other curves (Fig. 2). The shape of a restitution curve was also assessed by measuring the slopes of a curve at 5 segments of the total range of S1-S2 diastolic interval (0% to 10%, 10% to 30%, 30% to 50%, 50% to 75%, and 75% to 100%) from S2 refractoriness to baseline pacing. Because the baseline ARIs in different geographic segments were not identical, comparison between different curves was made after normalization of ARIs to percentage of baseline ARIs.

CV. The CV was calculated by dividing the distance from the site of earliest activation to the site of recording by the activation time between the two sites (11). The site of earliest activation was determined from isochronal mapping of the ventricle. The distance between these sites was taken as an average of three measurements of straight lines drawn along the geometric surface and perpendicular to the isochrones. Maximum CV restitution (difference of CV at baseline and shortest coupling intervals) has been used as a measure of steepness of CV restitution (11). We defined the

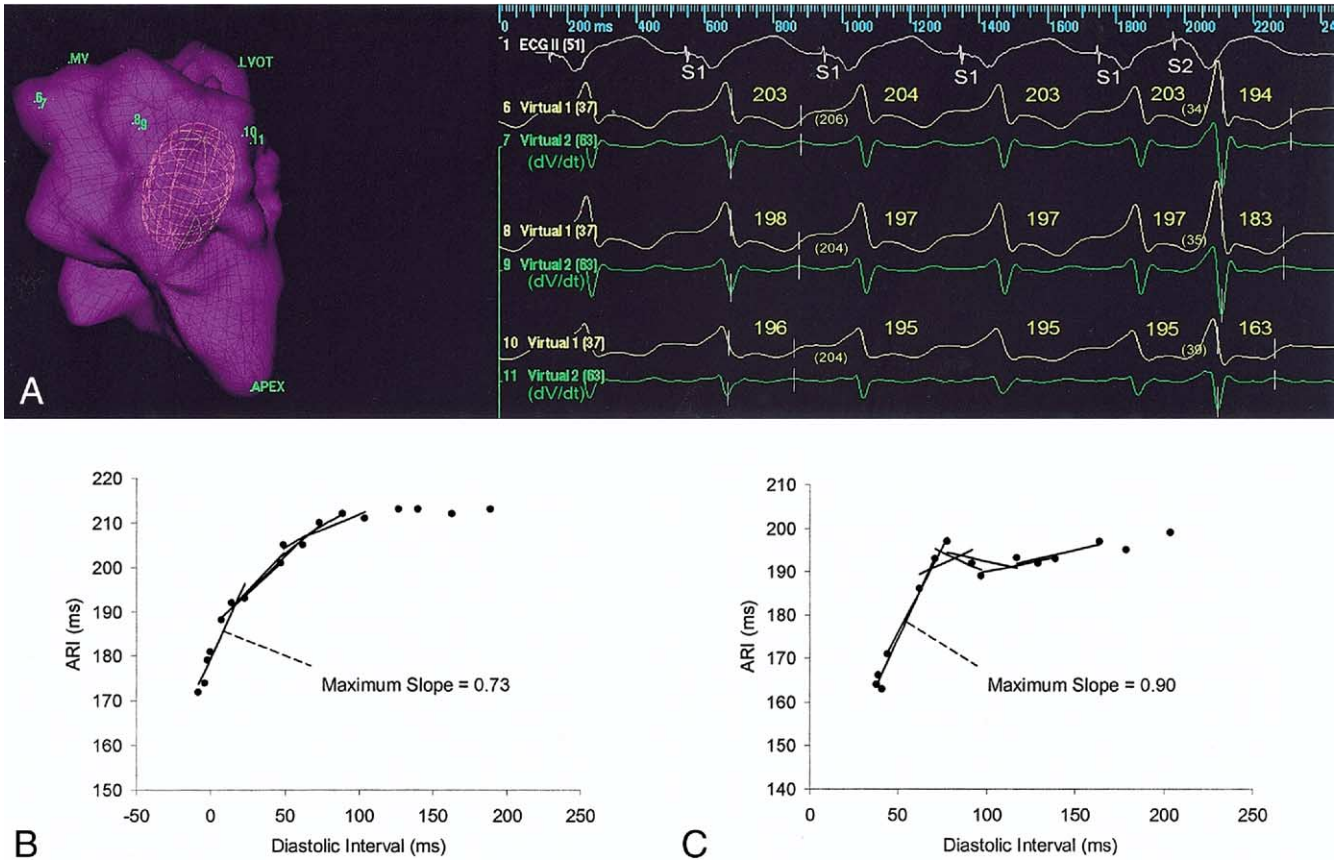

Figure 2. Activation-recovery interval (ARI) restitution and slope measurement. **(A)** Simultaneous measurement of ARIs at three sites in the posterobasal left ventricle during S1-S2 stimulation is shown. ARIs and diastolic intervals **(in parentheses)** from unipolar virtual electrograms—virtuals 6, 8, 10—are determined using their respective first derivatives (dV/dt)—virtuals 7, 9, 11 at the same sites. Maximum ARI restitution slopes from a right ventricular site **(B)** and left ventricular site **(C)** are measured by 16 overlapping least-squares linear segments. LVOT = left ventricular outflow tract; MV = mitral valve.

JACC Vol. 46, No. 6, 2005
September 20, 2005:1067–75

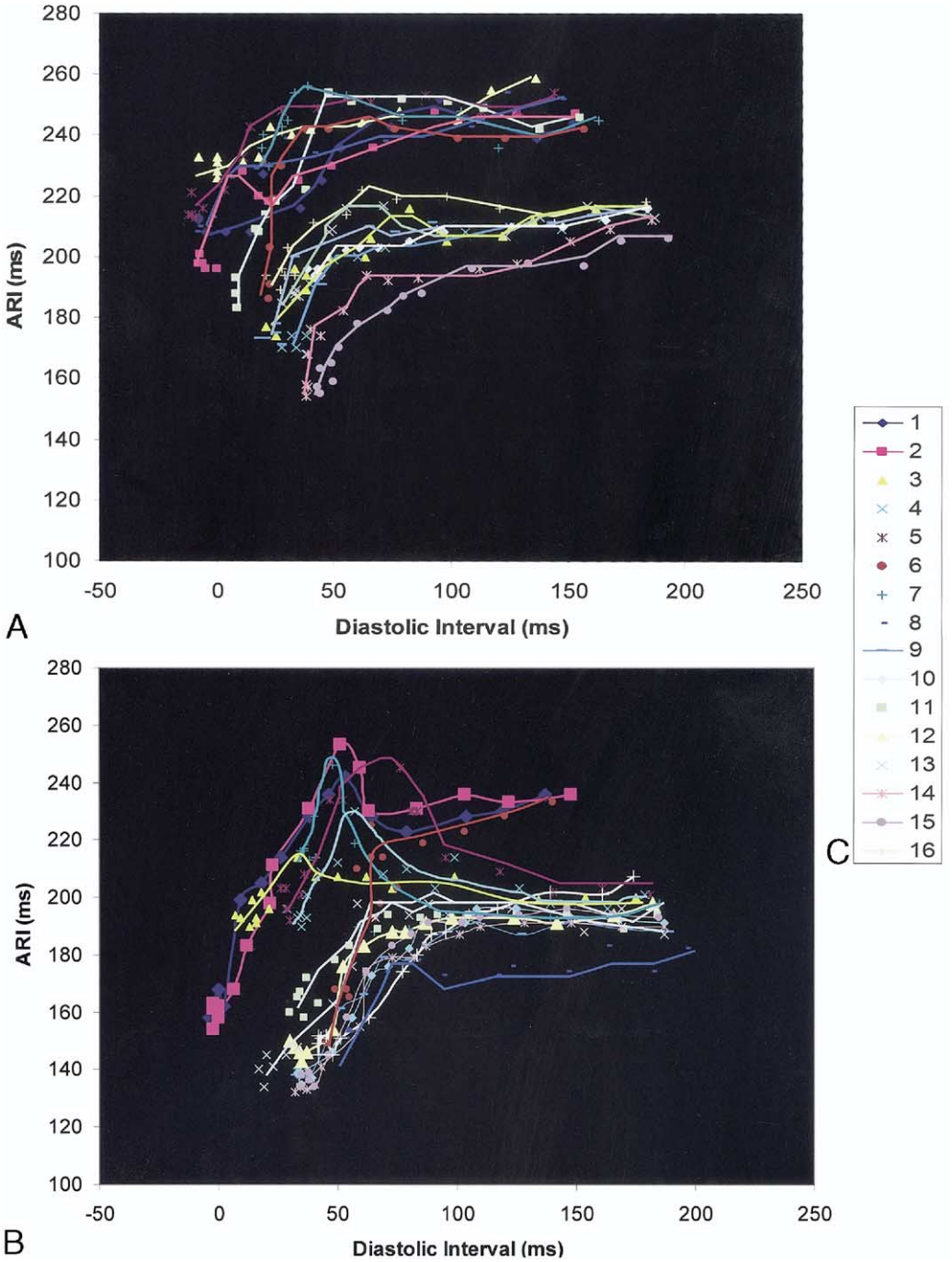

Figure 3. Global activation-recovery interval (ARI) restitution curves. Simultaneous restitution curves were constructed at 16 sites in a right ventricle **(A)** and left ventricle **(B)**. Color labels for the 16 regional segments are illustrated in **(C)**. Locations of the 16 segments are shown in Figure 1.

magnitude of CV restitution as a percentage of baseline value.

Statistical analysis. Continuous data were presented as means ± standard deviations. Dispersion was quantified using the standard deviation and the coefficient of variation (ratio of standard deviation and the mean, in percent). The dispersion of ARI restitution slope at each diastolic interval segment was used as an index for comparison within each ventricle and between patients. Activation-recovery interval restitution data were compared with CV restitution data in each patient using the paired *t* test, paired by sites and diastolic intervals. Left and right ventricular restitution data were compared by the unpaired unequal variance *t* test. A p value <0.05 was considered statistically significant.

RESULTS

Restitution curves were constructed using a basic drive cycle length of 400 ms from a total of 128 endocardial sites: 64 from the right ventricle of 4 patients and 64 from the left

ventricle of 4 patients. Of 1,968 recordings of ARIs made at these sites during construction of restitution curves, 22 (1%) were excluded from analysis because of flat or ambiguous T waves at short coupling intervals. Within-segment variability of ARI was 8 ± 11 ms during constant pacing and 6 ± 8 ms at the shortest S1-S2 coupling intervals.

Average ARI and regional variability in RV and LV. The mean ARI during steady-state pacing was 209 ± 11 ms. At the shortest S1-S2 coupling intervals, the mean ARI was 175 ± 16 ms. The mean global dispersion of ARI (coefficient of variation) at steady state was 7.7 ± 2.1%, and at minimum S1-S2 coupling interval it was 11.2 ± 3.7 % ($p = 0.01$). The duration of ARI at a specific site was inversely correlated with local activation time for the same preceding diastolic interval. For each specific site, however, properties of electrical restitution were observed, with ARI shortening with decreasing diastolic interval in a complex relationship.

The ARI restitution curves in each ventricle were variable in their shapes and slopes, and could not be systematically fitted with a simple exponential curve. Examples of global restitution curves from 16 sites determined simultaneously in the left ventricle or right ventricle are given in Figure 3. The steep initial phase of ARI restitution was found in the interval range between refractoriness and a diastolic interval of approximately 50 ms, with an early maximum approaching or exceeding steady state at a mean diastolic interval of 38 ± 13 ms. In 52 of 128 restitution curves (41%), there was a complex and "supranormal" response in the initial phase when the ARI temporarily exceeded the steady-state ARI.

ARI restitution slopes. The maximum restitution slope was >1 in 32 (25%) of all sites. The mean restitution slope of the left ventricle was significantly greater than the mean slope of the right ventricle (0.94 ± 0.49 vs. 0.66 ± 0.25, $p < 0.001$). The overall mean slope was 0.79 ± 0.49. In the three patients with inducible idiopathic LV (fascicular) tachycardia (Patients #5, #6, and #7), sites with the greatest slopes were located in the mid/basal septum of the LV adjacent to sites of catheter ablation of ventricular tachycardia. In the other five patients with focal RV or LV outflow tachycardia, sites of successful ablation were not located at segments with the steepest slopes (Fig. 4).

The shapes of restitution curves from different regions were analyzed after normalization of diastolic intervals and ARIs to steady-state values. The slope was steepest at 0% to 10% of baseline diastolic interval in both left and right ventricles with a mean of 0.76 ± 0.51 (Fig. 5A). In 78 restitution curves (70%), the steepest segment was located at 0% to 10% of baseline diastolic interval, whereas in 34 restitution curves (30%), it was situated at 10% to 30% of baseline diastolic interval. Dispersion of restitution slope as defined by the standard deviation of the mean was also greater with decreasing diastolic interval, ranging from 0.09 ± 0.03 over the plateau phase to 0.50 ± 0.15 over the steep initial phase of the restitution curve (Fig. 5B).

CV restitution. The CV restitution curves resemble ARI restitution curves in that a variable or supranormal initial phase could be demonstrated in 56 of 128 sites (44%) and could not be fitted with a simple mathematical function.

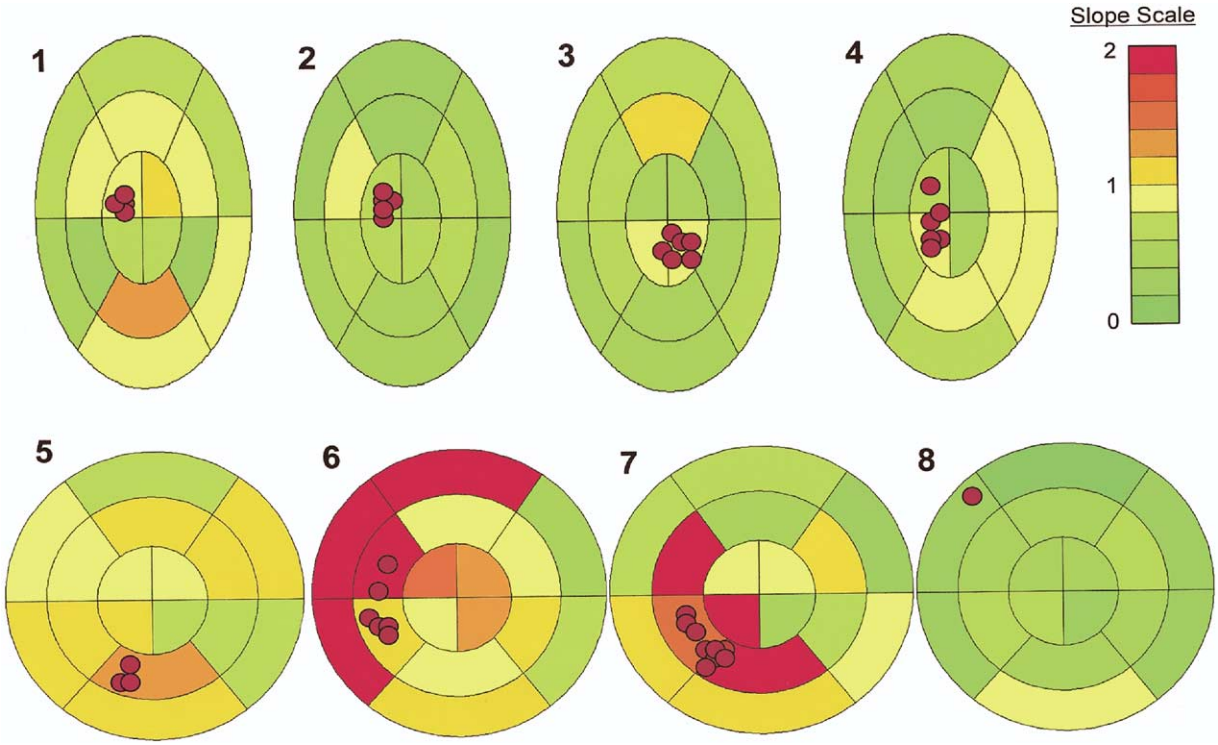

Figure 4. Distribution of activation-recovery interval restitution slopes. Maximal restitution slopes are shown in color in the 16 segments of the ventricle in patients 1 to 8. **Brown circles** = sites of ablation therapy. In patients with idiopathic left ventricular (fascicular) tachycardia (#5 to #7), sites of ablation are located in segments with a restitution slope >1.

However, CV restitution operated over a narrower range of diastolic intervals than did ARI restitution (Fig. 6). The steep initial ascending phase of CV restitution reached steady-state plateau after a diastolic interval of only 10 ± 6 ms from refractoriness, or the initial 6 ± 4% of the total range of diastolic intervals from refractoriness to steady-state pacing, compared with 38 ± 13 ms and 22 ± 7%, respectively, for ARI restitution ($p < 0.001$). The magnitude of CV restitution was greater (steeper) than ARI restitution at the same endocardial sites in all patients (25 ± 10% vs. 18 ± 9%, $p < 0.001$) (Table 2). There was no significant difference in the magnitude of CV restitution between left and right ventricles (24 ± 8% vs. 26 ± 12%, $p = 0.18$) or in the magnitude of ARI restitution between left and right ventricles (19 ± 12% vs. 17 ± 5%, $p = 0.23$).

DISCUSSION

We have systematically analyzed global repolarization data from the human left and right ventricles using noncontact mapping. The major findings are: 1) global restitution changes as derived by noncontact mapping cannot be represented by a simple mathematical function because of considerable heterogeneity of restitution curve characteristics; 2) although some ARI restitution slopes exceed 1, most LV and all RV slopes do not; and 3) compared to ARI restitution, early CV restitution is steeper and reaches a plateau over a much narrower range of diastolic intervals.

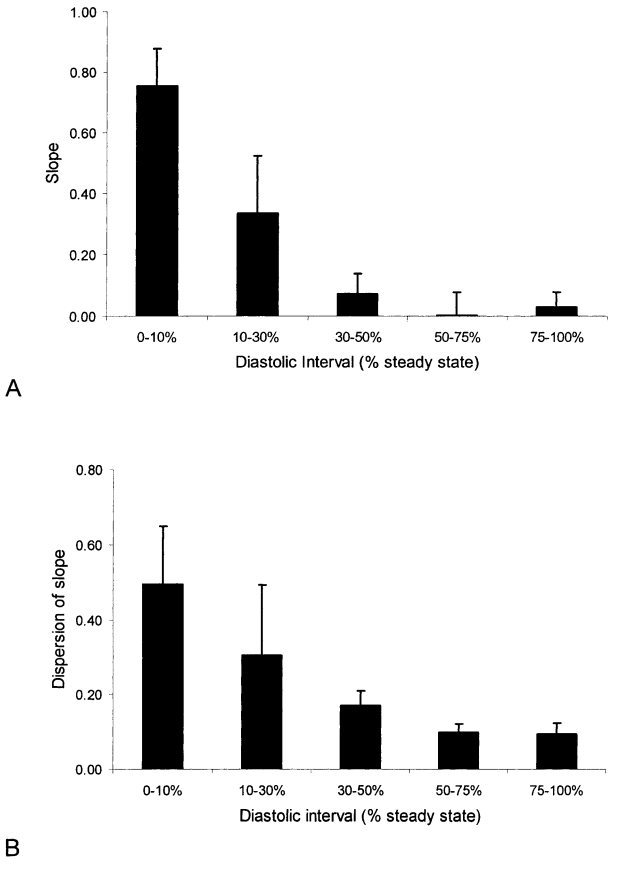

Figure 5. Activation-recovery interval restitution slopes at different diastolic intervals. Mean (±SD) restitution slopes **(A)** and dispersion of restitution slopes **(B)** are greatest in the initial 0% to 10% of the restitution curves.

The time course of APD changes with proximity to the refractory period of a preceding beat has been previously described in animal and human studies. In cat papillary muscle (23) and right ventricle of the in vivo human heart (3,8,14,15), the restitution curve assumes biphasic or triphasic characteristics, with a steep initial phase up to a diastolic interval of about 50 ms, then reaching a supernormal phase before the plateau phase toward the steady-state diastolic intervals. Our results using noncontact mapping are consistent with these studies.

In contrast to Purkinje fibers, which have a monotonic restitution response, the early time course of electrical restitution curves from the human ventricle may be biphasic or triphasic and variable between different endocardial segments. This lends further support to the assertion that restitution curves should not be fitted with a simple mathematical function (e.g., mono-exponential curve) because this would result in smoothing of physiological data (16). Biphasic or triphasic time course of early ARI restitution is observed in a minority of sites in our study probably because ARI measurement is validated at the 90% repolarization time point (18). This may not be as sensitive as the 70% repolarization time point, which has been used in monophasic action potential recordings to detect complexities of early restitution (8).

We have found restitution slopes of >1 at 25% of all sites without exogenous adrenergic stimulation. The restitution hypothesis in its original form proposes that, in a homogeneous two-dimensional medium without conduction uncoupling, a steep slope of >1 predisposes to APD alternans, spiral wave breakup, and degeneration into VF, whereas flattening of the restitution slope to <1 promotes stability of a spiral wave and transition from VF to monomorphic ventricular tachycardia (7,9). Thus far, studies in animal models and a study in the human ventricle at two sites have identified restitution slopes of >1 (17,24–26). However, the global electrical restitution patterns of patients at high risk of ventricular arrhythmias and sudden death have not yet been defined. Our results suggest that ARI restitution slope of >1 is found at only a minority of endocardial segments in patients at low risk of sudden cardiac death.

We have also shown that there is significant global heterogeneity of restitution slopes during the steep phase of APD restitution in the human heart. There is interventricular variation with the mean slope in the left ventricle significantly greater than the right ventricle with an overall mean of 0.79. Intraventricular variation of restitution slopes is also seen. Previous experimental work using optical mapping has shown a linear positive gradient of restitution with increasing distance from a pacing site, although restitution slope was not specifically calculated (27). Our results suggest that this relationship is less predictable but nevertheless heterogeneity exists. The steeper slopes in the LV

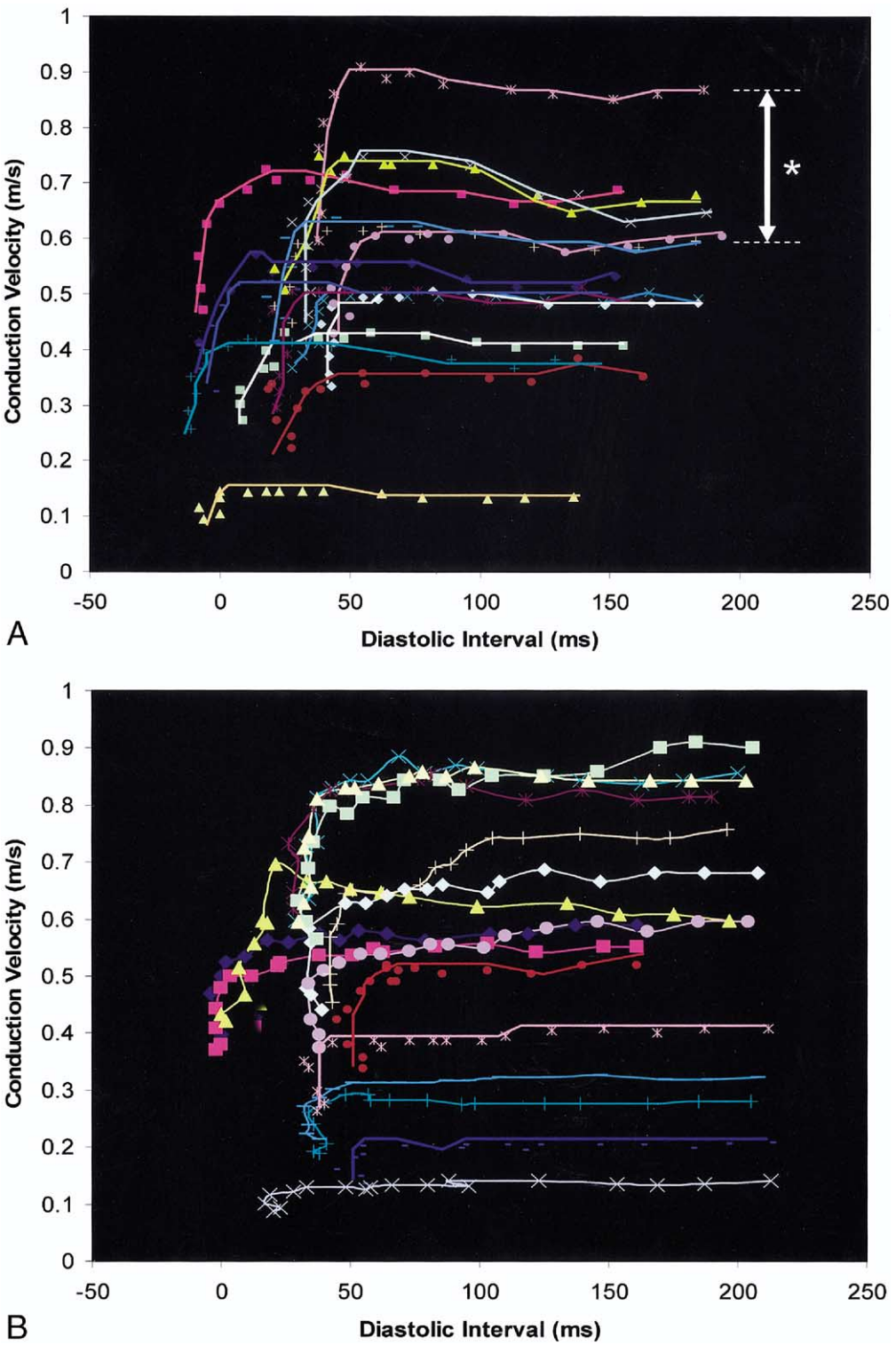

Figure 6. Global conduction velocity restitution curves from a right ventricle **(A)** and a left ventricle **(B)**. Measurements are taken from 16 segments in each ventricle at the same sites as in Figure 3. *Magnitude of CV restitution for site 14 of the right ventricle.

compared to RV could be consistent with a transventricular restitution gradient induced by premature stimulation at the RV apex, or it may be an intrinsic property of the LV. It is notable that restitution curves with the steepest slopes (>1) are located close to sites of ablation in three of three patients with idiopathic left ventricular (fascicular) tachycardia previously inducible by programmed electrical stimulation, but in 0 of 5 patients with focal ventricular outflow tachycardia. This suggests that dispersion of ARI restitution slope may represent a substrate for initiation of re-entrant ventricular

Table 2. ARI Restitution Slope and Magnitude of Restitution

Patient	Study Ventricle	Maximum ARI Slope Mean (Range)	Magnitude of ARI Restitution (Mean ± SD%)	Magnitude of CV Restitution (Mean ± SD%)
1	Right	0.78 (0.28–1.47)	18 ± 6	33 ± 8
2	Right	0.55 (0.28–0.91)	18 ± 7	12 ± 6
3	Right	0.61 (0.06–0.99)	19 ± 4	23 ± 7
4	Right	0.66 (0.33–1.00)	15 ± 4	39 ± 7
5	Left	0.99 (0.63–1.37)	24 ± 5	17 ± 3
6	Left	1.25 (0.45–2.14)	23 ± 12	34 ± 3
7	Left	1.03 (0.25–2.22)	25 ± 9	26 ± 5
8	Left	0.46 (0.14–0.91)	5 ± 6	19 ± 4
All		0.79 ± 0.41	18 ± 9*	25 ± 10*

Magnitude of restitution is presented as percentage of steady state value (see Fig. 6A). *$p < 0.001$ (see text).
ARI = activation-recovery interval; CV = conduction velocity.

arrhythmias as suggested by Pak et al. (17), but this supposition requires further evaluation.

The range of conduction velocities at specific segments during steady-state pacing are consistent with those measured in optical mapping studies (11,25). However, the magnitude of maximum CV restitution in our patients (25%) is greater than the rabbit model (5%, from 67 to 64 cm/s without pharmacological challenge) (11) despite the latter study being performed with a pacing drive cycle length down to 110 ms. In our patients, ARI restitution is heterogeneous, has a magnitude of 18% of steady-state ARI, and plateaus after the initial 38 ms (22% of the diastolic interval at resting state). In contrast, CV restitution has a greater magnitude of 25%, but reaches a plateau after only 10 ms (6% of the diastolic interval at resting state) in the initial phase of the curve and therefore operates at a very narrow range of diastolic intervals. Thus, ARI and CV restitution curves in this study resemble those in the experimental model of VF induction by rapid pacing (10) and may have important implications on the electrical stability of the normal ventricle (12). During very rapid pacing or ventricular tachycardia that results in diastolic intervals of <10 ms, ARI restitution is likely to engage CV restitution because of the greater magnitude and steepness of the latter, which may lead to discordant alternans and VF. But at longer and more physiological diastolic intervals, the presence of a flat CV restitution response may dampen the effects of ARI heterogeneity and thus maintain electrical stability.

Clinical implications. Global APD and CV restitution can be determined in the clinical setting. The S1-S2 pacing protocol in this study yields results similar to those achieved with dynamic pacing in the human ventricle (17). It is therefore unlikely that cardiac memory significantly complicates extrapolation of experimental restitution data to arrhythmogenesis in the human heart. Under physiological conditions, we have shown that CV restitution may be an important factor that maintains electrical stability despite heterogeneity of APD restitution. In cardiac ischemia, APD restitution is flattened but the steepness of CV restitution is increased, thereby resulting in the degeneration of ventricular tachycardia to type-2 VF (11). In right ventricular cardiomyopathy, exaggerated dispersion of APD restitution between adjacent myocardium (3) may overcome the stabilizing effects of CV restitution and serve as a mechanism for phase-2 re-entry and arrhythmia initiation. We propose that the global pattern of coupling between APD and CV restitution is more important than APD restitution slope per se in determining ventricular electrical stability. Further clinical studies of the interactions between APD and CV restitution in patients predisposed to VF may elucidate in vivo mechanisms that destabilize wavefront propagation and result in VF induction.

Study limitations. Potential errors may exist in estimating the distance of impulse propagation. These are minimized by measurements made perpendicularly to lines of isochrones to mimic the actual propagation pathway. Conduction velocity is inversely correlated with activation delay which may have two components: local capture delay and conduction time further downstream. Nevertheless, the local activation times and conduction velocities measured reflect the exact input of activation wavefront to the specific sites (11). Ventricular fibrillation can be induced by high-rate pacing (28) but this has not been performed in our patients because of ethical constraints. For the same reasons, short S1 drive pacing rate has not been used, but its absence could explain the discrepancy in restitution slopes between this study and animal models.

Conclusions. Noncontact mapping can be useful as a clinical tool to investigate spatial dispersion of APD and CV restitution in the human ventricle. In this study, we have demonstrated that ARI restitution is heterogeneous with a slope of >1 at 25% of all sites, whereas CV restitution is narrow and steep. This may provide insight into the instantaneous and global processes of activation and repolarization in patients at high risk of ventricular arrhythmias.

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