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Restitution Kinetics of Ventricular Action Potential Duration In the Human Heart

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Abstract: Recent animal experiments and computer modeling have suggested that cardiac tissues showing steep slope (>1) of action potential duration (APD) restitution would provide a dynamic instability of refractoriness causing a wave break, which is required for the genesis of polymorphic ventricular tachycardia or ventricular fibrillation. However, much remains to be clarified as to the APD restitution kinetics in the normal ventricular myocardium of humans. Monophasic action potentials were recorded from the right ventricular apex and outflow tract in five patients who had no ventricular tachyarrhythmias or structural heart disease. APD restitution kinetics was estimated by a standard S1-S2 protocol. The APD restitution curve was constructed by plotting APD_{90} for each premature stimulus (S2) as a parameter of the preceding diastolic interval. The average values of $slope_{max}$ of APD restitution curve were 0.44±0.09 in RVA and 0.49±0.10 in RVOT. The $slope_{max}$ did not exceed 1.0 at any recording sites. These results suggest that normal ventricular muscle in humans have minimal repolarization instability initiating wave break.

Key words: restitution, action potential duration, ventricular fibrillation

Polymorphic ventricular tachycardia (PVT) and ventricular fibrillation (VF) are life-threatening arrhythmias. These cardiac tachyarrhythmias are the result of meandering and breakdown of spiral-type functional reentry in the ventricle. A localized conduction failure (wave break) is necessary for initiation of these activities. In addition to the spatial variation of refractory periods (pre-existing heterogeneity of refractoriness), its temporal variation (dynamic instability of refractoriness) plays crucial roles in the genesis of wavebreak. Recent animal experiments and theoretical studies using compute modeling (Franz et al, 1988; Karma et al, 1994; Qu et al, 1999; Garfinkel et al, 2000; Weiss et al, 2000; Swissa et al, 2002) have suggested that dynamic change in action potential duration (APD) as a function of the preceding diastolic interval (DI) is critical; a steep (> 1) slope of the APD restitution curve would cause divergent fluctuations of APD, and conduction failure leading to wave break as the action potential upstroke (wave fronts) collides with the refractory of the preceding action potential (wave tails). Although the APD restitution properties have been relatively well characterized in experimental animals, limited information is available for the human heart (Kim et al, 2002; Taggart et al, 2003). The present study was designed to investigate this issue by recording monophasic action potentials (MAPs) from the right ventricular myocardium.

Materials and Methods

1. Patients:

The study was carried out in 5 patients who admitted to Shizuoka Saiseikai General Hospital (Shizuoka, Japan) for electrophysiological evaluation and treatment for supraventricular arrhythmias. All the patients were males and their ages were 55±7.2 years (29 to 72 years). None of the patients showed abnormal values in the echocardiographic parameters (Table 1). No ventricular tachyarrhythmia including VT or VF was documented in 24-hour Holter monitoring in any patient. The study was approved by the Ethical committee of Shizuoka

Table 1 Clinical and Electrocardiographic Characteristics of Patients

Pt. No.	Age,y	Sex	Arrhythmia	LV ejection fraction (%)	LA dimention (mm)
1	72	M	AFL	71	42
2	45	M	AVNRT	76	31
3	60	M	AVNRT	75	40
4	29	M	AVRT	74	35
5	69	M	AVRT	77	41

AFL = atrial flluter; AVNRT = atrioventricular nodal reentrant tachycardia; AVRT = atrioventricular reentrant tachycardia; LV = left ventricular; LA = left atrum

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Saiseikai General Hospital, and all patients gave written informed consent.

2. Electrophysiological Study

All patients were studied under sedation with intravenous midazolam, and all antiarrhythmic drugs were discontinued at least 5 half-lives before the measurements. A steerable Franz catheter (EP Technologies Inc., USA) was inserted through the femoral vein into the right ventricle. MAPs were recorded from the right ventricular apex (RVA) and outflow tract (RVOT). The heart was driven by the application of electrical stimuli through a pair of electrodes of the same catheter, twice the diastolic threshold in intensity and 1 msec in duration, at a basic cycle length of 600 msec. Single premature stimuli (S2) were introduced after 8 beat trains of basic stimuli (S1) with progressively shorter S1-S2 intervals from 550 msec until reaching the refractory period. MAPs were measured at 90% repolarization (APD_{90}) and DI was estimated as the S1-S1 interval minus the APD_{90} of S1 (Figure 1, top panel). The APD restitution curve was constructed by plotting the APD_{90} for S2 as a parameter of the preceding DI, and fitted using a mono-exponential equation: $APD_{90} = A0 + A1\ [1 - \exp(-DI/\tau 1)]$. The steepest slope was defined as $slope_{max}$ of the APD restitution curve.

Data are presented as mean±SEM. The statistical significance of difference was analyzed by the Student's two-tailed unpaired *t*-test and P values less than 0.05 was considered as significant difference.

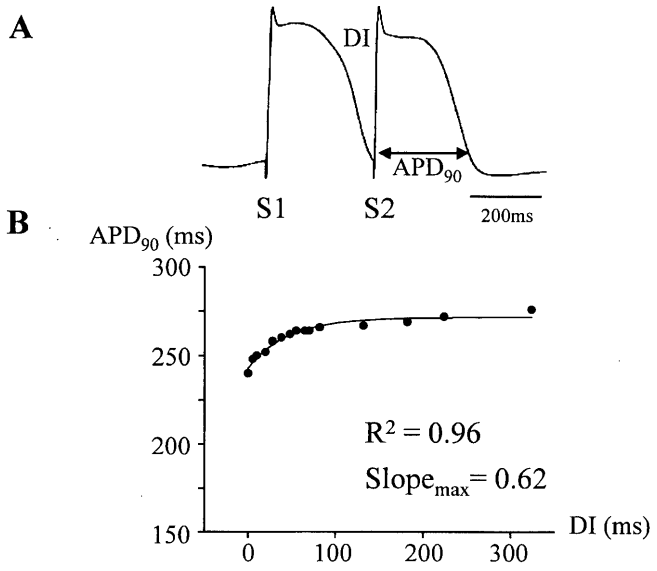

Fig. 1 Example of MAP (patient 1) obtained form RVOT.
A; The action potential duration induced by S2 with a S1-S2 interval of 20 ms was markedly abbreviated compared with the control action potential.
B; APD restitution curve at RVOT (patient 1)
The data points were reasonably well fitted by a single exponential function (R^2=0.96) and the curve gave a $slope_{max}$ of 0.62 at the shortest DI.

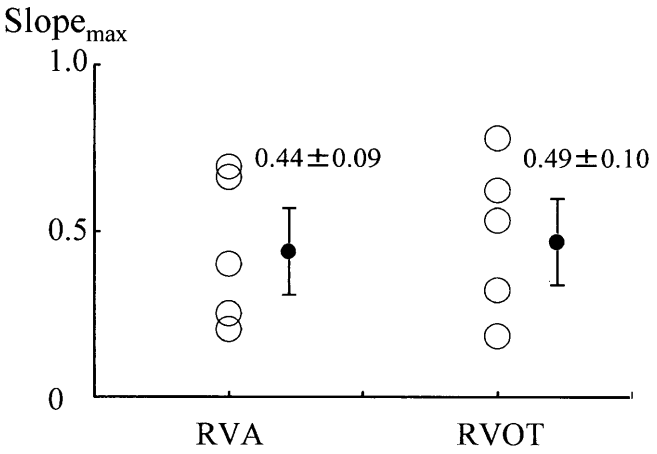

Fig. 2 $Slope_{max}$ of APD restitution in 5 patients
The values of $slope_{max}$ were 0.44±0.09 in RVA (left) and 0.49±0.10 in RVOT (right).

Results

Fig. 1A shows a representative tracing of MAPs recorded form RVOT of one subject. The action potential duration elicited by S2 with a S1-S2 interval of 20 msec was markedly abbreviated compared with the basal (S1) action potential. Fig. 1B shows a restitution of APD_{90} in this patient. The data points were well fitted with a single exponential function (R^2=0.96), giving rise to a $slope_{max}$ of 0.62 at short DIs.

Fig. 2 summarizes data obtained from RVA and RVOT of five patients. Values of $slope_{max}$ ranged from 0.20 to 0.69 (0.44±0.09, n=5) at RVA and from 0.18 to 0.78 (0.49±0.10, n=5) at RVOT. There was no significant difference between RVA and RVOT. All the values obtained from five patients did not exceed 1.0 at any recording sites.

Discussion

In the present study, we have shown that the $slope_{max}$ of the APD restitution curve is less than 1.0 at RVA and RVOT of human subjects who had no ventricular tachyarrhythmias. These results seem to suggest a dynamic electrical stability of normal human hearts in terms of minimal opportunity for the genesis of "wave break". It is important to note, however, other factors such as anatomical and electrophysiological heterogeneity and complex three-dimensional dynamics of spiral-type reentry also provide substrates for wavebreak initiating and maintaining VF and VT.

In contrast to our results, Taggart et al. (Taggart et al, 2003) have recently reported much higher values (1.053±0.092) in the $slope_{max}$ of the APD restitution curve from the right ventricular septum of humans. The discrepancy between these two studies could be explained by different methods to evaluate

the slope of the curve; in the study by Taggart et al. the restitution curves were fitted using overlapping least-squares linear segments, whereas they were fitted by single exponential curves in our study. However, it is possible that the different $slope_{max}$ values could reflect regional differences in the APD restitution kinetics in the ventricle. In guinea-pig hearts, regional differences in the APD restitution kinetics have been demonstrated by optical mapping on the ventricular epicardium (Laurita et al, 1996). Another explanation for their discrepant results from our present one is the effects of "cardiac memory"; APD is modulated not only by the immediate DI preceding the action potential but also by a history of previous excitations (Laurita et al, 1996; Koller et al, 1998; Riccio et al, 1999). Taggart et al. have shown that the $slope_{max}$ is lower at a shorter basic cycle length in humans. Nevertheless further studies will be needed to elucidate the restitution kinetics and their roles on the genesis of life-threatening arrhythmias in human ventricles.

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