Comprehensive Analyses of Arrhythmogenic Substrates and Vulnerability to Ventricular Tachycardia in Left Ventricular Hypertrophy in Salt-Sensitive Hypertensive Rats

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Background The contribution of conduction disturbances to susceptibility to ventricular tachycardia (VT) has not been directly examined in the process of left ventricular hypertrophy (LVH).

Methods and Results Dahl salt-sensitive (S) and -resistant rats were raised on a high-salt diet. After echocardiography, a fractionation study was conducted using wavelet transform analysis, which reflects conduction disturbances, recording of monophasic action potential (MAP), measurement of conduction velocity, and programmed extrastimuli for the induction of VT, as well as patch-clamp analysis at 10, 13 and 16 weeks (W) (n=7, each). Systolic blood pressure, wall thickness and MAP duration significantly increased at 10W in S rats, whereas conduction velocity decreased and MAP duration and the power of wavelet transform increased at 13W and 16W. Paired extrastimuli induced polymorphic VT only at 13W and 16W in S rats. VT frequency correlated inversely with conduction velocity and positively with MAP duration. Power of wavelet transform correlated negatively with conduction velocity and positively with VT vulnerability. The patch-clamp study revealed that the action potential duration significantly increased in S rats with aging, and correlated with MAP duration.

Conclusions Latently progressing slow and inhomogeneous conduction, as well as a repolarization abnormality, may contribute to VT vulnerability in hypertensive LVH. (Circ J 2007; 71: 390–396)

Key Words: Hypertrophy; Ventricular tachycardia; Wavelet analysis

Hypertensive left ventricular hypertrophy (LVH) is associated with an enhanced incidence of ventricular arrhythmia and an increased risk of sudden cardiac death^{1–3}. Although *in vitro* studies of hypertensive LVH have proposed various electrophysiological abnormalities (ie, impulse formation^{4,5} and conduction^{6–8} and repolarization abnormalities⁹) as arrhythmogenic substrates, it remains unclear how these factors directly relate to the vulnerability to ventricular tachyarrhythmia in the *in vivo* whole heart. In other words, it remains poorly understood just how these electrophysiological abnormalities develop and increase the vulnerability to ventricular tachyarrhythmia with progression of LVH. The arrhythmogenic potential in hypertensive LVH may be multifactorial, but susceptibility to ventricular tachycardia (VT) induction has not been simultaneously investigated in the same LVH preparations, and therefore the relationships between various underlying arrhythmogenic mechanisms and VT attack have not been clarified. A clear understanding of this pathophysiological linkage is essential for determining the therapeutic target for prevention of fatal ventricular tachyarrhythmia. To investigate this issue, we used Dahl salt-sensitive hypertensive rats in which concentric LVH develops in a relatively short

period¹⁰. Our preliminary study using this LVH model revealed that polymorphic VT was induced by programmed electrical stimulation, as shown by Coste et al in their clinical report¹. Thus, the objectives of this study were first, to quantify the vulnerability of VT to programmed extrastimuli, and the changes it undergoes during the development of hypertensive LVH; second, to clarify how this vulnerability of VT relates to arrhythmogenic substrates (ie, conduction disturbances defined by a decrease in conduction velocity and an increase in the fractionation of QRS complex, and repolarization abnormalities defined by increases in the absolute refractory period and monophasic action potential (MAP) duration); and third, to examine how cellular electrophysiological remodeling relates to conduction and repolarization abnormalities of the whole heart during the progress of LVH. For these purposes, we performed programmed electrical stimulation to induce VT at 3 different observation periods in Dahl salt-sensitive (S) rats and -resistant (R) rats, and compared the vulnerability to VT with the conduction velocity and the degree of inhomogeneous conduction evaluated by wavelet analysis^{12,13}, duration of MAP¹⁴ and absolute refractory period. In addition, myocytes were isolated from the same hearts, and patch-clamp analysis was performed for evaluation of resting membrane potential (RMP) and action potential (AP), as well as sodium (I_{Na}), calcium (I_{Ca}), and transient outward potassium currents (I_{to}).

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Fig 1. Schematic representation of the recording of the monophasic action potential (MAP). MAP was obtained from the central region of the left ventricular anterior wall. The time from the pacing spike (apical pacing rate: 600 beats/min) to the onset of upstroke of MAP recorded from the base of the left ventricle was defined as the conduction time.

Methods

This study conformed to the Fukushima Medical University Guidelines for Animal Experiments, the Japanese Government Animal Protection and Management Law (No. 115), and the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised 1996).

Animal Preparation

Six-week-old male S rats ($n=21$) and R rats ($n=21$) (Life Science Center, Japan) were used in this study. They were caged individually in a constant environment (room temperature, $23\pm 1.5^\circ\text{C}$; humidity, $55\pm 5\%$) and were allowed free access to a high-salt diet (NaCl 6%) and water up to 16 weeks of age. Experiments were performed at 3 different ages to investigate arrhythmogenic substrates during progression of hypertrophy: at 9–10 weeks (10W), 11–13 weeks (13W) and 14–16 weeks old (16W, $n=7$ for each period in both groups).

Experimental Protocol

On the day of an experiment, we measured the blood pressure of the tail artery and heart rate using an oscillometric method (UR 5000, Ueda, Japan) while the animal was conscious. The rats were then anesthetized with ether followed by intraperitoneal administration of sodium pentobarbital (50 mg/kg body weight). After anesthesia, hair was shaved in the precordial area for 2-dimensional echocardiography (DE), and on both sides of the chest, the back, head and sacral area for electrocardiogram (ECG) recording. After body surface ECG were recorded for wavelet analysis, 2-DE was performed with the rats supine. The right carotid artery was then cannulated (PE50, Intramedic, USA) for monitoring of aortic blood pressure and fluid supplementation. Next, the chest was opened under artificial ventilation using a rodent ventilator (683, Harvard, USA), and an electrophysiological study of the in situ heart was performed. Finally, the heart was isolated with Langendorff's perfusion, and ventricular myocytes were isolated for whole-cell patch-clamp analysis.

Body Surface ECG and Wavelet Analysis

Three bipolar ECGs (X lead: at left+ and right-axillary line in the 5th intercostal space; Y lead: on the thoracic spine+ and sternum- at the same level as X lead; and Z lead: on the sacral+ and occipital-region) were obtained

(0.03–10 kHz) in electrically shielded cages using a high-precision amplifier (RECTIGRAPH-8K, Sanei, Japan) and electrodes for electroencephalography (SEE101, Necmed, Japan). Data were recorded on a thermal printer (PC216Ax, Sony, Japan) and stored on magnetic tape (DT-120RA, Sony, Japan) for wavelet analysis. After the experiment, the QRS complex was digitized at 6 kHz, and the vector magnitude ($\sqrt{X^2 + Y^2 + Z^2}$) was averaged at approximately 20–40 consecutive beats as described previously.¹³ Wavelet transform was obtained at 40, 100, 160, 240, 320 and 400 Hz of the central frequency of the analyzing wavelet, and the area under the wavelet transform at each frequency was calculated as the increase in power with fine fractionation of the QRS complex reflecting inhomogeneous conduction.¹³

Transthoracic 2-DE

2-DE was performed using an echocardiographic system equipped with a 10-MHz transducer (Hewlett-Packard, SONOS 100CF, USA). Left ventricular (LV) end-diastolic (LVDD) and end-systolic diameters (LVDS), and wall thickness of the interventricular septum (IVS) were measured and shown as average values of 15 consecutive beats. The LV ejection fraction (LVEF) was calculated using the cubic method with the following formula: $\text{LVEF (\%)} = (\text{LVDD}^3 - \text{LVDS}^3) / \text{LVDD}^3 \times 100$.

MAP and Conduction Velocity

After the chest was opened, we used hook electrodes for detection of premature ventricular beats while monitoring and recording 3 epicardial orthogonal bipolar ECGs (LV lateral wall to right ventricular free wall; left anterior wall to inferior wall; LV apex to base in the lateral wall). For ventricular pacing, the paired hook electrodes were positioned 2 mm apart at the LV apex. Wilson's indifferent electrode was constructed from 3 needle electrodes at both upper limbs and the left leg.

After these preparations, the MAP of Wilson's indifferent electrode was obtained by manually pressing the sharp-edged Ag–AgCl electrodes on the epicardium in the center of the LV anterior wall. The duration of the MAP was measured at the level of 90% of the maximal amplitude at the base of the LV anterior wall under a ventricular pacing of 600 beats/min (Fig 1); when a ventricular pacing rate of 600 beats/min was impossible, the rate was decreased to 500 beats/min and then 400 beats/min. The time from the pacing spike to MAP onset was defined as the conduction

Fig2. Induction of ventricular tachycardia (VT) by the extrastimulus method. Paired extrastimuli with decreasing coupling interval were added after 10 bouts of pacing (600beats/min) in 13W rats. VT was hardly induced in salt-resistant (R) rats (Top panel). In contrast, polymorphic VT was easily induced in salt-sensitive hypertensive (S) 13W rats (Bottom panel).

Table 1 Comparisons of BW, Echocardiographic and Electrophysiological Variables Between S and R Rats

	R rats			S rats		
	10W	13W	16W	10W	13W	16W
BW (g)	303±29	360±26*	405±41**	312±31	336±24	361±40*
SBP (mmHg)	135±13	139±20	146±16	208±41##	226±27##	234±42##
HR (beats/min)	386±41	418±57	399±53	418±59	428±58	417±84
UCG IVS wall thickness (mm)	1.1±0.04	1.1±0.07	1.2±0.09	1.5±0.11#	1.6±0.33#	1.7±0.52*.,##
EDd (mm)	5.7±1.2	6.0±0.7	5.8±1.1	6.1±1.1	5.7±1.1	5.2±0.7
EF (%)	95±3	92±1	94±3	91±5	90±7	89±6
ECG MAP duration (ms)	66±4	73±3	77±8	81±11#	98±14*.,##	114±15*.,##
Conduction velocity (cm/s)	76±12	77±5	77±11	73±4	56±7##	50±12*.,##

BW, body weight; S, salt-sensitive; R, salt-resistant; SBP, systolic blood pressure; HR, heart rate; UCG, echocardiography; IVS, inter-ventricular septum; EDd, end-diastolic dimension; EF, ejection fraction; ECG, electrocardiogram; MAP, monophasic action potential.

* $p < 0.05$ vs 10W, ** $p < 0.001$ vs 10W, # $p < 0.05$ vs R rats in same period, ## $p < 0.001$ vs R rats in same period.

time (Fig1). After the distance of the epicardial surface from the pacing site to the MAP recording site was measured using cotton thread, the conduction velocity was calculated as the distance/conduction time (cm/s).

Measurement of Refractory Period and Induction of VT

Electrical stimulation was a square wave with a width of 1 ms at 3.5 V (Stimulator 3F51, Sanei, Japan). Extrastimuli were added after 10 round of pacing (S1) at 600beats/min. For induction of VT, 2 extrastimuli (S2 and S3) were added after 10 bouts of pacing at 600beats/min, and coupling intervals that were initially 90 (S1–S2) and 80 ms (S2–S3), as shown in Fig2, were reduced by 10ms, respectively, after 10 bouts of pacing; this form of extrastimuli was repeated 10 times. The reduction in the coupling intervals of extrastimuli was repeated until extrastimuli S2 and S3 failed to induce ventricular excitation, after which we increased both S1–S2 and S2–S3 by 2 ms to find the exact timing needed to induce no ventricular excitation. This period of S1–S2 was defined as the refractory period. VT was defined as equal to or more than 3 consecutive premature ventricular beats (Fig2). VT vulnerability was defined as the frequency of VT induction during 10 bouts of extrastimuli with certain coupling intervals.

Whole-Cell Patch-Clamp Analysis

Cell Preparation Single myocytes were enzymatically dissociated from the LV as described previously¹⁵ The excised hearts were perfused on a Langendorff apparatus with the following solutions in sequence: (1) normal Tyrode

solution for 2 min to wash excess blood from the heart; (2) nominally Ca^{2+} -free Tyrode solution for 5 min; (3) enzyme solution containing 0.01% WV^{-1} collagenase (Wako, Osaka, Japan), and 0.002% WV^{-1} alkaline protease (Nagase, Tokyo, Japan) for 60–80 min; and (4) Kraftbruhe (KB) solution for 3 min. The cells were kept in the KB solution at 4°C and were studied within 6h of isolation.

Whole-Cell Clamp The whole-cell patch-clamp technique was performed as described previously¹⁶ We generated ramp pulses to induce I_{Na} and I_{Ca} using a function generator (NF, Tokyo) as described previously¹⁷ AP was recorded at 10-s intervals using a K^{+} -pipette solution and Tyrode external solution as described previously¹⁶

I_{to} was elicited by depolarizing square pulses of 200-ms duration to the voltage range between -40mV and $+60\text{mV}$ with 10mV steps from the holding potential of -40mV . The pulse was given every 8 or 10 s. I_{to} was obtained as a 4-aminopyridine-sensitive current by subtracting the current in the presence of 4-aminopyridine from the control currents before applying 4-aminopyridine. The peak for I_{to} was extrapolated and its amplitude was measured between the peak and a steady state at the end of a 200-ms pulse. Because currents during the initial 2 ms after depolarization were capacitive transients, they were omitted. I_{to} density was obtained by dividing I_{to} amplitude by the cell capacitance (Cm) in each experiment¹⁶

Solutions and Drugs The composition of the Tyrode and pipette solutions has been described previously¹⁶ The composition of the modified KB solution was 70mmol/L KOH, 40mmol/L KCl, 50mmol/L L-glutamic acid, 20mmol/L

Fig 3. Comparison of wavelet transform of the QRS complex between salt-sensitive hypertensive (S) and salt-resistant normotensive (R) rats. (A) Wavelet transforms of the QRS complex at 40, 100, 160, 240, 320 and 400 Hz of the central frequency of the analyzing wavelet were superimposed on the S (13W, Top panel) and R (13W, Bottom panel) rats, showing that the duration and number of peaks increased in S rats compared with R rats. The area under the wavelet transform (ie, power) also increased in S rats compared with R rats [(B) 160 Hz (P160), (C) 240 Hz (P240)]. This suggests an increased fine fractionation of the QRS complex, reflecting inhomogeneous conduction. * $p < 0.05$.

taurine, 20 mmol/L KH_2PO_4 , 3 mmol/L MgCl_2 , 10 mmol/L glucose, 0.2 mmol/L ethylene glycol-bis (3-aminoethyl ether)- N,N,N',N' -tetraacetic acid, and 10 mmol/L HEPES (pH 7.2 adjusted with KOH). For recording APs, cells were perfused with Tyrode solution. For the measurements of whole cell I_{to} (Ca^{2+} -insensitive component of I_{to}), 10 $\mu\text{mol/L}$ nifedipine was added to the external solution to block the calcium current, and the pipette solution contained 10 mmol/L BAPTA to chelate intracellular Ca^{2+} .

Statistical Analysis

Data are expressed as mean $\pm$ standard deviation. For comparisons among data derived from the 6 groups (ie, 10W, 13W and 16W in both R and S groups), 1-way analysis of variance was used, followed by Fisher's exact probability test as a post hoc test. Relationships between 2 indices were analyzed by linear regression analysis. A level of $p < 0.05$ was regarded as statistically significant.

Results

One S rat died suddenly 16 weeks before the experiment. Therefore, 6 S rats were examined at 16W. Spontaneous ventricular premature beats were not observed in any rats during the approximately 60 min of ECG monitoring (ie, during recording of body surface ECG and the electrophysiological study after thoracotomy). As shown in Table 1, body weight and heart rate in the conscious state did not differ between the 2 groups of rats in each period.

Blood Pressure and LVH

Systolic blood pressure was much higher in S rats than in R rats in all 3 periods, and tended to increase from 10W

to 16W. The thickness of the IVS in S rats was greater than that in R rats in all 3 periods, and increased over time (1.7 ± 0.52 at 16W vs 1.5 ± 0.11 at 10W in S rats, $p < 0.05$). On the other hand, neither LVEF nor LVDd differed between the 2 groups in all 3 periods or among all 3 periods in each group (Table 1).

Wavelet Analysis of Body Surface ECG

Fig 3A shows the power profile of wavelet transform at each frequency. The power at 160 and 240 Hz, but not at other frequencies, tended to be different between R and S rats in all 3 periods. At 160 Hz, the comparative power in S rats significantly increased only at 16W (Fig 3B). The power of wavelet transform at 240 Hz increased over time in both R and S rats ($p < 0.05$ in S, but not in R), and there were significant differences in the power between R and S rats in all 3 periods as shown in Fig 3C ($p < 0.05$, each).

Electrophysiological Study in the In Vivo Heart

Systolic blood pressure, wall thickness and MAP duration (S: 81 ± 11 vs R: 66 ± 4 ms, $p < 0.05$) increased at 10W in S rats (Table 1). MAP duration in S rats was longer than that in R rats in all 3 periods ($p < 0.05$, each), and increased over time (Table 1, Fig 4A). On the other hand, conduction velocity did not decrease at 10W, but rather declined at 13W and 16W in S rats compared with R rats. VT was not induced at either 10W or 13W in R rats, whereas R rats at 16W showed monomorphic VT at low frequency, but not polymorphic VT, in response to extrastimuli (Fig 4C). Importantly, polymorphic VT was frequently induced at 13W and 16W in S rats, but not at 10W (Fig 4C). VT induction among 10 bouts of extrastimuli occurred most frequently at intervals of S1–S2 of 83 ± 18 ms at 13W and 94 ± 16 ms at

Fig4. Comparisons of monophasic action potential (MAP) (A), conduction velocity (B), and inducibility of ventricular tachycardia (VT) (C) between salt-sensitive hypertensive (S) and salt-resistant normotensive (R) rats among the 3 time periods. The duration of MAP increased at 10 weeks, and increased over time in S rats. On the other hand, conduction velocity did not decrease in S rats at 10 weeks, but decreased in 13 and 16W S rats. VT was not induced at 10 weeks in either R or S rats, but was easily induced in hypertensive rats after 13 weeks. * $p < 0.05$ vs 10W, ** $p < 0.001$ vs 10W, # $p < 0.05$ vs R rats in same period, ### $p < 0.001$ vs R rats in same period.

16W in S rats. Although all these VT inductions were associated with profound hypotension, they spontaneously recovered to sinus rhythm without exception (Fig 2).

Whole-Cell Patch-Clamp Analysis

Table 2 shows the results of whole-cell patch-clamp analysis. RMP and I_{Na} did not change over time in S rats (ie, there were no differences in RMP and I_{Na} between the 2 groups in all 3 periods (Table 2), whereas the AP duration at 600 beats/min of stimulation frequency significantly increased in S rats at 13W and 16W). I_{to} at 20 mV did not change at 10W between S and R rats, whereas it decreased over time in S rats, with a significant reduction at 16W compared with 10W ($p < 0.05$). On the contrary, the I_{Ca} tended to increase over time in S rats, but without reaching statistical significance.

Relationships Among the Electrophysiological Variables

Using data from both R and S rats at 10W, 13W and 16W, correlations between VT inducibility and conduction velocity, inducibility of VT and MAP duration, the power of wavelet transform and VT vulnerability, and power of wavelet transform and conduction velocity, were investigated. The inducibility of VT correlated negatively with conduction velocity, indicating that a slow conduction velocity induced VT vulnerability (Fig 5A, $r = -0.83$, $p < 0.001$). The frequency of VT correlated positively with MAP duration (Fig 5B, $r = 0.69$, $p < 0.001$). In addition, there was a significant correlation between conduction velocity and MAP duration ($r = -0.64$, $p < 0.01$, data not shown).

The power of wavelet transform, which indicates the degree of inhomogeneous conduction, correlated inversely with conduction velocity (Fig 6A, 240 Hz (P240): $r = -0.69$, $p < 0.01$) and positively with VT vulnerability (Fig 6B, 240 Hz (P240): $r = 0.66$, $p < 0.01$). AP duration obtained by the patch-clamp method correlated positively with MAP duration ($r = 0.69$, $p < 0.01$).

Discussion

This is the first study to comprehensively evaluate the linkage between various arrhythmogenic substrates and vulnerability to VT in hypertensive LVH. Despite the absence of a spontaneous ventricular premature beat in S rats, polymorphic VT was easily induced by paired extra-stimuli, which suggests that arrhythmogenic substrates sufficient to sustain reentrant VT are latently formed, even in compensatory LVH, without enhancement of abnormal impulse formation. In addition, this electrophysiological remodeling consistently progresses, even though the degree of LVH does not significantly increase, as shown from 10W to 13W in this study. The present study results suggest that not only repolarization abnormalities (ie, increases in MAP and AP duration), but also conduction disturbances (ie, slow conduction velocity) play important roles in the induction of VT in hypertensive LVH, whereas repolariza-

Table 2 Comparison of Cellular Electrophysiological Findings of S and R Rats

	R rats			S rats		
	10W	13W	16W	10W	13W	16W
RMP (mV)	-64 ± 3	-67 ± 8	-64 ± 8	-60 ± 6	-62 ± 7	-62 ± 6
AP duration (ms)	71 ± 21	69 ± 40	67 ± 12	83 ± 15	$127 \pm 30^{***}$	$139 \pm 51^{***}$
Na current (nA)	1.45 ± 0.21	1.99 ± 0.44	1.84 ± 0.58	1.79 ± 0.35	2.02 ± 0.76	2.15 ± 0.80
Ca current (nA)	0.48 ± 0.33	0.47 ± 0.17	0.46 ± 0.21	0.49 ± 0.42	0.70 ± 0.51	0.70 ± 0.33
I_{to20} (pA/pF)	4.44 ± 1.30	4.56 ± 1.20	4.28 ± 0.16	5.02 ± 1.53	3.47 ± 2.09	$2.08 \pm 1.04^{**}$

RMP, resting membrane potential; AP, action potential; I_{to20} , transient outward current in 20 mV. Other abbreviations see in Table 1.

* $p < 0.05$ and ** $p < 0.01$ vs 10W in same R or S rat group; # $p < 0.05$ and ### $p < 0.01$ vs R rat at in same period.

Fig 5. Relationships between inducibility of ventricular tachycardia (VT) and conduction velocity (A) or duration of monophasic action potential (MAP) (B) were obtained using data from both R and S rats in 10W, 13W and 16W. Both conduction velocity ($r = -0.83$, $p < 0.001$) and duration of MAP ($r = 0.69$, $p < 0.001$) were related to the inducibility of VT. S, salt-sensitive hypertensive; R, salt-resistant normotensive.

Fig 6. Relationships between power at 240 Hz (P240) and conduction velocity (A), inducibility of ventricular tachycardia (VT) and power of wavelet transform (B) were obtained using all data from R and S rats. There was a significant correlation between the power of wavelet transform at 240 Hz and conduction velocity ($r = -0.69$, $p < 0.01$; A). Moreover, a significant correlation ($r = 0.66$, $p < 0.01$; B) was found between inducibility of VT and power at 240 Hz. S, salt-sensitive hypertensive; R, salt-resistant normotensive.

tion abnormalities have been shown to be a major cause of polymorphic VT and ventricular fibrillation in hypertrophic cardiomyopathy.¹⁸ In addition, time-frequency analysis using a wavelet transform for the QRS complex of body-surface ECG may be a clinically useful method for detecting conduction disturbances that increase VT vulnerability in hypertensive LVH.¹⁹

In terms of determining conduction velocity, the limitation of this study is that we defined conduction velocity as the time from the pacing spike to the MAP onset between the center of LV anterior wall and apex, although recent mapping analysis can determine it accurately.^{20,21} In this study, we found that conduction velocity diminished at 13W and 16W, though it was not reduced at 10W. Previous studies have shown that conduction velocity is somewhat enhanced early in the hypertrophic process⁶ and that this is related to decreased intercellular junctional impedance and enhanced connexin expression.²² Thereafter, in the process of LVH, conduction velocity decreases with an increase in gap junctional resistance.⁶ In the present study, RMP determining cellular excitability and I_{Na} determining the velocity of AP upstroke did not change in rats with LVH, as in previous studies.^{23,24} Therefore, the decrease in conduction velocity we observed may relate to cell-to-cell conduction disturbances, presumably because of an increase in gap junctional resistance.²⁵ As previously reported,²⁶ cardiac interstitial fibrosis may also play a role in conduction disturbances.

The impairment of an intercellular connection can produce an inhomogeneous slow conduction and disruption of the excitation wavefront because of regional conduction blocking in the hypertrophied LV, which results in fine fractionations of the QRS complex of ECG. Wavelet analy-

sis is a time-scale technique that estimates the frequency content of a signal as a function of time.¹² It has been reported that highly fractionated local right ventricular electrograms in response to premature stimuli can identify hypertrophic cardiomyopathy patients at risk for sudden cardiac death.²⁷ Our results suggest that the fractionation study using wavelet analysis may be a useful non-invasive tool for risk stratification of fatal ventricular arrhythmia in hypertensive LVH.

The increase in AP duration in hypertrophied hearts has been a consistent finding.⁹ The duration of AP is primarily responsible for the time course of repolarization of the heart; prolongation of the AP produces delays in cardiac repolarization. It was estimated using computer simulation that the size of a meandering pattern increases, and the degree of VT polymorphism amplified, when AP duration is increased.²⁸ The results of the present study support this concept from the experimental point of view. If the electronic interaction between cells is impaired because of an increase in gap junctional resistance, as mentioned earlier, intrinsic differences in AP duration would be revealed, and the enhanced dispersion of repolarization would facilitate reentrant VT.²⁹ In addition, inhomogeneous conduction may further increase the dispersion of repolarization.

The reduction in the current density of I_{to} is the most consistent ionic current change in cardiac hypertrophy and failure.³⁰ Notable exceptions have been found in studies of compensated pressure overload hypertrophy, which were associated with either no change³¹ or an increase in I_{to} density.³² This discrepancy in our results seems to be explained by the duration of pressure overload (Tables 1, 2). The tendency toward an increase in I_{Ca} may also contribute to the prolongation of AP duration, which also seems to depend

on the duration of pressure overload.

Although it was also a study limitation to quantitatively estimate the relative role of each arrhythmogenic mechanism in a VT attack in this study, our results emphasize that arrhythmogenic substrates that facilitate reentrant VT would latently progress even in compensatory pressure overload LVH, without any manifestation of spontaneous ventricular premature beats, a finding that suggests the usefulness of the fractionation study in predicting the risks of fatal ventricular tachyarrhythmia.

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