Regional prolongation of ARI and altered restitution properties cause ventricular arrhythmia in heart failure

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Watanabe, Tetsu, Michiyasu Yamaki, Sou Yamauchi, Osamu Minamihaba, Takehiho Miyashita, Isao Kubota, and Hitonobu Tomoike. Regional prolongation of ARI and altered restitution properties cause ventricular arrhythmia in heart failure. Am J Physiol Heart Circ Physiol 282: H212–H218, 2002.—The mechanism of arrhythmogenicity in heart failure remains poorly understood. We examined the relationship between electrical abnormalities and ventricular arrhythmia by using experimental heart failure models. Sixty unipolar electrograms were recorded from the entire cardiac surface in control dogs (n = 13) and pacing-induced heart failure dogs (n = 16). In failing hearts, activation time (AT) was delayed at the apex, and AT dispersion increased in failing hearts. Activation-recovery intervals (ARI) were prolonged mainly at the apex and ARI dispersion was significantly augmented. The slope of the ARI restitution curve, interaction of diastolic interval, and ARI in failing hearts was significantly steeper than in control hearts. Ventricular fibrillation (VF) was easily induced by programmed stimulation in failing hearts, whereas no arrhythmia occurred in control hearts. Computer simulation studies could reproduce the experimental results. Altering the ARI restitution to the steep slope causes VF in a model heart. It is suggested that electrical remodeling, especially steepness of electrical restitution, may play a role in arrhythmogenicity in failing hearts.

restitution hypothesis; simulation

ADVANCEMENTS IN MEDICAL THERAPY have improved survival for patients with congestive heart failure in the past decade (4, 16a). However, total mortality is still high, and sudden deaths account for approximately half of the mortality (11). Ventricular arrhythmia contributes significantly to sudden death in patients with heart failure (11, 18) and alterations in electrophysiological properties have been demonstrated. Myocytes and isolated tissue from failing hearts of animals and humans consistently reveal abnormalities mainly in repolarization such as action potential prolongation (12, 16, 21). In general, action potential prolongation can predispose to dispersion of repolarization and the development of afterdepolarizations (22). Dispersion of repolarization leads to reentrant arrhythmia, and afterdepolarization leads to triggered arrhythmia. However, the relationship between electrical alteration and ventricular arrhythmia in failing hearts is poorly understood. The pacing-induced heart failure model reliably reproduces the resulting abnormalities similar to human heart failure (1, 27, 28), including biventricular dysfunction (1), increases in plasma norepinephrine and renin and atrial natriuretic factor (28), and altered gene expression (27). In the present study, we examined the relation between electrophysiological alterations and ventricular arrhythmia by use of this experimental model and a three-dimensional heart model to verify the mechanism of arrhythmogenicity in heart failure.

MATERIALS AND METHODS

Pacing-induced heart failure. Twenty-two adult mongrel dogs were anesthetized by intravenous administration of pentobarbital sodium (20 mg/kg body wt), and sterile unipolar endocardial leads were placed stereilery under fluoroscopic guidance at the right ventricular apex through the right internal jugular vein. A programmable pacemaker was connected to the leads and placed in a subcutaneous pocket at the base of the neck. Dogs were allowed to fully recover from surgery for 7 days, after which pacing was started at a cycle length of 300 ms for 3 wk. Thirteen dogs that underwent sham operation skin incisions were used as a control group. Experiments began a minimum of 2 days after the operation when the dogs had completely recovered. This study conformed to the guiding principles of animal experiments in Yamagata University School of Medicine, Yamagata, Japan.

Protocols and measurements. The dogs within the sham operation and heart failure groups (14–30 kg body wt) were anesthetized with pentobarbital sodium (25 mg/kg body wt) and received supplemental doses as needed. A respirator ventilated the dogs with room air supplemented with oxygen (3–5 l/min). Hemodynamic variables were measured with a micromanometer (Millar Instruments; Houston, Texas) after cessation of rapid ventricular pacing. Under controlled respiration, the thorax was opened in the fifth intercostal space, the pericardium was opened, and the pericardial cradle supported the heart at an appropriate position. The sinus node was crushed (19, 20, 23), and the right atrium was paced at
several basic cycle lengths using a model SEN-7203 stimulator (Nihon Koden; Tokyo, Japan). A sock-shaped electrode array was placed on the ventricular surface for simultaneous recording of electrograms from 60 epicardial sites. Each unipolar electrode consisted of fine silver wire (0.2 mm diameter) sutured to the electrode array (19, 20, 23), which consisted of 6 rows and 10 columns. All recording electrodes were referenced to the Wilson’s central terminal, and multichannel electrograms were digitized every millisecond using a multiplexed data processing system (CD-G015, Chunichi Denshi; Nagoya, Japan) as described in previous studies (19, 20, 23). The thoracic cavity was covered with plastic wrap to prevent cooling and dehumidifying, and body temperature was maintained at 37–38°C. An arterial line was inserted into the right femoral artery to continuously monitor mean arterial pressure. The electrocardiogram lead II and blood pressure were monitored throughout the study on a recorder (model 2G66, NEC San-ei, Tokyo, Japan).

Analysis of multichannel epicardial electrograms. Multichannel epicardial electrograms were processed on an off-line microcomputer (model SUN 4/2, SUN Microsystems; Mountain View, CA). Epicardial activation of each electrogram was defined as the minimal derivative of the QRS signal (17). The earliest activation was assigned to time 0, and the activation time (AT) was determined as the interval between time 0 and each activation. Recovery time (RT) was defined as the maximal derivative in the T wave. Activation-recovery intervals (ARI), defined as the time from AT to RT, were also measured (9). ARI is known to be well correlated to the action potential duration (APD) and effective refractory periods (9). We measured the dispersion of AT, RT, or ARI, defined as the difference between the longest and the shortest measured values in the same heart to evaluate electrical heterogeneity.

The relationship between ARI and diastolic interval (DI) was examined during atrial pacing at cycle lengths from 600 to 300 ms in steps of 100 ms and from 300 ms to the Wenckebach block in steps of 10 to 20 ms. The relationship between ARI and DI was fitted to a function of the type ARI = b(1 − e−a−DI), where b is a constant, to quantify them as an electrical restitution curve. The plateau level of b and the time course as the maximal slope of the restitution curve was derived in control and failing hearts.

Susceptibility of ventricular arrhythmia was investigated by programmed stimulation. The ventricular effective refractory period was determined with use of a driving train (S1) of 10 beats at a cycle length of 400 ms, followed by an extra stimulus (S2) that was decreased in 10 ms intervals. The ventricular effective refractory period was defined as the longest S1-S2 interval at which S2 failed to elicit ventricular activation. The second extrastimulus (S3) was started with the S1-S2 interval fixed at 40 ms longer than the ventricular effective refractory period. S2-S3 interval decrements until S3 failed to elicit ventricular activation. If double extrastimuli failed to initiate arrhythmia, a third extrastimulus (S3) was used.

At the end of the study, the heart was rapidly excised after induction of ventricular fibrillation (VF). At this point, biventricular weight was measured. The myocardium underlying the left and right ventricular free wall and apex was stained with hematoxylin-eosin for histological assessment of fibrosis and/or the size of myocardium.

Heart model and simulation protocol. A simulation study using the Wei-Harumi model was performed (8, 24). The model included atria and ventricles and was comprised of 50,000 discrete units (model cells). The model cells were categorized into eight types: sinus node, atria, atrioventricular node, bundle of His, bundle branch, Purkinje fibers, ventricular cells, and connective element. The electrophysiological properties of each model cell were specified as in previous reports (29) and were also specified as measurements in a representative pacing-induced heart failure model. Excitation automaticity was assigned only to sinus node cells. Other types of cells were activated from neighboring cells when those cells became excitable. When cells were absolutely refractory, conduction was completely blocked.

A parameter called the dynamic coefficient (DC) was associated with the coupling interval (CI)-dependent APD change (6). DC was defined as the difference in APDs divided by the difference in CIs. This parameter yields APD change with CI and is uniquely determined for each cell type.

The value of APD at time t is defined as APD(t) = APD(t − 1) + DC ∆CI where ∆CI is the change in CI for the model cell at time t.

Surface electrocardiograms were simulated by the heart model under the following simulation protocols: 1) normal condition (N) slow conduction and prolonged APD; or 3) slow conduction, prolonged APD, and greater DC. Each was the simulation of “normal heart,” “failing heart with normal restitution,” or “failing heart with abnormal restitution.” Parameters of ventricular cells, APDs, or DCs were determined based on the present experimental data to replicate the experimental observations. Parameters of Purkinje fibers, including 80% of DC, were determined based on the reported experimental data (7).

Trains of electrical stimuli were delivered to an anterior apex cell at a cycle length of 160 ms. The heart model was considered to be located inside a homogeneous torso model (Fig. 1). Surface potentials on the model torso generated by the heart model were calculated by means of the prescribed transmembrane action potential distribution (8, 24). This simulation generated a torso surface electrocardiogram, because we employed the boundary element method for calculation.

Statistical analysis. Quantitative data are reported as means ± SD. Statistical analysis was performed with ANOVA. A confidence level of 95% was considered statistically significant.

RESULTS

Clinical features and hemodynamics at the basal state. Thirteen sham-operated dogs had no apparent signs of pump failure throughout the observation period. Among 22 tachypacing dogs, six dogs (27%) suddenly died (four during pacing period and two due to the second surgical procedure). The remaining 16 dogs of the heart failure group were studied.

Hemodynamic measurements at baseline are summarized in Table 1. Compared with the control group, there were reduced left ventricular systolic pressure, elevated left ventricular end-diastolic pressure, and decreased peak positive and negative first derivatives of left ventricular pressure (dP/dt) in failing hearts. Hemodynamic results confirmed the presence of both systolic and diastolic dysfunction in the heart failure group.

Heterogeneity of ARI. In the 13 control and 16 failing dogs, surface distributions of AT, RT, and ARI were examined during right atrial pacing at a cycle length of 300 to 600 ms. Representative traces of AT, RT, and ARI maps in a control heart are shown in Fig. 2A.
earliest activation appears on the anterior right ventricle. Conduction delay is not recognized, and distribution of RT or ARI was almost uniform. A maximal ARI of 198 ms was located on the left anterior base. Figure 2B shows representative traces of AT, RT, and ARI maps in a failing heart. Prolongation of both RT and ARI is recognized mainly at the ventricular apex. Maximal ARI was 238 ms. Delayed ATs were also observed at the ventricular apex.

The maximal ARI in the failing group was significantly longer than in the control group at a cycle length of 300 to 600 ms (Fig. 3). We measured dispersion (d) of RT, AT, and ARI (ATd, RTd, and ARId) to evaluate spatial heterogeneity (Fig. 4). ATd, RTd, or ARId significantly increased in the failing group compared with the control group.

Restitution property of ARI. The restitution relation between ARI and DI was examined at the apical and the basal myocardium. Figure 5A shows the representative ARI restitution curves in two control and two failing hearts, and Fig. 5B shows the group difference in the maximal slopes between control (n = 6) and failing hearts (n = 6). In the representative curves, the slopes of the ARI restitution in failing hearts were steeper at short DI compared with control hearts. Average data confirmed that the slope of the ARI restitution curve at the apex of failing hearts was significantly steeper than that of control hearts (Fig. 5B). However, the slope of the ventricular base, where ARI was not prolonged, was almost equal to that of the control hearts.

Programmed electrical stimulation. Programmed electrical stimulation was performed to examine arrhythmogenicity in failing hearts. Ventricular tachycardia (VT) was easily initiated by double extrastimuli at a drive cycle length of 400 ms in all failing hearts (10 of 10 dogs), whereas no ventricular arrhythmias were initiated by the same extrastimuli in control hearts (0 of 8 dogs). Induced VT in failing hearts degenerated into VF (9 of 10 episodes). Figure 6 illustrates the initiation of VF caused by double extrastimuli on the left ventricle (Fig. 6A) or the right ventricle (Fig. 6B) in a failing heart. In the S3 excitation, conduction was blocked on the left posterior ventricular wall (Fig. 6A). Spontaneous excitation (VT1) initiated near the block line of the beat S3. Excitation of VT1 was again blocked on the left posterior ventricular wall, widely rotated around the apex, and reached the opposite site. Figure 6B shows a case of right ventricle stimuli. Block line was located on the right anterior wall. The excitation was blocked on this area and then rotated around the apex. In this dog, the excitation easily degenerates to VF.

Simulation study using a heart model. We performed simulation studies in following three setups: 1) normal heart, simulation 1; 2) heart with slow conduction and prolonged APD, simulation 2; and 3) heart with slow conduction, prolonged APD, and an increase in DC, simulation 3.

In simulation 1, we assigned 255 ms of APD, 0.5 m/s conduction velocity, and 0.4 of DC to each ventricular cell. In simulation 2, we assigned 295 ms of APD and...
0.4 m/s of conduction velocity to apical ventricular cells, and assigned 255 ms of APD and 0.5 m/s of conduction velocity to basal ventricular cells. APDs were gradually changed between apical and basal in the experimental study. Therefore 265, 275, or 285 ms of APD were assigned to transitional cells between apical and basal. In this simulation, the other setups were the same as simulation 2.

Figure 7A shows simulation results after four trains of stimulation are applied to each model heart. VF continued only when greater DC was applied (simulation 3). Increase in DC is essential for the induction of VF in the model heart. Figure 7B shows activation sequences at the initial phase of VF induction. These activation patterns support reentry as a mechanism of the arrhythmia.

Pathological findings in failing hearts. The hearts of the failing dogs showed visible dilation and pericardial effusion. However, there was no significant difference in either total ventricular weight or weight normalized for body weight between control and failing groups (Table 1). No significant change in body weight was recognized between the control and failing group. On histological examination, myocyte length, width and nuclear size appeared to be increased in the failing hearts.

DISCUSSION

In the present study, we examined the relation between electrophysiological alterations and ventricular arrhythmia in heart failure using a pacing-induced tachycardia heart failure model, which exhibited lethargic behavior, cardiac dysfunction, and fluid retention. The results suggested that 1) regional conduction disturbance, 2) augmented inhomogeneity of refractoriness, and 3) steepness of electrical restitution curve are important for arrhythmia vulnerability in heart failure. The simulation study verified that an increase in DC was essential for the induction ofVF. Altered electrical restitution properties may play an important role for arrhythmogenicity in heart failure.

Inducibility of ventricular arrhythmia. In the present study, applying double extrastimuli induced VF in failing but not in normal hearts. It has been postulated that triggered activity and automaticity are the mechanisms of ventricular tachyarrhythmia in failing hearts (13, 22, 30). Indeed, VT was not sustained, and VF was reproducibly induced (12, 30).
However, analysis of the activation sequence (Fig. 6) suggested that the VT1 wave was blocked at the apex along the border of prolonged ARI and then rotated around the apex. We assumed that the prolonged refractoriness at the apex might contribute to the formation of the conduction block and reentrant arrhythmia.

Restitution hypothesis and electrical instability in failing hearts. Recently, restitution properties have been focused on the transition between VT and VF (the restitution hypothesis) (15, 25). In a case of steep slope of the restitution curve, small changes of DI (extrastimuli) produced a larger change in the APD of the next beat. The larger the APD changes, the larger the DI changes. Therefore, alteration in the APD and DI was augmented, and finally VF occurred. Riccio et al. (15) reported that a steep slope of the electrical restitution curve was a prerequisite for VF, and reduction of the restitution slope prevented the development of VF. The simulation study using a model is an important process for linking the hypothesis to the observed phenomena. Therefore, we constructed the three-dimensional heart model simulating failing heart electrophysiology. The simulation results showed that increase in a parameter DC was essential for VF in heart failure. Because an increase in DC is compatible with steepness of ARI restitution, it confirmed the importance of restitution hypothesis on the mechanism of VF in heart failure. In the present study, the slope of ARI restitution at the ventricular base was almost equal to that of control hearts. It became steep only at the apex where the repolarization remodeling was seen.

It is suggested that a slope over 1 of restitution relation facilitates the induction of APD alternans (15). In the present study, the mean steepness of the ARI restitution slope was 0.74 at the apex in the failing heart during atrial pacing. However, VF was induced by ventricular extrastimuli. Because CIs were definitely shorter during ventricular extrastimuli than during atrial pacing, the slope of restitution relation

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Fig. 4. Dispersion (d) of ATd, RTd, and ARId in control or failing hearts. †P < 0.05 vs. control; ‡P < 0.05 vs. BCL of 300 ms.

Fig. 5. A: representative ARI restitution curves in control and failing hearts measured at the apical myocardium. Slopes of the ARI restitution curves in failing hearts were steep at short diastolic interval (DI) compared with control hearts. B: maximal slopes of the restitution curves in control (n = 6) and failing hearts (n = 6) on apical or basal myocardium. NS, not significant.
Spatial dispersion of refractoriness. Action potential prolongation is a consistent finding in human heart failure (3, 21) and experimental cardiac insufficiency (12–14, 30). In the present study, ARI, a compatible measure of APD, was prolonged mainly at the apex of the failing heart. The mechanism of action potential prolongation has been increasingly investigated on experimental failing myocytes (12, 26). These studies suggest a concomitant reduction in the transient outward current ($I_{to}$) density with a reduction in channel density. Because $I_{to}$ is an important current in setting the level of plateau currents, a decrease in this current contributes to early deviation of action potential configuration and action potential prolongation. The reduction on inward rectified K$^+$ current (3, 12) and slow inactivation of L-type calcium channel current are also reported in failing hearts (16). Total balance of these altered ion channels may determine the APD on failing hearts.

Slowing of ventricular conduction and an increase in dispersion of refractoriness were also seen. Clinically, interlead variability in the Q-T interval (Q-T dispersion) is a more powerful indicator of sudden death than the Q-T interval itself (2, 5). Q-T dispersion thoroughly reflects inhomogeneous recovery and should be the substrate of ventricular arrhythmia in chronic heart failure (2). A difference in ARI between the apex and the base contributed to augmented dispersion in repolarisation in the present experiments. APD significantly increased in failing hearts. This may be explained by histological changes characterized by interstitial edema and fibrosis. Both conduction delay and an increase in dispersion of recovery should be the substrate of arrhythmia in failing hearts.

In conclusions, the present study suggested that the restitution hypothesis is important for the development of VF in heart failure. Weiss et al. (25) suggested that pharmacological therapy that reduces the slope of the restitution relationship would be expected to suppress the development of VF. The approach for controlling arrhythmia based on the restitution hypothesis...
may provide new insights into the antiarrhythmic strategy in patients with heart failure.

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REFERENCES


15. Scamps F, Mayoux E, Charlemagne D, and Vassort G. Calcium current in single cells isolated from normal and hyper-}


