

Chapter 8

Electrophysiological Alterations in Cardiac Hypertrophy

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1. Introduction

Cardiac hypertrophy is one of the adaptive responses to mechanical, hormonal, and sympathetic stresses. If these stresses are persistent, the heart becomes decompensated, thereby leading to heart failure. During the structural and cellular remodeling, the electrophysiological alterations as well as disturbance of Ca^{2+} handling also proceed in the diseased hearts. These changes are likely to be responsible for the arrhythmogenic substrates seen in hypertrophied/failing hearts.

2. Arrhythmogenic Substrate in Hypertrophied/Failing Hearts

a. Action Potential Parameters

Prolongation of action potential duration (APD) is one of the most common electrophysiological features in hypertrophied and/or failing ventricular myocytes¹⁻⁵⁾. For example, our previous study revealed that APD of rat hypertrophied left ventricular myocytes (SHR: spontaneously hypertensive rat) was prolonged compared to that of normal one (WKY: Wistar-Kyoto rat) (Figure 1)⁴⁾. In some studies, decreases in resting membrane potential (RMP) and maximal rate of depolarization (max dV/dt) have been reported in hypertrophied/failing myocardium. However, in most studies, there have been no significant differences in RMP, action potential (AP) amplitude, and max dV/dt between hypertrophied/failing and normal hearts.

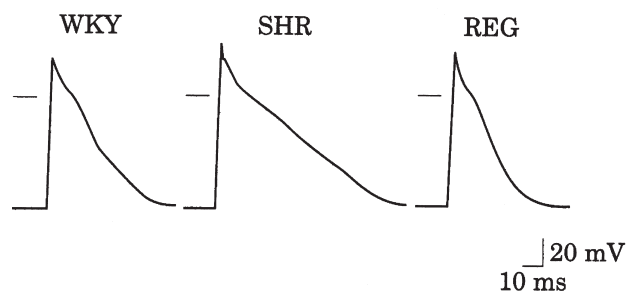


Figure 1 Action potentials in left ventricular subendocardial cells of WKY, SHR and SHR treated with captopril (REG). The cells were stimulated at 0.1 Hz and action potentials were recorded in the current-clamp mode.

Reproduced from Yokoshiki et al. (1997)⁴⁾.

b. Factors related to Propagation Velocity

According to the one-dimensional cable theory, the hypertrophied myocyte (i.e., greater cell diameter) promotes faster propagation because propagation velocity is a function of the square root of cell diameter. However, it has been reported that the conduction velocity in hypertrophied myocardium is lower probably due to the increase in cell-to-cell coupling resistance^{6), 7)}. For example, in rat hypertrophied ventricle, the longitudinal conduction velocity was reduced in parallel to the decrease in the gap junction protein, connexin 43, thereby changing the property of anisotropic conduction⁷⁾.

The decrease in fast Na^+ channel current (I_{Na}) has been reported in hypertrophied canine ventricular myocytes remodeled after myocardial infarction⁸⁾. In addition, the proportion of the inactivated Na^+ channels was increased in that study. Such a decrease in Na^+ channel availability may also be involved in the reduced conduction velocity.

c. Factors related to APD Prolongation and Unstable RMP

The ionic mechanisms of APD prolongation in hypertrophied/failing hearts have been investigated by the patch-clamp study as well as the molecular biological approaches. Most of these studies have revealed that the density of transient outward current (I_{to}) in hypertrophied/failing myocytes is decreased compared to normal one^{2), 4), 5)}. Depending on the inactivation property, I_{to} is classified as $I_{\text{to,f}}$ and $I_{\text{to,s}}$. The former inactivates faster, and the latter does slower. The molecular component of $I_{\text{to,f}}$ were thought to be Kv4.2 or Kv4.3, and that of $I_{\text{to,s}}$ was Kv1.4.

It has been reported that the expression level of mRNA of Kv4.2 and Kv4.3 is decreased in left ventricular hypertrophy due to renovascular hypertension⁹⁾ and hypertrophied myocardium adjacent to infarction¹⁰⁾, i.e., the remodeled myocardium. Moreover, expression of dominant-negative construct of Kv4.2 subunit in Kv1.4 knockout mouse has a phenotype similar to hypertrophied/failing hearts¹¹⁾. That is, it exhibited prolonged APD and early afterdepolarization (EAD), degenerating into ventricular tachycardia. Similar results have been reported in the transgenic mouse inhibiting the I_{to} ^{12), 13)}.

APD in rat and mouse is very brief, ranging 50 to 100 ms. In these small mammals, the contribution of I_{to} in repolarization process is relatively large. We also reported that prolongation of APD in rat left ventricular hypertrophy could result from the reduction of current density of I_{to} (Figure 2)⁴⁾. However, there are some differences in the components of membrane currents responsible for AP formation among distinct species. In general, APD becomes prolonged in association with increase in the heart size. For example, in human ventricular myocytes, APD reaches up to 300 ms. According to the simulation study by Priebe and Beuckelmann¹⁴⁾, the reduced current density of I_{to} was not likely to reproduce APD prolongation seen in human failing hearts. They proposed important components responsible for APD prolongation in those diseased hearts: a) increase in forward

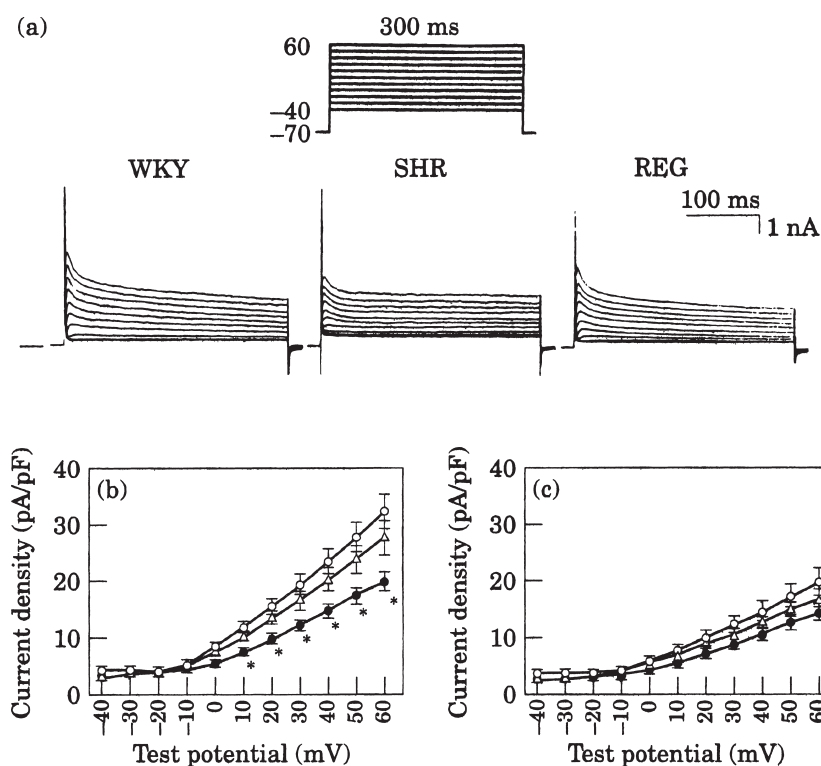


Figure 2 Voltage-dependent activation of transient outward current. (a) Voltage-clamp protocol and representative current tracings recorded during depolarizing steps from a holding potential of -70 mV to test potentials ranging between -40 and +60 mV in WKY, SHR and REG cells. REG indicates regression of left ventricular hypertrophy in SHR by chronic treatment with captopril. Cell capacitance was 109 pF in WKY cell, 170 pF in SHR cell and 102 pF in REG cell. Peak and steady-state current-voltage relation for WKY (open circle) ($n=12$), SHR (filled circle) ($n=13$) and REG (open triangle) ($n=13$) cells are shown in panel (b) and panel (c), respectively. * $P < 0.05$ vs. WKY. Reproduced from Yokoshiki et al. (1997)⁴.

mode of Na-Ca exchange current ($I_{Na/Ca}$), b) alterations in intracellular Ca^{2+} transients (especially the slower decay of Ca^{2+} transient, thereby increasing in intracellular Ca^{2+} during diastolic period), c) decrease in inward rectifier K^+ current (I_{K1}), and d) decrease in Na-K pump current (I_{Na-K}). In addition, high vulnerability to EAD-related arrhythmias in failing human hearts was shown because of the smaller repolarization reserve.

I_{K1} plays an important role in maintenance of RMP and promotion of repolarization especially at the late phase of AP. It has been reported that the current density of I_{K1} is decreased in hypertrophied/failing hearts^{5), 15)}. Inhibition of I_{K1} not only prolongs APD, but also decreases important background conductance. That

is, such a high membrane resistivity (i.e., a less leaky membrane) could facilitate the genesis of abnormal automaticity as well as delayed afterdepolarization (DAD). Furthermore, reappearance of hyperpolarization-activated inward current (I_h or I_f) has been reported in hypertrophied/failing ventricular myocytes¹⁶. I_f is usually expressed only in the conduction system that possesses automaticity.

3. Modulation of Arrhythmogenic Substrate

The electrophysiological substrates in hypertrophied/failing hearts are characterized as prolongation of APD (reduced repolarization reserve), unstable RMP and propagation abnormality (delay). These are based on the ionic channel remodeling as well as the disturbance of intracellular Ca^{2+} handling^{14, 17}. In combination to the delayed conduction velocity, the abnormalities and possible heterogeneity in K^+ channels and Ca^{2+} transients could result in augmented APD dispersion. Moreover, the affected substrates by modulating factors, such as ischemia, acidosis, catecholamine, and electrolyte abnormality, would generate fatal ventricular tachyarrhythmias, i.e., ventricular fibrillation (VF) and ventricular tachycardia (VT).

For example, in Langendorff perfused hypertrophied rat hearts (SHR), VT/VF occurred more frequently vs. normal hearts (WKY) within 15 minutes after left coronary artery ligation (Figure 3)³. Using papillary muscle preparations of left ventricle, the greater abbreviation of APD during simulated ischemia was observed

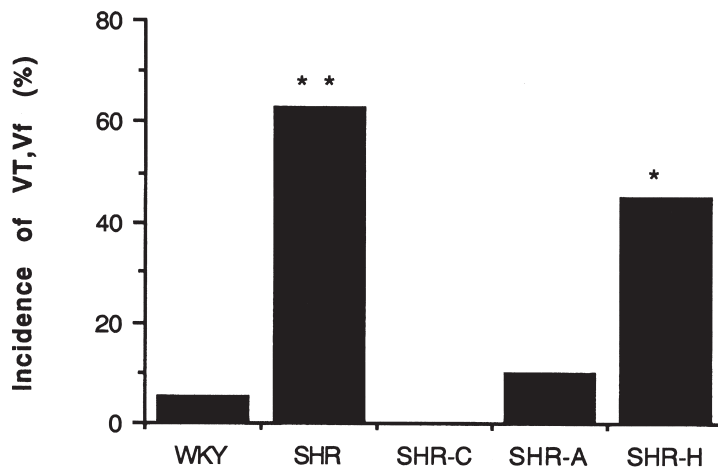


Figure 3 Bar graph showing the incidence of ventricular tachycardia (VT) or ventricular fibrillation (VF) during the 30-minute period after left coronary ligation. WKY indicates Wistar-Kyoto rats; SHR-N, spontaneously hypertensive rats (SHR) without treatment; SHR-C, SHR treated with captopril; SHR-A, SHR treated with angiotensin II receptor antagonist TCV-116; and SHR-H, SHR treated with hydralazine. * $P < 0.05$ and ** $P < 0.005$ vs. WKY. Reproduced from Kohya et al. (1995)³.

in these hypertrophied hearts which was in contrast to prolonged APD under oxygenated condition (Figure 4)³⁾. This greater shortening of APD at the area of regional ischemia could deteriorate APD dispersion, because APD in the non-ischemic zone is to be prolonged in hypertrophied/failing hearts. These alterations in the electrical substrate are likely to trigger the reentrant arrhythmias.

Although the mechanism of greater abbreviation of APD during ischemia remains to be determined, one possible explanation is due to changes of the property of ATP-sensitive K⁺ (K_{ATP}) channels. In the normal heart, the K_{ATP} channels¹⁸⁾ are masked (closed, inhibited) by the high intracellular ATP concentration ([ATP]_i) and become unmasked (opened, disinhibited) during ischemia (lower [ATP]_i), thus serving to protect ischemic myocardial cells. That is, increasing the total outward K⁺ current shortens the APD and thereby decreases Ca²⁺ influx and contraction and so conserves ATP.

It has been reported that the sensitivity of K_{ATP} channels to ATP becomes lower (i.e., higher IC₅₀ value) in hypertrophied feline left ventricular myocytes^{19), 20)}. The lower ATP sensitivity would facilitate openings of the channels even when decrease in [ATP]_i is small. These alterations of K_{ATP} channels may contribute to enhanced APD shortening in hypertrophied hearts during ischemia. On the other hand,

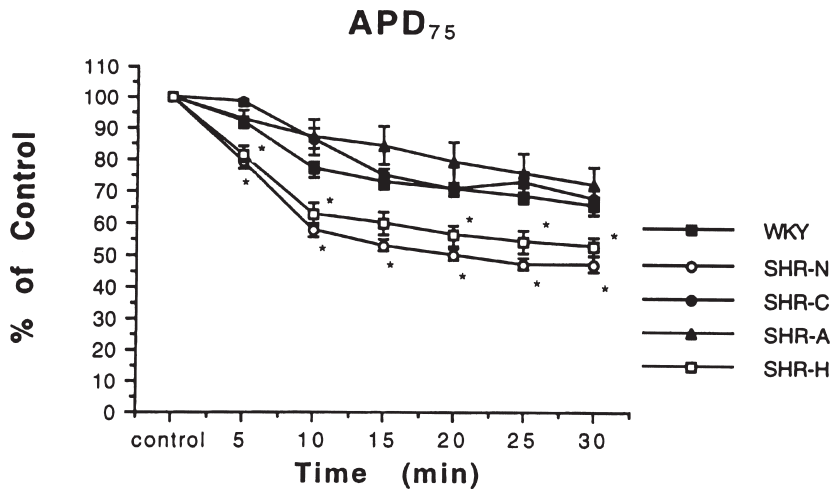


Figure 4 Graphs showing changes in action potential duration at 75 % repolarization (APD₇₅) during 30 minutes of superfusion with the hypoxia/no-glucose solution. WKY indicates Wistar-Kyoto rats; SHR-N, spontaneously hypertensive rats (SHR) without treatment; SHR-C, SHR treated with captopril; SHR-A, SHR treated with angiotensin II receptor antagonist TCV-116 at 30 mg/kg per day; and SHR-H, SHR treated with hydralazine. Percent changes from control values (before hypoxia) are indicated. Numbers of experiments are as follows: WKY, 10; SHR-N, 11; SHR-C, 10; SHR-A, 7; and SHR-H, 7. Values are mean ± SEM. *P < 0.05 vs. WKY. Reproduced from Kohya et al. (1995)³⁾.

a recent study has demonstrated that APD in mouse failing hearts induced by transgenic expression of tumor necrosis factor α fails to abbreviate during hypoxia probably due to the metabolic dysregulation such as mitochondrial and creatine kinase deficits²¹. Therefore, ischemia-induced changes in electrical substrates in hypertrophied/failing hearts remains to be clarified.

4. Clinical Evidence of Altered Electrical Substrate in Cardiac Hypertrophy

Transmembrane action potentials of in situ dog ventricular cells during VF exhibited lack of a stable resting period, as if cells were reexcited as soon as they had become excitable²². In this respect, it has been reported that the cycle length (CL) of VF is closely correlated with local ventricular refractoriness²³⁻²⁵. In addition, a significant linear correlation has been found between the core size and the CL of reentry^{26, 27}.

We thus hypothesized that analysis of successive changes of the CL during VF reflects the degree of electrophysiological heterogeneity, and that such changes are enhanced in hypertrophied hearts prone to VT/VF recurrence. To this end, we analyzed ventricular electrograms (which were recorded by the screw-in electrode placed at the endocardium of right ventricular apex) during VF in patients receiving implantable cardioverter defibrillator (ICD). As shown in Figure 5B, the

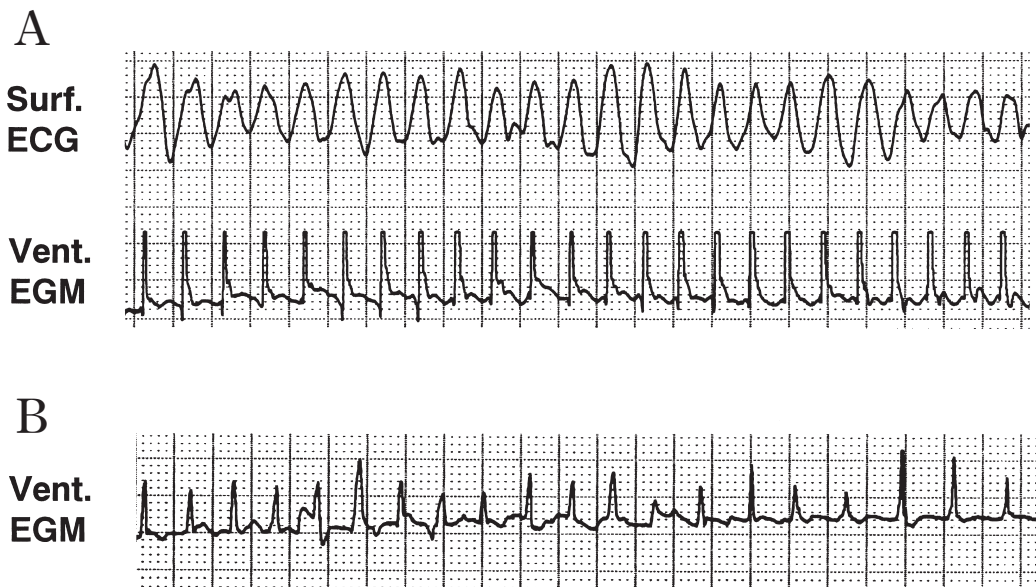


Figure 5 Examples of VF during defibrillation testing in patients with and without arrhythmia recurrence. (A) VF in a patient without recurrence who has no structural heart disease. From the top, surface ECG (Surf. ECG) and bipolar electrogram recorded by a transvenous lead located at the right ventricular apex (Vent. EGM). (B) VF in a patient with recurrence who has a hypertrophied heart.

Reproduced from Yokoshiki et al. (2003)²⁸.

temporal CL variability during VF was greater in a patient with hypertrophied cardiomyopathy who had arrhythmia recurrence²⁸⁾.

5. Concluding Remarks

Persistent mechanical, hormonal, and sympathetic stress would produce hypertrophied/failing hearts, thereby leading the hearts to decompensation. During the cellular remodeling against these stresses, changes in ionic channels, pumps, exchangers, and Ca²⁺ handling proteins occurs. These electrical and structural alterations appears to be responsible for arrhythmogenic substrates in hypertrophied/failing hearts. In addition, the modulating factors such as ischemia, catecholamines, and electrolyte abnormality could facilitate the genesis of fatal ventricular tachyarrhythmias which are the most common cause of sudden cardiac death. Recent remarkable advances in non-pharmacological therapy, i.e., ICD implantation, have actually prevented sudden cardiac death in high risk patients. However, another approach such as reversal of arrhythmogenic substrate by regression of hypertrophy may be promising³⁾. Sub-analysis of the HOPE study²⁹⁾ has demonstrated for the first time (as we proposed in the experimental study³⁾) that regression and/or prevention of left ventricular hypertrophy reduces the incidence of sudden cardiac death in the clinical settings. In order to prevent the development of arrhythmogenic substrates, it is required to elucidate the basic mechanisms of hypertrophied/failing hearts as well as their electrical remodeling.

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