**Diminished Transient Outward Currents in Rat Hypertrophied Ventricular Myocytes**

Fumishi Tomita, Arthur L. Bassett, Robert J. Myerburg, Shinichi Kimura

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**Abstract** Action potential duration is prolonged in ventricular hypertrophy induced by sustained pressure overload. Since the transient outward current (I_{to}) is a major factor for determining action potential duration in rat ventricular cells, we used patch-clamp techniques to compare the characteristics of I_{to} in normal and hypertrophied left ventricular cells of the rat. Left ventricular pressure overload was induced by partial ligation of the abdominal aorta for 4 to 6 weeks before study. Age-matched normal rats served as controls. Pressure overload increased the heart weight-to-body weight ratio by 47.7%. I_{to} was significantly smaller in hypertrophied cells than in normal cells (20.0±1.3 versus 31.0±2.1 pA/pF, respectively, at a test potential of +60 mV; P<0.001). There were no differences in the steady-state inactivation, the inactivation time course, and the time course of recovery from inactivation between normal and hypertrophied cells. At the single-channel level, there were no differences in the unitary current amplitude of the single I_{to} channel between normal and hypertrophied cells, and the slope conductance was 13.7 pico Siemens in normal cells and 13.4 pico Siemens in hypertrophied cells. The maximum open-state probability, which was estimated from the ratio of the peak of the ensemble-averaged currents to the single-channel current amplitude, was similar for normal and hypertrophied cells (0.66±0.03 and 0.69±0.04, respectively, at a test potential of +40 mV; P=NS). We conclude that diminished I_{to} contributes to action potential prolongation in hypertrophied ventricular cells from pressure-overloaded rat hearts. Reduced I_{to} channel density may be responsible for the diminished whole-cell I_{to}. (Circ Res. 1994;75:296-303.)

**Key Words** • pressure overload • patch clamp • single channel

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It is well recognized that cardiac hypertrophy induced by pressure or volume overload is associated with various alterations in mechanical and electrophysiological properties of the heart. Prolongation of the action potential is the alteration observed most consistently in hypertrophied myocardium. Our previous study and studies by others have demonstrated altered characteristics of L-type Ca^{2+} current (I_{Ca}) and delayed rectifier K^{+} current (I_{K}) in hypertrophied feline ventricular myocytes, which at least in part appear to be responsible for the prolonged action potential duration. However, because ionic currents and thus action potential configuration differ markedly among animal species, it is probable that the underlying ionic current mechanisms for prolonged action potential duration are diverse, depending on the animal species.

Transient outward current (I_{to}), which is generally assumed to be a voltage-dependent potassium current, has been observed in several cardiac tissues, including rat, rabbit, cat, dog, and human cardiac cells. I_{to} activates and inactivates rapidly on depolarization and thus contributes to the initial phase of repolarization of the action potential. In rat ventricular cells, it is well known that I_{to} plays an important role in repolarization and in the control of action potential duration. Therefore, the present study was designed to test the hypothesis that I_{to} is decreased in hypertrophied cells of the rat heart. Using the whole-cell and cell-attached configurations of the patch-clamp techniques, we compared the characteristics of I_{to} in normal and pressure-overload-induced hypertrophied left ventricular cells in the rat.

**Materials and Methods**

**Animals and Surgical Procedure**

Sprague-Dawley rats weighing 200 to 220 g (8 to 9 weeks old) at the time of surgery were used for aortic banding. The study was carried out 4 to 6 weeks after surgery, when the rats weighed 360 to 510 g. Age-matched normal rats weighing 350 to 520 g served as controls.

Pressure overload was induced by partial ligation of the abdominal aorta. Our surgical procedure has been previously reported in detail. In brief, under pentobarbital sodium anesthesia (35 mg/kg IP), the abdominal aorta was exposed just above the renal arteries and looped with 3-0 silk suture. The suture was tied against a 25-gauge needle, and the needle was then withdrawn. After closure of the incision, the rats were kept in a colony until the day of study.

**Cell Isolation**

On the terminal day, the rats were anesthetized with pentobarbital sodium (35 mg/kg IP), and then they were anticoagulated with heparin sodium (300 U/kg IP). The heart was rapidly excised and mounted on a Langendorff apparatus. It was perfused retrogradely via the aorta for 5 minutes with a modified Tyrode’s solution equilibrated with 100% O₂ at 37°C at a rate of 5 to 10 mL/min, followed by perfusion for 5 minutes with nominally Ca²⁺-free Tyrode’s solution. The heart was then perfused with collagenase (80 to 100 U/mL, Yakult) and 0.1 to 0.2 mg/mL protease (type XIV, Sigma Chemical Co) dissolved in nominally Ca²⁺-free Tyrode’s solution. Exposure to the enzyme was continued until the solution flowed freely (8 to 10 minutes), after which the collagenase was washed out with 100 mL of a Kraftrühe (KB) solution. After removing
the atria, the left ventricular free wall was dissected and minced in a beaker containing KB solution. The tissue pieces were gently stirred, and isolated single cells were then filtered through a nylon mesh (250 μm). Isolated left ventricular free wall cells were stored in the KB solution at 4°C and were studied within 24 hours after isolation.

**Solutions**

The composition of the modified Tyrode's solution was (mmol/L) NaCl 144, KCl 4, CaCl₂ 1.8, MgCl₂ 0.5, NaHPO₄ 0.33, glucose 5.5, and HEPES 5.5 (pH 7.4 with NaOH). The nominally Ca²⁺-free Tyrode's solution was prepared by omitting CaCl₂ from the modified Tyrode's solution. The composition of KB solution was (mmol/L) KOH 70, KCl 40, t-glutamic acid 50, taurine 20, KH₂PO₄ 10, MgCl₂ 0.5, glucose 11, EGTA 0.5, and HEPES 10 (pH 7.4 with KOH). For recording action potentials, cells were perfused with Tyrode's solution at 37°C. The pipette solution contained the following (mmol/L): KCl 140, MgCl₂ 5, ATP 5, EGTA 5, and HEPES 10 (pH 7.3 with KOH). For the measurements of the whole-cell I_m current (Ca²⁺-insensitive component of I_m), a Na⁺-free solution was used as an external solution to eliminate the Na⁺ current contamination and exclude the possible contribution of either Na⁺-activated K⁺ currents or of transient currents generated through the Na⁺-K⁺ pump. The solution was prepared by replacing NaCl in the modified Tyrode's solution with equimolar choline chloride. To eliminate a weak cholinergic effect of choline chloride, atropine (5 mmol/L) was added in the Na⁺-free external solution. I_m was blocked by the addition of 0.3 mmol/L CdCl₂ to the external solution. The pipette solution contained (mmol/L) potassium aspartate 120, KCl 20, MgCl₂ 1, K₂-ATP 4, EGTA 10, and HEPES 5 (pH 7.4 with KOH). The composition of the bath solution for the cell-attached single-channel recording was (mmol/L) KCl 140, MgCl₂ 1, EGTA 5, glucose 5, and HEPES 5 (pH 7.4 with KOH). The bath solution that contained 140 mmol/L K⁺ was used to zero the membrane potential. The pipette solution was the Na⁺-free solution containing 0.3 mmol/L CdCl₂ as described above for the whole-cell experiments. The pH of the solution was adjusted after all chemicals were added. The whole-cell patch-clamp experiments were performed at 37°C, whereas single-channel current recordings were made at room temperature (20°C).

**Recording Techniques**

The whole-cell membrane voltage and current and the single-channel current in the cell-attached membrane patch mode were recorded by the patch-clamp method described by Hamill et al. Glass pipette electrodes were forged by a micropipette puller (model P-87, The Sutter Instrument Co), and the resistance was 2 to 3 MΩ (whole-cell current recordings) or 3 to 5 MΩ (single-channel current recordings) after heat polishing of the pipette tip and filling with the internal solution. The pipette electrode was connected to the input stage of a patch-clamp amplifier (Axopatch-1D, Axon Instruments, Inc) with a feedback resistance of 100 MΩ for whole-cell current recordings and 10 GΩ for single-channel current recordings. The electrode potential was adjusted to give zero current between the pipette solution and bath solution immediately before each cell was attached. The sealing resistance of 5 to 100 GΩ was established by applying a negative pressure. In whole-cell current recordings, the cell membrane capacitance was determined by applying 10-mV hyperpolarizing pulses from a holding potential of 0 mV and integrating the area under the capacity transient. The series resistance was compensated by minimizing the duration of the capacitive surge on the current tracing. The junction potential between the pipette and the bath solution was ~−5 mV, and it was not corrected. Current and voltage were monitored on an oscilloscope (Tektronix). The current signals were filtered with a low-pass filter with cutoff frequency of 1 to 2 kHz at −3 dB, digitized at a conversion rate of 25 to 50 kHz with a 12-bit resolution Labmaster A-D converter (Tecmar Inc) under the control of an IBM-AT computer, and stored on a hard disk for later analysis. Data were analyzed by using the software program PC-LAMP (Axon Instruments).

Data are presented as mean±SEM. Statistical significance was evaluated by analysis of Student’s unpaired t test. Differences with values of P<.05 were considered significant.

**Results**

**Animal and Cell Characteristics**

Table 1 provides the characteristics of normal and aorta-banded rats. There was no difference in body weight between normal and operated rats. However, the heart weight was significantly heavier (P<.001) and the ratio of heart weight to body weight (HW/BW) was significantly higher (P<.001) in the operated rats compared with the control rats. HW/BW was increased 47.7% in rats with chronic pressure overload.

The cell membrane capacity was 149±4 pF (n=39) in normal cells and 192±6 pF (n=33) in hypertrophied cells. This difference was statistically significant (P<.001).

Fig 1 shows action potentials recorded from myocytes isolated from normal and hypertrophied left ventricles, and Table 2 summarizes data on their action potential characteristics. The cells were stimulated by passing depolarizing currents (1-millisecond pulse width, twice diastolic threshold) through the pipette at a rate of 1 Hz. Action potential duration was significantly prolonged in hypertrophied cells. However, there were no differences in resting membrane potential or action potential amplitude between the two cell types.

![Figure 1](image-url)
TABLE 2. Characteristics of Action Potentials

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=10)</th>
<th>Hypertrophy (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMP, mV</td>
<td>-78.7±0.6</td>
<td>-77.8±0.7</td>
</tr>
<tr>
<td>APA, mV</td>
<td>102.8±1.1</td>
<td>101.2±1.2</td>
</tr>
<tr>
<td>APD₉₀, ms</td>
<td>18.5±1.5</td>
<td>28.5±1.8*</td>
</tr>
<tr>
<td>APD₉₀, ms</td>
<td>44.7±1.9</td>
<td>69.3±2.3*</td>
</tr>
</tbody>
</table>

RMP indicates resting membrane potential; APA, action potential amplitude; and APD₉₀ and APD₉₀, action potential duration measured at 50% and 90% repolarization, respectively. Values are mean±SEM. The cells were stimulated at 1 Hz.

*P<.01 vs corresponding normal value.

Iₒ in Normal and Hypertrophied Myocytes

To study the activation of Iₒ, we clamped the membrane potential for 300 milliseconds to a test potential ranging from -40 to +60 mV in 10-mV steps from a holding potential of -80 mV at an interval of 5 seconds (Fig 2A inset). Fig 2A shows representative current recordings from normal and hypertrophied cells. The amplitude of Iₒ was measured as the difference between the peak of Iₒ and the minimum current level during the depolarizing pulse after the peak. The averaged current-voltage relations of 29 normal cells and 22 hypertrophied cells are shown in Fig 2B. In both normal and hypertrophied cells, the threshold for the activation of Iₒ was -20 mV; the peak current amplitude increased as a test potential was made more positive. However, the current density (the amplitude normalized to cell membrane capacitance) of Iₒ was significantly smaller in hypertrophied cells than in normal cells at test potentials from +20 to +60 mV. At a test potential of +60 mV, the current density of Iₒ was 20.0±1.3 pA/pF in hypertrophied cells and 31.0±2.1 pA/pF in normal cells (P<.001).

Fig 3A illustrates the protocol used to determine the voltage dependence of steady-state inactivation of Iₒ and shows representative current tracings. The membrane was voltage-clamped to different conditioning potentials (from -100 to 0 mV) for 1 second and then

![Figure 2](http://circres.ahajournals.org/)

**Fig 2.** Voltage-dependent activation of transient outward current (Iₒ). A, Voltage-clamp protocol and representative current tracings recorded during depolarizing steps from a holding potential of -80 mV to test potentials ranging between -40 and +60 mV (10-mV steps, 300-millisecond duration) in normal (middle) and hypertrophied (bottom) cells. Normal cell capacitance was 134 pF, whereas that for the hypertrophied cell was 201 pF. B, Graph showing average peak current-voltage relation for Iₒ for normal (○, n=29) and hypertrophied (○, n=22) cells. Values are mean±SEM (*P<.01 and **P<.001).

![Figure 3](http://circres.ahajournals.org/)

**Fig 3.** Steady-state inactivation of transient outward current (Iₒ). A, Voltage-clamp protocol and representative current tracings from a normal cell. From a holding potential of -80 mV, cells were depolarized to various conditioning potentials for 1 second. The conditioning pulse was followed by a standard test pulse to +60 mV. B, Graph showing voltage dependence of steady-state inactivation for normal (○, n=10) and hypertrophied (○, n=10) cells. The data are normalized to the largest peak Iₒ value obtained in each cell (Iₒ/Iₘₐₓ). The curve was fitted to a Boltzmann distribution. Values are mean±SEM.
stepped to +60 mV for 300 milliseconds, at which time \( I_{\text{in}} \) was fully activated. The holding potential was −80 mV, and the interval between test pulses was 5 seconds. In Fig 3B, the current elicited by the test pulse was expressed as a fraction of the maximum current obtained, and the normalized magnitude of \( I_{\text{in}} \) was plotted against conditioning potentials. The data points were fit with the Boltzmann distribution equation:

\[
\frac{I}{I_{\text{max}}} = \frac{1}{1 + \exp[(V-V_{0.5})/k]}^{-1}
\]

where \( I \) is the current at a conditioning potential of \( V \), \( I_{\text{max}} \) is the maximal current, \( V_{0.5} \) is the half-inactivation potential, and \( k \) is a slope constant. The inactivation curve of \( I_{\text{in}} \) for normal and hypertrophied cells was nearly identical. \( V_{0.5} \) and \( k \) were −34.6 mV and 9.2, respectively, for normal cells \((n=10)\) and −33.8 mV and 9.1, respectively, for hypertrophied cells \((n=10)\). No differences were found in the steady-state inactivation of \( I_{\text{in}} \) between normal and hypertrophied cells.

We next compared the time course of inactivation of \( I_{\text{in}} \) in normal and hypertrophied cells. The analysis of current inactivation was performed by fitting a sum of exponential decays to experimental data by using the Marquard-Levenberg algorithm of CLAMPFIT. As shown in Fig 4A, for both normal and hypertrophied cells, two exponential terms were required to describe the inactivation time course of currents; i.e., the data were best fit by an equation in the following form:

\[
I_{\text{in}}(t) = A_1 \exp(-t/\tau_1) + A_2 \exp(-t/\tau_2) + A_c
\]

where \( I_{\text{in}}(t) \) is the amplitude of \( I_{\text{in}} \) at time \( t \); \( \tau_1 \) and \( \tau_2 \) are the time constant and initial amplitude of the fast phase of inactivation, respectively; \( A_1 \) and \( A_2 \) are the corresponding parameters for the slow phase of inactivation; and \( A_c \) is a constant. The \( \tau_1 \) and \( \tau_2 \) are plotted against test potentials in Fig 4B. At all test potentials, there were no differences in either \( \tau_1 \) or \( \tau_2 \) between normal \((n=19)\) and hypertrophied \((n=14)\) cells.

The time course of recovery of \( I_{\text{in}} \) from inactivation was studied by a double-pulse protocol. Two 200-millisecond pulses, each to +60 mV with a varying interpulse interval, were applied every 10 seconds from a holding potential of −80 mV (Fig 5A). The interpulse interval ranged from 0 to 100 milliseconds. The magnitude of \( I_{\text{in}} \) elicited by the second pulse was expressed as a fraction of the \( I_{\text{in}} \) during the first pulse and plotted against the interpulse duration. The averaged results are shown in Fig 5B. The recovery from inactivation for normal and hypertrophied cells was almost identical.

**Single-Channel Currents Underlying \( I_{\text{in}} \)**

To determine whether the difference in the whole-cell \( I_{\text{in}} \) amplitude was due to a difference in unitary current amplitude and/or the probability of channel opening, we initiated single-channel recordings of \( I_{\text{in}} \) by use of the cell-attached membrane-patch mode. The single-channel events were evoked by depolarizing the patch for 300 milliseconds to test potentials of +20, +40, +60, or +80 mV from a holding potential of −120 mV at an interval of 5 seconds. Fig 6A shows seven tracings of the single-channel currents recorded from the same patch at a test potential of +40 mV. The channel was activated immediately after the depolarizing stimulus, and channel activity continued for a relatively short time after depolarization. Ensemble-averaged current of this channel constructed from 60 successive tracings yielded an outward current that activated almost instantaneously to reach its peak am-

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**Fig 4.** Inactivation time course of transient outward current \( (I_{\text{in}}) \). A, Theoretical curves superimposed on the data points of the inactivation phase of \( I_{\text{in}} \) in normal (left) and hypertrophied (right) cells. \( \tau_1 \) and \( \tau_2 \) are fast and slow time constants, respectively. The data were fit by a two-exponential function in both normal and hypertrophied cells. B, Graph showing voltage dependence of fast (\( \tau_{\text{fast}}, \) left) and slow (\( \tau_{\text{slow}}, \) right) time constants for normal \((c, n=19)\) and hypertrophied \((\sigma, n=14)\) cells. Values are mean±SEM.
macroscopic $I_{}\text{in}$, and we compared the current amplitude of this channel between normal and hypertrophied cells. Membrane patches showing only one-channel activity and no overlaps of the unitary current throughout the entire period of recording were subjected to analysis.

Fig 7A shows representative recordings of single-channel $I_{\text{in}}$ current at various test potentials in patches from normal and hypertrophied cells. In Fig 7B, the current-voltage relations averaged from 32 normal and 28 hypertrophied cells are shown. There was no significant difference in unitary current amplitude between channels from normal and hypertrophied cells. In both normal and hypertrophied cells, the current-voltage relations were linear, and the slope conductances were 13.8 picoeimens (pS) in normal cells and 13.5 pS in hypertrophied cells.

The maximum open-state probability ($P_{\text{max}}$) was estimated from the ratio of the peak of the ensemble-averaged currents to the single-channel current amplitude. The ensemble-averaged currents were obtained from 30 successive single-channel currents. Fig 8 shows representative recordings of ensemble-averaged currents at test potentials of +40 and +60 mV in patches from normal and hypertrophied cells. $P_{\text{max}}$ at test potentials of +40 and +60 mV were $0.65\pm0.02$ and $0.63\pm0.06$ in normal cells ($n=20$) and $0.68\pm0.04$ and $0.66\pm0.04$ in hypertrophied cells ($n=20$), respectively ($P=\text{NS}$).

**Discussion**

Prolonged action potential duration is a typical finding in hypertrophied myocardium. The duration of cardiac action potential is controlled by a precise balance of inward currents and outward currents. We and Kleiman and House* have shown that delayed inactivation of $I_{\text{Ca}}$ as well as decreased amplitude, delayed activation, and enhanced deactivation of $I_{\text{K}}$ contribute to the prolongation of action potential in feline hypertrophied myocytes. However, these data do not exclude a possible role of other ionic currents in prolongation of action potential.* In rat ventricular cells, one of the
Fig 7. Current-voltage relations of single transient outward current (I_o) channels. A. Representative tracings of single-channel currents at test potentials of +20, +40, +60, and +80 mV from a normal (left) and a hypertrophied (right) cell. B. Graph showing current-voltage relations of single I_o channels from normal (○, n=32) and hypertrophied (●, n=28) cells. Values are mean±SEM.

The Ca^{2+}-insensitive component of I_o between single myocytes isolated from normal and hypertrophied rat left ventricular free wall and demonstrated that it was diminished in cells from hypertrophied left ventricles induced by chronic pressure overload. We did not compare the Ca^{2+}-sensitive component of I_o, because it has been shown that the characteristics of I Ca and sarcoplasmic reticulum function are altered in hypertrophied cells^{6,7,26-28} which may bias measurements of Ca^{2+}-sensitive I_o.

Xu and Best^{29} have shown that I_o is decreased in hypertrophied right ventricular cells from rats with growth hormone–secreting tumors induced by subcutaneous inoculation of GH3 cells, a finding consistent with our results. Also, very recent studies reported decreased whole-cell I_o in human ventricular myocytes from patients with terminal heart failure^{30} and in myocytes from hypertrophied rat left ventricles induced by chronic pressure overload,^{31} the same model of hypertrophy as ours. However, Ten Eick et al^{16} have reported enhanced I_o in long-term feline right ventricular hypertrophy induced by partial ligation of the pulmonary artery. They suggested that increased I_o is responsible for the prolonged action potential in right ventricular hypertrophy. Although I_o abbreviates action potential duration in rat ventricle^{9,10} and rabbit atrium,^{14} it has the opposite effect in canine epicardium^{19} and human atrium^{22}: I_o exerts a prolonging influence on action potential duration. The role of I_o in the control of the duration of the action potential and the alteration of I_o in hypertension thus may differ depending on animal species and type of hypertrophy.

In the present study, the measurements of I_o might have included other currents such as chloride current and I_K. However, the contribution of chloride currents was probably minimal, because of the absence of Ca^{2+} (Cd^{2+} in the external solution and 10 mmol/L EGTA in the pipette solution) and the lack of adrenergic stimulation. Also, I_K activates slowly, and its magnitude is relatively small in rat ventricular cells (<10% of I_o, authors' unpublished observation). Since I_o activated after 50 to 100 milliseconds, the portion of I_K that might have been included in our measurements appears negligible.

There are some differences in I_o characteristics of rat ventricular cells between our data and those of others. We found that the time course of inactivation of I_o was fitted by a two-exponential function. These findings are consistent with those reported by Tohse et al.^{10} However, Apkon and Nerbonne^{11} and Dukes and Morad^{12} have noted that inactivation of I_o was best fit by a single-exponential function. The discrepancy may be ascribed to the different experimental conditions. A major difference was the temperature at which the experiments were carried out. The currents were recorded at 36°C to 37°C by us and Tohse et al^{10} and at room temperature by the latter groups.^{11,12}

Although the current density of I_o was decreased in hypertrophied left ventricular cells, there were no differences in kinetic properties, such as the steady-state inactivation, the inactivation time course, and the time course of recovery from inactivation between normal and hypertrophied cells. The decrease of the whole-cell I_o in hypertrophied cells could result from either a lower density of channels or from modified properties...
of single channels. The present data on single-channel \( I_\text{Ca} \) currents demonstrate that the current-voltage relation of single-channel currents is very similar for normal and hypertrophied cells. Neither unitary current amplitude nor maximum open-state probability was different between normal and hypertrophied cells in the cell-attached membrane-patch mode. Therefore, the difference in the whole-cell \( I_\text{Ca} \) density appears to be due to the difference in the number of functional channels between normal and hypertrophied cells. However, this interpretation is made with caution, because we did not measure single-channel currents and whole-cell currents simultaneously from the same cell.

We suggest that the single-channel events obtained in the present study underlie the generation of the whole-cell \( I_\text{Ca} \), because there was a similarity in the time courses, especially the inactivation phase, between the ensemble-averaged single-channel currents and the whole-cell \( I_\text{Ca} \). In addition, it seems unlikely that the single-channel currents are responsible for generating outward current components other than \( Ca^{2+} \)-insensitive \( I_\text{Ca} \) in the rat left ventricle, i.e., \( Ca^{2+} \)-sensitive \( I_\text{Ca} \) and \( I_\text{K} \). Our recording conditions were arranged to minimize \( Ca^{2+} \)-sensitive \( I_\text{Ca} \); e.g., \( I_\text{Ca} \) was inhibited by the \( Ca^{2+} \)-free bath solution and the existence of \( Cd^{2+} \) in the pipette solution. Furthermore, the single-channel conductances of \( I_\text{K} \) described for mammalian heart cells are substantially much smaller than the value observed by us: 5.4 pS\(^{32}\) at 4.5 mmol/L external \( K^+ \) and 11.1 pS\(^{33}\) or 13.2 pS\(^{34}\) at 150 mmol/L external \( K^+ \). We found a single-channel conductance of 13.7 pS for normal cells and of 13.4 pS for hypertrophied cells, which compare quite well with the values reported for \( I_\text{K} \) in cardiac cells.\(^{35}\)

Recently, expressed \( K^+ \) channels cloned from ventricular myocardium in Xenopus oocytes, which have properties similar to the 4-aminopyridine-sensitive \( Ca^{2+} \)-insensitive component of \( I_\text{Ca} \), have been studied to gain insight into the molecular basis of cardiac repolarizations.\(^{36-37}\) Furthermore, the mechanisms of the kinetics of the channel have been explored by combining channel protein subunits.\(^{37}\) Our findings that there are no differences in channel kinetics and single-channel properties of \( I_\text{Ca} \) between normal and hypertrophied cells suggest that the channel proteins are not altered in hypertrophied cells. Our data simply indicate suppressed functional expression of \( I_\text{Ca} \) in hypertrophied rat myocytes.

\( I_\text{Ca} \) is a major factor for determining action potential duration in rat ventricular cells.\(^{38,39}\) Thus, it is conceivable that the diminished \( I_\text{Ca} \) demonstrated in the present study contributes to the prolongation of action potential duration in hypertrophied left ventricular cells in rats. Tohse et al.\(^{40}\) have suggested that \( Ca^{2+} \) influx through the \( Ca^{2+} \)-sensitive \( I_\text{Ca} \) channel increases indirectly as a consequence of \( I_\text{Ca} \) inhibition by \( a_\text{1}- \)adrenergic receptor stimulation, which, in turn, may contribute to an \( a_\text{1}- \)adrenergic receptor-mediated positive inotropic effect in rat heart. Shibata et al.\(^{41}\) have shown that inhibition of \( I_\text{Ca} \) by 4-aminopyridine increases steady-state phase tension in human atrium. Therefore, diminished \( I_\text{Ca} \) in hypertrophy, together with delayed inactivation of \( I_\text{Ca} \), may result in an increase in total \( Ca^{2+} \) inflow in myocytes and play a role in maintaining contractile function in cardiac hypertrophy.

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**References**


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