Alterations of K⁺ Currents in Isolated Human Ventricular Myocytes From Patients With Terminal Heart Failure

Dirk J. Beuckelmann, Michael Näbauer, Erland Erdmann

Prolongation of the action potential has been postulated to be a major reason for the altered diastolic relaxation of the heart in patients with severe heart failure. To investigate the electrophysiological basis for this action potential prolongation in terminal heart failure, K⁺ currents were recorded in single ventricular myocytes isolated from 16 explanted hearts of patients undergoing transplantation. Results from diseased hearts were compared with ventricular cells isolated from six undiseased donor hearts. Action potential duration was significantly prolonged in cells from patients with heart failure. A delayed rectifier K⁺ current was hardly detectable in most cells, and if it could be recorded, it was very small in both diseased and undiseased cells. When currents were normalized for cell surface area, the average current density of the inward rectifier K⁺ current was significantly reduced in diseased cells when compared with normal control cells (hyperpolarization at −100 mV, −15.9±2.2 vs −9.0±1.2 μA/cm²; *P < .01). In addition, a large transient outward K⁺ current could be recorded in human myocytes. The average current density of the time-dependent component of this transient outward K⁺ current was significantly reduced in heart failure (depolarization at +40 mV, 9.1±1.0 vs 5.8±0.64 μA/cm²; *P < .01).

Action potential prolongation in severe heart failure may partially be explained by a reduction in current densities of the inward rectifier K⁺ current and of the transient outward K⁺ current. These alterations may thereby have a significant effect on cardiac relaxation. (Circulation Research 1993;73:379-385)

**KEY WORDS**  •  K⁺ currents  •  heart failure  •  action potentials  •  human ventricular myocytes

Prolongation of the action potential is a prominent feature of human ventricular myocardium from patients with severe heart failure. Gwathmey et al² have shown that such a prolongation can be found in isometrically contracting ventricular muscle from patients with terminal heart failure or with severe cardiac hypertrophy. This has also been reported to occur in a variety of species and animal models of cardiac failure and hypertrophy.²-⁶ Although the mechanism of excitation-contraction coupling in the heart is thought to be through Ca²⁺-induced Ca²⁺ release,⁷,⁸ prolongation of the action potential may have a pronounced effect on excitation-contraction coupling, especially on diastolic [Ca²⁺], decline and on the Ca²⁺ load of the sarcoplasmic reticulum.⁹

We have previously demonstrated that, in myocytes isolated from myocardium of patients with terminal heart failure, action potentials are prolonged at all frequencies when compared with cells isolated from undiseased hearts.⁹ Furthermore, when Ca²⁺ currents were corrected for cell surface area, the unstimulated Ca²⁺ current density was found to be unchanged,⁹ thus supporting indirect findings of other groups.¹⁰ Characteristics of the L-type Ca²⁺ current in human ventricular myocytes were found to be similar to those in other mammalian species.¹¹ Therefore, it seemed plausible that K⁺ currents might be altered in cardiac failure. However, until now, sarcolemmal K⁺ currents in human myocardium have only been recorded in atrial cells.¹²-¹⁴ Single-channel recordings from reconstituted human K⁺ channels could not differentiate between channels isolated from the sarcoplasmic reticulum or the sarcolemmal membrane of the heart.¹⁵ The aim of this study was to test the hypothesis that K⁺ currents are altered in ventricular myocytes isolated from hearts of patients with terminal heart failure and that this might contribute to the changes of the action potential in heart failure observed in humans.

**Patients**

Cells were prepared from 16 hearts of patients with end-stage heart failure due to dilated cardiomyopathy (n=10) or ischemic cardiomyopathy (n=6) undergoing transplantation. Patients' age was 46.6±3.6 years; 14 patients were male, 2 patients were female; cardiac index was 2.4±0.2 L · min⁻¹ · m⁻²; and ejection fraction was 25±3%. All patients received digoxin and diuretics and were under vasodilator therapy. No catecholamines or β-adrenoceptor blocking drugs were given during the 48 hours before the operation. Informed consent was obtained before organ explantation. The experimental protocol was approved by the ethical committee of the university. Results were compared with cells isolated from six normal human hearts without cardiac disease.
that could not be transplanted for technical reasons. The isolation procedure was identical in all hearts used.

**Cell Isolation**

The isolation procedure has been described in detail before. A part of the left ventricular wall was excised together with its arterial branch. The wall segment was then perfused via this arterial branch: 30 minutes with a nominally Ca$^{2+}$-free modified Tyrode's solution (mM: NaCl, 138; KCl, 4; MgCl$_2$, 1; glucose, 10; Na$_2$HPO$_4$, 0.33; and HEPES (sodium salt) 10; pH 7.3 with addition of NaOH, 37°C), followed by 40 minutes with the same solution added with collagenase (type I, 70 mg/50 mL, Worthington Biochemical Corp, Freehold, NJ) and protease (type XIV, 6 mg/50 mL, Sigma Chemical Co, St Louis, Mo). Finally, the enzyme was washed out for 15 minutes with modified Tyrode's solution that contained 200 µM Ca$^{2+}$. Tissue digestion was maximal within the ventricular wall, with the endocardial and epicardial layers often left undigested. Therefore, tissue was taken from the central one third of the myocardial thickness. Ventricular cells were disaggregated by mechanical agitation and, after filtering through a nylon mesh, stored in Tyrode's solution containing 2.0 mM Ca$^{2+}$ at room temperature (21° to 23°C).

The living-cell yield was approximately 5% to 8%. Only cells with clear cross striations without significant granulation that did not contract spontaneously were selected for experiments. Cells that fulfilled these selection criteria did contract on field stimulation as judged by visual control.

**Solutions**

Cells were superfused with a modified Tyrode's solution containing (mM) CaCl$_2$, 2.0; NaCl, 138; KCl, 4; Na$_2$HPO$_4$, 0.33; MgCl$_2$, 1; CdCl$_2$, 0.3; glucose, 10; and HEPES (sodium salt) 10; pH was 7.3 with the addition of NaOH. Cd$^{2+}$ was included to block Ca$^{2+}$ currents that might interfere with the measurement of K$^+$ currents. BaCl$_2$ (2 mM) to block the inward rectifier K$^+$ current (I$_{K}$) or 4-aminopyridine (3 mM) to block the transient outward K$^+$ current (I$_{to}$) was added when indicated. For recordings of action potentials, solutions did not contain Ca$^{2+}$. The temperature was 35°C for recordings of action potentials, delayed rectifier K$^+$ current (I$_{K}$), and I$_{to}$ and was 21° to 23°C for recordings of I$_{K}$.

After establishing whole-cell recordings, the electrode solution was allowed to exchange with the intracellular environment for at least 2 minutes. The electrode solution contained (mM) potassium glutamate, 120; KCl, 10; MgCl$_2$, 2; HEPES (K$^+$ salt), 10; EGTA (K$^+$ salt), 5; and Mg-ATP, 2; pH 7.2. After this time, the contraction after stimulation had ceased, and the [Ca$^{2+}$], was calculated to be <10 nM.

**Recording Techniques**

Experiments were carried out by standard whole-cell recording techniques using a patch-clamp amplifier (model EPC-7, List Instruments, Germany) with a 100 MΩ feedback resistor. Microelectrodes were pulled from borosilicate glass capillaries and had resistances of 2.0 to 3.0 MΩ. Series resistance was compensated as much as possible (30% to 80%). Currents were low pass-filtered at 3 kHz, and current recordings were digitized (1 to 5 kHz) and stored for off-line analysis. Membrane capacitance was determined in each cell by integrating the capacitance current on repolarizing to −80 mV from hyperpolarizing pulses. Currents were sampled at 10 kHz.

**Statistical Analysis**

Values are shown as mean±SEM. Mann-Whitney nonparametric analysis was used for statistical evaluation of the data, and values of P<.05 were considered significant.

**Results**

**Action Potential**

When action potentials were recorded in current-clamp mode, different shapes could be distinguished. In some cells, action potentials had a shape similar to guinea pig cells, but most cells had a prominent notch immediately after the upstroke between phases 1 and 2. The latter type was suggestive of I$_K$ being present in these cells, like the one described in rat or feline, but not in guinea pig or frog ventricular cells. Fig 1 shows typical examples of action potentials recorded from a cell isolated from undiseased myocardium (A) and from a patient with dilated cardiomyopathy (B). Action potential duration was significantly prolonged in myopathic cells as compared with control cells (action potential duration at 90% repolarization, 0.65±0.10 seconds [control cells, n=4] vs 1.09±0.09 seconds [myopathic cells, n=9], P<.05).

To investigate the possible effects of I$_K$ on action potential shape and duration, 3 mM 4-aminopyridine was added to the external solution. Fig 1, C, shows the effects of 4-aminopyridine during the wash-in phase at the time when the notch during phase 1 of the action potential was completely abolished. This was taken as indicative of a complete block of I$_{to}$. During successive recordings, a further increase in action potential duration could be recorded without affecting the shape during phase 1.

**Transient Outward K$^+$ Current**

When isolated myocytes were submitted to 500-millisecond depolarizing clamp pulses after a prepulse to −60 mV from a holding potential of −80 mV, at potentials positive to −20 mV, an early I$_{to}$, could be observed that decayed with time (Fig 2, A). Details of electrophysiological characteristics of this current have been described elsewhere. To precisely detect the peak of this current, experiments were carried out at room temperature (21° to 23°C), because activation was strongly temperature dependent. When recordings were attempted at 35°C, it was not possible to reliably differentiate the peak of the ionic from the capacitance current. After 500 milliseconds of depolarization, inactivation of the time-dependent component of the current was complete at room temperature. Combined intracellular and extracellular substitution of K$^+$ with Cs$^+$ completely blocked this I$_{to}$ (not shown). The non-inactivating steady-state current had a comparable current-voltage relation as the time-dependent component of I$_{to}$ (Fig 2, B).

When the current was normalized to cell surface area, the current density, measured on depolarization to +40 mV (plateau of the action potential), was significantly
smaller in cells isolated from hearts of patients with terminal heart failure when compared with control cells. This was true whether the absolute current densities or only the time-dependent components were compared. Steady-state currents at the end of the 500-millisecond pulse were unchanged (Table 1). Quantitative recordings of $I_{o}$ were done in a total of 60 cells.

**Inward Rectifier K⁺ Current**

To measure $I_{K1}$, a prepulse to $-30$ mV was applied to the membrane to largely inactivate $I_{o}$. After this prepulse, the membrane was clamped to voltages between $-120$ and $+60$ mV in 10-mV steps for 500 milliseconds. On hyperpolarization to membrane potentials negative to $-70$ mV, an inward current could be recorded (Fig 3, A). At membrane potentials negative to $-90$ mV, this current was slightly time dependent. It exhibited pronounced inward rectification. Intracellular and extracellular substitution of K⁺ with Cs⁺ completely blocked this current (not shown). When cells were superfused with a solution containing 2 mM BaCl₂, this inward current was completely blocked (Fig 3, B). Fig 3, C, depicts the current-voltage relation of this current, typical of $I_{K1}$. All outward current in the voltage range of $-70$ to $-40$ mV was completely blocked by Ba²⁺.

When the amplitude of this current was normalized to the cell surface area, the average current density, measured on hyperpolarization to $-100$ mV, was significantly smaller in cells isolated from hearts of patients with terminal heart failure compared with control cells. This was true whether the maximal current densities or the time-independent components (end of the 500-millisecond pulse) were compared. When current densities were compared on clamping the cell membrane to $-60$ mV, the difference did not quite reach statistical significance because of large variations of the current in this voltage (Table 2). Quantitative recordings of $I_{K1}$ were performed in 35 cells.

**Delayed Rectifier K⁺ Current**

To measure $I_{K}$, a prepulse to $-30$ mV was applied to largely inactivate $I_{o}$. After this prepulse, the membrane was depolarized for 4500 milliseconds to $-30$ to $+80$ mV, followed by an 800-millisecond repolarization to $-30$ mV. During depolarization, a small outward current could be recorded that activated with time (Fig 4, A). Twenty-seven cells were investigated with this protocol. In 11 cells, a tail current on repolarization could be recorded. However, in 15 cells, no significant tail current was detectable, and in these cells the current on depolarization was time independent (not shown). Almost no tail currents were recorded in those myocytes isolated from control hearts (n=6). To minimize the influence of current "run-down" on $I_{K}$, this protocol was always applied 2 minutes after establishing whole-cell recording.

Fig 4, B, represents the voltage-dependent activation of the current shown in Fig 4, A, as determined from measurements of current tails. In 11 cells in which a small tail current could be recorded, half-maximal activation of $I_{K}$ was at $7.4±2.1$ mV.

To study the time dependence of activation of $I_{K}$, the membrane voltage was clamped to $+40$ mV for various durations before repolarization to $-20$ mV. Activation of $I_{K}$ was assessed from current measurements of current tails on repolarization. Fig 4, C, depicts an original recording in a cell in which $I_{K}$ could be recorded. The time dependence of current activation (envelope) is shown in Fig 4, D. At $35°C$, this current was completely activated within 250 milliseconds.

**Discussion**

The duration of the cardiac action potential is controlled by a precise balance of inward currents and outward currents at any given time of the cardiac cycle. Prolongation of the action potential has been shown to be a prominent feature of the heart in states of hypertrophy or cardiac failure in a variety of species. It has been demonstrated in multicellular preparations of human ventricular myocardium and in isolated ventricular myocytes from hearts of patients with severe heart failure. However, the cellular basis for such retarded repolarization has remained obscure. Quantitative measurements of currents have been difficult until isolated.

FIG 1. Action potential recorded in single cells isolated from an undiseased heart (A) and from the heart of a patient with dilated cardiomyopathy (B). V, voltage. Stimulation frequency was 0.5 Hz. Action potential duration in myocytes from patients with heart failure was significantly prolonged (cells: AM40, control; BM4, myopathic). The effects of 4-aminopyridine on the action potential are shown (C). Stimulation frequency was 0.5 Hz at mammalian temperature. During wash in of 4-aminopyridine (3 mM), the prominent notch during phase 1 of the action potential was abolished. At the same time, action potential duration was increased by approximately 15% to 20%. During continuous incubation, a further increase in action potential duration could be observed without any significant change of the action potential shape during phase 1.
human ventricular cells have become available. Single myocytes now allow for a quantitative determination of current densities. We have shown before that Ca^{2+} current densities in these cells are unchanged. Therefore, an increased Ca^{2+} influx may not be responsible for the prolonged action potential duration. Our results indicate that a reduction of current densities of I_{K1} and I_{to} may contribute to action potential prolongation in failing human hearts.

I_{to} has been recorded not only in Purkinje cells but also in human atrial cells and in ventricular cells of a variety of species, like rat, dog, and rabbit. The shape of the ventricular action potential was indicative of the presence of an I_{to} in these cells. Our experiments show that in human ventricular myocytes this current is present with a large current density. Details of current characteristics are described elsewhere. Regional variability of current density of I_{to} has been reported in rabbit, canine, and feline ventricular cells. Similar observations were made for I_{K} in feline myocytes. In hearts of these animals, a substantial difference of current size between endocardial and epicardial cells was found. However, to prevent an influence of sampling localization on the size of the measured currents, cells used in these experiments were obtained from the central one third of the myocardial wall.

To accurately measure size and kinetics of K+ currents, contaminating Ca^{2+} currents had to be eliminated. This was achieved by the use of 300 μM Cd^{2+}. Although Cd^{2+} may cause a shift in activation and inactivation parameters of I_{to}, other blockers of the L-type Ca^{2+} current are not of any advantage, as they also affect size and kinetics of K+ currents. Reports of the effect of Cd^{2+} on I_{K} suggest that I_{K} is increased in the presence of Cd^{2+} indicating that the small size of I_{K} in the present study is not caused by the use of CdCl_{2} as a Ca^{2+} channel blocker. Furthermore, a possible effect of Cd^{2+} on K+ currents would not weaken our results of a reduced current density in heart failure, because the experimental conditions for current recordings in diseased and undiseased cells were identical.

The functional significance of I_{to} can best be estimated by considering its time course and size compared with other currents. The peak of the action potential varied between +20 and +50 mV; the plateau was recorded between +10 and +40 mV (Fig 1). The current density of I_{to} (9.1±1.0 μA/cm² on depolarization to +40 mV) was rather large when compared with the maximal Ca^{2+} current density in these cells (3.8±1.2 μA/cm²). Therefore, it is likely that a major determinant of repolarization is not only inactivation of the Ca^{2+} current but rather activation of a large I_{to}. Although the transient nature of I_{to} makes a significant contribution of this current at the time of repolarization unlikely, it has an important role in setting the voltage of the early plateau, thus influencing the activation of other currents such as Ca^{2+} and outward currents. The important role of I_{to} in controlling the action potential duration has been demonstrated in studies of other species. A prolongation of the action potential has also been reported in experiments after blockade of I_{to} by 4-aminopyridine. Our results show that I_{to} is decreased in heart failure. Addition of 4-aminopyridine led to an increase in action potential duration of approximately 15% to 20% at a time when the “notch” during phase 1 was abolished. The action potential prolongation was further increased on continuous incubation, presumably because of the effects of 4-aminopyridine on other K+ currents. Furthermore, a significant steady-state current could be recorded at the end of the 500-millisecond pulse. This current had a comparable

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**Table 1. Current Density of the Transient Outward Current**

<table>
<thead>
<tr>
<th>I_{to}</th>
<th>Peak (μA/cm²)</th>
<th>Steady state (μA/cm²)</th>
</tr>
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<tbody>
<tr>
<td>Control (n=6)</td>
<td>9.2±1.0</td>
<td>2.1±0.3</td>
</tr>
<tr>
<td>Heart failure (n=15)</td>
<td>5.8±0.6</td>
<td>1.7±0.1</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

I_{to}, transient outward current; n, number of hearts. Values are mean±SEM.

I_{to} density was taken as the peak current and steady-state current at the end of a 500-millisecond pulse per square centimeter cell surface after depolarization to +40 mV, assuming a surface area of 10^{-9} cm²/pF membrane capacity.

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**Fig 2. Transient outward current. I, current; V, voltage. A, Original recording from a holding potential of −80 mV. Interfering Ca^{2+} currents were blocked with 0.3 mM CdCl_{2}; temperature was 23°C. After a 100-millisecond depulse to −60 mV, the cell membrane was depolarized to −30 to +80 mV. After the 500-millisecond pulse depolarization, the cell was repolarized to −60 mV. B, Plot showing that the I–V relation of the peak current was typical of transient outward current as was the I–V relation of the steady-state current at the end of the pulse. The inset represents the pulse protocol of the original recordings shown in A (cell: KM3, control).**
TABLE 2.  Current Density of the Inward Rectifier K+ Current

<table>
<thead>
<tr>
<th></th>
<th>$I_{K1}$</th>
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<tbody>
<tr>
<td></td>
<td>$-100$ mV</td>
</tr>
<tr>
<td></td>
<td>$\mu$A/cm$^2$</td>
</tr>
<tr>
<td>Control (n=5)</td>
<td>$-13.9 \pm 1.9$</td>
</tr>
<tr>
<td>Heart failure (n=7)</td>
<td>$-8.5 \pm 1.0$</td>
</tr>
<tr>
<td>$P$</td>
<td>$&lt;.01$</td>
</tr>
</tbody>
</table>

$I_{K1}$, inward rectifier K+ current; n, number of hearts. Values are mean±SEM.

The current-voltage relation as the time-dependent component (Fig 2, B). At this time, it is not clear whether the steady-state current at the end of the 500-millisecond pulse represents a nonactivating part of $I_{K1}$ or if it is a different current.

Alterations of $I_{K1}$ have been described in rat ventricular myocytes. Some authors have reported a decrease of the current density in animals with acromegaly.28 Because the Ca$^{2+}$ current and outward currents were unchanged in this animal model, prolongation of the action potential was most likely due to the decrease in $I_{K1}$. Other authors have described a marked reduction in the current size of $I_{K1}$ in canine myocytes after large myocardial infarctions.

Because of the degree of the current reduction in severe cardiac failure (the peak current was reduced by approximately 36%), it is likely that the prolongation of the action potential is partially due to this reduction of $I_{K1}$. The specific mechanism by which the current is reduced remains to be elucidated. The current is strongly regulated by $\alpha$-adrenergic stimulation.30,31 However, most authors could not find an alteration of the $\alpha$-adrenergic pathway in severe heart failure.32 Two different types of $I_{K1}$ have been found in other species.33,34 One type has been shown to be Ca$^{2+}$ dependent. It has been demonstrated before that intracellular Ca$^{2+}$ handling is profoundly altered in heart failure.9 One of the prominent features in heart failure is a marked reduction of intracellular Ca$^{2+}$ transients on depolarization. To avoid any possible influence of altered intracellular Ca$^{2+}$ handling on current measurements, intracellular Ca$^{2+}$ transients were abolished by block of Ca$^{2+}$ currents using Cd$^{2+}$ and Ca$^{2+}$ influx through the Na$^{+}$-Ca$^{2+}$ exchange system35 (by intracellular perfusion with a Na$^{+}$-free solution). Furthermore, the Ca$^{2+}$ chelator EGTA at a concentration of 5 mM was included in the intracellular perfusion to minimize possible Ca$^{2+}$-dependent $I_{K1}$. For these reasons, in this report we have compared the (larger) Ca$^{2+}$-insensitive $I_{K1}$ in myocytes from hearts with contractile failure and from control hearts. The present study is therefore confined to changes of K+ currents in failing human heart cells independent of effects secondary to alterations of intracellular Ca$^{2+}$ handling in myocytes from failing hearts. Whether a Ca$^{2+}$-sensitive $I_{K1}$ also exists in
human ventricular myocytes can only be answered by further investigations.

\( I_k \) was almost completely activated within 250 milliseconds of depolarization (Fig 4), but in most human ventricular cells investigated, only a minimal or no \( I_k \) could be recorded. This is in accordance with results in other species that exhibit a large \( I_{so} \), like rat. In these species, the major current responsible for membrane repolarization appears to be \( I_{so} \). Therefore, this current differs from the slowly activating outward current (\( I_{so} \)) found in guinea pig ventricular myocytes.\(^{36}\) \( I_k \) was not observed in any of the cells isolated from nondiseased hearts. Therefore, we did not think that a comparison of current densities of \( I_k \) between undiseased and failing ventricular myocytes was appropriate under these circumstances.

To prevent any influence of run-down of \( I_k \), recordings were started 2 minutes after establishing whole-cell recording. It is unlikely that the small size of \( I_k \) measured in human ventricular myocytes was due to rundown during that time, since measurements done immediately after breaking into the cell did not reveal a larger \( I_k \). These measurements, however, were not used for analysis because buffering of intracellular \( Ca^{2+} \) required 1 to 2 minutes of internal perfusion with the electrode filling solution (as judged by a complete stop of contraction). However, at the present time, it cannot be excluded that fast run-down occurs, leading to underestimation of \( I_k \) even after a short period of internal dialysis.

A large \( I_{ki} \) that was blocked by Ba\(^{2+} \) could also be recorded in human ventricular myocytes (Fig 3). Data from human atrial cells have been in conflict with respect to the size of this current. Some authors have found a large \( I_{ki} \) similar to our results in human ventricular cells;\(^{33}\) others have reported a very high input resistance in these cells with hardly any inward current at very negative potentials.\(^{14}\) The characteristic outward current in the voltage range between -70 and -30 mV was also observed in human ventricular myocytes. Our results indicate that \( I_{ki} \) is reduced in myocytes isolated from hearts of patients with severe heart failure. This outward current is thought to be responsible for the last 40 mV of membrane repolarization during the action potential. Therefore, the reduction of \( I_{ki} \) in heart failure may also contribute to the prolongation of the action potential in these cells.

A reduction of \( I_{ki} \) would be expected to alter the rate of repolarization in the voltage range between -30 and -80 mV. This rate of repolarization was indeed faster in most action potentials recorded from undiseased cells. In the examples shown in Fig 1, A and B, the time for the membrane potential to repolarize from -30 to -70 mV was 90 milliseconds in the undiseased myocyte and
170 milliseconds in the myopathic cell, indicating a relevant influence of the reduction of I_{Ks} density on the final repolarization of the action potential.

No significant difference in resting potential between cells isolated from undiseased hearts or from organs of patients with terminal heart failure was observed. This was most likely due to the influence of other currents on the cardiac resting potential (Na⁺-K⁺ pump current, Na⁺-/Ca²⁺ exchange current, and Cl⁻ current), which have not yet been investigated. Changes in these currents might counterbalance the effects of a reduced I_{Ks} on the resting membrane potential. Because of our experimental conditions (buffering of intracellular Ca²⁺ by EGTA and inhibition of Ca²⁺ entry), only a Ca²⁺-insensitive I_{Ks} would have been measured. Therefore, at the present time, we cannot exclude the possible existence of a Ca²⁺-dependent I_{Ks}, which has been found in other species.37

Alterations of I_{Ks} and I_{Op} seem to be important in changing the shape of the action potential in severe heart failure in humans. These currents may thereby have a significant effect on cardiac contractility. However, further work will be necessary to determine whether other currents are involved in action potential prolongation and to clarify their role in human heart failure.

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