Characteristics of Transient Outward Current in Human Ventricular Myocytes From Patients With Terminal Heart Failure

Michael Nábauer, Dirk J. Beuckelmann, Erland Erdmann

A variety of outward currents exists in ventricular myocardium of different species influencing action potential duration and electrical activity. Transient outward currents have been reported in ventricular tissue of some animals but are small or absent in others. This study was conducted to investigate whether a transient outward current exists in human ventricular myocardium and to characterize its basic electrophysiological properties. Currents were recorded from enzymatically isolated human ventricular myocytes obtained from explanted hearts of 22 patients with terminal heart failure. In almost all cells studied, a transient outward current could be recorded on depolarization to between −20 and +80 mV. The size of the transient outward current was usually large enough to mask the Ca$^{2+}$ current. It could be recorded under conditions in which Ca$^{2+}$ influx and intracellular Ca$^{2+}$ transients were suppressed. Basic current characteristics were similar to transient outward currents observed in other species. Inactivation of the transient outward current was monoeponential, with a time constant of 54.8±3.7 milliseconds at +40 mV. Half-maximal activation occurred at 16.7±1.6 mV; half-maximal steady-state inactivation occurred at −34.5±2.3 mV. Frequency-dependent reduction of peak transient outward current was 29.8±1.4% at 2 Hz compared with resting conditions. Recovery from inactivation was voltage dependent and had a biexponential time course; the faster time constant (41.0±6.5 milliseconds at −80 mV) accounted for 86.0±5.2% of total current. The transient outward current was sensitive to 4-aminopyridine (IC$_{50}$, 1.15 mM). These results indicate that a large Ca$^{2+}$-independent transient outward K$^{+}$ current is present in human ventricular myocytes that might be regulated by physiological or pathological events and is a potential site for pharmacological intervention. (Circulation Research 1993;73:386-394)

KEY WORDS • transient outward currents • human ventricular myocytes • 4-aminopyridine

Outward currents in the heart are responsible for repolarization of membrane voltage and therefore influence action potential duration and electrical activity. However, presence and density of different outward currents in the heart vary with species and tissue. Transient outward currents have been recorded in ventricular myocardium of rat, dog, cat, and rabbit, whereas a clear transient outward current appears to be absent in guinea pig ventricular myocytes.1

In several cardiac tissues including human atrial cells, two types of transient outward currents have been identified; one is Ca$^{2+}$ dependent, and the other is Ca$^{2+}$ independent.7,8,10,12 The Ca$^{2+}$-independent transient outward current, carried predominantly by K$^{+}$, has been postulated to be a major determinant of cardiac action potential duration because of its size and pronounced frequency dependence.1,8,13,15 Recent studies also indicate an important role of the transient outward current in the electrophysiological heterogeneity of subendocardial and subepicardial myocardial cells.4,6,15 Furthermore, it may be important in age-related changes of the cardiac action potential or subjected to modulation by pathological events such as myocardial infarction or ischemia.16,17

On the other hand, the Ca$^{2+}$-dependent transient outward current, which may be related to intracellular Ca$^{2+}$ release, is usually found to have a much smaller current density.4,8 Its functional role has not yet been defined. Recent evidence suggests that this current may be regulated via cellular cAMP and be due to a chloride conductance.18,19

Action potential recordings from human ventricular myocardium often display a characteristic notch after the upstroke of the action potential, suggesting the presence of a transient outward current.20-22 Successful isolation of human ventricular myocytes suitable for use with the patch-clamp technique now allows for separation of currents and quantitative measurements.23 The present study was conducted to investigate whether a transient outward current exists in human ventricular myocardium and to characterize its basic electrophysiological properties.

Subjects and Methods

Patients

Cells were prepared from hearts of 22 patients with end-stage heart failure due to dilated cardiomyopathy (n=12) or ischemic cardiomyopathy (n=10) undergoing transplantation. Patients’ age was 41.4±3.5 years; one

Received March 19, 1992; accepted April 22, 1993.
From the Department of Medicine I, University of Munich (Germany), Klinikum Grosshadern.
Previously presented in part as an abstract (Circulation. 1992;86[suppl 1]:I-617).
Correspondence to Marchioninistr. 15, D-8000 Munich 70, FRG (Dr Nábauer).
was female. Cardiac index was \(2.3\pm0.18\ \text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}\) and ejection fraction was \(24.7\pm3\%\). All patients received digoxin and diuretics and were under vasodilator therapy. No catecholamines or \(\beta\)-adrenoceptor blocking drugs were given during 48 hours before the operation. Informed consent was obtained before organ explantation. The protocol was approved by the ethical committee of the university.

**Cell Isolation**

The isolation procedure has been previously described in detail. A part of the left ventricular wall was excised together with its arterial branch. The wall segment was then perfused via its arterial branch: 30 minutes with a nominally \(\text{Ca}^{2+}\)-free modified Tyrode’s solution (mM: NaCl, 138; KCl, 4; MgCl\(_2\), 1; glucose, 10; NaH\(_2\)PO\(_4\), 0.33; and HEPES, 10; pH 7.3 with addition of NaOH, 37\(^\circ\)C), followed by 40 minutes with the same solution with added 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 \(\mu\text{M}\) Ca\(^{2+}\). To prevent an influence of regional current variability, due to the location of the tissue sample, cells used in this study were taken from the central one third of the myocardial wall, thus excluding endocardial and epicardial layers. Ventricular cells were disaggregated by mechanical agitation and, after filtering through a nylon mesh, stored at room temperature in Tyrode’s solution containing 2.0 mM Ca\(^{2+}\). The living-cell yield was approximately 5\% to 8\%. Only cells with clear cross striations without spontaneous contractions or significant granulation were selected for experiments. When field-stimulated, those cells contracted as controlled visually. A total of 73 cells yielded results for these experiments; mean cell capacity was \(163.3\pm7.6\ \text{pF}\).

**Solutions**

Cells were superfused with a modified Tyrode’s solution containing (mM) Ca\(_{\text{Cl}}\), 2.0; NaCl, 138; KCl, 4; NaH\(_2\)PO\(_4\), 0.33; MgCl\(_2\), 1; CdCl\(_2\), 0.3; glucose, 10; and HEPES, 10; pH was adjusted to 7.3 with the addition of NaOH. For determination of activation curves, NaCl was replaced with equimolar amounts of choline chloride to eliminate contamination of tail current readings by Na\(^+\) current; steady-state inactivation was determined under identical conditions. In external solutions containing elevated concentrations of KCl (20, 40, and 80 mM) or tetraethylammonium chloride (TEA-Cl) (40 mM), NaCl was reduced accordingly. Cd\(^{2+}\) was included to block Ca\(^{2+}\) currents that might interfere with the measurement of \(K^+\) currents. Tetrodotoxin (3 \(\mu\text{M}\), Sigma) was added to the external solution to partially block the fast Na\(^+\) current. 4-Aminopyridine and diisothiocyanostilbene-2,2’-disulfonic acid (DITS, 200 \(\mu\text{M}\)) were freshly dissolved just before use in Tyrode’s solution. Experiments were performed at room temperature (21\(^\circ\) to 23\(^\circ\)).

For current recordings, cells were dialyzed internally for at least 2 minutes via the micropipette electrode with (mM) potassium glutamate, 120; KCl, 10; MgCl\(_2\), 2; HEPES, 10; EGTA, 5; and Mg-ATP, 2; pH was adjusted to 7.2 with KOH. After this time, the contraction on depolarization had ceased even in the absence of external Cd\(^{2+}\).

**Recording Technique**

Experiments were carried out by standard whole-cell recording techniques using a patch-clamp amplifier (model EPC-7, List Instruments, Germany) with a 100-M\(\Omega\) feedback resistor. Microelectrodes were pulled from borosilicate glass and had resistances of 2.0 to 3.0 M\(\Omega\). Series resistance was compensated as much as possible (30\% to 80\%). For determination of current activation, small cells were selected (mean capacity, 118.1±18.6 pF; \(n=7\)) to minimize the time required to charge the membrane capacitance to ensure accurate measurement of decaying current tails. Analog filtering of current recordings was at 3 kHz. Currents were digitized at 1 to 10 kHz and stored for off-line analysis.

**Data Analysis**

Fits to the Boltzmann distribution and Goldman-Hodgkin-Katz and Hill equations were obtained by a nonlinear least-squares technique based on the Marquardt algorithm. Exponential fits were performed by nonlinear least-squares fitting using the simplex algorithm. Goodness of fit for single exponential current decay was judged by visual inspection and \(\chi^2\) testing. A two-exponential fit was adopted when it led to a significant (>1.5 times) decrease in \(\chi^2\) over a single exponential fit. Mean \(\pm\)SEM values are given for data when appropriate.

**Results**

**Voltage Dependence of Transient Outward Current**

To determine whether the observed notch in the action potential of human ventricular myocardium might be due to the presence of a transient outward current, 500-millisecond depolarizing pulses were applied under voltage-clamp conditions from a holding potential of -80 mV. In addition to 3 \(\mu\text{M}\) tetrodotoxin in the external solution, a 100-millisecond prepulse to -60 mV was used to partially inactivate the fast Na\(^+\) current. The size of the observed transient outward current showed significant variability between different cells and preparations but was often large enough to almost balance the Ca\(^{2+}\) current in the peak activation range of this current when Cd\(^{2+}\) was omitted from the external solution. Therefore, to prevent interference of the Ca\(^{2+}\) current with the measurement of the transient outward current, CdCl\(_2\) (0.3 mM) was included in the external solution.

CdCl\(_2\) has recently been reported to cause a shift in activation and steady-state inactivation parameters of the transient outward current in the depolarizing direction. Therefore, alternative ways to block the Ca\(^{2+}\) current were considered. However, organic Ca\(^{2+}\) channel antagonists have also been shown to profoundly affect peak transient outward current as well as current kinetics. Increasing intracellular Mg\(^{2+}\) to 15 mM was not sufficiently effective to block the Ca\(^{2+}\) current in human ventricular myocytes with contaminating Ca\(^{2+}\) current remaining. Therefore, it was decided to use an inorganic Ca\(^{2+}\) channel blocker, such as CdCl\(_2\), which has been used extensively by others to block Ca\(^{2+}\) current in studies of the transient outward current.
Activation of the transient outward current was first observed at membrane potentials of approximately −10 mV, increasing monotonically with voltage (Fig 1). Inactivation of the current was rapid with a small maintained current at the end of the clamp pulse that had no obvious time dependence. This current component had a similar voltage dependence as peak transient outward current, although little or no current could be recorded up to +10 mV (Fig 1). External application of 40 mM TEA-Cl did not cause any change in transient outward current or maintained current (not shown).

The transient outward current was also present when Na+ current was partially blocked by tetrodotoxin (3 to 50 μM) or completely eliminated by substitution of external NaCl by choline chloride, indicating that Na+ influx into the cell was not required to activate the transient outward current. A concentration of 3 μM tetrodotoxin, as usually used, will not completely block the fast Na+ current in ventricular myocytes, even from a prepulse potential of −60 mV.24 However, suppression of Na+ current was sufficient to achieve adequate voltage control in the voltage range where the transient outward current was activated. This can be inferred from current tracings such as in Fig 1, which clearly demonstrate that even at voltages of approximately −20 mV, where the Na+ current is expected to be much larger than at more positive voltages, the Na+ current had settled by the time the transient outward current reached its peak. This indicates that contamination of measurement of peak transient outward current by Na+ current is unlikely. As a further precaution, whenever possible, quantitative measurements of peak transient outward current were done at +40 mV, close to the reversal potential of the Na+ current, where only a small Na+ current would be expected, thus not disturbing voltage control or readings of the peak transient outward current.

Increase of temperature from room temperature to 35°C markedly speeded up activation and inactivation kinetics, making a discrimination of capacitance and ionic current transient difficult or even impossible (not shown). To ensure reliable measurement of the transient outward current experiments were performed at room temperature.

**Activation and Inactivation Parameters**

Steady-state inactivation and activation parameters of the transient outward current were determined using standard voltage protocols9,35 (Fig 2). The size of the transient outward current was measured as the difference between peak outward current and current at the end of the pulse. For calculation of steady-state inactivation and activation curves, the transient outward current measured after applying the appropriate prepulse was normalized to the respective maximal transient outward current to give I/I\max. For each individual cell, a Boltzmann distribution was fitted to these normalized currents:

\[ I/I_{\text{max}} = 1/[1+\exp((V_{1/2}-V_m)/S)] \]

where \( V_m \) is the membrane voltage, \( V_{1/2} \) is the voltage at half-maximal activation or inactivation, and \( S \) a slope factor at \( V_m = V_{1/2} \). Both steady-state inactivation and activation could be fitted with a single Boltzmann distribution with \( V_{1/2} = -34.5 \pm 2.3 \) mV and \( S = -5.5 \pm 0.5 \) for steady-state inactivation and \( V_{1/2} = 16.7 \pm 1.6 \) mV and \( S = 8.4 \pm 0.43 \) for activation (n=7).

The time course of inactivation could be fitted by a single exponential function with a time constant of 54.8±3.7 milliseconds (at +40 mV), with no obvious voltage dependence in the range of +20 to +80 mV (Fig 3). At voltages negative to +20 mV, transient outward currents were too small to obtain meaningful fits. In 2 cells (obtained from a single preparation) out of a total of 16 cells, a single exponential fit was inadequate. A double-exponential decay was required to describe the observed current kinetics in these 2 cells (not shown).

**Ion Selectivity of the Transient Outward Current**

The ion selectivity of the transient outward current was determined by measuring the reversal potential of the current at various levels of [K+]o, using a tail-current protocol (Fig 4). To eliminate a contamination by steady-state inward rectifier current, transient outward current...
current--dependent tail currents were calculated as the difference between peak tail current and current at the end of the pulse. Reversal of this difference current occurred at 64.8±0.84 mV (n=12) at [K\(^+\)], of 4 mM, slightly less than what would be expected for a pure potassium conductance, indicating a permeability for ions other than potassium. Assuming that, in addition to potassium, sodium may also be permeable, the relative permeabilities for potassium and sodium were estimated by fitting the Goldman-Hodgkin-Katz equation to the reversal potential (V\(_{rev}\)) measured at different levels of [K\(^+\)]. (Fig 4):

\[
V_{rev} = 58 \cdot \log\left(\frac{P_{Na} \cdot [Na^+] + [K^+] \cdot [Na^+]}{P_{Na} \cdot [Na^+] + [K^+]}\right)
\]

where \(P_{Na}\) is the relative permeability of sodium to potassium, [K\(^+\)] is 130 mM, [Na\(^+\)] is 138 mM, and [Na\(^-\)] is 5 mM (estimated). \(P_{Na}\) obtained by this procedure was 0.043.

Because contamination of tail currents by a time-dependent component of the inward rectifier current in the voltage range negative to −60 mV might cause an overestimation of the potassium selectivity of the transient outward current, the reversal potential of transient outward current--dependent tail currents was also determined by extrapolation from the linear part of the relation voltage to tail currents in the range between −30 and −55 mV. Using this procedure, the reversal potential of the transient outward current was −58.2±2.1 mV (n=8), indicating a slightly larger relative Na\(^+\) permeability of 0.066.

To assess a possible contribution of a chloride conductance to the transient outward current, the chloride channel blocker DIDS (200 \(\mu\)M) was studied.\(^9\) No effect was seen on peak currents, kinetics, or reversal potential. This indicates that the transient outward current in human ventricular myocytes has a high selectivity for potassium, similar to what has been reported in other species and tissues.\(^{1,4,9,36}\)

**Recovery from Inactivation**

To measure the time and voltage dependence of recovery from inactivation, a double-pulse protocol was used. After initial depolarization to +40 mV, the membrane was held for increasing intervals at −60, −80, or −100 mV, followed by a second pulse to determine the fraction of available transient outward current. Recovery from inactivation was voltage dependent, with recovery being faster at more negative potentials. A double-exponential fit was required to adequately describe the time course of recovery (Table). Initial recovery was fast, with 79.4±8.4% recovery of the transient outward current within 100 milliseconds at −80 mV (Fig 5). The remaining small current component recovered with a much slower time course (Table). Because of the very slow time course and small size of this second component, its accurate determination was difficult.
Frequency Dependence of the Transient Outward Current

Frequency dependence of the transient outward current was determined by applying 300-millisecond pulses to +40 mV from a holding potential of −80 mV. A 50-millisecond prepulse to −60 mV was given to partially inactivate Na⁺ current. Measurements of the peak transient outward current were made after steady-state level had been reached (usually three to six beats) and were normalized to the peak transient of the first depolarization in the train. These “rested state” currents were obtained after 20 seconds of rest at a holding potential of −80 mV. In a total of 16 cells, the mean reduction of peak transient outward current at 2 Hz compared with rested state conditions was 29.8 ± 1.4% (Fig 6).

Effect of 4-Aminopyridine

4-Aminopyridine is commonly used to rather selectively block the transient outward current in mammalian cardiac cells. To determine the 4-aminopyridine sensitivity of the transient outward current in human ventricular myocytes, 4-aminopyridine in concentrations from 0.1 to 5 mM was applied to myocytes depolarized to +40 mV from a holding potential of −80 mV at a frequency of 0.2 Hz. A concentration of 5 mM 4-aminopyridine was sufficient to completely eliminate the fast transient component of the outward current. Block by 4-aminopyridine was determined by calculating the

<table>
<thead>
<tr>
<th>Voltage (mV)</th>
<th>τfast (ms) ± SEM</th>
<th>Amplitudefast (%) ± SEM</th>
<th>τslow (ms) ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>−60</td>
<td>66.6 ± 10.5</td>
<td>80.8 ± 5.1</td>
<td>18.124</td>
</tr>
<tr>
<td>−80</td>
<td>41.0 ± 6.6</td>
<td>86.0 ± 5.2</td>
<td>4425</td>
</tr>
<tr>
<td>−100</td>
<td>30.7 ± 3.1</td>
<td>89.7 ± 3.4</td>
<td>2331</td>
</tr>
</tbody>
</table>

τ, time constant. Values are mean±SEM.
difference between the peak outward current and the current measured at the end of the pulse, which was then normalized to this current difference before application of 4-aminopyridine. The results are shown in Fig 7. Fitting of a Hill equation to the data indicated a half-maximal inhibition of the transient outward current at 1.15 mM 4-aminopyridine.

**Discussion**

The present report describes the presence of a transient outward current in human ventricular myocytes and gives its basic electrophysiological characterization. The large current density, frequently masking the Ca\(^{2+}\) current in the peak range of this current, makes this current a major outward current at plateau voltages in human ventricular myocardium. Its existence and large size may have important implications for the understanding of electrical phenomena of the human heart.

Transient outward potassium currents similar to that described in this report have been observed previously in atrial,\(^9,11\) crista terminalis,\(^25\) and pacemaker\(^28\) cells, in cardiac Purkinje fibers,\(^3,10\) and in ventricular myocytes.\(^1,2,7,8\) The similarities are based on its transient nature with fast activation and inactivation, its voltage dependence, potassium conductance, current density, and pharmacological sensitivity. In cardiac tissue, this type of transient outward current is usually denoted \(I_{to}\)\(^3,16,39\) which will also be used thenceforward in this article. However, some specific characteristics should be noted.

In several animal species as well as human atrial tissue, Ca\(^{2+}\)-independent and Ca\(^{2+}\)-dependent types of transient outward current have been reported.\(^4,11,13\) The Ca\(^{2+}\)-dependent transient outward current is up to an order of magnitude smaller than the Ca\(^{2+}\)-independent current and is usually identified only when this current has been blocked.\(^8,10,11,38\) Because of our experimental conditions, it is very likely that only the Ca\(^{2+}\)-independent transient outward current has been observed in the present study. Inclusion of 5 mM EGTA in the internal solution and block of Ca\(^{2+}\) influx via Ca\(^{2+}\) channels (by
FIG 7. Sensitivity of the transient outward current to 4-aminopyridine. I, current; Imax, peak current. A, Application of 5 mM 4-aminopyridine (4AP) completely suppressed the transient component of the outward current in human ventricular myocytes. Repetitive clamp steps from -80 to +40 mV at 0.2 Hz were shown during wash in of 5 mM 4AP. The dotted line indicates zero current level; the remaining outward current at the end of the pulse is 190 pA. B, Concentration-effect curve for 4AP on the transient outward current. The transient outward current was measured as the difference between peak outward current and the current at the end of the pulse. I/Imax is the ratio of these difference currents before and after application of 4AP. The line is the best fit of a Hill equation to the data points with a half block at 1.15 mM 4AP and a Hill coefficient of 1.4. Data are from nine cells exposed to two to three concentrations of 4AP.

use of external Cd²⁺ and Na⁺-Ca²⁺ exchange (by internal dialysis with nominally Na⁺-free internal solution) would have minimized a Ca²⁺-dependent transient outward current. The existence of such a Ca²⁺-dependent transient outward current in human ventricular myocardium, possibly due to a chloride conductance, 18,19 must await further investigation.

When examining the voltage dependence of Iw, a maintained component was noted after settling of the transient current. Although the voltage dependence of this component was similar to the transient component, the maintained current did not show changes corresponding to those of the transient current in its steady-state inactivation, recovery from inactivation, or frequency-dependent reduction. Therefore, it seems unlikely that it is related to Iw, even though a small nonactivating component of the transient outward current cannot be excluded by our experiments. A maintained current component in rat ventricular myocytes has recently been reported to be due to a novel depolarization-activated extracellular TEA⁺-sensitive outward K⁺ current. 40 However, there was no evidence for this type of outward current in human ventricular myocytes under our experimental conditions. This is based on the monosigmoidal shape of the steady-state inactivation curve, lack of effect of prepulse voltage on the late outward current (Fig 2), and absence of an extracellular TEA⁺-sensitive outward current component.

Because of the complex state-dependent blocking properties of 4-aminopyridine, the pedestal current component remaining after application of 5 mM 4-aminopyridine cannot be simply regarded as current going through channels other than the transient outward K⁺ channel. Since 4-aminopyridine appears to bind with higher affinity to the resting state of the transient outward K⁺ channel than to the open state, a significant number of channels will become available during the depolarizing pulse contributing to the observed outward current, 41 even in the presence of 4-aminopyridine. Therefore, 4-aminopyridine may not be a suitable tool to assess the size of a possible pedestal outward current not carried by transient outward K⁺ channels.

Reported inactivation kinetics of Iw were variable, depending on animal species used and, possibly, experimental conditions. Although some studies found a biexponential decay of Iw, 1,7,9,10 the transient outward current in human ventricular myocardium described here followed a single exponential time course, thus being similar to results in human atrium and rat 11,30. The time course of inactivation was largely independent of voltage, in agreement with most other reports. 1,11,30 Voltage-independent inactivation kinetics were also reported for the kinetically similar A-type K⁺ outward current in neuronal cells. 35,42 These channels are thought to inactivate via a “ball and chain” mechanism plugging the internal opening of the channel pore without being significantly influenced by membrane voltage. 42 To explain the observed kinetics of this current, a coupled model of activation and inactivation transitions has been successfully used. 42,43 This may indicate that a similar coupled model may be applicable to the human ventricular transient outward K⁺ channel. 44

The transient outward current has been suggested to be responsible for frequency-dependent effects on repolarization of the action potential. 4,8,13,15,45 Within a physiological range of frequencies, Iw varied by approximately 30% (Fig 6). Such a reduction may appear too small to account for major effects on the action potential. However, considering the large density of Iw, a small fractional reduction results in significant changes in absolute current (several hundred picoamperes). Because of its fast activation, the transient outward current has an important influence on the initial repolarization of the action potential (phase 1) and the early plateau. Current changes of several hundred picoamperes during this early phase of the action potential may profoundly affect activation of other plateau currents, eg, Ca²⁺ and delayed rectifier K⁺ currents, influencing action potential duration in a complex manner. The lack of a specific blocker of the transient outward current, however, hinders attempts to determine its physiological role for action potential duration. Because of the fast inactivation of the transient outward current, espe-
cially at physiological temperatures, its direct contribution to the final repolarizing phase of the action potential is probably small.

The frequency-dependent changes of $I_{to}$ are also reflected in the time course of recovery from inactivation. More than 80% of $I_{to}$ recovered with a rapid time course of $41\pm 6.5$ milliseconds (at $-80$ mV), which is similar to what has been reported for dog ventricle (94 milliseconds$^{38}$) or human atrial myocytes (54 milliseconds$^{39}$) at comparable voltages. This contrasts to the more than 10 times slower recovery reported in rabbit atrial and ventricular myocytes (780 milliseconds$^{10}$ to 5700 milliseconds$^{10}$). Biphasic recovery from inactivation has also been reported for rabbit atrial and ventricular$^{8}$ and canine Purkinje$^{3}$ cells. This and the initial delay in the time course of recovery (Fig 6, most noticeable at $-60$ mV) indicate that the recovery process probably involves more than one transition through inactivated states. Although most of $I_{to}$ recovered within 100 milliseconds, use-dependent inactivation due to the slow component of recovery and its accumulation appears to be sufficient to account for the frequency-dependent reduction of $I_{to}$. A relevant contribution of the fast component of recovery to frequency-dependent reduction of $I_{to}$ would only be expected if the time spent at resting membrane voltages gets significantly shorter than 100 milliseconds.

The presence of a large transient outward current in human ventricular myocardium may have important clinical implications. Even though the physiological role of the transient outward current has not been fully defined, partly because of the lack of a specific blocker of the transient outward current, a number of important functions have been attributed to the transient outward current. It is held responsible for early repolarization of the action potential, determining the voltage of the early plateau. This in turn affects activation of other plateau currents, most importantly Ca$^{2+}$ and delayed rectifier K$^{+}$ currents, influencing action potential duration and Ca$^{2+}$ influx, hence, cardiac contractility. Under normal and pathological conditions, eg, ischemia with extracellular K$^{+}$ accumulation and partial depolarization, the availability of the transient outward current may affect conduction and spontaneous electrical activity. Alteration of the transient outward current has been reported to occur during developmental stages and in cell layers adjacent to infarcted areas. Furthermore, substantial regional variability of $I_{to}$ has been reported for myocardium at different locations within the myocardial wall, being much larger in epicardial than endocardial layers, possibly related to differences in action potential duration of these layers. This variability may provide a basis for selective pharmacological modification of electrical properties in different areas of the heart. The presence of a large transient outward current may be important for concepts of arrhythmogenesis and arrhythmic drug action in the human heart, especially since some of the drugs used to treat ventricular arrhythmias have been shown to also act on the transient outward current at therapeutic concentrations (quinidine$^{48}$ and propafenone$^{49}$).

The role of the transient outward current in ventricular arrhythmias and frequency-dependent phenomena of the human heart and its possible modulation during physiological or pathophysiological conditions merits further investigation. Possible changes in the density of the transient outward current in the failing human heart are described in the accompanying article$^{20}$ in this issue of Circulation Research.

Acknowledgments

This study was supported by a grant of the Deutsche Forschungsgemeinschaft (Be 1113/2-2). The expert technical assistance of Johann Rausch is gratefully acknowledged. Special thanks are due to Prof Bruno Reichart and his colleagues (Department of Cardiac Surgery) for providing the myocardial tissue.

References


Characteristics of transient outward current in human ventricular myocytes from patients with terminal heart failure.
M Näbauer, D J Beuckelmann and E Erdmann

Circ Res. 1993;73:386-394
doi: 10.1161/01.RES.73.2.386
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/73/2/386

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/