Effects of carvedilol on transient outward and ultra-rapid delayed rectifier potassium currents in human atrial myocytes

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Abstract

Carvedilol is a β- and α1-adrenoceptor antagonist. It is widely used in the treatment of cardiovascular diseases including atrial arrhythmias. However, it is unclear whether carvedilol may affect the repolarization currents, transient outward K+ current (Ito) and ultra-rapid delayed rectifier K+ current (IKur) in the human atrium. The present study evaluated effects of carvedilol on Ito and IKur in isolated human atrial myocytes by whole-cell patch-clamp recording technique. We found that carvedilol reversibly inhibited Ito and IKur in a concentration-dependent manner. Carvedilol (0.3 μM) suppressed Ito from 9.2±0.5 pA/pF to 4.8±0.5 pA/pF (P < 0.01) and IKur from 3.6±0.5 pA/pF to 1.9±0.3 pA/pF (P < 0.01) at +50 mV. Ito was inhibited in a voltage-dependent manner, being significantly attenuated at test potentials from +10 to +50 mV, whereas the inhibition of IKur was independent. The concentration giving a 50% inhibition was 0.50 μM for Ito and 0.39 μM for IKur. Voltage-dependence of activation, inactivation and time-dependent recovery from inactivation of Ito were not altered by carvedilol. However, time to peak and time-dependent inactivation of Ito were significantly accelerated, indicating an open channel blocking action. The findings indicate that carvedilol significantly inhibits the major repolarization K+ currents Ito and IKur in human atrial myocytes.

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Introduction

The voltage-gated repolarizing K+ currents include rapid and slow components of delayed rectifier K+ currents (IKr and IKs), 4-aminopyridine-sensitive transient outward K+ current (Ito) and ultra-rapid delayed rectifier K+ current (IKur) in human atria (Li et al., 1996; Wang et al., 1993). Ito and IKur appear to play important roles in human atrial repolarization, and their quantity or kinetic properties have significant effects on action potential duration. In addition, IKur has been reported to be present in the atrium, but not in the ventricle of human heart (Nattel et al., 1999). Therefore, blockade of IKur may have implications for the treatment of patients with atrial fibrillation.

Carvedilol is a β- and α-adrenergic blocker with clinically important antiarrhythmic properties. It possesses anti-ischemic, anti-oxidant/anti-apoptotic (Kawai et al., 2004), anti-proliferative (Ohlstein et al., 1993) and anti-inflammatory (Yuan et al., 2004) activities. It can inhibit a number of cationic channels, including the L-type Ca2+ current (Ica), IKr, IKs and Ito in rabbit ventricular myocytes (Cheng et al., 2001), the HERG K+ channel expressed in HEK293 cells (Karle et al., 2001; Kawakami et al., 2006) and the voltage-dependent sodium channel in cultured bovine adrenal medullary cells (Kajiwara et al., 2002). It is widely used for treatment of patients with hypertension, acute myocardial infarction and heart failure. Recent studies have reported that carvedilol is effective in patients with atrial fibrillation (Joglar et al., 2001; Ramaswamy, 2003). However, the direct effect of carvedilol on Ito and IKur currents in human atrial myocytes remains unknown. Therefore, the aim of the present study was to examine whether carvedilol directly influences Ito and IKur in isolated human atrial myocytes by using whole-cell patch-clamp recording technique.
Materials and methods

Myocyte isolation

Atrial cells were isolated from specimens of human right atrial appendage obtained from 19 patients (52.3±4.3 years old, range from 28 to 70 years) undergoing coronary artery bypass grafting. The procedure for obtaining the tissue was approved by the Ethics Committee of Guangdong Provincial People’s Hospital. All atrial specimens were grossly normal at the time of cardiac surgery, and all patients were free of supraventricular tachyarrhythmias and symptomatic congestive heart failure. After excision, the samples were quickly immersed in oxygenated, nominally Ca2+-free cardioplegic solution for transport to the laboratory. Atrial myocytes were enzymatically dissociated with a modified technique as described previously (Tian et al., 2006). Briefly, atrial tissue was chopped into cubic chunks in Ca2+-free Tyrode solution (4 °C), then placed in a 25 ml beaker containing 10 ml of the Ca2+-free Tyrode solution (36 °C), and gently agitated by continuous bubbling with 100% O2 and stirred with a magnetic bar. After 20 min (5 min at a time in fresh solution) the chunks were reincubated in a similar solution containing 150 to 300 U/ml collagenase (CLS II, Worthington Biochemical, Freehold, NJ), 4 U/ml protease (type XXIV, Sigma Chemical, St. Louis, MO) and 1% albumin (Sigma) for 50 min. The supernatant was then removed and discarded. The chunks were reincubated in a fresh enzyme solution without protease. The medium was examined microscopically every 5 to 10 min to determine the number and quality of the isolated cells. When the yield appeared to be maximal, the chunks were suspended in a “Kraftbrühe” (KB) storage solution and gently pipetted. The isolated atrial myocytes were maintained in the medium at least 1 h before study.

Electrophysiology

Electrophysiological experiments were performed essentially as previously described (Hamill et al., 1981). Myocytes were transferred into an experimental chamber (~3 ml) mounted on the stage of an inverted microscope (Olympus IX70, Japan) and allowed to adhere to the glass bottom of the chamber. Cells were perfused with extracellular solution. $I_{\text{Na}}$ and $I_{\text{K}}$ were recorded by the whole-cell patch-clamp technique. Patch pipettes were fabricated from borosilicate glass capillaries (Corning 7740, 1.5 mm OD). Tip resistances were 2–3 MΩ when filled with the internal solution. A 3 M KCl-agar bridge was used as reference electrode. Tip potentials were compensated before the pipette touched the cell. After a gigaseal (10 GΩ) was obtained, the cell membrane was ruptured by gentle suction to establish the whole cell configuration. The series resistance ($R_s$) was 3–5 MΩ and was compensated by 70–80% to minimize voltage errors. Current signals were recorded with an Axopatch 200B amplifier using the Digidata 1200B-pClamp 7.0 data-acquisition system (Axon Instruments, USA). The signals were filtered at 5 kHz and stored on the hard disk of a computer.

Drugs and chemicals

Ca2+-free cardioplegic solution for specimen transport contained (in mM): 50 KH2PO4, 8 MgSO4, 5 adenosine, 10 HEPES, 140 glucose, 100 mannitol, and 10 taurine, with the pH adjusted to 7.3 with KOH. Tyrode solution contained (in mM): 140 NaCl, 5.4 KCl, 1 MgCl2, 1.8 CaCl2, 0.33 NaH2PO4, 5 HEPES, and 10 glucose, with the pH adjusted to 7.4 with NaOH. For washing of atrial tissue chunks, Ca2+ was omitted. KB storage solution contained (in mM): 10 KCl, 10 KH2PO4, 20 glucose, 120 K-glutamate, 10 taurine, 0.5 EGTA, 10 HEPES, 10 mannitol, and 1.8 MgSO4, with the pH adjusted to 7.2 with KOH. The pipette solution contained (in mM): 20 KCl, 110 K-aspartate, 1.0 MgCl2, 10 HEPES, 5 EGTA, 0.1 GTP, 5 Na2-phosphocreatine, and 5 Mg-ATP, with the pH adjusted to 7.2 with KOH. For $I_{\text{Na}}$ and $I_{\text{K}}$ determination, BaCl2 (200 μM, Sigma) and CdCl2 (200 μM, Sigma) were added to the superfusion to block $I_{\text{K1}}$ and $I_{\text{Ca}}$. Atropine (1.0 μM, Sigma) was used to minimize possible $I_{\text{K,ACH}}$ contamination during the current recording. Carvedilol was from Qilu Pharmaceutical Company (Jinan, Shandong, China). All experiments were performed at room temperature (25±1 °C).

Statistical analysis

All data are expressed as mean±S.E.M and were analyzed using Graphpad PRISM 3.0 (Graphpad, San Diego, CA).
CA, USA) or Clampfit (Axon). Paired and/or unpaired Student’s *t*-test was used as appropriate to evaluate the statistical significance of differences between two group means, and ANOVA was used for multiple groups. Values of *P*<0.05 were considered to indicate statistical significance.

**Results**

**Time-dependent effect of carvedilol on I_{to}**

Fig. 1A shows voltage-dependent $I_{to}$ elicited by 300-ms at 0.2 Hz in voltage steps from −50 mV to +50 mV in a representative human atrial myocyte under control conditions (Fig. 1A(a)), in the presence of carvedilol (Fig. 1A(b)) and after drug washout (Fig. 1A(c)). The current was measured from current peak to the steady-state current level at end of depolarization step. $I_{to}$ was substantially inhibited by the application of 0.3 μM carvedilol, and almost fully recovered after washout of the drug.

Fig. 1B illustrates the time-dependent effect of carvedilol on $I_{to}$ activated by a 300-ms voltage step from −50 mV to +50 mV in a representative cell. Carvedilol (0.3 μM) gradually reduced $I_{to}$ density (normalized by individual cell membrane capacitance) and the effect reached steady-state level within 2 min. The current almost completely recovered upon 3-min drug washout. Similar results were obtained in another four cells.

**Effect of carvedilol on current–voltage (I–V) relationship of I_{to}**

Fig. 2A illustrates the I–V relationships of $I_{to}$ density in six cells before and after the application of 0.1, 0.3, 0.5, 1 and 3 μM carvedilol. $I_{to}$ was suppressed by carvedilol in a concentration-dependent manner, and recovered to 95% upon washout. Carvedilol (0.1, 0.3, 0.5, 1 and 3 μM) significantly inhibited $I_{to}$ at voltages from +10 to +50 mV.

**Voltage-dependent effect of carvedilol on I_{to}**

The percentage of $I_{to}$ reduction by the application of 0.1, 0.3, 0.5, 1 and 3 μM carvedilol are shown in Fig. 2B at test potentials from +10 to +50 mV. Carvedilol significantly decreased $I_{to}$ at all concentrations. Effects of drug were voltage-dependent at the four lower concentrations, showing a significant attenuating effect at test potentials from +10 to +50 mV.

**Concentration-dependent effect of carvedilol on I_{to}**

The concentration–response relationship for inhibition of $I_{to}$ by carvedilol is illustrated in Fig. 2C. Carvedilol at 0.01, 0.1, 0.3, 0.5, 1 and 3 μM in the extracellular solution decreased peak $I_{to}$ by 4.1%, 19.2%, 43.1%, 48.2%, 70.2% and 93.9%, respectively, at test potential of +50 mV. On the basis of cell-by-cell fitting with the Hill equation in six cells, IC$_{50}$ was 0.50 μM with a Hill coefficient of 1.02.

**Effect of carvedilol on time-dependent activation and inactivation of I_{to}**

Fig. 3A shows effects of carvedilol on time-dependent activation and inactivation of $I_{to}$. Current decay of the $I_{to}$ was well fitted by a mono-exponential function with time constant shown under control conditions and in the presence of 1 μM carvedilol. The inactivation time constant was substantially reduced in the presence of carvedilol. Mean values of time constants observed in six cells under control conditions and at 0.1, 0.3, and 1 μM carvedilol are
shown in Fig. 3C. Carvedilol significantly accelerated $I_{\text{to}}$ inactivation in a concentration-dependent manner.

Carvedilol also reduced the time from the onset of depolarization to peak $I_{\text{to}}$ significantly (Fig. 3B). Fig. 3D displays analysis of the time from the onset of depolarization to peak $I_{\text{to}}$ before and after exposure to 1 μM carvedilol, and shows that carvedilol significantly reduces the time to the peak current at potentials from +10 to +50 mV ($P<0.05$ or $P<0.01$ vs. control).

**Effect of carvedilol on voltage-dependent activation and inactivation of $I_{\text{to}}$**

The voltage-dependence of $I_{\text{to}}$ activation can be determined from the ratio of $g/g_{\text{max}}$, where $g$ is the conductance and $g_{\text{max}}$ is the full-scale value of $g$, by using the $I-V$ relation of $I_{\text{to}}$. The relationship between $g/g_{\text{max}}$ and membrane potential was fit to Boltzmann equation: $g/g_{\text{max}} = 1/[1 + \exp((V_{0.5} - V)/S)]$, where $V_{0.5}$ is the estimated half-maximum activation voltage, $V$ is the test potential, and $S$ is the slope factor, which were determined under control conditions and after carvedilol perfusion. The voltage protocol and representative recordings used to assess $I_{\text{to}}$ inactivation are illustrated in Fig. 4A. The voltage dependence of the steady-state inactivation relationship was examined by using a standard two-pulse protocol, 1000-ms preconditioning pulses between −120 and +30 mV from the holding potential of −80 mV, followed by a 300-ms test pulse to +50 mV. The inactivation variability ($I/I_{\text{max}}$) was determined as $I_{\text{to}}$ at a given prepulse potential divided by the maximum $I_{\text{to}}$ in the absence of a prepulse. The inactivation curve was fit by a Boltzmann function with the following equation: $I/I_{\text{max}} = 1/[1 + \exp((V - V_{0.5})/S)]$, where $V_{0.5}$ is the estimated half-maximum inactivation voltage, $V$ is the prepulse potential, and $S$ is the slope factor.

**Fig. 3.** Effects of carvedilol on time course of inactivation and time to peak of activation of $I_{\text{to}}$. (A) Representative $I_{\text{to}}$ tracing from one cell upon depolarization to +50 mV from −50 mV under control conditions and in the presence of 1 μM carvedilol. Inactivation raw data under control conditions and in the presence of carvedilol were well fit to mono-exponential functions with time constants shown. (B) Expanded $I_{\text{to}}$ tracings at +20 mV, showing that the time to peak from the onset of activation of $I_{\text{to}}$ is reduced by 1 μM carvedilol in a typical experiment. (C) Time constants of $I_{\text{to}}$ inactivation in the absence and presence of 0.1, 0.3, and 1.0 μM carvedilol. Carvedilol accelerated $I_{\text{to}}$ inactivation as the concentration increased ($**P<0.01$ vs. control). (D) The time to peak of $I_{\text{to}}$ activation at +10 to +50 mV under control conditions (○) and in the presence of 1 μM carvedilol (●). Carvedilol reduced $I_{\text{to}}$ activation time course ($**P<0.01$ or *$P<0.05$ vs. control).

**Fig. 4.** Effects of carvedilol on $I_{\text{to}}$ kinetics. (A) Representative current traces and protocol used to evaluate voltage dependence of $I_{\text{to}}$ inactivation. (B) Mean data for voltage dependence of $I_{\text{to}}$ inactivation and activation in the absence (○) and presence (●) of 1 μM carvedilol in five cells. Line curves shown are fits of mean data by Boltzmann distribution function. (C) Representative current traces and protocol used for assessing time-dependent recovery of $I_{\text{to}}$ from inactivation. (D) Mean data for time course of recovery of $I_{\text{to}}$ from inactivation in the absence (○) and presence of 1 μM carvedilol (●) in five cells. Data are best-fit to monoexponential function.
The voltage dependence of \( I_{to} \) activation and inactivation was not affected by the application of 1 \( \mu \)M carvedilol (Fig. 4B).

Mean values of \( V_{0.5} \) and \( S \) were 23.0±1.4 and 13.2 ±0.3 mV for activation, and \(-8.6±1.2 \) and \(-5.0 ±0.6 \) mV for inactivation under control conditions. In the presence of 1 \( \mu \)M carvedilol, corresponding values were 23.5±0.9 mV and 14.0 ±0.4 mV for activation (\( n=5, P<0.05 \)), and \(-8.1 ±1.4 \) mV and \(-4.9±0.8 \) mV for inactivation (\( n=5, P>0.05 \)).

**Effect of carvedilol on time-dependent recovery of \( I_{to} \) from inactivation**

The time-dependent recovery of \( I_{to} \) from inactivation was studied with a paired-pulse protocol (P1, P2). The current during P2 (\( I_{2} \)) relative to the current during P1 (\( I_{1} \)) was plotted as a function of the P1–P2 interval (Fig. 4C). The time course of recovery was well fitted to an exponential function. Time constant (\( \tau \)) was 38.4±2.6 ms in control and 37.4 ±3.2 ms in the presence of 1 \( \mu \)M carvedilol (\( n=5, P>0.05 \)). This indicates that carvedilol has no effect on recovery of \( I_{to} \) from inactivation (Fig. 4D).

**Frequency-dependent effect of carvedilol on \( I_{to} \)**

The frequency-dependent effect of 1 \( \mu \)M carvedilol was studied by a series of 10 depolarizing pulses (150 ms duration) from a holding potential of \(-50 \) mV to \(+50 \) mV at three different stimulation frequencies (0.2, 0.5 and 1 Hz). No significant frequency-dependent effect was observed at any frequency (\( n=3, P>0.05 \)).

**Time-dependent effect of carvedilol on \( I_{Kur} \)**

\( I_{Kur} \) was elicited by a 100-ms prepulse to \(+40 \) mV to inactivate \( I_{to} \), followed by 150-ms test pulses between \(-40 \) and \(+60 \) mV after a 10-ms interval from \(-50 \) mV at 0.2 Hz. Fig. 5A displays voltage-dependent \( I_{Kur} \) recorded by the voltage protocol in a typical experiment. Carvedilol at 0.3 \( \mu \)M substantially

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**Fig. 5. Effects of carvedilol on \( I_{Kur} \).** (A) Representative voltage-dependent \( I_{Kur} \) recorded with voltage protocol shown in an atrial myocyte (a) under control conditions, (b) in the presence of 0.3 \( \mu \)M carvedilol, and (c) after washout. The \( I_{Kur} \) was substantially inhibited by carvedilol application (2 min) at all voltages, and almost fully recovered after drug washout for 2 min. (B) Time-dependent effect of 0.3 \( \mu \)M carvedilol on \( I_{Kur} \) in a representative myocyte. The \( I_{kur} \) was evaluated at peak amplitude during test pulse.

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**Fig. 6. Concentration-dependent effect of carvedilol on \( I_{Kur} \).** (A) \( I–V \) relationship of \( I_{Kur} \) under control conditions, in the presence of carvedilol at 0.1, 0.3, 0.5, 1, and 3 \( \mu \)M, and drug washout. Carvedilol inhibited \( I_{Kur} \) in a concentration dependent manner, and the effect was reversed by 92% upon drug washout. (B) Voltage-dependent percentage of \( I_{Kur} \) reduction by carvedilol with multiple concentrations. Carvedilol significantly inhibited \( I_{Kur} \) throughout concentrations (\( n=7, **P<0.01 \) vs. control), and no voltage dependence was observed for the drug effect (\( n=7, P>0.05 \), at \(+10 \) mV vs. at \(+50 \) mV). (C) Concentration–response relation for carvedilol inhibition of \( I_{Kur} \). Symbols are mean experimental data at \(+50 \) mV. Solid line is best-fit equation of the form \( E = E_{max}/ [1+(D/C)^b] \). The results for plotted mean data: IC50=0.39 \( \mu \)M, \( b=0.98 \).
inhibited $I_{\text{Kur}}$ (Fig. 5A(b)) and the inhibitory effect was significantly reversed by drug washout (Fig. 5A(c)).

Fig. 5B shows the time-dependent effect of 0.3 μM carvedilol on $I_{\text{Kur}}$ activated by a 100-ms prepulse to 0 mV to inactivate $I_{\text{to}}$, followed by a 150-ms test pulse to +50 from −50 mV after a 10-ms interval to record $I_{\text{Kur}}$ in a representative myocyte. $I_{\text{Kur}}$ was gradually inhibited by carvedilol, and recovered upon the drug washout. Similar results were obtained in five myocytes.

**Effect of carvedilol on current–voltage (I–V) relationship of $I_{\text{Kur}}$**

Fig. 6A shows current–voltage relationship of $I_{\text{Kur}}$ density (normalized by individual cell membrane capacitance) in seven cells studied under control conditions, in the presence of 0.1, 0.3, 0.5, 1 and 3 μM carvedilol, and after drug washout. Carvedilol markedly produced a concentration-dependent inhibition of $I_{\text{Kur}}$, and the effect was reversible upon washout. For example, at a test potential of +50 mV, 0.3 μM carvedilol decreased the $I_{\text{Kur}}$ current density by 44.3±4.6%, from 3.5±0.51 pA/pF to 1.9±0.3 pA/pF ($n=7$, $P<0.05$).

**Voltage-dependent effect of carvedilol on $I_{\text{Kur}}$**

Fig. 6B shows percent changes of $I_{\text{Kur}}$ by carvedilol with various concentrations at test potentials from +10 mV to +60 mV. Inhibition of $I_{\text{Kur}}$ by carvedilol was significant at all concentrations, but no significant voltage-dependent effect was observed at any concentration.

**Concentration-dependent inhibition of $I_{\text{Kur}}$ by carvedilol**

The concentration–response relationship for inhibition of $I_{\text{Kur}}$ by carvedilol is illustrated in Fig. 6C. Carvedilol at 0.01, 0.1, 0.3, 0.5, 1 and 3 μM in the extracellular solution decreased peak $I_{\text{Kur}}$ by 7.23%, 30.28%, 44.37%, 53.52%, 76.76% and 83.80%, respectively, at a test potential of +50 mV. On the basis of cell-by-cell fits with the Hill equation in five cells, IC50 was 0.39 μM with a Hill co-efficient of 0.98.

**Discussion**

In the present study, we have demonstrated that carvedilol significantly inhibits native $I_{\text{to}}$ and $I_{\text{Kur}}$ in human atrium in a concentration-dependent manner. Carvedilol does not affect the voltage dependence of activation, inactivation or recovery from inactivation of $I_{\text{to}}$. However, it significantly accelerates $I_{\text{to}}$ activation and inactivation processes, indicating an open channel blocking action.

Carvedilol is known to exert an antiarrhythmic effect. The electrophysiological properties of carvedilol include moderate prolongation of action potential duration and effective refractory period; slowing of atroventricular conduction; and reduced dispersion of refractoriness (Naccarelli and Lukas, 2005). Although the mechanism is still unclear, it is conceivable that carvedilol interacts with voltage-gated ion channels and therefore modifies the electrophysiological properties of excitable cells. It has been reported that carvedilol is a multi-channel blocker with relative selectivity for $I_{\text{Kr}}$. The IC50 for carvedilol to inhibit $I_{\text{Kr}}$ is 0.35 μM, which is much lower than the concentration required to inhibit other ion channels. However, carvedilol inhibited $I_{\text{Ca}}$, $I_{\text{to}}$, $I_{\text{Ks}}$ with IC50 of 3.59, 3.34, and 12.54 μM, respectively in rabbit ventricular myocytes (Cheng et al., 1999). Carvedilol inhibited HERG current in a concentration-dependent manner with an IC50 of 0.51 μM (Kawakami et al., 2006). In the present study we have found that carvedilol produces a significant block of $I_{\text{Kur}}$ and $I_{\text{to}}$ in human atrial myocytes.

Our observation has showed that carvedilol at 0.1–3 μM substantially inhibits $I_{\text{to}}$ in human atrial myocytes, and significantly accelerates the inactivation of $I_{\text{to}}$, and reduces the time to peak of the activation, indicating an open channel blocking action (Dukes et al., 1990). Carvedilol has no significant effect on the kinetics of voltage-dependent activation and inactivation, and the rate of recovery from inactivation of $I_{\text{to}}$ in human atrial myocytes. Interestingly, carvedilol also significantly inhibits $I_{\text{Kur}}$ in a concentration-dependent manner. It should be noted that the IC50 for carvedilol to inhibit $I_{\text{Kur}}$ is 0.39 μM and that is similar to the concentration required to inhibit $I_{\text{Kr}}$ in rabbit ventricular myocytes (Cheng et al., 1999). The inhibitory effect of carvedilol on $I_{\text{Kur}}$ at lower concentrations might make the drug a desirable therapeutic agent.

It is well known that $I_{\text{to}}$ and $I_{\text{Kur}}$ are major repolarizing currents in the human atrium. Inhibition of the two currents, especially $I_{\text{Kur}}$, would prolong action potential duration and refractory period. Therefore, a decrease of $I_{\text{Kur}}$ would be expected to inhibit atrial tachyarrhythmias, including fibrillation induced by reentrant activity. In addition, $I_{\text{Kur}}$ is found in the atrium, but not in the ventricle of the human heart, and therefore $I_{\text{Kur}}$ is believed to be a potential target in the development of selective antiarrhythmic drugs.

The measurement of the peak plasma concentration of carvedilol after a single oral dose or daily dose of 12.5, 25 or 50 mg revealed that it was in a range of 32–252 μg/l in hypertensive patients (McPhillips et al., 1988; Morgan et al., 1990). This corresponds to concentrations of 0.1–0.6 μM. Therefore, it is speculated that at therapeutic dosage, carvedilol may exert not only β- and α-adrenoceptor antagonistic effects, but also a potent $I_{\text{to}}$ and $I_{\text{Kur}}$ blocking effect in atrium (Cheng et al., 1999). Recent evidence also suggests that the antiarrhythmic actions of certain β-receptor blockers such as carvedilol and metoprolol extend beyond the ventricular tissue to encompass atrial cells and help maintain sinus rhythm in patients with atrial fibrillation, especially in combination with potent antiarrhythmic agents such as amiodarone. This introduction provides a current perspective on these recent developments in the understanding of the antiarrhythmic and antiarrhythmic actions of beta-blockers (Singh, 2005).

The limitation of this study is that it sheds no light on the effects of carvedilol on $I_{\text{Ks}}$ and $I_{\text{Kr}}$, because the cells obtained with the current isolation procedure were not favorable for recording $I_{\text{Kr}}$ and $I_{\text{Ks}}$. Whether carvedilol would regulate $I_{\text{Kr}}$ and $I_{\text{Ks}}$ remains to be defined.
In summary, the present observation demonstrates that the carvedilol can block $I_{K_{Ca}}$ and $I_{Na}$ via open channel block. Therefore, carvedilol can exert an antiarrhythmic effect through both its β-adrenoceptor-blockade activity and ion channel modulating effects, which provides a basis for the wide use of carvedilol in the treatment of heart disease, especially atrial fibrillation.

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