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Review

Carvedilol and vesnarinone: new antiarrhythmic approach in heart failure therapy[1]

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ABSTRACT

Carvedilol and vesnarinone are drugs attracting recent interest in the treatment of chronic heart failure. Electrophysiologic studies have revealed that these drugs cause a moderate prolongation of action potential duration (APD) of ventricular muscles with minimal "reverse frequency-dependence" through different ionic mechanisms. Carvedilol blocks *L*-type Ca^{2+} current (I_{Ca}), transient outward K^+ current (I_{to}), and delayed rectifier K^+ current (I_K) preferentially for the rapidly activating component (I_{Kr}). Vesnarinone is a selective blocker of I_K with a unique drug-channel interaction. From the voltage- and time-dependence of I_K inhibition, vesnarinone is considered to bind the I_K(mainly I_{Kr}) channel during the activated state and unbind during the closed state. These electropharmacologic profiles provide a new approach for the development of an ideal antiarrhythmic drugs in patients with structural heart diseases.

INTRODUCTION

Congestive heart failure (CHF) is the final stage of various structural heart diseases with a series of clinical syndromes resulting from decompensation of the underlying pathologic conditions. The purpose of treatment for CHF is not only to reduce symptoms and to increase functional capacity but also to prolong the survival of individual patients. Among many CHF treating drugs investigated, angiotensin-converting enzyme (ACE) inhibitors, carvedilol (an α, β-adrenoceptor blocking agent), and vesnarinone (a positive inotropic agent) have been shown to reduce the mortality of the patients[1-5]. A common electrophysiologic feature of carvedilol and vesnarinone is a moderate prolongation of action potential duration (APD) of cardiac muscle with minimal "reverse frequency-dependence"[6-7]. Ionic mechanisms underlying the class Ⅲ action of the two drugs are, however, different. It is the result of a balanced multi-channel blocking effect for carvedilol, whereas the result of a unique drug-channel interaction for vesnarinone[6-7]. These pharmacologic profiles may be of potential importance in the clinical management of CHF patients in terms of preventing sudden arrhythmic death and progressive hemodynamic deterioration.

MANAGEMENT OF VENTRICULAR ARRHYTHMIAS IN CHF

Patients with chronic CHF have a high incidence of ventricular arrhythmias causing sudden cardiac death (SCD)[8-12]. In patients who survive acute myocardial infarction (MI), over 50 % of the deaths are due to fatal ventricular tachyarrhythmias[13]. Effective antiarrhythmic treatment is, therefore, essential in the clinical management of these patients for prevention of SCD as well as for improvement of the quality of life and long-term prognosis.

The use of class Ⅰ antiarrhythmic drugs (Na^+ channel blockers) has always been limited by their proarrhythmic potential owing to the depression of conduction[14]. These drugs have reportedly even increased mortality in patients with recent MI[15]. Class Ⅲ agents

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(eg, sotalol, E-4031, dofetilide, UK-66914, and almokalant), which exert antiarrhythmic action by prolonging APD and effective refractory period (ERP), possess a common unfavorable feature, a "reverse frequency-dependence"; wherein the APD prolongation is greatly enhanced at low but diminished at high stimulation frequencies[16,17]. Although these drugs have been shown to exert beneficial antifibrillatory effects in patients with atrial fibrillation, they also produce a variable incidence of *torsades de pointes*, resulting in either a neutral (*eg*, dofetilide) or deleterious (*d*-sotalol) effect on mortality in patients with post MI and CHF[17]. Emphasis is, therefore, now shifting to compounds that have the propensity to block more than one kind of ion channels (so called complex class Ⅲ agents, such as amiodarone, tedisamil, and azimilide). Such a property may not be associated with reverse use- or frequency-dependence of APD prolongation, and could be less "torsadogenic" compared with specific I_{Kr} blockers[18].

In the 1990's amiodarone emerged as one of the few antiarrhythmic drugs effective in suppressing and preventing life-threatening ventricular tachyarrhythmias without increasing mortality. The electrophysiologic basis for amiodarone's exceptionally high antiarrhythmic efficacy and low proarrhythmic propensity is not fully understood. It is well known that the electrophysiologic effects of amiodarone administered acutely and those after a long-term administration differ markedly[19,20]. Long-term treatment of rabbits with amiodarone was reported to cause a moderate and frequency-independent APD prolongation of ventricular muscle (Fig 1A). The APD prolongation by chronic amiodarone is most likely due to a decrease in the current density of I_K (especially the slowly activating component, I_{Ks}) and I_{to}[19,20]. Chronic amiodarone has been shown to cause a down-regulation of Kv1.5 mRNA in rat hearts, suggesting a drug-induced modulation of K^+ channel gene expression (pharmacologic remodeling of ion channels)[19,20]. Induction of early afterdepolarization in isolated cardiac muscles at lower stimulation frequencies was also shown to be prevented by long-term pretreatment of the animal with amiodarone[21]. These observations may explain, at least in part, the potent antiarrhythmic and the low proarrhythmic potential of amiodarone compared with other class Ⅲ agents[22]. Clinical usefulness of amiodarone is, however, greatly limited by its complex extracardiac toxicity involving the liver, lungs, and thyroid. Efforts to develop alternative new class Ⅲ agents are therefore continuing.

MULTI-CHANNEL BLOCKING ACTIONS OF CARVEDILOL

Carvedilol is a non-selective adrenoceptor (α, β) blocking agent with vasodilatory properties[23,24]. This drug was originally designed and developed as a vasodilating compound for efficacious and safe treatment of hypertension and coronary artery disease[23]. Recently, interest in carvedilol has been focused on the potential utility of the drug in CHF. Many clinical analyses have revealed that carvedilol produces a significant reduction in mortality of CHF patients, especially from progressive deterioration of left ventricular function and SCD[4,5]. Carvedilol has been shown to prevent ventricular arrhythmias in various animal models including ischemia/reperfusion- and digitalis-induced arrhythmias[25-27].

Action potential recording experiments in rabbit ventricular muscle at different stimulation frequencies have revealed that carvedilol causes a moderate APD prolongation with minimal reverse frequency-dependence (Fig 1B). When the stimulation frequency was changed in steps from 0.1 to 3 Hz, the APD_{90} (APD at 90 % repolarization) in control conditions initially increased and then decreased, showing a normal bell-shaped frequency-response curve in the rabbit ventricular muscle with the longest APD at 0.5 Hz. Carvedilol prolonged APD_{90} by 7 % – 12 % at 1 μmol/L and by 12 % – 24 % at 3 μmol/L over the entire range of stimulation frequencies tested, and the bell-shaped frequency-response curve was well preserved. The ionic currents responsible for the APD prolongation by carvedilol were investigated in rabbit ventricular myocytes[7]. *L*-type Ca^{2+} current (I_{Ca}), inward rectifier K^+ current (I_{K1}), rapidly and slowly activating components of I_K (I_{Kr} and I_{Ks}), and 4-aminopyridine (4-AP)-sensitive I_{to} were recorded using a whole-cell voltage clamp technique. Carvedilol inhibited I_{Ca}, I_{Kr}, I_{Ks}, and I_{to} in a dose-dependent manner without affecting I_{K1}. The potency of inhibition was highest for I_{Kr} (IC_{50} 0.35 μmol/L). The inhibition of I_{Ca} and I_{to} was about 10 fold less potent (IC_{50} 3.34 – 3.59 μmol/L), and the inhibition of I_{Ks} was least potent (IC_{50} 12.54 μmol/L). The voltage-dependence of activation of these ionic currents were unaffected by carvedilol. These observations indicate that the APD prolongation by carvedilol at low concentrations (0.3 – 1 μmol/L) is primarily attributed to a direct inhibition of I_{Kr}. The K^+ channel blocking effects of carvedilol should have led to a profound APD prolongation at higher concentrations.

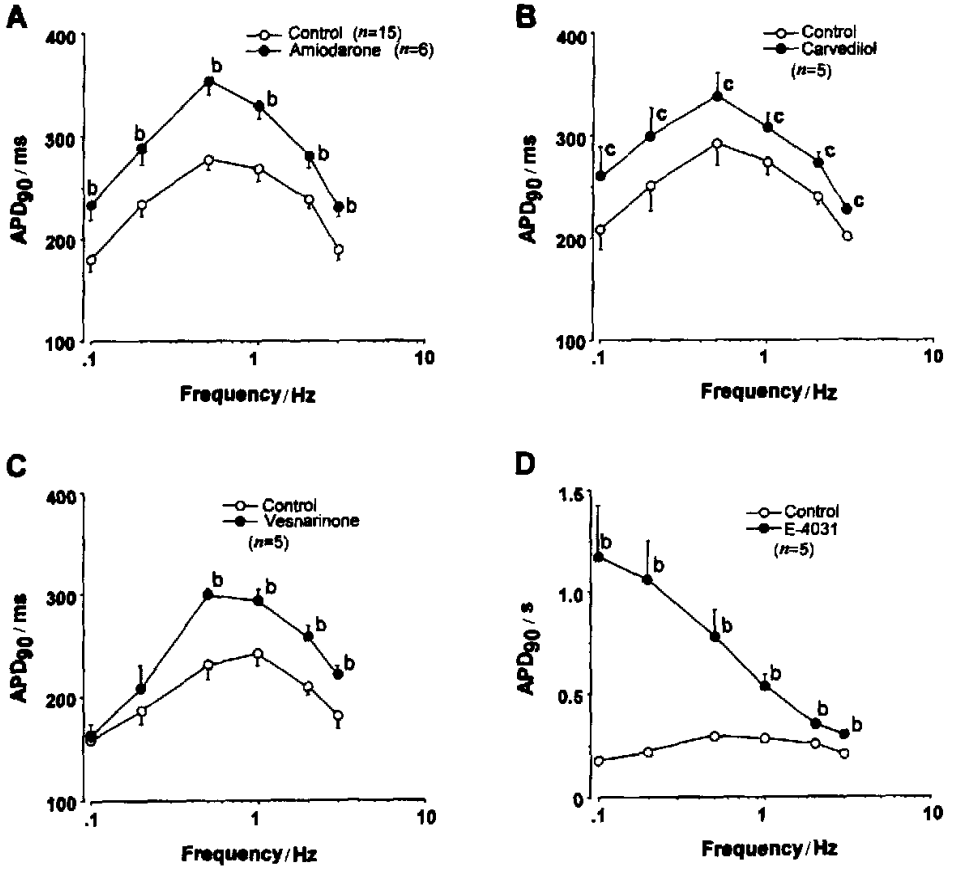

Fig 1. Comparison of the frequency-dependence of APD prolongation by amiodarone, carvedilol, vesnarinone, and E-4031 in rabbit papillary muscles. A: Chronic effects of amiodarone. Amiodarone was administered for 4 weeks at an oral dose of 100 mg·kg^{-1}·d^{-1}. B: Effects of carvedilol (3 μmol/L). Both carvedilol and amiodarone induced a moderate prolongation of APD with minimal reverse frequency-dependence. C: Effects of vesnarinone (10 μmol/L). Vesnarinone prolonged APD significantly at frequencies higher than 0.5 Hz, but had no significant effects at low frequencies of 0.1 and 0.2 Hz. D: Effects of E-4031 (0.3 μmol/L). E-4031 prolonged APD more prominently as the stimulation frequency was reduced, resulting in a marked reverse frequency-dependence. $^bP<0.05$, $^cP<0.01$ *vs* each control value.

However, a concomitant blocking of I_{Ca} may have resulted in a limited increase in APD at higher concentrations ($\geqslant 3$ μmol/L).

The blocking of I_{Kr} with carvedilol, like that with E-4031[28], was not enhanced by a prolongation of the depolarizing voltage-clamp pulse. This suggests that carvedilol may have already blocked I_{Kr} channel at the holding potential when the channel was in the closed state or that the block by carvedilol occurs very rapidly (during the first depolarizing pulse). More extensive voltage-clamp studies will be required to discriminate the two possibilities. In any case, the minimal reverse frequency-dependence of APD prolongation by carvedilol cannot be interpreted by the drug-I_{Kr} channel interaction. Instead, it may be the result of counteracting reduction of inward Ca^{2+} current, which would be more prominent at lower stimulation frequencies.

In patients with CHF, the level of sympathetic drive to the heart is elevated[29]. This preferential activation of cardiac sympathetic outflow contributes to arrhythmia development and probably to the progression of heart failure. Under such a pathologic condition, treatment with carvedilol may produce an antiarrhythmic action through both its intrinsic class Ⅱ antiarrhythmic activity associated with β-adrenoceptor blockade and direct ionic channel

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modulating effects. Indeed, carvedilol has been reported to significantly reduce the frequency of the premature ventricular contractions in patients with mild to moderate essential hypertension, stable angina or chronic heart failure[30]. Carvedilol is also reported to be effective in the treatment of ventricular tachyarrhythmia in a patient with dilated cardiomyopathy without causing significant deterioration of cardiac function or exercise capacity[31]. Furthermore, inhibition of Ca^{2+} and K^+ channels by carvedilol will reduce sinus node firing, as is evidenced by a significant reduction in heart rate in patients of acute MI[32]. Both prolongation of APD and reduction of sinus node pacemaking activity may facilitate cardiac pumping function and improve the prognosis of CHF.

CHANNEL STATE-DEPENDENT BLOCKING AND UNBLOCKING OF I_{Kr} WITH VESNARINONE

Vesnarinone is a quinolinone derivative developed as a phosphodiesterase (PDE) inhibitor. In a multicenter study initiated in 1990, treatment of CHF patients with vesnarinone for 6 months was reported to improve both morbidity and mortality[3]. This effect was observed at low doses below the range at which ventricular contractility and pumping functions are augmented though its PDE inhibitory action. The latest large clinical trial for longer follow-up period (286 d in average), however, has shown a decrease of survival of severe CHF patients by the drug treatment[33].

Vesnarinone has been shown to prolong APD of guinea pig, rabbit, and human ventricular cells[6,34,35]. This APD prolongation is attributed mainly to an inhibition of I_{Kr}, since the effects of vesnarinone on Na^+ inward current (I_{Na}), I_{Ca}, I_{to} and I_{Ks} at clinically relevant concentrations (3 – 10 μmol/L) are minimal or negligible[6,35]. In rabbit ventricular myocytes, vesnarinone inhibited I_K (composed mainly of I_{Kr}) in a dose-dependent manner (IC_{50} 0.91 μmol/L) without affecting the voltage-dependence of its activation[6]. The stimulation frequency-dependence of APD prolongation by vesnarinone was studied most extensively in rabbit ventricular muscle (Fig 1C). Vesnarinone (10 μmol/L) prolonged APD moderately (by 20 % – 30 %) at the physiologic range (0.5 – 3 Hz) of stimulation but not at very low frequencies (0.1 – 0.2 Hz). This is in a good contrast with the APD prolongation by E-4031 (0.3 μmol/L) showing a typical reverse frequency-dependence; it was only 38 % at 3 Hz, but enhanced to 89 % at 1 Hz, and to 511 % at 0.1 Hz (Fig 1D).

Toyama *et al* examined the mode of I_K block by vesnarinone in rabbit myocytes isolated from the apex of the left ventricle, since I_K in this region was shown to be composed mainly of I_{Kr} (Fig 2)[6,36]. To observe the development of I_K channel block by vesnarinone (3 μmol/L), depolarizing prepulses to + 10 mV of variable duration (0.05 – 3 s) were applied from the holding potential (– 75 mV), and tail current ($I_{K,tail}$) was evoked at – 50 mV step after the depolarization. Reduction of $I_{K,tail}$ (I_K block) by vesnarinone was enhanced progressively as the prepulse duration was prolonged; the progress of I_K block was approximated by a single exponential function with a time constant of 365 ms. Recovery of I_K block was tested by a paired pulse protocol; following a 1-s depolarization to + 10 mV, the membrane was hyperpolarized to – 75 mV for variable duration, and then a test depolarization to + 10 mV for 0.2 s was applied to see $I_{K,tail}$ on subsequent repolarization back to – 50 mV. In controls (no drug), the amplitude of $I_{K,tail}$ was decreased gradually reflecting slow deactivation of I_K. In the presence of vesnarinone (3 μmol/L), the $I_{K,tail}$ amplitudes were increased with a prolongation of the hyperpolarization. The ratio of $I_{K,tail}$ blocked by vesnarinone was decreased as a single exponential function of the duration of hyperpolarization with a time constant of 1.87 s. It was also shown in voltage-clamp experiments with a train of depolarization (200 ms, + 10 mV) at 0.2 – 2 Hz for 30 s that the I_K block by vesnarinone is enhanced in a frequency- and use-dependent manner; the block ratio of $I_{K,tail}$ was increased from 15.7 % at 0.2 Hz to 48.9 % at 2.0 Hz[6]. These observations can be interpreted most likely by a state- or voltage-dependent drug-channel interaction; vesnarinone may bind to I_K channel during the activated (open) state at around the plateau phase of action potential, and unbind from the channel during the deactivated (closed) state at around the resting membrane potential level.

To be effective against reentrant arrhythmias with minimal proarrhythmic potential, an antiarrhythmic drug should have a greater class Ⅲ action (APD prolongation) at higher heart rates (during sustained tachycardia). This goal can be attained if the drug block I_K with appropriate blocking and unblocking kinetics: relatively slow onset of block development during depolarization and rapid recovery from the block (unblock) during the

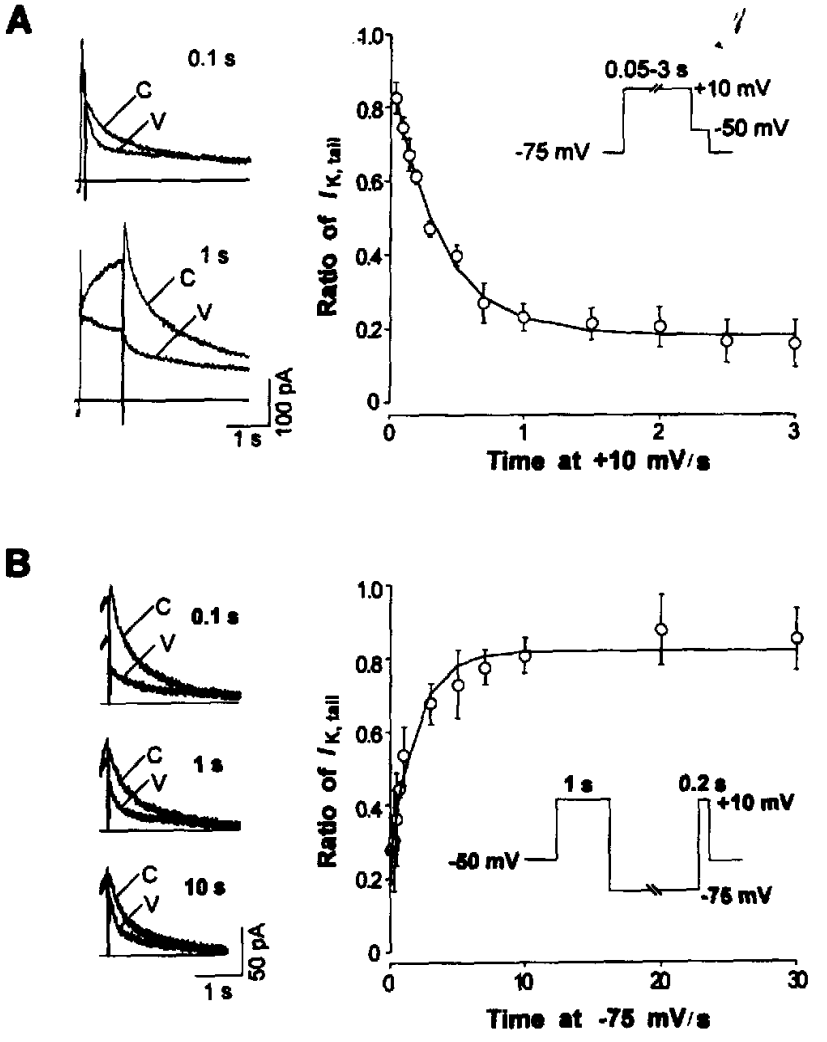

Fig 2. Development of block and recovery from block on I_K by vesnarinone. A: Development of block on I_K by vesnarinone (3 μmol/L). Envelopes of tail current were generated by applying depolarizing pulses of variable durations (from 0.05 to 3 s) from a holding potential of −75 mV. Superimposed tracings represent envelopes of tail current in the control condition (C) and during the application of vesnarinone 3 μmol/L (V). Ratios of tail current amplitudes in the presence of vesnarinone against control conditions were plotted as a function of the duration of the depolarizing pulse. B: Recovery from the block on I_K by vesnarinone (3 μmol/L). The block was induced by applying a 1-s depolarizing pulse to +10 mV, and a test depolarization at the same amplitude was applied for 0.2 s after variable rest durations at −75 mV. Superimposed tracings represent tail currents in the control condition (C) and during the application of vesnarinone 3 μmol/L (V). Tail current amplitudes as a percentage of control are plotted as a function of the rest duration.

electrical diastole. Dofetilide and almokalant have been shown to bind to the open state of I_{Kr} channel with fast kinetics, but they unbind very slowly (time constants ~ 14 s) at partially depolarized membrane potentials (about −50 mV); there is no substantial recovery from the block at the normal resting potential level[37,38]. E-4031 also shows fast binding to the open state but no recovery (unbinding) during the closed state at the resting potential level[28]. Vesnarinone is the first drug that unblocks I_K channels almost completely during the electrical diastole

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at a physiological resting membrane potential level. This unique binding and unbinding kinetics is responsible at least in part for the frequency-dependent APD prolongation by vesnarinone (Fig 1C)[6].

DESIRABLE PROFILES OF ANTIARRHYTHMIC DRUGS IN THE MANAGEMENT OF CHF

For the prevention and suppression of arrhythmias in patients with CHF, class Ⅲ drugs that prolong APD via K^+ channel block are supposed to be more beneficial than the drugs that inhibit Na^+ or Ca^{2+} inward currents (class Ⅰ and Ⅳ drugs) in terms of life-threatening proarrhythmia and dangerous deterioration of cardiac contractility. The benefit of class Ⅲ drugs, however, depends on the frequency- and use-dependent characteristics of the drug-induced APD prolongation; ideally they should cause substantial APD prolongation only during tachyarrhythmias with minimal effect at normal sinus rhythm. Unfortunately, most of the class Ⅲ drugs currently available have the opposite characteristics; their effects to prolong APD are most during slow heart rates, whereas minimal or even negligible during tachyarrhythmias. Vesnarinone could be a model in the future development of ideal class Ⅲ drugs. If the vesnarinone-like I_{Kr} blocking and unblocking kinetics were improved in a newly designed compound (to obtain a faster I_{Kr} recovery during the electric diastole), it would provide more desirable frequency-dependence of APD prolongation.

The pharmacologic characteristics shared by carvedilol and amiodarone may provide alternative approach for the development of ideal antiarrhythmic drugs. These drugs have many different types of molecular targets including Na^+, Ca^{2+}, K^+ channels and receptors, resulting in a moderate APD prolongation with minimal reverse frequency-dependence. For the moment, the right kind of combination of ion channel and receptor blockade fundamental and salutary for their antiarrhythmic activity is not known. This is an important current research subject on antiarrhythmic drugs.

Another important issue to be addressed is drug actions on the "remodeled" cardiac cells. The most consistent electrophysiological abnormality of hypertrophied or failing hearts is APD prolongation of ventricular cells[39]. The APD prolongation itself may be expected to decrease the propensity to reentrant arrhythmias. However, this no longer holds when the prolongation becomes excessive, thereby leading to early afterdepolarizations, or when the prolongation is regional and thereby increases dispersion in APD and also refractoriness[40]. Changes in membrane currents underlying the APD prolongation are incompletely understood. A decrease in I_{to} density (down regulation) has been shown most frequently in experiments using CHF animal models[40,41] whereas I_{Ca} density was reported to be unchanged or decreased[40]. Regarding the change in I_{Kr} and I_{Ks}, information available is still limited. Interestingly, it was recently demonstrated in a canine model of biventricular hypertrophy that I_{Ks} was decreased by about 50 % in both right and left ventricular myocytes, whereas the I_{Kr} density was decreased by only 45 % in myocytes from the right ventricle[42]. Effects of class Ⅲ drugs (pure or complex K^+ channel blockers) on these abnormal (remodeled) ventricular cells are expected to be different from normal cells; the data obtained from animal hearts under physiologic condition cannot be simply extrapolated to such pathologic conditions. More experimental studies are required to shed light on this aspect.

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关键词 卡维地洛；维司力农；充血性心力衰竭；动作电位；抗心律失常药

卡维地洛和维司力农是近年来受到瞩目的慢性充血性心力衰竭治疗药．电生理学研究表明这些药物可适度延长心室肌的动作电位时程(APD)而无明显的逆频度依存性，然而其产生这一作用的离子机制是不同的．卡维地洛可阻断 *L*-型钙电流(I_{Ca})，一过性外向钾电流(I_{to})以及延迟整流钾电流(I_K)，特别是其快速激活成份(I_{Kr})．维司力农是一个选择性的 I_K 阻滞剂，具有独特的药物-通道相互作用．根据维司力农对 I_K 的电位与时间依存性抑制作用，该药被认为在 I_K(主要是 I_{Kr})通道处于激活状态时与其结合，而在通道关闭时则发生解离．这些电生理学特性将为器质性心脏病患者理想的抗心律失常药的开发提供新的途径．

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