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Effect of carvedilol on atrioventricular conduction in the ischemic heart

Toru Horio [a,*], Shigenori Ito [a], Michihiko Aoyama [b], Yutaka Takeda [a], Hiroshi Suzumura [a], Koutarou Nakata [c], Yoshiaki Yamada [a], Shogo Suzuki [a], Tatsuya Fukutomi [a], Makoto Itoh [a]

[a] *The First Department of Internal Medicine, Nagoya City University Medical School, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi-ken, Japan*
[b] *Division of Internal Medicine, Inabe Kosei Hospital, Inabe, Mie, Japan*
[c] *Division of Internal Medicine, Midori Municipal Hospital, Nagoya, Japan*

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Abstract

We compared the effects of carvedilol on atrial-His and His-ventricular conduction with those of propranolol in isolated rat hearts. Hearts were perfused retrograde, and atrial-His and His-ventricular intervals were measured. The effective doses that increased conduction times by 25% were 10^{-6} M for atrial-His and 3×10^{-6} M for His-ventricular for propranolol, and 8×10^{-8} M for atrial-His and 10^{-8} M for His-ventricular for carvedilol. Prazosin did not affect the atrial-His and His-ventricular intervals. After ischemia–reperfusion, atrial-His and His-ventricular intervals increased to a greater extent with 10^{-6} M carvedilol. To determine the direct membrane effect, we examined the transmembrane action potential in guinea pig papillary muscle. Both drugs decreased the maximum upstroke velocity equally. Our data indicate that carvedilol had a greater effect on atrioventricular conduction in the setting of ischemia–reperfusion than did propranolol. This effect of carvedilol was not due to its α-adrenoceptor blocking property or to a direct membrane effect.
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Keywords: β-Adrenoceptor antagonist; Carvedilol; Propranolol; Atrioventricular conduction; Ischemia–reperfusion

1. Introduction

Carvedilol is a "third-generation" non-selective β-adrenoceptor antagonist with additional vasodilating properties mediated through α_1-adrenoceptor blockade. In addition, carvedilol has antioxidant and free radical scavenging properties, which may be cardioprotective. In several species, carvedilol markedly reduces infarct size (Feuerstein et al., 1992). Furthermore, the cardioprotective effects of carvedilol during prolonged reperfusion are more marked than those of pure β-adrenoceptor blocking agents such as propranolol (Bril et al., 1992). However, few studies have examined the effects of carvedilol on the cardiac conduction system, which may restrict its use. The purpose of this study was to compare the electrophysiologic properties of carvedilol with those of propranolol on the atrioventricular conduction system in a Langendorff ischemia–reperfusion model. To determine the cause of the differences, the α_1-adrenoceptor blocking potency of carvedilol was compared with that of prazosin. The transmembrane action potential was measured to determine the direct membrane effect.

2. Materials and methods

2.1. Animal preparation

2.1.1. Atrioventricular conduction model

Male Sprague–Dawley rats weighing 220–250 g were anesthetized with 25 mg/kg of thiopentone sodium. Hearts were rapidly excised via a midsternal thoracotomy and placed in modified Krebs–Henseleit buffer containing (in mmol/l) NaCl 118, KCl 4.7, $MgSO_4$ 1.66, KH_2PO_4 1.18, $CaCl_2$ 2.52, $NaHCO_3$ 24.88, glucose 5.55, and pyruvate 2.0. Hearts were attached to a Langendorff apparatus via the aorta for retrograde perfusion with modified Krebs–Henseleit buffer equilibrated with 95% O_2/5% CO_2 at 37°C. The coronary perfusion pressure was maintained at 80 mm Hg. A bipolar electrode was attached to the right atrium to pace the heart at a rate of 333 beats/min. A single needle bipolar recording electrode (UB-9007, Nihon

* Corresponding author. Tel.: +81-52-853-8211; fax: +81-52-852-0952.
E-mail address: horioto@rcs.tokai.west.ntt.co.jp (T. Horio).

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Kohden, Tokyo, Japan) was inserted into the tricuspid valve annulus through the right atrium in order to record the His-bundle electrogram. The electrograms were displayed on a dual-beam oscilloscope (V-525, Hitachi, Tokyo, Japan) triggered by the driving stimulus. The electrograms were recorded on paper and atrial-His and His-ventricular conduction intervals were measured during the following protocols.

2.1.2. Transmembrane action potential model

Guinea pigs weighing 250–300 g were killed by a blow on the head, and the papillary muscles (2–3 mm in length and < 1 mm in diameter) were isolated from the right ventricle. The preparation was fixed in a tissue bath and superfused continuously with Krebs–Ringer solution equilibrated with 95% O_2/5% CO_2. The composition of the solution was as follows (in mmol/l): NaCl 120.3, KCl 4.0, $CaCl_2$ 1.2, $MgSO_4$ with $7H_2O$ 1.3, $NaHCO_3$ 24.2, glucose 5.5 (pH 7.4).

The temperature of the tissue bath was maintained at 34°C. The preparations were stimulated by a pair of 1.0 mm Ag–AgCl wire electrodes placed 1 mm apart on either side of the papillary muscles. By means of this field stimulation technique, the whole muscle was excited simultaneously, and no conduction occurred within the preparation. Pulses used for stimulation were 0.5–1.0 ms in duration and twice the diastolic threshold in intensity unless specified otherwise. Transmembrane potentials were recorded through two glass microelectrodes filled with 3 M KCl, one intracellularly and the other extracellularly, placed close together. These electrodes were each connected by Ag–AgCl wire to a high-input impedance buffer amplifier, connected to a differential amplifier. The maximum upstroke velocity ($\dot{V}_{max}$) of the action potential was obtained by electronic differentiation.

2.2. Experimental protocols

2.2.1. Protocol 1: control and dose effects model

Hearts ($n = 6$) were perfused for 30 min with modified Krebs–Henseleit buffer, and atrial-His and His-ventricular intervals were measured as baseline control values. Hearts were then perfused with β-adrenoceptor antagonist for 20 min. The concentration of the drug was increased every 20 min (10^{-7}, 3×10^{-7}, 10^{-6}, 3×10^{-6} M for propranolol; 3×10^{-8}, 10^{-7}, 3×10^{-7}, 10^{-6} M for carvedilol; and 10^{-8}, 3×10^{-8}, 10^{-7}, 3×10^{-7}, 10^{-6} M for prazosin). Atrial-His and His-ventricular intervals were measured at the end of each infusion stage. As a control, modified Krebs–Henseleit buffer without drug was perfused for 110 min and atrial-His and His-ventricular intervals were measured at the same five points (Fig. 1).

2.2.2. Protocol 2: ischemia–reperfusion model

Hearts ($n = 6$ for each concentration) were perfused with modified Krebs–Henseleit buffer for 30 min without additions and then perfused with drugs for 10 min at a concentration of 10^{-7}, 3×10^{-7}, 10^{-6}, or 3×10^{-6} M for propranolol; 3×10^{-8}, 10^{-7}, 3×10^{-7}, or 10^{-6} M for carvedilol; and 10^{-8}, 3×10^{-8}, 10^{-7}, 3×10^{-7} or 10^{-6} M for prazosin. Hearts were perfused with only modified Krebs–Henseleit buffer as control. Hearts were then subjected to 30 min of global ischemia followed by 30 min of reperfusion at the same concentration of drugs. Atrial-His and His-ventricular intervals were measured before the infusion of β-adrenoceptor antagonists, after global ischemia, and every 10 min during reperfusion. To determine the cumulative effects of each drug after ischemia–

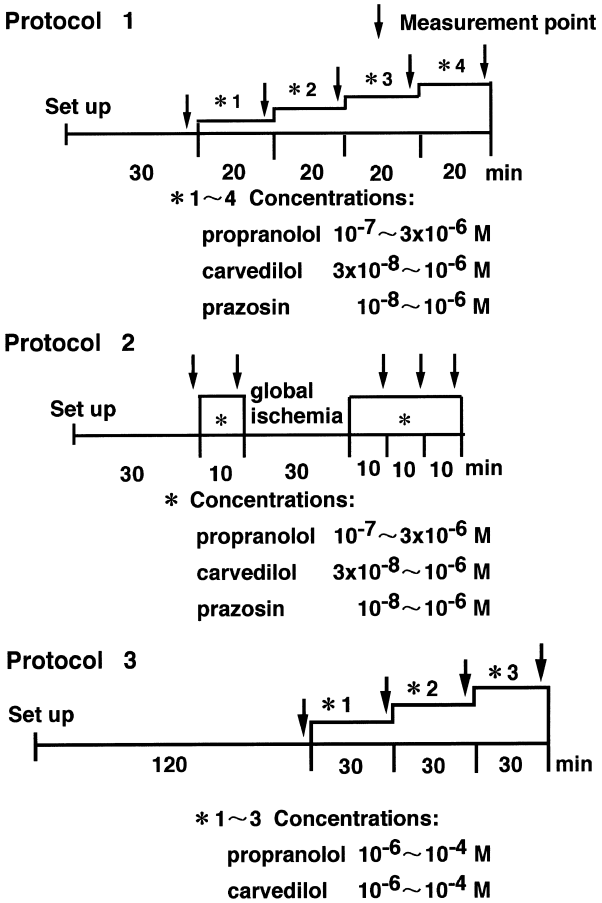

Fig. 1. Study protocol. Summaries of the dose–effect model (Protocol 1), ischemia–reperfusion model (Protocol 2) and transmembrane action potential model (Protocol 3) are shown. In Protocols 1 and 2, atrial-His and His-ventricular intervals were measured under steady conditions. In Protocol 1, hearts were equilibrated with modified Krebs–Henseleit buffer for 30 min and then perfused with increasing doses of propranolol, carvedilol or prazosin over an 80-min period. The concentration of each drug was increased every 20 min. In Protocol 2, hearts were infused with either of the two β-adrenoceptor antagonists or prazosin for 10 min before global ischemia and during reperfusion. All experiments were performed during right atrial pacing at a cycle length of 180 ms. Black arrows indicate the time points for atrial-His and His-ventricular interval measurements. In Protocol 3, right ventricular papillary muscles of guinea pigs were superfused with Krebs–Ringer solution. Action potential, action potential duration at 80% repolarization (APD 80), resting potential and maximum upstroke velocity ($\dot{V}_{max}$) were measured.

reperfusion, we compared the serial changes in atrial-His and His-ventricular intervals. These changes were determined as the Δatrial-His and ΔHis-ventricular intervals and defined as atrial-His or His-ventricular interval at 10, 20 or 30 min after ischemia–reperfusion minus atrial-His or His-ventricular interval before ischemia. The Δatrial-His and ΔHis-ventricular intervals were used to eliminate the effects of the individual variance in atrial-His and His-ventricular intervals at baseline.

2.2.3. Protocol 3: transmembrane action potential model

Transmembrane action potential was examined in six preparations for each drug. After 2 h of equilibration, control measurements were performed, and then the preparations were superfused with Krebs–Ringer solution containing the drug at the lowest concentration for 30 min. The concentration of the drug (10^{-6}, 10^{-5}, 10^{-4} M for both propranolol and carvedilol) was increased every 30 min.

2.3. Drugs

Carvedilol was solubilized in dimethylsulfoxide with further dilution in 0.9% NaCl. Propranolol was dissolved in normal saline. Prazosin was dissolved in purified water. Vehicle control groups were pooled from all vehicle experiments as no consistent variations were observed between the different vehicle groups.

2.4. Statistical analysis

Data are expressed as the means ± S.E.M. Continuous variables of both the dose–response model and the ischemia–reperfusion model were analyzed by repeated-measures analysis of variance (ANOVA) followed by Dunnett's test or contrasts. Stat View 5.0 and Super ANOVA (Abacus Concepts) were used to compute these analyses. Differences were considered significant at P values less than 0.05.

3. Results

3.1. Control and dose–effect model

Fig. 2 shows representative His-bundle electrograms. Table 1 shows actual data of atrial-His and His-ventricular intervals. Fig. 3 summarizes the dose–response curves for atrial-His and His-ventricular intervals normalized to the baseline values. A time-dependent change was not found in the control groups. At every concentration of either carvedilol or propranolol, atrial-His and His-ventricular intervals increased significantly. Carvedilol suppressed atrioventricular conduction to a greater extent than propranolol at equimolar doses. There were significant differences between the two groups ($P < 0.0001$). At concentrations higher than 10^{-6} M for carvedilol and 3×10^{-6} M for propranolol, atrioventricular block occurred. The effective doses that prolonged the conduction time by 25% (ED_{25}) were 10^{-6} M for atrial-His and 3×10^{-6} M for His-ventricular for propranolol, 8×10^{-8} M for atrial-His and 10^{-8} M for His-ventricular for carvedilol. Prazosin had no effect on atrioventricular conduction at concentrations lower than 10^{-6} M.

3.2. Ischemia–reperfusion model

Table 2 summarizes changes in atrioventricular conduction with ischemia–reperfusion (Protocol 2). In the control group, there was little effect of global ischemia on atri-

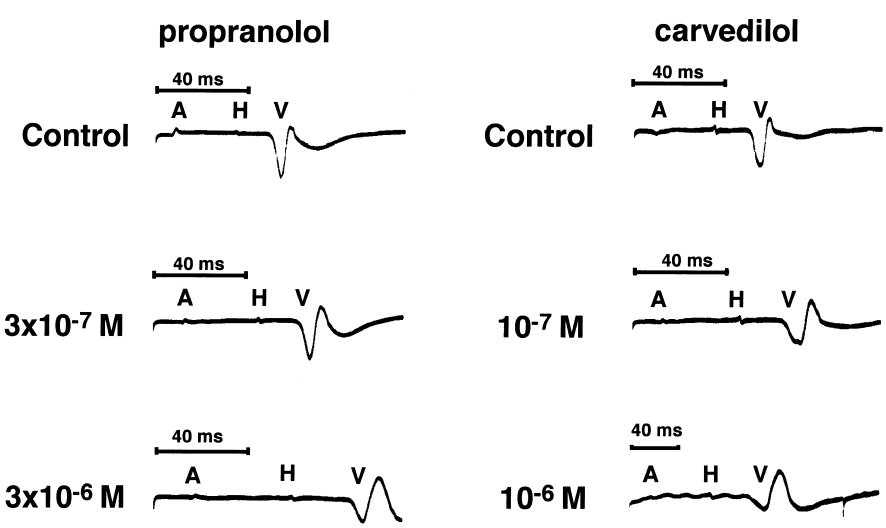

Fig. 2. Representative His-bundle electrograms. Atrial-His and His-ventricular intervals progressively increased with increasing concentrations of propranolol and carvedilol.

Table 1
Effects of propanol, carvedilol and prazosin on atrioventricular conduction ($n = 6$ for each drug)

Concentration	Control	Atrial-His interval			Mean ± S.E.M. (ms)	
		3×10^{-8} M	10^{-7} M	3×10^{-7} M	3×10^{-6} M	3×10^{-6} M
Propranolol	25.7 ± 1.1		28.7 ± 0.8	28.7 ± 1.0	31.6 ± 1.2	38.0 ± 0.8
Carvedilol	26.4 ± 0.7	31.1 ± 1.2	36.8 ± 2.3	46.9 ± 4.1	62.1 ± 4.3	
Prazosin	28.1 ± 0.6	28.4 ± 0.8	30.8 ± 1.9	27.4 ± 0.9	33.7 ± 2.3	
Concentration	Control	His-ventricular interval			Mean ± S.E.M. (ms)	
		3×10^{-8} M	10^{-7} M	3×10^{-7} M	10^{-6} M	3×10^{-6} M
Propranolol	13.3 ± 0.2		14.7 ± 0.3	15.5 ± 0.3	17.7 ± 0.7	23.4 ± 0.6
Carvedilol	14.2 ± 0.8	15.9 ± 0.7	17.3 ± 0.9	19.7 ± 1.4	32.1 ± 1.2	
Prazosin	13.3 ± 0.3	13.0 ± 0.4	14.4 ± 0.4	14.5 ± 0.4	15.8 ± 1.3	

oventricular conduction. Fig. 4 summarizes the normalized serial changes in atrial-His and His-ventricular intervals during ischemia–reperfusion. Atrioventricular conduction was prolonged by each drug. However, the increases were similar for carvedilol and propranolol. Fig. 5 illustrates the serial changes in Δatrial-His and ΔHis-ventricular intervals after 10, 20 and 30 min of reperfusion for each concentration of carvedilol and propranolol. Δatrial-His and His-ventricular intervals increased during reperfusion in a time-dependent fashion for all concentrations of carvedilol and propranolol. Carvedilol at a concentration of 10^{-6} M prolonged Δatrial-His and ΔHis-ventricular intervals to a greater extent than propranolol at a concentration of 3×10^{-6} M (From a two-way repeated measures ANOVA: for drug effect, $P < 0.0001$; for concentration effect, $P < 0.0001$; for interaction, $P < 0.0001$. From contrasts: $P < 0.05$.). At lower concentrations, both drugs seemed to have a similar influence on atrioventricular conduction during ischemia and reperfusion. The effects on atrial-His and His-ventricular intervals were generally greater for carvedilol than for propranolol.

3.3. Transmembrane action potential model

Fig. 6 shows the effects of propranolol and carvedilol on transmembrane action potentials of papillary muscle. Fig. 7 summarizes the normalized serial changes in the action potential, action potential duration at 80% repolarization (APD_{80}), resting potential and the maximum upstroke velocity ($\dot{V}_{max}$). The effects of both drugs on the membrane action potential configuration were examined in six papillary muscles constantly stimulated at 1.0 Hz. After exposure to each concentration of propranolol and carvedilol for 30 min, no significant changes were observed. Propranolol at 10^{-4} M shortened APD_{80} with no significant change in the other parameters. Resting membrane potential was unchanged. $\dot{V}_{max}$ was decreased at

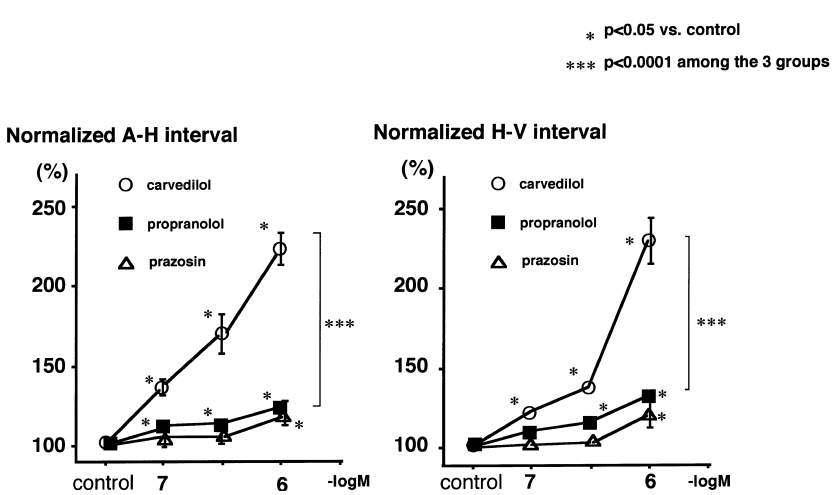

Fig. 3. Effects of propranolol, carvedilol and prazosin on atrial-His and His-ventricular intervals ($n = 6$ for each drug). Values are means ± S.E.M. Both intervals increased compared to baseline ($P < 0.05$) after the administration of β-adrenoceptor antagonist. Carvedilol prolonged the atrial-His and His-ventricular intervals to a greater extent than propranolol. From a two-way repeated measures ANOVA: for drug effect, $P < 0.0001$; for concentration effect, $P < 0.0001$; for interaction, $P < 0.0001$.

Table 2
Effects of propranolol, carvedilol and prazosin on atrioventricular conduction during ischemia–reperfusion ($n = 6$ for each concentration)

	Atrial-His interval		Mean ± S.E.M. (ms)	
	Before ischemia	Reperfusion (10 min)	Reperfusion (20 min)	Reperfusion (30 min)
Control				
	27.1 ± 2.2	28.7 ± 3.7	29.1 ± 3.3	30.5 ± 2.7
Propranolol				
3×10^{-7} M	27.2 ± 1.9	26.0 ± 2.2	27.8 ± 1.3	28.0 ± 1.1
10^{-6} M	33.7 ± 5.9	34.5 ± 5.9	38.7 ± 7.1	39.3 ± 7.3
3×10^{-6} M	31.5 ± 3.4	36.5 ± 2.9	39.3 ± 3.5	41.6 ± 3.0
Carvedilol				
10^{-7} M	30.2 ± 2.4	30.1 ± 2.3	34.7 ± 2.5	36.5 ± 2.4
3 ± 10^{-7} M	25.5 ± 2.2	28.7 ± 1.2	36.9 ± 3.7	39.1 ± 4.5
10^{-6} M	36.7 ± 1.0	45.5 ± 3.7	56.7 ± 4.9	61.1 ± 4,8
Prazosin				
10^{-7} M	30.8 ± 1.9	26.4 ± 0.6	30.6 ± 1.0	31.6 ± 1.5
3×10^{-7} M	27.4 ± 0.9	25.4 ± 1.7	31.2 ± 3.6	32.6 ± 4.6
10^{-6} M	33.7 ± 2.3	30.2 ± 1.9	36.6 ± 2.5	38.6 ± 2.8
	His-ventricular interval		Mean ± S.E.M. (ms)	
	Before ischemia	Reperfusion (10 min)	Reperfusion (20 min)	Reperfusion (30 min)
Control				
	14.0 ± 1.1	14.5 ± 1.1	14.8 ± 0.6	14.9 ± 0.9
Propranolol				
3×10^{-7} M	14.9 ± 0.3	15.4 ± 0.3	15.0 ± 0.4	15.2 ± 0.5
10^{-6} M	19.2 ± 3.3	22.0 ± 4.1	22.0 ± 4.2	22.1 ± 4.4
3×10^{-6} M	18.9 ± 1.5	21.1 ± 1.7	23.5 ± 2.3	22.1 ± 1.3
Carvedilol				
10^{-7} M	17.5 ± 2.4	18.4 ± 2.3	19.5 ± 2.9	20 ± 2.4
3×10^{-7} M	13.6 ± 0.6	15.7 ± 0.8	17.2 ± 1.6	16.9 ± 1.0
10^{-6} M	17.6 ± 2.2	21.6 ± 2.2	25.3 ± 2.6	27.7 ± 2.6
Prazosin				
10^{-7} M	14.4 ± 0.4	14.3 ± 0.3	14.6 ± 0.5	14.5 ± 0.4
3×10^{-7}	14.5 ± 0.4	14.9 ± 0.3	15.2 ± 0.5	15.5 ± 0.8
10^{-6} M	15.8 ± 1.3	15.6 ± 1.1	16 ± 1.0	16.5 ± 1.2

each concentration of both drugs in a dose-dependent manner, while no significant differences were observed between the two drugs.

4. Discussion

The effects of β-adrenoceptor antagonists on cardiac conduction have been extensively studied. There is general agreement that β-adrenoceptor blockade prolongs the atrial-His interval, indicating suppression of atrioventricular nodal conductivity, while β-adrenoceptor stimulation enhances atrioventricular nodal conduction. The change in atrial-His interval has been shown to be dependent on the dose of propranolol (Brorson et al., 1981). In contrast, His-Purkinje conductivity is not affected by β-adrenoceptor stimulation or blockade (Wit et al., 1975a). Propranolol consistently increases the atrial-His interval but does not affect the His-ventricular interval in humans (Ciemniewski et al., 1989; Kirkorian et al., 1988; Seides et al., 1974) and in dogs (Jaillon et al., 1978; Priola, 1973). Other β-adrenoceptor antagonists, such as metoprolol (Camm et al., 1982; Ciemniewski et al., 1989; Marchlinski et al., 1984; Rizzon et al., 1978), acebutolol, oxprenolol, pindolol (Gulker et al., 1981), and atenolol (Hombach et al., 1982; Robinson et al., 1978), have electrophysiologic potencies similar to that of propranolol.

In this study, carvedilol had stronger effects on atrioventricular conduction than propranolol. Carvedilol increased the atrial-His interval at low doses, suggesting that it has strong β-adrenoceptor blocking activity. The relative β-adrenoceptor blocking potency of carvedilol has been reported to be three to five times higher than that of propranolol (Tomlinson et al., 1988). In our study, the ED_{25} values of carvedilol and propranolol for the atrial-His interval were 8×10^{-8} and 10^{-6} M, respectively. There-

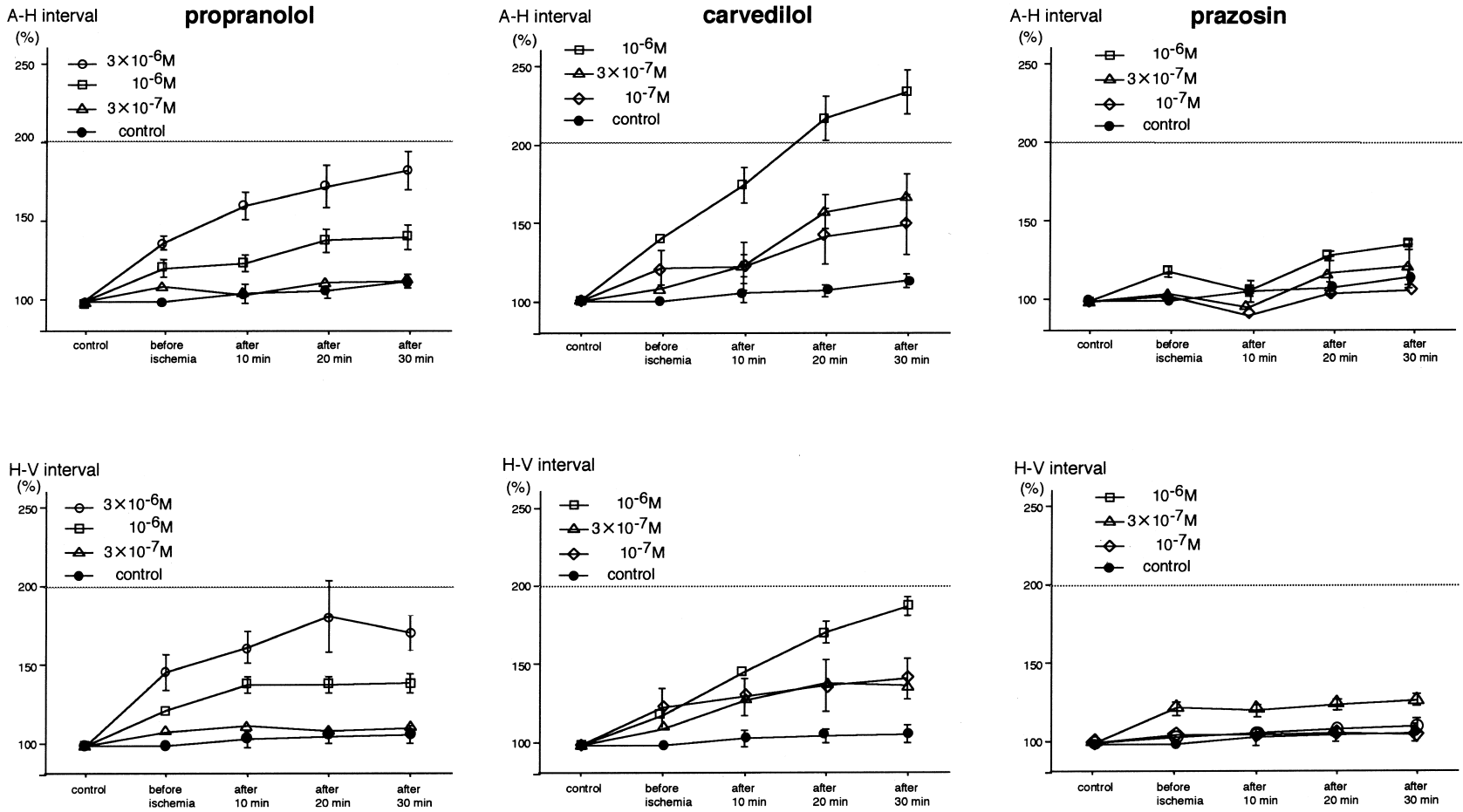

Fig. 4. Serial changes in atrial-His and His-ventricular intervals in the ischemia–reperfusion model ($n = 6$ for each concentration of the drug). All data were normalized to the baseline value. Values are means ± S.E.M. In the drug-free control models, neither the atrial-His interval nor the His-ventricular interval was altered.

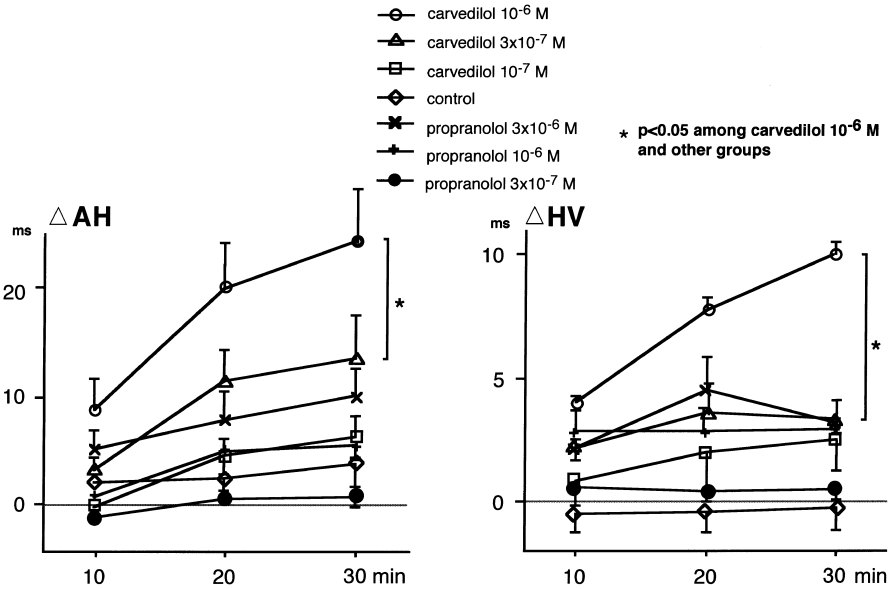

Fig. 5. Normalized serial changes in Δatrial-His and ΔHis-ventricular intervals after reperfusion. The Δatrial-His or ΔHis-ventricular interval was defined as the atrial-His or His-ventricular interval at after 10, 20 or 30 min of reperfusion minus atrial-His or His-ventricular interval before ischemia. Values are means ± S.E.M. Carvedilol 10^{-6} M increased Δatrial-His and ΔHis-ventricular intervals to a greater extent than propranolol 3×10^{-6} M. From a two-way repeated measures ANOVA: for drug effect, $P < 0.0001$; for concentration effect, $P < 0.0001$; for interaction, $P < 0.0001$. From contrasts: $^{*}P < 0.05$.

fore, carvedilol was 10 times more potent than propranolol in prolonging atrioventricular nodal conduction. Carvedilol also suppressed His-ventricular conduction at doses $> 10^{-7}$ M ($P < 0.05$). It has been reported that carvedilol also antagonizes α_1-adrenoceptors both in vitro and in vivo (Bristow et al., 1992). The ratio of the potency of carvedilol to block β_1 and α_1-adrenoceptors is 8:1 (Tomlinson et al., 1988). Under physiologic conditions, the effects of the adrenergic nervous system on the electrophysiologic properties of the sinus node, atrioventricular node, and atrium are mediated primarily by β_1-adrenoceptors (Ciemniewski et al., 1989). Spiers et al. (1990) demonstrated that the pure α_1-adrenoceptor antagonist prazosin decreased the atrial-His interval, but did not affect the His-ventricular interval (in dogs, in vivo). In our study, prazosin did not affect either the atrial-His interval or the

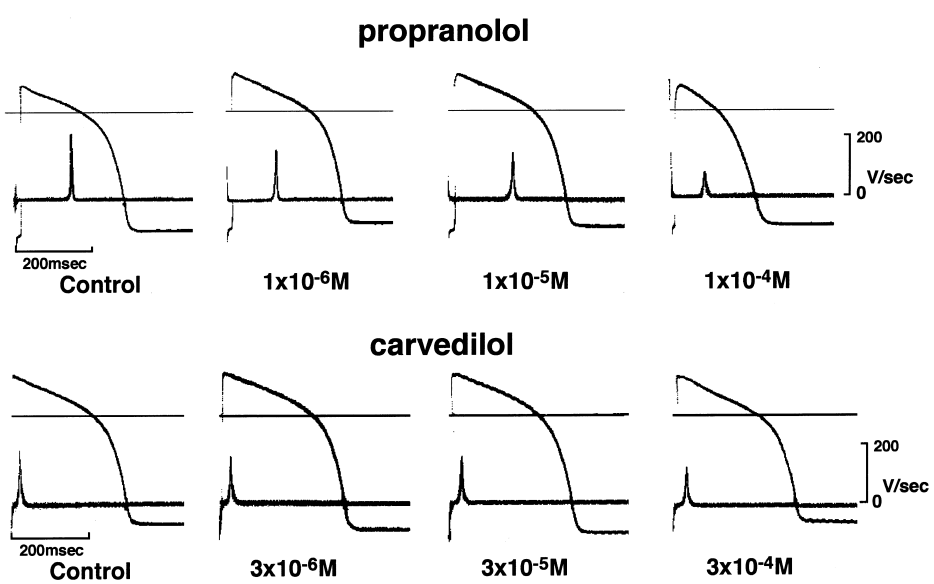

Fig. 6. Effects of propranolol and carvedilol on the transmembrane action potential of guinea pig papillary muscle ($n = 6$ for each drug). The preparation was constantly driven at 1.0 Hz. Membrane potential was recorded before and 30 min after the application of each drug concentration.

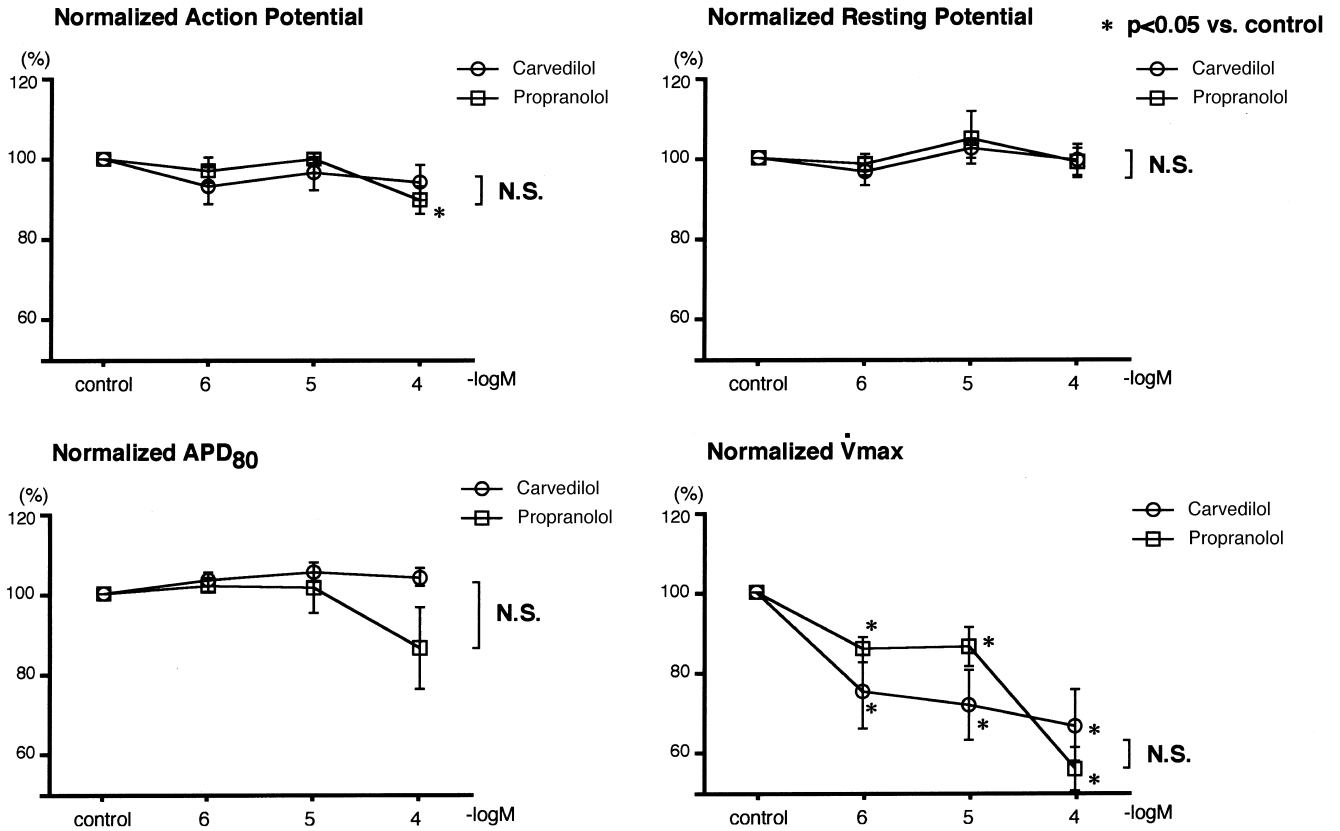

Fig. 7. Effects of propranolol and carvedilol on action potential, action potential duration at 80% repolarization (APD_{80}), resting potential and the maximum upstroke velocity ($\dot{V}_{max}$). All data were normalized to the baseline value. Values are means ± S.E.M. $\dot{V}_{max}$ was decreased at each concentration of both drugs in a dose-dependent manner, while no significant differences were observed between the two drugs.

His-ventricular interval at concentrations lower than 10^{-6} M, and carvedilol prolonged the atrial-His interval consistently. The α_1-adrenoceptor blockade potency of carvedilol on atrioventricular conduction may be negligible under physiologic circumstances.

Jaillon et al. (1978) found that both timolol and propranolol increase the His-ventricular interval only at higher doses. They hypothesized that the effect, which is not altered by isoprenaline, may be related to the membrane depressant effect of the drugs. Dawson et al. (1984) reported that infusion of D-propranolol produces a greater prolongation of the His-ventricular interval than infusion of DL-propranolol, suggesting that this action is not mediated by β-adrenoceptors. However, previous investigations have indicated that, within the therapeutic range, the direct membrane effects of propranolol are negligible and probably do not play a role in the electrophysiologic action of the drug in vivo (Wit et al., 1975b).

In other studies, propranolol had stronger effects on His-Purkinje conductivity in vitro. Stark et al. (1989) studied the effects of propranolol enantiomers on the intracardiac electrophysiologic activity in perfused guinea pig hearts. At an L-propranolol concentration of 10^{-6} M, the atrial-His and His-ventricular intervals increased by 20 ± 8% and 19 ± 7%, respectively, while 10^{-6} M D-propranolol did not change conductance. At an L-propranolol concentration of 10^{-5} M, there was a further increase in the atrial-His (38 ± 6%) and His-ventricular (63 ± 9%) intervals (Stark et al., 1989). In our study, 10^{-6} M DL-propranolol increased the atrial-His and His-ventricular intervals by 23 ± 4% and 32 ± 9%, respectively. At a DL-propranolol concentration of 3×10^{-6} M, the atrial-His and His-ventricular intervals increased by 49 ± 1% and 76 ± 9%, respectively. The discrepancy between the results of our studies and those of Jaillon and Dawson may reflect differences in the model used, namely an isolated heart model versus an in vivo model.

Vaughan–Willams defined the local anesthetic effect as a reduction in the height and rate of rise of the transmembrane action potential (Dohadwalla et al., 1969), which is due to the ability of drugs to decrease Na^+ conductance. To determine the direct membrane effect as a possible cause of the prolongation of the His-ventricular interval, we examined the effect of propranolol and carvedilol on the transmembrane action potential. Although, the species and subjects were different from those of the atrioventricular conduction model, the transmembrane action potential model showed that both propranolol and carvedilol decreased $\dot{V}_{max}$ in a dose-dependent manner. In cardiac muscle, the main ion current crossing the cell membrane at the

time of $\dot{V}_{max}$ is the Na^+ current; other membrane currents make no significant contribution.

Davis and Tempe, using graded concentrations of DL-propranolol, noted that depression of phase 0 of the transmembrane action potential appeared at free drug concentrations of 3000 ng/ml. At a concentration of 10,000 ng/ml, a small but statistically significant increase in the action potential duration occurred (Davis and Temte, 1968). In our study, propranolol and carvedilol decreased $\dot{V}_{max}$ equally, so that propranolol and carvedilol have a similar potential for blocking Na^+ channels. This means that the Na^+ channel blocking property cannot explain the difference in the suppression of the His-ventricular interval by the two drugs.

During ischemia and reperfusion, 10^{-6} M propranolol and 10^{-7} M carvedilol had similar effects. Both increased atrial-His and His-ventricular intervals by about 20% before ischemia and further increased them by 40% after reperfusion. The doses that caused atrioventricular block were far higher than the clinical doses. In humans, the plasma concentration of carvedilol obtained after an oral dose of 60 mg is 76.0 ± 20.0 ng/ml (1.87×10^{-7} M) (Fujimaki et al., 1990). Because the adrenoceptor blockade effect of carvedilol is about three to five times greater than that of propranolol, carvedilol had a similar potency in prolonging atrioventricular conduction.

Our data indicate that carvedilol has a greater effect than propranolol on atrioventricular conduction in the setting of ischemia–reperfusion.

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