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Comparison of the Effects of Pancuronium and Vecuronium in Canine Coronary and Renal Arteries

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Background: **Pancuronium has sympathomimetic actions but does not change or lowers systemic blood pressure in some studies of anesthetized humans and dogs. The present study was done to determine the actions and mechanisms of action of pancuronium on coronary and renal arteries other than those as a sympathomimetic agent.**

Methods: **Helical strips of coronary and renal arteries from mongrel dogs were suspended in oxygenated, warmed Ringer-Locke solution, and changes in the isometric tension were recorded. In some strips, transmural electrical stimulation (5 Hz for 40 s) was applied to activate perivascular adrenergic nerves.**

Results: **Pancuronium (10^{-7} to 10^{-5} M) caused dose-dependent relaxation in coronary and renal arteries contracted with prostaglandin (PG) $F_{2\alpha}$, whereas no significant response was induced with vecuronium. The relaxation was endothelium independent and abolished by indomethacin or tranylcypromine, a PGI_2 synthase inhibitor. Transmural electrical stimulation caused coronary arterial relaxation, which was augmented by pancuronium and vecuronium. Desipramine also increased the response, and additional potentiation of the response was not elicited by pancuronium and vecuronium. In renal arteries, electrical stimulation caused contraction, which was also augmented by pancuronium and vecuronium. With desipramine treatment, these muscle relaxants did not potentiate the response. Endothelium-dependent coronary arterial relaxation caused by bradykinin was not affected by pancuronium.**

Conclusions: **Pancuronium-induced relaxations in canine coronary and renal arteries appear to be mediated by PGI_2 released from subendothelial tissues. Potentiations by pancuronium and vecuronium of the response to adrenergic nerve stimulation are expected to be due to an inhibition of the norepinephrine uptake but not to facilitated release of the amine. (Key words: Dog; norepinephrine uptake; prostaglandin I_2; transmural electrical stimulation.)**

THE principal action of nondepolarizing muscle relaxants is competitive antagonism against acetylcholine at nicotinic receptors in the neuromuscular junction, and the agents are considered to have no direct actions on vascular smooth muscle. However, pancuronium bromide is reported to have sympathomimetic actions by blocking atrial muscarinic receptors, stimulating catecholamine release, inhibiting its uptake by adrenergic nerve terminals, or both; and interfering with the action of acetylcholine on inhibitory muscarinic receptors in sympathetic ganglia.[1] Administration of pancuronium consistently increases the heart rate, whereas data concerning the action on blood pressure are conflicting: an increase in pithed rats[2] and anesthetized patients,[3] no significant change in anesthetized patients,[4–6] or a decrease in anesthetized patients[7] and dogs.[8] However, mechanisms underlying the inconsistent effect of pancuronium on blood pressure have not been explained. In addition, actions of this agent on adrenergic nerves innervating arteries in vital organs such as the heart and kidney have not been reported.

Therefore, the present study was done to determine whether pancuronium acted directly on vascular smooth muscle, modified the adrenergic nerve function and had actions *via* the release of relaxing factors from the endothelium. We provided isolated endothelium-intact and endothelium-damaged coronary and renal arteries from dogs, applied transmural electrical stimulation to activate perivascular adrenergic nerves, and used pharmacologic inhibitors to analyze mechanisms of pancuronium's action. Because it has been reported that vecuronium does not affect the heart rate or blood pressure in clinical doses, the agent was also used to compare its vascular action with that of pancuronium.

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Materials and Methods

Preparation

The Animal Care and Use Committee of the Shiga University of Medical Science approved the use of blood vessels for the present study. Mongrel dogs of either sex that weighed 8–14 kg were deeply anesthetized with intravenous injections of sodium pentobarbital (30 mg/kg) and killed by bleeding from the common carotid arteries. The heart and kidney were rapidly removed. Circumflex branches of the left coronary artery were isolated from the heart, and intrarenal, interlobar branches of the renal artery were isolated from the kidney. The arteries were cut helically into 20-mm-long strips. The specimens were fixed vertically between hooks in a 20-ml muscle bath containing modified Ringer-Locke solution that was maintained at 37 ± 0.3°C and aerated with a mixture of 95% oxygen and 5% carbon dioxide. The hook anchoring the upper end of the strip was connected to the lever of a force-displacement transducer (Nihonkohden Kogyo, Tokyo, Japan). The resting tension was adjusted to 1.5 g for both artery strips, which was optimal for inducing maximal contraction. Constituents of the solution included 120 mM NaCl, 5.4 mM KCl, 25 mM $NaHCO_3$, 2.2 mM $CaCl_2$, 1 mM $MgCl_2$, and 5.6 mM dextrose. The *p*H of the solution was 7.35–7.45. Before the start of the experiments, all strips were allowed to equilibrate for 60–90 min in control media, during which time the solutions were replaced every 10–15 min.

In the experiments on transmural electrical stimulation, artery strips were placed between stimulating electrodes. The gaps between the strip and electrodes were wide enough to allow undisturbed contraction and relaxation and yet sufficiently narrow to stimulate intramural nerve terminals effectively. A train of 0.2-ms square pulses of supramaximal intensity (10 V) were transmurally applied at a frequency of 5 Hz for 40 s, which produced submaximal responses.[9,10] The stimulus pulses were delivered by an electronic stimulator (Nihonkodhen Kogyo, Tokyo, Japan).

Recordings of Vascular Responses

Isometric contractions and relaxations were displayed on an ink-writing oscillograph (Nihonkohden Kogyo). Contractile responses to 30 mM KCl were obtained first and then the preparations were repeatedly washed and equilibrated for 30–40 min. Concentration–response relations for pancuronium, vecuronium, and bradykinin were obtained by adding the agent directly to the bathing media in cumulative concentrations. The agents were added after the artery strips had been partially contracted with prostaglandin (PG) $F_{2\alpha}$ (10^{-7} to 2×10^{-6} M); the contraction ranged from 20% to 40% of the contraction induced by 30 mM KCl. Papaverine (10^{-4} M) was added at the end of each experimental series to obtain the maximal relaxation.

The pancuronium- or bradykinin-induced relaxation relative to that caused by 10^{-4} M papaverine and the contraction by vecuronium relative to that elicited by 30 mM KCl are presented. In the experiments of transmural electrical stimulation, relaxation is presented as a relative value to that caused by 10^{-4} M papaverine, and change of contraction is presented as a relative value to the response without treatment. The preparation had been treated for 20–30 min with blocking agents before the agonist was added.

Protocol

Concentration–response relations for pancuronium and vecuronium were obtained in endothelium-intact coronary and renal artery strips partially contracted with $PGF_{2\alpha}$. To determine whether the effect induced by pancuronium was endothelium dependent, the intimal surface of artery strips from the same dog were gently rubbed with a cotton ball to remove the endothelium and the strips were used for comparison. Endothelium denudation was verified by abolishment of relaxation caused by acetylcholine (10^{-6} M).[11,12] To determine the involvement of cyclooxygenase products in the pancuronium-induced relaxation, the strips were treated with indomethacin (10^{-6} M)[13,14] and the responses before and after the treatment were compared. Then tranylcypromine in a concentration of 5×10^{-4} M, sufficient to inhibit PGI_2 synthesis,[15,16] was used to determine whether the induced relaxation was mediated by PGI_2.

Transmural electrical stimulation was applied to $PGF_{2\alpha}$-contracted coronary artery strips that responded to relaxations and to renal artery strips under resting conditions in which contractions were induced. The artery strips were electrically stimulated repeatedly at 10-min intervals until steady responses were obtained. Then pancuronium, vecuronium, or desipramine (2×10^{-7} M), an inhibitor of norepinephrine uptake by adrenergic nerve terminals,[17] was applied. To determine whether pancuronium and vecuronium inhibited the neural uptake or facilitated the release of norepinephrine, responses to the agents were compared before and after the amine uptake was inhibited by desipramine.

In coronary artery strips partially contracted with $PGF_{2\alpha}$, we have reported that bradykinin (10^{-9} to 10^{-7} M) causes an endothelium-dependent relaxation that is markedly suppressed by methylene blue, indicating the involvement of endothelium-derived relaxing factor.[11] We used this peptide to determine if pancuronium influenced the endothelium-derived relaxing factor-mediated relaxation.

Statistics and Drugs

The results shown in the text and figures are expressed as mean values ± SD. Statistical analyses were done using the Student's paired and unpaired *t* test or Tukey's method after one-way analysis of variance. Probability values < 0.05 were considered significant.

The drugs used were $PGF_{2\alpha}$, beraprost sodium (Toray Industries, Tokyo, Japan); indomethacin (Sigma Chemical, St. Louis, MO); bradykinin (Peptide Institute, Minoh, Japan); papaverine hydrochloride (Dainippon Pharmaceutical, Osaka, Japan); acetylcholine chloride (Daiichi Pharmaceutical, Tokyo, Japan); pancuronium, vecuronium (Organon Teknika, Boxtel, the Netherlands); tetrodotoxin (Sankyo, Tokyo, Japan); desipramine, prazosin hydrochloride (Wako Pure Chemical Industries, Osaka, Japan); and timolol maleate (Banyu Pharmaceutical, Tokyo, Japan).

Results

Direct Effects on Coronary and Renal Arteries

Pancuronium (10^{-7} to 10^{-5} M) produced relaxations in coronary and renal artery strips partially contracted with $PGF_{2\alpha}$ in a dose-dependent manner, whereas vecuronium in the same concentration range did not relax the arteries (fig. 1). The relaxant responses to pancuronium did not significantly differ in control and de-endothelialized strips. Mean values of the maximal response in endothelium-intact and endothelium-removed coronary arteries were 50.8 ± 12.2% and 52.2 ± 11.1% (n = 6), respectively, and those of the median effective concentration values were 7.3 ± 4.2 × 10^{-7} M and 5.2 ± 1.4 × 10^{-7} M (n = 6), respectively. Similar results were obtained in renal arteries with and without the endothelium (53.3 ± 20.1% *vs.* 52.3 ± 7.1% [n = 6] and 4.5 ± 2.9 × 10^{-7} M *vs.* 5.1 ± 1.9 × 10^{-7} M [n = 6]). The relaxations caused by pancuronium in these arteries were abolished or markedly suppressed by treatment with 10^{-6} M indomethacin or tranylcypromine (5 × 10^{-4} M), an inhibitor of PGI_2 synthesis.[16]

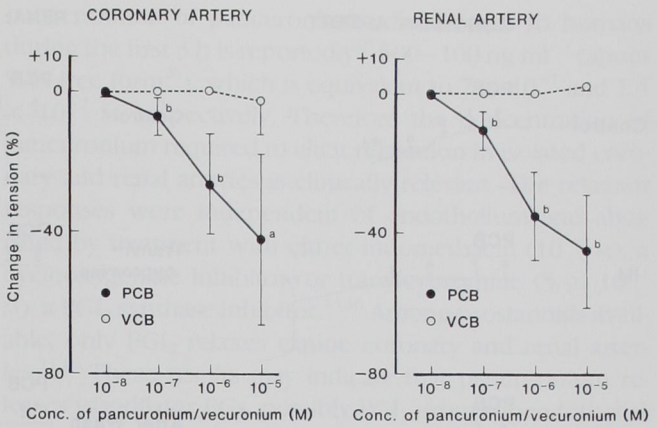

Fig. 1. Concentration–response relations for pancuronium and vecuronium in canine coronary (*left panel*, n = 5) and renal artery strips (*right panel*, n = 7). The arteries were partially contracted with prostaglandin $F_{2\alpha}$. Relaxations induced by 10^{-4} M papaverine were taken as 100% relaxation. Contractions induced by 30 mM KCl were taken as 100% contraction. Relaxations and contractions are expressed in minus and plus values, respectively. Significantly different from values with vecuronium: $^aP < 0.05$, $^bP < 0.01$, by unpaired *t* tests. Vertical bars represent SD. PCB, pancuronium bromide; VCB, vecuronium bromide; Conc., concentration.

Figure 2 illustrates typical recordings of the effects of the antagonists, and figure 3 summarizes data. Tranylcypromine (5 × 10^{-4} M) itself did not attenuate the relaxant response caused by beraprost sodium (10^{-9}, 10^{-8}, and 10^{-7} M), a stable analog of PGI_2, in coronary (n = 6) and renal arteries (n = 6).

Effects on Transmural Electrical Stimulation

Transmural electrical stimulation at 5 Hz produced a moderate relaxation in coronary artery strips treated with indomethacin (10^{-6} M) and prazosin (10^{-5} M) and partially contracted with $PGF_{2\alpha}$. The response was augmented by treatment with 10^{-5} M pancuronium or vecuronium and abolished by 3 × 10^{-7} M tetrodotoxin (n = 4) or 10^{-7} M timolol (n = 4). Figure 4 shows typical recordings, and figure 5 summarizes data. Pancuronium and vecuronium (10^{-5} M) augmented the relaxation caused by 2 × 10^{-8} M norepinephrine (n = 5). Desipramine (2 × 10^{-7} M), in a concentration sufficient to inhibit the uptake of catecholamine by sympathetic nerve terminals,[17] augmented the relaxant response to the electrical stimulation. Under desipramine treatment, additional potentiation by pancuronium or vecuronium (10^{-5} M) were not obtained (fig. 5). In contrast to coronary arteries, transmural electrical stimulation at 5 Hz in renal artery strips produced a contraction under resting

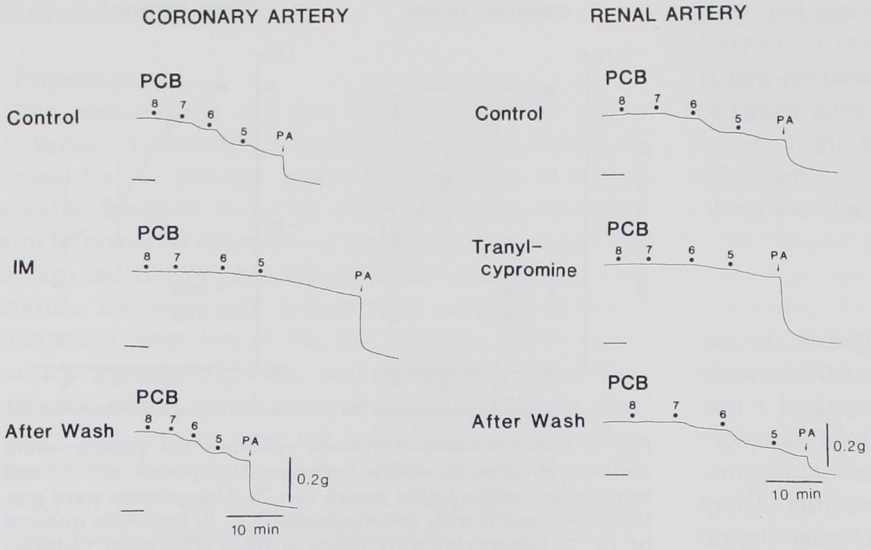

Fig. 2. Typical responses of a coronary (*left panel*) and a renal artery strip (*right panel*) to pancuronium (10^{-8} to 10^{-5} M) before (control) and after treatment with indomethacin (IM, 10^{-6} M) or tranylcypromine (5×10^{-4} M). The strips were partially contracted with prostaglandin $F_{2\alpha}$. Concentrations of pancuronium from 8 to 5 = 10^{-8} M, 10^{-7} M, 10^{-6} M, 10^{-5} M, respectively. The horizontal line just left of each tracing represents the level before the addition of prostaglandin $F_{2\alpha}$. PCB, pancuronium; PA, 10^{-4} M papaverine.

conditions treated with 10^{-6} M indomethacin. The response was potentiated by pancuronium or vecuronium (10^{-5} M) and abolished by 3×10^{-7} M tetrodotoxin (n = 5) or 10^{-5} M prazosin (n = 5). Figure 4 shows typical recordings, and figure 6 summarizes data. Desipramine (2×10^{-7} M) potentiated the response to the electrical stimulation, which was not significantly influenced by additional treatment with pancuronium or vecuronium (10^{-5} M; fig. 6).

Effects on Endothelium-dependent Relaxation

Pancuronium (10^{-5} M) did not significantly affect the relaxant response to bradykinin in coronary artery strips partially contracted with $PGF_{2\alpha}$ at any concentrations tested: mean values of the relaxation induced by 10^{-9} M, 10^{-8} M, and 10^{-7} M of the peptide were 16.2 ± 10.9%, 62.1 ± 25.9%, and 77.6 ± 19.2% (n = 6), respectively,

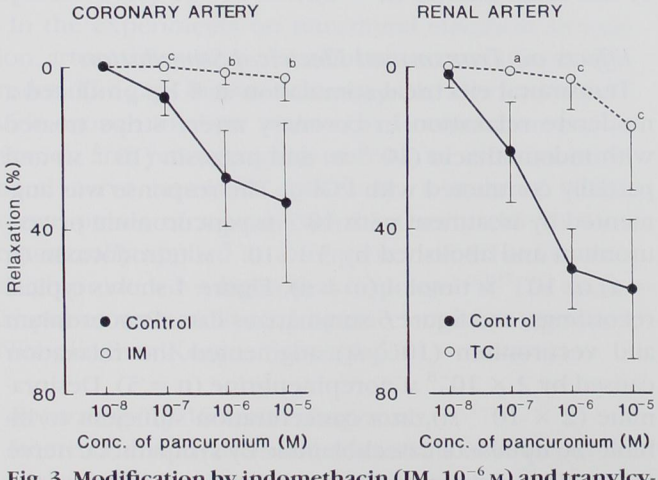

Fig. 3. Modification by indomethacin (IM, 10^{-6} M) and tranylcypromine (TC, 5×10^{-4} M) of the response to pancuronium of coronary (*left panel*, n = 7) and renal arteries (*right panel*, n = 6) partially contracted with prostaglandin $F_{2\alpha}$. Relaxations induced by 10^{-4} M papaverine were considered 100%. Significantly different from control: $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$, by paired *t* tests. Vertical bars represent SD. Conc., concentration.

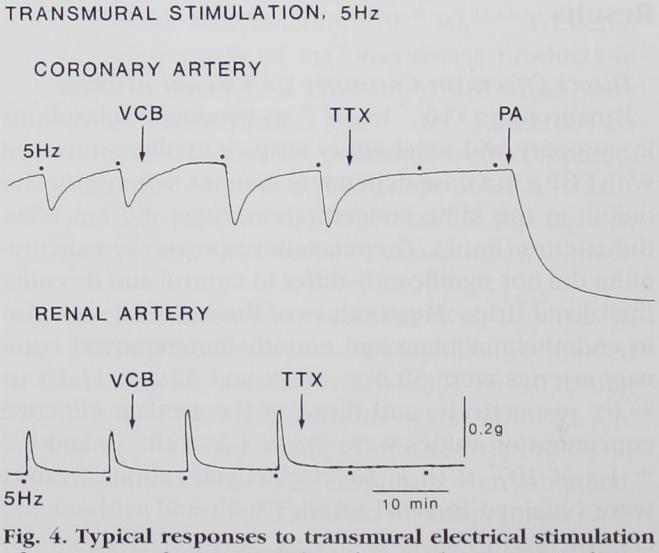

Fig. 4. Typical responses to transmural electrical stimulation of a coronary (*upper panel*) and a renal artery strip (*lower panel*) before and after 10^{-5} M vecuronium. The coronary artery strip was partially contracted with prostaglandin $F_{2\alpha}$. The renal artery strip was transmurally stimulated under resting conditions. The artery strips were pretreated with 10^{-6} M indomethacin plus 10^{-5} M prazosin and with indomethacin, respectively. TTX, 3×10^{-7} M tetrodotoxin; PA, 10^{-4} M papaverine.

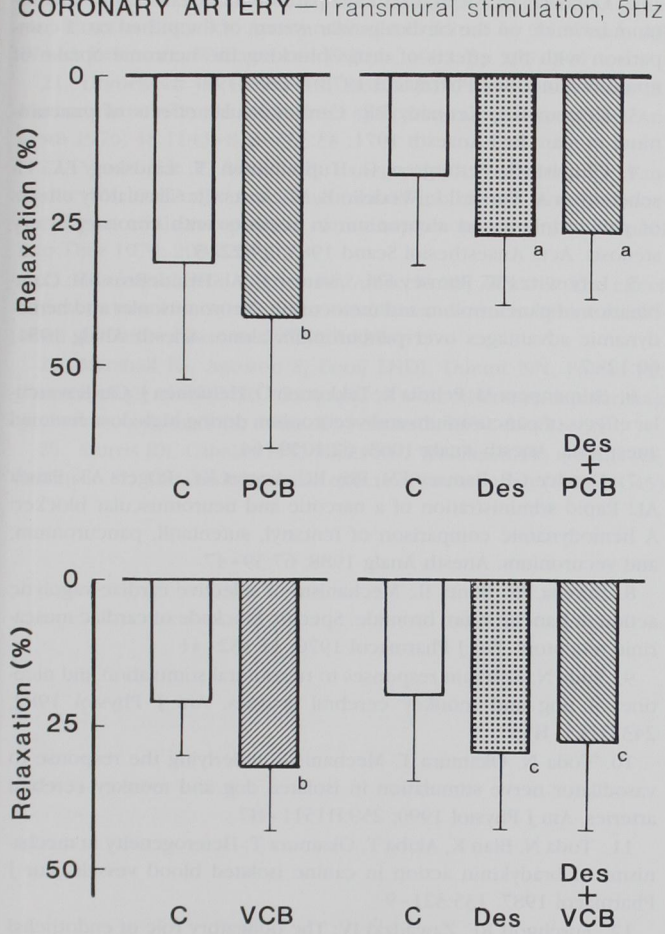

Fig. 5. Modification by pancuronium (PCB, 10^{-5} M), desipramine (Des, 2×10^{-7} M, n = 5; *upper panel*), vecuronium (VCB, 10^{-5} M) and desipramine (2×10^{-7} M, n = 5; *lower panel*) of the response to transmural electrical stimulation in coronary artery strips contracted with prostaglandin $F_{2\alpha}$. All strips were pretreated with 10^{-6} M indomethacin plus 10^{-5} M prazosin. Relaxations induced by 10^{-4} M papaverine were considered 100%. Significantly different from control (C), $^{b}P < 0.01$ (by a paired *t* test for upper and lower left) and $^{a}P < 0.05$, $^{c}P < 0.01$ (by Tukey's method for upper and lower right). Vertical bars represent SD.

in control strips and 9.5 ± 4.6%, 57.1 ± 23.3%, and 74.9 ± 15.8% (n = 6), respectively, in the treated strips.

Discussion

Pancuronium caused relaxations in canine coronary and renal arteries partially contracted with $PGF_{2\alpha}$, whereas these arteries did not significantly respond to vecuronium, a monoquartenary analog of pancuronium that lacks a quaternizing methyl group in the 2-position.[18] The plasma concentration of pancuronium administered to humans during the first 3 h is reportedly[19] 500 - 100 ng ml^{-1} (about 90% free form[20]), which is equivalent to 7×10^{-7} and 1.4×10^{-7} M, respectively. Therefore the concentration of pancuronium required to elicit relaxation in isolated coronary and renal arteries is clinically relevant. The relaxant responses were independent of endothelium and abolished by treatment with either indomethacin (10^{-6} M), a cyclooxygenase inhibitor, or tranylcypromine (5×10^{-4} M), a PGI_2 synthase inhibitor.[15,16] Among prostanoids available, only PGI_2 relaxes canine coronary and renal arteries.[11,16] These results may indicate that pancuronium releases vasodilator PGs, possibly PGI_2, from subendothelial tissues.

Transmural electrical stimulation (5 Hz) relaxed coronary arteries partially contracted with $PGF_{2\alpha}$ and, in contrast, contracted renal arteries under resting conditions. Because these responses were abolished by the blockade of β- or α_1-adrenoceptors, respectively, norepinephrine released from axon terminals by electrical stimulation is expected to mediate the responses. Treatment with either 10^{-5} M pancuronium or vecuronium augmented the coronary arterial relaxation and renal arterial contraction, suggesting that these agents affect the metabolism, release, or action of norepinephrine. Pancuronium and vecuronium increased the responsiveness to exogenous norepineph-

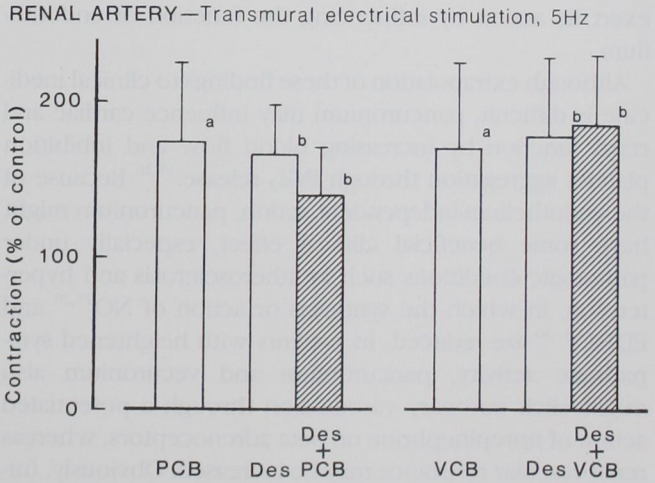

Fig. 6. Modification by pancuronium (PCB, 10^{-5} M), desipramine (Des, 2×10^{-7} M, n = 5; *left panel*), vecuronium (VCB, 10^{-5} M) and desipramine (2×10^{-7} M, n = 5; *right panel*) of the response to transmural electrical stimulation of renal artery strips under resting conditions. All strips were pretreated with 10^{-6} M indomethacin. Contractions of the strips before treatment (control) were taken as 100% in the ordinate. Significantly different from control, $^{a}P < 0.05$ (by paired *t* test), $^{b}P < 0.05$ (by Tukey's method). Vertical bars represent SD.

rine, when norepinephrine produced an amount of relaxation similar to that caused by transmural electrical stimulation. In coronary and renal arteries in which the neurogenic responses were augmented by desipramine, additional treatment with pancuronium or vecuronium failed to significantly alter the response. Desipramine is a potent inhibitor of norepinephrine uptake by adrenergic nerves,[17,21] thereby potentiating the response to endogenous and exogenous norepinephrine. Therefore the potentiation by pancuronium and vecuronium of the response to adrenergic stimulation appears to be due to the inhibition of the neural uptake of norepinephrine rather than the increased release of norepinephrine. It has been reported that pancuronium stimulates the release of norepinephrine from nerves and simultaneously inhibits the neural uptake in canine isolated saphenous veins[22] and in anesthetized dogs.[21] In accord with our results, inhibition by pancuronium of the catecholamine uptake is also demonstrated in isolated, perfused rat hearts[23] and pithed rats.[2] Effects of pancuronium seem to differ in blood vessels from various organs and tissues and from different mammals. Vecuronium in clinical doses does not have the vascular action that pancuronium does.[24,25] However, the present study suggests that high doses of vecuronium may work as a sympathomimetic agent.

Pancuronium did not affect the nitrous oxide-mediated endothelium-dependent relaxation induced by bradykinin in the canine coronary artery. The agent is unlikely to exert its action by influencing the function of endothelium.

Although extrapolation of these findings to clinical medicine is difficult, pancuronium may influence cardiac and renal function by increasing blood flow and inhibition platelet aggregation through PGI_2 release.[15,26] Because of the endothelium-independent action, pancuronium might have some beneficial clinical effect, especially under pathologic conditions such as atherosclerosis and hypertension, in which the synthesis or action of NO[27,28] and EDHF[28-30] are reduced. In patients with heightened sympathetic activity, pancuronium and vecuronium also might elicit coronary vasodilation through a potentiated action of norepinephrine on beta adrenoceptors, whereas renal vascular resistance may be increased. Obviously, further work is needed to determine whether these predictions are correct.

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