Positive Inotropic and Chronotropic Effects of Pancuronium and Vecuronium in the Canine Blood-pefused Papillary Muscle and Sinoatrial Node Preparations

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The positive inotropic and chronotropic potencies of pancuronium (Pc) and vecuronium (Vc) were compared with developed tension of the isolated papillary muscle (DT) and sinoatrial rate of the sinoatrial node preparation (SAR). Both Pc and Vc caused dose-dependent positive inotropic and chronotropic effects. Pc showed much more potent effect than Vc on DT (0.1, 0.3 mg; $P<0.05$) or SAR (0.03, 0.1, 0.3 mg; $P<0.05$). DT and SAR were increased by Pc and Vc, and the increase in DT was inhibited by propranolol or tetrodotoxin. These results suggest that the cardiac effects of Pc or Vc may be mediated by release of norepinephrine from the synpathetic nerve endings. (Key words: cardiac effects, beta-adrenargic effects, pancuronium, vecuronium)

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Pancuronium causes a moderate increase in heart rate[1] and in blood pressure[2]. Indirect (release of norepinephrine from adrenergic nerve endings[3,4]) and direct (blockade of neuronal uptake of norephinephrine[3,5]) mechanisms have been suggested. On the other hand, Iwatuki et al.[6] reported that pancuronium had a positive inotropic effect which may be mediated by beta adrenergic receptor stimulation, using an isolated canine heart muscle. Duke et al.[7] reported that pancuronium produced no change in isometric contraction of rabbit atrial or cat papillary muscle. Then to examine the effects of pancuronium and vecuronium (one of new muscle relaxants), we used a method in which an isolated papillary muscle and a sinoatrial node were perfused by the other donor dog.

With this method, we compared the positive inotropic and positive chronotropic potencies, and examined the mechanism of cardiac effects of pancuronium and vecuronium.

Methods

Experiments were carried out on six papillary muscle[8] (PM) and sinoatrial node[9] (SAN) preparations perfused by the circulating blood of halothane anesthetized donor dogs through the cannulated anterior septal artery (ASA) and right coronary artery (RCA).

The papillary muscle and sinoatrial node preparations were obtained from a mongrel dog of either sex, weighing 8–12 kg anesthetized with thiamylal (15 mg/kg intravenously) given sodium heparin (500 U/kg intravenously) and exsanguinated.

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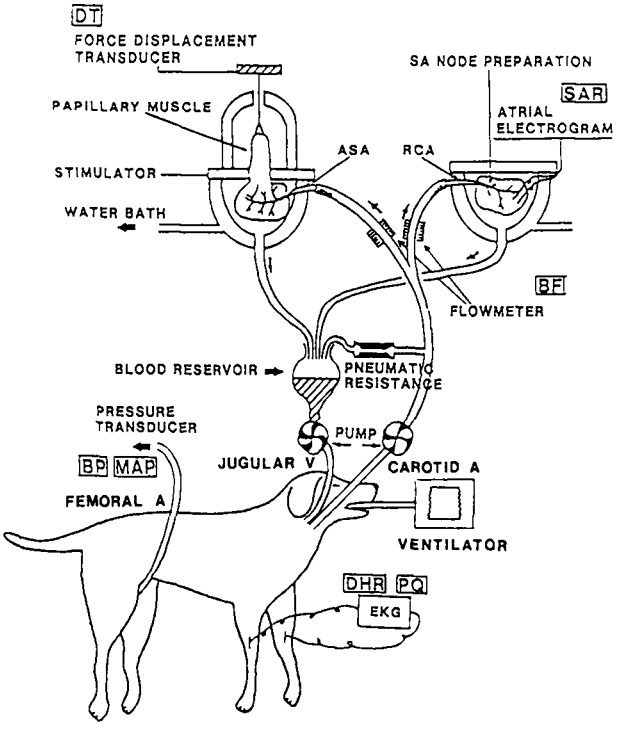

Fig. 1. A schematic representation of cross-circulation diagram of the isolated papillary muscle and sinoatrial node preparations. DT: developed tension of the papillary muscle, SAR: sinoatrial rate of the sinoatrial node preparation, ASA: the anterior septal artery, RCA: the right coronary artery.

The heart was excised and plunged into cold Tyrode's solution kept at about 4°C, then the preparations were made. The either preparation was placed in either doublewall glass jacket maintained at 38°C by circulating warm water.

The both papillary muscle and sinoatrial node preparations were simultaneously perfused through each cannulated artery with heparinized arterial blood from the donor carotid artery at a constant perfusion pressure of 120 mmHg with a Cole-Parmer Masterflex peristaltic pump and a Starling pneumatic resistance placed parallel to the perfusion system. Venous blood from the preparations and excess blood passing through the pneumatic resistance was collected in the blood reservoir and infused back into the jugular vein of donor dog.

The papillary muscle preparation was electrically driven by a stimulator (Nihon Kohden, SEN-3301) and an isolation unit (Nihon Kohden, SS-302J) with rectangular pulses of 1–3 V (about 20% above the threshold voltage) at 5 msec duration at a fixed rate of 2 Hz (120 beats/min) through bipolar silver-silver stimulating electrodes sutured onto the endocardium of the ventricular septum close to the base of the papillary muscle. Tension developed (DT) by the papillary muscle was measured with a force displacement transducer (Nihon Kohden TB-651 T). The muscle was loaded with a 2 g weight. The sinoatrial rate (SAR) of the sinoatrial node preparation was measured with a cardiotachograph triggered by bipolar atrial electrograms obtained from the right atrium close to the sinoatrial node. Donor dogs of either sex, weighing 13–17 kg, were obtained as follows: General anesthesia (thiamylal, 15 mg/kg i.v. for induction and halothane, 1% for maintenance) was given for placement of fluid-filled Tygon catheters in the carotid artery (for supplying arterial blood to the preparations) and the jugular vein (for returning venous blood), and of a polyethylene catheter in the femoral artery (for monitoring blood pressure).

Cross circulation experiments began with an initial 60 min stabilization period. The agents (pancuronium and vecuronium) were disolved with normal saline and they were

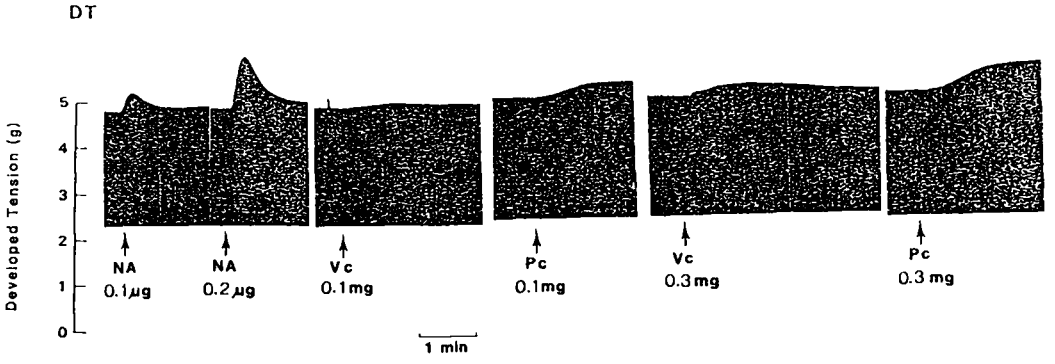

Fig. 2. Positive inotropic effect of Pc and Vc on DT.

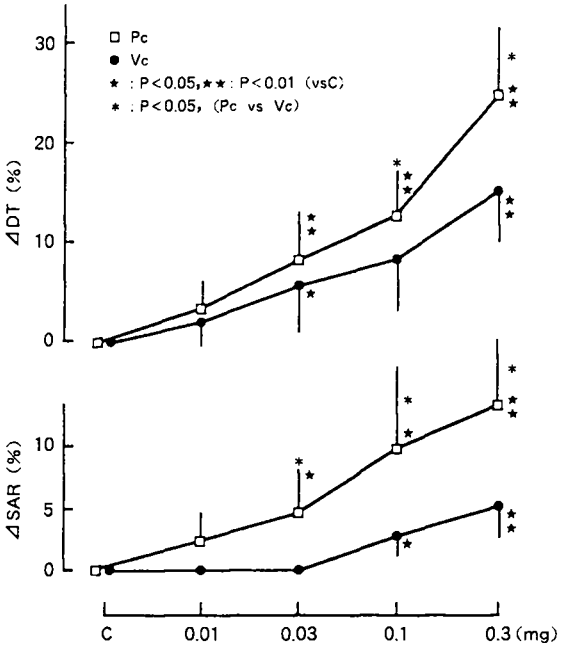

Fig. 3. Summarized results of Pc (open squares) or Vc (solid circles) on DT and SAR.

Asterisks (★) mean that values were significantly different from the values of control (C) at each doses. (★; $P<0.05$,★★; $P<0.01$).

Another asterisks (*) mean that values of Pc were significantly different from the values of Vc at each doses (*; $P<0.05$).

injected directly into the ASA and RCA which supplied arterial blood to the PM and the SAN, using Hamilton microliter syringe. The dose of the agents were increased in four steps (0.01, 0.03, 0.1 and 0.3 mg) each over a 5 min period. The interaction between propranolol or tetrodotoxin and Pc or Vc was also examined in same PM preparation by injecting of propranolol or tetrodotoxin for about 1–3 min prior to administration of Pc or Vc. For comparison of the positive inotropic or chronotropic effects of Pc and Vc, Student's t-test (dependent) was used. When P-values are smaller than 0.05, it is decided that a satistical significant difference is exist between two mean values.

Results

Both Pc and Vc had dose-dependent positive inotropic and chronotropic effects. (fig. 2)

Figure 3 summarizes results obtained from direct infusion of the agents into the arterial blood supplying the preparations. 0.01 mg of the both drugs had no significant effect on DT and SAR. 0.03 mg, 0.1 mg and 0.3 mg of the both drugs increased DT significantly and dose-dependently. Percent increases in DT on 0.1 mg and 0.3 mg of Pc were significantly greater than on the same dose of Vc. Pc showed much more potent effect on SAR than Vc.

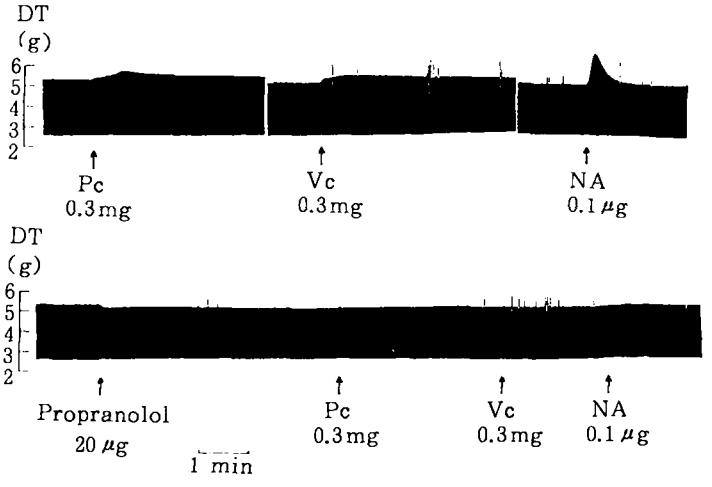

Fig. 4. Blocking effect of propranol on the positive inotropic effect of Pc or Vc.

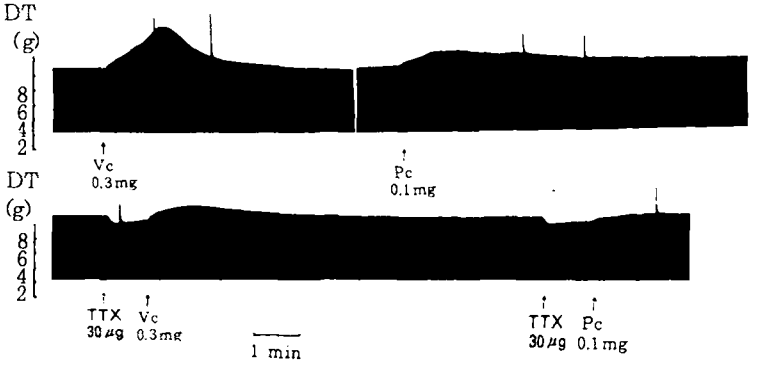

Fig. 5. Suppressing effect of tetrodotoxin on the positive inotropic effect of Pc or Vc.

Pretreatment of 20 μg propranolol inhibited the increase in DT on 0.3 mg Pc or Vc (fig. 4). Tetrodotoxin, in in a dose of 30 μg, suppressed positive inotropic effect of Pc or Vc (fig. 5).

Discussion

The model used in the present experiments is very suitable for determining the cardiac effects of drugs, because they are free of the influence of neurohumoral responses[8,9].

Pancuronium is well known to increase blood pressure and heart rate[1,2], but vecuronium causes little change[2].

The results in the present study indicate that the positive inotropic potency of Pc is about three times of that of Vc, and the positive chronotropic potency of Pc is about ten times of that of Vc.

Iwatsuki et al.[6] reported pancuronium to have a positive inotropic effect using an isolated canine heart muscle, too. They discussed positive inotropic effect of Pc from shortning of $\frac{dF}{dt}$, and from effect of propranolol.

DT and SAR were increased by Pc and Vc, and the increases in DT were inhibited by propranolol or tetrodotoxin (TTX) in the present study. TTX is known to block the sympathetic nerve conduction, thus suppress the release of norepinephrine from the sympathetic nerve endings.

These results suggest that the positive inotropic and chronotropic effects of Pc and Vc are induced by the facilitation of release of norepinephrine from the sympathetic nerve endings and by the indirect activation of beta-receptor. As Vc was shown to have less potent effect on heart, it is recommendable to anesthesia of cardiac operation. In conclusion the cardiac effects of Pc and Vc may be

mediated by noradrenergic nerve stimulation.

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References

1. Miller RD, Eger E, Stevens WC, Gibbons R: Pancuronium induced tachycaradia in relation to alveolar halothane, dose of pancuronium, and prior atropine. Anesthesiology 42:352–355, 1975
2. Palmer Taylar: Neuromuscular blocking agents, The Pharmacological Basis of Therapecutics (7th ed.), Edited by Gilman AG, Goodman LS, Roll TW, Murad F, p230 NEW YORK, 1986
3. Docherty JR, McGrath JC: Sympathomimetic effects of pancuronium bromide on the cardiovascular system of the pithed rat. Br J Pharmacol 64:589–599, 1978
4. Domenech JS, Garcia RC, Sasiain JMR, Loyola AQ, Oroz JS: Pancuronium bromide: An indirect sympathomimetic agent. Br J Anaesth 48:1143–1148, 1976
5. Ivankovich AD, Miletich DJ, Albrecht RF, Zahed B: The effect of pancuronium on myocardial contraction and catecholamine metabolism. J Pharm Pharmacol 27:837–841, 1975
6. Iwatsuki N, Hasimoto Y, Amaha K, Obara S, Iwatsuki K: Inotropic effects of nondepolarizing muscle relaxants in isolated canine heart muscle. Anesth Analg 59:717–721, 1980
7. Duke PC, Fung H, Gartner J: The myocardial effects of pancuronium. Can Anaesth Soc J 22:680–686, 1975
8. Motomura S, Kissin I, Aultman DF, Reves JG: Effects of fentanyl and nitrous oxide on contractility of blood-perfused papillary muscle of the dog. Anesth Analg 63:47–50,1984
9. Manabe M, Motomura S, Hashimoto K: Interaction between diltiazem and halothane or enflurane in the canine blood-perfused papillary muscle and sinoatrial node preparations cross-circulated by chronically instrumented conscious donor dog. J Anesth 2:50–62, 1988