

# Differential Effects of the Sedative Agents on the Heart Rate Response to Intravenous Isoproterenol Infusion.

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Bradycardia is one of the adverse events associated with the sedatives, dexmedetomidine (DM) and propofol (PF). Because PF and DM attenuate the heart rate (HR) response to intravenous (IV) atropine, isoproterenol may be required for the treatment of bradycardia during DM or PF sedation. Therefore, we conducted the current study to evaluate the effect of DM or PF on the response of HR to IV isoproterenol.

Male Sprague-Dawley rats were randomly allocated to one of three groups. Group C (n=7) received sodium pentobarbital intraperitoneally and IV saline. Group PF (n=7) received IV PF. Group DM (n=7) received IV DM. Then all groups received IV isoproterenol at incremental infusion rates (0.1, 0.3, 0.5, 1.0, and 3.0 ng/kg/min for 2 min each dose).

Blood pressure decreased significantly in the groups C and DM, and HR decreased significantly in group DM after administration of each sedative. The increases in HR at 0.5, 1.0, and 3.0 ng/kg/min isoproterenol in group DM were  $75 \pm 41$ ,  $86 \pm 36$ , and  $110 \pm 39$  beats/min, respectively, and were greater as compared with those in group C ( $35 \pm 29$ ,  $38 \pm 30$ , and  $57 \pm 32$  beats/min, respectively), but there were no significant differences between groups C and PF.

In conclusion, DM but not PF enhances the HR response to the continuous IV infusion of isoproterenol, suggesting that isoproterenol may be useful when atropine is ineffective for the treatment of bradycardia during DM or PF sedation. (245 words)

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## Introduction

Alpha 2-adrenergic agonist is of interest to anesthesiologists because they produce sedation, anxiolysis, analgesia, reduction of anesthetic requirement, and hemodynamic stabilization.<sup>1)</sup> Perioperative use of alpha 2-adrenergic agonist may result in a decreased risk of adverse cardiac events, including myocardial ischemia.<sup>2)</sup> Dexmedetomidine (DM), a highly specific and selective alpha 2-adrenergic agonist, is novel sedative agent for intensive care.<sup>3)</sup> It can provide hemodynamic stability and appears to have no clinically important adverse effects on respiration.<sup>4)</sup>

The efficacy of propofol (PF) in the sedation of adults in the intensive care unit (ICU) is well established, and clinical trials have demonstrated a similar quality of sedation to midazolam, and also a more rapid and predictable emergence time than midazolam.<sup>5)</sup> PF has been reported to have no direct negative inotropic effect at therapeutic concentrations in normal myocardium.<sup>6)</sup> In clinical study, PF causes no significant changes in cardiac output in patients with good cardiac function undergoing coronary artery bypass graft surgery.<sup>7)</sup> Thus PF is used with increasing frequency for anesthetic management or sedation in the ICU.

Bradycardia is one of the adverse events associated with both DM and PF. Furthermore, it has been reported that PF and clonidine, another alpha 2-adrenergic agonist, attenuate not only the heart rate (HR) response to intravenous (IV) atropine but also the reflex tachycardia and sympathetic response to hypotension.<sup>8–11)</sup> Thus isoproterenol may be required when atropine is ineffective for the treatment of bradycardia during DM or PF sedation. Therefore, we conducted the current study to evaluate the effects of DM and PF in comparison with pentobarbital on the response of HR to IV isoproterenol.

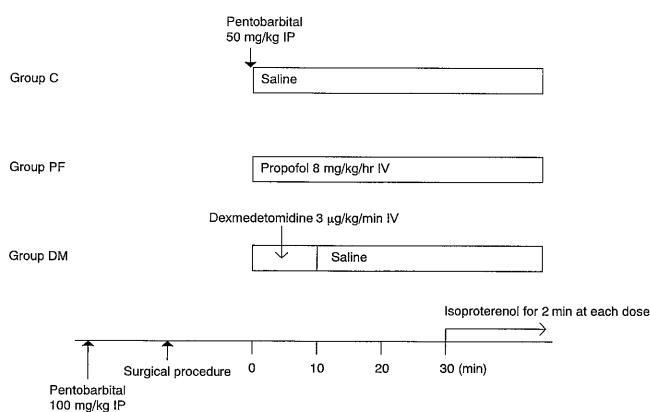
## Materials and Methods

All experimental procedures and protocols described

in this study were approved by the Animal Care and Use Committee of Nagasaki University School of Medicine. After male Sprague-Dawley rats weighing 350-400 g were anesthetized with sodium pentobarbital, intraperitoneal injection (IP) of 100 mg/kg, the rats were subjected to tracheotomy and ventilated with room air using a mechanical ventilator. Heparinised polyethylene catheters were inserted into the right carotid artery for recording arterial blood pressure (BP) and into the right external jugular vein for drug administration. Subcutaneous electrocardiograph electrodes were placed. Blood pressure (BP) and HR were monitored throughout the study (Nihon-Kohden RM-6000, Tokyo, Japan). Body temperature was maintained at  $37 \pm 1^\circ\text{C}$  with a heated pad controlled by a rectal thermistor.

The experimental protocol is shown in figure 1. After surgical preparation and a stabilization period, baseline hemodynamic data were collected. The rats were randomly allocated to one of three groups. Group C (n=7) received sodium pentobarbital, IP of 50 mg/kg followed by saline infusion. Group PF (n=7) received IV PF at a rate of 8 mg/kg/hr throughout the experimental period. Group DM (n=7) received IV DM at a rate of  $3 \mu\text{g}/\text{kg}/\text{min}$  for 10 min followed by saline infusion. Thirty minutes after starting administration of each sedative, the next measurement was done. Then all groups received continuous IV infusion of isoproterenol at incremental infusion rates (0.1, 0.3, 0.5, 1.0, and 3.0 ng/kg/min for 2 min each dose). BP and HR were measured at the end of each infusion period.

All values were expressed as mean  $\pm$  SD. Data within and among groups were analyzed with analysis of variance for repeated measures followed by Fisher's PLSD test. A p value less than 0.05 was considered statistically significant.



**Figure 1.** Experimental protocol. IV=intravenous; IP=intraperitoneal injection.

## Results

Table 1 shows the data of HR and systolic, mean, and diastolic BP (SBP, MBP, and DBP) in this study. There were no significant differences among groups in basal HR and BP (Table 1). SBP, MBP, and DBP decreased significantly in the groups C and DM, and HR decreased significantly in group DM after administration of each sedative. Isoproterenol increased HR in a dose-dependent manner in all groups. BP in groups PF and DM significantly decreased after isoproterenol infusion, but remained unchanged in group C.

The increases in HR after isoproterenol infusion at 0.5, 1.0 and 3.0 ng/kg/min in group DM ( $75 \pm 41$ ,  $86 \pm 36$  and  $110 \pm 39$  beats/min, respectively) were greater than those in group C ( $35 \pm 29$ ,  $38 \pm 30$  and  $57 \pm 32$  beats/min, respectively), but there was no significant difference between groups C and PF (Figure 2).

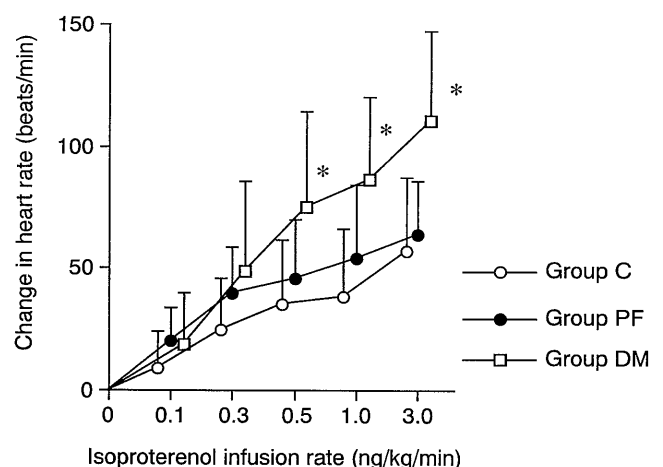
**Table 1.** Heart rate and blood pressure at each dose of intravenous isoproterenol

	Group	Baseline	Pre-isoproterenol	Isoproterenol infusion rate (ng/kg/min)				
				0.1	0.3	0.5	1.0	3.0
HR (bpm)	C	428 (18)	418 (17)	426 (25)	443 (35) *	453 (42) *	456 (42) *	475 (40) *
	PF	437 (14)	440 (15) #	460 (10) * #	480 (12) * #	486 (15) *	494 (22) *	504 (14) *
	DM	438 (14) *	315 (18) #	334 (27) #	364 (41) * #	390 (46) * #	401 (40) * #	425 (37) * #
SBP (mmHg)	C	151 (19) *	134 (11)	131 (10)	127 (14)	125 (19)	123 (20)	124 (22)
	PF	148 (21)	153 (17)	152 (17) #	154 (16) #	149 (15) #	150 (16) #	144 (9) * #
	DM	147 (11) *	128 (16)	126 (16)	120 (17)	116 (16)	111 (18)	111 (15) *
MBP (mmHg)	C	135 (15) *	119 (11)	118 (8)	113 (13)	110 (19)	110 (21)	107 (19)
	PF	128 (16)	133 (13)	130 (12)	131 (12) #	131 (13) #	129 (12) #	122 (9) *
	DM	130 (8) *	114 (13)	111 (13)	106 (11)	104 (12)	97 (9) *	100 (11) *
DBP (mmHg)	C	120 (13) *	104 (10)	102 (9)	98 (13)	95 (18)	95 (19)	91 (16)
	PF	111 (13)	116 (14)	112 (12)	113 (13) #	112 (14) #	109 (14) *	103 (11) *
	DM	115 (7) *	101 (12)	98 (12)	92 (8) *	92 (9) *	86 (8) *	90 (12) *

Values are mean (SD).

HR = heart rate; SBP = systolic blood pressure; MBP = mean blood pressure; DBP = diastolic blood pressure.

\* P < 0.05 versus Pre-isoproterenol; # P < 0.05 versus control.



**Figure 2.** Heart rate response to intravenous isoproterenol infusion at a rate of 0.1, 0.3, 0.5, 1.0, and 3.0 ng/kg/min.

All values were expressed as mean  $\pm$  SD.

\*Significantly (P<0.05) different from control.

## Discussion

The present study showed that DM enhanced the HR response to continuous IV infusion of isoproterenol. It was reported that clonidine augmented the alpha 1-adrenergic stimulated vasoconstriction and beta 1-adrenergic stimulated HR increase,<sup>11)</sup> and that the HR response to atropine was attenuated in adults and children receiving clonidine in a dose-dependent manner.<sup>10, 12)</sup> The difference of the HR responses to atropine and isoproterenol in the presence of clonidine might be due to the differential pharmacological interactions of these drugs with the alpha 2-adrenergic agonist. Atropine increases HR by suppression of postganglionic parasympathetic nervous activity. The HR response to atropine could be attenuated by age,<sup>13)</sup> sympathetic nerve activity,<sup>14)</sup> co-existing disease,<sup>15)</sup> basal HR,<sup>16)</sup> and background anesthesia.<sup>17)</sup> DM and clonidine reduce the central sympathetic outflow and the release of noradrenaline from peripheral presynaptic terminals,<sup>18, 19)</sup> resulting in a decrease in HR. Thus attenuation of the HR response to atropine in the presence of DM or clonidine may be due to reduced sympathetic nervous activity and lowered basal HR resulting from the alpha 2-adrenergic action.

In contrast to atropine, isoproterenol stimulates postsynaptic beta 1-adrenergic receptor. It has been demonstrated that DM and clonidine suppress the stress-induced increase in the blood catecholamine concentration,<sup>18, 19)</sup> and that these alpha 2-adrenergic agonists produce the up-regulation of the beta-adrenergic receptor of the heart at a clear short time.<sup>20)</sup> Thus it is possible that DM might enhance the HR response to isoproterenol through the up-regulation of the beta-adrenergic receptor.

PF does not change the HR response to isoproterenol as compared with group C in the present study. Horiguchi et al. reported that PF with nitrous oxide anesthesia enhanced the HR response to isoproterenol as compared with awake patients, and suggested that increased sympathetic tone during isoproterenol infusion might be accompanied by an increase in vagal tone in awake patients but not in propofol anesthetized patients.<sup>8)</sup> The discrepancy between our and their results may be due to the difference of the control. Our study used pentobarbital anesthetized rats as control, but theirs awake humans. The balance of autonomic nervous activity could alter the HR response to not only atropine<sup>14)</sup> but also isoproterenol<sup>21)</sup>.

BP in group DM significantly decreased after isoproterenol infusion, but remained unchanged in group C. A decrease in BP could cause a baroreceptor-mediated tachycardia. Thus the baroreflex might

enhance the HR response to isoproterenol in group DM. However, it is known that a continuous infusion of isoproterenol increases vagal tone. Furthermore, clonidine was shown to attenuate both the reflex tachycardia and the sympathetic response to hypotension.<sup>11)</sup> Thus the role of baroreflex seems to be minimum in the enhancing effect of DM on the HR response to isoproterenol.

In conclusion, DM enhances the HR response to a continuous IV infusion of isoproterenol, whereas PF has no significant effect on the response. These results suggest that isoproterenol would be useful when atropine is ineffective for the treatment of bradycardia during DM or PF sedation.

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