Selective $beta_1$ and $beta_2$ adrenoceptor blockade on epinephrine-induced arrhythmias in halothane anaesthetized dogs

Yukio Hayashi MD,* Koji Sumikawa MD,†
Takahiko Kamibayashi MD,† Atsushi Yamatodani MD,‡
Tadanori Mammoto MD,* Masakazu Kuro MD,*
Ikuto Yoshiya MD†

$Beta_2$ as well as $beta_1$ adrenoceptors have been recognized in the heart of vertebrates. They mediate a positive chronotropic action of catecholamines. We compared the effect of selective $beta_1$ and $beta_2$ adrenoceptor antagonists on the genesis of halothane-epinephrine arrhythmias in dogs. The arrhythmogenic dose (AD) of epinephrine was increased in the presence of l-metoprolol, a selective $beta_1$ antagonist (8.40 ± 1.13 $\mu g \cdot kg^{-1} \cdot min^{-1}$; mean ± SEM), compared with control value (2.62 ± 0.56) ($P < 0.05$). In contrast, ICI-118,551, a selective $beta_2$ antagonist, did not change the AD (2.36 ± 0.43). Adding ICI-118,551 to l-metoprolol did not affect the AD of epinephrine in the presence of l-metoprolol alone (6.34 ± 0.74 vs 8.40 ± 1.13). These results suggest that selective $beta_1$ blockade is effective in preventing halothane-epinephrine arrhythmias, but selective $beta_2$ blockade is not.

Des récepteurs adrénergiques B_2 autant que les B_1 ont été localisés dans le coeur des vertébrés. Ils transmettent l'action chronotrope positive des catécholamines. Nous avons comparé les effets d'antagonistes adrénergiques sélectifs B_1 et B_2 sur l'initiation des arythmies dues à l'association halothane-adrénaline chez le chien. La dose arythmogène (DA) de l'adrénaline a été accrue en présence de l-métoprolol, un antagoniste sélectif B_1 (8,40 ± 0,13 $\mu g \cdot kg^{-1} \cdot min^{-1}$, moyenne ±SEM), en comparaison avec des valeurs contrôle (2,62 ± 0,56) ($P < 0,05$). Au contraire, le ICI-118,551, un B_2 antagoniste sélectif n'a pas modifié la DA (2,36 ± 0,43). En ajoutant ICI-118,551 au l-métoprolol, la DA de l'adrénaline reste semblable à celle déterminée avec le l-métoprolol seul (6,34 ± 0,74 vs 8,40 ± 1,13). Ces résultats suggèrent qu'un bloc sélectif B_1 est efficace pour prévenir les arythmies dues à l'association halothane-adrénaline mais qu'une inhibition B_2 sélective ne l'est pas.

Key words
ANAESTHETICS, VOLATILE: halothane;
HEART: arrhythmias;
RECEPTOR: beta adrenergic;
SYMPATHETIC NERVOUS SYSTEM: catecholamines, epinephrine.

From the *Department of Anesthesiology, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita Osaka 565, Japan, and the †Department of Anesthesiology and the ‡Department of Molecular Physiological Chemistry and Pharmacology, Osaka University Medical School, 2-2 Yamadaoka, Suita Osaka 565, Japan.

Address correspondence to: Dr. Yukio Hayashi, Anesthesiology Service, VA Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304, U.S.A.

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Epinephrine exerts its effects on the heart through adrenergic receptors. Myocardial beta receptors have been considered to be one of the responsible receptors mediating the catecholamine-induced arrhythmias.[1–4] Propranolol, a nonselective beta antagonist,[1] and l-metoprolol, a selective $beta_1$ antagonist,[2] have been shown to prevent epinephrine-induced arrhythmia during halothane anaesthesia. Recent reports[5] have described the existence of both $beta_1$ and $beta_2$ adrenoceptors in the heart.[5–7] The effect of selective $beta_2$ antagonism on the genesis of the arrhythmias is controversial. Sharma,[3] using H 35/25 as a $beta_2$ antagonist, reported a weak protective effect against halothane-epinephrine arrhythmias and concluded that this action was attributed to its non-specific effect. On the other hand, we[8] examined the effect of a selective $beta_2$ antagonist, ICI-118,551, on the genesis of the arrhythmias provoked by various combinations of phenylephrine and isoproterenol, and showed that ICI-118,551 potentiated isoproterenol-induced arrhythmias in the presence of a low

dose of phenylephrine. The inconsistent results may be because different drugs produce different activation of myocardial adrenergic receptors. Thus, the present study was designed as an extension of our previous work, to compare the effects of $beta_1$ and $beta_2$ antagonism on the epinephrine-induced arrhythmias during halothane anaesthesia.

Methods

The studies were conducted under guidelines approved by the Animal Care Committee of Osaka University Medical School.

Thirty-nine adult mongrel dogs of either sex and weighing 8–11.5 kg were used in the study. Anaesthesia was induced with halothane alone and maintained at an end-tidal concentration of 1.3%, which was monitored continuously by an anaesthetic gas analyzer (Datex AA 102-30-00, Helsinki, Finland). The trachea of each dog was intubated with a cuffed tracheal tube, and the lungs were mechanically ventilated with air (Aika R60, Tokyo, Japan). The $PETCO_2$ was monitored continuously with an expired gas monitor (Minato 1H 21A, Osaka, Japan) and maintained at 35–40 mmHg. A heating lamp and a circulating water blanket were used to maintain nasal temperature between 37.0 and 38.5° C. Lead II of the ECG was monitored continuously. A femoral artery catheter was inserted for both pressure monitoring and blood sampling. A femoral vein was cannulated for the administration of both epinephrine and a solution of lactated Ringer's solution, infused at a rate of 10 $ml \cdot kg^{-1} \cdot hr^{-1}$. Serum K^+ concentration was maintained between 3.5 and 4.5 $mEq \cdot L^{-1}$ by infusion of K^+ at a rate of 1–10 $mEq \cdot hr^{-1}$. Arterial pH, PO_2, and serum Na^+ concentration were maintained within the range of 7.35–7.45, 85–95 mmHg, and 135–150 $mEq \cdot L^{-1}$, respectively.

The drugs used in the present study were l-metoprolol as a selective $beta_1$ antagonist,[9] d-metoprolol, a stereoisomer of l-metoprolol which has membrane stabilization effect but lacks $beta_1$ antagonistic effect, and ICI-118,551 a selective $beta_2$ antagonist.[10]

The arrhythmia threshold was achieved when four or more premature ventricular contractions occurred within 15 sec. The arrhythmogenic dose (AD) of epinephrine was defined as the lowest dose that achieved the arrhythmia threshold, as previously reported.[11] The AD of epinephrine was determined in each dog with standardized logarithmically spaced infusions of epinephrine lasting three minutes with 10–30 min recovery periods between infusions. The infusion was started at the minimum dose of 0.67 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and the dose was increased by $e^{0.4}$ (e = 2.72) until arrhythmias occurred. If arrhythmias did occur at one of these doses, a smaller dose, divided by $e^{0.2}$, was tested. The AD of epinephrine was determined under five different conditions: in the presence of l-metoprolol (0.4 $mg \cdot kg^{-1}$); d-metoprolol (0.4 $mg \cdot kg^{-1}$; ICI-118,551 (0.2 $mg \cdot kg^{-1}$); and both l-metoprolol and ICI-118,551; or with no antagonist (control). A 4 ml arterial blood sample was collected to allow measurement of arrhythmogenic plasma concentration (APC) of epinephrine at the time when the criterion for the AD had been satisfied. Plasma epinephrine was determined in a fully automated high-performance liquid chromatography-fluorometric system (model HLC-8030 Catecholamine Analyzer, Tosoh, Tokyo, Japan) using a diphenylethylenediamine condensation method.[12] This assay method has a limit of sensitivity of 10 $pg \cdot ml^{-1}$ for epinephrine. The inter- and intra-assay variations are less than 3%. As there was individual variability in both the AD and APC values, the mean AD and APC values were calculated.

Data are expressed as mean ± SEM. The results of multiple groups were analyzed by one-way analysis of variance, and comparison between groups was assessed by Scheffe's test. $P < 0.05$ was considered statistically significant.

Results

The AD and APC of epinephrine in the presence of various beta antagonists are shown in Figures 1 and 2, respectively. L-metoprolol prevented epinephrine-induced arrhythmias and increased the arrhythmia threshold to 3.2-fold of the control level ($P < 0.05$), whereas ICI-118,551 did not produce any change in AD and APC. The effect of

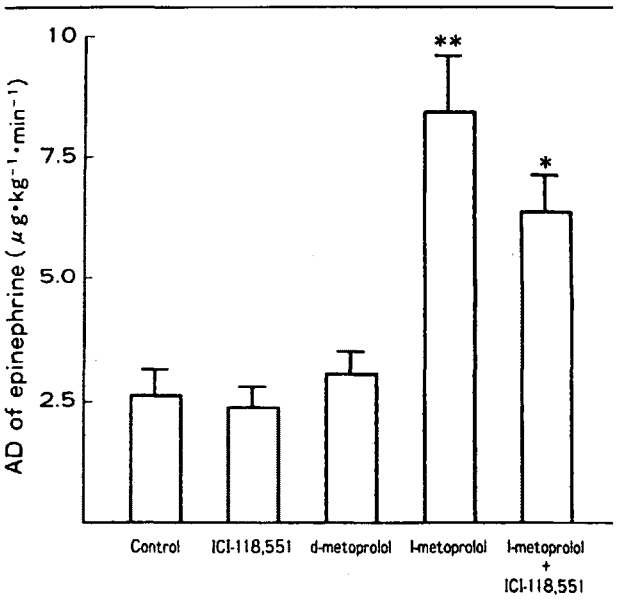

FIGURE 1 The arrhythmogenic dose (AD) of epinephrine required in the presence of various drugs (mean ± SEM; number of observations is shown in parentheses). *$P < 0.05$, **$P < 0.01$ compared with control.

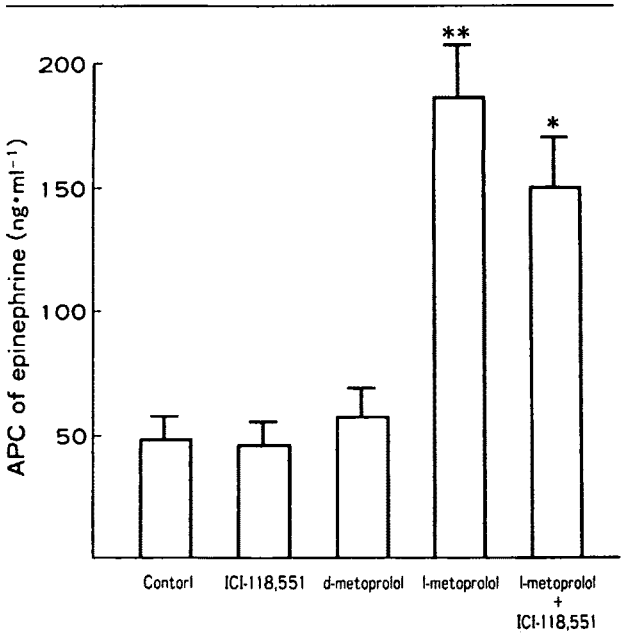

FIGURE 2 The arrhythmogenic plasma concentration (APC) of epinephrine in the presence of various drugs (mean ± SEM; number of observations is shown in parentheses). $*P < 0.05$, $**P < 0.01$, compared with control.

d-metoprolol was not also statistically significant. The combined administration of l-metoprolol and ICI-118,551 increased both AD and APC of epinephrine significantly, but the antiarrhythmic effect of combination of l-metoprolol and ICI-118,551 was not different from that of l-metoprolol alone.

Systolic and diastolic arterial pressure and heart rate at the time of the arrhythmias induced by epinephrine in the presence of various antagonists are shown in the Table. Systolic arterial pressure and heart rate did not vary in the presence of various antagonists, whereas diastolic arterial pressure in the presence of l-metoprolol plus ICI-118,551 was higher than that in control.

Discussion

Application of new selective adrenoceptor agonists and antagonists has contributed to knowledge of the adrenoceptor mechanism involved in epinephrine-induced arrhythmias.[13] It has been reported recently that $beta_2$ adrenoceptors are present in the hearts of vertebrates[6,7] and are classified as relatively epinephrine-selective compared with norepinephrine.[14] Therefore, the role of $beta_2$ adrenoceptors in the genesis of halothane-epinephrine arrhythmias should be evaluated. The present results show that $beta_1$ blockade by l-metoprolol increased AD and APC of epinephrine, whereas $beta_2$ blockade by ICI-118,551 did not prevent the epinephrine-induced arrhythmia (Figures 1, 2). Furthermore, ICI-118,551, when added to l-metoprolol, did not produce any change in the AD and APC of epinephrine compared with l-metoprolol alone (Figures 1, 2). Therefore, $beta_2$ blockade would be of no use in opposing halothane-epinephrine arrhythmias.

Sharma[3] reported that H 35/25, a selective $beta_2$ antagonist, prevented epinephrine-induced arrhythmias in halothane anaesthetized dogs to some degree. He attributed its inhibitory effect to the nonspecific action. Although our present findings seem to be contrary to his study,[3] and despite similar experimental models, this discrepancy may be due to a difference in $beta_2$ selectivity between the two antagonists used.[10,15] ICI-118,551 is considered to have a higher degree of $beta_2$ selectivity and the dose of ICI-118,551, 0.2 $mg \cdot kg^{-1}$ used in the present study was reported to be adequate to block $beta_2$ adrenoceptors selectively in dogs.[16] On the other hand, the dose of H 35/25 in Sharma's previous report appeared to be so great that a non-specific effect was involved in its antiarrhythmic activity.[3] Therefore, the results of the two studies may be compatible as regards the ineffectiveness of $beta_2$ adrenoceptor antagonism.

Membrane stabilization as well as $beta_2$ blockade could be involved in the effect of l-metoprolol.[17] In order to rule out the membrane stabilizing effect, we examined

TABLE The haemodynamic data at the time of arrhythmias induced with epinephrine after the various treatments during halothane anaesthesia

	n	*SAP (mmHg)*	*DAP (mmHg)*	*HR (beats · min⁻¹)*
Control	8	220 ± 12.2	125 ± 9.5	139 ± 14.2
D-metoprolol (0.4 mg · kg⁻¹)	7	244 ± 13.3	141 ± 7.5	135 ± 9.5
L-metoprolol (0.4 mg · kg⁻¹)	9	263 ± 8.4	146 ± 6.8	119 ± 5.5
ICI-118,551 (0.2 mg · kg⁻¹)	8	225 ± 16.2	124 ± 8.2	120 ± 19.9
L-metoprolol +ICI-118,551	9	245 ± 11.4	161 ± 7.1*	126 ± 12.2

SAP: systolic arterial pressure. DAP: diastolic arterial pressure. HR: heart rate. *n* = the number of observations. Values, are expressed as mean ± SEM. $*P < 0.05$ compared with control value.

the antiarrhythmic effect of d-metoprolol, which lacks receptor blocking action but preserves membrane stabilization. The results show that d-metoprolol had no effect on the arrhythmias, indicating that l-metoprolol exerts its antiarrhythmic effect by $beta_1$ receptor blockade. Maze and Smith[2] examined the effect of d-metoprolol in a similar way and reported that d-metoprolol increased the AD of epinephrine to three-fold of the control. This difference could have to do with the dosage of d-metoprolol, that is, we administered 0.4 $mg \cdot kg^{-1}$ of d-metoprolol as a single dose, whereas they injected 0.5 $mg \cdot kg^{-1}$ of it repeatedly at 30-min intervals.[2] In addition, ICI-118,551 might also have the membrane stabilizing effect, but this effect was reported to be insignificant in the dose range we used.[16]

It is well known that $beta_2$-receptors exist on vascular smooth muscle and they exert a vasodilating effect.[5,7] Inhibition of these receptors might enhance the epinephrine-induced arterial pressure elevation resulting in potentiation of its arrhythmogenicity.[8] However, in the present study systolic arterial pressures in each group were not different. Therefore, the effect of $beta_2$ antagonist was not involved in the modulation of myocardial sensitization by halothane.

Finally, the vulnerability to myocardial sensitization by halothane would vary between dogs and humans because of a species difference.[18] Thus we would like to address limited applicability of the present results to the clinical settings.

In conclusion, $beta_2$ sympathetic antagonism did not contribute to the prevention of the epinephrine-induced arrhythmias during halothane anaesthesia as did the $beta_1$ antagonist, l-metoprolol. Therefore, selective $beta_1$ antagonists are recommended for the treatment of halothane-epinephrine arrhythmias rather than nonselective beta antagonists, such as propranolol.

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