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Hemodynamic effects of KRN2391 (potassium channel opener) in halothane-anesthetized dogs

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Abstract: The cardiovascular responses to an infusion of KRN2391, a potassium channel opener, was studied in halothane-anesthetized dogs. Intravenous administration of KRN2391 at 1.0 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 60 min produced dose-dependent decreases in mean arterial pressure (MAP) and systemic vascular resistance (SVR) associated with dose-dependent increases in the cardiac index (CI) and stroke volume index (SVI) but was not accompanied by an increase in heart rate (HR). The maximum decrease in MAP during the infusion of KRN2391 at 1.0 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was $-13 \pm 7\%$ ($P < 0.01$) and $-37 \pm 10\%$ ($P < 0.01$), respectively. The maximum reduction in SVR after 1.0 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was $-20 \pm 11\%$ ($P < 0.01$) and $-60 \pm 16\%$ ($P < 0.01$), respectively. A KRN2391 infusion of 1.0 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increased CI a maximum of $11 \pm 13\%$ ($P < 0.05$) and $65 \pm 33\%$ ($P < 0.01$), respectively. KRN2391 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ showed a tendency to increase SVI but this change was not significant, KRN2391 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, however, produced a significant increase in SVI. The present results demonstrate that the decrease in MAP and the increases in CI and SVI caused by KRN2391 are due to a reduction in the afterload. Therefore, we conclude that these cardiovascular profiles of KRN2391 may be benificial in perioperative uses including the control of systemic blood pressure and the treatment of hypertension during halothane anesthesia in clinical practice.

Key words: KRN2391, Halothane anesthesia, Systemic hemodynamics, K^+ channels

Introduction

Hemodynamic stability and control of systemic blood pressure are important in ischemic heart conditions and in critically ill patients in the perioperative period. Vasodilators such as nitroprusside, nitroglycerin, calcium channel antagonists (verapamil, diltiazem, and nicardipine), and esmolol are frequently used to reduce systemic blood pressure during episodes of acute abnormal hypertension due to sympathetic stimulation during anesthesia and/or surgical procedures. Although both organic nitrates and calcium channel antagonists produce antihypertensive actions, their cardiovascular effects are different [1].

The characteristics of an ideal vasodilator agent include rapid onset and diminution of action, reduction of systemic vascular resistance, preservation of cardiac output, maintenance of adequate organ perfusion of all tissues, and the absence of tachyphylaxis.

Recently, it has been reported that the cardiovascular profile of a novel vasodilator, KRN2391 [*N*-cyano-*N'*-(2-nitroxyethyl)-3-pyridinecarboximidamide monomethanesulfonate, Fig. 1], satisfies all the above criteria.

The vasodilatory effect of KRN2391 is thought to be based on both a nitrate action and potassium channel opening action [2]. In anesthetized dogs, an intravenous administration of KRN2391 increased coronary, mesenteric, and renal blood flow and decreased their vascular resistances [3]. KRN2391 also showed decreases in myocardial oxygen consumption and total peripheral vascular resistance and an increase in oxygen supply to the heart [4]. However, these experimental results were obtained using dogs anesthetized with pentobarbital. Currently, volatile anesthetics such as halothane, enflurane, isoflurane, and sevoflurane are used in various types of procedures. Since these anesthetics are reported to affect calcium and potassium channels resulting in changes in hemodynamics [5], the interaction between vasodilator agents and volatile anesthetics are of importance. Therefore, this study was performed to elucidate the possibility of using KRN2391 as a vasodilator agent during halothane anesthesia.

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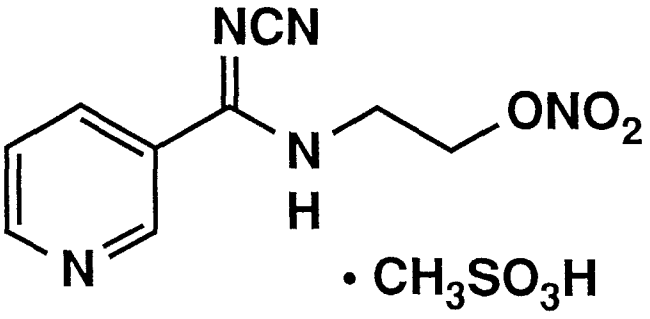

Fig. 1. Chemical structure of KRN2391

Materials and methods

Instrumentation

All experimental procedures and the protocol for this study were approved by the Animal Experiments Ethics Comittee of Showa University Fujigaoka Hospital.

Fourteen mongrel dogs weighing 12–23 kg were fasted overnight and then anesthetized with intravenous pentobarbital 25 mg·kg^{-1}. After intubation of the trachea, anesthesia was maintained with halothane at an inhaled concentration of 0.9% delivered through an Ohmeda Vaporizer (BOC Health Care, Windlesham, UK) using oxygen as a carrier gas at flow of 3–5 l·min^{-1}. The animals were mechanically ventilated with a constant volume respirator (Harvard Instruments, Chicago, IL, USA) to maintain normocapnia. The end-tidal halothane and CO_2 concentrations were continuously monitored with an infrared analyzer (Capnomac Ultima, Datex, Helsinki, Finland). A right femoral vein catheter was inserted for drug administration and 0.9% saline was infused at a rate of 7 ml·kg^{-1}·h^{-1} together with the infusion of KRN2391. The left femoral artery was cannulated for continuous systemic blood pressure (SBP) monitoring. A 7-F balloon-tipped triple-lumen pulmonary catheter (Baxter Healthcare Corporation, Irvine, CA, USA) was inserted via the right external jugular vein and positioned in a branch of the pulmonary artery for measurements of the central venous pressure (CVP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). CO was measured in triplicate using the thermodilution technique using a computer (Model MTC 6210, Nihon Kohden, Tokyo, Japan) and injection of 5 ml of 0.9% saline at 0°C into the right atrium at end-expiration. The cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated using standard formulas.

A 7-F pig-tailed catheter (Schneider, Minneapolis, MN, USA) was passed into the left ventricle via the right femoral artery and used for measurement of left intraventricular pressure (LVP). Left ventricular maximum rate of pressure change (LV dp/dt max.) was electrically derived from the left ventricular pressure wave signal with the use of an electronic differentiator (Model EQ 601G, Nihon Kohden). Heart rate (HR) was calculated from lead II of the electrocardiogram (ECG) using a cardiotachometer (Model AT 601G, Nihon Kohden) and was continuously monitored. Body temperature was monitored by a thermistor attached to the pulmonary artery catheter and was maintained at 37.0° ± 1.0°C with electric heating pads and lamps. Each pressure monitoring catheter was connected to a pressure transducer (UNIFLOW, Baxter Healthcare Corporation). SBP, ECG, LVP, and LV dp/dt max. were monitored continuously on a polygraph (Model RM 6200, Nihon Kohden) and recorded using an 8-channel pen recorder (Model VM-640G, Nihon Kohden).

Fourteen dogs, divided randomly into two groups, were studied in the following manner: group I ($n = 7$) received 1.0 μg·kg^{-1}·min^{-1} KRN2391 and group II ($n = 7$) received 5.0 μg·kg^{-1}·min^{-1} KRN2391. After completion of surgical preparation the animals were observed for approximately 60 min to allow hemodynamic variables (Stable SBP, MPAP, and HR) to stabilize. KRN2391, dissolved in 0.9% saline 50 ml, was infused for 1 h into the left femoral vein at constant rates of 1.0 or 5.0 μg·kg^{-1}·min^{-1} with an infusion pump (Model STG-521, Terumo, Tokyo, Japan). Baseline values were obtained before infusion of KRN2391. Hemodynamic variables were measured at 5, 30, and 60 min after commencement of infusion of KRN2391 and at 10, 30, and 60 min after termination of infusion.

Data are expressed as mean ± SD. Intragroup differences were analyzed by two-way analysis of variance from repeated measurements of the same variables followed by Dunnett's test when appropriate. Intergroup differences were analyzed by Student's unpaired t-test if the F test was significant. Differences were considered significant at $P < 0.05$.

Results

The baseline values of systemic hemodynamics including MAP, HR, CI, SVI, MPAP, PCWP, SVR, PVR, and LV dp/dt max. are shown in Table 1. These hemodynamic variables did not differ significantly between the groups. Hemodynamic changes during and after KRN2391 infusion, expressed as percentage of changes from baseline values are presented in Figs. 2 and 3. KRN2391 at 1.0 and 5.0 μg·kg^{-1}·min^{-1} produced decreases in MAP in a dose-related manner. With KRN2391 5.0 μg·kg^{-1}·min^{-1}, MAP changed by −30 ±

Table 1. Baseline values of hemodynamic variables before infusion of KRN2391 in groups I and II

	Group I ($n = 7$) 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Group II ($n = 7$) 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$
MAP (mmHg)	116 ± 11	121 ± 13
HR (beats·min^{-1})	159 ± 14	160 ± 28
CI (l·min^{-1}·m^{-2})	3.7 ± 0.8	3.6 ± 1.3
SVI (ml·beats^{-1}·m^{-2})	24 ± 5	23 ± 7
MPAP (mmHg)	16 ± 1	16 ± 3
PCWP (mmHg)	9 ± 1	10 ± 3
SVR (dyne·s·cm^{-5})	3451 ± 970	4556 ± 1770
PVR (dyne·s·cm^{-5})	194 ± 62	218 ± 73
LV dp/dt max (mmHg·s^{-1})	3457 ± 299	3457 ± 428

Values are the mean ± SD.
MAP, mean arterial pressure; HR, heart rate; CI, cardiac index; SVI, stroke volume index; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; LV dp/dt max, left ventricular maximum dp/dt.

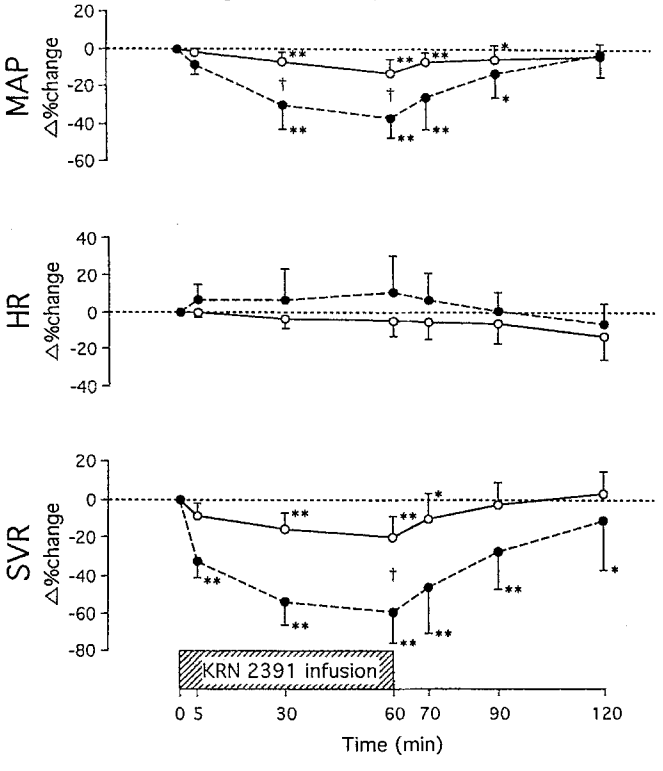

Fig. 2 Changes in mean arterial pressure (*MAP*), heart rate (*HR*), and systemic vascular resistance (*SVR*) during and after infusion of KRN2391. *Open circles*, 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$; *closed circles*, 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Each point represents the mean ± SD of 7 experiments. $^{*}P < 0.05$, $^{**}P < 0.01$ versus baseline values. $^{+}P < 0.05$ between 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$

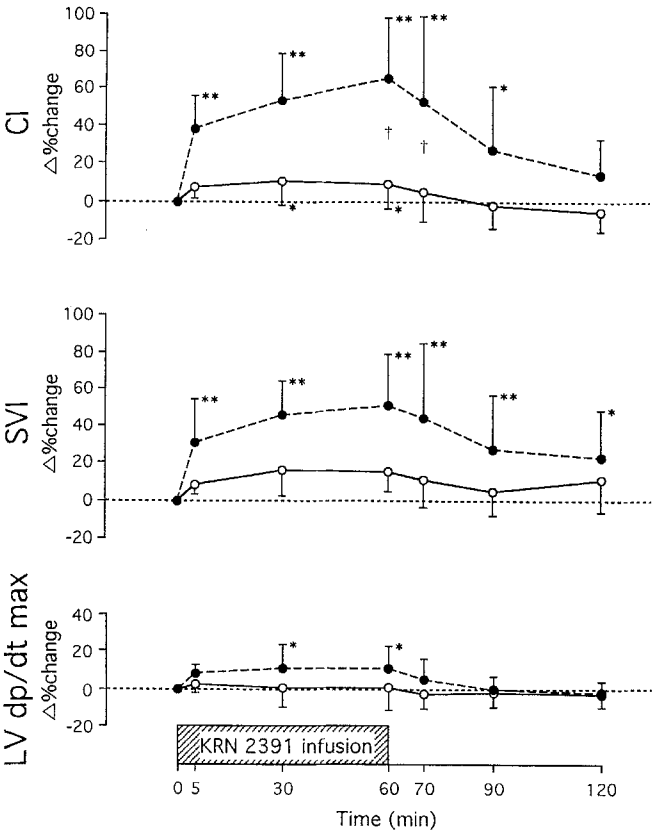

Fig. 3 Changes in cardiac index (*CI*), stroke volume index (*SVI*), and left ventricular maximum dp/dt (*LV dp/dt max*) during and after infusion of KRN2391. *Open circles*, 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$; *closed circles*, 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ $^{*}P < 0.05$, $^{**}P < 0.01$ versus baseline values, $^{+}P < 0.05$ between 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$

12% ($P < 0.01$) at 30 min and −37 ± 10% ($P < 0.01$) at 60 min, during the infusion period, −26 ± 17% ($P < 0.01$) at 10 min and −13 ± 13% ($P < 0.05$) at 30 min after the end of infusion from baseline values of 121 ± 13 mmHg. Further, MAP was significantly lower at 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ when compared with 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at 30 min and at 60 min during the infusion period. KRN2391 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ had no effects on HR. KRN2391 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ showed a tendency to increase HR, but this change was not significant. KRN2391 1.0 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced dose-dependent reductions in SVR. With KRN2391 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, SVR showed a significant reduction throughout the course of the experiment. This reduction of SVR at 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ decreased progressively from the baseline value of 4556 ± 1770 dyne·s·cm^{-5} to a nadir of 1772 ± 714 dyne·s·cm^{-5} at 60 min of the infusion period. SVR at KRN2391 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ showed significant reductions during the infusion period and at 10 min after the termination of infusion. Thereafter, SVR rapidly returned toward the baseline values.

In addition, SVR was significantly lower at 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ when compared with 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at 60 min of the infusion period.

Hypotension due to the doses of KRN2391 was accompanied by an increase in CI. KRN2391 1.0 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced increases in CI in a dose-related manner. CI of KRN2391 5.0$\mu g \cdot kg^{-1} \cdot min^{-1}$ increased significantly from the baseline value of 3.6 ± 1.3 $l \cdot min^{-1} \cdot m^{-2}$ to a maximum of 5.6 ± 1.3 $l \cdot min^{-1} \cdot m^{-2}$ at 60 min of the infusion period followed by an increase over the baseline values after termination. With KRN2391 at 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, CI significantly increased at 30 min and 60 min during the infusion period and then promply returned toward the baseline values. Further, CI was significantly greater at 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ compared with 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ both at 60 min of the infusion period and at 10 min after termination.

SVI with KRN2391 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increased significantly and progressively from baseline values of 23 ± 7 $ml \cdot beat^{-1} \cdot m^{-2}$ to a maximum ($50 \pm 28\%$, $P < 0.01$) at 60 min of the infusion period followed by a significant increase over the baseline values after termination. On the other hand, with KRN2391 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ SVI showed a tendency to increase but this increase was not significant.

LV dp/dt max. with KRN2391 at 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ significantly increased by $11 \pm 12\%$ ($P < 0.05$) at 30 min and $11 \pm 12\%$ ($P < 0.05$) at 60 min, respectively, during the infusion period from baseline values of 3457 ± 428 $mmHg \cdot s^{-1}$, but then decreased rapidly to the baseline values.

In contrast, KRN2391 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ resulted in no significant changes LV dp/dt max. throughout the course of the experiment. KRN2391 1.0 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ had no significant effects on MPAP, PCWP, or PVR throughout the course of the experiment.

Discussion

The present results demonstrate that a dose-dependent decrease in MAP induced by KRN2391 is due to a significant reduction in SVR but not accompanied by a reflexive increase in HR. In contrast, Kaneta et al. [6] reported that the decrease in blood pressure induced by KRN2391 was accompanied by an increase in HR in dogs anesthetized with sodium pentobarbital and this tachycardia was inhibited by pretreatment with propranolol, suggesting that the tachycardia induced by KRN2391 is due to a compensatory increase in sympathetic tone elicited by the lower blood pressure. This discrepancy in the effect of KRN2391 on HR appears to be based on the difference in anesthetic used in the experiments. Halothane is well known to inhibit the baroreceptor pathways, both centrally and peripherally [7–9]. In addition, it is reported that halothane decreases the rate of spontaneous discharge of slow action potentials in sinoatrial nodal tissue and prolongs atrioventricular conduction [10]. Therefore, this characteristic of halothane is thought to suppress the appearance of positive chronotropic action through the baroreflex and through a direct effect on the sinoatrial node of the heart.

In the present study, an increase in LV dp/dt max. was induced by KRN2391 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ but not by 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Since KRN2391 does not possess a positive inotropic action [11], the increase in LV dp/dt max. by KRN2391 is thought to be due to an increase in sympathetic tone and/or preload. However, the change in preload does not appear to contribute to the increase in LV dp/dt max. caused by KRN2391 because KRN2391 1.0 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ had no significant effects on CVP and MPAP in this study. Thus, it is considered that the increase in LV dp/dt max. induced by KRN2391 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is due to increased sympathetic discharge relating to a marked decrease in blood pressure.

KRN2391 decreased SVR as a consequence of vasodilation and increased CI and SVI. This result is in good agreement with earlier reports [4]. The increase in CI and SVI caused by KRN2391 appear to result in a reduction of afterload due to a decrease in SVR, because KRN2391 did not affect HR. However, the positive inotropic action induced by the increase in LV dp/dt max. is thought to partly contribute to the increase in CI and SVI caused by 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ KRN2391. KRN2391 is reported to have both a nitrate action and a potassium channel opening action. Todd et al. [12] showed that nitroglycerin produced decreases in MAP and SVR and an increase in CO without affecting HR and right atrial pressure in halothane-anesthetized dogs. Gotanda et al. [13] observed that the cardiovascular effects of cromakalim and pinacidil, both potassium channel openers, were characterized as vasodilators which preferentially reduced afterload and increased venous return in relating to increased cardiac output in pentobarbital-anesthetized dogs. Although there was a difference in anesthetics used in experiments, the hemodynamic profiles of KRN2391 in halothane-anesthetized dogs seem to be similar to those of nitroglycerin. However, the hemodynamic profiles of potassium channel openers may be affected by the anesthetic used. Indeed, nitroglycerin is reported to produce an increase in CO in halothane-anesthetized dogs as mentioned above but to produce a decrease in CO in pentobarbital-anesthetized dogs [14,15].

At present, nitroglycerin and nicardipine are used to control systemic blood pressure during anesthesia. For such purposes, the security of regional blood flow without an increase in myocardial oxygen consumption is

also important. Nitroglycerin has been shown to increase CO without affecting HR in halothane-anesthetized dogs [12]. However, the problem of tolerance to organic nitrates has been raised in human trials and in animal experiments [16–18]. Consequently, tolerance to nitrates may make it difficult to control the extent of hypotension during anesthesia. It has been reported that the increase in coronary blood flow caused by the intracoronary administration of KRN2391 was not affected by intravenous infusion of KRN2391, isosorbide dinitrate, or nitroglycerin in anesthetized dogs [19]. Further, the antihypertensive effect of KRN2391 is not affected by isosorbide dinitrate or nitroglycerin [19]. Therefore, these results suggest that KRN2391 does not induce acute tolerance by itself or cross-tolerance with other organic nitrates despite possessing a nitrate action in addition to a potassium channel opening action.

Currently, the most common clinically used antihypertensive agent is nitroprusside. However, rebound hypertension following the use of nitroprusside has been described [20]. Todd et al. [12] reported that nitroprusside produced increases in MPAP, PCWP, PVR, and right atrial pressure after stopping infusion in halothane-anesthetized dogs. This rebound phenomenon caused by nitroprusside was also observed in patients who have received nitroprusside for treatment of congestive heart failure [21]. On the other hand, in the present study KRN2391 did not induce the rebound phenomenon after stopping infusion. Thus, it is considered that KRN2391 does not induce the rebound phenomenon.

The interactions of calcium channel antagonists with volatile anesthetics have also been reported in experiments using dogs [22,23]. However, since there is a difference in selectivity between calcium channel antagonists and their effects on blood vessels and the myocardium, the cardiovascular profile differs with the type of calcium channel antagonist used. Hysing et al. [23] reported that nicardipine increased cardiac output, stroke volume, carotid blood flow, and coronary blood flow but decreased renal blood flow in isoflurane-anesthetized dogs. They also showed that the antihypertensive effect of nicardipine was accompanied by increases in HR and LV dp/dt max. during 1.6% end-tidal isoflurane anesthesia, but these were not seen during 3.0% isoflurane anesthesia. In contrast, verapamil produced decreased blood pressure without affecting CI and the systemic vascular resistance index but decreased LV dp/dt max. in halothane-anesthetized dogs [22]. These results suggest that nicardipine has preferential vasodilating properties but verapamil showed direct negative inotropic action in addition to a vasodilating action in dogs anesthetized with volatile anesthetics. In terms of the hemodynamic profile of KRN2391, Ogawa et al. observed that KRN2391 increases coronary, mesenteric, and renal blood flows and decreases myocardial oxygen consumption [3,4], although these experiments were performed in pentobarbital-anesthetized dogs. Further, it was confirmed that the decrease in myocardial oxygen consumption was not due to depressed cardiac function because the concentration of KRN2391 required to elicit cardiac effect was markedly higher than that to induce the vasorelaxant effects in vitro [11]. In the present study, KRN2391 had no significant effects on CVP, MPAP, PCWP, and PVR, suggesting that KRN2391 does not induce cardiac dysfunction in dogs anesthetized with halothane. These data also indicate that KRN2391 has no effects on right and left ventricular overload. Thus, these profiles of KRN2391 are thought to show the further possibility for its use as a vasodilator to control systemic blood pressure during halothane anesthesia.

In conclusion, the present study shows that KRN2391 produces a hypotensive action based on its potent vasodilating effect in halothane-anesthetized dogs. These profiles of KRN2391 suggest that KRN2391 may be a safe vasodilator suitable for perioperative use during general anesthesia with volatile anesthetics.

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