# Potentiation of the Cardiovascular Effects of Nicardipine by Enflurane Anesthesia in Canine Blood-perfused Heart Preparations

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The cardiovascular interaction betwenn nicardipine (N) and enflurae (E) was examinend with blood perfused isolated paplillary muscle preparations (PMP) and sinoatrial node preparations (SNP). Blood flow to these preparations was supplied by either conscious or 1.7% E-anesthetized-donor dogs. N was administerd continuously at a rate of 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ into the donor dogs for 60 min. Mesurements were as follows: mean arterial blood pressure (MAP), heart rate (DHR), PQ interval (PQ) in the electrocardiogram, developed tension (DT) in PMP, sinoatrial rate (SAR) in SNP and blood flow (BF) to PMP and SNP. There were no significant differences in PQ, SAR and BF between two groups. However, N further decreased MAP, DHR and DT that were already decreased by E significantly.

The authors conclude that the cardiovascular interaction between N and E was generally additive but that concerning negative inotropism was synergistic. (Key words: enflurane, nicardipine, contractility, heart rate)

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Previously we demonstrated that enflurane interacted with diltiazem to enhance its effects on mean arterial pressure and contractility of papillary muscle[1].

In healthy awake volunteers, nicardipine of 10 and 20 $\mu g \cdot kg^{-1}$ produced a dose dependent decrease in arterial blood pressure without depressing cardiac function[2]. In open chest dogs, Iwatsuki et al[3]. reported that the cardiovascular interaction between nicardipine and sevoflurane was additive. However, there have been no reports describing interactions between nicardipine and enflurane in the preparations as described below.

This study was designed to evaluate the interactions between nicardipine and enflurane using isolated papillary muscle preparations (PMP) and sinoatrial node preparations (SNP) perfused with blood of chronically instrumented conscious donor dogs or E-anesthetized ones.

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**Table 1.** Basal values of donor dogs and isolated heart preparations in conscious state

| | Conscious group (n=7) | Enflurane Anesthesia group (n=6) |
|---|---|---|
| Mean Arterial Pressure (MAP, mmHg) | 100 ± 11 | 96 ± 7 |
| Donor Heart Rate (DHR, beats·min$^{-1}$) | 144 ± 15 | 128 ± 26 |
| PQ Interval (PQ, msec) | 86 ± 12 | 95 ± 14 |
| Developed Tension (DT, g) | 2.8 ± 1 | 3.5 ± 1 |
| Sinoatrial Rate (SAR, beats·min$^{-1}$) | 105 ± 20 | 95 ± 13 |
| Blood Flow (BF, ml·min$^{-1}$) | 7.6 ± 2.0 | 6.7 ± 0.8 |

All parameters were not significantly different between two groups.

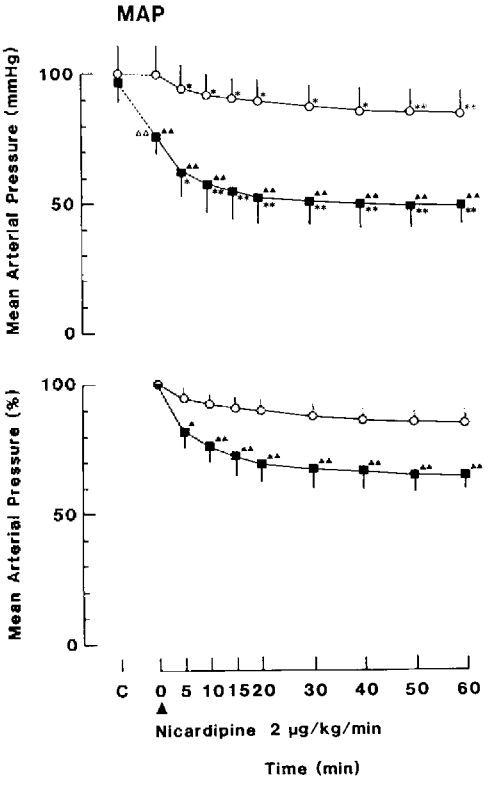


**Fig. 1.** The effects of nicardipine infusion on mean arterial pressure (MAP) in conscions (open circles) and enflurane anestheized (solid squares) donor dogs. Actual values of MAP are shown in the upper panel and the values are normalized as percentages in the lower panel. The vertical bars represent the standard deviation of the mean.

△; $P < 0.05$, △△; $P < 0.01$: vs Time C

▲; $P < 0.05$, ▲▲; $P < 0.01$: vs Conscious group

*; $P < 0.05$, **; $P < 0.01$: vs Time O

## Methods

**This study was approved by the animal research committee of Yamanashi Medical College. The model used here has been described previously[1]. Experiments were conducted on 13 canine, isolated, blood perfused PMP[4] and SNP[4] with blood supplied by chronically instrumented dogs[1,6]. Developed tension (DT) in PMP, the sinoatrial rate (SAR) in SNP, the blood flow (BF) through the anterior septal and right coronary arteries perfusing PMP and SNP, mean arterial pressure (MAP), heart rate (DHR) and the PQ interval (PQ) in electrocardiogram of donor dog were recorded. The preparations were allowed to stabilize for 60 min to obtain control recordings.**

**In group I, nicardipine, 2.0 μg·kg$^{-1}$·min$^{-1}$, was administered continuously for 60 min into seven conscious donor dogs that provided the isolated preparations with blood. In group II, the remaining six dogs that provided the isolated preparations with blood was administered 10 mg·kg$^{-1}$ thiamylal sodium and intubated. The animals were then connected to an anesthetic vaporizer (Enfluwick Muraco, Type 200) that was set to deliver enflurane at an inspired concentration of 2.0%. After ten min, the vaporizer was adjusted to deliver an inspired concentration of 1.7%. Thirty min after the start of enflurane all the pa-**

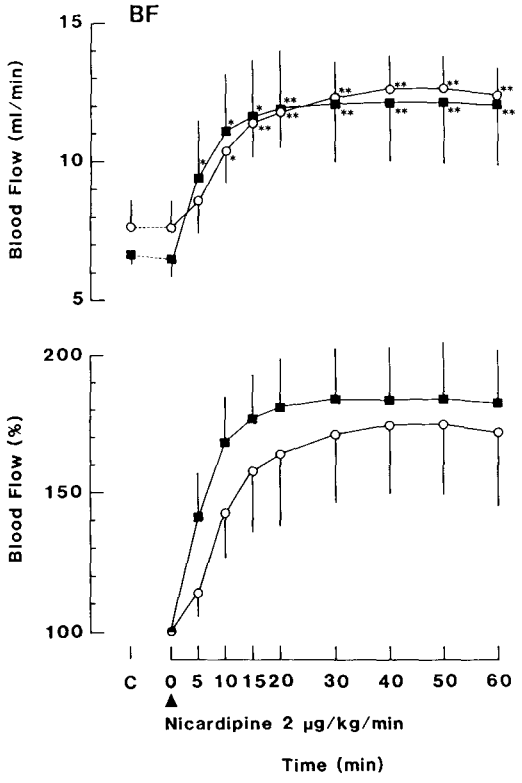


Fig. 2. The effects of nicardipine infusion on blood flow. All symbols and expressions are the same as those in figure 1.

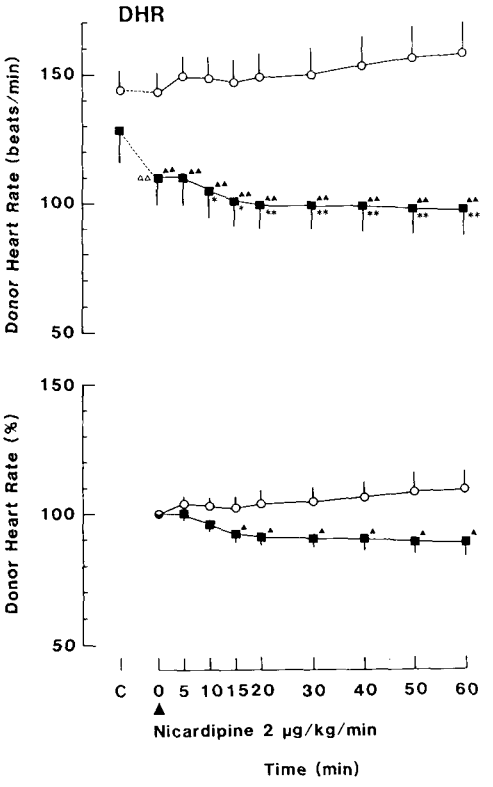


Fig. 3. The effects of nicardipinen infusion on heart rate of the donor dogs. All symbols and expressions are the same as those in figure 1.

rameters were measured and recorded. Nicardipine was then infused at the same rate as that in group I for 60 min. In both groups all the parameters were measured at five min intervals for the frist 20 min and at 10 min intervals during the following 40 min. Blood samples were obtained from all the animals at 10 min intervals for 60 min after the start of the nicardipine infusion and at 15 min intervals for 60 min after the nicardipine infusion was discontinued. Plasma concentrations of nicardipine were measured by gas chromatography[7].

All the data were normalized as percentage of the values at the start of the nicardipine infusion both in Group I and in Group II. Student's t-test for paired data was used for statistical analysis of differences in each group. Student's t-test for unpaired data was used for statistical analysis of differences between Group I and Group II. Differences were considered significant at $P < 0.05$.

## Results

There was no significant difference between control values measured at the end of the 60 min stabilization period both in Group I and in Group II (table 1). In Group I, MAP was progressively and significantly decreased during the 60 min nicardipine infusion period and BF to the isolated preparations was progressively and significantly increased (figs. 1,2). None of the other measured parameters were altered significantly by nicardipine infusion alone (figs. 3–6).

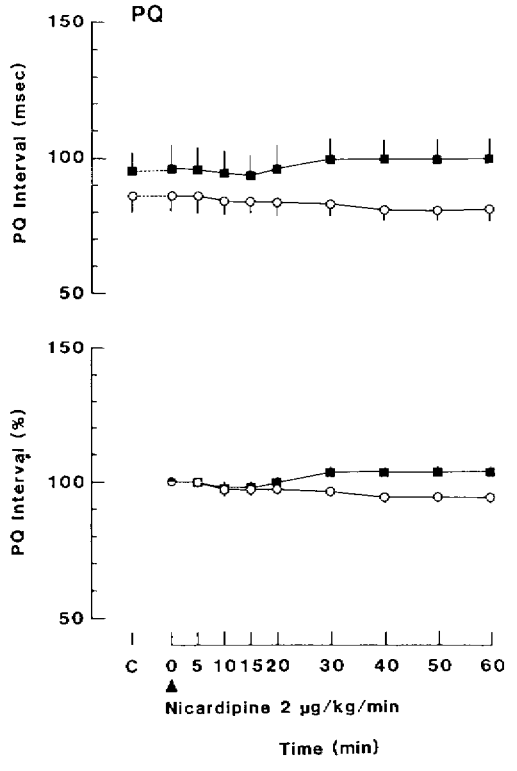


Fig. 4. The effects of nicardipine infusin on PQ interval in the donor dogs. All symbols and expressions are the same as those in figure 1.

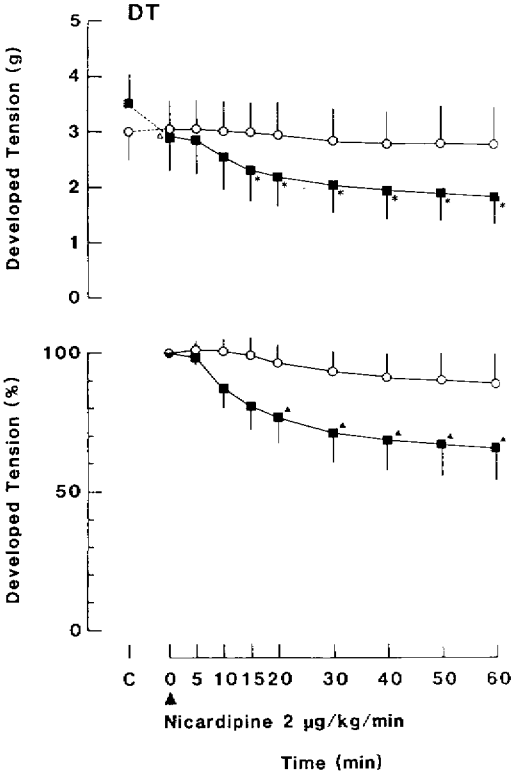


Fig. 5. The effects of nicardipine infusion on developed tension of the papillary muscles. All symbols and expressions are the same as those in figure 1.

In Group II, induction of anesthesia with thiamylal sodium produced transient alterations in all the parameters, which returned to control values within 15 min[1]. Thirty minutes after the start of enflurane, MAP, DHR and DT were significantly decreased (figs. 1,3,5), but PQ, SAR and BF changed only slightly (figs. 4,6,2). Nicardipine during enflurane anesthesia significantly decreased MAP, DHR and DT and significantly increased BF (figs. 1,3,5,2). There were no change in PQ and SAR (figs. 4,6).

The decreases in the normalized values of MAP, DHR and DT produced by the combination of N and E were significantly greater than those produced by N alone (figs. 1,3,5). Changes in the normalized values of PQ, SAR BF produced by the combination of nicardipine and enflurane were not significantly different from those produced by nicardipine alone (figs. 2,4,6).

Arterial plasma concentration of nicardipine obtained from the two groups increased progressively, and there was no significant difference between the two group (fig. 7).

## Discussion

Myocardial contractility as determined by DT in PMP was depressed to a grater degree by the combination of nicardipine and enflurane than was anticipated from the results of the two agents administered separately. The explaination for this potentiation might reside in the mechanisms of effect of the individual agents. Although enflurane is a potent, neg-

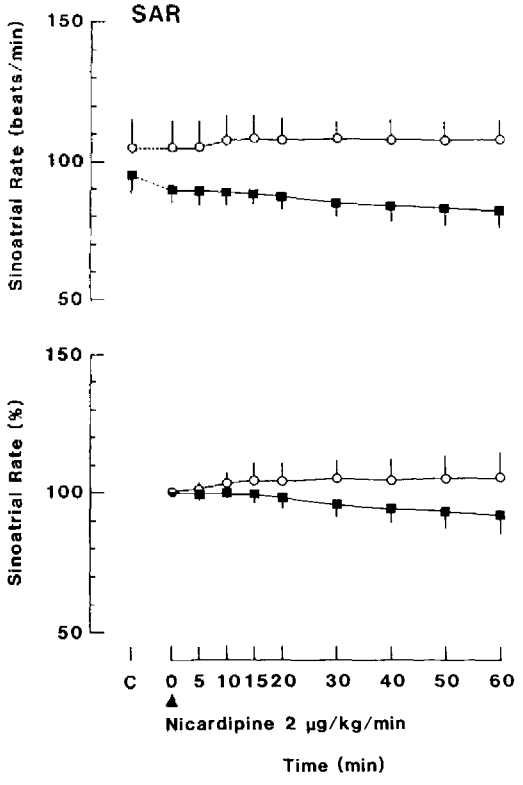


**Fig. 6.** The effects of nicardipine infusion on sinoatrial rate of the sinoatrial node preparations. All symbols and expressions are the same as those in figure 1.

ative, inotropic agent[8,9] whose suppressive mechanism (s) of enflurane's depressive effect is not certain, it may be due to a decrease in the rate of calcium entry, a decrease in the rate of release of calcium from the sarcoplasmic reticulum (SR) or a decrease in calcium available for release from the SR[10]. Nicardipine has a depressive effect on calcium entry through sarcolemmal channels (L-type $Ca^{++}$ channel)[11]. In addition, nicardipine binds to batrachotoxin-sensitive sodium channels and thereby reduces intracellural sodium and subsequently inhibits sodium-calcium exchange[11] resulting in a reduced intracellular calcium concentration. These may account for the potentiation of the negative inotropic effect observed in the present study.

The posibility that potentiation of nicardipine's negative inotropic effect might be due to an increase in the plasma concentration of nicardipine in the face of enflurane anesthesia was thought based on earlier hemodynamic studies[12–14]. Chelly et al.[13,14] proposed that the enhanced suppressive hemodynamic effects of varapamil by inhalatin anesthetics were due to an increase in plasma concentration of verapamil during the inhalation anesthesia. The increase resulted from the

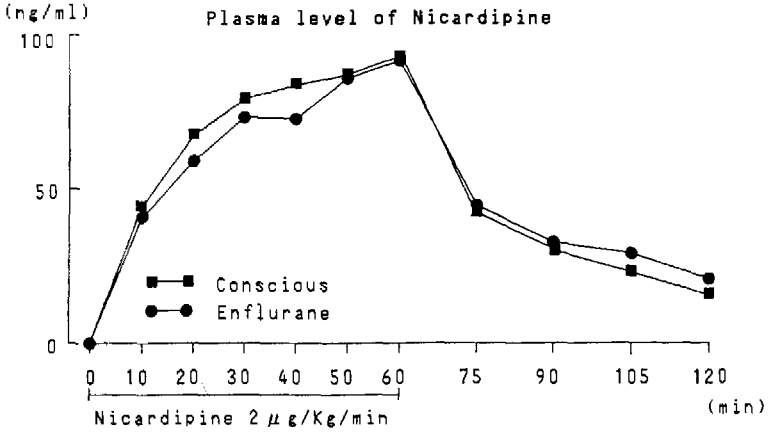


**Fig. 7.** The arterial plasma concentrations of nicardipine continuously infusion at a rate of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ into concious (solid squares) and enflurane anesthetized (solid circles) donor dogs.

reduced hepatic blood flow and from the reduced hepatic elimination of verapamil. The same explanation was proposed for diltiazem by Kapur et al.[12], since the plasma concentrations of diltiazem in enflurane-anesthetized dogs were higher than those in isoflurane-anesthetized dogs for the same diltizem infusion rates. In our previous report[1] arterial plasma concentration of diltiazem also was greater during enflurane anethesia than during the conscious state. In the present experiments, however, there was no difference in the plasma concentration of nicardipine at any time between the two groups (fig. 7).

The changes in SAR of SNP both during conscious state and during enflurane anesthesia reflects the direct effects of nicardipine. In the donor dog, DHR was increased by nicardipine in the conscious state, but not significantly. The DHR was suppressed by enflurane itself, and was further decreased significantly by nicardipne infusion during enflurane anesthesia. On the other hand, the SAR did not change either during conscious state or during enflurane anesthesia. These results suggest that reflex tachycardia was inhibited by enflurane anesthesia, and the SAR of isolated SNP did not change. Hysing et al.[15] reported that the tachycardiac properties of nicardipine were blunted in the presence of isoflurane. Kishi et al.[16] also reported that nicardipine did not affect heart rate in patients anesthetized with high doses of fentanyl.

In conclusion, enflurane may potentiate the cardiovascular effects of nicardipine and may eliminate compensatory reflex via the varoreceptors. Nicardipine should be used carefully during enflurane anesthesia, because severe hypotension could occur.

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