J Anesth (1994) 8:78–83

Journal of
Anesthesia

© JSA 1994

Effects and interaction of nicardipine and volatile anesthetics in the rat heart-lung preparation

Satoshi Kashimoto, Toshihiro Nakamura, Masaki Kume, Akihiko Nonaka, and Teruo Kumazawa

Department of Anesthesiology, Yamanashi Medical University, Shimokato 1110, Tamaho-cho, Nakakoma-gun, Yamanashi-ken, 409-38 Japan

Abstract: The effects of the calcium channel blocker nicardipine (N) and the volatile anesthetics halothane (H), enflurane (E), isoflurane (I), and sevoflurane (S) on myocardial metabolism after postischemic reperfusion were assessed in the isolated rat heart-lung preparation. Wistar-ST rats were randomly divided into six groups (each group $n = 9$) as follows: control (C) group, no drugs; N group, N (100 ng·ml^{-1}); H group, 1% H and N; E group, 2.2% E and N; I group, 1.5% I and N; and the S group, 3.3% S and N. In the presence of the volatile anesthetics, the preparations were perfused for 10 min, made globally ischemic for 8 min, and then reperfused for 10 min. N 100 ng·ml^{-1} was administered 5 min before ischemia except in the C group. Three hearts in the C and H groups (each $n = 9$) and one heart in the E group ($n = 9$) failed to recover from ischemia. The recovery times in the N, I and S groups were significantly shorter than controls. Although there was no significant difference in myocardial lactate concentrations among the groups, ATP content in the N, H, E, I and S groups was significantly higher than in controls. Glycogen content in the N, E, I and S groups was also significantly higher than in controls. These results suggest that N improves myocardial recovery from ischemia; however, in the presence of H or E it may cause significant myocardial depression.

Key words: Myocardial energy metabolism, Nicardipine, Volatile anesthetics

Introduction

Nicardipine is a water-soluble, light-insensitive dihydropyridine derivative and relatively selective for vascular smooth muscle [1,2]. It interferes with a calcium-dependent slow current across excitable cell membranes. Volatile anesthetics also decrease free calcium availability for contraction and probably interfere with several different steps in the excitation-contraction coupling process [3–6]. Significant cardiovascular interactions are likely to occur because of the similar pharmacological effects of these drugs. We knew of no other study of the direct effects of four volatile anesthetics and nicardipine on the isolated heart.

The aim of this study was to assess the direct cardiac effects of nicardipine in the presence of halothane, enflurane, isoflurane, and sevoflurane in the isolated heart-lung preparation. This technique eliminates any confounding neurohumoral effects of in vivo studies and can be used to determine any functional and metabolic effects of the interactions.

Materials and methods

The study was approved by the animal care committee of Yamanashi Medical University. The techniques used were almost identical to those used in earlier studies [7,8]. Briefly, 54 male Wistar-ST rats (300–320 g) were randomly divided into six groups (each group $n = 9$) as follows: (1) the control (C) group which received no drugs; (2) the nicardipine (N) group which received nicardipine (100 ng·ml^{-1}); (3) the halothane (H) group which received 1% halothane and nicardipine; (4) the enflurane (E) group which received 2.2% enflurane and nicardipine; (5) the isoflurane (I) group which received 1.5% isoflurane and nicardipine; and (6) the sevoflurane (S) group which received 3.3% sevoflurane and nicardipine. All rats, except in the C and N groups, were anesthetized with each volatile anesthetic in each group. Animals in the C and N groups were anesthetized with isoflurane during the preparation. Tracheostomy was performed, and intermittent positive pressure ventilation was adjusted to maintain P_aCO_2 at 4.7–5.3 kPa and P_aO_2 at 40–53 kPa with a 95% O_2 + 5% CO_2 gas mixture. The chest was opened and flooded with ice-cold saline and the heart arrested. Cannulae were inserted

Address correspondence to: S. Kashimoto
Received for publication on February 23, 1993; accepted on April 14, 1993

into the aorta and the superior and inferior vena cavae. The cannula in the superior vena cava was used for monitoring the right atrial pressure.

The heart-lung preparation was perfused with a solution containing red blood cells collected from another rat and Krebs-Ringer bicarbonate buffer, with hematocrit and pH of 25% and 7.4, respectively. The concentrations (mM) of the buffer constituents were: NaCl 127, KCl 5.1, $CaCl_2$ 2.2, KH_2PO_4 1.3, $MgSO_4$ 2.6, $NaHCO_3$ 15, glucose 5.5, and heparin. The perfusate blood pumped from the aorta passed through a pneumatic resistance and was collected in a reservoir maintained at 37°C and then returned to the inferior vena cava. In this model, no other organs except the heart and lung were perfused, cardiac output was determined by the inflow as long as the heart did not fail, and mean arterial pressure was regulated by the pneumatic resistance.

Heart rate was recorded with a bioelectric amplifier (AB-621G, Nihon Kohden, Tokyo, Japan) and cardiac output was measured with an electromagnetic blood flow meter (MFV-1200, Nihon Kohden). Arterial pressure and right atrial pressure were measured with transducers (TP101T and LPU-0.1A) and carrier amplifiers (AP-621G, Nihon Kohden).

All hearts were perfused initially with cardiac output of 30 ml·min^{-1} and mean arterial pressure of 80 mmHg. In the four anesthetic groups, each anesthetic was added to the gas mixture using calibrated vaporizers throughout the experiment. Nicardipine, 100 ng·ml^{-1}, was administered 5 min after the start of perfusion except in the C group. Ten minutes after the start of perfusion, all hearts were made globally ischemic for 8 min by clamping the venous return and reducing the pneumatic resistance to zero. Subsequently, the preparations were reperfused for 10 min by regulating the venous return and the pneumatic resistance. The recovery time was recorded when the cardiac output and the mean arterial pressure returned to preclamping values. At the end of the experimental period, the hearts were freeze-clamped and freeze-dried for 6 days. An aliquot was extracted with perchloric acid and centrifuged at 3000 rpm. Myocardial high energy phosphates (ATP, ADP and AMP) were measured by high performance liquid chromatography (HPLC) [9]. The lactate level was determined spectrophotometrically by standard techniques [10]. Another piece of freeze-dried sample was placed in 30% KOH and digested at 100°C. Tissue glycogen was extracted, hydrolyzed, and assayed as glucose equivalents [11]. The values were expressed as micromoles per gram of dry weight.

Hemodynamic data within groups were analyzed by two-way analysis of variance (ANOVA) with repeated measures. Recovery time was analyzed by the Kruskal-Wallis test. The other data were analyzed by one-way ANOVA followed by the Dunnett test for multiple comparisons. A probability of $P < 0.05$ was regarded as statistically significant. The data are given as mean ± S.D.

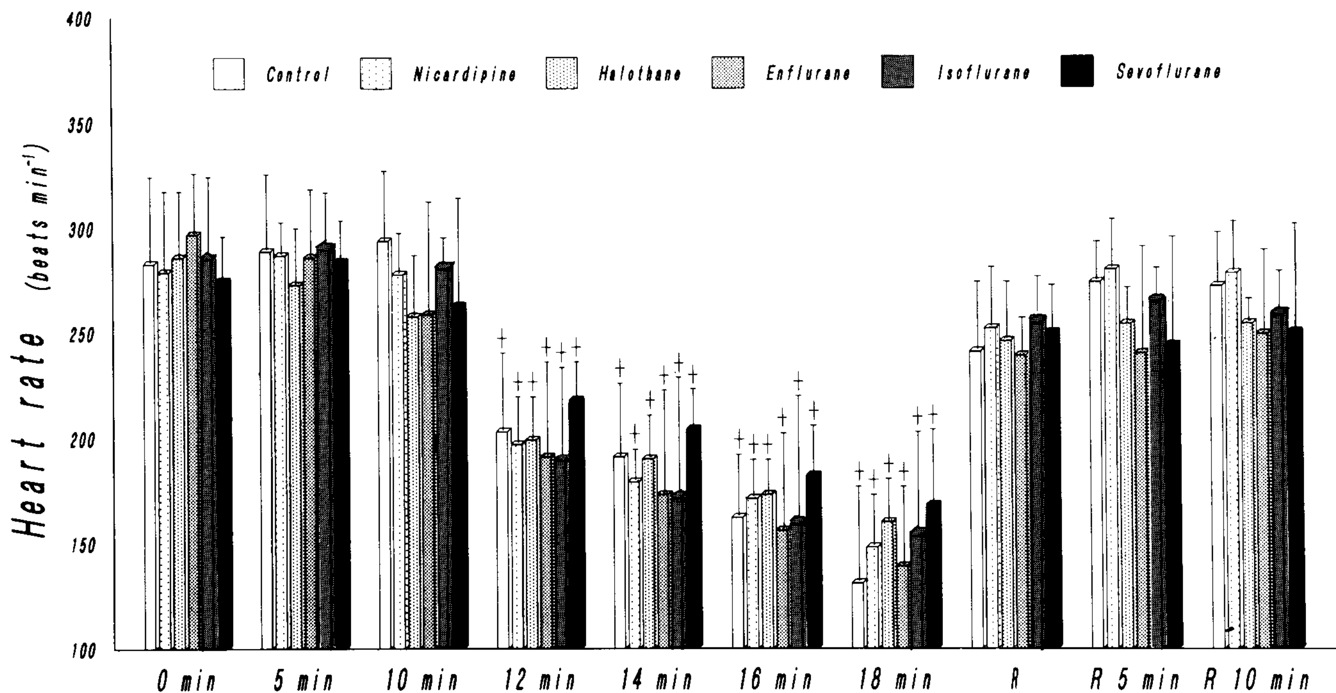

Fig. 1. Heart rate changes. Each group; $n = 9$. $^{+}P < 0.05$, as compared with the values at 0 min

Results

As expected, the heart rate in all groups decreased significantly during ischemia. However, there were no significant differences in heart rate among the groups (Fig. 1). Right atrial pressure in the E group increased significantly at 10 min and 5 min after the recovery (Fig. 2). Cardiac output in the C group decreased significantly after ischemia. Cardiac output in the N, I, and S groups were greater than that in the C group after ischemia, but those in the H and E groups were not (Fig. 3). Three of nine control hearts did not recover after ischemia. How-

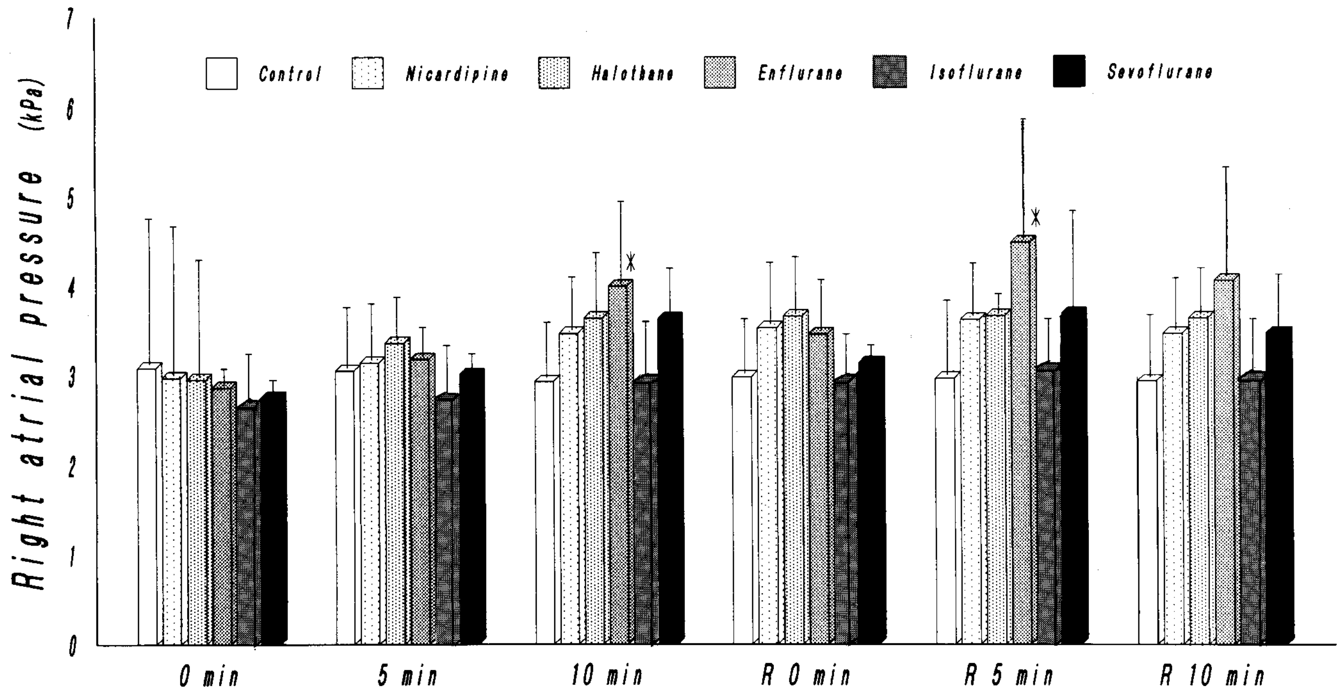

Fig. 2. Right atrial pressure changes. Each group; $n = 9$. $^{*}P < 0.05$, as compared with the control group

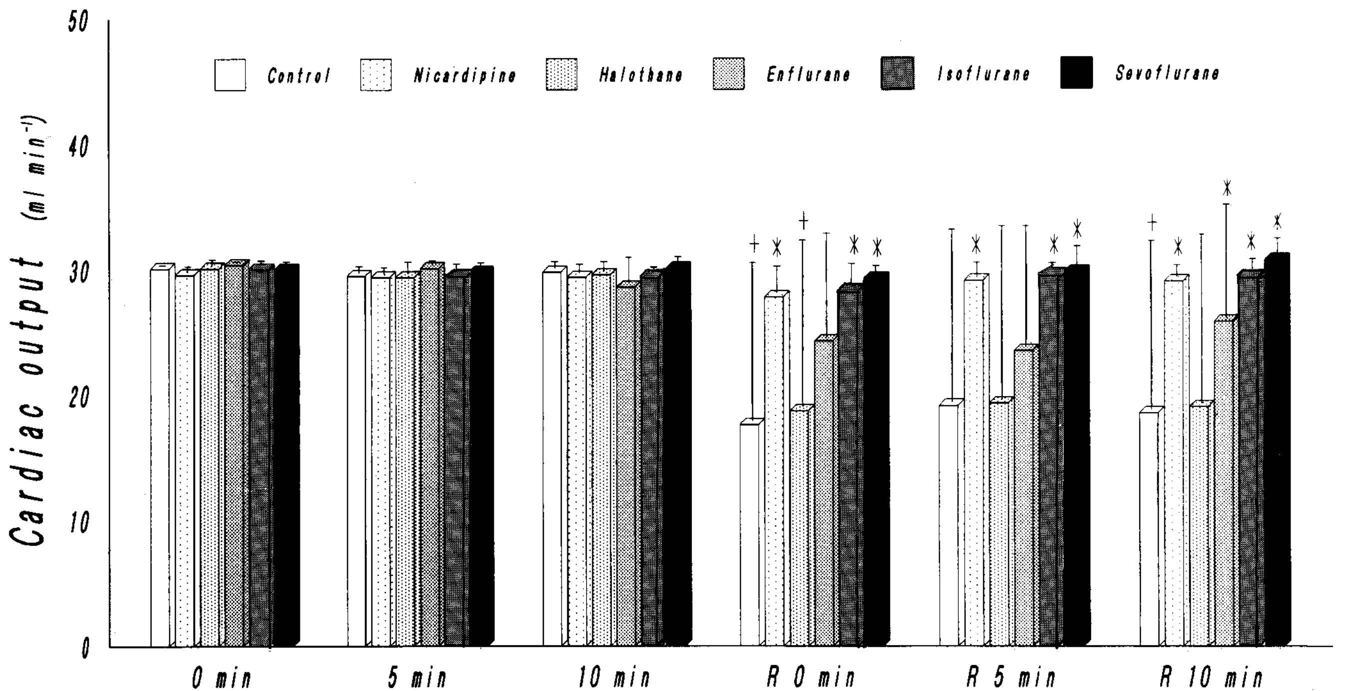

Fig. 3. Cardiac output changes. Each group; $n = 9$. $^{+}P < 0.05$, as compared with the values at 0 min; $^{*}P < 0.05$, as compared with the values in the control group

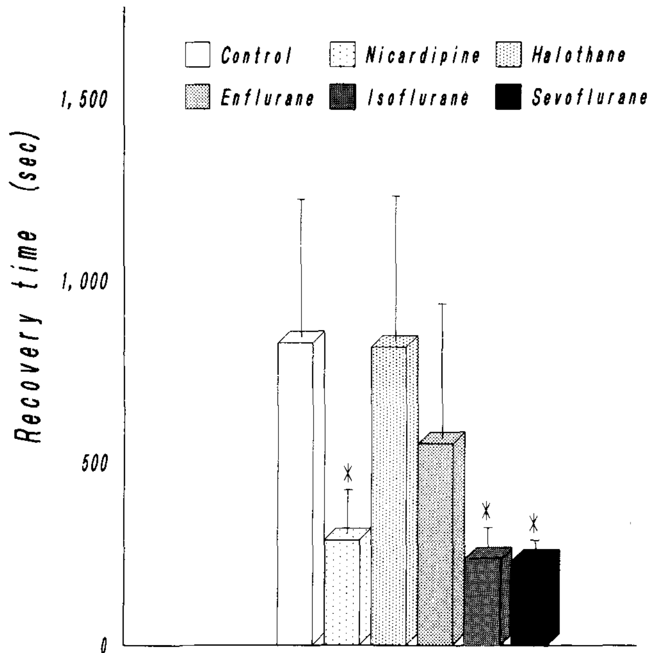

Fig. 4. Recovery time. Each group; $n = 9$. $^*P < 0.05$, as compared with the values in the control group

ever, all nine hearts in the N group recovered quickly. Three hearts in the H group and one in the E group did not recover after ischemia and the recovery time in the N, I, and S groups was significantly shorter than that in the C group (Fig. 4).

Although there were no significant differences in myocardial ADP and AMP levels among the groups, ATP in the N and in all anesthetic groups was significantly higher than that in the C group (Fig. 5). Myocardial glycogen content in the N, E, I, and S groups was significantly higher than that in the C group. There was no significant difference in lactate levels among any of the groups (Fig. 6).

Discussion

Nicardipine is a second-generation dihydropyridine calcium channel antagonist, which is relatively selective for vascular smooth muscle [1]. It appears to have little cardiodepressant action in the experimental animal [12], and has been shown to improve indices of cardiac performance in normal volunteers [13] and in patients with coronary artery disease [14,15]. Beneficial actions have also been described in acute myocardial infarction [16] and in chronic heart failure [17,18]. During anesthesia, the use of nicardipine is reportedly associated with a dose-dependent decrease in mean arterial pressure, without significant changes in filling pressures and heart rate [19,20]. However, van Wezel et al. [21] reported that nicardipine was associated with increases in heart rate after sternotomy during fentanyl anesthesia. However, in the present study, nicardipine did not show any significant changes in heart rate with or without volatile

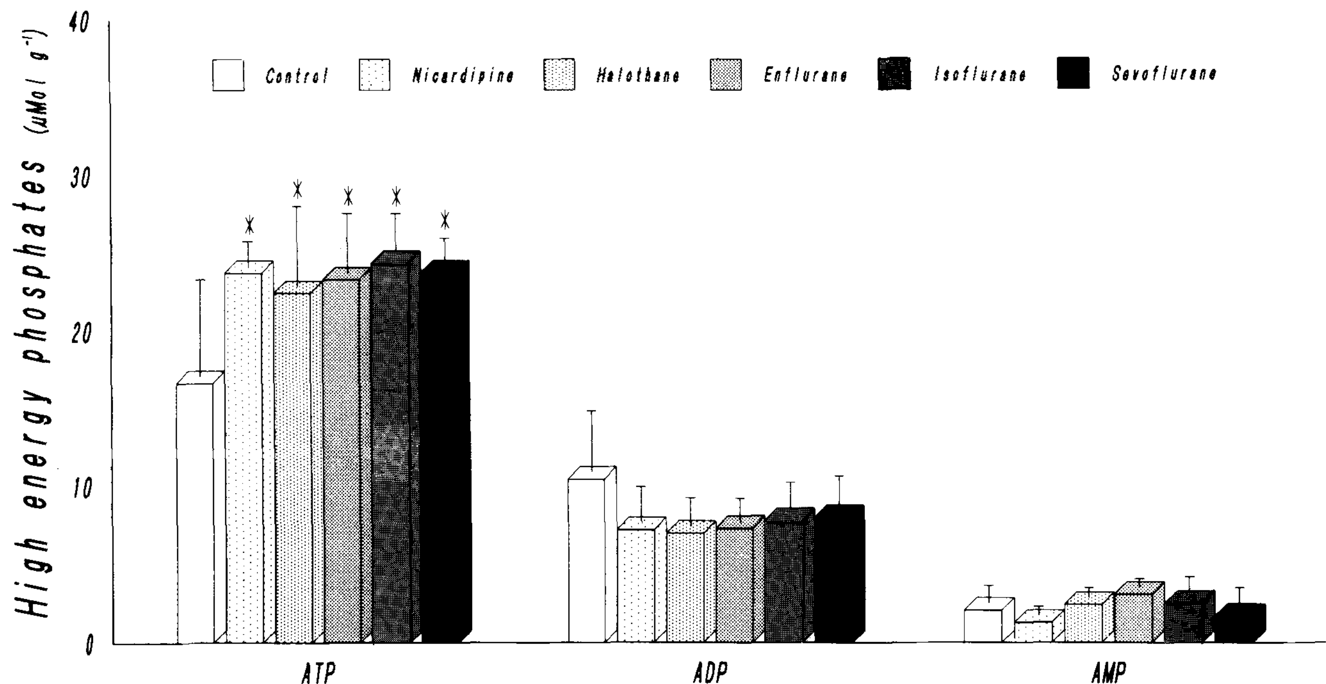

Fig. 5. Myocardial high-energy phosphate concentrations. Each group; $n = 9$. $^*P < 0.05$, as compared with the values in the control group

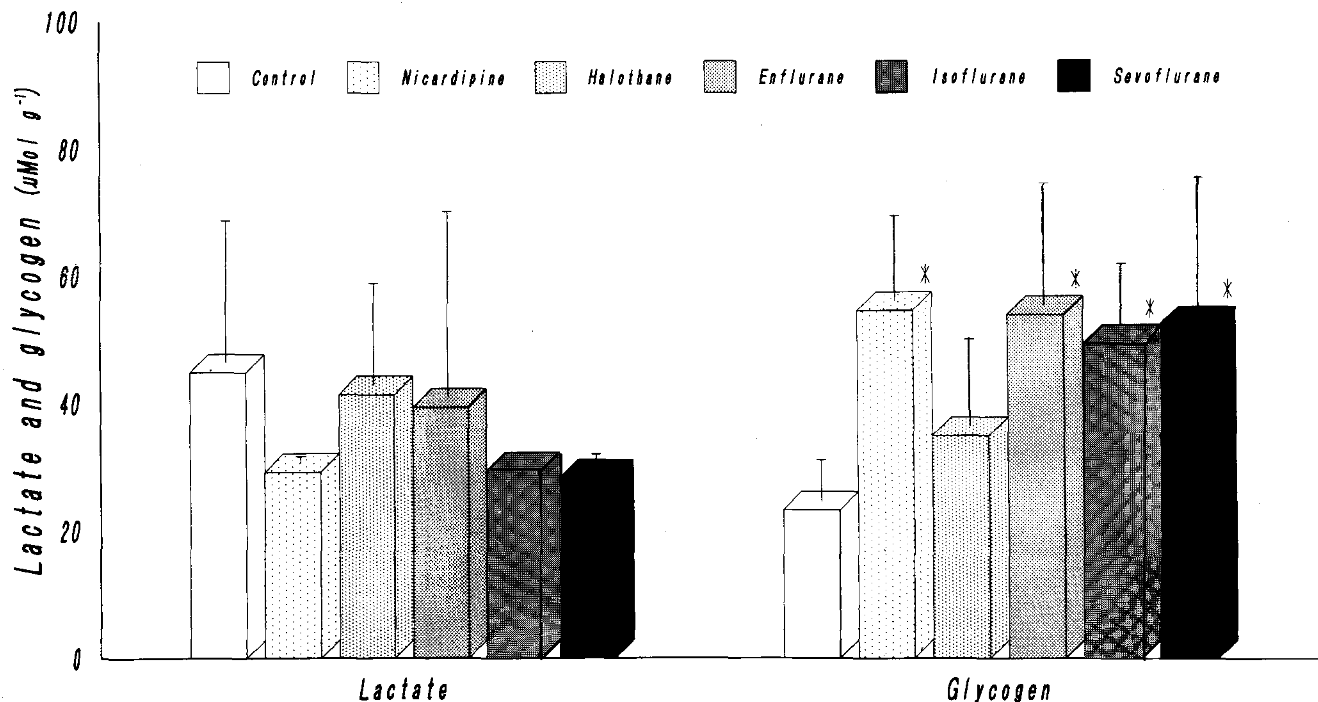

Fig. 6. Myocardial lactate and glycogen concentrations. Each group; $n = 9$. *$P < 0.05$, as compared with the values in the control group

anesthetics. This may be because autonomic, acid-base balance, and circulating hormonal influences were absent in the experimental model.

It is well known that ischemia results in a decrease in the intracellular concentration of high-energy phosphates [22,23]. In the present study, nicardipine enhanced the recovery from ischemia and increased the myocardial ATP level at the end of reperfusion. Calcium antagonists have been reported to have beneficial effects in models of isolated hearts [24]. These effects may result from a decrease in myocardial oxygen demand as well as an inhibition in transmembrane flux of calcium into the myocyte and preservation of sarcolemmal membrane permeability.

Nicardipine showed the beneficial effects on function and metabolism in the ischemic rat heart, but nicardipine plus halothane or enflurane lacked these beneficial effects during post-ischemic reperfusion. As a result, the combination of nicardipine and halothane showed, to a lesser extent, decreased glycogen metabolism in the myocardium, although enflurane did not indicate any metabolic derangement and there was no significant difference in high-energy phosphate compounds among the anesthetic groups. It is likely that anaerobic glycogenolysis during ischemia would have occurred more in the H group than the other groups. The difference between halothane and enflurane may be reflected in the fact that three hearts in the H group did not recover after ischemia wheares only one heart in the E group did not. Reves et al. [25] have suggested that there is considerable potential for drug interactions related to the cardiovascular system between general anesthetic drugs and calcium antagonists. We have also reported that the combination of verapamil and halothane caused a significant increase in recovery time together with decreases in the myocardial ATP and glycogen contents in the same model [8]. Halothane and enflurane may have more depressant effect on the heart than isoflurane or sevoflurane. In fact, there are many in vitro reports indicating that isoflurane is a weaker cardiac depressant than halothane or enflurane [26–30]. In addition, the cardiovascular effects of sevoflurane are comparable to those of isoflurane [31–33]. These results suggest that additive depressant effects of halothane or enflurane and calcium antagonists are more likely to occur than with isoflurane or sevoflurane.

There was no significant difference in myocardial lactate concentrations among the groups. We have previously reported that halothane or enflurane [7], but not isoflurane [34] or sevoflurane [35], increased intramyocardial lactate concentrations after postischemic reperfusion, suggesting a deterioration in myocardial oxidation-reduction state. In this study, however, halothane or enflurane plus nicardipine did not increase myocardial lactate levels after postischemic reperfusion. Nicardipine appears to have a protective effect possibly by maintaining cellular integrity by reducing

calcium influx and to have improved myocardial redox state.

Extrapolation of in vitro animal studies to human clinical experience is difficult, but our results suggest that the combination of nicardipine and halothane or enflurane should be used with caution.

Acknowledgments. The authors are indebted to Mr. Koshimizu and Miss Amemiya for their technical assistance and Miss Asakawa for her secretarial assistance. This study was presented at the XIV World Congress of the International Society for Heart Research in 1992.

References

1. Seki T, Takenaka T (1977) Pharmacological evaluation of YC-93, a new vasodilator, in healthy male volunteers. Int J Clin Pharmacol 15:267–274
2. Hof RP (1983) Calcium antagonist and the peripheral circulation: differences and similarities between PY 108-068, nicardipine, verapamil and diltiazem. Br J Pharmacol 78:375–394
3. Rusy BF, Komai H (1987) Anesthetic depression of myocardial contractility: a review of possible mechanisms. Anesthesiology 67:745–766
4. DeTraglia MC, Komai H, Rusy BF (1988) Differential effects of inhalation anesthetics on myocardial potentiated-state contractions in vitro. Anesthesiology 68:534–540
5. Shibata T, Blanck TJJ, Sagawa K, et al. (1989) The effects of halothane, enflurane, and isoflurane on the dynamic stiffness of rabbit papillary muscle. Anesthesiology 70:496–502
6. Lynch C, Frazer MJ (1989) Depressant effects of volatile anesthetics upon rat and amphibian ventricular mechanisms of action. Anesthesiology 70:511–522
7. Kashimoto S, Tsuji Y, Kumazawa T (1987) Effects of halothane and enflurane on myocardial metabolism during postischaemic reperfusion in the rat. Acta Anaesthesiol Scand 31:44–47
8. Kashimoto S, Oguchi M, Kume M, et al. (1990) Interaction between calcium blockers and volatile anaesthetics in the rat heart-lung preparation. Br J Anaesth 64:601–605
9. Wynants J, Belle HV (1985) Single-run high-performance liquid chromatography of nucleotides, nucleosides, and major purine bases and its application to different tissue extracts. Anal Biochem 144:258–266
10. Bergmeyer HU (1975) Neue Werte für die molaren Extinktions-Koeffizienten von NADH und NADPH zum Gebrauch im Routine-Laboratorium. Zeit Klin Chem Klin Biochem 13:507–508
11. Werner W, Rey H-G Wielinger H. (1970) Über die Eigenschaften eines neuen Chromogens für die Blutzuckerbestimmung nach der GOD/POD-Methode. Zeit Anal Chem 252:224–228
12. Schiantarelli P, Ferrari R, Razzetti R, et al. (1983) The "in vivo" and "in vitro" effects of nicardipine on coronary resistance and myocardial performance. J Mol Cell Cardiol 15 [Suppl. I]:228
13. Iliopoulou A, Turner P, Warrington SJ (1983) Acute haemodynamic effects of a new calcium antagonist, nicardipine, in man. A comparison with nifedipine. Br J Clin Pharmacol 15:59–66
14. Silke B, Verma SP, Nelson GIC, et al. (1984) Haemodynamic dose-response effects of i.v. nicardipine in coronary artery disease. Br J Clin Pharmacol 18:717–724
15. Silke B, Graham DJM, Verma SP, et al. (1986) Pharmacokinetic, haemodynamic and radionuclide studies with nicardipine in coronary artery disease. Eur J Clin Pharmacol 29:651–657
16. Silke B, Verma SP, Hafizullah M, et al. (1984) Haemodynamic effects of nicardipine in acute myocardial infarction. Postgrad Med J 60 [Suppl. IV]:29–34
17. Lahiri A, Robinson CW, Tovey J, et al. (1984) Intravenous nicardipine in patients with chronic heart failure: a nuclear stethoscope study. Postgrad Med J 60 [Suppl. IV]:35–38
18. Ryman KS, Kubo SH, Lystash J, et al. (1986) Effect of nicardipine on rest and exercise hemodynamics in chronic congestive heart failure. Am J Cardiol 58:583–588
19. Kishi Y, Okumura F, Furuya H (1984) Haemodynamic effects of nicardipine hydrochloride. Br J Anaesth 56:1003–1007
20. Hysing ES, Chelly JE, Doursout MF, et al. (1986) Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. III. Nicardipine and isoflurane. Anesthesiology 65:385–391
21. van Wezel HB, Koolen JJ, Visser CA, et al. (1989) Antihypertensive and anti-ischemic effects of nicardipine and nitroprusside in patients undergoing coronary artery bypass grafting. Am J Cardiol 64:22H–27H
22. Reimer K, Hill M, Jennings RB (1981) Prolonged depletion of ATP and of the adenine nucleotide pool due to delayed resynthesis of adenine nucleotides following reversible myocardial ischemic injury in dogs. J Mol Cell Cardiol 13:229–239
23. Schaper J, Mulch J, Winkler B, et al. (1979) Ultastructural, functional, and biochemical criteria for estimation of reversibility of ischemic injury: A study on the effects of global ischemia on the isolated dog heart. J Mol Cell Cardiol 11:521–541
24. Kloner RA (1988) Calcium channel blockade during ischemia-reperfusion sequences. J Mol Cell Cardiol 20:457–458
25. Reves JG, Kissin I, Lell WA, et al. (1982) Calcium entry blockers: Uses and implications for anesthesiologists. Anesthesiology 57:504–518
26. Marijic J, Bosnjak ZJ, Stowe DF, et al. (1988) Effects and interaction of verapamil and volatile anesthetics on the isolated perfused guinea pig heart. Anesthesiology 69:914–922
27. Housmans PR, Murat I (1988) Comparative effects of halothane, enflurane and isoflurane at equipotent anesthetic concentrations on isolated ventricular myocardium of the ferret. I: Contractility. Anesthesiology 69:451–461
28. Stowe DF, Marijic J, Bosnjak Z, et al. (1991) Direct comparative effects of halothane, enflurane, and isoflurane on oxygen supply and demand in isolated hearts. Anesthesiology 74:1087–1095
29. Stowe DF, Monroe S, Marijic J, et al. (1991) Comparison of halothane, enflurane, and isoflurane with nitrous oxide on contractility and oxygen supply and demand in isolated hearts. Anesthesiology 75:1062–1074
30. Bosnjak ZJ, Aggarwal A, Turner LA, et al. (1992) Differential effects of halothane, enflurane, and isoflurane on Ca^{2+} transients and papillary muscle tension in guinea pigs. Anesthesiology 76:123–131
31. Kazama T, Ikeda K (1988) The comparative cardiovascular effects of sevoflurane, halothane and isoflurane. J Anesth 2:63–68
32. Bernard J, Wouters PF, Doursout M, et al. (1990) Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically istrumented dogs. Anesthesiology 72:659–662
33. Conzen PF, Vollmar B, Habazettl H, et al. (1992) Systemic and regional hemodynamics of isoflurane and sevoflurane in rats. Anesth Analg 74:79–88
34. Kashimoto S (1988) Effects of isoflurane on myocardial metabolism during postischaemic reperfusion in the rat. Acta Anaesthesiol Scand 32:199–202
35. Kashimoto S, Oguchi T, Kume M, et al. (1989) Effects of sevoflurane on myocardial metabolism during postischemic reperfusion in the rat. J Anesth 3:23–26