J Anesth (1996) 10:199–203

Journal of
Anesthesia

Effect of nicardipine on vascular capacitance: comparison with sodium nitroprusside during induced hypotension

JU-TAE SOHN, SUMIO HOKA, KEN YAMAURA, and SHOSUKE TAKAHASHI

Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-82, Japan

Abstract: The purpose of this study was to examine the effects of nicardipine and sodium nitroprusside (SNP) on vascular capacitance in the rat. In ten rats anesthetized with pentobarbital, mean arterial pressure was lowered to about 70 mmHg and subsequently 50 mmHg by intravenous infusion of nicardipine or SNP. Vascular capacitance was assessed before and during nicardipine- or SNP-induced hypotension by measuring the mean circulatory filling pressure (MCFP). MCFP was measured during a brief period of circulatory arrest produced by inflating a balloon inserted in the right atrium. MCFP was significantly decreased by SNP from 7.1 ± 0.3 mmHg at control to 5.6 ± 0.4 mmHg and 4.4 ± 0.3 mmHg at mean arterial pressures of 70 mmHg and 50 mmHg, respectively. However, MCFP stayed at a similar level to that of the control during nicardipine-induced hypotension. These results suggest that nicardipine has a negligible influence on vascular capacitance during induced hypotension, whereas SNP has a potent vasodilating effect on the venous system as well as the arterial system.

Key words: Mean circulatory filling pressure, Sodium nitroprusside, Nicardipine, Induced hypotension, Vascular capacitance

Introduction

Vasodilator agents are used for induced hypotension during anesthesia in order to decrease blood loss, thereby improving operating conditions or decreasing the need for blood transfusion. Sodium nitroprusside (SNP), a drug commonly used to induce hypotension, has several advantages such as rapid onset, short duration of action, and easy controllability of blood pressure but also has undesirable side effects, including tachyphylaxis and cyanide toxicity [1]. On the other hand, nicardipine, a dihydropyridine calcium channel blocking agent, is widely used for the treatment of hypertension. It has recently been reported that nicardipine can be used for induced hypotension under anesthesia in patients undergoing orthopedic surgery [2,3]. These human studies have compared hemodynamic changes during hypotension induced by SNP and nicardipine [2,3]. However, there have been few studies concerning the effects of nicardipine on the venous system during induced hypotension. The venous system is necessary for control of circulation not only as a conduit but also as a reservoir of the circulatory blood [4]. Since a small change in vascular capacitance significantly alters venous return to the heart and thus affects cardiac output [4], it is important to know the effects of nicardipine and SNP on vascular capacitance, particularly during induced hypotension under general anesthesia. An alteration in vascular capacitance can be assessed by measuring mean circulatory filling pressure (MCFP) [5]. In this study, we examined the effect of nicardipine and SNP on MCFP during induced hypotension in rats.

Methods

Surgical preparation

Ten Wistar rats, weighing 300–400 g, were used for this experiment. The rats were anesthetized with pentobarbital 50 mg·kg^{-1} given intraperitoneally. When tail pinch responses were observed in the rats, a small supplemental dose of pentobarbital was given as necessary to maintain a constant and adequate anesthetic state during the experiment. After tracheostomy, the rats were mechanically ventilated using a Harvard res-

Address correspondence to: S. Hoka

Received for publication on December 25, 1995; accepted on March 22, 1996

Dr. Sohn is a visiting scientist from the Department of Anesthesiology, College of Medicine, Gyeong-Sang National University and Hospital, Chinju, Korea.

pirator with oxygen to maintain Pao_2 and $Paco_2$ at physiological levels. Two catheters (Argyle 20G, Nippon Sherwood, Tokyo, Japan) were placed in the left femoral artery and vein and connected to pressure transducers for recording arterial and central venous pressure, respectively. The arterial catheter was advanced to the iliac bifurcation, and the venous catheter was positioned in the abdominal inferior vena cava. The proper position of the venous catheter was confirmed by a synchronous change of the venous pressure with respiration. A balloon-tipped catheter was placed in the right atrium through the right external jugular vein, and the proper location was tested by injecting 0.3 ml of air into the balloon to stop the circulation completely. When the characteristic smooth increase in venous pressure and simultaneous decrease in arterial pressure to less than 30 mmHg were not observed, the balloon was repositioned. The right femoral vein was also cannulated (Argyle 20G, Nippon Sherwood) and used as a drug infusion route.

Measurement of MCFP

MCFP was measured by the method introduced by Yamamoto et al. [6]. Immediately after the balloon was inflated, arterial pressure decreased and venous pressure increased simultaneously (Fig. 1). Central venous pressure reached a plateau within 4–5 s. Since arterial and venous pressure during circulatory arrest were not in complete equilibrium, MCFP was calculated according to the following equation:

$$MCFP = VPP + K(FAP - VPP)$$

where VPP is the venous plateau pressure, FAP is the final arterial pressure, and K is the ratio of the arterial to venous compliance. In accordance with the report by Yamamoto et al. [6], a K value of 1/60 was used in this experiment.

Protocol

Mean arterial pressure (MAP), heart rate, and central venous pressure (CVP) were measured in the control state as well as during nicardipine- or SNP-induced hypotension. Each rat received both nicardipine and SNP. The order of drug administration was randomized. The drugs were diluted in normal saline. Two stages of induced hypotension such as moderate hypotension and deep hypotension were elicited at a MAP of approximately 70 mmHg and 50 mmHg, respectively. MCFP was obtained at control and during moderate and deep hypotension. At least 20 min was allowed between MCFP measurements, and more than 1 h was allowed after nicardipine infusion until the start of SNP infusion, because nicardipine has a relatively long half-life [7].

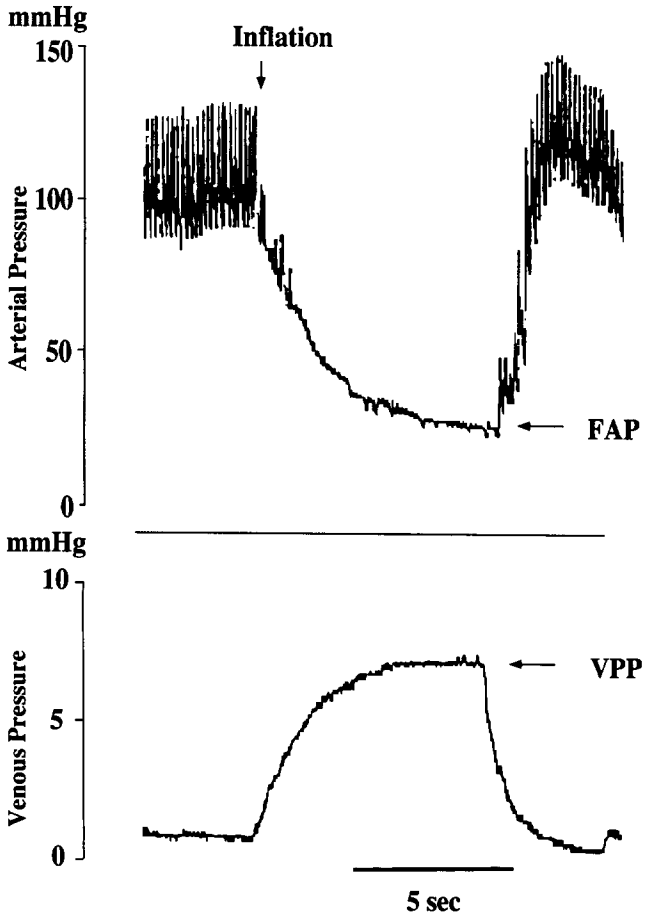

Fig. 1. Recording of arterial pressure and venous pressure during inflation of the balloon. Arterial pressure decreased and venous pressure increased and plateaued about 5 s after inflation. *FAP*, final arterial pressure; *VPP*, venous plateau pressure

Doses of nicardipine were 25 ± 9 and 55 ± 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at moderate and deep hypotension, respectively. Doses of SNP were 11 ± 3 and 25 ± 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at moderate and deep hypotension, respectively.

Statistical analysis

Data were expressed as mean ± SE (standard error of mean). Repeated measures of analysis of variance (ANOVA) were used for comparison of results, followed by Scheffé's test. $P < 0.05$ was considered as significant.

Results

Table 1 summarizes the values for MAP, heart rate, and CVP in the control state as well as during nicardipine- and SNP-induced hypotension. The MAP decreased

Table 1. Mean arterial pressure (MAP), heart rate, central venous pressure (CVP), and mean circulatory pressure (MCFP) at control and during moderate and deep hypotension induced by nicardipine or SNP (sodium nitroprusside)

	MAP (mmHg)	heart rate (beats·min^{-1})	CVP (mmHg)	MCFP (mmHg)
Control				
Nicardipine	103 ± 4	414 ± 9	1.3 ± 0.2	6.5 ± 0.2
SNP	98 ± 2	415 ± 8	1.6 ± 0.2	7.1 ± 0.3
Moderate hypotension				
Nicardipine	70 ± 2[a]	373 ± 15[a,c]	1.7 ± 0.2	6.6 ± 0.2[c]
SNP	69 ± 1[a]	413 ± 9	1.5 ± 0.2	5.6 ± 0.4[a]
Deep hypotension				
Nicardipine	54 ± 4[a,b]	317 ± 18[a,c]	1.5 ± 0.2	6.1 ± 0.2[c]
SNP	51 ± 2[a,b]	396 ± 11	1.4 ± 0.2	4.4 ± 0.3[a,b]

$n = 10$ for Nicardipine and SNP. Values are expressed as mean ± SE.
[a] $P < 0.05$ vs control.
[b] $P < 0.05$ vs moderate hypotension.
[c] $P < 0.05$ vs SNP.

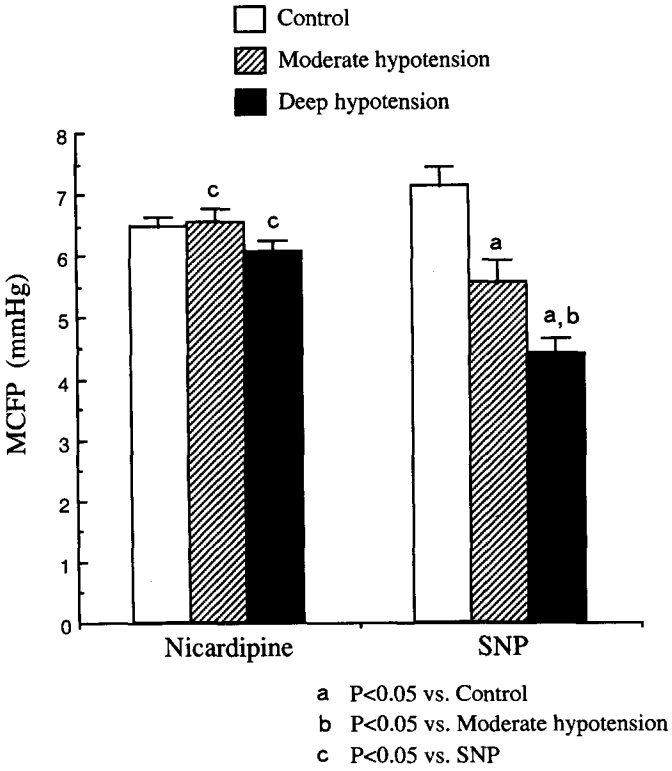

Fig. 2. Effects of nicardipine and sodium nitroprusside (*SNP*) on mean circulatory filling pressure (*MCFP*) during moderate hypotension at a mean arterial pressure of about 70 mmHg and during deep hypotension at mean arterial pressure of about 50 mmHg. Nicardipine did not alter MCFP during both moderate and deep hypotension as compared with the control, whereas SNP decreased MCFP depending on the extent of hypotension

to 70 ± 2 mmHg and 69 ± 1 mmHg at moderate hypotension and to 54 ± 4 mmHg and 51 ± 2 mmHg at deep hypotension in the nicardipine and SNP groups, respectively. The MAP and CVP were not significantly different between the nicardipine and SNP groups in the control state as well as at moderate and deep hypotension, but the heart rate significantly decreased during nicardipine-induced hypotension as compared with SNP-induced hypotension.

Figure 2 shows the values of MCFP in the control state and at moderate and deep hypotension produced by nicardipine and SNP. MCFP significantly decreased from 7.1 ± 0.3 to 5.6 ± 0.4 mmHg at moderate hypotension and to 4.4 ± 0.3 mmHg at deep hypotension in the SNP group, while MCFP in the nicardipine group was maintained from 6.5 ± 0.2 mmHg in the control, to 6.6 ± 0.2 mmHg at moderate hypotension, and to 6.1 ± 0.2 mmHg at deep hypotension. The MCFPs produced by nicardipine were significantly different from those in the SNP group at both moderate and deep hypotension.

Discussion

The principal finding of this study was that MCFP was maintained during nicardipine-induced moderate hypotension as well as deep hypotension at a level similar to that observed in the prehypotensive state. By contrast, during SNP-induced hypotension, MCFP significantly decreased and the decrease was greater at deep hypotension than that at moderate hypotension. MCFP is a function of total vascular capacitance and blood volume. Vascular capacitance is defined as the total contained volume of the vasculature at a given transmural pressure [4]. Capacitance vessels are primarily veins and venules. If blood volume is constant, the MCFP change reflects mostly an alteration of venous rather than arterial tone. Therefore, our results suggest that SNP increases vascular capacitance, but nicardipine does not alter it. This lack of effect of

nicardipine on the MCFP and vascular capacitance may contribute to maintaining venous return and thus cardiac output, since venous return to the heart is proportional to the difference between the MCFP and right atrial pressure.

The validity of this method for the measurement of MCFP has been discussed in previous reports [6,8]. It has been shown that MCFP obtained by this method is not different from MCFP obtained by the classical method using blood transfer from the arterial to the venous system after circulatory arrest [6]. A number of studies examining the effect of various vasoactive drugs [9–11] or anesthetic agents [8] on vascular capacitance have used this method.

Our results regarding the effect of SNP on MCFP or vascular capacitance are consistent with several previous reports [10,12]. D'Oyley et al. [10] found that SNP decreased MCFP in the conscious rat treated with hexamethonium but did not change MCFP in untreated rats, suggesting that SNP is an effective venous dilator but that its effect may be concealed by a reflex increase in sympathetic activity in the conscious state. Using extracorporeal circulation in deafferented dogs anesthetized with sodium thiopental, Hoka et al. [12] showed that SNP increased systemic blood volume by approximately $5\,ml \cdot kg^{-1}$ under constant CVP, indicating that SNP increases vascular capacitance. A plethysmography study has shown that SNP dilated human resistance vessels as well as capacitance vessels [13]. Thus, SNP is believed to cause venous dilatation and increase vascular capacitance.

Our results of the effect of nicardipine on MCFP are also in agreement with previous reports dealing with calcium antagonists. Waite et al. [14] reported that verapamil, nifedipine, and flunarizine caused an increase in MCFP compared with the corresponding control values in conscious rats, whereas after treatment of hexamethonium verapamil did not increase MCFP, suggesting that the calcium antagonists exert little effect on MCFP if the autonomic reflex modulation is excluded. In anesthetized open-chest dogs, a single dose of nicardipine has been shown to cause little effect on MCFP, although diltiazem was found to decrease MCFP [10]. The lesser effect of nicardipine on capacitance vessels than on resistance vessels is also supported by the finding that SK&F 24260, the same dihydropyridine derivative as nicardipine, preferentially dilates precapillary sphincter vessels to reduce resistance but has little effect on capacitance vessels [15]. In contrast, SNP has been shown to exert a powerful dilating effect on both resistance vessels and veins [16]. In addition, in patients receiving induced hypotension with nicardipine or SNP during total hip arthroplasty, Bernard et al. [3] have shown that the intravenous fluid volume required to maintain pulmonary capillary wedge pressure at 5 mmHg was larger in the SNP group than in the nicardipine group, which indirectly indicates that nicardipine has less of a dilatory effect on the venous system than SNP. However, there have been no studies examining the direct effect of nicardipine on MCFP in comparison with SNP at comparable hypotensive levels. Our study clearly shows that nicardipine maintains MCFP and thus vascular capacitance, whereas SNP decreases MCFP and thus increases vascular capacitance during induced hypotension in rats under pentobarbital anesthesia.

These differences between nicardipine and SNP in their effect on vascular capacitance should be taken into account when these drugs are used clinically. In patients with hypovolemia, SNP may accelerate a decrease in venous return and thus a decrease in cardiac output, whereas nicardipine may maintain venous return and cardiac output in that situation. On the other hand, in patients with congestive heart failure, an increase in vascular capacitance by SNP may be beneficial to reduce the preload and lessen the cardiac work simultaneously with the reduction of afterload, whereas the lack of venodilatation in nicardipine may be somewhat inconvenient in that condition.

References

1. Tinker JH, Michenfelder JD (1976) Sodium nitroprusside: pharmacology, toxicology and therapeutics. Anesthesiology 45:340–354
2. Bernard JM, Passuti N, Pinaud M (1992) Long-term hypotensive technique with nicardipine and nitroprusside during isoflurane anesthesia for spinal surgery. Anesth Analg 75:179–185
3. Bernard J-M, Pinaud M, François J, Macquin-Mavier I, Letenneur J (1991) Deliberate hypotension with nicardipine or nitroprusside during total hip arthroplasty. Anesth Analg 73:341–345
4. Rothe CF (1986) Physiology of venous return. An unappreciated boost to the heart. Arch Intern Med 146:977–982
5. Samar RE, Coleman TG (1978) Measurement of mean circulatory filling pressure and vascular capacitance in the rat. Am J Physiol 234:H94–H100
6. Yamamoto J, Trippodo NC, Ishise S, Frohlich ED (1980) Total vascular pressure-volume relationship in the conscious rat. Am J Physiol 238:H823–H828
7. Whiting RL, Dow RJ, Graham DJM, Mroszczak EJ (1990) An overview of the pharmacology and pharmacokinetics of nicardipine. Angiology 41:987–991
8. Hoka S, Takeshita A, Yamamoto K, Ito N, Yoshitake J (1985) The effects of ketamine on venous capacitance in rats. Anesthesiology 62:145–148
9. Ito H, Hirakawa S (1984) Effects of vasodilators on the systemic capacitance vessels, a study with the measurement of the mean circulatory pressure in dogs. Jpn Circ J 43:388–404
10. D'Oyley HM, Tabrizchi R, Pang CCY (1989) Effect of vasodilator drugs on venous tone in conscious rats. Eur J Pharmacol 162:337–344
11. Liang J, Hoka S, Okamoto H, Kawasaki T, Yoshitake J (1993) Changes in venous capacitance during prostaglandin E_1-induced hypotension; comparisons with trinitroglycerin. J Anesth 7:303–307
12. Hoka S, Siker D, Bosnjak ZJ, Kampine JP (1987) Alteration of

blood flow and vascular capacitance during induced hypotension in deafferented dogs. Anesthesiology 66:647–652
13. Miller RR, Vismara LA, Willaim DO, Amsterdam EA, Mason DJ (1976) Pharmacologic mechanisms for left ventricular unloading in clinical congestive heart failure. Differential effects of nitroprusside, phentolamine, and nitroglycerine on cardiac function and peripheral circulation. Circ Res 39:127–133
14. Waite RP, Pang CCY, Walker MJA (1988) Effects of calcium antagonists on mean circulatory filling pressure in the conscious rat. J Cardiovasc Pharmacol 12:499–504
15. Fielden R, Owen DAA, Taylor EM (1974) Hypotensive and vasodilator actions of SK&F 24260, a new dihydropyridine derivative. Br J Pharmacol 52:323–332
16. Verhaeghe RH, Shepherd JT (1976) Effect of nitroprusside on smooth muscle and adrenergic nerve terminals in isolated blood vessels. J Pharmacol Exp Ther 199:269–277