Sustained Effects of Plasma Norepinephrine Levels on Femoral-Radial Pressure Gradient after Cardiopulmonary Bypass

Ryosuke NAKAYAMA, Tomoko GOTO, Ichiro KUKITA and Ryuzo SAKATA

In order to determine the influence of the sympathetic nervous system upon the femoral-radial artery pressure gradient after cardiopulmonary bypass (CPB), we examined plasma norepinephrine levels in 34 adult male patients undergoing coronary artery bypass grafting. Cardiovascular parameters, including systolic arterial pressure, mean arterial pressure, cardiac index (CI), systemic vascular resistance index (SVRI), pulmonary artery pressure (PAP), hemoglobin (Hb) and peak dP/dt of radial and femoral artery pressures were measured after sternotomy, and immediately after the discontinuation of CPB and 90 min after CPB. Plasma norepinephrine levels were measured after sternotomy, after aortic declamping and 90 min after CPB.

The patients were divided into two groups. Group A consisted of 17 patients whose femoral minus radial systolic pressure difference was 15 mmHg or more at 90 min after CPB, while Group B consisted of 17 patients with the difference less than 15 mmHg. Group A patients had significantly longer time values in the duration of both CPB (Group A 175 ± 10 min; Group B 115 ± 12 min, $P < 0.001$) and aortic cross clamping (Group A 116 ± 7 min; Group B 71 ± 9 min, $P < 0.001$).

Although there was no significant difference in Hb or PAP of 90 min after CPB in Groups A and B, the following values, listed in the order of A to B, were obtained; CI, 2.79 ± 0.10 versus 3.46 ± 0.16 $l \cdot min^{-1} \cdot m^{-2}$ ($P < 0.01$); mean radial artery pressure (MRP), 58.7 ± 2.4 versus 65.1 ± 1.8 mmHg ($P < 0.05$); peak dP/dt of radial artery pressure, 568 ± 64 versus 1026 ± 61 $mmHg \cdot sec^{-1}$ ($P < 0.001$); and plasma norepinephrine concentration, 1.81 ± 0.25 versus 0.98 ± 0.10 $ng \cdot ml^{-1}$ ($P < 0.01$), which were statistically significant.

The higher femoral-radial artery pressure gradient after CPB was observed in patients with both a longer CPB time and a higher plasma norepinephrine concentration. These results suggest that a marked constriction of peripheral arteries might have produced a damped transmission of the pressure pulse to the radial artery. (Key words: plasma norepinephrine, femoral-radial artery pressure gradient, cardiopulmonary bypass)

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Departments of Anesthesiology and Cardiovascular Surgery, Kumamoto Chuo Hospital, Kumamoto, Japan

Address reprint requests to Dr. Goto: Department of Anesthesiology, Kumamoto Chuo Hospital, 1-16-1 Shinyashiki, Kumamoto, 862 Japan

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The radial artery has been routinely used for monitoring systemic arterial pressure in cardiac surgery. However, Stern et al. (1985) found that radial artery pressure after CPB was often lower than aortic pressure[1]. This differ-

ence could continue over 60 mmHg in some patient. Therefore, they warned that, if the pressure difference between the radial artery and the central aorta was overlooked after CPB, the patient might be inadequately treated on a basis of unrepresentative systolic radial artery pressure (SRP)[2]. Several mechanisms have been postulated for this pressure gradient. A low SRP might be due to a decrease in forearm vascular resistance[1]. On the contrary, Mohr et al. proposed a multifactorial hypothesis that the pressure difference might be caused by peripheral arterial constriction, decreased volume factors and proximal shunting, and suggest that an increased difference could be possibly corrected by volume loading with transfusion[2]. The clinical observation shows that SRP and MRP are elevated by wrist compression, and the pressure difference has been attributed to the decreased vascular resistance peripheral to the site of pressure monitoring[3]. Post CPB hemodilution could also contribute to the decrease of peripheral vascular resistance[4].

These controversies concerning the mechanism for the pressure gradient will mislead to opposite direction in the therapeutic aspect of the anesthesia and postoperative management. In this study, the influence of the sympathetic nervous system activity judged from plasma norepinephrine levels during and after CPB on the pressure gradient between femoral and radial arteries was investigated.

Methods

Thirty-four adult male patients undergoing coronary artery bypass grafting were included in this study. Anesthesia was maintained with 30 $\mu g \cdot kg^{-1}$ fentanyl and 0.5 $mg \cdot kg^{-1}$ diazepam. Upon arrival in the operating room, diltiazem 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and isosorbide dinitrate 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were started and, continuously administered during and after CPB. Volume loading with either Ringer Lactate or Blood was performed immediately after CPB according to PAP as an indicator of circulatory function. In order to maintain CI within normal range, a 1:1 dopamine-dobutamine mixture was continuously administered at a rate of 5–6 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Any patient who received a continuous drip infusion of norepinephrine (in even a small amount) before or after CPB, or one who required IABP or hemofiltration during the operation were not included in this study.

Cardiopulmonary bypass flow was regulated at 2.0 $l \cdot m^{-2}$ to 2.6 $l \cdot m^{-2}$ with nonpulsatile perfusion. The perfusion pressure was maintained between 50 and 70 mmHg by giving single norepinephrine shot of 0.05 mg each time, if necessary. The mean amount of norepinephrine ($mg \cdot kg^{-1} \cdot hr^{-1}$) used during CPB was recorded. The rectal temperature was kept between 28 and 32°C. Acid-base balance was held constant with an alpha-stat. Potassium and Hb were repeatedly measured and kept within adequate range (potassium 3.0–4.5 $mEq \cdot dl^{-1}$, Hb 6.0–9.0 $g \cdot dl^{-1}$). A 20 gauge plastic needle of 51 mm in length was inserted into the left radial artery and another was into the left femoral artery. The needles were connected to the transducer (Custom Kit Transpac II, Abbot Critical Care System, Chicago, Illinois) via three way stopcocks by a standard pressure monitoring tube, 160 cm in length. Data were recorded on a thermal array recorder (Nihonkohden, Tokyo, Japan). The midaxillary level was used as the zero point. The pressure monitoring circuit presented a frequency response of 25 Hz and a damping ratio of 0.25, both within the normal range[5]. After sternotomy, at the end of CPB and 90 min later, the systolic femoral artery pressure (SFP), mean femoral artery pressure (MFP), SRP,

Table 1. Clinical characteristics and operative data (Mean ± Standard Error).

	Group A (n=17)	Group B (n=17)
Age (yr)	61.1 ± 1.6	60.5 ± 2.1
Height (cm)	161.6 ± 1.5	164.4 ± 1.4
Weight (kg)	64.5 ± 1.9	66.9 ± 1.9
Body Surface Area (m^2)	1.68 ± 0.02	1.73 ± 0.03
Hypertension	11 (64.7%)	7 (41.2%)
Diabetes	4 (23.5%)	3 (17.6%)
No. of grafts per patient	3.6 ± 0.2**	2.4 ± 0.2
Aortic cross-clamp time (min)	116 ± 7**	71 ± 9
Bypass time (min)	175 ± 10**	115 ± 12
Norepinephrine during CPB ($mg \cdot kg^{-1} \cdot hr^{-1}$)	0.0028 ± 0.0003*	0.0052 ± 0.0010
Hb at 90 min after completion of CPB ($mg \cdot dl^{-1}$)	9.85 ± 0.22	9.73 ± 0.27

Mean ± SEM
*$P < 0.05$, **$P < 0.01$

MRP, peak dP/dt of the femoral and radial artery pressures, PAP, CI, and SVRI were measured. Plasma norepinephrine levels of blood samples taken from the pulmonary artery after sternotomy, after aortic declamping and 90 min after CPB were measured by high performance liquid chromatography. Peak dP/dt was calculated from the rate of change of pressure on the rising phase. Cardiac output was measured by the thermodilution method with a Model SAT-2 (Baxter International, Inc., Deerfield, Illinois). SVRI was calculated by the formula of 80 (MFP-CVP)/CI and expressed in dynes·sec·cm^{-5}·m^{-2}. Patients, whose SFR minus SRP values were 15 mmHg or more 90 min after CPB, were placed in Group A and those with values less than 15 mmHg in Group B. The parameters in two groups were statistically compared using the Student's unpaired t test, and any difference at the 5% P level or lower was considered significant.

Results

The values obtained before and during the operation were compared between two groups (table 1). Group A had a significantly longer aortic cross clamping time and CPB time. A larger number of grafts were performed and a significantly smaller amount of norepinephrine was used during CPB in Group A. The two groups were equal in the pre-CPB value as regards the MFP, MRP, SFP and SRP. The MRP value obtained immediately after CPB was 51.2 ± 2.6 mmHg for Group A and 57.8 ± 2.9 mmHg for Group B. The MRP value 90 min after CPB was 58.7 ± 2.4 mmHg for Group A, which was significantly lower than that of Group B, 65.1 ± 1.8 mmHg ($P < 0.05$). The SRP value immediately after CPB was 69.1 ± 3.9 for Group A and 90.8 ± 4.7 for Group B, and the value 90 min after that was 77.3 ± 3.7 for Group A and 102.2 ± 2.9 for Group B. Group B showed significantly higher SRP val-

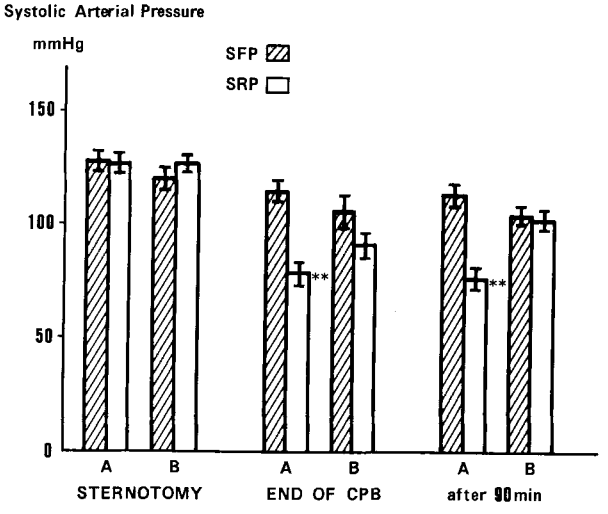
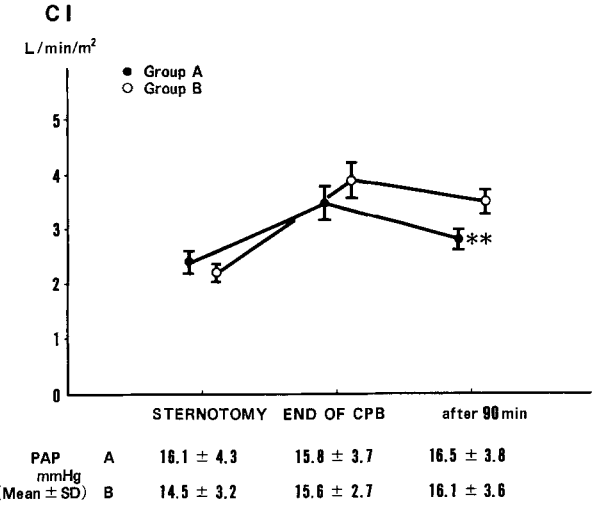


Fig. 1. Systolic radial artery pressure (SRP) and systolic femoral artery pressure (SFP) after sternotomy, at the end of CPB and 90 min after CPB (Mean ± Standard Error). A=Group A, B=Group B
**$P < 0.01$, Group A versus Group B.



PAP mmHg (Mean ± SD)	A	16.1 ± 4.3	15.8 ± 3.7	16.5 ± 3.8
	B	14.5 ± 3.2	15.6 ± 2.7	16.1 ± 3.6

Fig. 2. Cardiac index (CI) after sternotomy, at the end of CPB and 90 min after CPB (Mean ± Standard Error).
**$P < 0.01$, Group A versus Group B.

ues than Group A ($P < 0.01$ and $P < 0.001$, respectively). Ninety minutes after CPB, the SRP and SFP in Group B were nearly equal, whereas the pressure gradient between SRP and SFP in Group A was still as high as 36 mmHg (fig. 1).

After sternotomy and immediately after CPB, both groups did not differ in CI. The mean CI value 90 min after CPB was 2.79 ± 0.10 $l \cdot min^{-1} \cdot m^{-2}$ for Group A, and significantly lower than that of Group B, 3.46 ± 0.16 $l \cdot min^{-1} \cdot m^{-2}$ ($P < 0.01$, fig. 2). The SVRI value immediately after CPB was 1236 ± 65 for Group A versus 1161 ± 105 for Group B, and a value 90 min after that was 1685 ± 93 for Group A versus 1353 ± 81 for Group B. The SVRI value 90 min after CPB was significantly higher in Group A than that of Group B ($P < 0.05$).

Femoral peak dP/dt increased immediately after CPB in both groups and remained high even after 90 min, producing steep ascending curves of the femoral pressure wave forms, whereas radial peak dP/dt decreased

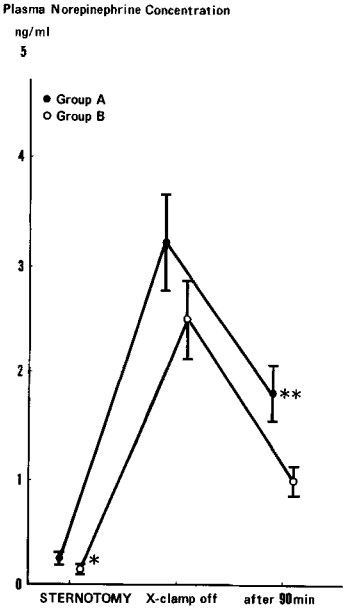


Fig. 3. Plasma norepinephrine concentration after sternotomy, upon aortic declamping and after CPB (Mean ± Standard Error).

*$P < 0.05$, **: $P < 0.01$, Group A versus Group B.

immediately upon completion of CPB in both groups and the radial pressure wave forms exhibited a tendency of damping. The radial peak dP/dt value immediately after CPB was 447 ± 38 mmHg·sec^{-1} for Group A versus 879 ± 79 mmHg·sec^{-1} for Group B, and the value 90 min after was 568 ± 64 mmHg·sec^{-1} for Group A versus 1025 ± 61 mmHg·sec^{-1} for Group B. Thus, the post-CPB radial peak dP/dt gradually returned to the pre-CPB value in Group B, however the low value was sustained even 90 min after CPB in Group A ($P < 0.001$).

In both groups, plasma norepinephrine levels increased immediately after aortic declamping and decreased 90 min after CPB, although the value of Group A 1.81 ± 0.25 ng·ml^{-1} was significantly higher than the value of Group B 0.98 ± 0.10 ng·ml^{-1} ($P < 0.01$, fig. 3).

Discussion

In this study, patients with a marked pressure gradient of 90 min after CPB (Group A) showed a significantly higher plasma norepinephrine concentration and significantly lower MRP, although there was no difference in the value of Hb. We speculated that constriction of the arterial branches proximal to the monitoring site of the radial artery pressure reduced the blood flow through the radial artery and increased the pressure gradient. Compared with other studies on pressure gradient between proximal and peripheral arteries, the significance of this study was quite reliable since there were only negligible variations in age, height, body weight and body surface area between the patients, and because the pressure gradient and plasma norepinephrine concentration were well correlated to the duration of CPB and aortic clamping time.

Previously proposed hypotheses for the pressure gradient between central and radial arteries after CPB can be divided into two major categories: vasodilation theories and vasoconstriction theories. Maruyama, et al. recognized that a pressure gradient became noticeable during continuous administration of nitroglycerin 0.25–0.5 μg·kg^{-1}·min^{-1} and nicardipine 0.25–0.5 μg·kg^{-1}·min^{-1}, and they concluded that peripheral vasodilation was the primary cause of the pressure gradient[6]. We administered diltiazem and isosorbide dinitrate 1.0 μg·kg^{-1}·min^{-1} to both groups upon arrival in the operating room in order to prevent coronary spasm. However, they are relatively weak vasodilators[7,8], and will not be the primary contributors of the pressure gradient. Hemodilution will decrease peripheral vascular resistance. However Hb of two groups had same values 90 min after CPB and would not develop the group difference

in the pressure gradient.

Ninety minutes after CPB, CI showed a significant difference in the two groups (Group A 2.79 ± 0.10, Group B 3.46 ± 0.16). However, in order to prevent peripheral constriction caused by a post-CPB low output and to maintain cardiac function, we administered dopamine and dobutamine, 5–6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, in the two groups. There was no difference in PAP between the two groups and almost a similar degree of volume loading was performed. Therefore, it is conceivable that the decreased ratio of cardiac output itself would not cause the pressure gradient after CPB. The difference in CI between the two groups may reflect the difference in after-load. It was our impression that the pressure gradient was not attributable to low cardiac output, but vascular vital response to a serious circulatory failure resembling shock, due to decreased blood pressure during the initiation of CPB, hemodilution[9], hypothermia[10], myocardial ischemia[11] , and nonpulsatile perfusion[12].

It has been reported that responses to most surgical stress, except for CPB, can be inhibited with large doses of fentanyl[13]. Reves et al. reported that myocardial ischemia was resulted in increases of epinephrine and norepinephrine, both were released from a three to ten minute period after aortic declamping and reached the peak[11]. In our study, the plasma norepinephrine levels of Group A were highest at the time of aortic declamping. The amount of norepinephrine used during CPB was significantly less in Group A. Therefore, it is unlikely that the administered norepinephrine caused the highest plasma norepinephrine concentration of Group A.

Philbin et al. reported that epinephrine and norepinephrine levels were significantly higher in cases with nonpulsatile perfusion than with pulsatile perfusion[12]. Minami et al. also reported the same result and subsequent vasoconstriction. They noted that water was transferred to the outside of the blood vessels with nonpulsatile perfusion more remarkably than with pulsatile perfusion due to decreased venous bed resistance as well as increased mean capillary pressure and filtration pressure[14]. Higher TPR (total peripheral resistance) with nonpulsatile perfusion, than with pulsatile perfusion, might be attributed to vasoconstriction caused by alpha-adrenergic stimulation. The increase in plasma norepinephrine concentration with nonpulsatile perfusion will remain for two to four hours after CPB. Although the time delay in blood pressure difference at the end of CPB as compared to plasma norepinephrine level at aortic declamping may consist, the most likely is that plasma norepinephrine remains at high level. In our study, the SVRI value 90 min after CPB was higher in the group showing a higher pressure gradient, and indicated a slower recovery from CPB (a shock condition). Although the increase in vascular resistance can be enhanced by other vasoacting compounds (renin-activity, angiotensin II, ADH etc.), we have not determined these in this study. Philbin reported that renin-activity had not been changed markedly during CPB, and thus renin-activity change would not be a contributing factor intraoperatively[12]. In both Groups A and B, SVRI was seemingly lower immediately after CPB than before CPB. However, it is not conclusive, because the patient immediately after CPB were suffering from vasomotor failure, cardiac depression and increased vasopermeability[14], and accurate determination of pre- and post-CPB vascular resistance with conventional TPR method was difficult.

A study comparing the post-CPB

pressures of the aorta, brachial artery and radial artery suggests that brachial artery pressure correlates well with aortic pressure, while the forearm arteries with many branches are constricted and cause damping of the radial artery pressure[15]. Alexander et al. stimulated the sciatic nerve to constrict the muscular artery and demonstrated that the pulses of the dorsalis pedis were weakened[16]. In our patients with a marked pressure gradient, radial peak dP/dt was low while femoral peak dP/dt was high. This indicates that true central pressure is not transmitted to the radial artery. Group A with a marked pressure gradient, significantly longer CPB and aortic clamping time, had significantly higher plasma norepinephrine concentration 90 min after CPB.

Though the causes of pressure difference between proximal and peripheral arteries after CPB are controversial, our study lead us to the following conclusions. Increased norepinephrine concentration, peripheral vasoconstriction and peripheral circulatory failure occurred in response to a stress caused by longer CPB. The higher pressure gradient might be caused by a decreased blood flow through the radial artery and decreased radial arterial pressure. In order to prevent this pressure difference, it is necessary to ameliorate peripheral circulatory failure during CPB. It may be achieved by reducing the periods of CPB and aorta clamping and by using pulsatile perfusion. We think that the pressure difference should be further investigated by measuring the inner diameter of a peripheral artery and its blood flow, during and after CPB.

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