THE EFFECTS OF PULSATILE AND NONPULSATILE SYSTEMIC PERFUSION ON RENAL SYMPATHETIC NERVE ACTIVITY IN ANESTHETIZED DOGS

It is still controversial whether to pulse or not to pulse for the establishment of ideal extracorporeal circulation. We directly measured the renal sympathetic nerve activity in mongrel dogs (n = 10, weighing from 13 to 21 kg) to determine the effects of pulsatile and nonpulsatile systemic perfusion on the control of the sympathetic nerve activity during left ventricular assistance. Pulsatile perfusion was generated with an air-driven, diaphragm-type blood pump, and nonpulsatile perfusion was generated with a centrifugal pump. Renal sympathetic nerve activity and the blood flow of the descending aorta were then recorded during pulsatile and nonpulsatile systemic perfusion. Other variables, such as mean arterial pressure, central venous pressure, left atrial pressure, and blood gas levels, were kept constant. At the same mean arterial pressure, renal sympathetic nerve activity during pulsatile perfusion decreased significantly to 80% of renal sympathetic nerve activity during nonpulsatile perfusion (26.8 ± 2.4 vs 33.4 ± 2.9 spikes/sec, $p < 0.01$). Total systemic vascular resistance during pulsatile perfusion decreased significantly to 85% of that during nonpulsatile perfusion (5700 ± 580 vs 6667 ± 709 dynes · sec · cm^{-5}, $p < 0.05$). These results suggest that pulsatile systemic perfusion, compared with nonpulsatile systemic perfusion, reduces sympathetic nerve activity and peripheral vascular resistance and thus may improve both microcirculation and organ function. (J THORAC CARDIOVASC SURG 1996;111:478-84)

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Pulsatile systemic perfusion during extracorporeal circulation (ECC) has been shown to be more beneficial than nonpulsatile perfusion with respect to hemodynamics, metabolism, organ function, hormonal responses, and microcirculation.[1-10] Some authors, however, claim that pulsatile perfusion does not improve either myocardial function or organ function.[11, 12]

A carotid sinus isolation model revealed that pulsatile perfusion sensitized the arterial baroreceptor more and as a result caused more inhibition of sympathetic nerve activity than seen with nonpulsatile perfusion.[13-16] So far, little is known about the effects of pulsatile and nonpulsatile systemic perfusion on renal sympathetic nerve activity (RSNA), which reflects the efferent activity of the sympathetic nerve, during ECC. In this study, we found directly measured RSNA to be reduced during pulsatile systemic perfusion, indicating the superiority of pulsatile over nonpulsatile systemic perfusion.

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Material and methods

Humane animal care. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985). This experiment was reviewed by the Committee of the Ethics on Animal Experiment in Faculty of Medicine, Kyushu University, and carried out under the control of Guidelines for Animal Experiments in the Faculty of Medicine, Kyushu University and the law (No. 105) and notification (No. 6) of the Japanese government.

Preparation of animals. Ten mongrel dogs weighing 13 to 21 kg (16.9 ± 0.7 kg) were used in this study. Anesthe-

sia was induced with an intravenous injection of thiamylal sodium (20 mg/kg) and α-chloralose (80 mg/kg) and was maintained with α-chloralose infusion (25 $mg \cdot kg^{-1} \cdot min^{-1}$). Because thiamylal sodium is rapid-acting barbiturate, its effect on nerve activity is negligible at the time of measurement of sympathetic nerve activity. After endotracheal intubation, the animals were ventilated mechanically with room air supplemented by 100% oxygen. Catheters were inserted into the right femoral artery and right femoral vein for sampling, pressure monitoring, and infusion. The left flank was opened to expose the left renal sympathetic nerves. After these nerves were separated from the surrounding connective tissues, one of the branches of the renal sympathetic nerve was placed on a stainless steel–stainless steel bipolar electrode and embedded in silicone gel (mixture of SILGEL 604 A & B; Eacker-Chemie GMBH, Munich, Germany). The wound was closed in layers.

Fig. 1 shows the preparation of the left ventricular assist system (LVAS) used in this experiment. A median sternotomy incision was made and 300 U/kg heparin was given intravenously. A cannula (no. 32F; Polystan A/S, Vårlöse, Denmark) was inserted into the left atrium through the appendage while another cannula (no. 28F Stöckert-Shiley; Stöckert Instrumente GMBH, Munich, Germany) was inserted into the left ventricle through the apex. An infusion cannula (6.5 mm Sarns; Sarns, 3M Health Care, Ann Arbor, Mich.) was placed at the ascending aorta. The pulsatile perfusion was generated with an air-driven, diaphragm-type blood pump (TCT 20; Toyobo Co., Ltd., Osaka, Japan), and the nonpulsatile perfusion was generated with a centrifugal pump (Bio-pump; Bio-Medicus, Inc., Eden Prairie, Minn.). These pumps were connected in series (Fig. 1). An ultrasonic flow probe was placed just distal to the origin of the left subclavian artery to measure the flow of the descending aorta in seven dogs (two-channel ultrasonic blood flowmeter T201; Transonic Systems Inc., Ithaca, N.Y.). (The flowmeter was not available for the first three dogs.) We measured the arterial pressure, left atrial pressure, and central venous pressure (CVP) through fluid-filled catheters. The arterial blood pH was maintained at around 7.4 by sodium bicarbonate injection as necessary. The arterial carbon dioxide tension was kept at around 35 and 45 mm Hg by regulating the tidal volume of the ventilator and the gas flow. Body temperature was measured at the nasopharynx and kept at around 37° C with a heating pad and the heat exchanger during ECC. The average hematocrit value was 34.8%.

Nerve recording. The technique for the amplification and quantification of sympathetic nerve activity has been described elsewhere.[17] In brief, the action potentials of the nerves were amplified with a Dual Channel Bioelectric Amplifier MEG-2100 (Nihon Kohden Corp., Tokyo, Japan). The amplified signals were fed into a nerve traffic analyzer (Pulse Counter MET-1100; Nihon Kohden), which discriminated each spike exceeding a preselected level (just above the noise level) so that the spikes could be counted. Each spike that crossed the lower window discriminator level triggered a voltage step independent of the spike amplitude. These voltage steps were integrated by a spike counter, which was digital in design and could be integrated linearly at instantaneous spike frequencies

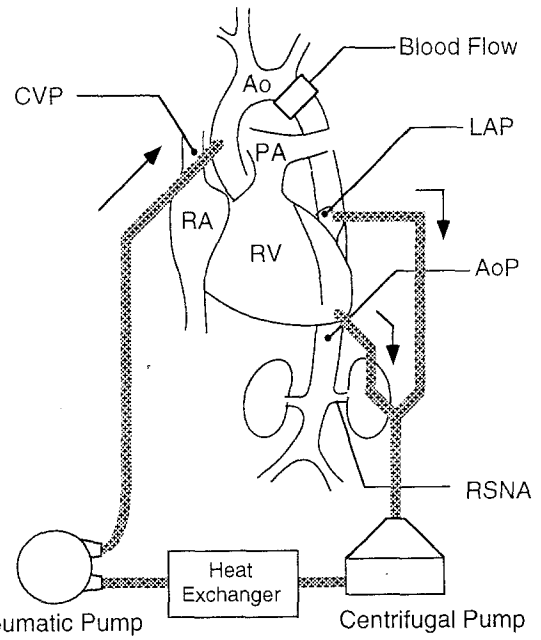

Fig. 1. Schematic diagram of the experimental scheme. *Ao,* Aorta; *AoP,* aortic pressure; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle, *LAP,* left atrial pressure.

of up to 10 kHz. The raw electroneurogram and the integrated output from spike counter were displayed on a recorder (Thermal Array Recorder RTA-1300; Nihon Kohden).

Procedure and measurements. The electrocardiogram, arterial pressure curve, CVP, and left atrial pressure, the blood flow of the descending aorta, RSNA, and integrated RSNA were all continuously monitored and recorded. The centrifugal pump flow was increased until a pulsatile wave form disappeared from the arterial pressure curve. The percentage of systole of the pneumatic pump was controlled to keep the mean arterial pressure (MAP) at the same level as the nonpulsatile flow. The pneumatic pump was driven during each diastolic phase by means of electrocardiographic synchronization. The mean pulse pressure was 37 ± 1 mm Hg. To adjust the MAP and left atrial pressure at the same level for the pulsatile and nonpulsatile modes, we required about 2 minutes after switching the perfusion mode from pulsatile to nonpulsatile or the reverse. The pulsatile and nonpulsatile flows were held constant for periods of 10 to 15 minutes for stabilization after the perfusion mode was switched. By the end of such periods, nerve activity and the systemic arterial and left atrial pressure were stable, and all measurements were then obtained for a period of 1 minute. The peripheral vascular resistance (PVR) was calculated as follows: (MAP − mean CVP)/blood flow of descending aorta) × 80 (in $dynes \cdot sec \cdot cm^{-5}$). The blood samples were analyzed for pH, oxygen tension, carbon dioxide tension, and oxygen saturation with the ABL 30 Acid-Base Laboratory (Radiometer A/S, Copenhagen, Denmark).

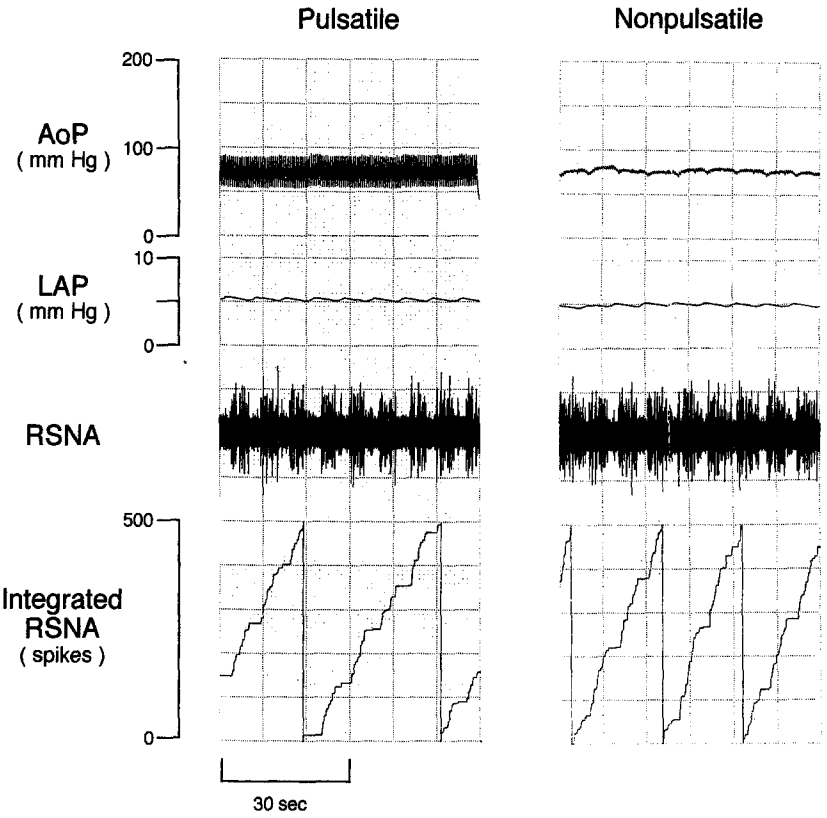

Fig. 2. Representative recording. *AoP,* Aortic pressure; *LAP,* left atrial pressure.

Table I. *Hemodynamic data*

	HR (beats/min)	*AoP (mm Hg)*	*LAP (mm Hg)*	*CVP (mm Hg)*	*Flow (ml/min/kg)*
Nonpulsatile	145 ± 5.2	82.5 ± 4.3	4.0 ± 1.1	4.3 ± 0.3	46.8 ± 3.6
Pulsatile	147 ± 4.6	81.8 ± 3.8	3.9 ± 1.1	4.2 ± 0.3	57.1 ± 2.3*

Mean ± standard error of the mean. *HR,* Heart rate; *AoP,* mean aortic pressure; *LAP,* left atrial pressure, *Flow,* blood flow of the descending aorta.
*$p < 0.01$ vs nonpulsatile.

Statistics. All values are expressed as the mean ± standard error of the mean. The measurements were compared by the paired Student's *t* test. Differences were considered significant when the *p* value was less than 0.05. A simple linear regression was used to estimate the relationship between RSNA counts and PVR.

Results

Table I summarizes the hemodynamic values during nonpulsatile and pulsatile perfusion. There were no significant differences in heart rate, arterial pressure, left atrial pressure, or CVP between each perfusion pattern. The blood flow of the descending aorta during pulsatile perfusion was significantly higher than that during nonpulsatile perfusion ($p < 0.01$).

Fig. 2 shows a representative recording. The shift from nonpulsatile to pulsatile perfusion decreased RSNA, whereas the shift from pulsatile to nonpulsatile perfusion increased RSNA. After 10 to 15 minutes, the perfusion pattern was switched and, when MAP and left atrial pressure were equal to those before the shift (accomplished by controlling the flow of LVAS), RSNA and the blood flow of the descending aorta were measured.

RSNA without LVAS was 33.5 ± 2.7 spikes/sec. RSNA during nonpulsatile perfusion was 33.4 ± 2.9 spikes/sec (99.7% of the value without LVAS), whereas RSNA during pulsatile perfusion was 26.8 ± 2.4 spikes/sec (80% of the value without LVAS; Fig. 3). RSNA during pulsatile perfusion significantly decreased to 80% of RSNA during nonpulsatile perfusion ($p < 0.01$).

PVR without LVAS was 6316 ± 602 dynes·sec·cm^{-5}. PVR during nonpulsatile perfusion was 6710 ± 485 dynes·sec·cm^{-5} (106% of the value

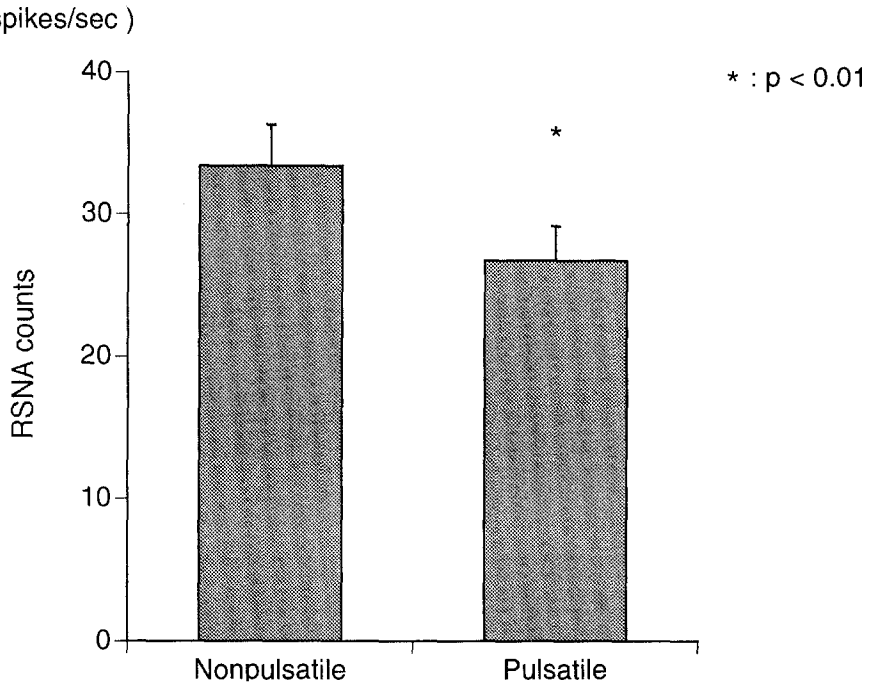

Fig. 3. The effect of pulsatile and nonpulsatile systemic perfusion on RSNA (n = 10). Values expressed as mean ± standard error of the mean.

without LVAS), and that during pulsatile perfusion was 5594 ± 501 dynes · sec · cm^{-5} (88.5% of the value without LVAS; Fig. 4). PVR during pulsatile perfusion decreased significantly, to 85% of that during nonpulsatile perfusion ($p < 0.05$). As shown in Fig. 5, there was a significant linear correlation between PVR and RSNA counts (PVR = 345RSNA + 389, r = 0.83).

Discussion

Baroreflex is a system that monitors change and minimizes fluctuations in blood pressure.[18] When blood pressure increases or decreases, the baroreflex system immediately senses this change and buffers it by altering sympathetic nerve activity. This reduction of sympathetic nerve activity induces vasodilatation. The factors that affect the sympathetic nerve activity during ECC are the dilution of blood (changes in hematocrit and electrolytes), the change of temperature, and activation of sinoaortic baroreceptors and cardiopulmonary receptors. The baroreflex function can be roughly broken down into the arterial baroreflex and the cardiopulmonary baroreflex. The former functions according to the arterial pressure and the latter functions according to the atrial pressure, pulmonary pressure, and ventricular diastolic pressure.

Felder and Thames[19] reported the interaction between cardiopulmonary receptors and sinoaortic baroreceptors in the control of sympathetic nerve activity. They concluded that cardiopulmonary receptors exert an inhibitory influence on cardiac sympathetic nerve activity and that this influence limits the arterial baroreceptor–mediated increases in cardiac sympathetic nerve activity. To determine the effects of any difference in perfusion characteristics on sympathetic nerve activity, left atrial pressure and CVP should be kept equal in each perfusion mode to exclude the effect of cardiopulmonary receptors. In this experiment, we changed only the perfusion characteristics and kept all other parameters equal in each perfusion mode.

Previous studies that used a carotid sinus isolation model[13-16] demonstrated that pulsatile perfusion sensitizes the arterial baroceptor more and, as a result, causes a greater inhibition of sympathetic nerve activity than does nonpulsatile perfusion. Chapleau, Hajduczok, and Abboud[16] also reported that pulsatile pressure imposed on the carotid sinus causes a greater inhibition of the sympathetic nerve activity than does nonpulsatile pressure when mean carotid sinus pressure is kept constant. In our in vivo model, the inhibition of the sympathetic nerve activity during pulsatile perfusion may result in the reduction of PVR, followed by a decrease in arterial

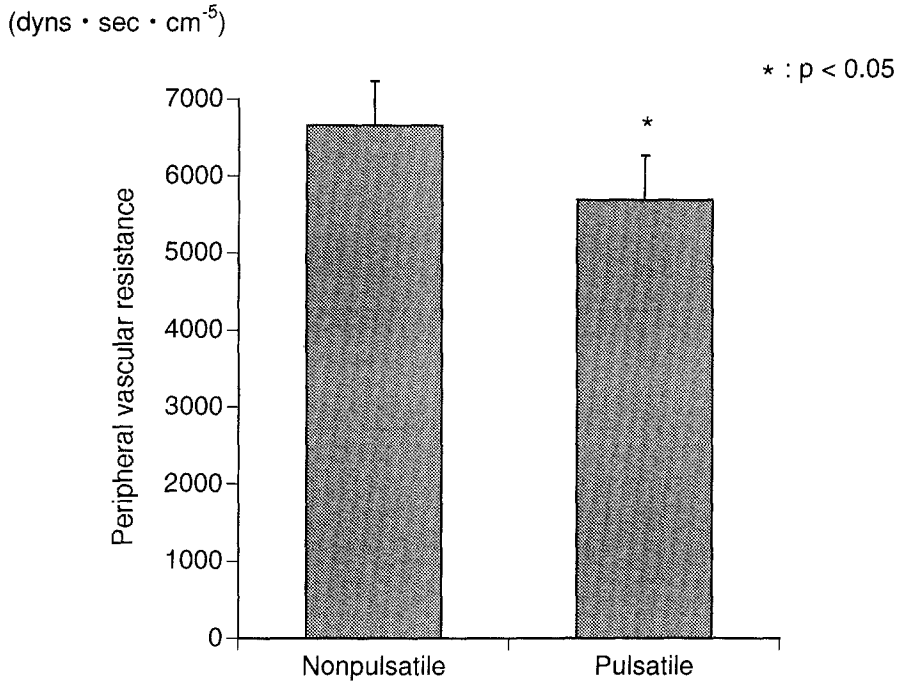

Fig. 4. The effect of pulsatile and nonpulsatile systemic perfusion on PVR (n = 7). Values expressed as mean ± standard error of the mean.

pressure. When we use the constant-flow model, this decrease in the arterial pressure may attenuate the inhibition of the sympathetic nerve activity during pulsatile perfusion. For this reason, we selected the constant-pressure model to clarify the differences between the effects of pulsatile and nonpulsatile perfusion on sympathetic nerve activity.

Hajduczok, Chapleau, and Abboud[20] reported that increases in flow result in increases in carotid sinus nerve activity in the carotid sinus isolation model and concluded that there are arterial rheoreceptors in the carotid sinus that respond to the flow at a constant distending pressure and strain. In their study to examine the influence of varying flow levels on carotid sinus nerve activity, carotid sinus pressure was kept at 50 mm Hg. Then, to examine the effect of flow on baroreceptor activity at varying levels of carotid sinus pressure, flow was set to 0 or 18 ml/min. In our study, the difference in the flow between pulsatile and nonpulsatile perfusion was about 10 $ml \cdot min^{-1} \cdot kg^{-1}$, whereas the arterial pressure was kept at 82 mm Hg. It is therefore not known whether the differences in flow levels between pulsatile and nonpulsatile perfusion may influence the differences in RSNA.

In addition to carotid sinus receptors, peripheral receptors such as aortic receptors, cardiopulmonary receptors, renal receptors, and liver receptors also affect the control of sympathetic nerve activity.[21] Little is known, however, about the integrated effects of these receptors on sympathetic nerve activity when they are exposed to nonpulsatile systemic perfusion. The carotid sinus isolation model therefore seems to be insufficient to determine the effects of pulsatile and nonpulsatile perfusion on neural regulation during ECC. In this study, we directly measured RSNA to delineate the effects of pulsatile and nonpulsatile systemic perfusion on sympathetic nerve activity during ECC. The results of this study show that RSNA during pulsatile perfusion decreases compared with that during nonpulsatile systemic perfusion. On the basis of the findings of the experiment with the carotid sinus isolation model, pulsatile systemic perfusion may increase baroreceptor activity, inhibit vasomotor discharge, and decrease RSNA.

It is generally accepted that PVR rises during conventional nonpulsatile cardiopulmonary bypass. Shepard and Kirklin[1] and Dunn and coworkers[2] showed lower PVR and higher oxygen consumption during pulsatile perfusion than during nonpulsatile perfusion. Taylor and colleagues[5] reported that pulsatile cardiopulmonary bypass prevented a rise in

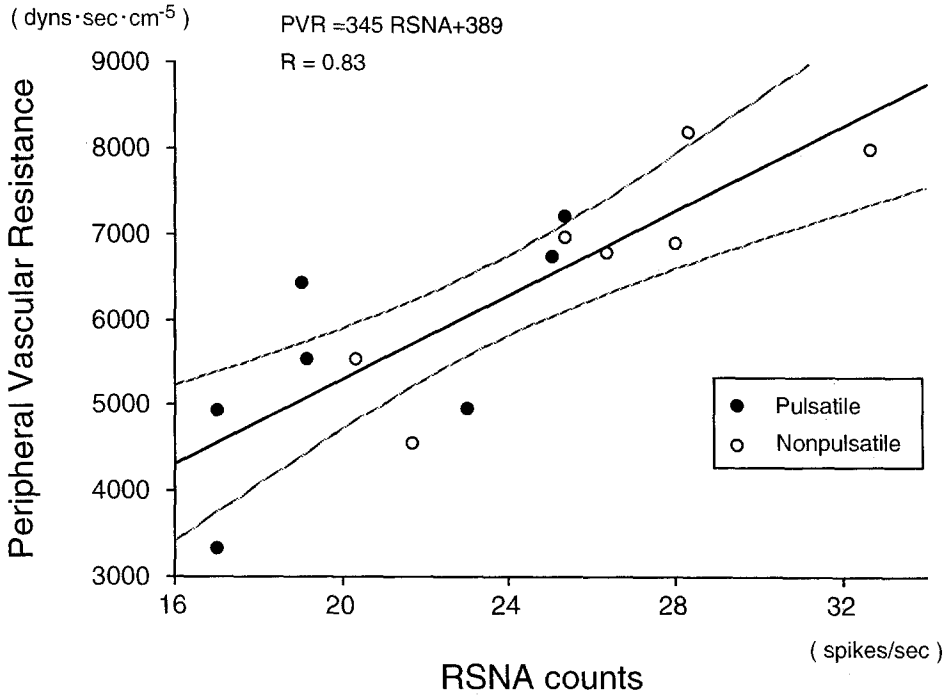

Fig. 5. Linear relationship of PVR to RSNA counts (n = 7). PVR correlated with RSNA (PVR = 345RSNA + 389, r = 0.83). The *dotted lines* express the 95% confidence limits.

either the PVR or the plasma concentration of angiotensin II. To examine the effects of pulsatile and nonpulsatile perfusion on the capacity system, Minami, Vyska, and Körfer[22] examined MAP, PVR, and venous blood volume. They reported that the change from pulsatile to nonpulsatile systemic perfusion increased MAP and PVR and that these effects were abolished after denervation of the pressure receptor and pharmacologic blockade of α and β receptors. Their finding thus supports the hypothesis that an autonomic vasomotor mechanism may be the cause of the change in PVR. In the carotid sinus isolation model used by Angell and Daly,[14] pulsatile pressure reduced the systemic vascular resistance. In our study, PVR during pulsatile perfusion decreased significantly, to 85% of that during nonpulsatile perfusion, and RSNA during pulsatile perfusion also decreased significantly, to 80% of that during nonpulsatile perfusion. There was a good correlation between the PVR and RSNA (Fig. 5). Such a good correlation may have been obtained because neural circulatory regulation system was a closed-loop system and MAP was held constant in our experimental setting. These data demonstrate that pulsatile systemic perfusion causes greater inhibition of the sympathetic nerve activity than does nonpulsatile perfusion and also decreases the PVR. In a clinical study, Minami, Vyska K, and Körfer[22] reported that peripheral resistance with pulsatile perfusion decreased to 85% of that with nonpulsatile perfusion, attenuated the catecholamine stress, reduced the fluid overload, and decreased the postoperative recovery period. The decreases in RSNA and PVR during pulsatile perfusion are therefore considered to be physiologically favorable.

A reduction of vascular resistance improves microcirculation, organ blood flow, and organ function.[1, 6, 7] In addition, pulsatile perfusion maintains better hormone metabolism[4, 5] and prevents increases in plasma catecholamine levels,[8] vasopressin levels,[9] and endotoxin levels[10] compared with nonpulsatile perfusion. Pulsatile perfusion may therefore reduce the fluid overloading of patients and shorten the postoperative recovery period, as evaluated by respiratory support time in adults[8] and infants.[23]

In the field of cardiovascular surgery, hypothermia is usually combined with ECC. Elsewhere, we reported on the effects of hypothermia during cardiopulmonary bypass on sympathetic nerve activity.[24] In that study, RNSA decreased according to the decrease in body temperature. In the study reported here, we used normothermia to exclude the effect of temperature on the relationship be-

tween RSNA and PVR. Further investigations are indicated to determine the effects on neural regulation during ECC of hypothermia during nonpulsatile systemic perfusion.

We conclude that pulsatile systemic perfusion can cause significantly greater inhibition of the sympathetic nerve activity than nonpulsatile perfusion and can also reduce PVR. Pulsatile perfusion may therefore improve microcirculation and organ function during ECC.

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