EXPERIMENTAL STUDIES

Hemodynamic Profiles During Concurrent Intraaortic Balloon Pumping and Venoarterial Bypass
— A Canine Study Comparing Subclavian and Femoral Artery Perfusion Sites —

Shinji Miyamoto, M.D., Tetsuo Hadama, M.D., Yoshiaki Mori, M.D.
Osamu Shigemitsu, M.D., Hidenori Sako, M.D.
and Uzo Uchida, M.D.

Concomitant use of venoarterial bypass (VAB) with centrifugal pump and intraaortic balloon pumping (IABP) is a common technique for cardiopulmonary resuscitation. This experimental study examines whether coronary perfusion and hemodynamics are affected by the site of the blood supply, comparing the subclavian artery and the femoral artery. VAB and IABP were performed in 11 mongrel dogs with cardiopulmonary failure induced by acute myocardial infarction and hypoventilation. Aortic root pressure (AP), left atrial pressure, central venous pressure and coronary sinus blood flow (CSF) were measured, and blood gas analysis was performed. Subclavian artery perfusion (SAP) and femoral artery perfusion (FAP) were compared at bypass ratios of 25, 50, 75, 85, 100%. At bypass ratios of 75% and 85% the mean systolic AP was higher with SAP than with FAP. The mean diastolic AP was higher with SAP than with FAP at a bypass ratio of 50% or higher. CSF was higher with SAP than with FAP at a bypass ratio of 50% or higher. The coronary arteriovenous O2 content difference was lower with SAP than with FAP at a bypass ratio of 85% or higher. In conclusion, at a high bypass ratio, SAP was more effective than FAP in achieving diastolic augmentation, thus enhancing myocardial oxygen balance, even though SAP had less of a systolic unloading effect. These data support the use of SAP over FAP in patients with severe cardiopulmonary dysfunction requiring high-flow bypass, and especially in patients with myocardial ischemia.

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INTRAARTIC balloon pumping (IABP) is useful for treating patients with low cardiac output syndrome (LOS) who do not respond to medical therapy. When treatment with IABP is ineffective, common options include venoarterial bypass (VAB), a left ventricular or a bi-ventricular assist device and IABP4 – 8

Recently, the use of VAB has increased markedly as percutaneous cardiopulmonary systems (PCPS) with a centrifugal pump have become more readily available. This type of device provides appreciable benefits in terms of cost, convenience, and suitability for emergency use. We have used VAB after open heart surgery in 5 patients in combination with IABP. In the first case, persistent LOS prevented termination of VAB until we changed the VAB access site device and IABP.

Key words:
Venoarterial bypass
Intraaortic balloon pumping
Cardiopulmonary failure
Low cardiac output syndrome

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The Second Department of Surgery, Oita Medical University, Oita, Japan
Mailing address: Shinji Miyamoto M.D., The Second Department of Surgery, Oita Medical University, Idaigaoka 1-1, Hazama-chou, OITA, 879-55, Japan

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Fig.1. Schematic diagram of experimental design for comparing the effect of the access site in venoarterial bypass on cardiac and systemic hemodynamics in a canine model. Raising or lowering the two-stage inflow syringe (※) controlled the preload to the native heart. R, reservoir; P, centrifugal pump; MO, membrane oxygenator; IABP, intra-aortic balloon pumping; AP, aortic root pressure; CO, cardiac output; LAP, left atrial pressure; CVP, central venous pressure; PF, pump flow, ECG, electrocardiogram.

from the femoral to the subclavian artery. We found that changing the access site to the subclavian artery increased diastolic augmentation, as reflected by a change in the left radial arterial pressure wave pattern. Subsequently, we successfully weaned 3 of the next 4 patients from VAB using the subclavian artery as the access site. All 3 of these patients were discharged from the hospital. This series led us to conclude that obtaining the blood supply from the subclavian artery had a greater positive effect on myocardial resuscitation than using the femoral artery.

The present study examines the effect of varying the site of the blood supply in the concomitant use of VAB and IABP on hemodynamics, and particularly coronary perfusion.

MATERIALS AND METHOD

Animal Preparation

Eleven adult mongrel dogs (15.7 to 20.3 kg) were given intramuscular ketamine hydrochloride (10 mg/kg) and intravenous pentobarbital sodium (25 mg/kg) to induce anesthesia. Anesthesia was maintained by the intermittent intravenous administration of pentobarbital sodium (10 mg/kg) at intervals of 90 to 120 min.

All of the animals used in this experiment 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 National Academy of Sciences and published by the National Institutes of Health (NIH Publication No. 80–23, revised 1978).

The animals were ventilated with a Harvard ventilator set at 10 to 15 cycles/min, a tidal volume of 20 ml/kg, and a fraction of inspired oxygen (FiO2) of 0.5. A catheter for measuring the central venous pressure was inserted via the right femoral vein, and a catheter for measuring the left atrial pressure was inserted via the left auricle. A 19-G silastic catheter was used to puncture the ascending aorta, and was fixed immediately superior to the aortic valve and anterior to the left coronary orifice. Cardiac output was measured by an electromagnetic blood flowmeter (FMV-1100, Nihon Kohden Co, Ltd, Tokyo, Japan) placed in the pulmonary artery. A 10-Fr blood-supply cannula was inserted into the right subclavian and right femoral arteries, and a 34-Fr blood-drawing cannula into the right auricle. A 14-Fr renal pelvis catheter was inserted via the right atrium into the coronary sinus to measure coronary sinus blood flow. A pediatric, 7cc, IABP balloon was inserted into the descending thoracic aorta via the left femoral artery.

The VAB bypass circuit removed blood from the right atrium and transported it to a reservoir via a two-stage inflow syringe. From there, blood was supplied bidirectionally to the subclavian and femoral arteries by a centrifugal pump (Bio-Pump, BioMedicus Inc, Eden Prairie, MN) and a membrane oxygenator (UNIBOX, Baxter Healthcare Corp, Irvine, CA). An electromagnetic blood flowmeter was installed in the supply circuit. The two-stage inflow syringe ensured that blood which overflowed from the inner syringe reached the reservoir. Thus, preload could be controlled by raising or lowering the syringe (Fig. 1).

The circuit was filled with 1,000 ml of autologous blood, 30 ml of Hespan, 150 ml of mannitol, and 60 ml of meylon.
Subsequently, 10 mg of heparin was added. In addition, the animals received a systemic injection of heparin (2 mg/kg) immediately prior to the insertion of the catheters. The IABP system was actuated with an electrocardiogram trigger using a Datascope System 90 (Datascpe Corp, Montvale, NJ). SCK-676 transducers (Viggo-Spectramed Inc, Oxnard, CA) were used to measure pressure.

After cannulation was completed, an acute myocardial infarction was induced by ligating the anterior descending branch of the left coronary artery immediately proximal to the first diagonal branch. In dogs with a maximum systolic pressure of 100 mmHg or greater and insignificant cardiac failure, the ramus circumflex was also ligated at the last branch. The sinus node was crushed, and 0.001-0.002 mg/kg per min of intravenous propranolol was administered continuously to suppress spontaneous beats. Atrial pacing was performed at a rate of 120 beats/min. Pulmonary failure, defined as a left intrapulmonary Po2 of 80 mmHg or less, was induced by changing the ventilator settings to 15 cycles/min, a tidal volume of 10 ml/kg, and a FiO2 ranging from 0.23 to 0.4. One liter/min of 100% O2 was passed through the oxygenator. Lidocaine (1 to 2 mg/kg) was administered as a prophylaxis against ventricular dysrhythmias and defibrillation was performed when necessary.

**Experimental Protocol**

The total circulation rate was set at 80 ml/kg per min (100%), and the bypass ratio varied between 25, 50, 75, 85 and 100%. By simultaneously adjusting the height of the inflow syringe, to increase or decrease preload, cardiac output could be adjusted to maintain the total circulation rate at 100%. Blood was initially supplied by subclavian artery perfusion (SAP) and then by femoral artery perfusion (FAP) at their respective bypass ratios. After maintaining a fixed cardiac output for 3 min, following 3 to 5 min to allow for stabilization, the central venous pressure (CVP), left atrial pressure (LAP), aortic root pressure (AoP), and coronary sinus blood flow (CSF) were measured under each condition. In addition, blood gas analysis was performed on arterial blood from the aortic root, coronary sinus blood, and pumped blood obtained just after it left the oxygenator. Electrocardiograms, cardiac pressures, and cardiac output were recorded using a 6-channel polygraph. Coronary sinus blood flow was measured directly by collecting coronary sinus blood in a measuring cylinder at 1-min intervals. The collected blood was placed immediately in an ice-water bath, and blood gas analysis was performed as soon as possible with a pH blood gas analyzer (ABL300, Radiometer Inc., Copenhagen, Denmark).

The tension-time index per min (TTI) and the endocardial viability ratio (EVR) were calculated as follows:

\[
\text{TIT} = \frac{\text{mSAoP} \times \text{ET} \times \text{HR}}{\text{mmHg} \cdot \text{sec/min}}
\]

\[
\text{DPTI} = \frac{(\text{mDAoP} - \text{mDLAP}) \times \text{DT} \times \text{HR}}{\text{mmHg} \cdot \text{sec/min}}
\]

\[
\text{EVR} = \frac{\text{DPTI}}{\text{TTI}}
\]

where mSAoP and mDAoP are the mean systolic and diastolic aortic root pressures (mmHg), respectively, mDLAP is the mean left atrial pressure in the diastolic phase (mmHg), ET and DT are the ejection time and diastolic time (sec), and HR is the heart rate (beats/min).

The left ventricular stroke work (LVSW) was calculated as

\[
\text{LVSW} = 0.0136 \times \text{mSAoP} \times \text{CO/HR} \quad \text{g \cdot m/beat}
\]

where mSAoP and HR are the same as defined above, and CO is the cardiac output of the native heart (L/min).

Coronary arterial-venous O2 content difference (AVDO2), myocardial O2 consumption (VO2), and myocardial O2 extraction rate (ExO2) were calculated as

\[
\text{AVDO2} = \text{Ca} - \text{Ccs} \quad \text{vol%}
\]

\[
\text{VO2} = \text{AVDO2} \times \text{CSF} \quad \text{ml/min per 100 g}
\]

\[
\text{ExO2} = \frac{\text{AVDO2}}{\text{Ca}}
\]

where Ca and Ccs are the O2 contents of aortic root blood and coronary sinus blood (vol%), respectively, and CSF is coronary sinus blood flow (ml/min per 100 g heart muscle).

The rate of mixing of the aortic root blood (Mx), which reflects the ratio of pumped blood to blood output from the heart, was
TABLE I THE HEMODYNAMIC EFFECTS OF MYOCARDIAL INFARCTION IN A CANINE MODEL

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>myocardial infarction</th>
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</thead>
<tbody>
<tr>
<td>Heat rate (beats/min)</td>
<td>134±6.2</td>
<td>120</td>
</tr>
<tr>
<td>Aortic root pressure (mmHg)</td>
<td>103.5±2.9</td>
<td>68.1±3.2*</td>
</tr>
<tr>
<td>Left atrial pressure (mmHg)</td>
<td>4.4±0.36</td>
<td>11.3±0.82*</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>4.1±0.34</td>
<td>9.1±0.62*</td>
</tr>
<tr>
<td>Cardiac output (ml/kg/min)</td>
<td>118.6±2.5</td>
<td>72.4±3.1*</td>
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The heart rate was fixed at 120 beats/min by atrial pacing in the myocardial infarction group. *p<0.01

calculated as

\[
M_x = (C_a - C_{LA}) / (C_p - C_a)
\]

where \( C_a \) is the same as defined above, and \( C_{LA} \) and \( C_p \) are the \( O_2 \) contents of left atrial blood and pumped blood, respectively.

At a bypass ratio of 100%, mSaOp, mDaOp, TTI, EVR, LVSW and \( M_x \) were not calculated because there was no output from the heart and it would have been meaningless to distinguish between the systolic and diastolic phase.

For statistical analysis, the paired t-test was used to compare variables. All variables are shown as the mean±SE (standard error), and a value of \( p<0.05 \) was considered statistically significant.

RESULTS

Coronary ligation produced a 40% decrease in cardiac output (Table I). Fig. 2 shows the actual pressures in the ascending aorta at each bypass ratio. The mean aortic root pressure (mAoP) decreased with FAP as the bypass ratio increased, but remained relatively constant with SAP, despite changes in the bypass ratio. At bypass ratios of 75% or higher, mAoP with SAP was significantly higher than that with FAP (Fig. 3-A). mSaOp significantly decreased with both SAP and FAP as the bypass ratio increased; however, the decrease with FAP was greater. At bypass ratios of 75% and 85%, mSaOp was significantly higher with SAP than with FAP (Fig. 3-B). mDaOp with SAP did not change with changes in the bypass ratio, but decreased with FAP as the bypass ratio increased. Accordingly, at bypass ratios of 50% or higher, mDaOp was significantly higher with SAP than with FAP (Fig. 3-C).

At bypass ratios of 75% and 85%, the TTI associated with SAP was significantly higher than that with FAP. The EVR with both SAP and FAP increased as the bypass ratio increased, and at each bypass ratio the EVR with SAP was significantly higher than that with FAP (Fig. 4-B). LVSW decreased as an inverse function of the bypass ratio, so that at a bypass ratio of 75%, LVSW was about one-third of that at a bypass ratio of 25% with both SAP and FAP. At bypass ratios of 75% and 85%, the LVSW associated with SAP was significantly higher than that with SAP.
Fig.3. Central arterial pressures as a function of the bypass ratio using the subclavian and femoral arteries as the access site for venoarterial bypass. A. Mean aortic root pressure (mAoP). B. Mean systolic aortic root pressure (mSaoP), and C. Mean diastolic aortic root pressure (mDaOP). Bars indicate the standard error. SAP, subclavian artery perfusion; FAP, femoral artery perfusion. *p<0.05, **p<0.01 comparing SAP to FAP at each bypass ratio; *p<0.05, **p<0.01 comparing SAP among bypass ratios; #p<0.05, ##p<0.01 comparing FAP among bypass ratios.

Fig.4. Cardiac work as a function of the bypass ratio using the subclavian and femoral arteries as the access site for venoarterial bypass. A. Tension time index (TTI), B. Endocardial viability ratio (EVR), and C. Left ventricular stroke work (LVSW). Bars indicate the standard error. SAP, subclavian artery perfusion; FAP, femoral artery perfusion. *p<0.05, **p<0.01 comparing SAP to FAP at each bypass ratio; *p<0.05, **p<0.01 comparing SAP among bypass ratios; #p<0.05, ##p<0.01 comparing FAP among bypass ratios.

FAP (Fig. 4-C).

CVP and LAP decreased as the bypass ratio increased because the outflow syringe was lowered to raise the bypass ratio and thereby reduce the cardiac output. No significant difference was observed between SAP and FAP at any bypass ratio (Fig. 5-A, B).

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Fig. 5. Central hemodynamics as a function of the bypass ratio using the subclavian and femoral arteries as the access site for venoarterial bypass. A. Central venous pressure (CVP). B. Left atrial pressure (LAP), and C. Coronary sinus flow (CSF). Bars indicate the standard error. SAP, subclavian artery perfusion; FAP, femoral artery perfusion. *p<0.05, **p<0.01 comparing SAP to FAP at each bypass ratio; *p<0.05, **p<0.01 comparing SAP among bypass ratios; #p<0.05, ###p<0.01 comparing FAP among bypass ratios.

CSF decreased with both SAP and FAP as the bypass ratio increased. At bypass ratios of 50% or more, the CSF with SAP was significantly higher than that with FAP (Fig. 5-C).

At a bypass ratio of 25%, the left intra-

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atrial partial pressures of oxygen (LA-PO$_2$) with SAP and FAP were 67.0 ± 5.9 mmHg and 66.6 ± 6.4 mmHg, respectively. These values increased as the bypass ratio increased, reaching 94.7 ± 10.6 mmHg and 99.5 ± 10.8 mmHg. No significant difference in LA-PO$_2$ was seen between SAP and FAP at any bypass ratio. In contrast to these changes in LA-PO$_2$, the partial pressure of oxygen in the pump blood decreased as the bypass ratio increased, but no difference was seen between SAP and FAP at any bypass ratio. The partial pressure of oxygen in the ascending aorta (AO-PO$_2$) with SAP was significantly higher than that with FAP at a bypass ratio of 85%.

Comparison of LA-PO$_2$ and AO-PO$_2$ revealed a significant step-up in the SAP AO-PO$_2$ at bypass ratios of 75% and more, while no significant change was observed in the FAP AO-PO$_2$ at any bypass ratios, except 100% (Fig. 6).

The mixing ratio reflects the proportion of blood in the ascending aortic blood pumped by the heart to that pumped mechanically. The mixing ratio increased with SAP from 0.419 ± 0.16 at a bypass ratio of 75% to 1.036 ± 0.35 at a bypass ratio of 85%. However, with FAP, even at a bypass ratio of 85%, the mixing rate was only 0.183 ± 0.09, which indicates almost no mixing (Fig. 7).

Coronary AVDO$_2$ decreased as the bypass ratio increased. At bypass ratios of 85% and 100%, AVDO$_2$ with SAP was significantly lower than that with FAP (Fig. 8-A). Oxygen saturation of the coronary sinus blood increased with both SAP and FAP as the bypass ratio increased. However, at bypass ratios of 75% or higher, oxygen saturation with SAP was significantly higher than that with FAP (Fig. 8-B).

The myocardial oxygen extraction with SAP at bypass ratios of 75% or higher was significantly lower than that with FAP (Fig. 8-C).

Myocardial oxygen consumption decreased with both SAP and FAP as the bypass ratio increased. At bypass ratios of 75% and 85%, myocardial oxygen consumption with SAP was significantly higher than that with FAP. However, no significant difference was found between myocardial oxygen consumption with SAP and FAP at a bypass level of 100% (Fig. 8-D).

**DISCUSSION**

VAB has the disadvantage of increasing afterload, although this can be ameliorated to some degree by using it in combination with IABP. When IABP does not provide adequate circulatory assistance, further blood flow augmentation is usually required. It is now common clinical practice to combine IABP and VAP in such patients. The ascending aorta, the subclavian artery and the femoral artery are common bypass sites, but no specific criteria exist for choosing between them during concurrent IABP and VAB.

We found that both systolic and diastolic aortic root pressures decreased significantly with FAP as the bypass ratio increased, while only the systolic aortic root pressure decreased significantly with SAP. Therefore, the difference between SAP and FAP was greatest during diastole. The systolic pressure decreased with SAP and FAP as the bypass ratio increased because the native cardiac output, which is reduced during systole because of preload reduction, is supplemented over the entire cardiac cycle when a pump is used. This leads to a decrease in blood flow into the aorta during systole. In addition, it is assumed that pump flow from the peripheral side of the balloon with FAP
increases as the bypass ratio increases, and that the amount of blood accumulated peripherally increases with balloon inflation. This is followed by a decrease in aortic root pressure with FAP during both systole and diastole. The balloon affects diastolic pressure more than systolic pressure because it inflates during diastole, thereby reducing diastolic augmentation. Since the total blood volume obtained from the central side of the balloon is constant during SAP, regardless of the bypass ratio, reductions in pressure such as those associated with FAP, do not occur, and diastolic pressure is maintained by the diastolic augmentation produced when blood accumulates central to the balloon. The disadvantage of central blood accumulation is that systolic unloading is reduced more with SAP than with FAP.

Afterload was greater with SAP than with FAP, which increased LVSW and myocardial oxygen consumption. Diastolic pressure, which represents coronary perfusion pressure, was higher, along with coronary sinus blood flow, with SAP. EVR, which is a noninvasive index of myocardial oxygen balance, was significantly higher with SAP at all bypass ratios. AVDO₂, which is a direct indicator of myocardial oxygen balance, was significantly lower at bypass ratios of 85% or greater. The O₂ saturation of coronary sinus blood, which represents the myocardial oxygen balance by combining AVDO₂ and coronary artery oxygen content, was also higher with SAP at a bypass ratio of 75% or greater. Braunwald et al. reported that myocardial oxygen consumption can be altered by changing the cardiac output and aortic pressure. Their investigations showed that coronary flow increases and AVDO₂ decreases when cardiac output is held constant and cardiac work and oxygen consumption are increased by elevating the aortic pressure. On the other hand, Sar- noff et al. found that autoregulation of the heart increases coronary flow in response to increased oxygen consumption resulting from an increase in aortic pressure, thereby
maintaining AVDO$_2$ in a steady-state condition. This autoregulation theory has been supported by several other studies.$^{15-18}$

In our investigation, measurements were performed after cardiac output had stabilized, following a 3-min wait to establish homeostasis. A significant difference was found in AVDO$_2$ at a bypass ratio of 85%. Either of two hypotheses may account for this finding. The first involves the range of arterial pressure required to establish homeostasis. Shaw et al.$^{17}$ demonstrated that a regulatory mechanism, such as oxygen-dependent cardiac performance which determines coronary flow, only operates within a physiologic pressure range of 70 to 145 mmHg in the anesthetized, thoracotomized dog, but not at higher or lower pressures. Our investigation was carried out at the lower limit of the physiologic range, and diastolic pressures less than 70 mmHg were observed, especially with FAP at a high bypass ratio. Clinically, most patients who undergo VAB are in shock and have an arterial pressure at the low end of the physiologic range.$^{8,9,12,19-22}$ The second hypothesis is that homeostasis may not be maintained in the ischemic heart. A reduction in AVDO$_2$ has been reported in ischemic heart supported by IABP, which leads to a decrease in systolic pressure and an elevation in diastolic pressure.$^{15}$ It has also been reported that IABP significantly increases collateral flow to ischemic areas$^{23,24}$; other studies have demonstrated that nutrient myocardial blood flow increases in animals treated with IABP, most dramatically in the intermediate and peripheral zones of an infarction$^{25-27}$ These findings suggest that autoregulation is not maintained in ischemic areas. In addition, it is assumed that the right coronary artery is drained almost entirely by the thebesian vessels, and that blood from the left coronary artery is drained into the coronary sinus largely through the superficial veins of the left heart$^{28,29}$ Consequently, it is possible that coronary sinus blood was affected by myocardial ischemia in the distribution of the left coronary artery, with resultant changes in AVDO$_2$.

The coronary blood supply consisted of a mixture of pumped blood and blood from the heart during SAP at bypass ratios of 75% to 85%, but not with FAP at bypass ratios of less than 100%. Takamoto et al.$^{30}$ showed that pumped blood and native cardiac output produce a "mixed zone" in the aorta. They suggested that the combination of VAB and IABP increases this "mixed zone". With SAP, the pumped blood is likely to expand the "mixed zone" and affect coronary blood flow as it gushes from the brachiocephalic trunk towards the ascending aorta. Thus, pumped blood, representing a rich oxygen supply, mixes with poorly oxygenated native cardiac output before supplying the coronary arteries. The use of SAP should be advantageous in patients with respiratory insufficiency with high-flow VAB.

Takamoto et al showed in animal and electrical simulation studies that the effects of afterload reduction are smaller, while those of diastolic augmentation are greater, with subclavian artery pumping than with femoral artery pumping when combined with IABP. They concluded that femoral artery perfusion, which has a large afterload reduction effect, is safer in patients who may be at risk of occlusive lesions.$^{31}$ However, they did not address the issue of myocardial oxygen supply and demand. Fukumura et al.$^{32}$ performed a study using a combination of constant-flow LA bypass and IABP under a bypass ratio of 100%. They found a greater increase in ascending aortic pressure and coronary flow volume with ascending aorta perfusion than with femoral artery perfusion. Clinically, coronary flow alone is insufficient for explaining oxygen balance. In our investigation, at high bypass ratios, SAP was more effective than FAP in achieving diastolic augmentation, reducing the coronary AVDO$_2$ and enhancing myocardial oxygen balance, even though SAP has a smaller systolic unloading effect. Moreover, under such high bypass ratios, SAP brings more highly oxygenated pumped blood to the coronary arteries than FAP.

When VAB is used clinically, a high bypass ratio is often required during the early stages of resuscitation.$^{33}$ Salisbury et al.$^{20}$ reported that only when VAB carried more than 75% of the total systemic flow was there an excess myocardial oxygen supply. Therefore, even when adequate cardiac function is maintained, we try not to maximize cardiac output and to reduce the cardiac work load at flow rates of 2 to 3.5 L/min.
(75% or higher bypass ratio) during the initial 12 to 24 h postoperatively to allow the ischemic heart to recover. A difference between FAP and SAP may exist in just this situation, although the application of such high-flow VAB is currently limited to only a short duration because of hemolysis.

The findings of this investigation support the use of SAP over FAP in patients with severe cardiopulmonary dysfunction requiring a high bypass blood volume, especially in those with myocardial ischemia. These findings may be applicable to left heart bypass in combination with IABP, which also uses a centrifugal pump with a constant flow.

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