Experimental Evaluation of the Influence of Complete Artificial Circulation on Renal Circulation and Tissue Metabolism—Comparative Study of Pulsatile vs Nonpulsatile Circulation—

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In this study, pulsatile and nonpulsatile assisted circulation were compared to evaluate renal circulation under complete artificial circulation. In addition, differences were also compared between animals supported by high (assist rate 80\%-)- and low (assist rate 60\%-)-level artificial circulation.

Using 20 pigs, ventricular fibrillation was induced after cardiogenic shock, assist by mechanical support by pulsatile and nonpulsatile artificial circulation. Hemodynamics and renal circulation were evaluated by measuring renal arterial blood flow, renal cortical blood flow, renal medullar blood flow, cortical/medullar flow ratio, serum urea nitrogen levels, blood creatinine levels, urinary \( \beta_2 \)-microglobulin (MG) levels, and serum \( \beta_2 \)-MG levels. Tissue metabolism was evaluated by comparing arterial ketone body ratios and lactic acid/pyruvic acid ratios.

During the acute stage of cardiogenic shock, redistribution of renal blood flow and tissue metabolism were improved in the pigs with pulsatile artificial circulation, suggesting the usefulness of pulse pressure. In nonpulsatile artificial circulation, the possibility of irreversible renal dysfunction was suggested. Although changes in renal blood flow were smaller in high-level artificial circulation than in low-level artificial circulation, physiological maintenance of renal circulation was better in pulsatile artificial circulation than in nonpulsatile artificial circulation. These results suggest that this effect of pulsatile assisted circulation may become more marked when evaluated in the early state after cardiogenic shock. (Ann Thorac Cardiovasc Surg 2003; 9: 355–64)

Key words: assisted circulation, VAD, pulsatile, nonpulsatile

Introduction

During the 1980s, it was reported experimentally that nonpulsatile circulatory support contributes to survival without inducing any physiological abnormalities,\(^1\) and the usefulness of nonpulsatile assisted circulation has been evaluated experimentally from various points of view.\(^2\)-\(^4\) However, all of these studies have been evaluated using normal hearts, and no previous studies have been conducted to research the usefulness of nonpulsatile assisted circulation in cardiogenic shock models.

After the onset of cardiogenic shock, redistribution of blood flow occurs as blood flow in the heart and brain is relatively maintained by the biological defense mechanism, though blood flow in the kidneys, liver, and skeletal muscles decreases proportionally. Prolonged uneven distribution of organ blood flow may cause multiple organ failure (MOF). In this institution, the usefulness of left ventricular assisted circulation for cardiogenic shock has been evaluated establishing that pulsatile assisted circulation was more useful for maintaining peripheral circulation (renal circulation in particular) and tissue metabolism than nonpulsatile assisted circulation.\(^5\)\(^6\) Particularly after the onset of cardiogenic shock, sufficient blood flow cannot be maintained by nonpulsatile assisted circulation in many patients.

In this study, to further compare the usefulness of pul-
Satellite and nonpulsatile assisted circulation, we excluded the influence of natural, and compared pulsatile and nonpulsatile assisted circulation under complete artificial circulation (biventricular assist under the state of ventricular fibrillation). In addition, assuming decreases in assisted blood flow that we frequently encounter in the clinical setting, two different levels of assisted circulation were established. Subsequently, experimental evaluation was performed focusing particularly on renal circulation and tissue metabolism.

Materials and Methods

All the experiments were performed according to the guidelines for animal experiments (Exp Anim 1987; 36: 285–8, JALAS).

Using 20 pigs (mean body weight: 43.2±3.2 kg), anesthesia was induced by administering sodium pentobarbital (20-25 mg/kg) via a vein in the right ear, followed by the maintenance of anesthesia with intravenous ketamine hydrochloride (1 mg/kg/hr). After tracheostomy, ventilation was regulated by maintaining the ventilation frequency and volume at 20-25 times/min and 10-15 ml/kg/ventilation, respectively, using a ventilator (Sarvo Ventilator 900E, Siemens Elema Inc., Stockholm, Sweden). A 7-Fr pigtail catheter was inserted through an internal carotid artery to measure aortic pressure and collect blood samples. A multi-lumen central venous catheter was inserted through an internal jugular vein to measure central venous pressure. Intravenous drip-infusion of electrolyte solution containing glucose was administered at a rate of 20 ml/kg/hr. Blood samples were collected 30 minutes later, and blood glucose levels were maintained at around 200 mg/dl while maintaining pH, PaO\textsubscript{2}, and PaCO\textsubscript{2} at specified levels.

The chest was opened by median sternotomy, and an electromagnetic flowmeter (FB type, Nihon Kohden Co., Tokyo, Japan) was placed at the base of the ascending aorta to measure aortic blood flow. Subsequently, the sum of native aortic blood flow and pump flow was used as a total cardiac output. Following systemic administration of heparin (1 mg/kg), on left heart bypass, an inflow cannula in was inserted into the left ventricle and an outflow cannula into the ascending aorta. On right heart bypass, an inflow cannula was inserted into the right ventricle and an outflow cannula into pulmonary artery. An acute myocardial infarction model was made by ligation of diagonal branches of the anterior descending branch of the left coronary artery. After failing of the ventricular fibrillated heart, all pigs were supported by artificial circulation for three hours. Pigs were divided into the following two groups: pigs supported by nonpulsatile artificial circulation (Group NP: n=10) and those supported by pulsatile artificial circulation (Group P: n=10). In both groups, right heart bypass was maintained using centrifugal pumps (HPM-15, Nikkiso Inc., Tokyo, Japan). To maintain left heart bypass, a centrifugal pump was used in Group NP, and a pneumatic ventricular assist device, (volume = 40 ml, Zeon Medical Inc., Tokyo, Japan) was used in Group P. Furthermore, Groups P and NP were subdivided into the following four groups assuming the possibility of sufficient and insufficient recovery of aortic blood flow obtained before the onset of cardiogenic shock: pigs in which 60% of aortic blood flow was supported by artificial circulation (Group P\textsubscript{60}: n=5, Group NP\textsubscript{60}: n=5) and those in which 80% of aortic blood flow was supported by artificial circulation (Group P\textsubscript{80}: n=5, Group NP\textsubscript{80}: n=5). Subsequently, the left kidney was exposed retroperitoneally, and a Doppler blood flowmeter (T206, Transonic Systems Inc., Ithaca, NY, USA) was attached to the left renal artery. To evaluate renal blood flow, tissue blood flow was measured using a tissue blood flowmeter (ALF21RD, Advance Inc., Tokyo, Japan) inserted into a portion 5 mm deep from the kidney surface (cortical area) and another blood flowmeter inserted into a portion 10 mm deep from the surface (medullary area) (Fig. 1). To evaluate the usefulness of pulsatile assisted circulation and to compare differences in the level of circulatory support, hourly urine volume, arterial ketone body ratios (AKBR), and levels of lactic acid, pyruvic acid, blood urea nitrogen (BUN), and serum creatinine (Cr) were measured, in addition to blood and urinary levels of β\textsubscript{2}-microglobulin (β\textsubscript{2}-MG). The results were expressed as the mean ± SD, and one-way ANOVA was used to evaluate serial changes and to test the significance among the respective groups. When significant differences were observed, multiple comparisons were performed using the Scheff method, and p<0.05 was considered statistically significant.

Results

Hemodynamics (Table 1)

After the onset of ventricular fibrillation, the mean aortic pressure significantly decreased to 30 mmHg in the respective groups. Three hours after the initiation of assisted circulation, the mean aortic pressure recovered to 90 mmHg in Groups NP\textsubscript{80} and P\textsubscript{80}, while it was main-
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Mean aortic pressure (mmHg)

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<td>92.3±9.7</td>
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Pulse pressure (mmHg)

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Total cardiac output (L/min)

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<td>3.5±0.25</td>
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<td>3.72±0.36</td>
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<td>3.60±0.60</td>
<td>0.29±0.12</td>
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<td>Group P 60% bypass</td>
<td>3.78±0.44</td>
<td>0.30±0.17</td>
<td>2.27±0.30</td>
<td>2.05±0.24</td>
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Fig. 1. Experimental model.

Table 1. Hemodynamics

tained at 75 mmHg in Groups NP80 and P80. Aortic pressure did not significantly differ among the groups. After the initiation of assisted circulation, pulse pressure did not significantly differ between Groups P80 and P60 (31.0±7.0 mmHg in Group P80 vs. 26.0±5.3 mmHg in Group P60). On the other hand, pulse pressure was maintained at 4 mmHg in Groups NP80 and NP60, and there were no significant differences between the two groups. After the induction of cardiogenic shock, the total cardiac output significantly decreased to 0.27 L/min in the respective groups. However, three hours after the initiation of assisted circulation, the total cardiac output decreased to a level 80% of that before cardiogenic shock in Groups NP80 and P80. In addition, the total cardiac out-
Renal arterial blood flow decreased to a level 60% of that before cardiogenic shock three hours after the initiation of assisted circulation.

Renal arterial blood flow (Fig. 2)
Renal arterial blood flow did not significantly differ between Groups NP$_{80}$ and P$_{80}$ during the three hours after the initiation of assisted circulation (31.0±7.5 ml/min in Group NP$_{80}$ vs. 40.3±7.9 ml/min in Group P$_{80}$). However, renal arterial blood flow tended to improve more in Group P than that in Group NP. Renal arterial blood flow significantly differed between Groups NP$_{60}$ and P$_{60}$ during the three hours after the initiation of assisted circulation (9.3±7.8 ml/min in Group NP$_{60}$ vs. 24.4±7.4 ml/min in Group P$_{60}$). Although renal arterial blood flow did not significantly differ between Groups P$_{80}$ and NP$_{80}$, it significantly differed between Groups P$_{60}$ and NP$_{60}$ during the first three hours after the initiation of assisted circulation. Renal cortical/medullar blood flow ratios obtained three hours after assisting were 0.40±0.9 in Group NP$_{80}$ and 0.53±0.08 in Group P$_{80}$, and there was no significant difference between the two groups. However, the ratio tended to improve more in Group P than in Group NP. Renal cortical/medullar blood flow ratios obtained three hours after the initiation of assisted circulation were 0.18±0.08 in Group NP$_{60}$ and 0.41±0.05 in Group P$_{60}$, and the ratio tended to improve more in Group P than in Group NP from the second hour of assisted circulation. Although the renal cortical/medullar blood flow ratio did not significantly differ between Groups P$_{60}$ and NP$_{60}$, it significantly differed between Groups P$_{80}$ and NP$_{60}$ during the first three hours after the initiation of assisted circulation.

Tissue blood flow in the renal cortex and medulla and their ratio (Fig. 3)
Renal circulation was evaluated by comparing tissue blood flows in the renal cortex and medulla obtained after the initiation of assisted circulation to those obtained before the induction of cardiogenic shock. Renal cortical tissue blood flow obtained one hour after the initiation of assisted circulation were 0.89±0.11 in Group P$_{80}$ and 0.68±0.04 in Group NP$_{80}$, and there was a significant difference between the two groups. Although the renal cortical tissue blood flow obtained two and three hours after assisting did not significantly differ between the two groups, renal tissue blood flow tended to improve more in Group P than in Group NP. Renal cortical tissue blood flow obtained three hours after the initiation of assisted circulation were 0.19±0.09 in Group NP$_{60}$ and 0.52±0.12 in Group P$_{60}$.
in Group P60. Therefore, renal cortical tissue blood flow significantly improved more in Group P60 than in Group NP60 during the first three hours after the initiation of assisted circulation. Although renal cortical tissue blood flow did not significantly differ between Groups P80 and NP80, it significantly differed between Groups P60 and NP60 during the first three hours after the initiation of assisted circulation. Tissue blood flow in the renal medulla slightly decreased in the respective groups immediately after assisting, however, it did not significantly differ among the respective groups thereafter.

**Changes in urinary and blood β2-MG levels** (Fig. 4)
Urinary β2-MG levels did not increase in Group P60 even after the initiation of assisted circulation, however, they increased in Group NP60. Therefore, urinary β2-MG levels obtained three hours after the initiation of assisted circulation significantly differed between Groups NP60 and P60 (24.43±2.1 μg/L vs. 20.42±1.81 μg/L in Group P60). Although urinary β2-MG levels did not significantly differ between Groups NP80 and P80, they were slightly lower in Group P than in Group NP. In addition, urinary β2-MG levels did not significantly differ between Groups P60 and NP80, however, they significantly differed between Groups P60 and NP60 two and three hours after the initiation of assisted circulation. During the first three hours after the initiation of assisted circulation, blood β2-MG levels did not significantly increase in any of these groups, and there were no significant differences among the four groups.

**AKBR and lactic acid/pyruvic acid (L/P) ratio** (Fig. 5)
Since AKBR was maintained at around the value obtained before the induction of cardiogenic shock even after the initiation of assisted circulation, it did not significantly differ among the four groups. Although AKBR decreased immediately after the induction of cardiogenic shock, it did not significantly differ between Groups P80 and NP80. However, it tended to improve more in Group P than in Group NP two hours after the initiation of assisted circulation (0.68±0.09 in Group P80 vs. 0.52±0.11 in Group NP80). In addition, AKBR significantly improved more in Group P60 than in Group NP60 from the second hour of assisted circulation (three-hour values: 0.53±0.09 in Group P60 vs. 0.33±0.04 in Group NP60). Although AKBR did not significantly differ between Groups P80 and NP80, it significantly differed between Groups P60 and NP60 during the first three hours after the initiation of assisted circ-
Fig. 4. Urine and serum β2-microglobulin.

Fig. 5. Arterial keton body ratio and lactate/pyruvic acid.
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Compared to the L/P ratio obtained before the induction of cardiogenic shock, it did not significantly change in any of these four groups even after the initiation of assisted circulation. Although mean L/P ratios obtained three hours after the initiation of assisted circulation were slightly higher in Group NP60 than in Group P80, they did not significantly differ between the two groups (34.5±10.1 in Group P80 vs. 47.8±8.1 in Group NP60). In addition, the mean L/P ratio increased significantly in Group NP60 from the third hour of assisted circulation (three-hour values: 62.5±7.2 in Group NP60 vs. 40.5±9.1 in Group P60). Although the L/P ratio did not significantly differ between Groups P60 and NP60, it significantly differed between Groups P80 and NP60 during the first three hours after the initiation of assisted circulation.

Changes in BUN and Cr levels
Compared to BUN and Cr levels obtained before the induction of cardiogenic shock, BUN and Cr levels did not significantly change in any of these four groups during the first three hours after the initiation of assisted circulation. In addition, BUN and Cr levels did not significantly differ among the four groups.

Urine volume (Fig. 6)
Urine volume slightly decreased in Groups P60 and NP60 after the initiation of assisted circulation, although it did not significantly differ between the two groups. Urine volume obtained three hours after the initiation of assisted circulation was higher in Group P60 than in Group NP60 (67.0±15.2 ml/hr in Group P60 vs. 45.0±12.0 ml/hr in Group NP60). However, urine volume significantly differed between Groups P60 and NP60, and it decreased markedly in Group NP60 three hours after the initiation of assisted circulation (11.0±9.2 ml/hr in Group NP60 vs. 46.0±12.8 ml/hr in Group P60). Although urine volume did not significantly differ between Groups P80 and NP80, it significantly differed between Groups P60 and NP60 during the first three hours after the initiation of assisted circulation.

Discussion
The number of patients with severe heart failure has increased with the advances in mechanical assist devices. However, a prolonged course of heart failure frequently results in fatal MOF. Currently, various methods of assisted circulation, including percutaneous cardiopulmo-
nary support (PCPS) and circulatory support by ventricu-
lar assist device (VAD), have been used in clinical set-
tings as potent supporting devices. In addition, many ba-
sic and clinical studies regarding these procedures have
been conducted to date. Recent clinical studies have re-
ported that nonpulsatile circulatory support is useful for
bridging to heart transplantation. Since long-term sur-

vival of animals supported by nonpulsatile assisted cir-
culation has been reported, several experimental studies
have reported the usefulness of nonpulsatile circulatory
support for normal hearts. However, no studies have eval-
uated the usefulness of nonpulsatile circulatory support in

cardiogenic shock models. In recent years, nonpulsatile
axial flow pumps have been clinically used as a VAD for
bridge to transplantation. Although some studies have
reported the usefulness of nonpulsatile axial flow pumps,
several cases of patient death caused by thrombosis or
MOF have also been reported to date. Therefore, the use-
fulness of nonpulsatile flow pumps is currently question-
able. Previously, a comparative study of pulsatile and
nonpulsatile assisted circulation has been conducted in
this institution. During left ventricular support for heart
failure, both pulsatile and nonpulsatile assisted circula-
tion were equally useful for supporting the failing heart.
However, pulsatile assisted circulation was more useful
for maintaining peripheral organ blood flow and tissue
metabolism than nonpulsatile assisted circulation. In par-
cular, pulsatile assisted circulation is markedly more
useful for maintaining renal circulation and tissue me-
tabolism than nonpulsatile assisted circulation. In the state
of shock, the biological defense mechanism maintains
organ blood flow in the heart and brain, while blood flow
decreases in the kidneys, liver, and skeletal muscles, re-
sulting in redistribution of organ blood flow. Since renal
blood flow decreases immediately after the onset of car-
diogenic shock, the kidneys are the target organ of shock.
In this experiment, a comparative study of nonpulsatile
and pulsatile assisted circulation has been conducted un-
der complete artificial circulation (biventricular bypass
method under the state of ventricular fibrillation). Fur-
thermore, renal circulation was compared between pigs
supported by high assist rate of 80% (high-assist) and
low assist rate of 60% (low assist) assisted circulation.
When mean aortic pressure and total cardiac output were
compared among pigs in which 80% and 60% of aortic
blood flow was supported by artificial circulation, they
did not significantly differ between pigs supported by
pulsatile and nonpulsatile artificial circulation. Although
mechanical ventilation produced approximately 4 mmHg
of pulse pressure in Groups NP50 and NP60 during artifi-
cial circulation, these pigs were successfully supported
by nonpulsatile assisted circulation.
Concerning renal arterial blood flow, pulsatile assisted
circulation was apparently predominant over nonpulsatile
assisted circulation particularly in pigs supported by low-
assist artificial circulation. In addition to factors previ-
ously known to influence renal blood flow such as the
renin-angiotensin-aldosterone system, sympathetic ner-
vous system, prostaglandins, and the kallikrein-kinin sys-
tem, atrial natriuretic peptides are also known to influ-
ence renal blood flow. However, much of this mechanism
remains unclear. These biological factors are involved in
changes in perfusion volume and pressure in renal blood
vessels, thus constructing complicated mechanisms of
autoregulation. However, following decreases in cardiac
output after the onset of cardiogenic shock, when perfu-
sion pressure decreases beyond the specified limit, renal
arterial blood flow decreases, resulting in redistribution
of renal blood flow. In humans, perfusion in the renal
cortex usually accounts for 90% of renal blood flow, how-
ever, cortical blood flow markedly decreases after the
onset of cardiogenic shock. It has been reported that re-
nal medullar blood flow is relatively resistant to the in-
fluence of cardiogenic shock. In this experiment, re-
distribution of renal blood flow was observed after the
induction of cardiogenic shock. That is, cortical blood
flow, which was predominant over medullar blood flow
before the induction of cardiogenic shock, decreased im-
mEDIATELY after the induction of cardiogenic shock, al-
though medullar blood flow was maintained thereafter.
Pulsatile assisted circulation was useful for recovering
the normal distribution of renal blood flow. In the state of
cardiogenic shock, the development of renal failure should
be prevented by rapidly improving uneven distribution
of renal blood flow. Pulsatile assisted circulation was use-
ful for this purpose, particularly in pigs supported by a
relatively low level of assisted circulation (60%).
Urinary β2-MG levels sharply reflected the presence
of tubular disorders. In addition, negative correlation be-
tween serum β2-MG levels and glomerular filtration rate
has been reported to date. In this experimental model,
increased urinary β2-MG levels suggested the occurrence
of proximal tubular disorders during the early stage of
cardiogenic shock. In addition, the severity of proximal
tubular disorders was higher in pigs supported by low-
assist nonpulsatile assisted circulation, suggesting the
usefulness of pulse pressure. In particular, the results of
this study suggested that low-assist nonpulsatile assisted circulation may cause irreversible nephropathy. After the induction of cardiogenic shock, blood levels of β2-MG, BUN, and Cr did not increase during artificial circulation, although blood levels of β2-MG, BUN, and Cr usually increase when the glomerular filtration rate decreases. In this study, however, blood levels of these biological markers were only evaluated during the first three hours after the induction of cardiogenic shock. Therefore, time factors should be considered during evaluation.

German et al. reported that nonpulsatile assisted circulation induced hypoxia in the renal tissue or metabolic acidosis. In addition, Funami et al. reported that nonpulsatile assisted circulation caused mitochondrial destruction in renal tubular epithelial cells and intracellular cavitation. Thus, many previous studies have reported tissue damages occurred during nonpulsatile assisted circulation. The L/P ratio is reported to reflect the hypoxic state in the tissue. In this experiment, the L/P ratio did not significantly change in pigs supported by high-assist pulsatile assisted circulation even after the induction of cardiogenic shock. Although the L/P ratio did not significantly differ between pulsatile and nonpulsatile assisted circulation, the pulsatile group showed better L/P ratios than the nonpulsatile group. Moreover, the L/P ratio tended to improve significantly in pigs in which 60% of aortic blood flow was supported by artificial circulation. These findings suggest that pulsatile assisted circulation is useful for supplying oxygen to the tissue supported by low-assist artificial circulation. Nonpulsatile assisted circulation may cause hypoxia in the tissue, probably resulting in irreversible cell damage. In addition, AKBR reflects the oxidation-reduction capacity of mitochondria in liver cells. Although AKBR did not recover to a value obtained before the induction of cardiogenic shock in any of these groups examined after the initiation of assisted circulation, it tended to improve in high-assist (80%) pulsatile assisted circulation. In low-assist (60%) nonpulsatile assisted circulation, AKBR decreased to a level below 0.4, which was a fatal condition. Therefore, AKBR significantly differed between high-assist pulsatile and low-assist nonpulsatile groups. Although urine volume did not decrease in pigs in which 80% of aortic blood flow was supported by pulsatile assisted circulation, it markedly decreased in pigs supported by low-level nonpulsatile assisted circulation. Therefore, it was found that pulsatile assisted circulation was indispensable to secure urine volume necessary for maintaining renal function.

In their chronic animal experiments using the normal heart, Nose et al. reported that increases in blood flow by 20% during nonpulsatile assisted circulation showed favorable results similar to those obtained by pulsatile assisted circulation. However, mechanical ventricular support is usually used in shocked patients with a higher tendency of fluid retention into the third space. Initially, an experiment using pigs completely supported by artificial circulation was planned, however, sufficient blood could not be pumped out during the acute stage of cardiogenic shock, and 100% blood flow was not maintained even when pigs were supported by nonpulsatile assisted circulation, although it has been reported that the blood is easily pumped out during nonpulsatile assisted circulation. Therefore, we abandoned this experimental plan. In this experiment, levels of assisted circulation were established at 60% and 80% of aortic blood flow obtained before the induction of cardiogenic shock. However, pulsatile assisted circulation was apparently predominant over nonpulsatile assisted circulation when pigs were supported by low-level artificial circulation, suggesting that nonpulsatile assisted circulation may cause irreversible tissue damages. During the acute stage of cardiogenic shock, the results of pulsatile assisted circulation were markedly better than those of nonpulsatile assisted circulation. However, even when nonpulsatile assisted circulation is used, better results can be expected if sufficient blood flow is maintained. For this purpose, at least 80% or higher level of aortic blood flow should be maintained during nonpulsatile assisted circulation.

In the future, the author would like to elucidate the influence of various biological factors such as the renin-angiotensin-aldosterone system, sympathetic nervous system, atrial natriuretic peptides, and cytokines on renal blood flow in detail.

Conclusions

A comparative study of the usefulness in pulsatile and nonpulsatile artificial circulation was conducted for cardiogenic shock from the perspective of renal circulation and tissue metabolism. Furthermore, their usefulness was also compared between pigs supported by different levels of artificial circulation.

During the acute stage of cardiogenic shock, redistribution of renal blood flow tended to improve more in pigs supported by pulsatile artificial circulation, demonstrating the usefulness of pulse pressure.

The effect of pulse pressure was marked particularly
in pigs supported by low-level artificial circulation, and the possibility of irreversible nephropathy was suggested in pigs supported by nonpulsatile artificial circulation.

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References