

## Efficacy and Adverse Effects of the Coronary Active Perfusion System—From a Viewpoint of Perfusional Timing—

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**We developed a coronary active perfusion system (CAPS) to avoid myocardial ischemia during off-pump coronary artery bypass (OPCAB). The purpose of this study was to determine the optimal timing of CAPS perfusion, and to investigate any adverse effects when it is driven within the systolic phase. Twenty-four pigs were divided into four groups: (A) systolic, (B) early-diastolic, (C) middle-diastolic, and (D) late-diastolic perfusion. Myocardial blood flow (MBF), hemodynamic and mechanical data were measured during 30 minutes of CAPS perfusion. MBF in group A was lower than in the other groups ( $p < 0.001$ ), but no significant differences were observed among groups B to D. End-systolic pressure-volume relation (Mw) and preload recruitable stroke work relation (Ees) in group A was lower than in groups B to D ( $p < 0.01$  and  $p < 0.05$ , respectively), but no significant differences were observed among groups B to D. CAPS could maintain regional MBF and left ventricular function if it was driven only within the diastolic phase and required no strict adjustment, but CAPS has an adverse effect when it is driven in the systolic phase. (Ann Thorac Cardiovasc Surg 2003; 9: 117–22)**

**Key words:** coronary active perfusion system (CAPS), off-pump coronary artery bypass (OPCAB), myocardial blood flow (MBF), optimal timing setting

### Introduction

Recently off-pump coronary artery bypass (OPCAB) has become a popular procedure,<sup>1,2)</sup> however, it is still a serious problem that temporary occlusion of the target coronary artery induces myocardial ischemia. To perform OPCAB safely without myocardial ischemia, we developed a coronary active perfusion system (CAPS).<sup>3,4)</sup> CAPS is a device to inject arterial blood into the coronary artery in a pulsatile manner using a computer-controlled syringe pump system (Fig. 1). The injection timing of CAPS is

adjusted by synchronizing with an electrocardiogram waveform, and it is designed to be within the diastolic phase. However, the diastolic phase has some width and what place within the diastolic phase is optimal for CAPS perfusion is unknown. On the contrary, adverse effects may occur if it is driven within the systolic phase.

The purpose of this study was to determine the optimal timing to perform CAPS perfusion, and to investigate any adverse effects in cases it is driven within the systolic phase.

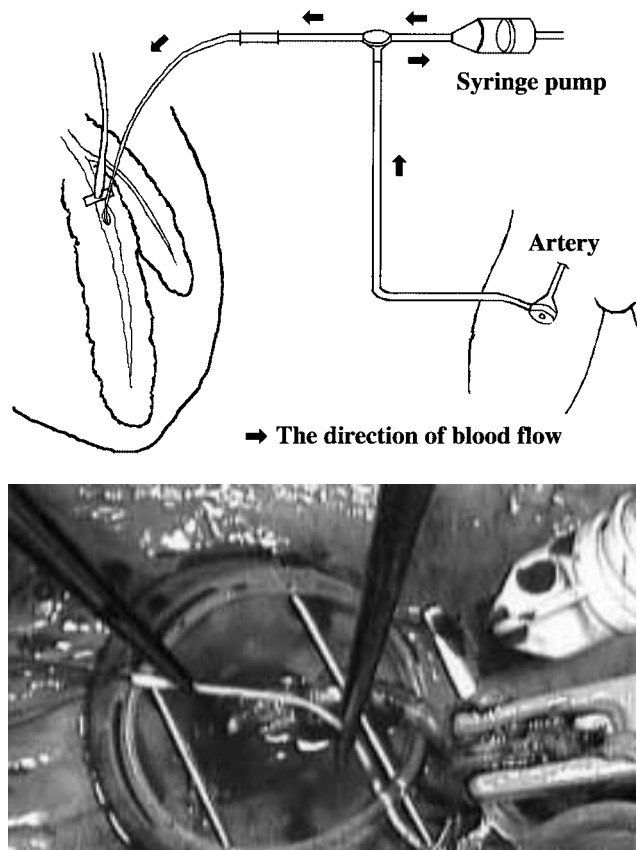
### Materials and Methods

All animals received human care in compliance with the 'Principles of Laboratory Animals 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 Institute of Health (NIH Publication No. 86-23, revised 1985).

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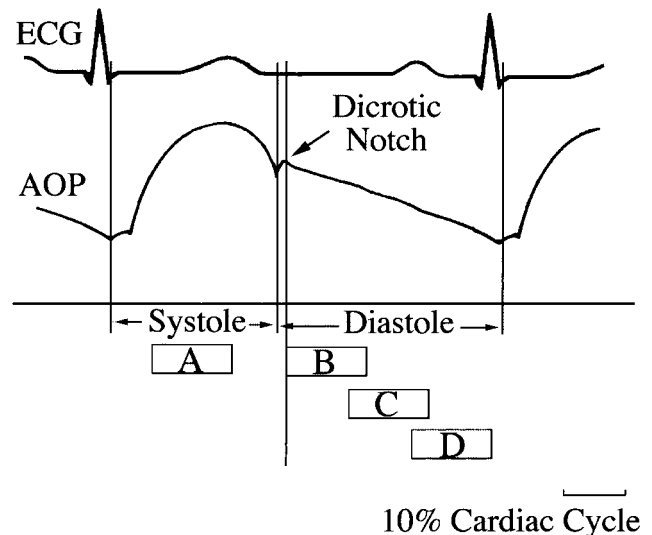
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**Fig. 1.** Upper, schematic presentation of the CAPS; lower, the usage of CAPS in clinical OPCAB.

Twenty-four Pigs were divided randomly into four groups: systolic phase perfusion group (group A, n=6), early-diastolic phase perfusion group (group B, n=6), middle-diastolic phase perfusion group (group C, n=6), and late-diastolic phase perfusion group (group D, n=6). The cardiac cycle was maintained between 80 and 90 bpm, and CAPS perfusion was performed with a 0.1 ml/stroke and 0.7 ml/sec setting in all the groups. The initiation of injection was adjusted at the dicrotic notch in group B, and that in groups A, C, D was adjusted at -20%, +10%, and +20% of the cardiac cycle from the dicrotic notch, respectively (Fig. 2).

Twenty-four pigs with a body weight of  $51.2 \pm 4.2$  kg were studied. The study protocol was the same as our previous study.<sup>3,4)</sup> Briefly, the CAPS cannula was cannulated into the left anterior descending coronary artery, and CAPS perfusion was performed for 30 min, and regional myocardial blood flow (MBF), hemodynamic and mechanical data were recorded. At the end of the experiment, the pigs were given a lethal intravenous injection

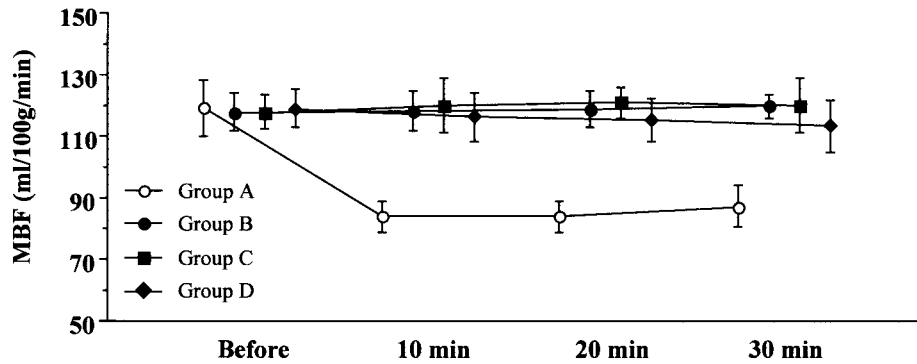


**Fig. 2.** The experimental protocol represented diagrammatically. The perfusion timing was divided into four pattern groups: systolic phase perfusion group (A), early-diastolic phase perfusion group (B), middle-diastolic phase perfusion group (C), and late-diastolic phase perfusion group (D). The square means the perfusion period. ECG, electrocardiogram; AOP, aortic pressure.

of pentobarbital and potassium, and transmural samples of the regional myocardium were taken for measurement of myocardial water content and histological examination.

Regional MBF was measured by a thermal diffusion probe connected to a thermal diffusion blood flow monitor (BTG-221, Biomedical Science Co. Ltd., Kanazawa, Japan) continuously during the experiments.<sup>4,5)</sup>

Hemodynamic data were acquired during disconnection of the ventilation in end-expiration to minimize the effects of intrathoracic pressure variations, and mechanical data were acquired during variable loaded beats by occluding the inferior vena cava for 10 seconds. The conductance catheter was connected to a Leycom Sigma-5 signal-conditioner processor (CardioDynamics BV, Zoetermeer, the Netherlands). The volume signal was corrected to absolute volume by calibrating the signal for parallel conductance and to the specific conductivity of the blood. The volume and pressure signals were processed and analyzed (Conductance-PC software, CardioDynamics BV, Zoetermeer, the Netherlands). Left ventricular contractility was quantitated by the slope of the end-systolic pressure-volume relation [Ees (mmHg/ml)], and the global left ventricular function was evaluated by the slope of the preload recruitable stroke work



**Fig. 3.** The changes in regional MBF during experiments. Data are presented as mean  $\pm$  standard deviation.

**Table 1. Hemodynamic data**

	Before	10 min	20 min	30 min
HR				
Group A	84.2 $\pm$ 2.8	86.0 $\pm$ 2.8	84.5 $\pm$ 1.6	84.5 $\pm$ 2.1
Group B	83.6 $\pm$ 3.0	83.0 $\pm$ 2.9	85.6 $\pm$ 2.1	85.3 $\pm$ 2.4
Group C	83.3 $\pm$ 1.9	83.8 $\pm$ 1.8	83.6 $\pm$ 3.2	81.5 $\pm$ 2.6
Group D	83.0 $\pm$ 1.3	83.6 $\pm$ 1.7	83.8 $\pm$ 2.9	82.7 $\pm$ 2.5
AOP				
Group A	99.2 $\pm$ 4.6	99.0 $\pm$ 10.1	97.5 $\pm$ 8.6	98.0 $\pm$ 7.5
Group B	102.0 $\pm$ 4.9	99.0 $\pm$ 8.7	98.8 $\pm$ 3.2	96.0 $\pm$ 6.9
Group C	97.0 $\pm$ 4.5	93.8 $\pm$ 5.7	94.2 $\pm$ 4.1	93.8 $\pm$ 7.7
Group D	96.2 $\pm$ 5.0	93.3 $\pm$ 6.3	93.6 $\pm$ 6.8	93.7 $\pm$ 8.3
CO				
Group A	2.30 $\pm$ 0.18	2.11 $\pm$ 0.19	2.10 $\pm$ 0.15	2.15 $\pm$ 0.24
Group B	2.21 $\pm$ 0.16	2.19 $\pm$ 0.21	2.27 $\pm$ 0.35	2.37 $\pm$ 0.39
Group C	2.23 $\pm$ 0.17	2.14 $\pm$ 0.20	2.22 $\pm$ 0.20	2.24 $\pm$ 0.31
Group D	2.21 $\pm$ 0.22	2.14 $\pm$ 0.19	2.15 $\pm$ 0.36	2.16 $\pm$ 0.15

HR, heart rate (bpm); AOP, mean aortic pressure (mmHg); CO, cardiac output ( $\times 10^3$  ml/min).

relation [Mw (erg/ml  $\times 10^3$ )].<sup>6,7</sup>

Transmural samples of the left ventricular anterior wall distal to the left anterior descending coronary artery were taken at the end of the experiment for measurements of wet weight/dry weight ratios. The water content (percent) was determined by the following formula:

$$\text{Myocardial water content} = (\text{wet weight} - \text{dry weight}) / \text{wet weight} \times 100 (\%)$$

The remaining heart tissues were fixed in phosphate-buffered 10% formalin overnight. Tissue was dehydrated, embedded, sectioned, and stained with hematoxylin-eosin. Myocardial edema and vessel injury to the endothelium and the intima were examined.

Results are presented as the mean  $\pm$  standard deviation. Paired comparisons with the Student's *t* test were used for comparisons versus baseline data in each group.

One-way ANOVA was used for comparisons of myocardial water content between groups, and repeated measures ANOVA was used for comparisons of other factors between the groups (StatView 5.0, Abacus Concepts Inc., Berkeley, CA, USA).

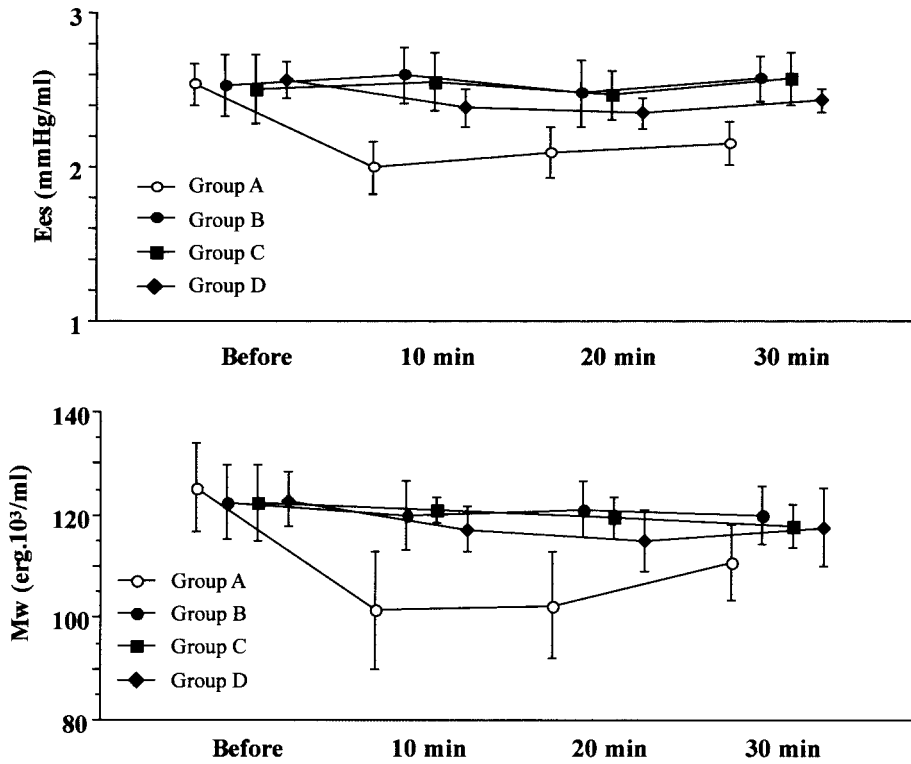
## Results

### Regional MBF

The changes in the regional MBF are shown in Fig. 3. The regional MBF in groups B to D were higher than in group A ( $p < 0.001$ ), however, there were no significant differences among groups B to D.

### Hemodynamics

All hemodynamic data are shown in Table 1. No differences were observed between changes in hemodynamic data in any of the groups.



**Fig. 4.** Upper, the changes in the slope of the end-systolic pressure-volume relation (Ees) during experiments; lower, the changes in the slope of the preload recruitable stroke work relation (Mw) during experiments. Data are presented as mean  $\pm$  standard deviation.

**Left ventricular function**

The changes in Ees and Mw are shown in Fig. 4. Ees in group A was significantly lower than in other groups ( $p < 0.01$ ), but Ees showed no significant difference among groups B to D. Mw in group A was significantly lower than in other groups ( $p < 0.05$ ), but Mw showed no significant difference among groups B to D.

**Myocardial water content**

Myocardial water contents in groups A to D were  $80.6 \pm 3.8\%$ ,  $75.2 \pm 2.5\%$ ,  $75.8 \pm 2.5\%$ ,  $76.6 \pm 2.0\%$ , respectively. Myocardial water content in group A was lower than in the other groups with significant difference ( $p < 0.03$ ), but no significant differences were observed among groups B to D.

**Histological examination**

The appearance of edema with interstitial space was observed only in group A (Fig. 5). At the left anterior descending coronary artery distal to the cannula tip, endothelium cells were well preserved in all the groups.

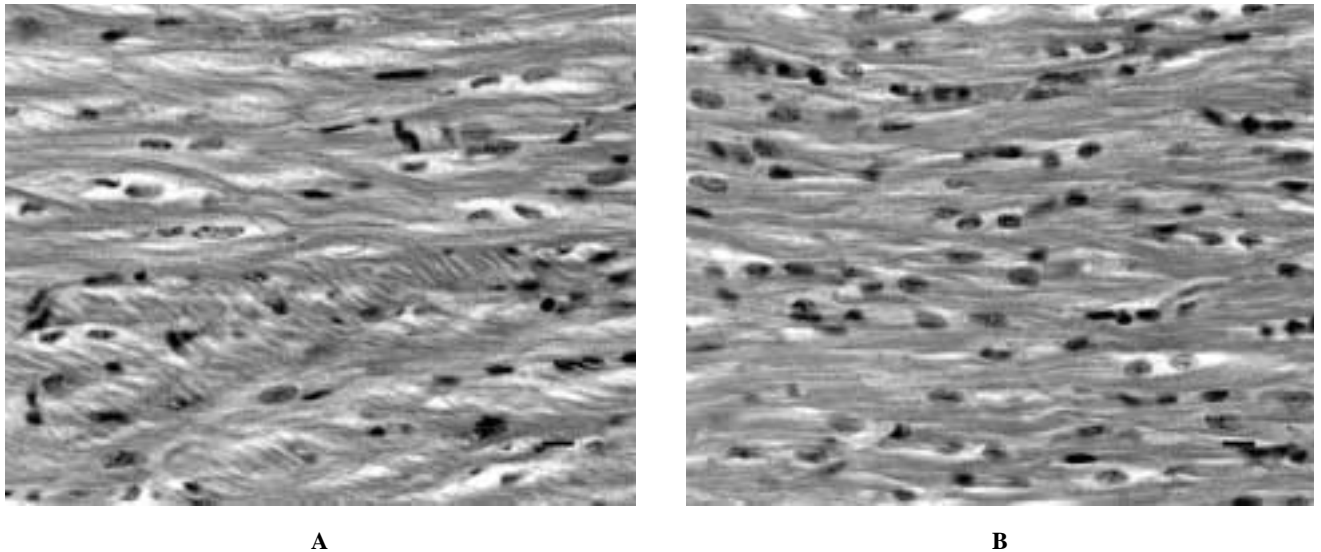
**Discussion**

In this study, regional MBF and left ventricular function

were better maintained in groups B to D than in group A, although there were no significant differences among the groups regarding hemodynamics. Analysis of myocardial water content and histological examination revealed myocardial edema in group A. Among groups B to D, no significant differences were observed in any factors.

Several methods have been devised to avoid or reduce myocardial ischemia during OPCAB, however, there has been no method to avoid it completely. The ischemic preconditioning method<sup>8,9)</sup> is well known, but requires too much time. Furthermore, it may not be a safe method in cases requiring a prolonged anastomosis time. The intracoronary shunt<sup>10,11)</sup> method has been popular for this purpose. However, we consider that the efficacy of an intracoronary shunt is doubtful because it should always be placed distal from stenosis lesion, and Muraki et al. described that the intracoronary shunt provided only 10-30% of baseline blood flow even if in a canine model without stenosis of the coronary artery.<sup>12)</sup> The external shunt<sup>13,14)</sup> method is also popular, but we demonstrated the poor perfusional capacity of the femoral artery shunt in a previous study,<sup>3)</sup> and the aorto-coronary shunt may be dangerous for some patients because it requires manipulation of the ascending aorta.

The CAPS generates active pulsatile blood flow syn-



**Fig. 5.** Photographs of longitudinal section of the left ventricular myocardium in groups A (left) and B (right). The appearance of edema with interstitial space was observed only in group A. Bar=10  $\mu$ m.

chronized with the diastolic phase. Up to the present, several authors have investigated non-pulsatile active coronary perfusion in the beating heart regarding coronary physiology,<sup>15-17)</sup> and it was applied clinically in the field of coronary angioplasty.<sup>18-20)</sup> Lehmann et al. reported that a clinical trial performed by delivery of blood perfusion at 60 ml/min to patients undergoing coronary angioplasty revealed lower levels of the maximum pain score and the maximum ST segment elevation than in the control group.<sup>20)</sup> However, this flow rate appeared to be too high. We investigated that the optimal stroke volume setting of CAPS was 0.1 ml in the previous study (data not shown), and its flow rate was approximately 15 ml/min in our preliminary study.<sup>3)</sup> The present study also supported this. Muraki et al. investigated the efficacy of active coronary perfusion with a constant-volume non-pulsatile pump during simulated OPCAB, but the flow rate was not described in their report.<sup>12)</sup> The CAPS may require less blood to maintain suitable myocardial perfusion than in a non-pulsatile active perfusion manner, and we consider that the pulsatile manner is prior to the non-pulsatile manner to maintain myocardial perfusion effectively.

For driving CAPS safely, the perfusion timing is considered very important. In this study, regional MBF was decreased resulting in deterioration of left ventricular function and myocardial edema in the systolic perfusion group. These facts indicate that the CAPS should not be driven in the systolic phase. Injection pressures were same in all groups, but coronary artery resistance may be in-

creased in the systolic perfusion group resulting in decreased regional MBF. On the contrary, regional MBF and left ventricular function were well maintained in the early to late diastolic groups, and it is considered that CAPS can be safely and effectively used if it is driven only within the diastolic phase. The CAPS required approximately a 150 msec perfusion period in the 0.1 ml stroke volume setting used in this study. This was within the diastolic phase with a large margin in males. Weissler et al. reported that the diastolic period in males was approximately from 340 to 860 msec at cardiac rates from 50 to 100 bpm.<sup>21)</sup> In this study, we demonstrated that the CAPS optimal timing had some latitude, which was anywhere in the diastolic phase. Some timing errors may occur in the clinical usage of CAPS, but these are considered to be allowable because the CAPS requires not strict, but easy adjustment of the perfusion timing within a permissible range.

In conclusion, CAPS could maintain regional MBF and left ventricular function if it was driven only within the diastolic phase, and it is considered that strict adjustments are not required. However, it should be warned that CAPS has an adverse effect when it is driven in systolic phase.

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