Effects of partial ischaemia and volume loading on myocardial efficiency and cardiac performance in dogs

Guangping Li, Xu Wang, Fuyong Du, Yi Ren, Gary Drzewiecki, John K.-J. Li, Joseph Kedem

Aims and methods: To determine whether volume loading may be beneficial for the performance of ischaemic heart, myocardial ischaemia was created by partial occlusion of the left anterior descending coronary artery (LAD) to reduce the blood flow to 30–40% of basal level in 11 open chest anaesthetised dogs. Global left ventricular function as well as regional performance were studied under four different levels of volume loading, euvolemia (EUVO), hypervolemia (HYPER), normovolemia and hypovolemia.

Results: Left ventricular dP/dt and cardiac output were decreased significantly during partial occlusion (3511.2±425.2 mmHg/s and 0.9±0.1 l/min) compared with pre-occlusion (4486.5±419.2 mmHg/s and 1.3±0.1 l/min) (P<0.05). Cardiac work was also lowered during partial occlusion (75.4±5.2 vs. 106.5±2.4 mmHg×l/min) (P<0.05). During volume loading, cardiac output and work were elevated (1.2±0.2 l/min and 94.0±5.4 mmHg×l/min) compared with EUVO (P<0.05). Local contractile dysfunction occurred in the LAD region after partial occlusion. There were no significant differences of dysfunction between any conditions of volume loading. Percentage shortening of the LAD region was decreased during partial occlusion (8.3±1.1 vs. 25.0±2.7%) and also was higher in HYPER (13.5±2.6%) than that in EUVO (P<0.05). Partial occlusion and different conditions of volume loading did not significantly change the force and local work in the LAD region. Myocardial O2 consumption (MVO2) in LAD region was decreased during partial occlusion with different levels of volume loading (P<0.05). Local myocardial efficiency (work/MVO2) was increased during partial occlusion compared with pre-occlusion (941.3±56.2 vs. 551.0±65.5 g×mm/ml O2/min/100 g, P<0.05) and was also higher in HYPER (1208.6±48.4 g×mm/ml O2/min/100 g) than that in EUVO (P<0.05). Local systolic work was decreased during partial occlusion compared with pre-occlusion (9.5±1.5 vs. 14.2±1.3 g×mm/beat), whereas local myocardial systolic mechanical efficiency was increased (496.3±45.7 vs. 667.2±39.8 g×mm/ml O2/min/100 g). There were no significant changes of local systolic work and local systolic myocardial efficiency between different volume loading, although they tend to be elevated with increasing volume loading. Conclusion: Increase of blood volume by 15% improved the impaired global performance caused by partial occlusion of the LAD in open-chest dogs. This improvement was not accompanied by further dysfunction or increased MVO2 of ischaemic myocardium, and therefore might be beneficial without causing further damage to the insulted myocytes.

Keywords: Coronary disease; Hemodynamics; Ischemia; Oxygen consumption; Ventricular function

1. Introduction

Myocardial ischaemia caused by incomplete occlusion of coronary artery due to the presence of coronary atherosclerotic plaque(s) is the most common type of coronary heart disease. Myocardial ischaemia may cause depressed regional and global function, and sometimes the dysfunction could be serious and immediate treatment is necessary. Inotropic agents such as digitalis may improve the regional and global functions of the ischaemic heart. However, this type of treatment may risk further injury to the ischaemic myocardium because inotropic agents increase the oxygen demand of the myocytes while the oxygen supply is still limited by the narrowed coronary artery. Therefore, it is desirable to improve the dysfunction.
of the ischaemic heart without increasing the oxygen demand.

It has been shown in previous studies that volume loading can improve postischaemic myocardial function without increasing myocardial oxygen consumption (MVO$_2$) or causing further damage to affected myocytes [1,2]. Those studies were performed during reperfusion, when coronary blood flow returned to normal. Thus, the ischaemic myocardium is different from the stunned myocardium in that the coronary blood flow remains limited. However, the mechanical dysfunction present in these two entities are very similar or almost the same. It is thus tempting to apply the same strategy to the ischaemic myocardium although these two entities are different in whether the oxygen supply is still limited. Therefore, the present study was designed to test the effects of volume loading on global and local function and metabolism as well as mechanical efficiency in ischaemic myocardium.

2. Materials and methods

2.1. Surgical procedure

Eleven mongrel dogs of either sex weighing 21.3–29.5 kg (25.46±2.75 kg) were used in this study. All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Research Council (National Academy Press, 1996) and approved by our Institutional Animal Care and Use Committee (IACUC). Each animal was anaesthetised with intravenous sodium pentobarbital (30 mg/kg) and placed under positive-pressure ventilation (Puritan-Bennett Corp., Los Angeles, CA, USA) after endotracheal intubation. During all experiments, arterial blood gases and also pH and oxygen saturation, were maintained within the normal physiological ranges by controlling respiratory rate, tidal volume, and the inspired fraction of oxygen. These parameters were monitored by periodic collection of arterial blood samples, which were analysed for pH, PaO$_2$, and PaCO$_2$ using a Radiometer ABL5 (Copenhagen, Denmark) blood gas anlyser. Oxygen saturation and haemoglobin concentration (Hb) were determined using a Radiometer OSM3 Hemoximeter.

The right femoral vein and artery were catheterised for systemic volume administration and blood sampling, respectively. The heart was exposed by a left thoracotomy at the fourth intercostal space. To measure the aortic and left ventricular pressures, one catheter-tip pressure transducer (Millar, Houston, TX, USA) was inserted into the left femoral artery and positioned at the aortic arch and another was inserted into the left ventricle through an apical stab wound, respectively. Mean aortic blood flow (cardiac output) and local coronary blood flow (LADFLOW) were measured by an ultrasonic volume flowmeter (Transonic T206, Ithaca, NY, USA) whose probes were placed around the ascending aorta and the isolated left anterior descending coronary artery (LAD) proximal to the second diagonal branch, respectively. Additionally, a snare was placed around the LAD to be used for subsequent partial occlusion. An anterior inter-ventricular branch of the great coronary vein was catheterised for sampling of local coronary venous blood. Oxygen saturation and Hb measurements taken from paired arterial and local coronary venous blood samples during each experimental stage, together with LAD flow, were used to calculate MVO$_2$ [3–5]. In order to normalise the measured LAD flow to 100 g wet tissue, at the end of the experiment, Evans Blue (2.5%) was slowly injected into the LAD at the point that occlusion was previously performed, and the total mass perfused by the LAD was determined by weighing the stained tissue.

2.2. Physiological measurements

For measurement of local myocardial segment work, both segment length and force of contraction were measured simultaneously in the anterior and posterior walls of the left ventricle. Ultrasonic transducers (Triton model 120, San Diego, CA, USA) for the measurement of myocardial segment length were inserted into the anterior wall of the left ventricle supplied by the LAD, and the posterior wall supplied by the circumflex branch of the left coronary artery (CFX). The crystals were placed in the short axis of the heart at a depth of 5 mm and separated by about 10 mm. Force of contraction for both LAD and CFX area was measured at a nearby site, at the same depth, and in the same orientation with miniature force transducers (Warren Instruments, Charlotte, SC, USA). The feet of the transducer were anchored to the myocardium with 3.0 silk sutures so that fibers were stretched by about 50% of their resting length, thus maintaining constant fiber length while force was measured throughout the cardiac cycle. The transducer was connected to a Wheatstone bridge (Warren Instruments). The bridge was balanced, and the device was calibrated with gram weights before each experiment [6].

The following parameters were recorded continuously and simultaneously on a multi-channel recorder (Gould TA 4000, Cleveland, OH, USA): lead II electrocardiogram, aortic blood pressure, left ventricular pressure, segment length and force in LAD and CFX regions of the left ventricle, aortic blood flow, and LAD coronary flow. All data were obtained at a sampling rate of 200 samples per seconds during experiment and digitised by Gould Acquisition Interface model ACQ-16 in real time for recording and monitoring (Ponemah Instrument System, Valley View, OH, USA). The digital signals were delivered to a Pentium computer and were analysed with the Ponemah physiology platform for further measurements and calculations.

Calculations performed included heart rate, mean aortic blood pressure, first derivative of the left ventricular pressure (dP/dt$_{max}$), peak isometric force, end-diastolic
length (EDL), end-systolic length (ESL), percentage segment shortening (defined as (EDL−ESL)/EDL×100%), and local myocardial work (local work) in the LAD and CFX region. Local work was calculated by determining the area under the force-length loop over the averaged cardiac beat. This was accomplished by multiplying each digitised value of force by its corresponding change in length and integrating all positive values (shortening only) during the cardiac cycle of the averaged beat (Local work=Σ positive (instant force×instant shortening)) [4]. Local systolic work is defined as the total local work done in the systolic phase. Local myocardial mechanical efficiency was calculated as local work divided by MVO₂ in the LAD region. Local myocardial systolic mechanical efficiency was calculated as local systolic work divided by MVO₂ in the LAD region. Left ventricular external work (global work) was calculated as aortic pressure×aortic blood flow.

In addition, several parameters describing local dysfunction, i.e. systolic bulge (Bulge), EDL, delayed onset of shortening (Delay), end shortening time delay (EST) and tail work ratio (TWR) were calculated using SAS System (statistical analysis system, SAS Institute Inc., Cary, NC, USA). These parameters [2] represent different characteristics of muscle contraction and may point to the nature of the lesion resulting in dysfunction. EDL is defined as the local segment length at the end of ventricular diastole that is marked by the closure of the mitral valve. Bulge is defined as the difference in segment length between the maximum length and the EDL in a cardiac cycle. Delay is defined as the time interval from the beginning of ventricular systole to the onset of local fiber shortening. EST is defined as the time period from end of ventricular systole to the end of local shortening. TWR is defined as the percentage of the local positive work performed by the regional myocardium after aortic valve has closed, to the local total work done in the same cardiac cycle.

2.3. Ischaemic model and changes of volume loading

In all animals, the very proximal LAD (origin) was partially occluded by tightening the snare (partial occlusion). Partial occlusion reduced the LAD blood flow to 30~40% of baseline [7,8] verified by the measurement of the LAD blood flow using an ultrasonic volume flowmeter (described above) placed around the isolated LAD. The state of partial occlusion was maintained constant during the whole experiment. The euvolemic (EUVO) stage was defined as 30 min after all the parameters were stabilised during partial occlusion. Volume loading was then given. Hespan (6% hetastarch in 0.9% sodium chloride injection, B. Braun Medical Inc., Irvine, USA) was infused intravenously over a period of at least 5 min to produce 15% increase of blood volume (Hypervolemia, HYPER). Normal volume (Normovolemia, NORMO) was produced by a removal of 15% blood volume following the HYPER and lowest volume (Hypovolemia, HYPO) by an additional removal of 15% volume following NORMO from femoral artery, respectively. Each stage of volume loading was maintained at a steady state for at least 15 min. All measurements of global, local function and blood gases were taken during each experimental stage.

2.4. Data analysis

Summaries of the data are presented as mean±S.E. Statistical analysis was carried out by using SAS system (SAS Institute Inc., Cary, NC, USA). The effect of ischaemia was analysed by paired t-test between the stage of pre-occlusion and that of euvoolemia. The effects of volume loading were compared by one-way analysis of variance (ANOVA) for repeated measurements. The comparison between stages of volume loading was made by paired t-test. The statistically significant changes were defined as P-value <0.05.

3. Results

3.1. Monitoring of arterial blood gas

Table 1 shows arterial blood gas parameters during the various stages of the experiments. Compared with pre-occlusion, there were no significant changes of oxygen saturation, PaCO₂, pH value and Hb during partial occlusion of LAD with different volume loading throughout the experiment.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-occlusion</th>
<th>Partial occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Euvolemia</td>
</tr>
<tr>
<td>SATaO₂ (%)</td>
<td>99.6±0.2</td>
<td>99.4±0.4</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>33.1±1.8</td>
<td>31.7±1.4</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>14.5±0.7</td>
<td>14.8±0.7</td>
</tr>
<tr>
<td>pH</td>
<td>7.27±0.01</td>
<td>7.27±0.02</td>
</tr>
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</table>

Table 2

Hemodynamics and global function during ischemia and different volume loading

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-occlusion</th>
<th>Partial occlusion</th>
<th>Hypervolemia</th>
<th>Normovolemia</th>
<th>Hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Euvolemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>146.3±9.3</td>
<td>146.5±4.4</td>
<td>145.6±5.2</td>
<td>144.9±4.9</td>
<td>142.8±5.7</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>85.3±4.8</td>
<td>97.3±5.7*</td>
<td>101.3±6.2*</td>
<td>90.1±2.7</td>
<td>77.9±7.1</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>95.6±2.7</td>
<td>104.2±4.8*</td>
<td>109.5±5.2*</td>
<td>98.0±2.1</td>
<td>84.9±2.6</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>4.4±1.9</td>
<td>4.6±2.2</td>
<td>4.7±2.1</td>
<td>4.6±2.0</td>
<td>4.2±2.0</td>
</tr>
<tr>
<td>dP/dt max</td>
<td>4486.5±419.2</td>
<td>3511.2±425.2†</td>
<td>3665.8±448.2†</td>
<td>3568.2±428.9†</td>
<td>3102.9±384.1†</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>1.3±0.1</td>
<td>0.9±0.1†</td>
<td>1.2±0.2§</td>
<td>0.9±0.1†</td>
<td>0.8±0.1†</td>
</tr>
<tr>
<td>Global work</td>
<td>106.5±2.4</td>
<td>75.4±5.2†</td>
<td>94.0±5.4§§</td>
<td>76.2±6.6†</td>
<td>74.6±7.5†</td>
</tr>
</tbody>
</table>

Note: HR: Heart rate. MBP: Mean blood pressure. LVSP: Left ventricular systolic pressure. LVEDP: Left ventricular end diastolic pressure. dP/dt max: First derivative of the left ventricular pressure. CO: Cardiac output, obtained by mean aortic blood flow (MABF). Global Work: External work. † Significant difference compared with pre-occlusion. ‡ Significant difference compared with euvolemia. § Significant difference compared with normovolemia. * Significant difference compared with Hypovolemia.

3.2. Haemodynamics and global function

Table 2 and Fig. 1 describes systemic hemodynamics and left ventricular global function during ischaemia and volume loading. The heart rate, mean blood pressure, left ventricular systolic pressure and left ventricular end diastolic pressures did not change after LAD occlusion. However, dP/dt max, cardiac output and global work during partial occlusion (EUVO) were decreased by 21.7, 30.1 and 29.2% compared with pre-occlusion (P<0.05).

Fig. 1 illustrates that increase of blood volume elevated both cardiac output and global work. Cardiac output and global work were higher in HYPER than that in EUVO and also higher than that in NORMO and HYPO (P<0.05). Table 2 shows that the different levels of volume loading were not accompanied by statistically different values of left ventricular dP/dt max. Left ventricular end-diastolic pressure was also unchanged, although mean blood pressure and left ventricular systolic pressure were lower in HYPO than that in HYPER and in EUVO (P<0.05).

3.3. Regional dysfunction

Table 3 shows that occlusion of LAD brought about regional dysfunction quantified by Delay, EST, Bulge and TWR, whereas alteration of volume loading condition had no effect on these parameters. In pre-occlusion, no significant Delay, Bulge, EST and TWR could be observed in the LAD and the CFX region, and the dysfunction appeared in the LAD region after partial occlusion of the LAD. There were no significant changes of Delay, Bulge, EST and TWR through all four different conditions of volume loading except EDL was longer in HYPER than that in NORMO and HYPO (P<0.05). Partial occlusion of the LAD and the changes of volume loading did not affect the performance of CFX region, i.e. no dysfunction appeared in the CEX region after occlusion.

3.4. Local function and segment work

Table 4 shows regional function and local work of the LAD and the CFX areas during partial occlusion of the LAD and change of volume loading conditions. Partial occlusion of the LAD decreased shortening in LAD area by 66.7% (P<0.05). Percent shortening in the LAD region...
was higher in HYPER than that in EUVO, NORMO and HYPO, whereas there were no significant differences of percent shortening among EUVO, NORMO and HYPO. Compared with pre-occlusion, regional force remained almost the same during partial occlusion. The alterations of volume loading did not change regional force in the LAD region compared with EUVO. Partial occlusion did not change local work in the LAD area. There were no statistical effects of different volume loading on local LAD work, although it tends to be higher at increased volumes compared with EUVO in the LAD region. Partial occlusion of the LAD and changes of volume loading also had no significant effects on the local percentage shortening, force and work in CFX area.

### 3.5. Regional efficiency and oxygen consumption

The changes of MVO$_2$, oxygen extraction, and coronary blood flow during partial occlusion of the LAD with different volume loading are shown in Table 5. As a reaction to ischaemia resulting from the coronary occlusion, oxygen extraction became higher in EUVO than that

### Table 3

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-occlusion</th>
<th>Euvolemia</th>
<th>Hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDL (mm)</td>
<td>10.0±0.1</td>
<td>12.2±0.3†</td>
<td>12.7±0.28‡</td>
</tr>
<tr>
<td>Delay (ms)</td>
<td>1.0±0.1</td>
<td>50.0±8.2†</td>
<td>51.5±7.5†</td>
</tr>
<tr>
<td>Bulge (mm)</td>
<td>0.2±0.0</td>
<td>1.7±0.3†</td>
<td>1.6±0.3†</td>
</tr>
<tr>
<td>EST (ms)</td>
<td>1.0±0.1</td>
<td>44.5±4.3†</td>
<td>48.0±4.0†</td>
</tr>
<tr>
<td>TWR (%)</td>
<td>0.8±0.1</td>
<td>29.3±4.4†</td>
<td>30.1±3.9†</td>
</tr>
</tbody>
</table>

Note: LAD: Left anterior descending. EDL: Segmental end diastolic length. Delay: Segmental systolic shortening onset delay. Bulge: Maximum segmental relaxation length during systolic period minus EDL. EST: Segmental end shortening time delay. TWR: Tail work ratio. † Significant changes compared with pre-occlusion. § Significant changes compared with normovolemia. * Significant changes compared with hypovolemia.

### Table 4

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-occlusion</th>
<th>Partial occlusion</th>
<th>Euvolemia</th>
<th>Hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Shortening (%)</td>
<td>25.0±2.7</td>
<td>8.3±1.1†</td>
<td>13.5±2.6‡ $*$</td>
<td>7.9±1.6†</td>
</tr>
<tr>
<td>Force (g)</td>
<td>9.9±0.1</td>
<td>10.6±2.3</td>
<td>10.5±1.7</td>
<td>9.0±1.8</td>
</tr>
<tr>
<td>Local work (g×mm/beat)</td>
<td>14.5±2.3</td>
<td>13.4±2.4</td>
<td>14.5±2.6</td>
<td>12.5±2.7</td>
</tr>
<tr>
<td>CFX region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Shortening (%)</td>
<td>14.9±1.2</td>
<td>14.2±1.4</td>
<td>15.1±1.5</td>
<td>14.2±1.5</td>
</tr>
<tr>
<td>Force (g)</td>
<td>10.8±0.2</td>
<td>11.4±1.3</td>
<td>11.1±1.2</td>
<td>10.5±1.2</td>
</tr>
<tr>
<td>Local work (g×mm/beat)</td>
<td>11.2±1.3</td>
<td>13.4±2.3</td>
<td>12.5±2.5</td>
<td>13.1±2.2</td>
</tr>
</tbody>
</table>

Note: LAD: Left anterior descending. CFX: Circumflex. percentage shortening: Segmental percent shortening. Force: Segmental peak force. Local work: Local work in a segment of the LAD or the CFX area. Systolic work: Local work minus tail work. † Significant difference compared with pre-occlusion. § Significant difference compared with normovolemia. * Significant difference compared with hypovolemia.

### Table 5

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-occlusion</th>
<th>Partial occlusion</th>
<th>Euvolemia</th>
<th>Hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>O$_2$ EXT (ml O$_2$ %)</td>
<td>11.2±0.8</td>
<td>14.3±0.9†</td>
<td>12.2±0.8</td>
<td>13.5±0.8</td>
</tr>
<tr>
<td>LADFLOW (ml/min/100 g)</td>
<td>74.5±6.6</td>
<td>31.6±4.6†</td>
<td>30.8±4.8†</td>
<td>31.4±4.1†</td>
</tr>
<tr>
<td>MVO$_2$ (ml O$_2$/min/100 g)</td>
<td>8.6±0.8</td>
<td>4.2±0.6†</td>
<td>4.2±0.4†</td>
<td>4.2±0.4†</td>
</tr>
<tr>
<td>EFFICIENCY (g×mm/ml O$_2$/min/100 g)</td>
<td>551.0±65.5</td>
<td>941.3±56.2†</td>
<td>1208.6±48.4†</td>
<td>883.4±58.3</td>
</tr>
</tbody>
</table>

Note: O$_2$ EXT: Oxygen extraction = coronary arterial oxygen content minus coronary venous oxygen content. LADFLOW: Blood flow of left anterior descending of coronary artery. MVO$_2$: oxygen consumption of 100 g myocardium. EFFICIENCY: Local myocardial mechanical efficiency, which was calculated as local myocardial work divided by MVO$_2$. † Significant difference compared with preocclusion. ‡ Significant difference compared with euvolemia. § Significant changes compared with normovolemia. * Significant changes compared with hypovolemia.
The local myocardial mechanical efficiency is shown in Table 5 and in Fig. 2. Efficiency in the LAD region was increased markedly during partial occlusion compared with pre-occlusion. Also, the efficiency was clearly higher in HYPER than that in the other volume loading stages, NORMO and HYPO as well as EUVO ($P<0.05$). Therefore, increase of volume loading did improve the efficiency in ischaemic myocardium.

Table 6 illustrates the changes of both local systolic work and local myocardial systolic mechanical efficiency in ischaemic region during partial occlusion of the LAD and different conditions of volume loading. Local systolic work is that portion of the total myocardial work performed during ventricular systole. Local systolic work in the LAD region was decreased after partial occlusion, whereas local myocardial systolic mechanical efficiency was increased compared with pre-occlusion. Hypervolemia also increased efficiency.

4. Discussion

4.1. Major finding of the present study

The major findings of the present study are that partial occlusion of the LAD causes increased metabolic efficiency, because work is decreased much less than oxygen consumption. Hypervolemia causing 15% increase of blood volume improved global function, although it did not improve the regional dysfunction caused by ischaemia. Volume loading did elevate local mechanical efficiency in ischaemic myocardium. These beneficial effects of volume loading were not accompanied by increased MVO$_2$ or oxygen extraction of the ischaemic myocardium, and therefore might not bring about further damage to the ischaemic myocardium.

4.2. Validity of the animal model used in the present study

Ischaemia created by partial occlusion in dogs is not a good model for the study of myocardial ischaemia because of the relatively well-developed collateral circulation, especially when quantitative measurement is involved. The
potential for collateral blood flow makes it difficult to determine the actual tissue blood flow. However, this also produces myocardial ischaemia in dogs more similar to that in patients with ischaemic heart disease since most of them may also develop collateral circulation of various extents to cope with the occluded coronary artery [9,10]. Therefore, the animal model should be of more clinical importance if the problem of collateral circulation is properly dealt with. In the present study, myocardial ischaemia was created by partial occlusion of the LAD. Under such a circumstance, one important potential source of collateral blood flow is from the CFX. We used the method described by Fujita et al. [11] and Yamanishi et al. [12] to determine the extent of collateral blood flow coming from the CFX to the LAD when ischaemia in the LAD region occurred. We found that there was no significant contribution from the CFX to the LAD during experiment, at least in all the animals included in the present study. Consistent with our results, Ramanthan et al. [13] also showed that during the first few days after myocardial ischaemia created by partial occlusion of the CFX, there was no significant collateral blood flow to the ischaemic region (CFX) coming from LAD. Another possible source of collateral blood flow is from the proximal part of the LAD when a more distal part of the LAD is occluded. Indeed, our own earlier experiments had shown that there was significant collateral blood flow coming from the proximal part of LAD to the ischaemic myocardium when the LAD was ligated more distally. In those pilot experiments, the LAD was occluded at a distal portion (between the first and second diagonal branch). It was found that under those circumstances, the regional function remained unimpaired even when the blood flow measured at the site of ligation was reduced by 80%. At the same time, the blood flow measured at the proximal end of LAD increased. On the other hand, if the LAD was occluded close to its origin, regional dysfunction would appear with about 60% decrease of blood flow. Therefore, in the present study, the very proximal part of the LAD was occluded to create coronary ischaemia thereby excluding the influence of collateral circulation from this possible source, the LAD itself. These actions thus assured that the decrease in blood flow measured by flowmeter correctly reflected the decrease in tissue blood flow, and verified the accuracy of quantitative measurements and calculation of MVO$_2$, mechanical efficiency, etc.

4.3. Dysfunction of the ischaemic myocardium

Consistent with previous studies [14–18], the present study showed that regional ischaemia caused depressed global and regional function. Our results showed that left ventricular dP/dt$_{max}$, external work and cardiac output all decreased during partial occlusion. The present study demonstrated that partial occlusion of the coronary artery resulted in regional shortening dysfunction of the ischaemic area (LAD area) similar to those of stunned myocardium, which are indicated by the presence of Delay, Bulge, EST, TWR and decreased percent shortening [2,14,15]. However, as in stunned myocardium, the local force remained almost the same. Depressed shortening in the ischaemic myocardial region was likely responsible for the impaired global function, because it decreased the contribution of the LAD region to global mechanics. Another mechanism for impaired global function is as follows: normal myocardial relaxation during the diastolic period of the heart makes it possible for the ventricle to be filled sufficiently and to maintain cardiac output within normal range. When regional ischaemia occurs, the ventricle as a whole loses its synchrony between pressure development and the segmental ischaemic myocardial shortening due to delayed shortening. The delayed shortening of the ischaemic myocardium persists into diastole. This will impede proper filling of the ventricle during diastole and consequently impair global function.

Depressed local systolic work is another reason for impaired global performance. During ischaemia, the presence of dysfunction caused the ischaemic region to contract asynchronously due to delayed shortening. Part of the local work was done after the closure of the aortic valve, which could not contribute to delayed shortening. Part of the local work was done after the closure of the aortic valve, which could not contribute to delayed shortening. Therefore, although the total local work did not change significantly during ischaemia, the systolic work, i.e. the work that occurred during the systole, which contributes to left ventricle pump function, was decreased significantly. Since the ischaemia was produced by ligation of the LAD almost at its origin, the affected myocardium included the whole region supplied by LAD, which constitutes a significant part of the left ventricle. Therefore, the depressed regional function also contributed significantly to the depressed global function.

4.4. Oxygen consumption and myocardial efficiency

The ‘oxygen consumption paradox’ has been regarded as one of the characteristics of stunned myocardium, in which the oxygen cost of stunned myocardial contraction was elevated primarily because the contractile function was markedly depressed, even as MVO$_2$ remains normal, decreased or increased [19–23]. However, in partial and complete occlusion of coronary artery, myocardial oxygen consumption was decreased (41%, Parsons et al. and 84%, Cave et al.) with corresponding reduction of coronary blood flow [7,14,24]. In our present study, although there was a slight increase in oxygen extraction, the MVO$_2$ still decreased by more than 50%. Since local myocardial mechanical efficiency and local myocardial systolic efficiency were calculated as local work and local systolic work divided by local MVO$_2$, the slightly depressed local work and dramatically decreased MVO$_2$ was therefore translated into elevated mechanical efficiency.
Previous studies have also shown elevated oxygen utilisation efficiency and decreased MVO₂ in ischaemic myocardium [25]. Casey and Arthur [26] in their study showed that cardiomyocytes are capable of downregulating energy-consuming processes other than contraction when oxygen supply is decreased. Chen et al. [27] observed that when regional coronary blood flow decreased by about 60%, wall thickening was maintained and the rate-pressure product was relatively constant, but MVO₂ was decreased. Although the exact mechanism underlying this phenomenon is still unclear, several hypotheses have been proposed [25,28–31], and the conversion of metabolic energy substrate from fatty acid to glucose seems to be the most promising one [32].

4.5. Beneficial effects of volume loading on ischaemic myocardium

Depressed global function caused by regional ischaemia may be very serious sometimes, and requires immediate treatment. Since oxygen supply is limited in ischaemic myocardium, any increase in oxygen consumption would imply further cell injury. Therefore, the most desirable method to improve the function should be one that would not increase the oxygen consumption. Hence, how to get better cardiac output with the limited oxygen resource, becomes a very important issue in the treatment of depressed function in ischaemic myocardium.

Utilisation of inotropic agents is the most commonly used method in improving heart function. This functional improvement is usually accompanied by increased oxygen consumption [33–39]. On the other hand, it is generally accepted that improving cardiac performance by increasing preload is usually accompanied by less increase in oxygen consumption [36,40–42]. In addition, our previous study [2] on stunned myocardium showed that increasing blood volume by 15% improves global and regional function without increasing MVO₂ of stunned myocardium, and these beneficial effects of volume loading could be attributed to the correcting effects of volume loading on regional dysfunction. Since the ischaemic myocardium shares similar dysfunction with stunned myocardium, it is reasonable to expect that volume loading will have similar effects in the ischaemic heart, although stunned myocardium is different from ischaemic myocardium in that the oxygen supply to the latter is still limited.

During partial occlusion and volume loading, MVO₂ was decreased and oxygen extraction was elevated in this study as described above. Nevertheless, MVO₂ and oxygen extraction was not changed with different volume loads when hypervolemia improved global function. Therefore, ischaemic myocardium seems not likely to consume more oxygen with the improvement of global function by hypervolemia. It indicated that the improvement of global function by volume loading did not cause further cell injury or death of jeopardised myocardium due to ischaemia. Thus, hypervolemia in our present study augmented global function without concomitant increase in regional oxygen consumption of ischaemic myocardium.

In contrast with our previous study in stunned myocardium, the beneficial effects of hypervolemia on global function were not observed on regional dysfunctional parameters in this study. Bulge, Delay, EST, TWR all remained unchanged with the variation of volume loading status. The mechanism for this discrepancy is not clear. The likely reason is probably the limited availability of oxygen consumption to ischaemic region, which prevent the recovery of dysfunction even with proper stimulation.

In conclusion, volume loading during partial occlusion of the LAD resulted in increased local myocardial efficiency, even while improving function. This may be the first quantitative description of increased energetic efficiency triggered by partial reduction of oxygen supply, and could be an obvious protective mechanism. Increase of blood volume by 15% improved the impaired global function caused by partial occlusion of LAD in open-chest dogs. This improvement was not accompanied by increasing MVO₂ of ischaemic myocardium, and therefore might not cause further damage to the insulted myocytes. The significant increase in stroke volume and cardiac output was accomplished without a large increase in either contractility or preload. This may imply that normal cardiac contraction uses more energy than necessary; thus, mild hypervolemia can significantly improve pump function without further energy input. We have no data regarding the longer term effects of mild hypervolemia in the clinical setting. Moreover, it must be emphasised that the data discussed herein were obtained from experimental animals under controlled conditions very different from the clinical situation. It would therefore not be appropriate to extend our conclusions to the clinical setting.

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