Effects of Sevoflurane on Regional Myocardial Blood Flow Distribution

Quantification with Myocardial Contrast Echocardiography

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Background: Using myocardial contrast echocardiography, the authors tried to determine whether sevoflurane causes myocardial blood maldistribution in humans and dogs.

Methods: In animal experiments, 15 mongrel dogs were organized into dipyridamole (n = 6) and sevoflurane (n = 9) groups. Sonoacoustic albumin was infused into the left main coronary artery. The peak gray level corrected for background was analyzed at the following intervals: (1) at baseline, (2) after stenosis of the left circumflex coronary artery (blood flow reduced by 40%), (3) after administration of dipyridamole (1 mg/kg given intravenously) or sevoflurane (1 minimum alveolar concentration) during stenosis, and (4) after phenylephrine during stenosis and administration of dipyridamole or sevoflurane. In human studies, nine patients undergoing coronary artery bypass grafting were studied. During partial extracorporeal circulation, the peak gray level was analyzed before and 20 min after sevoflurane (1 minimum alveolar concentration).

Results: In animal experiments, dipyridamole decreased significantly the inner/outer ratio of the peak gray level in the ischemic area and the ischemic ratio of the peak gray level. After arterial pressure was restored with phenylephrine, neither the inner/outer ratio nor the ischemic ratio improved. In contrast, after sevoflurane administration, the inner/outer ratio and the ischemic ratio remained unchanged, but these increased with phenylephrine. In human studies, sevoflurane did not change the inner/outer ratio in the area supplied by the most stenotic coronary artery.

Conclusion: These results suggest that dipyridamole, a potent coronary vasodilator, produces maldistribution of coronary blood flow in our dog models, whereas sevoflurane does not do this in animal or human studies. (Key words: Coronary steal; transesophageal echocardiography; vasodilators.)

POTENT coronary vasodilators, including adenosine, chromonar, and dipyridamole, have been shown to cause myocardial ischemia via a "coronary steal" mechanism, which is defined as redistriubution of myocardial blood flow from ischemic to normal zones or from subendocardial to subepicardial areas during constant aortic perfusion pressure and heart rate.1-5 All of these agents reduce arteriolar tone in the area supplying collateral flow or in the subepicardium, which has a vasodilator reserve. As a result, distal perfusion pressure at the origin of the collateral vessels decreases, reducing collateral flow and subendocardial blood flow in an ischemic region. Volatile anesthetics also possess vasodilating properties in isolated coronary artery segments, and they cause vasodilation of resistance coronary arterioles in vitro.1-5 Thus, research suggests that these agents may cause coronary steal and lead to exacerbation of myocardial ischemia in patients with coronary artery disease.6 However, despite many investigations,7-10 the hypothesis that inhalational agents may cause coronary steal in humans remains controversial, because the current techniques to measure regional coronary blood flow, including the radionuclide microsphere method, cannot be used in humans and animal models have been used. In contrast, investigators recently reported that, in animal experiments11-13 and in humans,14-16 myocardial blood flow distribution can be evaluated by injecting an
echocardiographic contrast agent into the coronary circulation and imaging the cardiac cross-sectional view with two-dimensional echocardiography (myocardial contrast echocardiography). By using myocardial contrast echocardiography, we first tried to determine whether dipyridamole causes marked redistribution of myocardial blood flow in our canine models with experimentally produced acute coronary artery stenosis. Then we studied the effects of sevoflurane, which induces direct vasodilation of the coronary arteries 

Methods

Animal Experiments

Fifteen unpremedicated mongrel dogs of both sexes that weighed 9–20 kg were organized into two groups: the dipyridamole group (n = 6) and the sevoflurane group (n = 9). Our protocol was approved by the Tokushima University Committee on the Use and Care of Animals. In both groups, anesthesia was induced with 20 mg/kg thiamylal given intravenously and maintained with an initial bolus (20 mg/kg) and then a continuous (0.3 μg·kg⁻¹·min⁻¹) infusion of fentanyl. The trachea was intubated and the lungs were ventilated with 100% oxygen using a Harvard pump. Muscle relaxation was obtained with vecuronium given intravenously. The arterial oxygen and carbon dioxide pressures were maintained at 350–450 mmHg and 35–40 mmHg, respectively. A catheter was placed in the right femoral vein for drug and fluid administration (10 ml·kg⁻¹·h⁻¹ lactated Ringer’s solution), and a solid-state, catheter-tip type of pressure transducer (Mikro-Tip PC 380; Millar Instruments, Houston, TX) was placed in the descending aorta through the right femoral artery. After a sixth intercostal thoracotomy, the heart was suspended in a pericardial cradle. The left circumflex coronary artery (CX) proximal to an obtuse marginal branch was isolated, and an electromagnetic flowmeter probe was placed around the CX. A screw constrictor was implanted around the CX distal to the flow probe to produce an acute stenosis. The absence of an arterial branch between the constrictor and the probe was confirmed. The CX blood flow was measured using an electromagnetic flowmeter (MFV-3200; Nihon Kohden, Tokyo, Japan) to confirm the magnitude of the coronary stenosis. Heart rate and the systolic, mean, and diastolic arterial pressures were displayed digitally on a Nihon Kohden RMC-1100 polygraph.

The regional distribution of coronary blood flow was measured using the myocardial contrast echocardiography. A 24-gauge catheter was placed in the left main trunk of the coronary artery to inject contrast medium. Heparin (100 U/kg) was administered intravenously to prevent thrombus formation. A left ventricular short-axis view at the level of the midpapillary muscle was obtained from the heart surface using a 5-MHz ultrasonic transducer (UST-5224+5; Aloka, Tokyo, Japan). Gain settings were optimized initially and held constant throughout the study period, and a maximal dynamic range of 60 dB was used. Postprocess and τ correction were established as linear. Automatic gain control and fast time constants were set off, and sensitivity time control was kept constant. According to the method of Feinstein et al., 5% human albumin was sonicated at 20 KHz and with an energy output of 25 W for 30 s using an ultrasonic processor (VC-50; Sonics & Materials, Danbury, CT). Two milliliters of sonicated 5% albumin were injected manually into the left coronary artery as contrast medium. The end-diastolic images synchronized to the peak of the R wave of the electrocardiography were recorded on SVHS videotape with a high-fidelity video recorder (AG-7300; Victor, Tokyo, Japan). The data were transferred to a computer and 40–60 consecutive images were digitized into a 640 × 480 pixel matrix with a 256–grayscale level/pixel to measure the degree of enhancement of the peak gray level after injection. To minimize motion of the heart, the respirator was turned off during measurement. Regions of interest (size = 200–300 pixels) of approximately equal thickness were designated in the inner and outer layers, excluding the endocardium and epicardium, of the area supplied by the CX (ischemic zone) and the left anterior descending coronary artery (LAD, normal zone). The time-intensity curve of each region was recorded, and the peak gray level, corrected for background obtained before injection of contrast medium, was analyzed and used as an indicator of regional distribution of coronary blood flow (fig. 1). The inner:outer blood flow ratio in the ischemic region was evaluated as the ratio between the peak gray level of the inner halves and that of the outer halves in the CX area (inner:outer ratio). The ischemic:control blood flow ratio was determined as the ratio of the mean of the peak gray level of the inner and outer halves in the CX area and that in the LAD area (ischemic:control ratio). The CX

Anesthesiology. V 90, No 5, May 1999
and LAD perfusion areas were identified by complete occlusion of CX when the experiments were complete.

Hemodynamic and myocardial contrast echocardiographic data were obtained simultaneously at the following intervals. (1) before CX stenosis (baseline), (2) 30 min after CX stenosis (with blood flow reduced by approximately 40%), (3) 5 min after intravenous administration of dipyridamole (1 mg/kg; the dipyridamole group) or 20 min after inhalation of 1 minimum alveolar concentration (MAC) sevoflurane (end-tidal concentration was 2.36% in dogs; the sevoflurane group) during CX stenosis, and (4) after arterial blood pressure was restored with phenylephrine to the level recorded immediately before administration of dipyridamole or sevoflurane.

Data are expressed as the mean ± SD. Statistical analysis was performed using two-way repeated-measures analysis of variance and the Scheffe F test to compare values among the four intervals and between the dipyridamole and sevoflurane groups. P < 0.05 was considered significant.

**Human Studies**

Nine patients (age, 60 ± 7 yr) scheduled for coronary artery bypass grafting agreed to participate in this study. Our protocol was approved by the Tokushima University Ethics Committee on Human Study, and written informed consent was obtained from all patients. Before induction of anesthesia, a 22-gauge catheter was placed in the radial artery to measure arterial blood pressure, and a pulmonary arterial catheter was inserted through the right internal jugular vein during local anesthesia.

Anesthesia was induced with fentanyl (200–500 µg) and thiopental (25–100 mg) and maintained with a continuous intravenous infusion of fentanyl (total dose, 70–100 µg/kg), oxygen, and air (or nitrous oxide). After tracheal intubation, the lungs were ventilated to maintain the arterial oxygen tension at more than 100 mmHg and the carbon dioxide pressure at 35–40 mmHg. A transesophageal echocardiographic probe (UST-52358-5, Aloka) was inserted orally. During partial extracorporeal circulation, the lungs were ventilated with 100% oxygen, and the pump flow, hematocrit, and rectal temperature were maintained at approximately 2.4 ± 1 · min⁻¹ · m⁻², 25%, and 35°C, respectively. Venous drainage to the cardiopulmonary bypass circuit was controlled to keep the arterial pressure constant during the study. After the stability of hemodynamic and echocardiographic variables was confirmed, inhalation of 1 MAC sevoflurane (end-tidal concentration, 1.71% in humans) in oxygen was started.

The regional distribution of coronary blood flow was measured using myocardial contrast echocardiography. A left ventricular short-axis view at the midpapillary muscle level was obtained by transesophageal echocardiography, and the end-diastolic images synchronized with the R wave of the electrocardiography were recorded. Five milliliters of 5% albumin was infused into the aortic root through the antegrade cardioplegia catheter as a contrast medium. The end-diastolic images were transferred to a computer and digitized into a 640 × 480 pixel matrix with a 256–gray level/pixel to measure the degree of enhancement of the peak gray level after injection. Regions of interest (size = 200–500 pixels) of approximately equal thickness were designated in the inner and outer layers, excluding the endocardium and epicardium, of the areas supplied by the coronary artery that had the most severe stenosis based on preoperative coronary angiographic findings. When the severity of stenosis was similar in some coronary arteries, regions of interest were designated in the segment without preoperative asynergy. The peak gray level corrected for background obtained before injection of contrast medium was analyzed. The inner/outer blood flow ratio in the ischemic region was evaluated as described in animal experiments.

Both hemodynamic and myocardial contrast echocardiographic variables, including heart rate; arterial pressure; systolic, mean, and diastolic pulmonary arterial pressures; and peak gray level, were obtained before and 20 min after inhalation of sevoflurane. In addition, the end-diastolic and end-systolic areas of the left ventricular short-axis view at the midpapillary muscle level were
SEVOFLURANE ON MYOCARDIAL BLOOD DISTRIBUTION

Table 1. The Changes in Hemodynamic Variables and Peak Gray Level of Myocardial Contrast Echocardiography in the Dipyridamole Group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Stenosis</th>
<th>Stenosis + Dipyridamole</th>
<th>Stenosis + Dipyridamole + Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats·min⁻¹)</td>
<td>94 ± 48</td>
<td>108 ± 49</td>
<td>134 ± 25*</td>
<td>106 ± 30</td>
</tr>
<tr>
<td>sAP (mmHg)</td>
<td>124 ± 23</td>
<td>123 ± 15</td>
<td>88 ± 22†</td>
<td>127 ± 7†</td>
</tr>
<tr>
<td>mAP (mmHg)</td>
<td>96 ± 19</td>
<td>97 ± 14</td>
<td>69 ± 18†</td>
<td>98 ± 12†</td>
</tr>
<tr>
<td>dAP (mmHg)</td>
<td>77 ± 19</td>
<td>83 ± 15</td>
<td>55 ± 16†</td>
<td>80 ± 14†</td>
</tr>
<tr>
<td>Peak gray level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CX Inner layer</td>
<td>60 ± 14</td>
<td>36 ± 16*</td>
<td>17 ± 19†</td>
<td>16 ± 12†</td>
</tr>
<tr>
<td>Outer layer</td>
<td>52 ± 13</td>
<td>44 ± 16</td>
<td>26 ± 22*</td>
<td>25 ± 16*</td>
</tr>
<tr>
<td>LAD Inner layer</td>
<td>66 ± 17</td>
<td>75 ± 18</td>
<td>90 ± 23*</td>
<td>86 ± 23*</td>
</tr>
<tr>
<td>Outer layer</td>
<td>58 ± 13</td>
<td>70 ± 11</td>
<td>81 ± 21*</td>
<td>71 ± 18*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

HR = heart rate; sAP = systolic arterial pressure; mAP = mean arterial pressure; dAP = diastolic arterial pressure; CX = left circumflex artery; LAD = left anterior descending artery.

* P < 0.05 versus baseline.
† P < 0.05 versus stenosis.
‡ P < 0.05 versus stenosis + dipyridamole.

obtained, and the fractional area change was calculated using the following formula:

\[
\text{fractional area change} = \frac{(\text{EDA} - \text{ESA})}{\text{EDA}}
\]

where EDA is end-diastolic area and ESA is end-systolic area. The percentage of systolic wall thickening was also calculated as follows:

\[
\text{percentage systolic wall thickening} = \left(\frac{(\text{ESWT} - \text{EDWT})}{\text{EDWT}}\right) \times 100
\]

where ESWT is end-systolic wall thickness and EDWT is end-diastolic wall thickness in the segments in which regions of interest for myocardial contrast echocardiography were designated. To detect myocardial ischemia, newly developed abnormalities in regional wall motion and electrocardiography (leads II and V5) were also evaluated throughout the study period.

Data are expressed as the mean ± SD. Statistical differences between the values obtained before (baseline) and 20 min after inhalation of 1 MAC sevoflurane were compared using paired t test, and P < 0.05 was considered significant.

Results

Animal Experiments

Tables 1 and 2 summarize the changes in hemodynamic variables and peak gray level of myocardial contrast echocardiography in the dipyridamole and sevoflurane groups, respectively. As shown in these tables, CX stenosis slightly increased heart rate in both groups, but these changes were not significantly different from baseline. Tables 1 and 2 also show that CX stenosis decreased peak gray level mainly and significantly in the inner halves and slightly in the outer halves of the CX area in both groups. In the dipyridamole group (table 1), subsequent administration of dipyridamole increased heart rate and decreased arterial blood pressure significantly. The peak gray level further decreased in the inner and outer halves of the CX area; although the decrease of the peak gray level in the outer halves did not differ significantly, the peak gray level in the inner halves was significantly less compared with that obtained before dipyridamole (after CX stenosis). In contrast, in the LAD area, peak gray level increased significantly in the inner and outer halves after dipyridamole. Intravenous administration of phenylephrine (3.1 ± 3.4 μg·kg⁻¹·min⁻¹) decreased heart rate and restored arterial blood pressure to the levels before dipyridamole, but peak gray levels in both layers of the CX area did not increase. In the sevoflurane group (table 2), inhalation of sevoflurane did not increase heart rate further, but it decreased arterial blood pressure significantly. The peak gray level further decreased in both layers of the CX area after sevoflurane. But these changes did not differ significantly compared with the peak gray level obtained before sevoflurane (after CX stenosis). Phenylephrine given intravenously

Anesthesiology, V 90, No 5, May 1999

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Table 2. The Changes in Hemodynamic Variables and Peak Gray Level of Myocardial Contrast Echocardiography in the Sevoflurane Group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Stenosis</th>
<th>Stenosis + Sevoflurane</th>
<th>Stenosis + Sevoflurane + Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>108 ± 35</td>
<td>128 ± 42</td>
<td>125 ± 31</td>
<td>98 ± 34</td>
</tr>
<tr>
<td>sAP (mmHg)</td>
<td>136 ± 20</td>
<td>128 ± 19</td>
<td>92 ± 13†</td>
<td>129 ± 20†</td>
</tr>
<tr>
<td>mAP (mmHg)</td>
<td>110 ± 15</td>
<td>106 ± 15</td>
<td>77 ± 12†</td>
<td>105 ± 17†</td>
</tr>
<tr>
<td>dAP (mmHg)</td>
<td>94 ± 14</td>
<td>91 ± 11</td>
<td>67 ± 12†</td>
<td>88 ± 16†</td>
</tr>
<tr>
<td>Peak gray level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inner layer</td>
<td>51 ± 24</td>
<td>34 ± 31*</td>
<td>31 ± 25*</td>
<td>31 ± 19*</td>
</tr>
<tr>
<td>Outer layer</td>
<td>35 ± 14</td>
<td>33 ± 23</td>
<td>26 ± 18*</td>
<td>23 ± 13*</td>
</tr>
<tr>
<td>LAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inner layer</td>
<td>50 ± 15</td>
<td>50 ± 16</td>
<td>54 ± 19</td>
<td>54 ± 23</td>
</tr>
<tr>
<td>Outer layer</td>
<td>41 ± 13</td>
<td>41 ± 17</td>
<td>37 ± 18</td>
<td>48 ± 17</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

HR = heart rate; sAP = systolic arterial pressure; mAP = mean arterial pressure; dAP = diastolic arterial pressure; CX = left circumflex artery; LAD = left anterior descending artery.

* P < 0.05 versus baseline.
† P < 0.05 versus stenosis.
‡ P < 0.05 versus stenosis + sevoflurane.

(0.53 ± 0.09 μg · kg⁻¹ · min⁻¹) restored arterial blood pressure to the level before sevoflurane, but peak gray levels in both layers of the CX area did not increase and were still significantly less than the baseline values. In contrast, in the LAD area, the peak gray level did not change significantly in either the inner and outer halves throughout the study period.

Figure 2 shows the changes in the inner:outer ratio of the peak gray level, obtained in the ischemic area (upper), and the ischemic:normal ratio of the peak gray level (lower). As shown in this figure, CX stenosis significantly reduced the inner:outer ratio in the areas supplied by the CX in the dipyridamole and sevoflurane groups. The ischemic:normal ratio also decreased significantly after stenosis of the CX in both groups. After intravenous administration of dipyridamole (during CX stenosis), the inner:outer ratio further decreased and was still significantly less than the baseline value even after arterial blood pressure was restored with phenylephrine ([1] 1.17 ± 0.14; [2] 0.81 ± 0.22; [3] 0.5 ± 0.36; [4] 0.55 ± 0.25). The ischemic:normal ratio also decreased significantly after dipyridamole and did not increase with phenylephrine ([1] 0.92 ± 0.15; [2] 0.55 ± 0.18; [3] 0.24 ± 0.18; [4] 0.27 ± 0.19). In contrast, after inhalation of sevoflurane (during CX stenosis), the inner:outer ratio tended to increase and significantly increased when the arterial blood pressure was restored by phenylephrine ([1] 1.46 ± 0.35; [2] 0.96 ± 0.32; [3] 1.24 ± 0.57; [4] 1.32 ± 0.37). There were significant differences in the inner:outer ratio between the dipyridamole and sevoflurane groups after dipyridamole or sevoflurane was administered. The ischemic:normal ratio remained unchanged after sevoflurane but tended to increase with phenylephrine ([1] 0.93 ± 0.32; [2] 0.50 ± 0.30; [3] 0.49 ± 0.32; [4] 0.67 ± 0.60).

**Human Studies**

Table 3 summarizes the demographic characteristics of each patient and designates the regions of interest. As shown in this table, six of nine patients had 90-100% occlusion in one or two coronary arteries, and five of these patients had angiographically visible collateral supply to the area distal to the occlusion. Table 4 summarizes hemodynamic variables, background-subtracted peak gray level in the inner and outer halves, and the inner:outer ratio of the peak gray level obtained before (baseline) and 20 min after sevoflurane. After inhalation of 1 MAC sevoflurane, heart rate, systolic pulmonary arterial pressure, and the end-diastolic area of the left ventricular short-axis view decreased slightly but significantly. Fractional area change and percentage of systolic wall thickening decreased significantly, suggesting that myocardial contractility was reduced during sevoflurane inhalation. There were no significant changes in peak gray level of the inner and outer halves during sevoflurane inhalation. Thus, the inner:outer ratio did not change significantly in areas supplied predominantly by the stenotic coronary artery (Table 4). None of the patients in this human study showed newly developed regional wall motion abnormalities or ST segment...
Sevoflurane on Myocardial Blood Distribution

Discussion

Our purpose was to determine whether sevoflurane causes abnormal redistribution of regional myocardial blood flow. In animal experiments, we first wanted to determine whether dipyridamole, which is a potent coronary vasodilator and is known to cause myocardial ischemia via a coronary steal mechanism, causes marked redistribution of myocardial blood flow from the subendocardial to subepicardial halves or from the ischemic to normal zones in our canine models with experimentally produced acute coronary artery stenosis. The administration of dipyridamole resulted in a significant reduction in the inner-outer ratio of peak gray level in the ischemic area (fig. 2). Furthermore, the decrease in the ischemic-normal ratio also was caused by dipyridamole administration. The deterioration of ischemia remained unchanged, even though heart rate and arterial pressure were restored to the values before dipyridamole administration. Dipyridamole caused transmural and intercoronary steal in our canine models with acute coronary stenosis. Using the same animal models, we determined whether sevoflurane, similar to dipyridamole, causes maldistribution of myocardial blood flow. Because sevoflurane reduces coronary vascular resistance and decreases pharmacologic coronary vasodilator reserve, this volatile anesthetic may exert coronary vasodilator activity similar to that of dipyridamole. However, contrary to our expectations, although arterial blood pressure decreased significantly after inhalation of 1 MAC sevoflurane during CX stenosis (table 2), the inner-outer ratio of the peak gray level in the ischemic area tended to increase, and significantly increased after arterial blood pressure was restored with phenylephrine. The ischemic-normal ratio did not change after sevoflurane but tended to increase with phenylephrine (fig. 2). These results suggest that blood flow to the ischemic myocardium was not worsened by the administration of 1 MAC sevoflurane. That is, in our canine models, sevoflurane induced neither transmural nor intercoronary steal, even though diastolic arterial blood pressure decreased significantly after sevoflurane.

A “steal-prone” coronary artery anatomy is characterized by total occlusion of one major epicardial coronary artery but adequate collateralization distal to the occlusion and simultaneous stenosis of the artery of origin of

Anesthesiology, V 90, No 5, May 1999

Fig. 2. (Upper) Circumflex coronary artery (CX) stenosis significantly reduced the ratio of the peak gray level in the inner halves to that in the outer halves (inner-outer ratio) in the areas supplied by the CX in the dipyridamole and sevoflurane groups. After intravenous administration of dipyridamole, the inner-outer ratio further decreased, and was still significantly less than the baseline value even after arterial blood pressure was restored with phenylephrine. In contrast, after inhalation of sevoflurane, the inner-outer ratio tended to increase, and it increased significantly when the arterial blood pressure was restored using phenylephrine. (Lower) The ratio of the peak gray level in the CX area to that in the left anterior descending artery (LAD) area (ischemic-normal ratio) was reduced significantly after stenosis of the CX in both groups. After dipyridamole, the ischemic-normal ratio decreased significantly and did not increase with phenylephrine. The ischemic-normal ratio remained unchanged after sevoflurane, whereas it improved after administration of phenylephrine. Sev = inhalation of sevoflurane (1 minimum alveolar concentration), Dipy = administration of dipyridamole (1 mg/kg).
the collateral vessels. To determine whether sevoflu- ranse produces coronary steal, Kersten et al. studied the effects of sevoflurane on regional myocardial perfusion in a model of dogs with steal-prone coronary artery anatomy that were fitted with instruments for long-term monitoring. They measured myocardial blood flow using a radioactive microsphere technique and showed that sevoflurane does not reduce collateral perfusion to the ischemic myocardium. In their experiments, coronary collateral development was enhanced by multiple brief occlusions of the LAD, and CX stenosis was produced by an amiodar constrictor. Subsequent total occlusion of the LAD was performed to create steal-prone coronary artery anatomy. In the current study, we used an acute experimental model with single coronary stenosis, which may not be suitable to study coronary steal. However, before we studied the effects of sevoflurane, we confirmed that diprydramole caused transmural and intercoronary steal in our experimental model (fig. 2). Gross et al. also reported that coronary steal could be caused by vasodilation in a model of a single coronary vessel with severe stenosis, such as the one we used.

Buffington et al. evaluated 16,249 patients whose coronary angiograms were recorded carefully as part of the Coronary Artery Surgery Study, and they reported that 23% of the patients in that registry had steal-prone coronary anatomy. In our human study, six of nine patients undergoing coronary artery bypass graft surgery had 99 to 100% occlusion in one or two coronary arteries, and five of these patients had angiographically visible collateral supply to the area distal to the occlusion (table 3). In addition, preoperative coronary angiograms revealed that at least two patients (patients 3 and 9) had steal-prone coronary anatomy, which is characterized as previously de-

scribed. However, when arterial blood pressure was kept constant by controlling the venous drainage to the cardiopulmonary bypass circuit, the inner:outer ratio of the peak gray level did not change significantly in areas supplied predominantly by the most stenotic coronary artery (table 4), and none of the patients evaluated in this study showed newly developed regional wall motion abnormalities or ST segment change during sevoflurane inhalation. These results suggest that sevoflurane does not produce abnormal redistribution of coronary blood flow from the subendocardial to the subepicardial halves in patients undergoing coronary artery bypass graft surgery.

Table 3. Patient Characteristics Undergoing Coronary Artery Bypass Graft Surgery

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Stenosed Coronary Artery</th>
<th>Preoperative Asynergy</th>
<th>NYHA</th>
<th>ROLs</th>
<th>Collateral Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>F</td>
<td>RCA 90%/LAD 90%</td>
<td>No</td>
<td>2</td>
<td>Anterior</td>
<td>RCA → LAD</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>LMT 50%/LAD 99%</td>
<td>No</td>
<td>3</td>
<td>Anterior</td>
<td>RCA → LAD</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>M</td>
<td>RCA 100%/LAD 99%/CX 50%</td>
<td>Anteroseptal, apex</td>
<td>3</td>
<td>Inferior</td>
<td>CX → RCA → LAD</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>LMT 75%</td>
<td>No</td>
<td>2</td>
<td>Inferior</td>
<td>RCA → LAD</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>F</td>
<td>RCA 75%/LAD 99%/CX 90%</td>
<td>Anteroseptal, apex, anterior</td>
<td>2</td>
<td>Inferior</td>
<td>RCA → LAD</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>F</td>
<td>RCA 100%/LAD 75%/CX 90%</td>
<td>No</td>
<td>2</td>
<td>Inferior</td>
<td>RCA → LAD</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>M</td>
<td>RCA 75%/LAD 90%/CX 90%</td>
<td>Inferoposterior</td>
<td>3</td>
<td>Anterior</td>
<td>RCA → LAD</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>M</td>
<td>RCA 75%/LAD 90%/CX 99%</td>
<td>Septal, apex</td>
<td>3</td>
<td>Posterior</td>
<td>RCA → CX</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>M</td>
<td>RCA 90%/LAD 100%/CX 90%</td>
<td>Septal, apex</td>
<td>3</td>
<td>Anterior</td>
<td>RCA → LAD</td>
</tr>
</tbody>
</table>

ROls = regions of interest for myocardial contrast echocardiography.

RCA = right coronary artery; LMT = left main trunk; LAD = left anterior descending artery; CX = left circumflex artery; NYHA = New York Heart Association Classification; M = male; F = female; ROLs = regions of interest for myocardial contrast echocardiography.

Table 4. The Hemodynamic Variables and Peak Gray Level of Myocardial Contrast Echocardiography in Human Study

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>73 ± 8</td>
<td>68 ± 9*</td>
</tr>
<tr>
<td>sAP (mmHg)</td>
<td>110 ± 19</td>
<td>103 ± 18</td>
</tr>
<tr>
<td>mAP (mmHg)</td>
<td>82 ± 11</td>
<td>79 ± 11</td>
</tr>
<tr>
<td>dAP (mmHg)</td>
<td>66 ± 11</td>
<td>65 ± 12</td>
</tr>
<tr>
<td>sPAP (mmHg)</td>
<td>19 ± 2</td>
<td>15 ± 3*</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>11 ± 2</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>dPAP (mmHg)</td>
<td>7 ± 2</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>EDA (cm²)</td>
<td>14.0 ± 5.2</td>
<td>12.2 ± 4.2*</td>
</tr>
<tr>
<td>ESA (cm²)</td>
<td>8.5 ± 4.6</td>
<td>8.1 ± 3.5</td>
</tr>
<tr>
<td>Fractional area change</td>
<td>0.42 ± 0.12</td>
<td>0.35 ± 0.09*</td>
</tr>
<tr>
<td>Systolic wall thickening (%)</td>
<td>35 ± 8</td>
<td>26 ± 6*</td>
</tr>
</tbody>
</table>

Peak gray level

Inner layer               | 37 ± 17   | 37 ± 22    |
Outer layer               | 29 ± 12   | 30 ± 19    |
Inner/outer ratio         | 1.25 ± 0.36 | 1.26 ± 0.22 |

Values are mean ± SD.

HR = heart rate; sAP = systolic arterial pressure; mAP = mean arterial pressure; dAP = diastolic arterial pressure; sPAP = systolic pulmonary arterial pressure; mPAP = mean pulmonary arterial pressure; dPAP = diastolic pulmonary arterial pressure; EDA = end-diastolic area of left ventricular short-axis view; ESA = end-systolic area of left ventricular short-axis view.

* P < 0.05 versus baseline.
SEVOFLURANE ON MYOCARDIAL BLOOD DISTRIBUTION

The results we obtained in our animal experiments suggest that sevoflurane induces neither transmural nor intercoronary steal, even though diastolic arterial blood pressure decreased significantly after sevoflurane (table 2, fig. 2). These results contradict those of Reiz et al. and Buffington et al., which were obtained using isoflurane. Priebe also reported that in animal experiments isoflurane can cause coronary steal. Hartman et al. reported that the redistribution of coronary blood flow away from the ischemic myocardium occurred during isoflurane anesthesia when diastolic arterial pressure was reduced. In our study, increases in the ratio of blood flow between the ischemic and normal zones or inner and outer halves in the ischemic zone were observed during 1 MAC sevoflurane with restoration of arterial pressure to the level before sevoflurane. These discrepancies between sevoflurane and isoflurane might occur because, during inhalation of sevoflurane, the decreased wall tension resulting from suppressed cardiac contractility and decreased blood pressure might have acted favorably in the ischemic area, especially in the subendocardial area. It is also possible that the net effect of sevoflurane on coronary vasomotor tone is determined not only by direct coronary vasodilator actions, but also by indirect reductions of coronary blood flow associated with decreased oxygen consumption caused by sevoflurane.

To determine regional myocardial blood flow, we used the myocardial contrast echocardiography technique in dogs and humans. The injection of contrast medium, containing microbubbles, into the coronary circulation enhances the backscattered signal from the myocardium and produces an ultrasonic contrast effect in the myocardium. With this technique, the perfusion area of the coronary artery is identified, and regional myocardial blood flow can be estimated. The early studies of myocardial contrast echocardiography used contrast agents containing large microbubbles that ranged from 10 μm to 20 μm. However, Feinstein et al. developed the technique of sonication to generate smaller microbubbles, which ranged in size from 5 μm to 12 μm (average, 6–8 μm). In the current study, based on the report of Feinstein et al., 5% human albumin was sonicated to create contrast medium. It has been reported that microbubbles of these sizes can pass through the microvasculature without sludging or significant delay. When contrast agents were regarded as deposit tracer, peak gray level corrected for background before injection of contrast medium was advocated as indicator. Several investigators recently studied the correlation between regional myocardial blood flow as determined by the microsphere method and each index determined by myocardial contrast echocardiography. They observed that the background-subtracted peak intensity correlates closely with normalized regional myocardial blood flow. Although half-time derived from the washout phase of the time-intensity curve has been used when contrast medium was regarded as free-passing tracer, it has been reported that peak gray level is more accurate than washout half-time. Cherif et al. also showed that peak contrast intensity after intracoronary injection of contrast medium provides a relative index of myocardial perfusion that allows regional coronary reserve to be assessed in patients with coronary artery disease. Thus, in the current study, we used the peak gray level corrected for background rather than the washout half-time as an indicator of regional myocardial blood flow distribution.

Myocardial contrast echocardiography appears to offer several advantages compared with other methods. One potential advantage is the ability of myocardial contrast echocardiography to provide simultaneous information about wall motion and myocardial perfusion with no risks from radiography or radioisotopes. In addition, Lim et al. showed that myocardial contrast echocardiography can provide useful information not only about intercoronary but also transmural myocardial blood flow distribution. In a model of critical coronary stenosis, Cherif et al. observed that the endocardial/epicardial ratio measured by contrast intensity or microspheres remained unchanged in regions supplied by a normal coronary artery, whereas it decreased in the segments supplied by the stenotic artery after administration of dipyridamole. Thus, myocardial contrast echocardiography seems to be a sensitive technique to detect changes in transmural and subendocardial perfusion. Although these data indicate that it may be feasible to quantify myocardial perfusion with myocardial contrast echocardiography, several methodologic limitations should be noted. First, enhancement of gray levels is affected by several factors, such as the size, homogeneity, and concentration of microbubbles contained in the contrast medium, the gain setting, angle of incidence, axial and lateral resolution, ultrasound attenuation, and the injection volume of the contrast agent. The lack of knowledge of the amount of microbubbles injected and the absence of an adequate mixing chamb-
ber preclude accurate measurement of absolute myocardial flow. Thus, we referred to the ratio of inner: outer layer peak gray level and the ratio of the ischemic:normal area peak gray level rather than the absolute values of peak gray level in the subendocardial and subepicardial halves, because the effects of aforementioned factors are thought to be reduced by calculating the ratio.

In conclusion, in dogs with acute coronary artery stenosis and in patients with multivessel coronary artery disease, sevoflurane did not cause transmural coronary steal or intercoronary steal. Myocardial contrast echocardiography appears to be useful to quantitate coronary blood flow and its transmural distribution.

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SEVOFLURANE ON MYOCARDIAL BLOOD DISTRIBUTION


