Cardioscopic Observation of Subendocardial Microvessels in Patients With Coronary Artery Disease

Yasuto Uchida, MD, Masahito Kanai, MD, Yuko Maezawa, MD, Yoshiro Maezawa, MD, Seiichiro Shirai, MD, Osamu Nakagawa, MD, and Yasumi Uchida, MD

SUMMARY

Coronary microvessels play a direct and critical role in determining the extent and severity of myocardial ischemia and cardiac function. However, because direct observation has never been performed in vivo, the functional properties of the individual microvessels in patients with coronary artery disease remain unknown.

Subendocardial coronary microvessels were observed by cardioscopy in 149 successive patients with coronary artery disease (81 with stable angina and 68 with old myocardial infarction).

Twenty-four arterial microvessels (AMs) and 27 venous microvessels (VMs) were observed in the left ventricular subendocardium. All 12 AMs and 13 of 14 VMs that were located in normokinetic-to-hypokinetic left ventricular wall segments were filled with blood during diastole and were collapsed during systole. In contrast, 8 of 12 AMs and 9 of 13 VMs that were located in akinetic-to-dyskinetic wall segments were filled with blood during systole and were collapsed during diastole. There were no significant correlations between the timing of blood filling and the severity of coronary stenosis and collateral development.

In patients with coronary artery disease, the timing of blood filling of AMs and VMs was dependent on the regional left ventricular contractile state; during diastole when contraction was preserved and during systole when it was not. It remains to be elucidated whether and how blood filling is disturbed in other categories of heart disease. (Int Heart J 2011; 52: 274-279)

Key words: Coronary microvessels, Diastolic and systolic blood filling, Left ventricular contraction, Interstitial pressure, Coronary artery disease

Coronary microvessels play a direct and critical role in determining the extent and severity of myocardial ischemia, cardiac function, and symptoms. However, because direct observation has never been performed in vivo, the dynamic properties of the individual coronary microvessels in patients with coronary artery disease remain unknown.

There are many diseases in which microvessel dysfunction is suspected to participate but not been proven, such as the no reflow phenomenon, which may be observed following coronary interventions, Takotsubo cardiomyopathy, peripartum cardiomyopathy, syndrome X, and small vessel angina.

Until recently, the coronary microcirculation has been evaluated by contrast echocardiography, radionuclide imaging, magnetic resonance imaging, computed tomography, electron beam computed tomography, pressure wire, Doppler guidewire, coronary angiography and left ventricular pressure. These techniques can evaluate coronary microcirculation as a whole, but functional evaluation of the individual microvessels has been beyond the scope of these imaging modalities.

Anatomically, a part of arterial microvessels (AMs; arterioles and small arteries), venous microvessels (VMs; venules and small veins) are located beneath the endocardium in humans, and can be seen through the endocardium.

If visualized directly, exactly what determines their functional properties can be objectively identified.

Cardioscopy enables the direct observation of the subendocardial microvessels. Therefore, the present cardioscopic study was performed to examine what determined dynamic changes in the subendocardial microvessels in patients with coronary artery disease.

METHODS

Cardioscopy system: The cardioscopy system (Figure 1A) was composed of a light source (CLV-A, Olympus Corporation, Tokyo), 9-F guiding balloon catheter (Clinical Supply Co, Gifu, Japan), 4.2-F fiberscope (AF 14, Olympus), and a color CCD camera (OTV-A, Olympus). This system could discriminate a target 20 μm or more in size. For the measurement of microvessel diameter, a 0.016 inch (approximately 40 μm) guidewire was introduced simultaneously with a fiberscope (Figure 1E). This technique is however not adequate for quantitative measurement of a target because the cardioscopic im-
No 5 CARDIOSCOPY FOR SUBENDOCARDIAL MICROVESSELS

Vol 52

The balloon was inflated with CO2. A 4.2-F fiberscope was then guided balloon was introduced into the left ventricle and the coronary angiography were performed. Subsequently, a 9-F

prevention of thrombus formation, left ventriculography and before being transferred to the catheterization laboratory. After approved by the Institutional Review Boards. All patients pro-

vided informed consent for the procedures.

The balloon catheter was gently pushed against the endocardial surface to create a dead space, saline solution was injected into the dead space to displace the blood, and the endocardial surface was observed by the fiberscope (a).

The Tebessian vessel was excluded because this vessel ejects the blood usually during diastole into the ventricular chamber. Before observation, color correction was performed by adjusting the white balance by using a gauze immersed in the saline solution as a standard white color. Details of the cardioscopy system have been described elsewhere.17-20

**Observation of subendocardial microvessels by cardioscopy:** Coronary microvessels that were observed by percutaneous cardioscopy in 149 successive patients with coronary artery disease were retrospectively evaluated [57 females and 92 males; mean age ± SD = 63 ± 6 years; 81 with stable angina and 68 with an old myocardial infarction (one month or more after the onset of acute myocardial infarction, complicated with or without stable angina] were evaluated retrospectively. Patients with acute coronary syndromes were not examined to avoid a time-delay in treatment.

The Tebessian vessel was excluded because this vessel ejects the blood usually during diastole into the ventricular chamber. Before observation, color correction was performed by adjusting the white balance by using a gauze immersed in the saline solution as a standard white color. Details of the cardioscopy system have been described elsewhere.17-20

**Observation of subendocardial microvessels by cardioscopy:** Coronary microvessels that were observed by percutaneous cardioscopy in 149 successive patients with coronary artery disease were retrospectively evaluated [57 females and 92 males; mean age ± SD = 63 ± 6 years; 81 with stable angina and 68 with an old myocardial infarction (one month or more after the onset of acute myocardial infarction, complicated with or without stable angina] were evaluated retrospectively. Patients with acute coronary syndromes were not examined to avoid a time-delay in treatment.

The cardioscopy was performed at Funabashi-Futawa Hospital, Toho University Medical Center Sakura Hospital, and Toho University Medical Center Ohmori Hospital and was approved by the Institutional Review Boards. All patients provided informed consent for the procedures.

The patients were pretreated with oral diazepam (10 mg) before being transferred to the catheterization laboratory. After administrating 50 mg of intravenous xilocaine for the prevention of ventricular arrhythmias and 5000 IU heparin for the prevention of thrombus formation, left ventriculography and coronary angiography were performed. Subsequently, a 9-F guiding balloon was introduced into the left ventricle and the balloon was inflated with CO2. A 4.2-F fiberscope was then advanced through the catheter to position the fiberscope tip at the tip of the catheter. Next, the balloon was gently pushed against the targeted wall segment of the left ventricle, and 50 to 100 mL of saline solution (heparin 10 IU/mL, 37°C) was injected through the catheter at 10 mL/second by a power injector to displace the blood between the balloon and the ventricular luminal surface to allow for observation (Figure 1). The anterior, apical, inferior, and lateral wall segments were observed. The guiding balloon catheter was preshaped so it could be easily placed on the targeted wall segment; either an “S”- or “crank”-configuration for anterior, apical, and inferior wall segments, or a “J”-configuration for the lateral wall segment was used.

The observed cardioscopic images were recorded using a color CCD camera on a DVD recorder while simultaneously recording fluoroscopic images and an electrocardiogram to determine the observed left ventricular wall segment, and to determine the relationship between the changes in microvessels during systolic and diastolic phases.17-20 The time from R to T terminal and the time from the T terminal to R in the electrocardiogram were determined to be systole and diastole, respectively.

**Wall motion:** After cardioscopic observation, a contrast material was injected toward the observed wall segment through the channel of the guiding balloon catheter that was used for the injection of saline solution to observe the regional wall motion. Regional left ventricular contraction was determined to be normokinetic-to-hypokinetic when inward motion was observed and akinetic-to-dyskinetic when no motion or outward motion was observed. Quantitative analysis of wall motion was not performed.

**Measurement of coronary stenosis:** The diameter stenosis of the coronary arteries was measured by quantitative coronary arteriography using TCS Symphony 2.02 (McKesson Co, North Charleston, NC, USA). The diameter was expressed as a percentage to correlate the changes in subendocardial microvessels to the severity of the stenosis of the irrigating epicardial coronary arteries. Collateral development was graded by Rentrop’s classification.31

**Determination of arterial (AMs) and venous microvessels (VMs):** Because the blood obtained from the human artery exhibited a red color and that from the vein was dark purple using the present cardioscopy system, the red vessels were defined as the AMs while the dark purple vessels were defined as the VMs.

**Statistical analysis:** The data were tested using the \( \chi^2 \) test. A \( P \) value < 0.05 was considered significant.

**Results**

Representative examples of subendocardial arterial (AMs) and venous microvessels (VMs): The diameter of subendocardial microvessels measured in 6 patients ranged from approximately 30-150 \( \mu m \). Diameter measurement was not performed in other patients.

Figures 2A-a and b show a vessel with branches and filled with red blood, namely an AM located in the subendo-
cardium of the normokinetic (normally contracting) anterior wall segment of the left ventricle in a patient with stable angi-
a. The AM was filled with blood during diastole (2A-a) and collapsed during systole (2A-b), indicating diastolic blood fill-
ing. Figures 2B shows a dark purple vessel, namely a VM lo-
A total of 51 microvessels were observed in the subendocardium in 149 patients. Of these, 7, 11, 14, and 19 were observed in the apical, anterior, inferior, and lateral walls of the left ventricle, respectively. Among them, 24 were red and 27 were dark purple, indicating that the former were AMs and that the latter were VMs. In addition to the microvessels located in the subendocardium, 7 AMs were observed exposed in the left ventricular cavity.

**Timing of blood filling and collapse**: By cardioscopy, microvessels became visible during diastole and were either not visible during systole, indicating blood filling during diastole and emptying due to collapse during systole, or remained visualized throughout one cardiac cycle, indicating sustained blood filling or blood retention (Table I).

The pressure measured through the guiding catheter during the injection of saline solution, which reflected both left ventricular luminal pressure and injection pressure, was not different between the group in which the microvessels were visible during diastole and the group in which the microvessels were visible during diastole (156 ± 21/43 ± 6 versus 160 ± 20/44 ± 5 mmHg).

**Blood filling during diastole and collapse during systole**: Diastolic blood filling was observed in the majority of AMs and VMs that were located in the normokinetic-to-hypokinetic wall segments (Table IIA). This phenomenon had no obvious relationship with the percentage stenosis of the irrigating epicardial coronary arteries (Table IIB) or collateral development (Table IIC).

**Blood filling during systole and collapse during diastole**: Blood filling during systole was observed in 8 of 11 AMs that were located in the akinetic-to-dyskinetic wall segments. The other 3 AMs remained visible throughout one cardiac cycle (Table IIA).

Blood filling during systole was also observed in 9 of 13 VMs that were located in the akinetic-to-dyskinetic wall segments. Blood filling of both AMs and VMs during systole had no obvious relationship with the percentage stenosis of the irrigating epicardial coronary arteries, or collateral development (Tables IIA, IIB).

**Red and purple patches that appeared during systole**: Multiple red patches, which appeared during systole and disappeared during diastole, were observed in 4 patients (Figures 3A and 3B). Also, multiple dark purple patches that appeared during systole and disappeared during diastole were observed in 2 patients (Figures 3C and 3D).

**Arterial microvessels (AMs) exposed in the left ventricular cavity**: Figures 4A and 4B show an AM that was exposed in the left ventricular cavity. Three and 4 AMs were detected close to the normokinetic-to-hypokinetic wall segments and akinetic-to-dyskinetic wall segments, respectively. In contrast to those located in the subendocardium, they remained visible throughout one cardiac cycle, although segmental narrowing was observed either during diastole or systole. The direction of the blood flow could not be determined.

**Complications**: When placing the balloon catheter tip onto the endocardial surface, ventricular arrhythmias appeared transiently. Although the balloon remained placed onto the endo-

**Table I. Relationship Between Cardiac Cycle and Blood Filling of Coronary Microvessels**

<table>
<thead>
<tr>
<th>Blood filling</th>
<th>Diastole</th>
<th>Systole</th>
<th>Both diastole and systole</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Subendocardial microvessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial microvessels</td>
<td>13</td>
<td>8</td>
<td>3’</td>
</tr>
<tr>
<td>Venous microvessels</td>
<td>14</td>
<td>10</td>
<td>3’</td>
</tr>
<tr>
<td>B. Cavity microvessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial microvessels</td>
<td>0</td>
<td>0</td>
<td>7’</td>
</tr>
</tbody>
</table>

*P < 0.05 versus diastole and systole.
cardium, the arrhythmias subsided within a few seconds. No serious complications related to cardioscopy were noted. The time required for cardioscopy ranged between 10 and 15 minutes. The total amount of saline solution required to complete the observation ranged from 300 to 500 mL.

**Discussion**

Previously, we investigated real-time changes in subendocardial myocardial blood flow by dye-staining cardioscopy, and subendocardial tissue fluid flow by fluorescent cardioscopy, but did not investigate dynamic flow changes in the individual microvessels.

Kaji, et al observed diastolic blood filling and systolic collapse of left ventricular subendocardial microvessels in open chest dogs by introducing a rigid scope through the left atrium into the left ventricle. However, they did not observe systolic blood filling and diastolic collapse. In the present study, diastolic blood filling and systolic collapse were observed in AMs and VMs located in normokinetic-to-hypokinetic segments but were reversed in those located in akinetic-to-dyskinetic segments. Furthermore, AMs that did not collapse throughout one cardiac cycle were observed.

The dependence of timing of blood filling on regional wall motion and the independence on left ventricular luminal pressure changes indicate that the left ventricular luminal pressure was not the determinant of the timing of blood filling or collapse of the subendocardial microvessels in patients with coronary artery disease.

The possible factors that may influence blood flow in subendocardial microvessels are the following: 1) autoregulation of the microvessels; 2) direct compression by the surrounding myocardium; 3) left ventricular luminal pressure; 4) blood pressure in the irrigating large arteries; 5) blood pressure gradient between the microvessels located in the normal wall and those located in the diseased wall; 6) interstitial pressure surrounding the microvessels, which is generated by contraction of the surrounding myocardium; 7) interstitial pressure gradient across the wall and between the normokinetic

---

**Table II. Relationships Between the Timing of Blood Filling of Subendocardial Microvessels and Regional Left Ventricular Wall Motion, Severity of Stenosis of Irrigating Artery, and Collateral Development**

<table>
<thead>
<tr>
<th>Wall motion</th>
<th>Normokinetic-to-hypokinetic</th>
<th>Akinetic-to-dyskinetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Arterial microvessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood filling</td>
<td>11</td>
<td>2'</td>
</tr>
<tr>
<td>Systolic blood filling</td>
<td>0</td>
<td>8'</td>
</tr>
<tr>
<td>Persistent blood filling</td>
<td>0</td>
<td>3'</td>
</tr>
<tr>
<td>B. Venous microvessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood filling</td>
<td>13</td>
<td>1'</td>
</tr>
<tr>
<td>Systolic blood filling</td>
<td>2</td>
<td>8'</td>
</tr>
<tr>
<td>Persistent blood filling</td>
<td>0</td>
<td>3'</td>
</tr>
</tbody>
</table>

P < 0.05 versus normokinetic-to-hypokinetic.

**B. Severity of stenosis of irrigating artery**

<table>
<thead>
<tr>
<th>Stenosis (%)</th>
<th>75 &gt;</th>
<th>75 ≤</th>
<th>≤ 99</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Arterial microvessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood filling</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Systolic blood filling</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Persistent blood filling</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>B. Venous microvessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood filling</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Systolic blood filling</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Persistent blood filling</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**C. Collateral development**

<table>
<thead>
<tr>
<th>Collateral development (Rentrop)</th>
<th>0-1</th>
<th>2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Arterial microvessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood filling</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Systolic blood filling</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Persistent blood filling</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>B. Venous microvessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood filling</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Systolic blood filling</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Persistent blood filling</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

---

**Figure 3.** Red and dark purple patches that appeared during systole. Red patches, that were not observed during diastole (A), appeared during systole (arrows in B). Dark purple patches, that were not observed during diastole (C) but appeared during systole (arrows in D).

**Figure 4.** An arterial microvessel (AM) located in the left ventricular cavity. An AM exposed in the left ventricular cavity that did not collapse throughout one cardiac cycle. A: Diastole. B: Systole. Arrow: the arteriole. Arrowheads in A and B: segmental narrowings that appeared either during diastole or systole.
and diseased walls; 8) tension-time index/diastolic pressure-time index; 9) pressure gradient between the microvessels and the venous trees, and 10) regional difference in microvessel density, which may be altered by angiogenesis. 30

In the present study, the timing of blood filling and collapse was closely related to the contractile state of the ventricular wall in which the microvessels were located; this resulted in blood filling during diastole and collapse during systole in normokinetic-to-hypokinetic wall segments as well as blood filling during systole and collapse during diastole in akinetic-to-dyskinetic wall segments. These changes can not be explained by the changes in the left ventricular luminal pressure.

Because vessel diameter measurement was not carried out systematically and because cardioscopy was not feasible for quantitative measurement, it was unclear whether or not there was a relationship between vessel diameter and the timing of blood filling. Although interstitial pressure was not measured, it is conceivable that in cases of normokinetic-to-hypokinetic wall segments, the surrounding contracting myocardium and the interstitial pressure rise caused by myocardial contraction overcame blood pressure in the microvessels to compress the microvessels to collapse and myocardial relaxation and a consequent fall in the interstitial pressure below the blood pressure of the microvessels during diastole caused blood filling. However, in cases of akinetic-to-dyskinetic wall segments, myocardial contractions were lost and direct compression by the myocardium did not occur and interstitial pressure did not rise. Therefore, the rise in interstitial pressure of the neighboring normally contracting wall segments squeezed the blood towards the akinetic-to-dyskinetic wall segment, thus causing systolic blood filling, and diastolic collapse due to the cessation of squeezing.

The AMs that were exposed in the left ventricular cavity did not collapse even during systole. The blood pressure in the AMs might have been higher than the ventricular luminal pressure or both ends of the AMs were obstructed by myocardial contraction resulting in the blood remaining in the vessels even during systole. Localized narrowing of the exposed AMs was observed during both diastole and systole. However, the mechanism of this phenomenon remains obscure.

Red or purple patches that appeared during systole were also observed in the present study. They were not thrombi or hematoma because they disappeared in synchrony to the cardiac cycle and because thrombi and hematoma do not disappear throughout the cardiac cycle and often protrude into the cavity. These patches resembled myocardial hemangiomas that are produced by angiogenic therapies using endothelial growth factors. 31,32 We believe that hemangiomas were produced by angiogenesis that was stimulated by myocardial ischemia, and became visible during systole filled with the blood from the normally contracting wall segments.

The timing of blood filling into AMs and VMs had no significant relationship with the severity of stenosis of the irrigating epicardial coronary arteries and collateral development. This finding also supports the possibility that coronary microvessel function was mainly controlled by regional myocardial function in these patients. Whether or not similar changes occur in AMs and VMs in patients with acute coronary syndrome or other heart disease remains to be elucidated.

By using cardioscopy, dilatation or contraction of microvessels and the presence of microemboli in the microvessels can be directly observed. Because damaged endothelial cells are stained blue by an intracoronary injection of Evans blue dye, 33 endothelial dysfunction can also be determined by cardioscopy.

Direct investigations of coronary microvessels by cardioscopy may therefore contribute to clarifying the mechanisms of heart diseases in which microvessel disease is suspected to participate.

The present study is, to the best of our knowledge, the first to perform direct in vivo visualization of coronary microvessels of a beating heart in humans.

**Study limitations:** Observation of the left ventricular endocardial surface was limited to at most 4 segments because of the limited volume of saline solution required for displacement of blood. We therefore could not examine whether or not any differences in functional properties existed between the microvessels in the same patient. The low detection rates of coronary microvessels in the present study are considered to be due to its retrospective nature.

**Conclusion:** Because direct observation has never been performed in vivo, functional properties of the individual coronary microvessels in patients with coronary disease have remained unclear. In the present study, subendocardial arterial microvessels (AMs) and venous microvessels (VMs) of the left ventricle were observed by percutaneous cardioscopy in patients with coronary artery disease.

The timing of blood filling of the subendocardial AMs and VMs was dependent on the contractile state of the regional myocardium; blood filled during diastole when contraction was preserved, and blood filled during systole when it was not. We believe that it was not the luminal pressure but rather direct compression by the surrounding myocardium and myocardial interstitial pressure primarily that determined the timing of the blood filling and collapse of AMs and VMs in these patients.

**References**


