Direct observation of epicardial coronary capillary hemodynamics during reactive hyperemia and during adenosine administration by intravitral video microscopy

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Submitted 2 February 2004; accepted in final form 29 August 2004

Intravital pencil-lens probe-charge-coupled device video microscopy, we visualized the epicardial capillary network of the beating canine heart in vivo to elucidate its functional role under control conditions, during reactive hyperemia (RH), and during intracoronary adenosine administration. The pencil-lens video-microscope probe was placed over capillaries fed by the left anterior descending artery in atrioventricular-blocked hearts of open-chest, anesthetized dogs paced at 60–90 beats/min (n = 17). In individual capillaries under control conditions, red blood cell flow was predominant during systole or diastole, indicating that the watershed between diastolic arterial and systolic venous flows is located within the capillaries. Capillary flow increased during RH and reached a peak flow velocity (2.1 ± 0.6 mm/s), twice as high as control (1.2 ± 0.5 mm/s), with enhancement of intercapillary cross-connection flow and enlargement of diameter (by 17%). With adenosine, capillary flow velocity significantly increased (1.8 ± 0.7 mm/s). However, the increase in volumetric capillary flow with adenosine estimated from red blood cell velocity and diameter was less than the increase in arterial flow, whereas that during RH was nearly equivalent to the increase in arterial flow. There was a time lag of ~1.5 s for refilling of capillaries during RH, indicating their function as capacitance vessels. In conclusion, the coronary capillary network functions as 1) the major watershed between diastolic-dominant arterial and systolic-dominant venous flows, 2) a capacitor, and 3) a significant local flow amplifier and homogenizer of blood supply during RH, but with adenosine the increase in capillary flow velocity was less than the increase in arterial flow.

microcirculation; in vivo imaging; watershed; unstressed volume

THE INFLOW OF CORONARY ARTERIAL blood into the myocardium is almost exclusively limited to diastole, and reverse flow is exhibited during systole (slosh phenomenon) (5, 22, 29). Conversely, venous outflow is predominantly systolic (5, 16, 17, 22, 28, 30). Thus arterial inflow into the myocardium during diastole must be stored in intramyocardial capacitance vessels, and an almost equal amount of stored blood must be squeezed out into coronary veins during the next systole (28). These findings suggest a substantial phasic volume change in intramyocardial capacitance vessels during the cardiac cycle (16).

We recently evaluated the intramyocardial microvessels of diastolic- and systolic-arrested rat hearts three-dimensionally by X-ray micro-CT and confocal laser scanning microscopy (36). The vascular volume fraction of the capillaries in diastolic mode was 10 times larger than that of other microvessels such as arterioles and venules and was reduced in systolic mode by ~30% without capillary collapse, indicating that capillaries are highly compliant and function as intramyocardial capacitance vessels to accommodate the majority of diastolic arterial inflow. However, the dynamic functional role of coronary capillaries during changes in hemodynamic conditions, such as an increase in flow, is unclear.

In the present study, to evaluate dynamic functions of coronary capillaries, we directly visualized epicardial coronary capillaries and their flow dynamics in vivo with our high-resolution, pencil-lens probe intravitral video microscope under control conditions, during reactive hyperemia (RH), and during adenosine administration.

METHODS

Intravitral pencil-lens probe-charge-coupled device video microscope system. Coronary capillaries were visualized using a pencil-lens probe video microscope coupled to a charge-coupled device (CCD) camera (Nihon Kohden, Tokyo, Japan). The system was modified for visualization of coronary capillary microcirculation from our previously reported needle-probe CCD video-microscope system (10, 40, 41). It consists of a pencil probe, a CCD camera, a light source and guide, a control unit, a monitor, and a videotape recorder (Fig. 1). The pencil-lens probe (1 mm tip diameter) is surrounded by eight light guide fibers arranged in an annulus. Epimyocardial tissue is illuminated by light from a xenon lamp via the light guide fibers. A green filter is used to accentuate the contrast between blood-filled vessels and surrounding tissue. The microscopic images are monitored and recorded on 8-mm videotape every 33 ms (30 frames/s). The spatial resolution of a static image of this system is 0.5 μm for ×600 magnification (42), whereas the resolution of a moving image is almost half that of the static image, i.e., 0.25 μm. The field of view is 367 × 248 μm, and the focal depth is ~50 μm.

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Animal preparation. This study conformed to the Guidelines of the Animal Research Committee of Okayama University Graduate School of Medicine and Dentistry and Kawasaki Medical School (Nos. 95-013, 96-003, and 97-058) and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Adult mongrel dogs (n = 17) of either gender weighing 19 – 32 kg were sedated with ketamine (10 mg/kg im) and then anesthetized with pentobarbital sodium (30 mg/kg iv). Depth of anesthesia was monitored by checking reflexes, and additional anesthesia was given when necessary. After tracheal intubation, the dogs were ventilated with a mixture of room air and oxygen by means of a jet ventilator. Blood gases and pH were measured regularly and kept within the physiological range (pH 7.35 – 7.45, 25 – 40 mmHg PCO2, >70 mmHg PO2) by adaptation of the ventilation. When necessary, sodium bicarbonate was given to avoid acidosis. Heparin sodium (1,000 U/h iv; Otsuka) was administered to prevent coagulation. The ECG was recorded from standard limb leads. An 8-Fr pig-tail double-lumen catheter was inserted via the right carotid artery to measure aortic pressure and left ventricular (LV) pressure. The thorax was opened through a medial sternotomy and a left thoracotomy between the third and fourth ribs. The pericardium was opened, and the heart was suspended in a pericardial cradle. The atrioventricular node was destroyed by an injection of 40% formaldehyde, and the heart was paced at a constant rate of 60 – 90 beats/min (31). The left anterior descending artery (LAD) and the great cardiac vein (GCV) were dissected free, and flow probes (Transonic Systems, Ithaca, NY) were placed around them for measurement of phasic coronary blood flow. Systemic hemodynamics and coronary blood flow were recorded on a data recorder (model R-81, TEAC, and LabView 3.1.1).

Flow visualization of coronary capillaries and analysis methods. The epicardial capillaries were visualized under control conditions, during RH (reperfusion after 20 s of LAD occlusion), and during adenosine administration (50 μg·kg⁻¹·min⁻¹ iv). A special plate with a hole (5 mm diameter) was fixed on the epicardial surface with an adhesive and pulled up gently to stabilize the observation area for the pencil-lens probe during the experiment. The tip of the probe, introduced through the hole, touched the epicardial surface softly and was withdrawn slowly and carefully within the focus length until a clear image of the capillary was obtained for recording (Fig. 1). At the end of the experiment, the sequence of capillary images was transferred from videotape to a personal computer (Power Macintosh, Apple Computer, Cupertino, CA) for measurement of velocity and diameter using appropriate software (NIH Image 1.62, National Institutes of Health, Bethesda, MD).

Fig. 1. A: schematic illustration of coronary microcirculation observation system and intravital pencil-lens probe video microscope coupled to a charge-coupled device (CCD) camera and videotape recorder (VTR). B: photograph of the tip of the video microscope. C: schematic illustration of lateral view of the system.
Red blood cell velocity in an individual segment of the coronary capillaries was analyzed using a specifically designed algorithm previously described (25). A line segment was set along a capillary bed in sequentially videotaped images, and a spatiotemporal image was constructed (the line-shift method), allowing us to discern differences in the gray level during the passage of red blood cells. The angle of the line-shift striped pattern was estimated for computation of the erythrocyte velocity vector.

Capillary diameters were determined from the images digitized near end diastole, where the heart motion was small, by manual border tracing or with an automated edge-detection procedure, in which the edge of the capillary was determined using a density profile (40). Because of the absorption of green light by hemoglobin, the light reflected by the blood in the capillary differed in intensity from that reflected by the surrounding tissue.

Validity of the methods. We eliminated the mechanical factors such that the coronary microcirculation was disturbed as little as possible. This system does not require insertion of the illumination fibers and the needles to stabilize the heart.

To evaluate the effect of application of the pencil-lens probe onto the epicardial surface, we set a miniature pressure gauge (model P-7, Konigsberg Instruments, Pasadena, CA) horizontal to the tip of the pencil lens and the epicardial surface while we monitored the epicardial pressure. The lens-tip pressure was nearly zero during pencil lens and the epicardial surface while we monitored the epicardial pressure. The pressure during systole increased <2.5 mmHg. Thus we believe that, with this observation system, we can obtain continuous images with minimum mechanical effect on the microcirculation.

Statistical analysis. Values are means ± SD. Student’s t-test was used for paired and unpaired comparisons. The criterion for statistical significance was P < 0.05.

RESULTS

Hemodynamics. Systolic and diastolic blood pressures, LV end-diastolic pressure, and LAD and GCV flows under control conditions, during peak RH, and during adenosine administration are shown in Table 1. Pressures did not increase during RH and during adenosine administration. LAD flows increased significantly to about three times their control values during RH. With adenosine administration, LAD flows increased significantly to ~4.2 times their control values.

Visualization of epicardial capillaries under control conditions. Figure 2 shows a representative image of the epicardial capillaries at end diastole and a schematic diagram of capillary branching patterns and diastolic flow directions. The capillary diameter and length were 5.3 ± 1.5 and 73 ± 16 μm, respectively, at end diastole. The distance between two adjacent capillaries was 15 ± 2.5 μm at end diastole. The capillaries were densely connected in patterns identified as H, Y, T, or hairpin (HP), through which cross-connecting flows were abundant. The flow directions of neighboring capillaries exhibited co- and countercurrents, indicating their blood homogenizing effect.

Table 1. Hemodynamic values under control conditions, during RH, and during adenosine administration

<table>
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<tr>
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<th>Control</th>
<th>RH</th>
<th>Adenosine</th>
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<tr>
<td>SBP, mmHg</td>
<td>106 ± 5</td>
<td>110 ± 4</td>
<td>108 ± 2</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>71 ± 8</td>
<td>68 ± 8</td>
<td>70 ± 6</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>8 ± 2</td>
<td>9 ± 2</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>LAD flow, ml/min</td>
<td>29 ± 5</td>
<td>88 ± 28*</td>
<td>123 ± 37†</td>
</tr>
<tr>
<td>GCV flow, ml/min</td>
<td>21 ± 12</td>
<td>89 ± 6</td>
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Values are means ± SD. RH, reactive hyperemia; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDP, left ventricular end-diastolic blood pressure; LAD, left anterior descending artery; GCV, great cardiac vein. *P < 0.05 vs. control; †P < 0.05 vs. RH.
also seen in capillaries proximal to the capillary sinus, but the peak flow was also detected in some other capillaries during systole.

Diameter and flow response of capillaries to RH. Figure 4 shows the capillary before LAD occlusion and during RH. Motion micrographs show capillaries before and during occlusion of the LAD and after its reopening (see supplementary movies 2 and 3 at http://ajpheart.physiology.org/cgi/content/full/00088.2004/DC1). Capillary flow stopped during LAD occlusion and rapidly reappeared after reperfusion. During occlusion of the LAD, however, collapse of capillaries was not observed. The increase in capillary flow is clearly seen in supplementary movie 3. During RH, intercapillary cross-connection flow was enhanced, but capillary recruitment was not detected. Figure 5 shows the end-diastolic flow velocity and diameter of capillaries under control conditions and at peak RH. Capillary flow velocities significantly increased by \(~85\%\) during RH compared with control conditions: from \(1.2 \pm 0.5\) to \(2.1 \pm 0.6\) mm/s. Capillary diameter significantly increased by \(~17\%\) compared with control conditions: from \(5.5 \pm 1.0\) to \(6.4 \pm 1.1\) \(\mu\)m. The time lag from resumption of LAD flow to reappearance of capillary and venous flow was \(0.3 \pm 0.1\) and \(2.2 \pm 0.7\) s, respectively. Thus the transit time of the capillaries during RH is estimated as \(~1.5\) s, if the refilling time of small veins and venules is assumed to be similar to that of small arteries and arterioles. The volumetric flow increase during RH of \(~2.5\) times control, which was estimated from the increase in capillary red blood cell velocity (\(85\%\) increase) and diameter (1.17 times), is compatible with the flow augmentation, because arterial flow at peak RH increased about threefold.

Diameter and flow response of capillaries to adenosine. Capillary flow velocities significantly increased by \(~50\%\) during adenosine administration compared with control conditions: from \(1.2 \pm 0.5\) to \(1.8 \pm 0.7\) mm/s (Fig. 5A). Capillary diameter significantly increased by \(~23\%\) compared with con-

Fig. 3. Representative image (A) and schematic diagram (B) of a capillary network with a capillary sinus in a beating canine heart in vivo. Arrow in A indicates a capillary sinus. Areas enclosed in dashed circles in A and B show an overlapping part of a distal end of the capillary sinus and an ordinary capillary. Arrows in B indicate flow directions with phasic preponderance. Black and gray lines, systolic- and diastolic-predominant flows, respectively. Supplementary movie 1 illustrates capillary network with capillary sinus with flows. Flow of the capillary overriding the capillary sinus is obviously recognized to be predominantly systolic.

Fig. 4. Representative images of a capillary network under control and reactive hyperemic (RH) conditions in a beating canine heart in vivo. A: capillary network before left anterior descending artery (LAD) occlusion. Great cardiac vein (GCV) flow, LAD flow, ECG, and aortic pressure, in descending order, are superimposed. Supplementary movie 2 illustrates the capillary network before and during LAD occlusion. No collapse of capillaries was observed. B: image of the capillary network just after release of the LAD. Arrow, release point. Time lag from resumption of LAD flow to reappearance of venous flow is shown. Venous flow was absent for a few seconds after the release of the LAD and then gradually increased. Supplementary movie 3 illustrates the capillary network during LAD occlusion and after release of the LAD. No capillary recruitment was observed.
of diastolic and systolic flow-predominant capillaries with adenosine administration, by administration. Capillary diameter was significantly increased during RH and respectively, compared with control conditions. Velocity was increased by 85 and 50% during RH and adenosine administration, respectively, compared with control conditions. Values are means ± SD.

**DISCUSSION**

The major new findings in this study are 1) the coexistence of diastolic and systolic flow-predominant capillaries with concurrent, countercurrent, and interconnecting flows, 2) the increase in capillary diameter and flow velocity during RH, with equivalent increases between capillary volumetric flow and arterial flow, and 3) during adenosine administration, an increase in capillary diameter and flow velocity approximately similar to that during RH, with less increase in volumetric capillary flow than in arterial flow.

**Visualization of the coronary capillary network and its red blood cell velocity.** Tillich and associates (33) used high-speed cinematography with transillumination to measure red blood cell velocity in the LV wall and the left atrial appendage. They observed that capillary red blood cell velocity increased during systole and decreased during diastole. Subsequently, Ashikawa and co-workers (1), using their unique floating-objective cinematography system, observed that capillary red blood cell velocity was relatively steady through a cardiac cycle except for retrograde flow at the QRS complex. We also observed a transient reverse flow during early systole (1, 5). We found the coexistence of diastolic and systolic flow-predominant capillaries; it is likely that the former are mainly arteriolar capillaries and the latter mainly venular capillaries. The coexistence of flow predominance indicates that the watershed between arterial and venous flows is located within the capillary network. In most of the capillaries, the capillary flow was predominantly diastolic (65%); in other fractions of the capillaries (17%), the capillary flow was predominantly systolic. The phasic flow preponderance in the remaining capillaries (18%) was not clearly determined. However, our observation was confined to the epicardium. The number of capillaries with systolic-dominant flow may change in the deeper myocardium, where mechanical stress is greater than in the epicardium. The coexistence of flow predominance may explain, at least partly, the discrepancy in capillary flow patterns between earlier observations.

Because of the relatively stable flow patterns during diastole and the limitation of our temporal resolution, we measured capillary red blood cell velocity during diastole, resulting in a mean velocity of ~1 mm/s. Because capillary red blood cell velocities in earlier studies were 0.9–4.0 mm/s (1, 32, 34), our data lie at the lower end of the reported range. This may reflect the differences of measurement sites, species, and experimental conditions, together with the use of diastolic velocity measurement in our study.

A capillary sinus is thought to be a bulbous enlargement located in the intramyocardial capillary network, with a diameter of 30–50 μm (18, 19, 24). The sinuses exhibited large diameter changes from end diastole to end systole, and the blood flow into the sinuses occurred during diastole. This finding indicates that capillary sinuses can function as capacitance vessels, which accommodate the diastolic arterial inflow and squeeze out the pooled blood in the next systole. However, our observation was confined to the epicardium. Because capillary sinuses are reported to be predominantly distributed in intramyocardial layers (24), where mechanical stress is greater than in the epicardium (9, 14), capacitance effects may be even greater than suggested by our present observations. Indeed, we found a more remarkable volume change in the capillaries in our previous study of deeper layers (see Fig. 4 in Ref. 36).

The coronary capillaries were connected in patterns identified as H, Y, T, and HP (Figs. 2 and 3), consistent with earlier findings (2, 20, 35). The diameter and unbranched unit capillary length in our observations ranged within their previously reported values. We also observed co- and countercurrent flow directions in neighboring capillaries with interconnections, helping homogenize and enhance blood supply to myocardial cells (12).

**Function of coronary capillaries in RH.** In our previous study, we evaluated the RH responses of subendocardial and subepicardial arterioles in dogs with our prototype needle-probe intravital microscope (41) and found that arteriolar vasodilation during RH is greater in the subendocardium. However, the functional characteristics of capillaries during RH were not elucidated because of the limited spatial resolution of the system (5 μm). In the present study, we were able to observe capillary responses to RH with our new, higher-resolution system. However, we have not succeeded in holding the new probe on the subendocardial surface. Accordingly, the present observations were confined to subepicardial capillaries.

In RH, the peak flow velocity in capillaries was increased by ~85% compared with the control condition, and the end-diastolic capillary diameter increased by ~17% (Fig. 5). Tillich et al. (33) reported that capillary flow velocity increased from 110 to 230 μm/s during functional RH induced by norepinephrine. Their observation was made in the left atrial appendage of the cat, and the velocity was lower than that obtained for the LV wall in the present study, but the approximately twofold increase during RH is compatible with our data.
Coronary capillary volume changes greatly through the cardiac cycle (36). However, Kassab et al. (21) reported that the distensibility of epicardial capillaries, measured during diastole in the isolated, potassium-arrested pig heart with an elastomer technique, is small: $2.3 \times 10^{-3}/\text{mmHg}$. The diameter change from control to RH in this study was $\sim 17\%$, which is much higher. Capillaries under in vivo beating conditions may be more compliant than capillaries filled with Microfil in the arrested heart, and the systolic-diastolic interaction of the diameter change might exert influences on the diastolic diameter change during RH in vivo. Bosman et al. (3) reported a capillary diameter increase of $\sim 12\%$ during RH in the rabbit tenuissimus muscle, which is compatible with our data. Because the aspect ratio, i.e., the vertical-to-horizontal axis ratio of the capillaries, could not be evaluated in our study, some diameters may have been underestimated. Because the perpendicular vascular density increased during RH, however, the vertical diameters may increase as well (see supplemental movie 3).

The time lag of $\sim 1.5$ s in capillary flow at the beginning of RH indicates the existence of unstressed volume (UV) (16) in the beating heart. The unfilled state of UV can be presumed from an absence of venous flow, because the UV pressure must be equal to or lower than venous pressure, whereas the appearance of venous flow implies the filled state of UV, with an elevation of UV pressure above venous pressure. In our previous study (16), we demonstrated the existence of UV, i.e., highly compliant intramyocardial vessels, during diastole. Because capillaries are compliant and their volume partition is much larger than that of arterioles and venules, they may function as the major UV in the RH response of the beating heart.

**Response of coronary capillaries to adenosine.** Peak red blood cell velocity during adenosine administration increased by 50% compared with control conditions, and end-diastolic capillary diameter increased by $\sim 23\%$ (Fig. 5). The degree of increase in estimated capillary volumetric flow ($\sim 2.6$ times) was remarkably less than the increase ($>4$-fold) in arterial flow, in contrast to arterial and capillary flow increases during RH. Ashikawa et al. (1) also reported that the increase in capillary red blood cell velocity from control to adenosine administration was $\sim 30\%$, which is much less than the increase in arterial flow. Klassen (23) reported that adenosine induced an increase in epicardial coronary arterial blood flow, but the flux of red blood cells through capillaries, which was measured by an optical-fiber laser-Doppler device, decreased. He explained the discordance between arterial and capillary red blood cell flows by a possible spatial heterogeneity of plasma and red blood cell flows in the capillary network. Pries et al. (27) also indicated a similar response in the microcirculation, i.e., that red blood cell movement was different from plasma movement. Vasodilation of terminal arterioles by adenosine may facilitate this phenomenon (15). The decrease in transcapillary pressure by adenosine could also influence the red blood cell velocities in capillaries (4).

There is increasing evidence that the glycocalyx, which is the luminal gel-like layer of the vascular endothelium, can interfere with coronary flow control (6, 8, 38). Platts and Duling (26) reported that adenosine causes a rapid and profound decrease in the ability of the glycocalyx to exclude dextran but affects red blood cell exclusion only via the $\text{A}_3$ receptor at pharmacological levels. Van den Berg et al. (37) demonstrated that the rat coronary capillary endothelial surface is coated with a $0.2$- to $0.5\mu$m-thick glycocalyx layer, and its degradation instantly causes tissue edema. Thus adenosine may cause the change in fluid shift from the plasma of the red blood cell column to the retarded plasma layer in the vicinity of the endothelial cell and from intra- to extracapillary compartments, contributing to the discordance between arterial flow and capillary red blood cell velocity increment (37). An increase in hematocrit with red blood cell velocity may also contribute to the discordance (8). Further studies are needed to elucidate the exact mechanism responsible for the discordance.

**Clinical implications and concluding remarks.** Using the cryoscopic technique, Honig and Gayeski (13) reported a large fall in $\text{HbO}_2$ saturation across the coronary capillary network, indicating that the major oxygen delivery takes place in capillaries, despite the significant drop in $\text{HbO}_2$ in the arterial and arteriolar system in many other organs and tissues.

The rate at which oxygen exits capillaries is determined by its diffusion constant, which is approximately the same for blood and soft tissues. Thus oxygen delivery depends greatly on blood transit. Accordingly, the flow velocity increase in capillaries (co- and countercurrent), with augmentation of flow through dense interconnections, may facilitate oxygen supply to the myocardium during RH. A possible intercapillary shunting through myocardial tissue may also increase in this situation (39). At the same time, the function of capillaries as capacitance vessels may be beneficial to local oxygen delivery by releasing oxygen from stored blood. The increase in capillary diameter during RH is probably caused by an increase in transmural pressure. Conversely, this may indicate that the passive distension of the capillaries is a possible mechanism to stabilize capillary pressure.

Interestingly, adenosine augmented coronary arterial flow greatly, with less increase in capillary red blood cell flow, whereas arterial flow and capillary red blood cell flow increased concomitantly during RH. Maximal flow at normal perfusion pressure is higher in subepicardium than in subendocardium (11). Thus the smaller increase in capillary flow by adenosine is not likely due to diversion of flow from the epicardium to the subendocardium. Although the exact mechanism responsible for the discordance between arterial and capillary flows remains uncertain, this phenomenon is clinically important. Adenosine administration has been associated with angina-like chest pain (7). The smaller increase in capillary than in arterial flow by adenosine may cause insufficient local myocardial supply under various conditions, such as atherosclerosis and small vessel diseases.

In conclusion, during RH with increased oxygen requirement, peak capillary flow velocity increased by $\sim 85\%$, and there was considerable increase in diameter together with augmentation of intracapillary interconnecting flows, facilitating oxygen supply to the myocardial cells. On the other hand, during adenosine administration, capillary red blood cell velocity increased, but less than proximal arterial flow. Thus oxygen supply to the myocardium is smaller than that estimated from the increase in arterial flow. Furthermore, the capillaries, including capillary sinuses, function as the major capacitance vessels and form the watershed between arterial and venous flows.
REFERENCES


