Diameter Change and Pressure–Red Blood Cell Velocity Relations in Coronary Microvessels During Long Diastoles in the Canine Left Ventricle

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The objective of this study was to determine whether coronary vascular resistance remains constant during long diastoles and whether critical closure of arterial microvessels occurs at zero-flow pressure. For this purpose, we directly measured internal diameters and red blood cell velocities in arterial and venous coronary microvessels during long diastoles under maximal vasodilation. The epicardial coronary microcirculation was viewed in anesthetized, open-chest mongrel dogs through an intravital microscope equipped with a newly developed floating objective. Coronary microvascular diameters and red blood cell velocities were measured with high-speed cinematography. During maximal vasodilation (150 μg/kg body wt i.v. dilazep), long diastoles were induced by vagal nerve stimulation. Internal diameters of all small arteries and arterioles (n=12) gradually declined with decreasing aortic pressure during long diastoles, and the reduction of the diameter was greatest when aortic pressure was less than 35 mm Hg. The mean internal diameter (88.8±52.2 μm) at minimal aortic pressure (19.2±6.4 mm Hg) was significantly less than that at an aortic pressure of 100 mm Hg (116.2±68.5 μm, p<0.01). The internal diameters of small veins and venules remained nearly constant during long diastoles. When red blood cell progression in coronary microvessels stopped at the nadir of aortic pressure, all arterial coronary microvessels remained open; that is, there was no evidence of “critical closure.” Zero-flow pressure (13.6±1.7 mm Hg), at which red blood cell progression in coronary microvessels stopped, was higher than right atrial pressure (3.2±4.4 mm Hg, p<0.01) and left ventricular end-diastolic pressure (3.6±2.7 mm Hg, p<0.05). The relations between pressure and red blood cell velocity in arterioles, capillaries, and venules were curvilinear at lower aortic pressures. These results indicate that coronary vascular resistance does not remain constant during long diastoles but gradually increases with the decline in perfusion pressure even in the maximally vasodilated condition and that, in the epimyocardium, zero-flow pressure is not caused by critical closure of arterial microvessels. (Circulation Research 1990;66:503–510)

Bellamy1 has reported that in an awake chronically instrumented dog, diastolic coronary flow is a linear function of aortic pressure and that this flow ceases at a perfusion pressure of 20–50 mm Hg. This report has kindled substantial interest in coronary pressure-flow relations. Subsequently, it was shown that coronary capacitance contributed to the slope of the pressure-flow relation and to zero-flow pressure.2 Even though, during a long diastole, coronary venous outflow continues after coronary arterial flow stops,3 it is still postulated that critical closure of arterial microvessels is the explanation for why coronary flow ceases at higher perfusion pressure than coronary sinus pressure.4

In the analysis of a pressure-flow relation, especially during vasodilation, it is often assumed that coronary vascular resistance remains relatively constant.1,2 This is a critical assumption that has not been substantiated by direct experimental measurements.

Studies in microvascular beds of organs other than the heart indicate that antegrade red blood cell movement persists at very low driving pressure and that critical closure of vessels does not occur.5,6 In the coronary circulation it has been shown that the large

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Received September 2, 1988; accepted September 11, 1989.
epicardial coronary diameter decreases linearly with declining aortic pressure during diastole.7 For technical reasons, such measurements in the coronary microcirculation have not been possible. Nevertheless, direct measurement of diameters and velocities of coronary arterioles during diastoles would offer important information in this area.

In this study, we measured red blood cell velocities and vessel diameters in the coronary microcirculation during long diastoles by a direct visualization method using our newly developed floating objective.8,9 These studies were directed toward the following specific questions: 1) Does coronary arterial microvascular resistance remain constant during long diastoles? 2) At what coronary driving pressure does antegrade red blood cell movement stop in the coronary microcirculation? 3) In the coronary arterial microvessels does critical closure occur at low perfusion pressure?

Materials and Methods

Microscope System

Complete details of the microscope system using our floating objective have been reported previously.8,9 Our floating objective consists of a pair of convex lenses aligned on a same-optic axis and transmits the real image of the epimycardium of the beating heart to a fixed position without a change in magnification. The image on the front focus of a convex lens facing the heart is transmitted to the back focus of another convex lens. This transmitted real image is not affected by a change in the distance between these two convex lenses. This transmitted real image is then observed with a standard microscope. A convex lens facing the heart is mounted in a thin aluminum tube (floating objective), and its total weight is reduced to approximately 16 g. This minimal weight, by reducing the inertial force in vertical movement, permits the floating objective to follow cardiac motion. The floating objective is supported by six low-resistance ball bearings and is suspended by a weight-adjusting coil spring that permits the lens to move easily in unison with the cardiac motion. The distance between the lens and the heart was adjusted to the focal distance of this lens.

Direct visualization of the coronary microcirculation was accomplished by transillumination of the epimycardium of the left ventricle with a xenon arc lamp. A light-conducting glass fiber (0.6 mm in diameter), which was introduced through the lumen of a 20-gauge stainless steel needle, was inserted into the subepicardial muscle layer of the left ventricle. The needle was fixed to a needle holder that allowed its tip to move up and down in unison with the cardiac motion. To avoid compression of the tissue, the floating objective was lifted just above the surface of the heart by an arm connected to the needle holder.8,9

The microscopic images were recorded on film at 128–500 frames/sec with a 16-mm high-speed motion picture camera (model DBM-5D, Milliken, Arcadia, California). High-speed Ektachrome film (7251, Eastman Kodak, Rochester, New York) was used with a 100–400-μsec exposure time. Timing lights every 10 msec and signals synchronized with the R wave of the ECG were simultaneously recorded on the edges of the film to confirm film speed and to correlate with hemodynamic data. The optical magnification was ×100 or ×150 with an eyepiece of ×10. When the high-speed camera was used, a relay lens reduced the optical magnification by three fourths.

Measurement of Red Blood Cell Velocities and Diameters of Microvessels

Red blood cell velocities in coronary microvessels were calculated by frame-to-frame analysis of the distance of red blood cell progression on a projection screen and by the numbers of frames required. When aortic pressure was high in the early phase of a diastole, these measurements were done only in vessels smaller than 30 μm in diameter (arterioles, venules, and capillaries) because it was difficult to track fast red blood cell or plasma-pocket progression in vessels larger than 30 μm in diameter. When aortic pressure was reduced in the late phase of a diastole, tracking in large arterioles and venules was possible. Therefore, zero-flow was confirmed both in large and small arterioles and in large and small venules. Antegrade red blood cell movement was judged as stopped (zero-flow) when red blood cells in a microvessel did not progress antegrade for an interval of 1 second. Because the resolution on the projection screen is about 2 μm with the optical magnification of ×100, minimal velocity, which we can detect by this criterion, is about 2 μm/sec. Internal diameters of microvessels were also measured on the projection screen. The magnification on the projection screen and the film speed were confirmed with a reference scale (Nikon, Tokyo, Japan) and timing lights, respectively.

General Preparation

Experiments were performed with 16 young mongrel dogs of both sexes weighing 4.5–8.5 kg. Animals were anesthetized with an intravenous injection of urethane (500 mg/kg) and chloralose (60 mg/kg). Additional doses were given as needed throughout the experiment. Ventilation was controlled by a positive-pressure respirator (model NSH-34RH, Harvard Apparatus, South Natick, Massachusetts) at an end-expiratory pressure of 2–4 cm H2O. Metabolic acidosis during anesthesia was prevented by intravenous infusion of sodium bicarbonate, which maintained arterial pH at approximately 7.4. Arterial blood gases and pH were kept within the physiological range (pH 7.4±0.1, PaO2 94.6±10.0 mm Hg, and PaCO2 36.0±3.0 mm Hg) by adjusting the rate and volume of the respirator and/or using oxygen-enriched air. Aortic pressure was measured at the aortic root with a catheter passed through the right carotid artery and connected to a strain-gauge pressure transducer (MPU 0.5, Toyo Sokki, Tokyo,
A polyvinyl tube (3 mm in internal diameter) was introduced into the right atrium via the external jugular vein to measure or regulate right atrial pressure. A left thoracotomy was performed in the fifth intercostal space. The pericardium was opened, and the heart was suspended in a pericardial cradle. A 16-gauge Teflon tube was inserted into the left ventricle through the apex and connected to a strain-gauge pressure transducer (MPU 0.5, Toyo Sokki) to measure left ventricular pressure. The sinus node was suppressed by local injection of formaldehyde (0.3–0.5 ml), and then atrial pacing was induced at 140 beats/min. A plastic wrapping was used to separate the lung from the heart and to keep the lung moist. The exposed cardiac surface was kept moist during the experiment by a continuous drip of warm physiological solution (mM): NaCl 118.2, KCl 4.7, CaCl2 2.5, MgSO4 1.2, KH2PO4 1.2, NaHCO3 25, calcium disodium EDTA 0.026, and glucose 5.5, maintained at 37°C and pH 7.40. To reduce excessive cardiac movement, two 24-gauge steel needles were inserted horizontally (5–7 mm apart) through the midmyocardium of the left ventricle. Both ends of each needle were fixed to a needle holder held with coil springs. This apparatus allowed the heart to move perpendicularly but limited excessive horizontal movement; thereby, the transilluminated area was kept in the microscopic field of view.

Aortic, left ventricular, and right atrial pressures as well as the ECG were recorded simultaneously on a rectigraph (model 8K 12-15-1S ME, San-Ei Sokki, Tokyo, Japan) at a paper speed of 50–100 mm/sec.

Introduction of Long Diastole

Both vagal nerves were isolated in the neck, and two pairs of platinum electrodes were attached bilaterally and connected to a nerve stimulator. Prolonged diastole was obtained by bilateral nerve stimulation and abrupt cessation of atrial pacing. Stimulation parameters were as follows: frequency, 30 Hz; duration, 3 msec; and voltage, 3–15 V.

Experimental Protocol

In all cases, the basic heart rate was kept at 140 beats/min by means of atrial pacing. After hemodynamic parameters had stabilized, an adenosine potentiator (150 μg/kg i.v. dilazep) was administered to cause maximal coronary vasodilation.10 In two dogs, the maximal increase in the left circumflex coronary blood flow was measured by electromagnetic flowmeter after release of 20-second circumflex occlusion before and after the administration of dilazep to determine if maximal coronary vasodilation was present. The maximal increases were 192% and 193% at control and −7% and 26% at 13 minutes after dilazep. Thirteen minutes after the administration of dilazep, prolonged diastole was induced while motion pictures and hemodynamics were recorded simultaneously. It was difficult to measure the vessel diameters and red blood cell velocities from a single preparation. In eight dogs, diameters of arterial microvessels (six dogs) and/or venous microvessels (five dogs) were measured. In the other eight dogs, red blood cell velocities in arterial microvessels (three dogs) and/or in venous microvessels (five dogs) and/or in capillaries (four dogs) were measured. Zero-flow pressures were obtained from five dogs. In three dogs in which zero-flow pressure was measured, the tube introduced into the right atrium was opened to air at the height of the right atrium to keep the right atrial pressure at zero. After these protocols were completed, dipyridamole (0.8 mg/kg i.v.) was given to confirm maximal vasodilation by dilazep in three dogs. This dose of dipyridamole, which caused no further reduction of aortic pressure, did not cause further dilation in arterial microvessel diameters (68±27 μm before injection, 68±28 μm after dipyridamole; n=5.0, p=NS).

Statistical Analysis

All data were presented as mean±SD. Student's t test for paired and unpaired samples was used when appropriate. Differences between means were considered to be statistically significant at values of p<0.05.

Calculation of Hindrance

Hindrances were calculated from microvessel diameters (l/radius3)11 and expressed as percent, according to the following expression:

\[
\text{Hindrance (\%)} = \frac{l(r_2)^3}{l(r_1)^3} \times 100
\]

where r100 is the radius at an aortic pressure of 100 mm Hg and r2 is the radius of same vessel at each aortic pressure. Although hindrance change is not a perfect representation of the resistance change (because such factors as vessel length or blood viscosity are not included), it is more useful for estimation of the alterations of vascular resistance than change of radius or cross-sectional area.11

Results

Hemodynamics Before Long Diastole

Table 1 shows systemic hemodynamics, left ventricular end-diastolic pressure, and right atrial pressure before long diastole. Heart rate was kept constant at 140 beats/min by atrial pacing.

Changes in Internal Diameter of Arterial Microvessels During Long Diastole

The internal diameters of 12 arterial microvessels were measured in six dogs. They ranged from 40 to
Changes in Internal Diameter of Venous Microvessels During Long Diastole

The internal diameters of seven venous microvessels were measured in five dogs. These ranged from 48 to 183 μm at the beginning of a long diastole. Internal diameters of all venous microvessels were nearly constant throughout long diastoles (Figure 4). The internal diameters of venules at the end of a long diastole (82±46 μm) were similar to those at the beginning of a long diastole (85±46 μm) (Table 2).

Pressure–Red Blood Cell Velocity Relations

In eight dogs, red blood cell velocities were measured (three arterioles in three dogs, five venules in five dogs, and 13 capillaries in four dogs). Figure 5 shows typical examples of pressure–red blood cell velocity plots of an arteriole, a venule, and capillaries. Pressure–red blood cell velocity relations became curvilinear when aortic pressure was less than 30 mm Hg. At an aortic pressure higher than 30 mm Hg, the relation between red blood cell velocity and aortic pressure was linear (r=0.99±0.02).

Zero-Flow Pressure and Critical Closure

In five dogs, aortic pressure was measured when antegrade red blood cell progression stopped in the microvessels. Zero-flow pressures were always higher than the right atrial pressures and the left ventricular end-diastolic pressures (Table 3). The right atrial pressure was kept at zero by opening the right atrial tube to air in three dogs, but zero-flow pressure was not influenced.

In eight different-sized arterial microvessels (8, 17, 40, 61, 74, 149, 183, and 221 μm in diameter at an aortic pressure of 100 mm Hg), we observed the cessation of antegrade red blood cell progression. The closure of the vessel lumen did not occur in any of these vessels.

Discussion

There are five important observations in this study: 1) The internal diameters of small arteries and arterioles did not remain constant but gradually narrowed when perfusion pressure decreased during a long diastole. 2) Critical closure did not occur either in small arteries or arterioles at the zero-flow pressure. 3) The internal diameters of small veins and venules did not change during a long diastole. 4) Pressure–red blood cell velocity relations in epimyocardial microvessels (arterioles, venules, and capillaries) were curvilinear. 5) Zero-flow pressures, at which antegrade red blood cell progression stopped in coronary microvessels, were higher than left ventricular end-diastolic pressures and right atrial pressures.

Critique of Methods

In our experimental preparation, mechanical factors that may alter the coronary microcirculation were minimized as much as possible.8,9 In particular, the floating objective did not contact with the
microvessels. However, it was possible that the insertion of an illumination fiber (0.9 mm in outer diameter) had some influences on the microvessels by producing trauma or by changing intramyocardial pressure. We previously reported the viability of the vessels that were located on the illumination fiber.\textsuperscript{9} In this study, arterial microvessels responded well to a low dose of dilazep (50 $\mu$g/kg i.v.), the vessel diameter increased by 30.6±4.8%, and red blood cell

**Figure 3.** Graphs showing relations between aortic pressure and normalized internal diameter of arterial microvessels. Arterial microvessels were classified into two groups according to vessel sizes. Panel A: Vessels larger than 100 $\mu$m (n=6). Panel B: Vessels less than 100 $\mu$m (n=6). Diameters were expressed as the percent of the value at an aortic pressure of 100 mm Hg. There were no significant differences between two groups at the same aortic pressure.

**Figure 4.** Graph showing relations between aortic pressure and internal diameter of venous microvessels (n=7) of all dogs (n=5) during long diastoles. Each symbol represents one of the seven venous microvessels. Internal diameters of all venous microvessels were nearly constant throughout the long diastoles.
velocity in small arterioles, capillaries, and small venules increased. However, those observations were done by use of an illumination fiber; therefore, we could not completely assess the effect of an inserted illumination fiber. Tillmanns et al.12 inserted a 23-gauge illumination fiber into the left atrial muscle and an intraluminal light pipe into the atrial lumen of the cat and dog heart and compared the mean capillary red blood cell velocity. In these experiments, red blood cell velocity was not significantly influenced by the intramuscular needle. Nellis et al.13 examined the effects of two different holding systems of right ventricular free wall, that is, the fixed-position and free-motion methods. In either method, a holding rod was inserted into the right ventricular lumen and was fixed to the endomyocardium by a vertically inserted tiny needle. When this rod prevented the vertical wall motion (fixed position), small venous pressure increased compared with the free-motion method, in which the rod was allowed to move in unison with the wall motion. Our transillumination system was comparable with the free-motion technique because the illumination fiber moved in unison with the vertical wall motion. However, in our experiments, we used a 20-gauge needle that was horizontally inserted into the left ventricular free wall. Therefore, it was still uncertain whether the inserted needle had some influences on the observed microvessels due to the trauma around the fiber and the changes in intramyocardial pressure. Also, the interpretation of results in the present study must be carefully done because our observations were limited to the superficial layer of the left ventricle and because vasomotor tone was eliminated.

**Changes in Arterial Microvessel Diameter**

We postulate that changes in the arterial microvessel diameter are mainly due to changes in intraluminal pressure. There are several other factors that may affect the diameter changes. The effects of autoregulation, which may occur because of changes in perfusion pressure during long diastoles, are negligible because the coronary vessels were maximally dilated by an adenosine potentiator. The gradual increase in left ventricular diastolic pressure during a long diastole may influence the diameter change.14,15 However, the left ventricular diastolic pressure was relatively low at the end of the long diastoles (8.5±2.7 mm Hg). Moreover, perfusion pressure–diameter relation curves in the present study showed a pattern similar to the stress-diameter curves, which were

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**TABLE 3. Zero-Flow Pressure, Left Ventricular End-Diastolic Pressure, and Right Atrial Pressure**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Zero-flow pressure (mm Hg)</th>
<th>Left ventricular end-diastolic pressure (mm Hg)</th>
<th>Right atrial pressure (mm Hg)</th>
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<tr>
<td>1</td>
<td>12</td>
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<tr>
<td>5</td>
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</table>

Mean±SD 13.6±1.7† 8.6±2.7 3.2±4.4

†p<0.05 vs. left ventricular end-diastolic pressure.
†p<0.01 vs. right atrial pressure.

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**FIGURE 5.** Graphs showing pressure–red blood cell velocity relations of an arteriole, a venule, and capillaries (n=3). Red blood cell velocities in capillaries were obtained from three capillaries in the same microscopic view and averaged. Pressure–red blood cell velocity relations became curvilinear when aortic pressure was less than 30 mm Hg.
obtained by using isolated, autoperfused cat mesenteric arteriole,\textsuperscript{16} and to the transmural pressure–diameter curves, which were obtained from isolated cylindrical segments of canine left circumflex coronary artery.\textsuperscript{17} This similarity also suggests the passive nature of changes of arterial microvessel diameters caused by reduction in perfusion pressure. Because resistance increases as a function of the fourth power of the vessel radius, these diameter changes of arterial microvessel must cause significant changes of coronary vascular resistance. This result is basically consistent with the study of Hanley et al.,\textsuperscript{18} who showed the pressure dependency of coronary vascular resistance by using isolated nonworking heart. These diameter changes also indicate continuous discharge of blood from arterial microvessels because the cross-sectional area of arterial microvessels was less than 50% of initial value when blood flow ceased.

**Constancy of Venous Microvessel Diameter**

In contrast with arterial microvessels, the diameters of venous microvessels remained constant during a long diastole. Although microvascular pressures were not measured in this study, a lack of diameter changes may suggest the constant intraluminal pressure of venous microvessels because venous microvessels have been known to have high distensibility in other organs.\textsuperscript{19,20} Such a lack of venous pressure change may be related to a large downstream (i.e., right atrium) capacitance. High compliance of venous microvessels will generate very low driving pressure, which throttles the venous blood into the right atrium; therefore, the venous blood may be very slowly expelled into the right atrium, otherwise a vascular waterfall phenomenon in the coronary sinus may be responsible for such a constant venous pressure.\textsuperscript{21}

**Zero-Flow Pressure and Critical Closure**

In this study, zero-flow pressures were assessed by directly observing the cessation of antegrade red blood cell progression in coronary microvessels. Therefore, the effect of capacitance in arterial vessels on zero-flow pressure was negligible.\textsuperscript{2} Nevertheless, zero-flow pressures were always higher than right atrial pressures and left ventricular end-diastolic pressures. These zero-flow pressures were consistent with the reported zero-flow pressures that were measured by using capacitance-free methods during pharmacologically induced maximum vasodilation\textsuperscript{22,23} and were also the same as stop-flow pressure measured from stop of venous outflow.\textsuperscript{3}

When aortic pressure reached zero-flow pressure, we observed eight arterial microvessels, ranging from 8 to 220 \textmu m in diameter. The closure of the vessel lumen did not occur in any of the vessels. It is clear from our results that, at least in the epiomyocardium, zero-flow pressure was not caused by closure of arterial microvessels. The closure of resistance vessels has been reported only under intense vasoconstriction.\textsuperscript{24,25} Moreover, Haack and Johnson\textsuperscript{6} recently reported that closure of microvessels did not occur during occlusion of the mesenteric artery. Another investigator\textsuperscript{9} has also postulated that cessation of flow is not due to collapse of vessels but due to rheological factors. Sherman et al.\textsuperscript{26} calculated the interfascial tension effects between blood and capillary endothelium assuming the capillary diameter as 5 \textmu m; the calculated value was 10.1±4.6 mm Hg, which was in agreement with critical closing pressure. Grayson et al.\textsuperscript{27} also obtained flow cessation at positive perfusion pressure even with noncellular perfusate. Narrowing of capillary due to reduced distending pressure may also contribute to cessation of capillary red blood cells because such reduction in diameter will increase the interfascial tension effects between blood cells and capillary endothelium. Even after the cessation of red blood cell flow in the capillaries, plasma flow, which we did not measure in the present study, may conceivably continue. However, this should not be the case, because red blood cell flow in arterial or venous microvessels, which were floating in plasma, stopped almost simultaneously when capillary red blood cell flow stopped. These observations indirectly but strongly suggest that plasma flow also stopped when red blood cell flow stopped in the capillaries. Is there any possibility of precapillary sphincters responsible for zero-flow pressure? Detection of such closure may be difficult because precapillary sphincters may be located in very small regions. However, in the study by Van Citters et al.,\textsuperscript{28} closure of a very wide region of small arterioles was observed in dog mesentery. Our microcirculatory system has sufficient resolution to detect such a case. For the explanation of zero-flow pressure that is higher than right atrial pressure, rheological phenomena may be reasonable, otherwise the coronary sinus may act as a Starling's resistor, as suggested by Uhlig et al.\textsuperscript{21}

**Pressure–Red Blood Cell Velocity Relation**

Pressure–red blood cell velocity relations were curvilinear, and curvilinearity was most prominent at lower pressures. This result is consistent with independent observations noted in standard pressure-flow relations in epicardial coronary artery obtained with capacitance-free methods.\textsuperscript{15,23,28} One postulated explanation for this curvilinear relation is that reduction of perfusion pressure may lead to sequential dropout of vessels by transmural layers and cause a change of total coronary vascular resistance.\textsuperscript{14,29,30} However, such sequential dropout of vessels cannot explain the curvilinearity of the pressure–red blood cell velocity relations because red blood cell velocities were measured at epicardial microvessels. Therefore, this curvilinear relation must be explained by the gradual increase in coronary vascular resistance caused by the gradual reduction in each arterial microvessel diameter. At an aortic pressure higher than 30 mm Hg, the relation between red blood cell velocity and aortic pressure was almost linear. Nevertheless, calculated hindrance increased approximately 60% when an aortic pressure decreased from
100 to 30 mm Hg. These results suggest that, even at the linear portion, pressure–red blood cell velocity relations are a composite of pressure–flow points from a family of different pressure–flow relations, each characterizing a different steady-state resistance at a different aortic pressure.

Acknowledgments
We are grateful to Dr. Melvin L. Marcus for his critical review of the manuscript and to Mrs. Maureen Kent for preparation of the manuscript.

References

KEY WORDS • intravital microscope • floating objective • epicardial microvessel • critical closure
Diameter change and pressure-red blood cell velocity relations in coronary microvessels during long diastoles in the canine left ventricle.
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doi: 10.1161/01.RES.66.2.503
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