Effect of Intracoronary Nitroglycerin Administration on Phasic Pattern and Transmural Distribution of Flow During Coronary Artery Stenosis

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Background. Nitroglycerin is effective in relieving myocardial ischemia; however, intracoronary nitroglycerin often fails to relieve angina and has been reported to have deleterious effects on subendocardial blood flow. To understand the mechanisms involved, we evaluated the direct effect of nitroglycerin on coronary circulation of the ischemic hearts.

Methods and Results. We measured the phasic pattern of intramyocardial coronary arterial flow with an 80-channel, 20-MHz pulsed Doppler ultrasound flowmeter under moderate to severe coronary artery stenosis (distal perfusion pressure = 45 mm Hg group 1, n=6) and transmural blood flow distribution using radioactive microspheres while maintaining coronary pressure at a low constant level (40 mm Hg, group 2, n=6). In anesthetized open-chest dogs, the left main coronary artery was perfused directly from the right carotid or femoral artery. In this bypass circuit, pressure was controlled with an occluder or a reservoir was connected to the circuit. In group 1, the systolic and diastolic pressures distal to the stenosis decreased significantly after intracoronary administration of nitroglycerin at maximal coronary flow from 66.5±18.5 to 56.5±13.8 mm Hg (p<0.01) and from 36.6±14.4 to 27.5±8.9 mm Hg (p<0.01), respectively. The phasic pattern of the septal artery flow was predominantly diastolic and was characterized by systolic reverse flow even in the absence of stenosis. Coronary stenosis increased systolic reverse flow. Nitroglycerin increased diastolic forward flow (p<0.05) but augmented systolic reverse flow markedly (p<0.001). In group 2, nitroglycerin increased subepicardial flow (p<0.05) but failed to increase subendocardial flow. With the administration of nitroglycerin, the subendocardial-to-subepicardial flow ratio decreased significantly from 0.73±0.19 to 0.32±0.14 (p<0.01).

Conclusions. The increased systolic reverse flow after intracoronary administration of nitroglycerin may be closely related to failure of subendocardial blood flow to increase with increased subepicardial flow.

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KEY WORDS • septal artery • coronary flow • systolic reverse flow • myocardial blood flow

Nitroglycerin is one of the most widely used drugs in the treatment of angina. Although there is no doubt about its effectiveness, its mechanism in alleviating angina is still unclear. Two mechanisms have been considered: 1) increase in blood flow to the ischemic myocardium through a direct effect of nitroglycerin on the coronary vessels and 2) a reduction in energy expenditure of ischemic myocardium through an effect of nitroglycerin on systemic vessels. Therefore, results may vary, depending on the experimental preparations studied and the route of administration of the drug. Regarding the direct effect of nitroglycerin on the coronary vessels, Forman et al\(^1\) reported that intracoronary administration of nitroglycerin caused a significant reduction in subendocardial blood flow with a decrease in the subendocardial-to-subepicardial blood flow ratio and depression of subendocardial contractile force in dog hearts with partial coronary artery occlusion. In their experiments, because intracoronary administration of nitroglycerin did not change systemic hemodynamics, these adverse effects of nitroglycerin were considered to be results of direct effect of nitroglycerin on the coronary blood flow. In the clinical study of Ganz and Marcus,\(^2\) intracoronary administration of nitroglycerin failed to relieve angina.

Although these studies suggested the possibility that the direct effect of nitroglycerin on the coronary vessels...
could be deleterious, the effects of nitroglycerin on coronary hemodynamics have not been evaluated in detail. Intracoronary administration of nitroglycerin may decrease coronary perfusion pressure distal to stenosis while dilating coronary vessels. A decrease in coronary perfusion pressure would be expected to decrease myocardial blood flow in subendocardium relative to that in subepicardium. Because nitroglycerin dilates extramural coronary arteries predominantly, it may increase systolic reverse flow by increasing the capacity of extramural coronary arteries to store blood squeezed out of deep myocardial vessels by cardiac contraction. This may decrease the end-systolic diameter of resistance vessels in subendocardium relative to that in subepicardium. Therefore, diastolic resistance to flow may be higher in the subendocardium than in the subepicardium. Other factors, for example, the impaired diastolic property of the left ventricle after stenosis, may also increase diastolic resistance to coronary arterial flow.

If the stenosis is not fixed, nitroglycerin might increase total coronary inflow by dilating the stenotic region, and myocardial ischemia could be relieved. However, if the stenosis is fixed, this relief mechanism is no longer available. In the present study, we focused on the fixed coronary artery stenosis. Recently, we investigated the effect of fixed coronary artery stenosis of different severities on phasic velocity waveforms of the intramyocardial coronary artery in dogs. Increasing the severity of the coronary artery stenosis increased systolic reverse flow. We also observed an increase in the systolic reverse flow after intravenous adenosine administration. It should be noted that adenosine dilates mainly smaller coronary arteries, but nitroglycerin dilates relatively larger coronary arteries.

To understand the direct effect of nitroglycerin on coronary hemodynamics, we measured coronary perfusion pressure and the phasic pattern of inflow to the myocardium with coronary artery stenosis before and after intracoronary injection of nitroglycerin in different dogs from those in the experiment by Kimura et al. We especially focused on the change in the degree of systolic reverse flow. To evaluate the effects of nitroglycerin on the transmural myocardial distribution of blood flow independent of changes in coronary perfusion pressure, we also measured the transmural blood flow distribution while maintaining coronary pressure at a low constant level.

Methods

Experimental Preparation

Twelve mongrel dogs of either sex weighing 19–38 kg were premedicated with an intramuscular injection of ketamine (200 mg) or 2–3 ml of fentanyl droperidol (Innovar-Vet, Pitman-Moore). The dogs were then anesthetized by intravenous injection of pentobarbital (30 mg/kg). After a cuffed endotracheal tube was inserted and connected to a Harvard respirator pump, the animals were artificially ventilated with 0.5–1.0% halothane and 3 ml/min oxygen at a rate sufficient to maintain arterial oxygen tension within the physiological range. A midline or a left thoracotomy was performed. The heart was exposed and suspended in a pericardial cradle. The left main coronary artery (LMCA) was carefully isolated. Heparin (5,000 units i.v. and 3,000 units hourly) was injected intravenously.

Group 1: Effect of Nitroglycerin on Phasic Pattern of Intramyocardial Coronary Artery Flow During Fixed Coronary Stenosis

In six dogs, the effects of nitroglycerin on the poststenotic coronary arterial pressure and the phasic flow pattern of the septal artery were evaluated. The LMCA was perfused directly from the right carotid artery by a direct shunt circuit (Figure 1). A cannula placed in the right carotid artery was connected by plastic tubing to a Gregg cannula. The Gregg cannula was introduced into the aorta through a left subclavian arteriotomy, advanced into the ostium of the LMCA, and secured with a ligature. An occluder was placed just proximal to the Gregg cannula near the LMCA. The coronary arterial pressure was measured both proximal and distal to the occluder; the proximal coronary arterial pressure was measured in the cannula, and the distal coronary arterial pressure was measured through a shunt cannula that was inserted into a diagonal branch of the left anterior descending coronary artery or at the tip of the Gregg cannula (Nihon-Kohden DHC pressure transducer). Phasic flow pattern in the septal artery was measured with an 80-channel, 20-MHz pulsed Doppler ultrasound flowmeter. This pulsed Doppler system has been previously described in detail. In brief, the transducer consists of a 20-MHz piezoelectrical crystal with a 20-MHz carrier frequency. Because the depth resolution was 0.2 mm, the sample volume for each sampling point was πr2×0.2 mm3. To avoid the influence of wall motion, a low-cut filter with 375 kHz was used. This system detects Doppler signals from 80 channels by a zero-crossing method and analyzes Doppler signals from one channel by a fast Fourier transform (FFT) method, both in real time. There are two modes of choice of an FFT method. One of them is fixed mode, in which an FFT analysis is performed for a fixed sampling point selected in advance. The other one is automatic mode, in which the sampling point changes automatically to follow the maximum velocity among sampling points in the vessel. In the present study, the velocity waveform was measured by the automatic mode. The probe of the Doppler system was placed between the LMCA and the pulmonary artery with the aid of a specially designed holder. The ultrasonic beam was directed toward the septal artery, and the probe was kept in the same position throughout each measurement from before to after administration of nitroglycerin. Using this method, blood velocity measurements in the septal artery were obtained successfully in all the dogs. The velocity waveform analyzed by an FFT method was measured for the systolic forward (SF) and reverse velocity components (SR) and the diastolic velocity component (DF). Systole was defined as the period from the onset of isovolumic contraction to the time of aortic valve closure. Diastole was the remainder of the cardiac cycle. Each component was defined as the envelope of the FFT display (see the left upper panel of Figure 1). The blood velocity analysis after nitroglycerin administration was carried out when the LMCA flow reached its maximum value, because nitroglycerin has varying effects with time.
Left ventricular pressure was measured by a catheter-tip micromanometer (model PC-470, Millar, Houston, Tex.), which was calibrated after reaching a steady state in a water bath kept at 37°C. To check the drift of the pressure signal, left ventricular pressure was also measured through a lumen of the catheter using a strain-gauge pressure transducer (Nihon-Kohden DHC), and zero pressure was set at midstread level. All measurements were recorded simultaneously on a data recorder (model R-81, TEAC, Tokyo), and direct writing was made by a multichannel recorder (model RIJ 5608, Nihon-Kohden, Tokyo).

Group 2: Effect of Nitroglycerin on Transmural Distribution of Coronary Flow With Perfusion Pressure at Constant Low Level

In six dogs, the effect of nitroglycerin on the myocardial blood flow distribution was evaluated under constant coronary perfusion pressure (40 mm Hg). The mean coronary perfusion pressure was maintained independent of aortic pressure. A right femoral artery to LMCA perfusion circuit was used. Blood from the right femoral artery was pumped through a filter into a reservoir, then passed through a Gregg cannula, which was inserted via a subclavian arteriotomy into the LMCA and secured in place with the external ligature (see Figure 1 of Reference 12). Air pressure in the reservoir was controlled to achieve a mean coronary arterial pressure of 40 mm Hg using a Servo system. The LMCA pressure was measured at the tip of the Gregg cannula (Hewlett-Packard solid-state transducer) and was used as the input to the servo system. Radionuclide-labeled microspheres were injected into the Gregg cannula. The LMCA flow was measured using an in-line electromagnetic flow transducer (Howell Instruments) connected to a flowmeter (model RT500, Narcomatic Instruments). Mechanical zero was determined by frequent occlusions. A short bypass circuit allowed determination of the occlusion zero without cessation of coronary inflow. The aortic pressure was measured (Hewlett-Packard solid-state pressure transducers) in the descending aorta with a fluid-filled catheter inserted from the left femoral artery. Heart rate was kept constant (range, 100–125 beats per minute) throughout the experiment by pacing the left atrium.

The intramyocardial blood flow distribution was measured with radionuclide-labeled microspheres (3M Company, New England Nuclear). Each dog received four intracoronary injections of 3 to 5 × 10^5 microspheres
(15±1 μm in diameter, mean±SD) selected from $^{153}$Gd, $^{57}$Co, $^{114}$In, $^{51}$Cr, $^{113}$Sn, $^{85}$Sr, $^{95}$Nb, $^{54}$Mn, or $^{65}$Zn. Microspheres were suspended in saline containing 0.01% Tween-80 to help prevent aggregation. After vigorous vortex mixing, microspheres were injected slowly to avoid any changes in perfusion pressure; injections had no discernible effect on coronary pressure and flow. After the final microsphere injection, each dog was given an overdose of KCl, and the heart was removed. The left ventricular free wall was trimmed into a square of side length approximately 6 cm, fixed in formaldehyde, and subsequently cut into subendocardial, middle, and subepicardial layers. Radionuclide emissions were counted for each layer as previously described by Baer et al.\textsuperscript{13} using an NaI (TI) detector (Tracor Analytic), multichannel pulse-height analyzer (Inotech), and a NOVA-3 minicomputer (Data General). All samples were counted for 3 minutes. Flow to each tissue sample was calculated using radionuclide counts referenced to the LMCA flow as measured by the electromagnetic flowmeter.\textsuperscript{14}

**Experimental Protocol**

**Group 1.** After the measurements of the coronary pressures and the phasic coronary arterial flow during control conditions, nitroglycerin (0.2 mg) was injected into the coronary arteries through the Gregg cannula, and the measurements were repeated when the LMCA flow reached its maximum value, which was observed within 5 seconds after the nitroglycerin administration in all the animals. After allowing flow to return to its control level, a stenosis was made. Measurements were then performed before and after administration of nitroglycerin. After the flow returned to its control level after release of the stenosis, the degree of stenosis was changed, and the above measurements were repeated. To avoid the effect of nitroglycerin on systemic hemodynamics, aortic pressure was maintained by squeezing the descending aorta, if necessary. Coronary and systemic pressures after the administration of nitroglycerin were measured when the phasic coronary arterial flow was measured.

**Group 2.** After injection of the radionuclide-labeled microspheres under control conditions, nitroglycerin (0.2 mg) was injected into the coronary arteries. The mean LMCA pressure was maintained at 40 mm Hg. Coronary blood flow, which increased rapidly after the bolus injection of nitroglycerin into the coronary artery, was relatively stable during the peak phase. As soon as the LMCA flow reached its maximum value, measurement of the myocardial flow was repeated. In some dogs in this group, phasic blood velocity pattern in the septal artery or distal portion of the diagonal branch of the left anterior descending coronary artery was also measured with an 80-channel, 20-MHz Doppler method or a suction cup-type, 20-MHz pulsed Doppler ultrasound flowmeter.

**Statistical Analysis**

Data are reported as mean±SD. Coronary and aortic pressures, heart rates, systolic, reverse, and diastolic velocity areas, subepicardial and subendocardial flows, and subendocardial-to-subepicardial flow ratios were compared by Student's t test. Where appropriate, figures are given as box plots to indicate nonnormality of the data. A value of $p<0.05$ was considered statistically significant.

**Results**

**Group 1**

Representative tracings of the phasic septal arterial blood flow velocity measured before and after administration of nitroglycerin are shown in Figure 2. Before administration of nitroglycerin, forward flow into the myocardium was mainly in diastole. In systole, a small amount of reverse flow was present. After administration of nitroglycerin, the diastolic forward flow increased, but the systolic reverse flow was also augmented. These findings were consistent in all the dogs. Figure 3 shows the areas of phasic velocity waveforms before and after administration of nitroglycerin. The systolic reverse velocity area (Figure 3A) increased significantly after nitroglycerin ($p<0.001$). The net systolic velocity areas decreased after nitroglycerin, although the change was not statistically significant (Fig-
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FIGURE 3. Graphs show areas of phasic velocity waveforms during coronary stenosis before and after administration of nitroglycerin. Panel A: Systolic reverse velocity area (SR); panel B: net systolic velocity areas (SR+SF); panel C: diastolic velocity area (DF). Data are presented as box plots: Upper bound of the rectangle is the upper quartile, lower bound is the lower quartile, and the line between them is the median; the two small horizontal lines at the ends of the vertical lines projecting above and below the rectangle indicate the 90th and the 10th percentiles, respectively. Circles indicate the extreme values lying above the 90th percentile or below the 10th percentile. Sometimes two of these values coincide so that one or other of the lines or circles do not appear.

ure 3B). The diastolic velocity area (Figure 3C) was increased significantly by the administration of nitroglycerin (p<0.05).

There were no significant differences in heart rate before (110.3±8.5 beats per minute) and after nitroglycerin (108.5±9.6 beats per minute). There were no significant differences in the systolic pressures proximal to the coronary stenosis before (85.3±9.6 mm Hg) and after administration of nitroglycerin (80.3±13.7 mm Hg). The diastolic pressure proximal to the coronary stenosis decreased significantly after administration of nitroglycerin from 61.7±9.8 to 56.2±12.9 mm Hg (p<0.01). The systolic and diastolic pressures distal to the stenosis decreased significantly after nitroglycerin from 66.5±18.5 to 56.4±13.8 mm Hg (p<0.01) and from 36.6±14.4 to 27.5±8.9 mm Hg (p<0.01), respectively (Figure 4). The mean distal perfusion pressures before and after nitroglycerin were 46.6±15.4 and 39.2±9.9 mm Hg, respectively. Left ventricular end-diastolic pressures during blood velocity measurements were not different before (1.43±1.97 mm Hg) and after nitroglycerin administration (1.07±1.34 mm Hg, NS).

Group 2

The LMCA flow increased significantly after intracoronary administration of nitroglycerin from 64.0±18.8 to 107.7±25.8 ml/min at a coronary perfusion pressure of 40 mm Hg (p<0.001). Figure 5 shows the transmyocardial distribution of coronary flow before and after intracoronary nitroglycerin administration when the perfusion pressure was kept constant at a low level. Before nitroglycerin administration, the myocardial flows were low, especially in the subendocardium. With the administration of nitroglycerin, the subepicardial flow increased significantly from 0.71±0.34 to 1.27±0.51 ml/min/g (p<0.05). On the other hand, the subendocardial flow did not change significantly, being 0.48±0.20 and 0.42±0.30 ml/min/g before and after administration of nitroglycerin, respectively. With the administration of nitroglycerin, the subendocardial–to–subepicardial flow ratio decreased significantly from 0.73±0.19 to 0.32±0.14 (p<0.01). Regarding phasic coronary velocity waveform in the septal artery, nitroglycerin increased the diastolic flow and augmented the systolic reverse flow (Figure 6). This was consistent in all the dogs examined and similar to the result shown in Figure 2. There were no significant differences in the systolic aortic pressures between before (72.3±6.3 mm Hg) and after administration of nitroglycerin (74.0±6.1 mm Hg).

Discussion

This study supplies two major findings relating to the coronary hemodynamic effects of intracoronary administration of nitroglycerin that increased the diastolic velocity but more greatly augmented the systolic reverse velocity and increased the subepicardial flow but failed...
Our conclusions and interpretations depend on three factors, which include a critique of our methods of measuring blood velocities, the effect of intracoronary nitroglycerin administration on the phasic pattern of intramyocardial artery flow and transmural distribution of coronary flow, and a clinical interpretation.

Critique of Methods

Myocardial perfusion was investigated by measuring the phasic pattern of inflow to the myocardium and the transmyocardial blood flow distribution. To evaluate the phasic pattern of the inflow to the myocardium, we need to avoid modification of the flow pattern by the capacitance effect of the extramural coronary arteries. For this, we measured the intramural septal artery blood velocities, assuming that the septal artery flow reflects the flow in intramyocardial coronary arteries. Chilian and Marcus measured the blood velocity in the septal artery and in small distal coronary arteries just before their penetration into the myocardium. They found that the velocity waveforms in the two arteries were similar. This may support the use of the septal artery as a model for the analysis of phasic intramyocardial flow. In this study, we compared the velocity waveform in the septal artery with that in the distal diagonal branch measured by a 20-MHz Doppler method with a suction cup and also confirmed that the two velocity waveforms were similar.

To measure the phasic flow pattern in the septal artery, we used the 20-MHz, 80-channel pulsed velocimeter. This pulsed Doppler system has been extensively validated. In steady-flow calibration experiments using a rotating turntable, we compared the velocity output with known water or blood velocities. In pulsatile flow calibration experiments in dogs, we compared the femoral arterial blood flow measured by the Doppler system with the blood flow measured by an electromagnetic flowmeter. In both studies, a good linear relation was obtained between the two. However, variability in the angle of incidence of the ultrasonic beam with blood flow in the septal artery could alter the estimate of the blood velocity waveform. Therefore, an effort was made to keep the angle of the probe (40°) constant throughout each measurement by the use of a specially designed probe holder. The 80-channel monitor was used to manipulate the holder so that the maximum flow diameter was obtained at the time of peak flow. This ensures that the ultrasound beam passes near the central axial region of the vessel. We used the envelope of the FFT display of blood velocities near the central axial region for the quantitative evaluation of blood velocity waveforms. The envelope may indicate the maximum velocity in the sample volume (the maximum negative velocity in reverse flow) and therefore the maximum velocity within the vessels, because we measured the blood velocity at the central axial region.

![Graph shows myocardial flows in subepicardium and subendocardium while maintaining perfusion pressure at a low level before and after intracoronary administration of nitroglycerin. Epi-NG(-), subepicardial flow under basal condition; Epi-NG(+), subepicardial flow with nitroglycerin; Endo-NG(-), subendocardial flow under basal condition; Endo-NG(+), subendocardial flow with nitroglycerin. Data are presented as box plots: Upper bound of the rectangle is the upper quartile, lower bound is the lower quartile, and the line between them is the median; the two small horizontal lines at the ends of the vertical lines projecting above and below the rectangle indicate the 90th and the 10th percentiles, respectively. Circles indicate the extreme values lying above the 90th percentile or below the 10th percentile. Sometimes two of these values coincide so that one or other of the lines or circles do not appear.](image1)

![Typical recordings of the septal arterial blood velocities before (top) and after nitroglycerin administration (bottom) while maintaining perfusion pressure at a low constant level (40 mm Hg). Nitroglycerin increased the diastolic flow and augmented the systolic reverse flow. The changes in the phasic patterns were consistent with Figure 2.](image2)
and the velocity profile was nearly parabolic (see the left lower panel of Figure 1).

Our focus was on coronary hemodynamics under a condition of significant flow effects by nitroglycerin. Therefore, the phasic coronary inflow pattern and intramyocardial blood distribution were measured at peak coronary blood flow, although the vasodilatory effect of nitroglycerin on the epicardial coronary arteries lasted beyond the point at which coronary blood flow returns to the control level. With regard to time, intramyocardial blood flow might differ from that in the epicardial coronary arteries. Furthermore, after the increase of coronary blood flow with nitroglycerin, systemic hemodynamics could start to change even when the nitroglycerin is administrated directly. Because we intended to evaluate the effect of nitroglycerin on intramyocardial blood flow distribution without its influence on systemic hemodynamics, the intramyocardial blood flow was measured in the early phase after intracoronary nitroglycerin administration.

To assess the intramyocardial blood flow distribution, the microsphere technique was used. Although steady-state conditions may be ideal for this technique, it is possible to use radioactive microspheres to assess changes in regional flows such as in reactive hyperemia. Downey et al.16 showed dynamic variation in the transmural distribution of myocardial blood flow during the course of coronary reactive hyperemia. Falsetti et al.17 investigated the temporal heterogeneity of myocardial blood flow in anesthetized dogs by using the microsphere technique. In the present study, coronary blood flow increased rapidly after the bolus injection of nitroglycerin into the coronary artery, and this was relatively stable during the peak phase. Therefore, we think that the measurement of myocardial blood flow at peak coronary blood flow is reliable, although it may be a quasi-steady state.

Effect of Intracoronary Nitroglycerin Administration on Phasic Pattern of Intramyocardial Artery Flow and Transmural Distribution of Coronary Flow

In the normal coronary artery, the phasic arterial blood flow waveforms in intramyocardial arteries and in peripheral epicardial arteries exhibit almost exclusively diastolic forward flow, and systolic reverse flow is frequently observed.15,18,19 With coronary arterial stenosis, the systolic reverse flow increased, whereas diastolic forward flow decreased (Figure 2). The most plausible explanation of the increased systolic reverse flow after coronary arterial stenosis may be that decreased distal pressure first reduces the back pressure to systolic reverse flow2 and second increases coronary arterial capacitance because of the pressure-dependent capacitance change.20 so that the poststenotic epicardial vessels accommodate more blood from the myocardium during systole. Inertial properties and wave propagation might also contribute to the systolic reverse flow.21

Intracoronary administration of nitroglycerin augmented the systolic reverse flow, whereas it increased the diastolic flow (Figure 3A and 3C). The increase in systolic reverse flow after nitroglycerin administration may be explained in two ways. First, nitroglycerin dilates relatively large coronary arteries and decreases poststenotic pressure during diastole by an increase in the diastolic flow. This may result in reduction of the end-diastolic pressure and early systolic pressure.22,23 Consequently, this systolic pressure drop should increase the systolic reverse flow by lowering the back pressure to the flow. Second, the dilating effect of nitroglycerin on the coronary arteries may contribute to the increase in systolic reverse flow independently of the coronary arterial pressure. The observation of an increase in the systolic reverse flow after nitroglycerin (Figure 6), when the coronary arterial pressure was maintained at a low constant level, may support this hypothesis. In this protocol, because back pressure to the systolic reverse flow was kept constant, the increase of the systolic reverse flow after intracoronary administration of nitroglycerin should be attributed to the direct effect of nitroglycerin on the coronary arterial vessels, although the dilating effect on epicardial arteries is not steady state in our experimental protocol. In our other study,7 adenosine administration increased systolic reverse flow, but the degree of the increase was smaller than that caused by nitroglycerin. In contrast, a greater decrease in the distal perfusion pressure was caused by adenosine than by nitroglycerin. This may also indicate the contribution of vasodilation to the increase in the systolic reverse flow caused by nitroglycerin. Several studies that used direct visualization of the coronary vessels showed that the primary site of coronary autoregulation resides in smaller coronary arterial vessels (<100 μm),24 whereas nitroglycerin dilates relatively larger coronary arterial vessels (≥100 μm).25,26 An increase in intramyocardial arterial blood volume by nitroglycerin may contribute to the systolic reverse flow, because a greater volume may imply a greater store of blood as a source of the reverse flow as blood is squeezed out of the myocardium by cardiac contraction.

Regarding the transmural distribution of coronary flow, the intracoronary administration of nitroglycerin failed to increase the subendocardial flow even though a decrease in poststenotic pressure was avoided by maintaining the pressure constant (Figure 5). This may be due to the augmented systolic reverse flow from the subendocardium or a relative increase in the resistance of subendocardial vessels to diastolic flow or a regional steal.27 Origin of the systolic reverse flow from the myocardium to the extramural coronary arteries is not entirely known. However, recent studies on phasic blood flow pattern in the superficial myocardial layer give important information.28,29 In the superficial myocardium, Ashikawa et al.28 measured phasic red cell velocity in the small arterioles by using an intravital microscope system and showed that systolic flow is characterized by sustained forward flow velocity after momentary reverse flow velocity during the isovolumic contraction phase. Therefore, contribution of systolic reverse flow from the superficial layer of the myocardium to the total systolic reverse flow from the myocardium to the extramural coronary arteries is much smaller than that from the deeper layer of the myocardium.

The increased systolic reverse flow from the deep myocardial layer might result in a more pronounced decrease in the diameter of subendocardial vessels than occurs in the normal state, thus resulting in a further increase in vascular resistance. This might also increase resistance during diastole, thereby decreasing diastolic
flow as explained by the theory of "systolic–diastolic interaction" proposed by Hoffman et al. When the heart rate is high, because the diastolic interval is shortened, this mechanism is enhanced and may explain the failure to relieve pacing-induced angina. Conversely, if the heart rate is in the physiological range of about <80 beats per minute, as observed in conscious dogs or in humans, the increase in the diastolic interval may compensate considerably for the early diastolic underperfusion. Decrease in poststenotic pressure caused by intracoronary administration of nitroglycerin might also increase systolic translocation of blood flow from the deep myocardial layer to the superficial layer. Therefore, the subepicardial layer may receive blood flow during systole arising from the squeezing of blood out of the subendocardial vessels. We conclude that the increase in systolic intramyocardial translocation of blood from subendocardium to subepicardium and/or relative change in resistance to diastolic flow between subepicardium and subendocardium may result in an increase in the subepicardial flow and the failure to increase the subendocardial flow after nitroglycerin administration.

**Clinical Interpretation**

Nitroglycerin has been used as one of the most effective drugs for the relief of angina. The predominant mechanism may be that nitroglycerin reduces energy expenditure of the ischemic myocardium through the reduction of end-diastolic left ventricular wall tension by decreasing venous return. In addition, the increase in myocardial blood flow through dilatation of the coronary arteries and coronary collateral channels may contribute to the relief of angina. Nitroglycerin also alters the transmural distribution of myocardial perfusion. It has been reported that intravenous administration of nitroglycerin improved subendocardial underperfusion, i.e., redistribution of blood flow toward the subendocardium in the ischemic heart. On the other hand, there have been reports that intracoronary administration of nitroglycerin did not improve the pacing-induced angina in humans, and that it rather worsened the subendocardial underperfusion and contractile function in ischemic dog hearts. Thus, the effects of nitroglycerin on the coronary circulation may be altered by the route of administration of the drug.

In this study, we focused on analyzing the direct effect of nitroglycerin on the coronary circulation. As the results show, intracoronary administration of nitroglycerin did not improve subendocardial perfusion in the ischemic hearts. In our experimental preparation, intramyocardial blood flow was measured by injecting radio-nuclide-labeled microspheres from the LMCA and so does not measure the contribution of any collateral flow from the right coronary artery. Thus, the measured flow distribution might reflect the distribution of antegrade flow, excluding the collateral flow. However, the contribution of collateral flow from the right coronary artery to the left coronary artery seems negligible. Murray et al. reported the amount of the collateral flow rate from the right coronary artery to the left coronary artery as 0.04±0.01 ml/min/g even when the LMCA was occluded.

When the intramyocardial blood flow was measured, the systolic aortic pressures did not change by the administration of nitroglycerin. At coronary perfusion pressure of 40 mm Hg, left ventricular end-diastolic pressures before (range, 12.5–15.0 mm Hg) and after nitroglycerin administration (range, 10.0–12.5 mm Hg) might contribute to decrease the subendocardial flows in each condition. Decrease in left ventricular end-diastolic pressure tends to increase the subendocardial flow more than the subepicardial flow. Because the decrease in the left ventricular end-diastolic pressure by nitroglycerin administration was negligible when the intramyocardial flow was measured, influence of the systemic hemodynamics on the change in the distribution of intramyocardial blood flow may be small. Therefore, the increased systolic reverse flow that was consistently observed after nitroglycerin may be closely related to a reduction of the subendocardial–to–subepicardial flow ratio.

**Summary**

We measured coronary perfusion pressure, phasic pattern of inflow to the myocardium, and transmural distribution of blood flow to understand the direct effect of nitroglycerin on coronary hemodynamics. Intracoronary administration of nitroglycerin 1) decreased the poststenotic coronary arterial pressure, 2) increased the diastolic velocity but more greatly augmented the systolic reverse velocity, and 3) increased the subepicardial flow but failed to increase the subendocardial flow. These findings may explain the possible deleterious effect of intracoronary administration of nitroglycerin and failure to relieve angina.

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