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Assessment of Coronary Conductance and Resistance Vessel Reactivity in Response to Nitroglycerin, Ergonovine and Adenosine: In Vivo Studies With Simultaneous Intravascular Two-Dimensional and Doppler Ultrasound

KRISHNANKUTTY SUDHIR, MD, PHD, JOHN S. MACGREGOR, MD, PHD,
SOPHIE D. BARBANT, MD, ELYSE FOSTER, MD, FACC, PETER J. FITZGERALD, MD, PHD,
KANU CHATTERJEE, MB, FRCP, FACC, PAUL G. YOCK, MD, FACC

San Francisco, California

Objectives. The aim of this study was to determine the differential effects of nitroglycerin, ergonovine and adenosine on the resistance vessels in vivo by using a Doppler-tipped guide wire in combination with an ultrasound imaging catheter.

Background. Catheter-based two-dimensional intravascular ultrasound yields images of the coronary arteries from which cross-sectional areas can be measured. Intravascular Doppler ultrasound techniques allow measurement of coronary blood flow velocity. The simultaneous use of the two techniques can yield anatomic and physiologic information on conductance and resistance vessels but has not been tried in the coronary arteries.

Methods. In 15 dogs, we studied coronary flow and vascular reactivity in response to pharmacologic agents using two approaches: 1) a 30-MHz, 4.3F imaging catheter placed alongside a 0.018-in. (0.046 cm) Doppler wire in the circumflex or left anterior descending coronary artery (n = 5); 2) the ultrasound imaging catheter introduced directly over a 0.014-in. (0.036 cm) Doppler wire (n = 10). Vasodilator and vasoconstrictor responses were studied by using intracoronary nitroglycerin (50, 100 and 200 μg), ergonovine (200 μg) and adenosine (6 mg).

Results. Nitroglycerin caused a dose-dependent increase in epicardial coronary artery cross-sectional area and, to a lesser extent, in average peak flow velocity, resulting in an increase in volumetric coronary blood flow of 39% and 50% at the doses of 100 and 200 μg, respectively. With these doses of nitroglycerin, the decrease in diastolic to systolic velocity ratio and the increased change in cross-sectional area from end-diastole to end-systole suggested an enhanced epicardial coronary artery compliance. With ergonovine, a 12% reduction in epicardial coronary artery cross-sectional area was seen, without a significant change in average peak velocity, resulting in a 15% decrease in volumetric coronary blood flow. Adenosine caused a 270% increase in average peak velocity but no change in epicardial coronary artery cross-sectional area, resulting in a 270% increase in volumetric blood flow.

Conclusions. This study demonstrates that nitroglycerin and ergonovine predominantly influence coronary conductance arteries whereas adenosine mainly dilates coronary resistance vessels. These findings also demonstrate that the combined use of a two-dimensional and a Doppler ultrasound transducer within one catheter assembly can provide information on the differential effects of vasoactive agents on the epicardial and microvascular coronary circulation.

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Catheter-based intravascular Doppler ultrasound has been used to measure coronary blood flow velocity, particularly in studies of coronary flow reserve (1,2), and to assess regional flow after balloon angioplasty (3). The contribution of normal epicardial vessels to overall coronary vascular resistance is <10% (4). Changes in flow velocity, as measured by Doppler ultrasound, primarily reflect effects on resistance vessels <400 μm in diameter (4). In nonstenosed vessels, therefore, intravascular Doppler velocimetry does not provide information on the epicardial coronary circulation. However, a related technique, intravascular two-dimensional ultrasound imaging permits real-time visualization of "slices" of the epicardial coronary arteries (5,6) and provides quantitative measurements of lumen cross-sectional area (7,8). Unlike angiographic measurements, which have limited accuracy (9–11), especially in the presence of eccentric lesions, intravascular ultrasound yields lumen areas that show a high degree of correlation with areas directly determined by histologic examination, irrespective of vessel geometry (7,8).

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Address for correspondence: Krishnankutty Sudhir, MB, PhD, Box 0124, University of California at San Francisco, San Francisco, California 94143.

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JACC Vol. 21, No. 5
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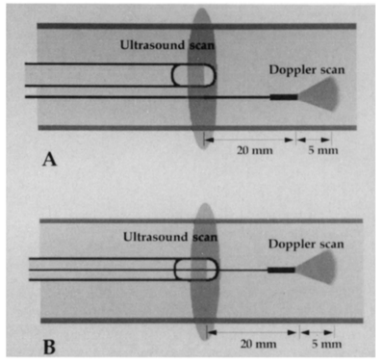

Figure 1. Schematic representation of relative positions of imaging catheter and Doppler wire. **A,** Two-dimensional imaging catheter placed alongside a 0.018-in. Doppler wire. **B,** Two-dimensional imaging catheter introduced over a 0.014-in. Doppler wire.

The effects of vasoactive agents on the coronary arteries may vary with vessel size (12–14). The combination of catheter ultrasound imaging and Doppler velocimetry is a potentially useful means of studying the selective responses of epicardial and resistance vessels to pharmacologic interventions. Until recently, however, the size of the Doppler catheters (3F) and the imaging devices (≥3.5F) have precluded simultaneous imaging and velocity recordings in a coronary artery. In this study, we describe the differential effects of nitroglycerin, ergonovine and adenosine on the coronary conductance and resistance vessels in vivo, by applying a new technology—a Doppler-tipped guide wire (15)—used for the first time in combination with an imaging catheter. The study also demonstrates the ability of this combined modality to obtain simultaneous measurements of velocity and cross-sectional area, allowing direct determination of coronary blood flow.

Methods

Fifteen mongrel dogs were anesthetized with Innovar (0.04 mg/kg subcutaneously) and sodium pentobarbital (15 mg/kg intravenously), with additional doses as needed to maintain the level of anesthesia. They were mechanically ventilated with room air. Blood pressure was continuously monitored from a cannula placed in the right internal carotid artery, and heart rate was monitored from the electrocardiogram (ECG). All studies conformed to the "Position of the American Heart Association on Research Animal Use" adopted November 11, 1984 by the Association.

Catheterization procedures. Under fluoroscopic guidance, the left main coronary artery was cannulated via the transfemoral approach by using an 8F canine guiding catheter (Advanced Cardiovascular Systems). One of the following approaches was then used to introduce both a two-dimensional ultrasound catheter and a Doppler guide wire into a coronary artery (Fig 1). 1) In five dogs, a 0.018-in. (0.046 cm) Doppler wire was introduced through the guiding catheter into the left anterior descending or circumflex coronary artery. The guiding catheter was then withdrawn several centimeters from the left main ostium, and a second guiding catheter was introduced through the opposite femoral artery and seated in the left main coronary artery. The two-dimensional catheter was then introduced over a standard 0.014-in. (0.046 cm) guide wire into the coronary circulation alongside the Doppler guide wire already within the coronary artery. 2) In 10 dogs, a 0.014-in. Doppler wire was first introduced through the guiding catheter, after which the two-dimensional imaging catheter was introduced directly over the Doppler wire into the left anterior descending or circumflex coronary artery. With both approaches, the Doppler transducer was positioned 2 cm distal to the tip of the imaging catheter (see Discussion).

Two-dimensional ultrasound system and image analysis. The 4.3F ultrasound catheter (Cardiovascular Imaging Systems) has a fixed 30-MHz transducer and a rotating mirror assembly. Images are displayed on a video monitor; resolution in the axial direction is approximately 150 μm and lateral resolution approximately 250 μm. Gain, contrast and reject settings can be adjusted by the operator to yield a well balanced gray scale appearance on the video display. Real-time images were stored on high quality super VHS videotape for subsequent off-line analysis. As previously described (16), selected portions of the videotape were digitized (12 bits, Rasterops 324) and stored on a computer disk. Off-line determination of lumen cross-sectional area at baseline and after administration of drugs was performed by computer-assisted planimetry with cursor-controlled calipers.

Doppler ultrasound system. Doppler-derived blood flow velocities were measured with a steerable Doppler guide wire (FloWire, Cardiometrics Inc.). This guide wire system has a miniature ultrasound crystal that transmits signals at a carrier frequency of 12 or 15 MHz (depending on the guide wire size) and receives pulsed wave Doppler ultrasound signals. The ultrasound beam has an angular width of approximately 25°, and the sample volume is located at a distance of 5 mm from the guide wire tip. The Doppler signals are analyzed by the FloMap instrument in which dedicated digital signal processing chips perform the fast Fourier transformation required for the spectral display. The spectral values are transformed into a gray scale, and the resultant spectrum is displayed on a monitor. The ECG and arterial pressure waveform are simultaneously displayed on the monitor. Also displayed were quantitative measurements of average peak velocity, which represents the velocity time integral divided by time, that is, $[\int v(t)dt]/t$ and diastolic to

Table 1. Effects of Nitroglycerin on Hemodynamic and Coronary Artery Variables in Nine Dogs

	Baseline	Nitroglycerin Dose (μg)		
		50	100	200
Heart rate (beats/min)	147 ± 10	144 ± 10	159 ± 13	154 ± 16
MAP (mm Hg)	87 ± 12	85 ± 13	83 ± 12	80 ± 9
Mean CSA (mm²)	8.05 ± 0.56	8.40 ± 0.66*	8.86 ± 0.76*	9.05 ± 0.87*
% ΔCSA (end-diastole to end-systole)	12.5 ± 2.4	10.1 ± 1.9	15.2 ± 2.9	20.4 ± 2.8*
fDTI/fSTI	0.67/0.33	0.70/0.30	0.68/0.32	0.66/0.34
APV (cm/s)	35.8 ± 4.3	35 ± 3.2	44.9 ± 5.0*	48.4 ± 7.4*
CBF (ml/min)	78.1 ± 9.4	84.0 ± 12.7	108.6 ± 16.1*	117.4 ± 20.7*
DSVR	1.56 ± 0.1	1.36 ± 0.1	1.31 ± 0.1*	1.33 ± 0.1*

*Significantly different from baseline at $p < 0.05$. APV = average peak velocity; CBF = coronary blood flow; CSA = cross-sectional area; Δ = change; DSVR = diastolic/systolic velocity ratio; fDTI = duration of diastole as a fraction of the cardiac cycle length; fSTI = duration of systole as a fraction of the cardiac cycle length; MAP = mean arterial pressure.

systolic velocity ratio, which represents the average diastolic peak velocity divided by the average systolic peak velocity. The monitor display was continuously recorded on a VHS videotape for further off-line analysis and comparison with corresponding cross-sectional ultrasound images.

Vasoactive agents. Drugs were administered as a bolus injection directly into the coronary circulation through the guiding catheter in the left main coronary artery. Intracoronary nitroglycerin was given in bolus doses of 50, 100 and 200 μg (n = 9) and intracoronary ergonovine in a bolus dose of 200 μg (n = 9). Intracoronary adenosine was given as a bolus dose of 6 mg to cause coronary hyperemia (n = 6). Measurements of coronary artery cross-sectional area and flow velocity were made 2 min after nitroglycerin and ergonovine administration to minimize the effect of a bolus injection on blood flow. Preliminary experiments with saline infusions of similar volume suggested that the bolus effect had little influence on flow after 30 s. With adenosine, the maximal response achieved after injection was the hyperemic response. Off-line measurements were obtained by an observer who had no knowledge of the drug and dose administered.

Calculations and statistical analysis. Measurements of lumen area were gated to the time points in the cardiac cycle when cross-sectional area was minimal and maximal, representing end-diastolic and end-systolic dimensions, respectively. Off-line analysis of Doppler spectra was performed on a commercially available computer (Freeland Systems, Prism Imaging Inc.) to determine systolic and diastolic time intervals. The mean value of cross-sectional area was obtained by correcting for the fractional diastolic time interval (fDTI, the duration of diastole as a fraction of the cardiac cycle length) and the fractional systolic time interval (fSTI, the duration of systole as a fraction of the cardiac cycle length) as follows:

Mean cross-sectional area =

(fDTI × End-diastolic cross-sectional area) +
(fSTI × End-systolic cross-sectional area).

Our method for computing mean cross-sectional area accounts for changes in vascular dimensions with the cardiac cycle, which may vary from 10% to 15% (17). Volumetric coronary blood flow (CBF) was determined from the relation

CBF = Cross-sectional area × Average peak velocity × 0.5

as previously described (15). The factor of 0.5 has been empirically validated and corresponds to the correction for a parabolic velocity profile by compensating for the ratio of spectral peak velocity as measured by the Doppler system and the spatial average velocity required for calculation of volumetric flow (15). This method assumes a parabolic flow velocity profile, with its peak within the Doppler sample volume throughout the cardiac cycle; however, the velocity profile in pulsatile arterial flow is not of the same parabolic form found in steady laminar flow, and it changes as a function of vessel size (18). Nevertheless, Doucette et al. (15) showed only minor effects of changes in pulsatility on average peak velocity in an in vitro system using tubes with a diameter of 3.17 mm, similar in size to the coronary arteries.

Responses to nitroglycerin at the three doses used were analyzed by using either analysis of variance for repeated measures with normally distributed data (blood pressure, heart rate responses, cross-sectional area) or the Friedman test for nonparametric data (flow velocity, volumetric flow). Multiple comparisons were made using a post-hoc Student Neumann-Keuls test. Responses to ergonovine and adenosine were analyzed using a Student t test or a Wilcoxon sign rank test for paired observations. Values are expressed as mean value ± SEM, and differences were considered significant at $p < 0.05$.

Results

There were no instances of arrhythmias, spasm, thrombosis or perforation during catheter/Doppler wire placement.

Ultrasound image quality. Simultaneous two-dimensional images and Doppler flow spectra were obtained during all animal experiments. In three dogs, the ultrasound image displayed a radial pattern of interference that disappeared when the Doppler transducer was switched off. Insertion and

JACC Vol. 21, No. 5
April 1993:1261–8

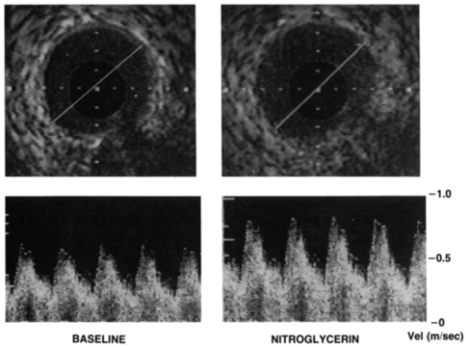

Figure 2. Two-dimensional ultrasound images **(top panels)** showing cross sections of the left circumflex coronary artery and spectral display **(bottom panels)** showing simultaneous Doppler velocimetry in the same coronary artery at baseline **(left)** and 2 min after administration of 200 μg of intracoronary nitroglycerin **(right)**.

positioning of the devices were considerably easier with the over-the-Doppler wire approach, but ultrasound image and Doppler spectral quality were acceptable with both techniques. Sequential 5-mm pullbacks of the imaging catheter from a distance of 20 mm from the Doppler transducer to a position back in the guiding catheter showed no significant change in measured average peak velocity.

Coronary artery dimensions and flow at rest. Mean values for coronary artery cross-sectional area, average peak velocity, average volumetric coronary blood flow and diastolic/systolic velocity ratio at rest are indicated in Table 1. The systolic/diastolic time interval ratio was 0.67/0.33 at baseline. Variability among baseline flow measurements within animals did not exceed 6%.

Effects of nitroglycerin. Nitroglycerin caused a dose-dependent increase in coronary artery cross-sectional area, average peak velocity and calculated volumetric coronary blood flow (Table 1, Fig. 2). The systolic/diastolic time interval ratio remained unchanged with nitroglycerin; however, there was a significant decrease in diastolic/systolic velocity ratio at the higher doses (100 and 200 μg) administered. In addition, the percent change in cross-sectional area between end-systole and end-diastole was increased at doses of 100 and 200 μg and was significant with the latter dose. No significant changes in systolic, diastolic and pulse pressures or heart rate were observed with any dose.

Table 2. Effects of Ergonovine on Hemodynamic and Coronary Artery Variables in Nine Dogs

	Baseline	Ergonovine (200 μg)
Heart rate (beats/min)	153 ± 16	153 ± 19
MAP	93 ± 15	95 ± 14
CSA (end-diastole)	8.26 ± 0.63	7.23 ± 0.65*
% ΔCSA (end-diastole to end-systole)	13.5 ± 2.6	12.5 ± 3.2
fDT/fST	0.68/0.32	0.67/0.33
APV (cm/s)	42 ± 6.6	39.9 ± 7.2
CBF (ml/min)	82.6 ± 21.9	69.9 ± 20.6
DSVR	1.70 ± 0.2	1.72 ± 0.19

*Significantly different from baseline at $p < 0.05$. Abbreviations as in Table 1.

Effects of ergonovine. Ergonovine caused a decrease in epicardial coronary artery cross-sectional area and calculated volumetric coronary blood flow but caused no change in average peak velocity (Table 2, Fig. 3). No changes in systemic arterial pressure, heart rate, diastolic/systolic time interval ratio or diastolic/systolic velocity ratio were observed.

Effects of adenosine. Adenosine caused a 270% increase in average peak velocity and in calculated volumetric blood flow but caused no change in epicardial coronary artery cross-sectional area (Fig. 4). No significant changes in systemic arterial pressure, diastolic/systolic time interval ratio, diastolic/systolic velocity ratio or percent change in cross-sectional area between end-systole and end-diastole were observed with adenosine. There was a transient decrease in heart rate (range 20 to 40 beats/min) lasting 5 to 10 s, with full recovery by 30 s. Maximal hyperemia was observed between 30 and 45 s after administration of adenosine.

Discussion

The present study shows that nitroglycerin and ergonovine predominantly influence coronary conductance arteries, whereas adenosine mainly dilates coronary resistance vessels. In addition, this study demonstrates that the use of simultaneous intravascular two-dimensional and Doppler ultrasound yields beat to beat measurements of coronary artery cross-sectional area and flow velocity and thus information on epicardial and resistance arteries.

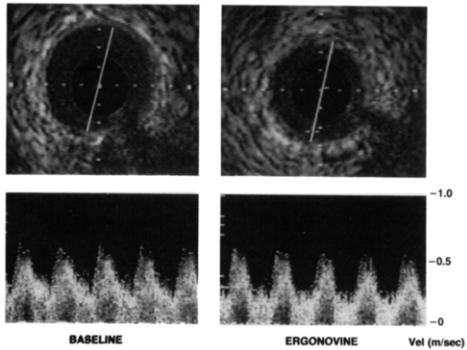

Figure 3. Two-dimensional ultrasound images (**top panels**) showing cross sections of the left circumflex coronary artery and spectral display (**bottom panels**) showing simultaneous Doppler velocimetry in the same coronary artery at baseline (**left**) and 2 min after intracoronary administration of 200 μg of ergonovine (**right**).

Effects of Vasoactive Agents on the Coronary Arteries

Studies of coronary vascular reactivity. The technique described in the present study provides a useful model to study the clinical pharmacology of vasoactive substances in the coronary circulation. As the drugs are administered by the intracoronary route, systemic effects on blood pressure and heart rate are minimized. Such effects have been confounding variables in studies of the effects of intravenously administered vasoactive agents on the coronary circulation (19). In a recent study of nitroglycerin-induced coronary vasodilation in heart transplant recipients (20), intravascular ultrasound was demonstrated to be useful in assessing real time coronary vasomotion. However, in that study, measurements were made of epicardial coronary artery dimensions, but not of flow velocity, so that information on resistance arteries could not be obtained. The technique we have described in the present study provides instantaneous information on coronary artery cross-sectional area and blood flow, allowing conclusions to be drawn on the major site of activity of the agents studied in the coronary circulation, that is, epicardial coronary arteries versus the microcirculation. The contribution of the epicardial coronary arteries to overall coronary vascular resistance is <10%; hence an increase in flow velocity implies a vasodilator effect on coronary resistance vessels (4). Drugs that have large effects on flow velocity but minimal effects on cross-sectional area presumably act on the microcirculation, whereas drugs that cause increases in cross-sectional area with smaller effects on flow velocity possibly act predominantly on the epicardial coronary circulation. Such information is useful in defining the mechanism and specific sites of action of vasoactive agents affecting the coronary circulation.

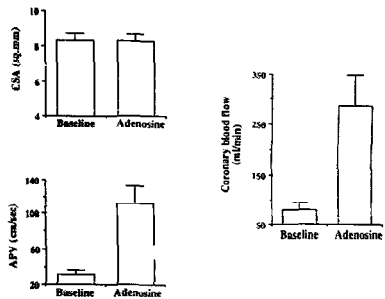

Figure 4. Left, Effect of intracoronary adenosine (6 mg) on epicardial coronary artery cross-sectional area (CSA, **above**) and average peak velocity (APV, **below**), showing a 270% increase in flow velocity, with no change in epicardial coronary artery dimensions. **Right,** Effect of intracoronary adenosine (6 mg) on calculated volumetric coronary blood flow, showing a 270% increase from baseline.

In the present study, the higher doses of nitroglycerin (100 and 200 μg) caused an increase in both cross-sectional area and flow velocity, suggesting effects in both epicardial coronary arteries and resistance vessels. The occurrence of endothelium-mediated flow-dependent epicardial vasodilation (21) resulting from an action on resistance vessels alone cannot be ruled out by our approach. However, previous reports suggest that although large vessel tone is markedly diminished by low concentrations of nitrates, small vessels dilate only with higher nitrate concentrations (22–27). Kurz et al. (28) have suggested that a lack of available sulfhydryl

groups (which are required for conversion of nitroglycerin to its vasoactive metabolite) may be responsible for the lack of response of small coronary arterioles to nitroglycerin. Indeed, in the present study, nitroglycerin had no effect on flow at the 50-μg dose despite epicardial coronary vasodilation and increased flow by only 39% and 50%, respectively, at the 100- and 200-μg doses, far short of the 270% maximal increase achieved with adenosine. This observation suggests that the predominant effect of nitroglycerin is on the epicardial coronary arteries. Ergonovine caused a decrease in epicardial coronary artery cross-sectional area with no change in flow velocity, suggesting again that its major site of action is the epicardial coronary vasculature. However, it is possible that an effect of ergonovine on the microcirculation may have been masked by local autoregulatory mechanisms (29), but this is unlikely in the absence of changes in heart rate and blood pressure. Adenosine caused an increase in flow velocity, with no change in epicardial coronary artery dimensions, suggesting that its predominant site of action is the coronary microcirculation, as previously described in isolated coronary artery strips and in the isolated perfused heart (23,24). In the present study, flow-dependent endothelium mediated vasodilation (21) was not observed in the epicardial circulation after adenosine, despite administration of a dose in excess of that reported to produce maximal hyperemia (30). The reason for the lack of flow-dependent vasodilation is unclear; it may be that the time course of such an effect lags behind the hyperemic response, which occurs within 45 s. Alternatively, it is possible that adenosine tended to constrict the epicardial vessels, but this effect was offset by flow-dependent vasodilation, so that no net effect was observed.

Determination of coronary artery compliance. Nitroglycerin caused an increase in the percent change in cross-sectional area between systole and diastole without a change in pulse pressure. This effect probably resulted from a nitroglycerin-induced increase in coronary artery compliance, which has been reported in peripheral medium-sized arteries (31,32). Doppler signal analysis, which provides information on diastolic and systolic velocities, showed that nitroglycerin reduced the diastolic/systolic velocity ratio by increasing systolic flow. The increased systolic flow was also probably due to enhanced compliance induced by nitroglycerin: a greater reservoir capacity of the epicardial coronary vessels would in turn result in greater extramural systolic flow when the intramyocardial vessels are compressed during ventricular contraction. In an open chest canine model of coronary stenosis, Goto et al. (33) recently showed that intracoronary nitroglycerin increased diastolic flow but augmented systolic reverse flow in the intramyocardial coronary arteries. The increase in systolic reverse flow was attributed to the dilating effect of nitroglycerin on the epicardial arteries. Our findings, and those of Goto et al. (33), may explain the observations that intracoronary nitroglycerin does not improve pacing-induced angina in humans (34) and may worsen subendocardial ischemia in dog hearts (35): a greater amount of blood squeezed out of the subendocardium into a compliant epicardial reservoir reduces effective subendocardial perfusion in the next diastole. In contrast to nitroglycerin, adenosine did not cause any change in epicardial coronary compliance, because neither the percent change in cross-sectional area between systole and diastole nor the diastolic/systolic velocity ratio was altered. Once again, this finding suggests that the predominant effect of adenosine is on resistance vessels, with minimal vasodilation in epicardial coronary arteries.

Advantages of the Combined Two-Dimensional and Doppler Ultrasound Approach

Simultaneous information on coronary artery morphology and flow velocity. The technique described in this study permits simultaneous assessment of both structure and function in the coronary circulation. Intravascular ultrasound imaging can provide real time images of the entire architecture of the vessel from lumen to adventitia (5–8). Simultaneous Doppler velocimetry provides information on blood flow, thus supplying the physiologic correlates of the structural changes seen with two-dimensional imaging (1,2,36). An experimental single catheter delivery system for both two-dimensional and Doppler ultrasound has been developed for use in the aorta (37) but has not been used in the coronary vasculature. In the system described in the present study, the ability to position the two modalities independently gives operational flexibility. For example, if the presence of the imaging catheter is interrupting flow, it can be withdrawn into the guiding catheter and velocity can be measured with the Doppler guide wire alone.

Determination of volumetric coronary blood flow. Recent studies (15,38) have shown excellent correlation in vivo between Doppler-derived volumetric flow and electromagnetic flow. In addition, the average peak velocity obtained by spectral analysis was found to be the best determinant of coronary flow, rather than the mean velocity, which significantly underestimated flow (38,39). The product of Doppler-derived coronary flow velocities and angiographic measurements of coronary cross-sectional area has been used in human studies as a measure of coronary flow (40). However, angiographic measurements have limited accuracy and reproducibility (9–11) and show considerable variability even with automated quantitation (41,42). Furthermore, because the measured variable in angiographic cross-sectional area determinations is diameter (d), a value squared in the area calculation ($\pi d^2/4$), small errors in d are magnified in flow calculations (17). Ultrasound-determined cross-sectional area may therefore be desirable in measuring absolute coronary blood flow, as these have been shown to correlate accurately with histologic measurements, even in the presence of lesions (43). Intravascular ultrasound also circumvents other problems with angiographic measurements such as the necessity for intracoronary injections of contrast media that have vasodilator properties (44,45) and the use of

catheters as calibration devices (46). In a recent in vitro study using a coronary flow model, coronary blood flow measured by sequential ultrasound imaging to determine cross-sectional area and pulsed Doppler velocimetry (47) showed excellent correlation with flow measured by timed collection in a graduated cylinder. However, in vivo, with beat-to-beat variability in cross-sectional area, especially in pharmacologic studies, it is desirable to obtain both cross-sectional area and velocimetry measurements *simultaneously*, an advantage of the technique described in this study. Although we did not directly validate our measurements of volumetric blood flow in this study, two recent studies from our institution have shown excellent correlation between electromagnetic flow and Doppler-derived volumetric flow measured by either a 3F Doppler catheter (38) or a 0.018-in. Doppler wire (15). In assessing coronary vascular reactivity, any errors of estimation would be likely to affect measurements both at baseline and after drug administration, so that differences from baseline are probably reasonable estimates of vascular responsiveness.

Technical Limitations and Developmental Needs

Local flow disturbance caused by the imaging catheter. In the combination two-dimensional and Doppler system, a potential source of error in the measurement of flow velocity is lumen obstruction by the imaging catheter proximal to the velocity measurement, leading to a lower velocity reading than would occur without the catheter. The disruption of blood flow would also tend to flatten the velocity profile, leading to reduced peak velocity measurements (48). In vitro studies have shown that interference to Doppler flow velocity measurements from local disturbances produced by the intravascular location of a catheter are minimal at a distance of about 10 catheter diameters downstream from the catheter tip (48). Hence, at a distance of ≥15 mm downstream from a 1.38-mm (4.3F) imaging catheter, the disturbance to flow due to the catheter should theoretically be minimal. This hypothesis was confirmed by our pullback studies, which showed no significant variation in measured average peak velocity when the imaging catheter was at least 20 mm from the Doppler transducer. Thus, as shown in Figure 1, the imaging plane cannot be at the same site as the Doppler sample volume, so that an inherent assumption with the present technique is that cross-sectional area is similar at both locations. In practice, the cross-sectional area at both sites should be measured initially with the imaging catheter to confirm this assumption. When absolute coronary blood flow is measured, the imaging catheter and guide wire should ideally be placed in a large proximal vessel with at least a 15-mm long disease-free segment and with no branches. Future technical developments that will facilitate our technique include further miniaturization of the imaging transducer, use of forward-viewing two-dimensional systems that allow measurements to be made at sites distal to the catheter tip (49) and emergence of a single catheter delivery system incorporating both the two-dimensional and Doppler ultrasound transducers.

Problems likely to be encountered in abnormal coronary arteries. Our technique has not been applied to blood flow measurements in tortuous or diseased vessels. In such situations, variations in lumen size and inhomogeneous flow patterns may result in errors in flow estimation. In the case of a significant stenosis, it may be necessary to perform two-dimensional imaging and Doppler velocity measurements in sequence, rather than simultaneously. The velocity of the stenotic jet could first be estimated by the Doppler wire, followed immediately by cross-sectional area measurement with two-dimensional imaging, so that both structural and flow information are obtained at the site of the stenosis.

Radiofrequency interference between the two-dimensional and Doppler transducers. An additional problem encountered with a simultaneous two-dimensional and Doppler ultrasound system is radiofrequency interference. Cross-talk created by harmonics from the Doppler transducer presented as radial spokes on the two-dimensional ultrasound image. Although this interference pattern was significant in only a minority of cases, image quality was degraded in these cases. Alternating the excitation of the Doppler and two-dimensional ultrasound transducer at different times, reconfiguring the excitation pulse waveform to produce out-of-band harmonics and common mode rejection shielding could be used in future combined catheter systems.

Thus, this study demonstrates that vasoactive agents have different effects on the epicardial and microvascular coronary circulation. Whereas nitroglycerin and ergonovine predominantly influence coronary conductance arteries, adenosine mainly dilates coronary resistance vessels. The combined use of a two-dimensional and a Doppler ultrasound transducer within one catheter assembly can provide information on the differential effects of vasoactive agents on the coronary epicardial and resistance arteries.

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