Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man

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ABSTRACT Assessment of coronary blood flow and the vasodilator reserve capacity of individual coronary arteries in the catheterization laboratory has been hampered by methodologic limitations. We have developed and validated a small Doppler catheter that can subselectively measure phasic coronary blood flow velocity (CBFV). In seven anesthetized calves, CBFV was varied from 0.1 to 5.7 times control CBFV. Changes in mean CBFV measured intraluminally by catheter in the left anterior descending and left circumflex arteries were similar to those measured simultaneously with an epicardial Doppler probe on the surface of the same vessel (n = 85, r = .95, slope = 1.04) and to changes in coronary sinus flow (n = 69, r = .97, slope = 1.06) measured with timed venous collections. Identical maximal coronary reactive hyperemic responses with the catheter present and absent in the artery being studied demonstrated that coronary obstruction by the catheter was minimal. Safety studies in six additional calves demonstrated that the catheter caused small changes in coronary endothelial permeability. Histologic studies revealed no endothelial denudation or thrombus formation. Stable phasic recordings of coronary blood flow velocity have been obtained in 58 of 70 patients studied. One of the 70 patients studied had abrupt coronary occlusion probably related to catheter-induced vasospasm. In 10 normal patients, intracoronary meglumine diatrizoate increased CBFV to 3.5 times that at rest (range 2.8 to 5.0). CBFV rose 5.0-fold after an intravenous infusion of dipyridamole (range 3.8 to 7.0). In each patient, dipyridamole produced greater vasodilation than meglumine diatrizoate. The time- and dose-response characteristics to dipyridamole infusion were heterogeneous, underscoring the advantage of continuous on-line measurement of CBFV in the measurement of vasodilator reserve. This method of measuring CBFV and assessing vasodilator reserve in the catheterization laboratory should facilitate studies of the coronary circulation in man.


MEASUREMENT OF phasic coronary blood flow velocity (CBFV) and the flow reserve capacity of individual coronary vessels has been hampered by methodologic limitations. Such data, if obtainable, could provide a means of assessing the physiologic significance of obstructive coronary artery disease at the time of cardiac catheterization.

Current methods of measuring coronary blood flow in conscious man have many limitations. Inert gas clearance techniques measure global myocardial blood flow but cannot detect rapid changes in flow.1–3 Radioisotope techniques (e.g., 133Xe clearance) measure regional blood flow, but do not permit on-line continuous assessment of coronary blood flow and are not accurate if blood flow is greater than 200 ml/min/100 g tissue.4,5 The coronary sinus thermodilution technique measures coronary venous effluent, but, except for that in the left anterior descending artery, cannot relate flow to an individual coronary artery. The technique is hampered further by catheter movement within the coronary sinus and inconsistencies in venous drainage patterns.6,7 These methodologic problems have prevented accurate measurements of coronary blood flow and the flow reserve capacity of individual vessels in conscious humans. Furthermore, the inability to obtain on-line flow measurements has prevented characterization of the time- and dose-response characteristics of coronary vasodilators.
Previous techniques of measuring instantaneous phasic changes in coronary blood flow in conscious humans have used pulsed Doppler technology to measure CBFV. CBFV has been shown to correlate highly with volumetric measurements of coronary blood flow. The Doppler technique of measuring flow velocity is advantageous because rapid changes in flow can be detected, on-line recordings can be obtained, and the method lends itself to miniaturization.

In 1974, Hartley and Cole developed a No. 5F (tip) Doppler catheter capable of measuring CBFV at the coronary ostium by placing a piezoelectric crystal at the tip of a Sones catheter. A major limitation of this and other coronary Doppler catheters available was that they were too large to place subselectively into coronary arteries. Furthermore, because the Doppler crystal is mounted on the catheter tip and the tip position is unstable, signal instability over time was a significant problem. Additionally, validation studies over a wide range of coronary flows have not been presented.

The purpose of our study was twofold: to develop and validate a coronary Doppler catheter that could be subselectively placed into individual coronary vessels to measure instantaneous changes in CBFV and to develop a method for determining subselective coronary vasodilator reserve at the time of cardiac catheterization.

**Methods**

The subselective coronary Doppler catheter was constructed by placing a 20 MHz piezoelectric crystal into the wall of a Rentrop reperfusion catheter (United States Catheter and Instrument Co.) and used a 20 MHz pulsed Doppler meter (Bioengineering Department, University of Iowa) to measure blood flow velocity. The woven Dacron catheter is 120 cm in length and has a 1.6 mm outer diameter at the proximal end; the distal 20 cm tapers to 1.0 mm outer diameter (figure 1). This catheter has been approved for investigational use in humans by the U.S. Food and Drug Administration. Details of the catheter construction and specifications of the pulsed Doppler meter are contained in the Appendix.

To determine the relationship between mean flow velocity and Doppler frequency shift measured with the coronary Doppler catheter, the catheter was placed into the lumen of a 1.8 mm internal diameter polyethylene tube system filled with a mixture of water and laundry starch and connected to a roller pump (Sarns Co.). A windkessel chamber was used to minimize pulsatile flow. The starch has ultrasonic reflective characteristics similar to blood. Mean flow velocity was calculated with the use of timed volume collections of tube flow. Paired measurements of flow velocity and Doppler frequency shift, obtained over a broad range of flows, were closely correlated (r = .99, figure 2).

**Animal validation studies.** Seven calves were anesthetized with ketamine (20 mg/kg im and iv) and pentobarbital sodium (10 mg/kg iv) and mechanically ventilated. A left thoracotomy was performed and a 6.5 mm internal diameter catheter passed through the right atrial appendage into the proximal coronary sinus and secured with a ligature. Blood from the coronary sinus catheter could be returned to the jugular vein or diverted to a graduated cylinder for timed volume collections. Catheters were placed in the left femoral artery and both femoral veins for measurement of arterial pressure, withdrawal of blood samples, and drug infusions. A metal introducer was placed into the right

![FIGURE 1. Top. Schematic diagram of the distal portion of the coronary Doppler catheter. The copper wires attached to the piezoelectric crystal exit from the proximal end of the catheter and are connected to a pulsed Doppler meter. Bottom, Photograph of the distal 3 cm of the catheter. A very flexible coiled wire has been attached to the tip to enhance safety in human studies.](image-url)
internal carotid artery and positioned at the ostium of the left main coronary artery. Heparin sodium (15,000 units) was given intravenously. Under fluoroscopy, the coronary Doppler catheter was passed into the left anterior descending or circumflex coronary artery. The catheter position and range control were adjusted to obtain an audio signal of phasic CBFV. An acceptable phasic signal had the following qualities: the systolic signal was less than 25% of the diastolic signal, the CBFV in early systole approximated 0, the mean flow velocity with the artery occluded proximal to the catheter tip approximated 0, and the audio signal did not contain phasic low-frequency sounds caused by reflection of the ultrasonic pulse from the vessel wall. In all experiments the range control was adjusted to obtain the maximal frequency shift.

An epicardial suction Doppler probe was then placed over the same coronary vessel distal to the catheter tip. Its signal was adjusted in a manner similar to the catheter signal. In each of three animals an epicardial suction Doppler probe was also placed over an artery in a perfusion field separate from the artery containing the catheter. Changes in CBFV measured with these epicardial suction Doppler probes have previously been shown to correlate highly with changes in myocardial perfusion measured with microspheres, timed volume collections of coronary sinus fluid, and electromagnetic flowmeters.

Alterations in coronary blood flow were produced by three methods. First, with use of a snare placed around the left main coronary artery, reactive hyperemic responses were obtained by 5 to 40 sec vessel occlusions. Second, global coronary flow was altered pharmacologically with adenosine (1 to 6 μM/kg/min iv) and epinephrine (0 to 3 μg/kg/min). Finally, hemorrhagic hypotension and the severe anemia following massive volume replacement with normal saline were also used to change coronary blood flow.

We compared results obtained with the coronary Doppler catheter with those by two standard techniques: measurement of CBFV with an epicardial Doppler probe and volumetric measurements of coronary sinus flow. If, during an experiment, the phasic CBFV signal from the catheter failed to meet criteria for an acceptable signal, the data collection was interrupted, the catheter was repositioned, and measurements resumed.

We assessed the extent and physiologic significance of flow obstruction resulting from the presence of the catheter in the vessel by two methods. First, using the epicardial Doppler probe, the maximal reactive hyperemic response with the catheter in the vessel was compared with that after removal of the catheter. Second, using pharmacologically induced global changes in CBFV, we compared simultaneous measurements of the change in blood flow velocity obtained with the epicardial Doppler probe and the Doppler catheter placed in separate perfusion fields.

**Safety studies**

*Studies in vitro.* Electrical isolation of the coronary Doppler catheter was evaluated by immersing the tip of the catheter in a beaker of saline and measuring the impedance between each lead and the saline. In the 10 catheters tested, the impedance was infinity.

*Studies in vivo.* To determine if the catheter produced changes in endothelial permeability, six calves (40 to 60 kg) were prepared in a manner similar to that described above. The coronary Doppler catheter was passed through the introducer into the mid left anterior descending or circumflex coronary artery with fluoroscopic guidance. Adjustments in catheter position were made and the catheter was left in the artery for 30 min. The catheter was withdrawn from the artery and inspected microscopically for thrombus. Evans blue dye (100 to 150 mg/kg) was then infused intravenously over 10 to 20 min. Thirty minutes after infusion of the dye, the animal was killed with intravenous KCl. The chest was opened and the heart removed. The epicardial coronary arteries were bluntly dissected from the heart, opened by a longitudinal incision, and carefully inspected for evidence of thrombus or staining. Sections were taken from any stained portion of the artery and also from arteries that had not come into contact with the catheter. Seven micron sections from these vascular segments were stained with hematoxylin and eosin or toluidine blue and microscopically examined for evidence of endothelial erosion by an observer blinded to the source of the sample.

*Studies in dogs instrumented over the long term.* We measured subselective coronary vasodilator reserve in many patients immediately after they received ergonovine maleate. To determine whether ergonovine maleate alters resting blood flow velocity or maximal coronary vasodilation after dipyridamole infusion, we studied five mongrel dogs (18 to 22 kg in weight) previously instrumented over the long term with indwelling left atrial and aortic catheters, a pneumatic arterial occluder placed circumferentially about the circumflex coronary artery, and a Doppler flow probe placed proximal to the occluder.

The animals were brought to the laboratory in an awake state. Recordings of the aortic pressure, heart rate, and phasic and mean circumflex flow velocity were obtained at rest. Arterial pressure and mean blood flow velocity were recorded during a 20 sec circumflex occlusion. Three 0.1 mg boluses of ergonovine maleate were infused into the left atrium. One minute after the final ergonovine bolus, the circumflex artery was occluded for 20 sec and the resultant reactive hyperemic response was measured. After a 2 min recovery, dipyridamole (0.56 mg/kg) was infused into the left atrium of each animal over 4 min and the increase in blood flow velocity was recorded. Ten minutes after the completion of the infusion, the 20 sec coronary occlusion was repeated and the reactive hyperemic response was measured.

The following day, animals were returned to the laboratory. The hyperemic response following a 20 sec circumflex occlusion was again recorded. After a 2 min recovery time, dipyridamole was infused as above. Ten minutes after completion of the infusion the 20 sec vessel occlusion was repeated.

An index of coronary resistance was calculated for each intervention as the quotient of (mean aortic pressure at peak flow/
peak blood flow velocity) and (resting aortic pressure/resting
blood flow velocity).

Studies in humans. We studied 70 patients with the coronary
doppler catheter. All patients underwent cardiac catheterization
and coronary angiography for the diagnosis of chest pain syn-
dromes. In this article, we report the measurement of coronary
vasodilator reserve in 10 patients with angiographically normal
or minimally stenosed (<25% luminal diameter narrowing)
coronary vessels. A separate informed consent form for the
doppler studies was obtained from each patient. All clinical
studies were approved by the human use committee of the
University of Iowa.

Patients were brought to the catheterization laboratory in a
fasting state. Although a variety of sedatives were administered
(tab. 1), no patient received atropine. After local anesthesia
with 1% lidocaine, diagnostic coronary angiography was per-
formed. After completion of the diagnostic catheterization, a
judkins No. 8F guiding catheter (United States catheter and
instrument Co.) was positioned in the right or left coronary
ostium of each patient. Heparin sodium (5 to 10,000 units iv)
was given before intracoronary catheterization to increase the
activated clotting time to at least twice control. The coronary
doppler catheter was passed through the guiding catheter into
the coronary artery. The catheter position and doppler meter
range control were adjusted to obtain a good audio signal and
phasic tracing of maximal resting CBFV. The catheter position
and doppler meter settings were not varied between measure-
ments.

Measurement of vasodilator reserve. To assess vasodilator
reserve, we measured changes in CBFV after intracoronary
administration of meglumine diatrizoate and an intravenous
infusion of dipyridamole. After baseline recordings of phasic
and mean CBFV, 2 to 6 ml of meglumine diatrizoate was injected
through the guiding catheter into the coronary ostium. The
resultant changes in blood flow velocity were continuously
recorded. After flow velocity returned to its baseline value, 0.56
mg/kg of dipyridamole was infused over 4 min by an infusion
pump into the femoral vein. Recordings were continued until
the increase in mean flow velocity appeared stable. In two
patients, an additional dose of dipyridamole (0.4 mg/kg and
0.28 mg/kg) was given after the increase in mean flow velocity
appeared stable for several minutes.

In six patients, arterial pressure was continuously recorded
from the guiding catheter. Only mean arterial pressure could
be accurately measured because of the marked damping of phasic
pressure by the presence of the coronary doppler catheter within

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical diagnosis</th>
<th>Electrocardiogram</th>
<th>Medication</th>
<th>Vessel studied</th>
<th>Meglumine diatrizoate</th>
<th>Dipyridamole</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. S.</td>
<td>Atypical chest pain; hypertension; diabetes mellitus</td>
<td>Normal</td>
<td>Dipyridamole; ergonovine; nitroglycerin</td>
<td>Cx</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>C. C.</td>
<td>Atypical chest pain; hypertension</td>
<td>Normal</td>
<td>Ergonovine; nitroglycerin</td>
<td>RCA</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>C. B.</td>
<td>Atypical chest pain</td>
<td>Normal</td>
<td>Ergonovine; nitroglycerin</td>
<td>RCA</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>R. W.</td>
<td>Atypical chest pain; hypertension</td>
<td>Anterior ST-T changes</td>
<td>Ergonovine</td>
<td>Cx</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>N. B.</td>
<td>Angina pectoris; hypertension</td>
<td>Normal</td>
<td>Nitroglycerin; nifedipine; hydrochlorothiazide</td>
<td>LAD</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>F. Y.</td>
<td>6 months post LAD PTCA; asymptomatic Graves disease</td>
<td>Normal</td>
<td>Nifedipine; propranolol; dipyridamole; aspirin; hydrochlorothiazide</td>
<td>LAD</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>M. C.</td>
<td>Atypical chest pain</td>
<td>Nonspecific ST-T changes</td>
<td>Ergonovine; nitroglycerin</td>
<td>LAD</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>C. H.</td>
<td>Atypical chest pain; bronchitis</td>
<td>I° AV block; nonspecific ST-T changes</td>
<td>Ergonovine; nitroglycerin</td>
<td>RCA</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>C. F.</td>
<td>Atypical chest pain</td>
<td>Normal</td>
<td>Dipyridamole; aspirin; secobarbital; promethazine; atropine</td>
<td>RCA</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>K. M.</td>
<td>Atypical chest pain</td>
<td>Normal</td>
<td>Ergonovine; nitroglycerin</td>
<td>Cx</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>

ΔCBFV = change in CBFV; Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; RCA = right coronary artery; AV = atrioventricular; PTCA = percutaneous transluminal coronary angioplasty.
the guiding catheter lumen. After removal of the catheter, the catheter tip was examined microscopically for the presence of adherent thrombus.

For each intervention, an index of the change in coronary resistance was calculated as described above.

Results

Animal validation studies. Paired measurements of CBFV (peak frequency shift/resting frequency shift) obtained with the coronary Doppler catheter and with an epicardial Doppler probe placed immediately distal to the catheter correlated highly \((r = .95, \text{range } = 0.1\) to 5.7 times resting blood flow velocity, slope = 1.04). The correlation coefficients for studies done in individual animals varied from .90 to .99.

Changes in CBFV assessed with the coronary Doppler catheter were also highly correlated with changes in volumetric coronary sinus flow over a wide range \((r = .97, \text{range } = 52 \text{ to } 924 \text{ ml/min, slope } = 1.06; \text{figure 3}).

Assessment of coronary obstruction produced by the catheter. The extent of coronary obstruction produced by the catheter was assessed by two approaches. Maximal reactive hyperemic responses after transient vessel occlusions with the catheter present and absent in the artery under study were measured by an epicardial Doppler probe. If any significant coronary obstruction was produced by the catheter, then the maximal flow response with the catheter present in the artery should have been less than when it was removed. We found, however, that the maximal flow responses were identical \((n = 9, r = .99, \text{slope } = 1.03).\)

When global myocardial flow was altered pharmacologically, changes in CBFV assessed by the catheter were highly correlated with simultaneous measure-

ments of flow velocity measured using an epicardial Doppler probe placed in a separate perfusion field \((r = .94, n = 17, \text{slope } = 1.04; \text{figure 4}).\) These findings suggest that coronary obstruction produced by the catheter was minimal and of no physiologic significance.

Safety studies. We assessed the safety of this Doppler catheter system in several ways. First, we measured the amount of current leakage emanating from the catheter; we found none. Second, we looked for evidence of clot deposition in the artery or on the catheter after 30 min of intracoronary placement. We found no evidence of clot deposition in either the artery or on the catheter. Third, we looked for histologic evidence of endothelial erosion caused by the catheter. These studies revealed the endothelium to be intact without evidence of erosion. Fourth, we looked for changes in the permeability of coronary endothelium to Evans blue dye. In five of six animals, small linear streaks of endothelial staining were found in the artery containing the catheter. These streaks occurred in the proximal coronary artery and were not circumferential. The magnitude of staining was minimal compared with that seen in the aorta and coronary ostium resulting from coronary catheterization by the Seldinger technique and a Judkins diagnostic coronary catheter. These findings suggest that, although changes in endothelial permeability can be produced by the coronary Doppler catheter, the changes are minimal.

Studies in dogs instrumented over the long term. We studied five dogs instrumented over the long term to determine whether prior ergonovine administration

FIGURE 4. Effect of the coronary Doppler catheter on regional blood flow assessed by measuring changes in CBFV in two perfusion fields (one containing the catheter and an adjacent field with an epicardial Doppler probe). While flow was altered with systemic pharmacologic agents, changes in blood flow velocity assessed with the catheter in one field were equivalent to changes in velocity measured with an epicardial Doppler probe in an adjacent field.

FIGURE 3. Validation of the coronary Doppler catheter in vivo with timed-volume collections of coronary sinus flow. Changes in CBFV assessed with the coronary Doppler catheter were highly correlated with simultaneously measured changes in coronary sinus blood flow over a wide range of flows.
TABLE 2

Effect of ergonovine on vasodilator reserve

<table>
<thead>
<tr>
<th></th>
<th>HR (bpm)</th>
<th>MAP (mm Hg)</th>
<th>CBFV (× resting)</th>
<th>CVRI (× resting)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1 (n = 5)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before ergonovine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>108 ± 27</td>
<td>92 ± 13</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Reactive hyperemia</td>
<td>110 ± 27</td>
<td>89 ± 16</td>
<td>2.7 ± 0.4</td>
<td>0.35 ± 0.06</td>
</tr>
<tr>
<td>After ergonovine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>116 ± 35</td>
<td>104 ± 14</td>
<td>1.3 ± 0.3</td>
<td>0.98 ± 0.11</td>
</tr>
<tr>
<td>Reactive hyperemia</td>
<td>122 ± 24</td>
<td>109 ± 17</td>
<td>3.2 ± 0.7</td>
<td>0.38 ± 0.06</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>138 ± 25</td>
<td>90 ± 10</td>
<td>3.1 ± 1.0</td>
<td>0.34 ± 0.10</td>
</tr>
<tr>
<td>Dipyridamole and reactive hyperemia</td>
<td>132 ± 26</td>
<td>89 ± 8</td>
<td>4.1 ± 1.2</td>
<td>0.25 ± 0.06</td>
</tr>
<tr>
<td><strong>Day 2 (n = 3)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>105 ± 34</td>
<td>91 ± 13</td>
<td>1.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Reactive hyperemia</td>
<td>108 ± 28</td>
<td>89 ± 6</td>
<td>3.4 ± 0.8</td>
<td>0.30 ± 0.08</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>136 ± 18</td>
<td>79 ± 3</td>
<td>2.7 ± 0.6</td>
<td>0.32 ± 0.01</td>
</tr>
<tr>
<td>Dipyridamole and reactive hyperemia</td>
<td>135 ± 14</td>
<td>75 ± 4</td>
<td>3.3 ± 0.8</td>
<td>0.26 ± 0.07</td>
</tr>
</tbody>
</table>

All values are mean ± SEM.
HR = heart rate; MAP = mean arterial pressure; CVRI = coronary vascular resistance index.
\( ^{a}p = NS \) vs resting CVRI before ergonovine.
\( ^{b}p = NS \) vs CVRI after reactive hyperemia before ergonovine.
\( ^{c}p = NS \) vs CVRI after dipyridamole on day 2.
\( ^{d}p = NS \) vs CVRI after dipyridamole and reactive hyperemia on day 2.

might alter resting coronary flow velocity or change measurements of coronary vasodilator reserve (table 2). Resting blood flow velocity and coronary vascular resistance were unchanged after ergonovine. Similarly, vasodilator reserve, measured after transient vessel occlusion and after administration of dipyridamole, was not altered by ergonovine.

**Studies in humans.** Studies of 70 patients in the cardiac catheterization laboratory have shown that measurements of phasic CBFV could be readily obtained in 58 of 70 patients (figure 5). Inability to "steer" the catheter away from a small branch vessel accounted for most instances of poor signal quality. A stable signal was recorded for up to 30 min (the arbitrary length of the study). As expected, the ratio of systolic to diastolic CBFV was higher when measurements were obtained from the right coronary artery as compared with the left coronary artery (systolic/diastolic signal ratio of 0.67 ± 0.11 [± SEM] in the right coronary and 0.17 ± 0.05 in the left anterior descending coronary).

**Subselective measurement of coronary vasodilator reserve in normal vessels.** Intracoronary injection of meglumine diatrizoate resulted in a 3.5-fold increase in CBFV compared with control velocity (range 2.8 to 5.0 times resting blood flow velocity; figure 6). The average time from onset of injection to peak change in flow velocity was 17 sec (range 12 to 22 sec). Flow velocity returned to baseline within a mean of 50 sec (range 39 to 69 sec). The peak flow responses did not significantly vary with the coronary vessel studied.

Intravenous dipyridamole resulted in an average fivefold increase in resting flow velocity (range 3.8 to 7.0 times resting velocity; figure 7). Similarly, the coronary resistance index fell to 17% of baseline resistance (range 0.10 to 0.22 times resting coronary resistance index). In each patient, dipyridamole produced a greater rise in blood flow velocity and a greater fall in resistance than did meglumine diatrizoate.

Figure 8 depicts the time course of the change in...
flow velocity in each patient after infusion of dipyridamole. Although the mean time from onset of infusion to peak flow velocity was 6.5 min, the temporal course of the response was variable (range 2.5 to 8.7 min). Furthermore, at the end of the 4 min infusion, average mean flow velocity had increased to only 67% of the eventual peak velocity.

In nine of 10 patients, 0.56 mg/kg of dipyridamole increased CBFV to more than 3.8 times resting velocity. In one patient, however, 0.56 mg/kg dipyridamole increased flow velocity to only 2.3 times resting velocity. An additional 0.4 mg/kg of dipyridamole further increased flow velocity to 4.2 times resting velocity (figure 9). Thus, the conventional dose of dipyridamole did not produce maximal vasodilation in all patients.

Safety. Sixty-nine of 70 patients underwent subselective coronary catheterization and flow velocity measurement without adverse effects. One patient had abrupt occlusion of the left anterior descending coronary artery during flow velocity measurements. The occlusion was unresponsive to intracoronary streptokinase and balloon angioplasty. The patient had a history of chest pain suggestive of myocardial ischemia and a normal coronary angiogram. An ergonovine test to exclude vasospasm was not performed before the flow study. After coronary occlusion the catheter was immediately withdrawn and microscopically examined for adherent thrombus. None was found. The angiogram did not suggest dissection and the distal vessel was normal. The patient underwent emergency coronary artery bypass surgery. At surgery no visible changes in the arterial wall were observed. Although the patient sustained an anterior myocardial infarction, he recovered from surgery and at present is asymptomatic.

Discussion

In animal studies, we have shown that a No. 3F coronary Doppler catheter can accurately measure instantaneous changes in phasic CBFV in individual coronary arteries without producing physiologically significant coronary obstruction. In subsequent studies in awake patients, we have shown that phasic flow velocity and coronary vasodilator reserve can be measured at the time of cardiac catheterization. We have also demonstrated that dipyridamole produces a greater fall in coronary vascular resistance than does meglumine diatrizoate. More importantly, we have characterized the temporal characteristics of the coronary dilative responses to meglumine diatrizoate and dipyridamole in man.

Our No. 3F coronary Doppler catheter offers several advantages over existing methods of measuring CBFV. First, use of the Doppler technique permits continuous on-line recording of instantaneous phasic
flow velocity. Consequently, transient changes in CBFV in response to neural or humoral stimuli can be readily measured. Second, because of its small diameter, the No. 3F coronary Doppler catheter can measure phasic flow velocity in individual coronary vessels well beyond the left main coronary artery without obstructing maximal coronary blood flow. Previous Doppler catheters have been unable to reproducibly measure flow beyond the coronary ostium without producing significant coronary obstruction. As a consequence, studies in patients with obstructions in the left anterior descending or circumflex coronary arteries were difficult to interpret. Third, signal stability over time has been improved.

The subselective pulsed Doppler coronary catheter methodology has several potential limitations. Movement of the catheter within the vessel could change the angle of the piezoelectric crystal relative to flow, thus artifactualy changing the measured CBFV. When the quality of the phasic tracing remained intact, however, we found that changes in flow velocity correlated directly with coronary sinus flow. Since pulsed Doppler methodology measures flow velocity in only a small portion of the stream, movement of the catheter with myocardial contraction could change the sample window over the cardiac cycle. Previous studies, however, have shown that the velocity profile in the proximal coronary arteries is parabolic. Thus, small changes in the sample window could not be expected to result in significantly different velocity measurements unless the sample window was immediately adjacent to the vessel wall. In our validation studies, wall movement was easily recognized by a characteristic audio signal. The catheter might also change the blood flow velocity profile of the stream, producing velocities that may not linearly follow CBFV. Results of our study in normal vessels, however, confirm that changes in the maximal flow velocity in the stream parallel changes in both coronary sinus flow and CBFV measured in a vessel not containing the catheter. It is possible, however, that diffuse vascular disease could change the relationship between maximal flow velocity and mean flow velocity.

Changes in vessel caliber during interventions might alter the linear relationship between velocity and flow. In particular, large epicardial coronary vessels could dilate in direct response to agents producing vasodilation or to ascending dilation resulting from the increased coronary flow produced by vasodilation. Studies by Hintze and Vatner in awake dogs suggest that the magnitude of large coronary dilation produced by dipyridamole (arterial cross-sectional area increased by 28%) might significantly alter the flow:flow velocity relationship. However, our studies and those by Marcus et al. have shown a good correlation between maximal flow velocity and flow even at high flow rates. Other studies in animals and man suggest that dipyridamole produces only minor changes in large vessel size. Brown et al. found that dipyridamole increased arterial cross-sectional area by only 4% in patients. Nonetheless, to compensate for changes in vessel size, arterial cross-sectional area could be measured with quantitative coronary angiography so that a relationship between flow velocity and flow could be determined.

Another theoretical problem is that the catheter itself could cause partial coronary obstruction and result in distal arteriolar vasodilation. We showed that this does not occur in an animal with coronary vessels of slightly smaller diameter than those of an adult human with normal coronary vessels. Calculation of the magnitude of obstruction likely to be produced by the catheter in
humans similarly suggested that significant obstruction would not result from the presence of the catheter in the proximal or middle portion of normal major epicardial coronary arteries. The cross-sectional area of the distal catheter (less than 0.8 mm$^2$) is less than 7% of the cross-sectional area of a normal human proximal left anterior descending artery and less than 22% of the area of a normal left anterior descending artery in its mid course.\textsuperscript{16} Since maximal coronary blood flow is not diminished until at least 36 $\pm$ 10% luminal area narrowing is present,\textsuperscript{17} physiologically significant coronary obstruction in normal human coronary arteries is unlikely. However, if diffuse luminal narrowing were present, then the additional obstruction produced by the catheter could restrict maximal flow. Determination of the cross-sectional area of the artery containing the catheter would provide a means of estimating the likelihood of flow restriction by the catheter in diffusely narrowed vessels.

**Measurement of coronary vasodilator reserve.** Measurement of vasodilator reserve with the coronary Doppler catheter has many advantages over currently available techniques. Unlike coronary sinus thermodilution or the inert gas methods, the coronary Doppler catheter can measure vasodilator reserve in individual coronary vessels. This subselective measurement of reserve is essential in measuring the impairment in flow reserve caused by an individual coronary stenosis. Another advantage, the ability to measure instantaneous changes in blood flow velocity, enables investigation of the time-response characteristics of a variety of agents used to unmask vasodilator reserve in man. This information should enhance the use of these drugs in noninvasive testing, in which time to maximal drug response and dosing must be approximated.

Our study confirms previous reports in animals and man that dipyridamole produces greater coronary vasodilation than iodinated contrast material. We also found that dipyridamole increased coronary flow velocity to at least 3.8 times resting velocity in each patient. These results in awake patients are similar to those in other studies of coronary vasodilator reserve in anesthetized patients\textsuperscript{7} and animals.\textsuperscript{17, 18} Recent measurements of coronary vasodilator reserve in normal awake patients by digital subtraction angiography have found only a 1.9-fold increase in flow after intracoronary administration of radiographic contrast material.\textsuperscript{19, 20} This small rise in flow is inconsistent with that observed in studies in animals and our studies in patients. Several methodologic problems may account for these inconsistencies. Since the time at which peak flow is measured must be approximated with the digital subtraction method, peak flow velocity could be missed. Furthermore, the time required for measurement of flow (several seconds) reduces the frequency response of the system, potentially underestimating the effects of short-acting vasodilators. Finally, methodologic problems related to contrast injection and streaming may impair measurements of high coronary flows with currently available digital subtraction angiographic methods.

Many investigators have assumed that dipyridamole produces maximal coronary vasodilation in a predictable fashion.\textsuperscript{21-23} Noninvasive studies with dipyridamole (e.g., \textsuperscript{20}$^{20}$Tl-dipyridamole scintigraphy) are based on the premise that near maximal vasodilation will occur in all patients after a single dose of dipyridamole. We found, however, that the response to dipyridamole varied among patients (figure 8). On average, more than 2 min elapsed from the completion of the drug infusion into the femoral vein until 90% of the eventual peak/flow velocity was reached. In three of 10 patients, 90% of the eventual peak/resting flow velocity was not reached for 3 min after completion of the infusion. One of our patients had only a 2.3-fold rise in resting velocity after 0.56 mg/kg of dipyridamole. After an additional 0.4 mg/kg infusion of dipyridamole, flow velocity rose an additional 170% to 4.2 times control velocity. This heterogeneity in the response to dipyridamole underscores the advantage of instantaneous on-line measurements of blood flow velocity in measuring vasodilator reserve in man.

Several potential problems are inherent in this method of measuring vasodilator reserve. They include changes in resting blood flow velocity, changes in arterial pressure between measurements, prolonged effects of vasodilator agents, concomitant exposure to drugs that may effect vasodilator reserve, and, as previously discussed, dilation of large coronary vessels. First, since a ratio of peak to resting flow velocity is measured, an elevated resting velocity could falsely suggest a diminished vasodilator reserve. This is unlikely, however, in the absence of conditions that increase myocardial oxygen demand (e.g., tachycardia, hypertension, thyrotoxicosis) or diseases associated with high resting flow rates (e.g., severe anemia).\textsuperscript{24-27} Second, changes in arterial pressure between measurements of resting and peak velocities could change the ratio of peak to resting flow. Calculation of an index of resistance can compensate for the changes in coronary perfusion pressure and better reflect the true change in coronary resistance.

Third, the prolonged increase in coronary flow after infusion of dipyridamole makes repeat measurements
or studies of other vessels during the same procedure impossible. This represents a major disadvantage to the routine use of dipyridamole in measuring coronary vasodilator reserve. Use of other agents with shorter lasting effects, such as papaverine, may be more advantageous. The time- and dose-response characteristics of any potential agent, however, will need to be thoroughly studied in man before it can be used routinely.

Fourth, many of the patients we studied had immediate prior exposure to ergonovine. Theoretically, ergonovine could have altered resting flow or limited maximal vasodilation. Our studies in dogs instrumented over the long term, however, show that ergonovine does not change the maximal vasodilator response to dipyridamole or resting flow.

**Safety considerations.** There are several potential dangers when this Doppler catheter is used to measure CBFV. First, the catheter could act as a stimulus for clot formation. In animal and human studies we found no evidence of clot formation in the artery containing the catheter or on the catheter itself. Second, the catheter could cause serious endothelial injury. By light microscopy, we found no evidence of endothelial injury in arteries containing the catheter. We did find that the catheter produced a change in endothelial permeability in small areas of the coronary artery containing the catheter. Previous studies by others and in our laboratory have shown that the technique we used (endothelial staining with Evans blue dye) is a very sensitive technique in detecting even minor changes in endothelial permeability and that endothelium disruption need not be present to produce a change in endothelial permeability to the dye.

A third potential problem is that the catheter could cause coronary vasospasm or dissection. Prior experience has demonstrated that intracoronary cannulation very infrequently results in vasospasm or dissection of angiographically normal vessels. Nevertheless, one patient of the 70 patients we have studied developed coronary occlusion at a site where the catheter was present and required emergency coronary bypass surgery. We presume this was related to vasospasm, as opposed to dissection or thrombosis. To minimize the likelihood of this complication in future studies, the possibility of coronary vasospasm should be excluded before intracoronary cannulation in all patients without significant obstructive coronary artery disease. The need for excellent radiographic visualization and an operator experienced in techniques of subselective coronary catheterization is self evident. The incidence of coronary occlusion in standard catheterization laboratory procedures varies from 0.25% with routine coronary angiography to 3% to 8% during coronary angioplasty. Additional experience with the coronary Doppler catheter will need to be obtained to determine if the complication rate we observed (1.3%) is reflective of the true incidence of complications resulting from this procedure.

**Future applications.** Measurements of CBFV in individual coronary vessels of conscious humans should facilitate studies of the coronary circulation in man. We anticipate that use of this coronary Doppler catheter system will enable direct measurement of coronary vasodilator reserve and permit characterization of the physiologic significance of coronary artery stenoses during routine coronary angiography. Furthermore, instantaneous on-line coronary flow velocity recordings should be of great value in studying neural and humoral control of the coronary circulation.

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**Appendix**

**Doppler catheter construction.** Two insulated copper wires (38 G) were passed through the length of the catheter and brought out through a V-shaped notch cut into the catheter wall 7 to 10 mm from the catheter tip (figure 1). To give the terminal ends of the two conductors more flexibility, the distal ends of these wires were tinned and soldered to a 1 cm length of 48-gauge insulated gold-plated copper wire. These short wires were then pulse-dot soldered to either side of a 0.7 to 1.0 mm × 0.7 to 1.0 mm fine-ground compressional piezoelectric 20 MHz crystal that was gold-plated on either side (Valpey-Fischer, Inc.). The back of the crystal was coated with an 180 degree lens of epoxy (No. 795-Hy-Sol) mixed with air-filled glass beads (FT 102, Emerson and Cuming). The beads provided insulation so that the ultrasound pulse was unidirectional. The crystal assembly was pulled into the notch in the catheter wall and placed at a 30 to 45 degree angle to the long axis of the lumen so that the insulated side of the crystal faced toward the tip of the catheter. Using this configuration, the ultrasonic pulse was projected at a 30 to 45 degree angle toward the proximal portion of the catheter. A lens of vacuum-degassed epoxy was placed about both sides of the crystal to fill the unoccupied space within the notch of the catheter. An epoxy plug (No. 795-Hy-Sol) was placed into the tip of the catheter lumen. To harden the epoxy, the distal end of the catheter was heated to 70° C for 30 min. The rough edges of the crystal were then filed and polished so that the catheter profile was similar to its "native" state.

To provide greater flexibility for human studies, we attached a 15 mm flexible guidewire 0.016 inch in diameter (United States Catheter and Instrument Co., angioplasty spring guide tip) to the catheter tip.

**Doppler meter.** The pulsed Doppler meter is a modification of a circuit described by Hartley and has been described in detail elsewhere. Briefly, a 20 MHz carrier frequency is provided by a crystal-controlled oscillator. A digital integrated circuit divides the basic frequency by 320 to produce a pulse repetition frequency of 62.5 kHz. A gate of 0.8 msec duration passes 16 cycles of 20 MHz to the transmitter, which amplifies
the signal and couples it to a transducer. Energy returning to the transmitter is detected, amplified by the receiver, and passed to a dual-face detector. There, two reference signals locked to the transmitted frequency and separated in phase by 90 degrees are compared with the returning signal. During each 16 msec receive cycle, the phase difference between the received and transmitted signals is converted to a voltage. The time during each received cycle at which this voltage is sampled is variable. By adjusting the range control the operator can move the sample window over a distance of 1 to 10 mm from the crystal face. Sample and hold circuits are used to extract the Doppler audio signal from the phase detector outputs. The signals are then filtered to remove the pulse repetition frequency component. Thereafter the audio signals are passed to a dual-polarity frequency-to-voltage converter that is phase sensitive. The output of the converter, a voltage corresponding to the instantaneous velocity, is displayed on a strip-chart recorder. The audio signal is amplified and fed to a speaker. The audio signal is used to initially position the catheter.

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