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EXPERIMENTAL STUDIES

# Coronary Flow Reserve as a Physiologic Measure of Stenosis Severity

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**PART I: Coronary flow reserve indicates functional stenosis severity, but may be altered by physiologic conditions unrelated to stenosis geometry. To assess the effects of changing physiologic conditions on coronary flow reserve, aortic pressure and heart rate-blood pressure (rate-pressure) product were altered by phenylephrine and nitroprusside in 11 dogs. There was a total of 366 measurements, 26 without and 340 with acute stenoses of the left circumflex artery by a calibrated stenoser, providing percent area stenosis with flow reserve measured by flow meter after the administration of intracoronary adenosine.**

**Absolute coronary flow reserve (maximal flow/rest flow) with no stenosis was 5.9 ± 1.5 (1 SD) at control study, 7.0 ± 2.2 after phenylephrine and 4.6 ± 2.0 after nitroprusside, ranging from 2.0 to 12.1 depending on aortic pressure and rate-pressure product. However, relative coronary flow reserve (maximal flow with stenosis/normal maximal flow without stenosis) was independent of aortic pressure and rate-pressure product. Over the range of aortic pressures and rate-pressure products, the size of 1 SD expressed as a percent of mean absolute coronary flow reserve was ±43% without stenosis, and for each category of stenosis severity from 0 to 100% narrowing, it averaged ±45% compared with ±17% for relative coronary flow reserve. For example, for a 65% stenosis, absolute flow reserve was 5.2 ± 1.7 (±33% variation), whereas relative flow reserve was 0.9 ± 0.09 (±10% variation), where 1.0 is normal.**

**Therefore, absolute coronary flow reserve by flow meter was highly variable for fixed stenoses depending on aortic pressure and rate-pressure product, whereas relative flow reserve more accurately and specifically described stenosis severity independent of physiologic conditions. Together, absolute and relative coronary flow reserve provide a more complete description of physiologic stenosis severity than either does alone.**

**PART II: Coronary flow reserve directly measured by a flow meter is altered not only by stenosis, but also by physiologic variables. Stenosis flow reserve is derived from length, percent stenosis, absolute diameters and shape by quantitative coronary arteriography using standardized physiologic conditions. To study the relative merits of absolute coronary flow reserve measured by flow meter and stenosis flow reserve determined by quantitative coronary arteriography for assessing stenosis severity, aortic pressure and rate-pressure product were altered by phenylephrine and nitroprusside in 11 dogs, with 366 stenoses of the left circumflex artery by a calibrated stenoser providing percent area stenosis as described in Part I. Stenosis flow reserve was measured by quantitative coronary arteriography and coronary flow reserve by flow meter after intracoronary adenosine before and during ±40% change in aortic pressure.**

**Absolute coronary flow reserve by flow meter for fixed stenosis geometry varied significantly depending on aortic pressure and rate-pressure product. In contrast, stenosis flow reserve by quantitative arteriography was not affected by these variables. For example, for all 65% stenoses, coronary flow reserve by flow meter was 5.2 ± 1.7 (±33% variation); by comparison, stenosis flow reserve by quantitative arteriography was 5.0 ± 0.5 (±10% variation). For 366 stenoses, the size of 1 SD, expressed as a percent of the mean coronary flow reserve by flow meter for each category of stenosis severity from 0 to 100% narrowing, averaged ±45% compared with ±12% of mean stenosis flow reserve by quantitative arteriography for the same categories of stenosis severity.**

**Therefore, absolute coronary flow reserve by measured flow meter is highly variable for fixed stenosis geometry depending on aortic pressure and rate-pressure product, but reflects actual flow capacity due to stenosis severity and physiologic conditions at the time of measurement. Stenosis flow reserve determined by quantitative coronary arteriography more specifically reflects functional stenosis severity under standardized physiologic conditions.**

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# Part I: Relative and Absolute Coronary Flow Reserve During Changing Aortic Pressure and Cardiac Work Load

The concept of coronary flow reserve, defined as maximal flow divided (normalized) by control flow at rest, has evolved into an accepted functional measure of stenosis severity since first proposed 15 years ago (1). Its validity has been confirmed and applied clinically by noninvasive imaging (2–15) and invasive methods such as coronary sinus thermodilution (16), Doppler-tip catheters (17–19) and digital subtraction angiography (20–22). These clinical methods measure pharmacologically induced increases in coronary blood flow, most commonly with intravenous dipyridamole for noninvasive studies and intracoronary papaverine for invasive studies. Coronary flow reserve has also been theoretically and experimentally related to the geometric dimensions of stenoses (8–12).

However, changes in aortic pressure and heart rate are known to alter cardiac work load and, therefore, baseline coronary blood flow, as well as altering maximal coronary flow under conditions of maximal vasodilation (23,24). Consequently, absolute coronary flow reserve as measured by flow meter has also been hypothesized to vary with aortic pressure and heart rate independent of stenosis geometry due to differential effects of these variables on rest and maximal coronary flow (25,26). Consequently, under varying physiologic conditions, or from patient to patient, coronary flow reserve may not reliably or specifically reflect the severity of coronary artery narrowing because it may be altered by physiologic factors unrelated to stenosis geometry.

*In contrast, relative maximal coronary flow or relative flow reserve*, defined as maximal flow in a stenotic artery divided (normalized) by the normal maximal flow in the absence of stenosis, should theoretically be more independent of aortic pressure, heart rate or varying baseline flow caused by changing cardiac work load. Physiologic variables unrelated to stenosis severity, such as aortic pressure, heart rate, metabolic demand or vasomotor tone, alter distal coronary bed resistance in series with and independent of proximal stenosis resistance. During maximal coronary vasodilation, distal coronary bed resistance is equally minimized for both normal and stenotic arteries. When the maximal flow in the stenotic artery is normalized by normal maximal flow, the effects of pressure, heart rate or vasomotor tone on flow in the numerator and denominator of this ratio cancel out. Therefore, relative differences in regional maximal flow, or relative flow reserve, are determined primarily by differences in proximal stenosis resistance. Relative flow reserve should then measure stenosis severity independent of physiologic variables.

Although the potential effects of changing physiologic conditions on absolute maximal flow have been recognized in principle (25,26), their effects on flow reserve for assessing stenosis severity are complex and have not been previously described experimentally. Accordingly, the purpose of this study was to test in an animal model the hypotheses that 1) absolute coronary flow reserve, defined as maximal flow divided (normalized) by baseline flow at rest, is so highly dependent on aortic pressure and baseline heart rate-blood pressure (rate-pressure) product that it is not a specific measure of stenosis severity when these physiologic variables are different or changing; and 2) relative maximal coronary flow or relative flow reserve, defined as the maximal flow in a stenotic coronary artery divided (normalized) by normal maximal flow in the absence of a stenosis, reflects stenosis severity independently of varying aortic pressure and baseline rate-pressure product.

## Methods

**Instrumentation.** Eleven mongrel dogs (weighing 26 to 35 kg) underwent anesthetic induction with 20 to 30 mg/kg body weight of intravenous thiopental for acute experimental study. After endotracheal intubation, general anesthesia was maintained with 0.1% to 0.5% methoxyflurane (Penthrane) with approximately 2 liters/min of nitroprusside and 3 liters/min of oxygen, using a Met-O-Matic veterinary anesthesia ventilator (Ohio Medical Products). Through a left thoracotomy, the left circumflex coronary artery was dissected free and instrumented with a Zapeda perivascular electromagnetic flow transducer, a precision-machined, external, eccentric, variable stenoser providing a measure of percent area narrowing and a more distal 1-0 silk snare occluder. A left coronary artery Judkins catheter adapted for dogs was inserted through the left femoral artery and positioned at the left coronary ostium for coronary arteriography. Aortic pressure was monitored with an Ail Tec pressure transducer through the coronary catheter. Intravenous catheters were inserted for administration of drugs. Standard electrocardiographic (ECG) leads were attached to the limbs.

**Measurements.** Standard ECG lead II, mean and phasic left circumflex coronary artery blood flow and aortic pressure were monitored continuously with multiple zero flow baseline measurements recorded throughout the experiment using the snare occluder. For each study, pressure transducers were calibrated by comparison with 100 mm Hg pressure by mercury column. Zero baseline checks were recorded for

each experimental step in the protocol, including decreased aortic pressure. Zero flow baseline measurements determined repeatedly throughout each experiment were stable, indicating consistently good electrical contact between the flow meter electrodes and the arterial wall. In addition, flow meter readings were calibrated in situ at the end of each experiment by passing known volumes of blood through the artery over timed intervals. Flow meter recordings were made in all experiments with the perivascular flow transducer upstream from the stenosis. Calibration recordings were made with upstream perfusion pressures of approximately 60, 100 and 160 mm Hg to demonstrate constant flow calibration at different pressures.

**Data processing.** Standard ECG lead II, mean and phasic left circumflex coronary artery flow and aortic pressure were recorded on a VR-16 Electronics for Medicine physiologic recorder with a direct writer and a Honeywell tape recorder for analog to digital conversion and subsequent computer processing. Biplane coronary arteriograms were optically magnified and digitized on a Spatial Data Eyecom II videocamera system on line to a Vax 11/780 computer. Digitized arteriograms were analyzed by completely automated border recognition and densitometric techniques as previously described and validated (8,9,27–29) to be reproducible to within ±2% to 3% and accurate to ±0.1 mm for absolute dimensions.

**Experimental protocol.** After a 30 min stabilization period following acute surgical preparation, baseline ECG, rest control coronary flow and aortic pressure were recorded. Adenosine in a concentration of 2 mg/ml was continuously infused selectively into the left coronary artery at an increasing rate until coronary flow no longer increased with increasing infusion rates. This rate of intracoronary adenosine infusion was then used to achieve maximal coronary vasodilation at subsequent times during the remainder of the experiment. After establishing the intracoronary dose rate for maximal coronary vasodilation, adenosine infusion was terminated and coronary flow allowed to return to baseline values.

*Control measurements of rest and maximal coronary flows after intracoronary adenosine* were made before and during a sequence of progressively severe coronary artery stenoses. For each stenosis, aortic pressure, coronary artery flow, heart rate and coronary arteriograms were obtained until the artery was completely occluded. The stenosis was then progressively released in steps while the same data were obtained until there was no arterial narrowing. The adenosine infusion was then terminated and conditions allowed to return to baseline. Control ECG, coronary artery flow and aortic pressure were again recorded in absence of a stenosis, with a zero flow baseline determined by snare occlusion.

*Phenylephrine (0.05 mg/ml) was then infused intravenously* to increase aortic pressure by approximately 40% while the ECG, coronary flow and aortic pressure were recorded. When aortic pressure was stable at approximately 40% above the control value during intravenous phenylephrine infusion, the predetermined intracoronary dose of adenosine was infused to produce maximal coronary vasodilation during recording of the ECG, coronary artery flow and aortic pressure. A sequence of progressively severe coronary artery stenoses was then repeated as before. Phenylephrine and adenosine infusions were terminated and conditions allowed to return to baseline, with control measurements again obtained.

*Nitroprusside (0.5 mg/ml) was then infused intravenously* until aortic pressure stabilized at approximately 40% below control values. The predetermined dose of adenosine was infused into the coronary artery until maximal flow at the reduced pressure was obtained while the ECG, coronary flow and aortic pressure were recorded. The sequence of progressive stenoses was again applied while data were recorded and coronary arteriograms performed until complete occlusion. The stenosis was progressively released in steps, again while obtaining data until no stenosis was present. Nitroprusside and adenosine infusions were terminated and conditions allowed to return to baseline. Not all animals tolerated the entire sequence of infusions for the series of stenoses. After each experiment was completed, the animals were killed. Because 30 to 50 stenoses were applied in each dog, arteriograms were obtained only for every 4 or 5 stenoses after flow reserve began to diminish for purposes of confirming the percent area narrowing determined by the mechanical constrictor.

**Data analysis.** After processing of data as described, the following measurements were made. Absolute coronary flow reserve was calculated as maximal flow measured by flow meter during adenosine infusion divided by baseline control flow at rest, with units from 1.0 to 9.0. Relative maximal coronary flow or relative flow reserve was calculated as maximal flow in the stenotic left circumflex artery during adenosine infusion divided by normal maximal flow in the absence of a stenosis; units of relative coronary flow reserve ranged from 1.0 to 0.1 with stenoses (that is, a fraction of normal maximal flow). Percent area narrowing for each stenosis was determined by the machined external arterial constrictor, which provided on-line measurements as previously described (1–3) of increments from a baseline setting with no stenosis to complete occlusion.

*Although we have emphasized the importance of integrated geometric analysis of stenoses* using not only percent narrowing but also length and absolute dimensions (8–12,27–30), those dimensions of length and normal arterial diameter were constant for each progressively severe stenosis in each animal throughout each experiment. Accordingly, for the sake of simplicity, we report progressive percent area narrowing by the mechanical constrictor in relation to varying physiologic conditions. The effects of other dimensions are

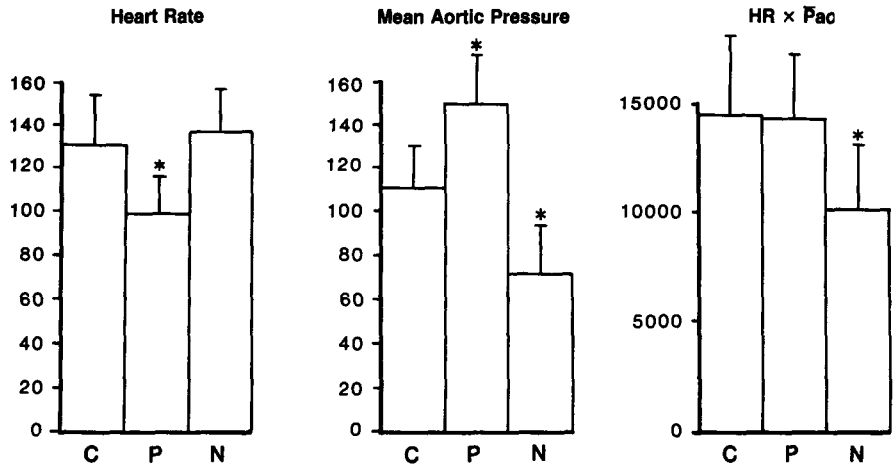



**Figure 1.** Effects of nitroprusside (N) and phenylephrine (P) on aortic pressure, heart rate and aortic pressure (Pao)-heart rate (HR) product. C = control; *p < 0.01. Values are mean ± 2 SD.

described subsequently. Mean values ± SD of grouped data were calculated with standard statistical software (Minitab, Inc.) on an IBM PC.

**Clinical examples.** To demonstrate the potential clinical relevance of these experimental findings, we also report on positron emission tomography of rubidium-82 carried out at rest and after dipyridamole stress (9,11,12) in patients undergoing clinical cardiac evaluation. These examples illustrate the value of absolute and relative coronary flow reserve for quantifying 1) a localized stress perfusion defect, 2) balanced three vessel disease, and 3) reduced flow reserve due to left ventricular hypertrophy with normal coronary arteries. Generator-produced rubidium-82, 40 to 50 mCi, was injected intravenously before and after intravenous dipyridamole (0.142 mg/kg per min over 4 min) followed by a 2 min delay and 2 min handgrip exercise. Images were interpreted without knowledge of the patient's name, clinical data or catheterization results, and analyzed quantitatively as previously described (9,11,12).

## Results

### *Experimental Coronary Flow Measurements*

**Control measurements.** A total of 340 stenoses and 26 recordings without coronary artery narrowing constitute the data set of 366 observations in the 11 dogs. Figure 1 shows mean values ± 1 SD for heart rate, mean aortic pressure and rate-pressure product during the control period and during phenylephrine and nitroprusside infusions. Figure 2 shows mean values ± 1 SD for coronary artery flow at rest, maximal coronary flow during intracoronary adenosine infusion and coronary flow reserve in the absence of stenosis. Mean coronary flow reserve for all values of aortic pressure and rate-pressure product without coronary stenosis was 5.9 ± 2.5 (1 SD), with a range of 2.2 to 12.1 depending on aortic pressure and baseline rate-pressure product.

**Measurements during progressive coronary stenosis.** Figure 3A shows absolute coronary flow reserve in one experiment during control conditions and during phenyleph-

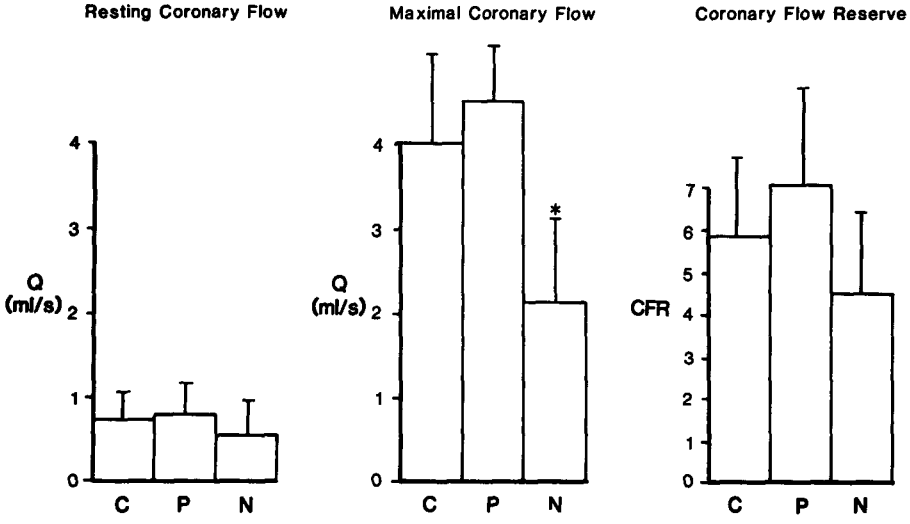



**Figure 2.** Effects of nitroprusside (N) and phenylephrine (P) on rest and maximal coronary flow (Q) and coronary flow reserve (CFR) defined as the ratio of maximal to rest flow. C = control.

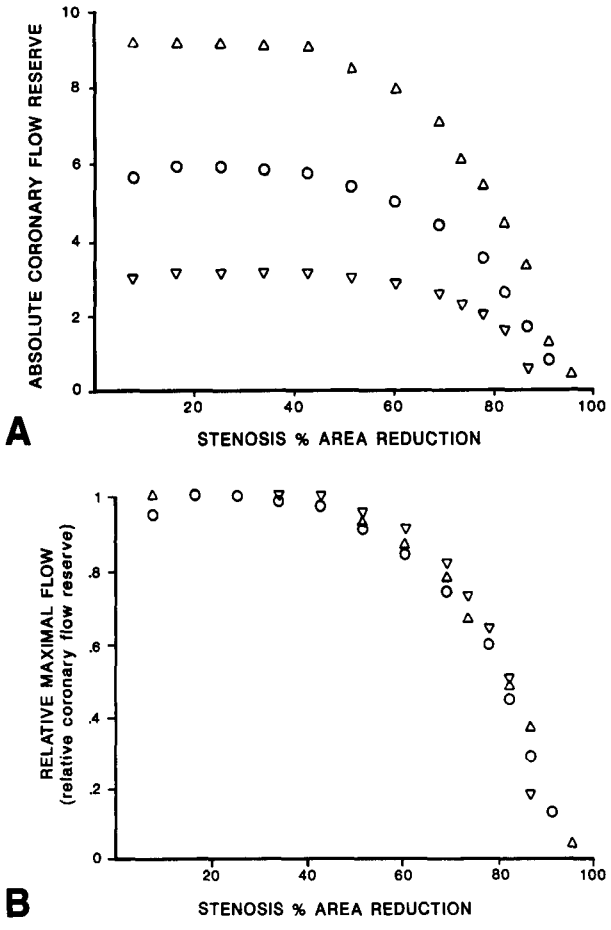



**Figure 3.** **A**, Changes in coronary flow reserve during phenylephrine and nitroprusside infusion during progressive coronary artery stenosis in one experiment. Absolute coronary flow reserve is plotted on the **vertical axis**, defined as maximal flow divided by coronary flow at rest measured by flow meter. Percent area stenosis is plotted on the **horizontal axis**, measured by the arterial constrictor and confirmed by arteriography, with length and normal diameter remaining constant. Absolute coronary flow reserve showed marked variation for any given fixed stenosis depending on aortic pressure. **B**, Relative maximal coronary flow or relative flow reserve, defined as maximal flow in the stenotic artery divided (normalized) by normal maximal flow in the absence of the stenosis, showed little variation over a wide range of aortic pressures. **Upright triangles** = phenylephrine; **inverted triangles** = nitroprusside; **circles** = control.

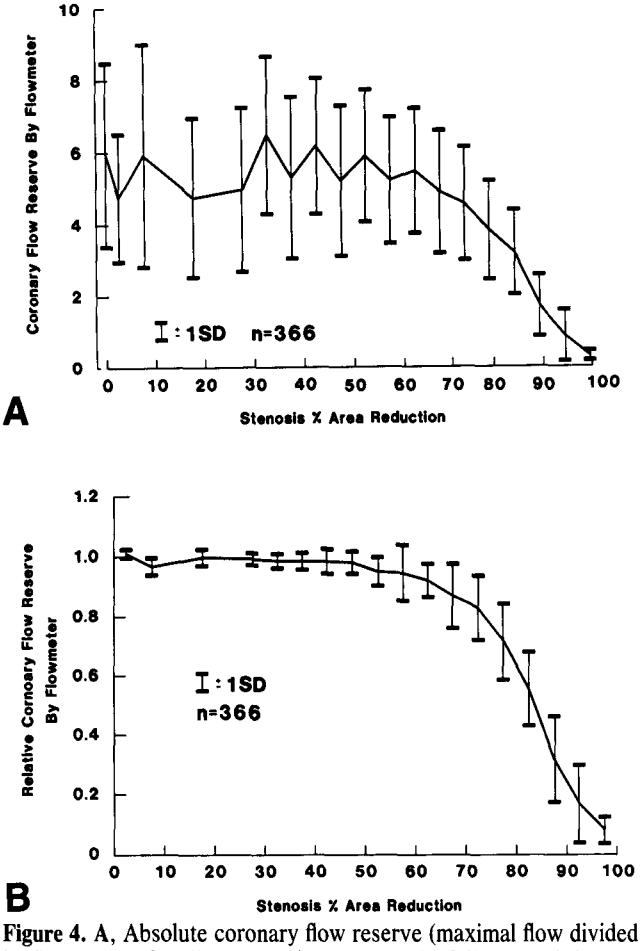



**Figure 4.** **A**, Absolute coronary flow reserve (maximal flow divided by flow at rest) for all 366 experiments over the full range of changes in aortic pressure and stenosis severity. **B**, Relative maximal coronary flow or relative flow reserve (maximal flow in stenotic artery divided by normal maximal flow in absence of stenosis) for all 366 experiments over the range of changes in aortic pressure with progressive coronary artery stenosis.

rine and nitroprusside infusions as the coronary artery was progressively narrowed, with length and normal arterial diameter being constant. Absolute coronary flow reserve for a given stenosis ranged from low to high values depending on aortic pressure and rate-pressure product. For example, for a 65% area narrowing, absolute coronary flow reserve during control conditions was approximately 5.0. For the same stenosis, absolute coronary flow reserve during phenylephrine infusion was approximately 8.0 and during nitroprusside infusion it was 3.0. Thus, for a given fixed stenosis of 65% area narrowing and constant length and absolute dimensions, absolute coronary flow reserve ranged from 3.0 to 8.0 depending on aortic pressure and heart rate. However, relative maximal flow or relative flow reserve was independent of aortic pressure and heart rate (Figure 3B). Relative coronary flow reserve was approximately 0.90 for the 65% stenosis regardless of physiologic conditions.

*For all stenoses with 65% area narrowing*, absolute coronary flow reserve averaged 5.2 ± 1.7 (1 SD), a ±33% variation over the range of aortic pressures and rate-pressure products. By comparison, for the same 65% area stenoses, relative flow reserve averaged 0.90 ± 0.09, a variation of only ±10% over the same range of physiologic variables.

*Figure 4A shows absolute coronary flow reserve measured by flow meter from all experiments for all stenoses under all conditions.* Standard deviations are large, indicating great variability of absolute coronary flow reserve by flow meter for any given geometrically fixed stenosis. Figure 4B shows corresponding values of relative coronary flow reserve, defined as maximal flow in the stenotic artery divided by normal maximal flow in the absence of a stenosis.

**Table 1.** Variability of Absolute Coronary Flow Reserve*

| % Area Stenosis† | No. of Stenoses | Absolute Coronary Flow Reserve | | |
|---|---|---|---|---|
| | | Mean | 1 SD | 1 SD as % of Mean |
| 0 | 26 | 5.94 | 2.54 | 43% |
| 5 | 5 | 5.45 | 2.44 | 45% |
| 15 | 9 | 4.62 | 2.11 | 45% |
| 25 | 6 | 4.97 | 2.27 | 46% |
| 35 | 41 | 6.16 | 2.24 | 36% |
| 45 | 44 | 5.89 | 1.97 | 33% |
| 55 | 39 | 5.57 | 1.80 | 32% |
| 65 | 43 | 5.18 | 1.72 | 33% |
| 75 | 56 | 4.17 | 1.50 | 36% |
| 85 | 68 | 2.34 | 1.24 | 53% |
| 95 | 29 | 0.72 | 0.67 | 93% |
| Mean | — | — | — | 45% |

*Maximal coronary flow/coronary flow at rest. †% area stenosis indicates the center of a range of 10% diameter narrowing from 0 to 100%.

**Table 2.** Variability of Relative Maximal Coronary Flow or Relative Coronary Flow Reserve*

| % Area Stenosis | No. of Stenoses | Relative Maximal Flow | | |
|---|---|---|---|---|
| | | Mean | 1 SD | 1 SD as % of Mean |
| 0 | 26 | — | — | — |
| 5 | 5 | 0.99 | 0.032 | 3% |
| 15 | 9 | 1.00 | 0.025 | 3% |
| 25 | 6 | 0.99 | 0.020 | 2% |
| 35 | 41 | 0.99 | 0.024 | 2% |
| 45 | 44 | 0.98 | 0.039 | 4% |
| 55 | 39 | 0.95 | 0.072 | 8% |
| 65 | 43 | 0.90 | 0.089 | 10% |
| 75 | 56 | 0.77 | 0.132 | 17% |
| 85 | 68 | 0.42 | 0.180 | 43% |
| 95 | 29 | 0.14 | 0.119 | 83% |
| Mean | — | — | — | 17.5% |

*Maximal flow stenotic artery/normal maximal flow with no stenosis. Abbreviations as in Table 1.

The standard deviations of relative flow reserve show much less variability during marked changes in aortic pressure and rate-pressure product.

**Variability of absolute versus relative coronary flow reserve.** Table 1 shows the systematic variability in absolute coronary flow reserve over the range of aortic pressures and rate-pressure products for all stenoses from mild to severe narrowing. One standard deviation ranged from 2.5 for no coronary narrowing to 0.7 for the more severe narrowings. As a more standardized measure of variability, 1 SD was expressed as a percent of the mean absolute coronary flow reserve for each category of stenosis severity. The size of 1 SD as percent of mean absolute coronary flow reserve for each stenosis severity ranged from ±32% to ±93%, with a mean of ±45% for all stenoses. In other words, a single measurement of coronary flow reserve, on average, varied by ±45% for fixed stenosis geometry depending on aortic pressure and rate-pressure product. In contrast, Table 2 shows corresponding variability in relative maximal coronary flow or relative flow reserve over the same range of aortic pressures and rate-pressure products for these same stenoses. The standard deviations are markedly lower, averaging ±17.5% of mean relative flow reserve values for each stenosis category of severity compared with ±45% for absolute coronary flow reserve.

*In the intermediate range of severity, from 15% to 75% area stenosis, where quantitation of severity is most important clinically*, the variability of relative flow reserve ranged from ±2% to ±17%, with a mean of ±6.6%, compared with ±32% to ±46%, with a mean of ±37% for absolute coronary flow reserve. For severe stenoses of ≥85% area stenosis, the variability of both absolute and relative coronary flow reserve for fixed stenoses is fairly large because maximal flows are so markedly reduced that small variations of flow meter measurements during baseline conditions at rest cause large changes in the denominator of the flow reserve ratio or relative maximal flow ratio. However, these values of flow reserve are so low that this variability does not interfere with the diagnostic indication of severe stenosis.

## *Clinical Coronary Flow Reserve Measurements*

**Patients with mild "balanced" three vessel disease (Fig. 5).** To illustrate the application of assessing both absolute and relative coronary flow reserve clinically, Figure 5 illustrates an example of a positron emission tomographic study at rest and after dipyridamole stress using generator-produced rubidium-82 and showing mild "balanced" three vessel disease. The rest study (S1) (upper left polar map) is normal. Because it was obtained after infusion of dipyridamole, the stress study (S2) (lower left polar map) reflects regional relative coronary flow reserve on the same scale of 0 to 100% and is abnormal. Every quadrant in the stress study shows a decrease in relative minimal intensity from 81% to 70% of normal in the anterior (A) quadrant, from 73% to 65% of normal intensity in the septal (S) quadrant, from 68% to 50% of normal intensity in the apex (X) and from 74% to 67% of normal intensity in the inferior quadrant, with the high lateral quadrant showing no relative defects (that is, from 67% to 66%).

*However, how does one know that the high lateral myocardium is a normal reference area?* The upper right polar map (Fig. 5) labeled ABS S2/S1 shows the absolute activity in the stress study (S2) divided by the absolute activity in the rest study (S1) expressed as absolute coronary flow reserve using a model accounting for radionuclide extraction, dose and cardiac output changes. In this in-

**Figure 5.** Positron emission tomograms of generator-produced rubidium-82 in horizontal (**upper left**) and vertical (**upper right**) long-axis views of the heart of a patient with moderate "balanced" three vessel coronary artery disease. In the **top half** of the figure, rest images are shown in the **top row** and dipyridamole stress images in the **lower row**. In the color coding, **white** is the highest level of flow, **red** is next highest, **yellow** is intermediate and **green** and **blue** are lowest. Horizontal long-axis tomograms (**upper left**) are oriented as if looking down from above, with the anterior wall or apex at the top of each image, the left lateral free wall on the left (LAT) and the muscular septum (SEP) on the right, with the atrioventricular (AV) ring or inferior myocardium, or both, at the bottom. The vertical long-axis tomograms (**upper right**) are oriented as if looking at the left side of the body cut head to toe. Anterior myocardium is at the top, inferior at the bottom, apex at the left and the AV ring on the right.

In the **lower half** of the figure, tomographic data are summarized in a polar display as if looking up from below at the apex of the left ventricle located in the center of the bull's-eye, where the outer rim of the bull's-eye corresponds to the AV ring. Polar displays on the left (**lower half** of figure) show the relative activity on a scale from 0 to 100%, with rest being the **upper** (scaled study 1) and stress the **lower** (scaled study 2) of the polar maps on the **left** of the panel. The polar map on the **right** (absolute S1/S2 ratio) shows the absolute counts of the stress image divided by the rest image displayed on a scale from 0 to 2 and the corresponding absolute coronary flow reserve (CFR). An increase in activity is shown by **warm colors**, indicating ratios >1 or an increase in absolute activity reflecting increased perfusion due to dipyridamole. The **lower right** polar display (relative S2/S1 ratio) shows the relative distribution of flow at rest divided by the relative distribution on the stress image (instead of absolute values) on a scale of 0 to 2. It therefore maps the relative change in activity from rest to stress.

Letters and numbers beside each polar map show quantitative results. For regions of the heart, A = anterior; I = inferior; L = lateral; S = septal; W = whole heart; X = apex. The numbers beside each region indicate the minimal activity as a percent of normal areas (100%).

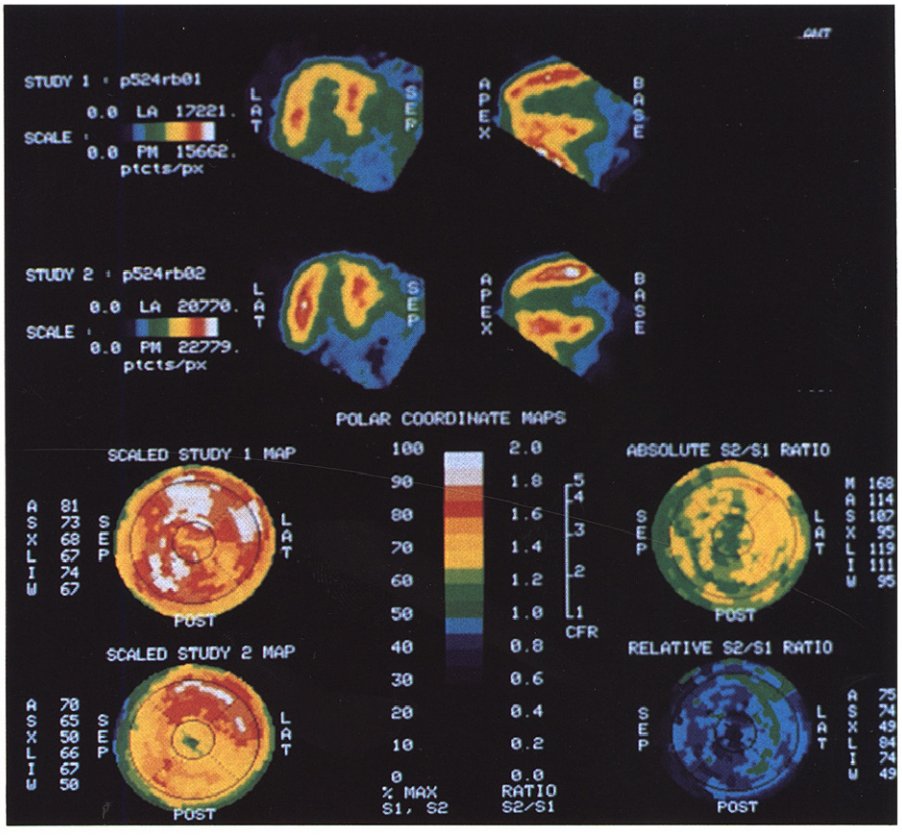
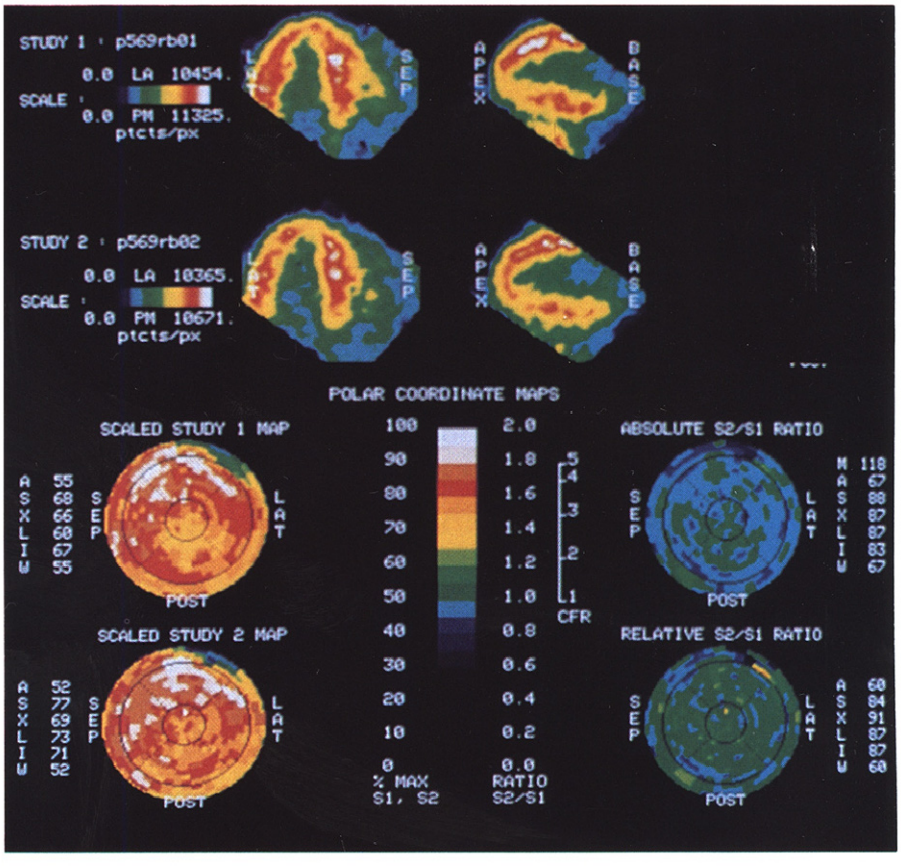



**Figure 6.** Positron emission tomograms from a patient with diffuse reduction of coronary flow reserve associated with left ventricular hypertrophy due to hypertension. Display as in Figure 5.



stance, the maximal regional coronary flow reserve located in the anterolateral area of the heart in response to dipyridamole was 4.0 (times rest levels), indicating that this patient responded well to dipyridamole in a small artery to the high anterior lateral myocardium. Because flow reserve was reduced to every quadrant of the heart except to this high anterior lateral area, the tomographic scan was interpreted without knowledge of clinical data or arteriograms as showing mild to moderate "balanced" three vessel disease. Thus, despite balanced three vessel disease affecting all major arteries of the heart, at least some part of the myocardium responded well to this vasodilatory stimulus as a normal reference area. Coronary arteriography confirmed 50% to 60% diameter narrowing of the three major coronary arteries, thereby allowing medical management and cholesterol-lowering therapy.

**Patient with left ventricular hypertrophy (Fig. 6).** The upper right polar map (ABS S2/S1) shows that the maximal coronary flow reserve in the heart at stress was only 1.18, indicating a diffuse moderately reduced response to dipyridamole, with no abnormality of relative coronary flow reserve in the lower left polar map (S2). The long-axis views show an enlarged hypertrophied heart. This pattern suggests diffuse nonatherosclerotic reduction in flow reserve associated with left ventricular hypertrophy. The coronary arteriograms of this patient were normal, with the echocardiogram and left ventriculogram also showing left ventricular hypertrophy and confirming this conclusion.

*Thus, for assessing diffuse impairment of flow capacity,* absolute coronary flow reserve is essential despite its potential dependence on physiologic variables. These examples illustrate the potential clinical differences and complementary value of both absolute and relative coronary artery flow reserve as systematically shown by our experimental data.

## Discussion

**Absolute versus relative coronary flow reserve.** Rather than considering absolute coronary flow reserve to be competitive or antithetical to relative flow reserve, our data indicate that these measurements are independent variables providing complementary information. Absolute flow reserve reflects the flow capacity of the entire coronary vascular bed under whatever conditions of pressure, work load, hypertrophy, vasomotor tone or stenoses are present. It reflects the cumulative summed effects of these various factors without being specific for the mechanism or cause of altered flow reserve. Relative coronary flow reserve reflects more specifically the effects of the stenosis independent of and not affected by the other physiologic variables if normal maximal flow is high enough. Thus, absolute and relative coronary flow reserve are complementary.

"Balanced" three vessel coronary artery disease may theoretically cause a false negative stress perfusion test depending on the stress stimulus and the imaging technology, particularly its spatial and contrast resolution. In most hearts affected by coronary artery disease, there is some area supplied by even a small artery that is unaffected and that serves as a reference area based on our experience with positron emission tomography. However, small vessel disease, left ventricular hypertrophy or theoretically "balanced" three vessel coronary artery disease are potential causes of diffusely impaired flow reserve that must be accounted for in individual patients. For this purpose, some measure of absolute as well as relative coronary flow reserve is necessary. Relative flow reserve more accurately defines physiologic stenosis severity because it is not affected by variability in pressure or heart rate within the same patient or among patients.

Although maximal coronary flow has been related to perfusion pressure (23,24), the effects of varying aortic pressure and cardiac work load on the ratio of maximal to rest flow (flow reserve) in the presence of stenoses has not been previously described despite controversy about the expected effects (25,26). This study shows that maximal and rest flows may change in different directions or to different degrees, in the same direction, or both, with different alterations in pressure and work load. Consequently, absolute coronary flow reserve may change significantly as a result of physiologic conditions despite fixed stenosis geometry, whereas relative flow reserve shows much less variability.

*The explanation for relative coronary flow reserve being independent of aortic pressure and cardiac work load is provided by the following readily derived simple equations relating flow reserve to pressure and distal bed resistance:*

$$Qr,s = (Pa - \Delta Pr)/Rr = \text{flow in stenotic artery at rest}$$

$$Qm,s = (Pa - \Delta Pm)/Rm = \text{maximal flow in stenotic artery}$$

$$Qm,n = Pa/Rm = \text{maximal flow in normal artery}$$

where Pa = aortic pressure, ΔPr = pressure decrease across the stenosis at resting flow, ΔPm = pressure decrease across the stenosis at maximal flow, Rr = distal vascular bed resistance at rest, and Rm = minimal distal vascular bed resistance at maximal flow. By dividing and rearranging:

$$\text{Absolute CFR} = \frac{Qm,s}{Qr,s} = \frac{Pa - \Delta Pm}{Pa - \Delta Pr} \times \frac{Rr}{Rm} \qquad \text{(equation 1)}$$

$$\text{Relative CFR} = \frac{Qm,s}{Qm,n} = \frac{Pa - \Delta Pm}{Pa} \times \frac{Rm}{Rm} \qquad \text{(equation 2)}$$

$$= 1 - \frac{\Delta Pm}{Pa}$$

Equation 1 for absolute coronary flow reserve (CFR) contains two terms. The first is related to pressure and pressure

decrease across the stenosis at rest and at maximal flow; the second term is related to distal coronary vascular bed resistance at rest and maximal flow and is, therefore, dependent on the state of the distal bed. However, equation 2 for relative coronary flow reserve has only one term that is related to pressure and pressure decrease across the stenosis. The resistance terms for the distal coronary vascular bed cancel out. These equations explain why absolute flow reserve is altered by characteristics of the distal coronary vascular bed independent of and in addition to stenosis severity. Relative coronary flow reserve is altered only by stenosis severity.

**Limitations and comparison of absolute and relative coronary flow reserve in clinical application.** Although the experimental methods of this study are well established with unequivocal results, the limitations of the study are related to their clinical applications. There is some controversy (10,25,26,30–33) about the usefulness of coronary flow reserve for assessing stenosis severity, some of which may be related to methodologic differences. However, as this study suggests, some of those differences may be due in part to determining absolute coronary flow reserve under different conditions or considering relative versus absolute flow reserve without specifying which one was measured under what conditions.

Awake humans with intact vasomotor reflexes may not show as great changes in coronary flow reserve with altered pressure and heart rate as those observed in open chest anesthetized animals. Nevertheless, for whatever variations there are in aortic pressure and heart rate, relative coronary flow reserve reflects physiologic stenosis severity despite large variation in absolute flow reserve from whatever cause provided that normal maximal flow is reached in some part of the heart as a normal reference area. The conditions under which absolute and relative coronary flow reserve might fail to reflect stenosis severity would be failure of normal arteries to respond to a vasodilatory stimulus (34), or diffuse global impairment of flow reserve due to small vessel disease (35), and adrenergic coronary vasoconstriction (36), for which absolute flow reserve is necessary.

*Absolute coronary flow reserve may also be reduced because of increased flow at rest with no change in maximal flow capacity in left ventricular hypertrophy* both experimentally (37–39) and clinically (40–43). In this instance, relative flow reserve is normal in the absence of stenosis (37,39,43) and is abnormal in the presence of a stenosis. However, in advanced severe hypertrophy due to hypertension or cardiomyopathy, maximal flow may be reduced globally in nonstenotic coronary arteries (38,40,41). Small vessel disease also reduces maximal flow in the absence of stenosis (37,44,45). Consequently, absolute coronary flow reserve in these conditions is impaired, but relative flow reserve is normal. Although theoretically possible, balanced three vessel or diffuse coronary artery disease (45) would require hemodynamically equal right ostial and left main coronary artery disease that impaired flow reserve to the same extent. Because flow reserve depends on percent narrowing, absolute luminal radius raised to the fourth power, length and shape, exactly balanced lesions would be unlikely and have not been seen in our experience. In that instance, absolute flow reserve would be reduced, whereas relative flow reserve would be normal.

**Clinical implications.** A stress myocardial perfusion image shows relative maximal perfusion (radiotracer uptake) or relative coronary flow reserve. One of the limitations of radionuclide perfusion imaging is considered to be its inability to measure absolute coronary flow and absolute coronary flow reserve. However, despite this purported limitation, perfusion imaging of relative maximal coronary flow or relative coronary flow reserve has been useful for assessing physiologic stenosis severity despite greatly changing or widely variant physiologic conditions seen during upright treadmill exercise, bicycle stress, supine exercise or various pharmacologic stresses such as dipyridamole and papaverine. The results of our study explain this observation. The stress perfusion image shows relative coronary flow reserve, which is independent of physiologic variables. What has long been considered the limitation of stress perfusion techniques is, in fact, its greatest advantage.

Although direct measures of absolute coronary flow reserve by invasive techniques have provided important research data, they have been of limited diagnostic benefit for assessing stenosis severity in individual patients. The poor correlation between coronary flow reserve and percent narrowing has been ascribed in part to the inadequacy of percent narrowing as a measure of severity (17–22,30–32). However, there is considerable variability in expected coronary flow reserve even when all other dimensions such as integrated length and absolute dimensions as well as percent narrowing are accounted for (8,27,28). Such variability in directly measured coronary flow reserve for stenoses appears to be out of proportion to their anatomic severity (10,17–22) despite potential limitations in the arteriographic analysis of anatomic stenosis severity in some studies (30,31). This variability has been directly examined in a recent clinical study (32) as an unresolved problem (33). The relatively poor correlation between absolute coronary flow reserve and the anatomic severity of stenosis has been reported from so many different laboratories utilizing several different methods (such as thermodilution, Doppler-tip catheters and transit time measurements) that physiologic differences not previously recognized or accounted for might be playing a role.

To be optimally effective over the wide range of conditions seen clinically, a method for assessing physiologic stenosis severity should be able to provide measures of both relative and absolute coronary flow reserve. For example, measurement of absolute flow reserve in a coronary artery

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by a Doppler-tip catheter gives the flow response to dipyridamole or papaverine or the effects of diffuse coronary artery disease. However, it may change as a result of varying afterload and baseline rate-pressure product or because of physiologic differences among patients that affect coronary flow reserve separate from stenosis geometry. On the other hand, relative coronary flow reserve as assessed by current standard thallium perfusion imaging does not adequately reflect the absolute coronary flow response to vasodilatory stimuli or diffuse processes affecting all areas of the heart. Most invasive or noninvasive clinical methods as now used provide measurements of either absolute or relative coronary flow reserve, but not both (10,12,46,47).

*The optimal noninvasive method* would utilize relative coronary flow reserve to assess physiologic stenosis severity *and* absolute coronary flow reserve to assess response to dipyridamole, small vessel disease, left ventricular hypertrophy and "balanced" three vessel disease. Positron emission tomography as illustrated in Figures 5 and 6 demonstrates the concepts. Further clinical investigation in patients will be necessary to establish the importance of this approach for clinical use, documented here conceptually in an animal model.

**Conclusions.** Our experimental data demonstrate that absolute and relative coronary flow reserve are independent complementary variables that, together, more completely describe physiologic severity of coronary artery narrowing that either one alone. These results have important implications for assessing physiologic stenosis severity noninvasively by perfusion imaging as described here and by invasive methods using quantitative coronary arteriography as described in Part II of this report.

# Part II: Determination From Arteriographic Stenosis Dimensions Under Standardized Conditions

As just shown, coronary flow reserve reflects physiologic stenosis severity, but is altered by several physiologic factors unrelated to stenosis severity. Because coronary flow reserve is defined as maximal flow divided (normalized) by baseline flow at rest, any conditions that alter either maximal or rest flow may also change flow reserve unrelated to stenosis severity (25,26). Accordingly, a change in flow reserve could reflect a change or difference in aortic pressure or work load, rather than a change or difference in stenosis severity.

Utilizing standard orthogonal, calibrated, coronary arteriograms, we previously proposed (27–30) an anatomic-geometric method for determining coronary stenosis severity in terms of pressure-flow characteristics, or what we have termed stenosis flow reserve, derived from integrated arteriographic stenosis dimensions of length, absolute dimensions and percent narrowing. The problem of changing physiologic variables was obviated by assuming "standardized" theoretical values for aortic pressure and normal maximal flow in the absence of coronary artery stenosis (8–12). These assumed or standardized values were used in the equations for determining coronary stenosis flow reserve from geometric dimensions alone. Accordingly, there can be no variability in stenosis flow reserve as a result of extraneous physiologic variables unrelated to stenosis severity. However, stenosis flow reserve determined by quantitative analysis of stenosis dimensions might not equal directly measured coronary artery flow reserve in a given patient at a specific time because the physiologic variables for the patient might not be the same as those arbitrarily assumed for the "standardized" geometric analysis. On the other hand, stenosis flow reserve based on anatomic geometry using standardized values of aortic pressure and normal flow reserve should theoretically reflect anatomic severity with sufficient precision to make interventional decisions or to compare stenosis severity between patients or in the same patient at different times because it should theoretically be independent of varying or different physiologic conditions.

*Based on this brief overview, the following are the central questions for assessing physiologic stenosis severity by invasive methods:* 1) Is accurate direct measurement of absolute coronary flow reserve, as by flow meter, Doppler-tip catheter or microspheres, the optimal, accurate measure of physiologic stenosis severity? Should we, therefore, focus on better methods to measure directly absolute coronary flow or absolute flow reserve? Or, 2) is stenosis flow reserve derived from all stenosis dimensions on arteriograms with assumed "standardized" aortic pressure and normal maximal flow reserve the optimal, accurate and consistent measure of physiologic stenosis severity needed clinically?

## Methods

**Experimental preparation.** In 11 open chest dogs, 366 stenoses were studied. Surgical preparation, instrumentation, physiologic measurements, experimental protocol and physiologic data analysis are described in Part I of this report, with clinical implications for noninvasive perfusion imaging. The basis for Part II of this report is quantitative coronary arteriography carried out during the same experiments, but reported here as a separate study involving different concepts, theoretical basis, methodology, results,

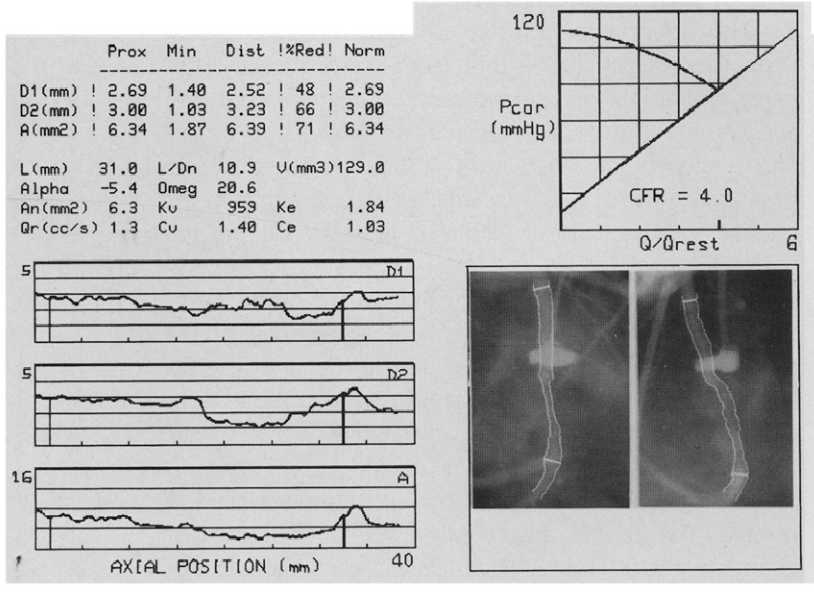


**Figure 7.** Quantitative coronary arteriographic analysis of a coronary artery stenosis, taking into account relative percent narrowing, absolute cross-sectional luminal area and integrated length effects to derive coronary stenosis flow reserve (CFR) for standard physiologic conditions of 110 mm Hg aortic pressure and a normal maximal flow reserve of 6.0 for these experimental animals. **Upper left**, Orthogonal single plane diameters ($D_1$, $D_2$) and cross-sectional luminal area (A) by both biplane border recognition and densitometry for proximal (Prox), minimal (Min), distal (Dist) and normal (Norm) coronary segments with percent reduction (% Red). An = normal cross-sectional area; Qr = rest flow; Kv and Cv are coefficients related to viscous losses dependent on geometry of the stenosis; Ke and Ce are coefficients of momentum losses dependent on entrance and exit geometry of the stenosis; V is intraluminal volume in the stenotic segment; L = length; L/Dn = length/diameter ratio. **Lower left**, Diameters in two orthogonal views ($D_1$, $D_2$) and cross-sectional luminal area (A) plotted as a function of lesion length (L) along the artery (axial position). **Upper right**, Distal coronary perfusion pressure (Pcor) on **vertical axis** and coronary flow (Q) as a ratio to normal flow at rest (Qrest) on **horizontal axis**. Calculated coronary flow reserve (CFR) was 4.0 compared with a normal value of 6.0 (see text). **Lower right**, Orthogonal arteriographic views of canine stenotic coronary artery with automatically defined borders. The radiopaque object is the flow meter around the artery.

limitations and clinical implications related to invasive approaches for assessing functional severity of coronary artery stenoses.

**Quantitative coronary arteriography.** Orthogonal biplane coronary arteriograms were made at end-diastole on cut film, with alternating exposures electronically sequenced from a single 2 to 3 ml injection of radiopaque contrast medium (Renografin-76) into the coronary artery from a Viamonte-Hobbs programmable power injector triggered from the electrocardiogram (ECG). X-ray films were obtained with a Machlett 62 U X-ray tube having a 0.6 mm focal spot, a 12% target angle and a 26 to 32 in. (66 to 81 cm) tube to film distance. Exposures were at 20 to 32 ms, 350 mA and 75 to 85 kV using Konica AOG X-ray film and X-O-Matic cassettes with either Dupont Ultra Detail screens or Konica KF Rare Earth screens. The cut films have a resolution of 8 to 10 line pairs/mm. Because of the limited load of arteriographic contrast medium tolerated by the experimental preparation, 52 of the 366 stenoses were studied by arteriography.

*The arterial borders of each stenosis were automatically defined* using simultaneous border recognition and densitometry techniques previously described and validated (8–12,27–30) to be reproducible to within ±2% to 3% in vivo in animals and accurate in phantoms in scattering media to ±0.1 mm for absolute dimensions. Dimensions of absolute cross-sectional luminal area, percent narrowing, integrated length effects and shape were determined, from which stenosis flow reserve was calculated as previously described. Mean and standard deviations of grouped data were calculated with standard statistical software (Minitab, Inc.) on an IBM PC.

## Results

**Arteriographic quantitative coronary flow reserve analysis.** Figure 7 illustrates the printout from the automatic quantitative coronary arteriographic analysis utilizing simultaneous border recognition and densitometry calibrated for absolute dimensions of the coronary segments by border recognition of orthogonal arteriographic views. Dimensions and cross-sectional luminal area of the proximal, minimum, distal and normal segments and percent reduction were measured and plotted as a function of length along the artery in the lower left side of Figure 7. Coronary stenosis flow reserve was calculated at standardized conditions of aortic pressure and expected normal flow reserve in the absence of the stenosis. Because mean control aortic pressure was 110 mm Hg in these animal experiments, the standardized aortic pressure was set at 110 mm Hg for all arteriographic determinations of stenosis flow reserve regardless of the actual aortic pressure, which varied over a wide range. Because the normal coronary flow reserve in the control group in the

absence of a stenosis was 6.0, this value was used as the normal reference for all arteriographic determinations of stenosis flow reserve based on stenosis dimensions.

Distal coronary perfusion pressure was calculated from stenosis dimensions (upper right side of Fig. 7) against coronary artery flow expressed as a ratio to normal flow at rest. The straight line in this graph shows the observed experimental relation between coronary perfusion pressure and coronary flow under conditions of maximal coronary vasodilation in the absence of a stenosis, as previously described (8–12). The downward curved line is a plot of the relation between coronary perfusion pressure and flow derived by stenosis geometry. Arteriographic stenosis coronary flow reserve is given by the intersection of the downward curving line characterizing stenosis severity, with the straight upward slanted line characterizing the flow reserve-coronary pressure relation in the absence of a stenosis. In this case, arteriographic stenosis coronary flow reserve was 4.0 compared with a normal value of 6.0.

**Arteriographic versus direct flow meter measurement of coronary flow reserve.** Figure 8A shows directly measured coronary flow reserve by flow meter in one experiment at 148 and 93 mm Hg as the coronary artery was progressively narrowed. Flow meter-measured coronary flow reserve for any given stenosis ranged from low to high values depending on aortic pressure and heart rate-blood pressure (rate-pressure) product. For example, for a 68% area narrowing, directly measured coronary flow reserve by flow meter at 148 mm Hg was 5.8, whereas at 93 mm Hg it was approximately 3.8. Thus, for a given fixed stenosis of 68% area narrowing, constant length and normal proximal and distal diameter, directly measured coronary flow reserve by flow meter ranged from 3.8 to 5.8 depending on afterload. Therefore, directly measured flow reserve did not specifically define functional stenosis severity.

*Figure 8 also exhibits values of arteriographic stenosis flow reserve derived from arteriographic stenosis dimensions* using a fixed standardized aortic pressure of 110 mm Hg and a fixed maximal normal flow reserve of six times baseline values for all analyzed stenoses, regardless of the actual aortic pressure or normal maximal flow reserve. The arteriographically derived values for stenosis flow reserve correspond closely to those directly measured by flow meter at the higher pressure. This equivalency of arteriographic stenosis flow reserve and directly measured coronary flow reserve by flow meter illustrates the accuracy of the arteriographic method in an example where the physiologic and "standardized" conditions were comparable.

*Figure 8B illustrates that for the 68% area stenosis,* relative maximal flow or relative flow reserve by flow meter is 0.9 (90%) of normal maximal flow reserve regardless of afterload conditions. The relative flow reserve can also be derived from the arteriographic dimensions and expressed as a fraction of the normal "standardized" value of 6 by

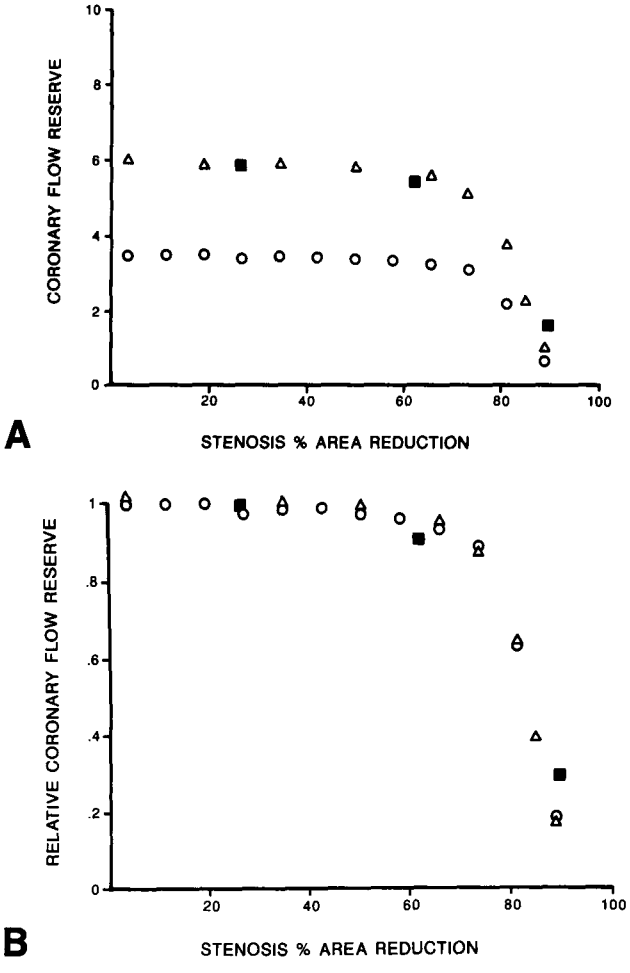


**Figure 8. A,** Changes in coronary flow reserve at high and low aortic pressure as a function of percent area narrowing. The **triangles** are directly measured coronary flow reserve by flow meter at an aortic pressure of 148 mm Hg and the **open circles** are measurements at 93 mm Hg during progressively severe coronary stenosis. **B,** Directly measured relative maximal flow or relative coronary flow reserve by flow meter at the two different aortic pressures. The **vertical axis** shows relative flow reserve in the stenotic artery with progressive coronary stenosis as a fraction of normal maximal flow as measured by flow meter. **Solid squares** indicate arteriographically determined relative stenosis flow reserve (QCA) based on geometric dimensions.

dividing arteriographic stenosis flow reserve by 6 for each stenosis. When arteriographically determined values for relative stenosis flow reserve are plotted against values of relative flow reserve by flow meter for progressively severe stenosis, there is close correspondence of the values measured by both methods.

*Figure 9 shows the arteriographic stenosis flow reserve for progressively severe stenoses with bars indicating ±1 SD for all experiments.* In Figure 9A, the size of the standard deviations for arteriographic stenosis flow reserve is much smaller than for direct flow meter measurements over the range of pressure and rate-pressure products observed. Therefore, arteriographic measurements using standardized

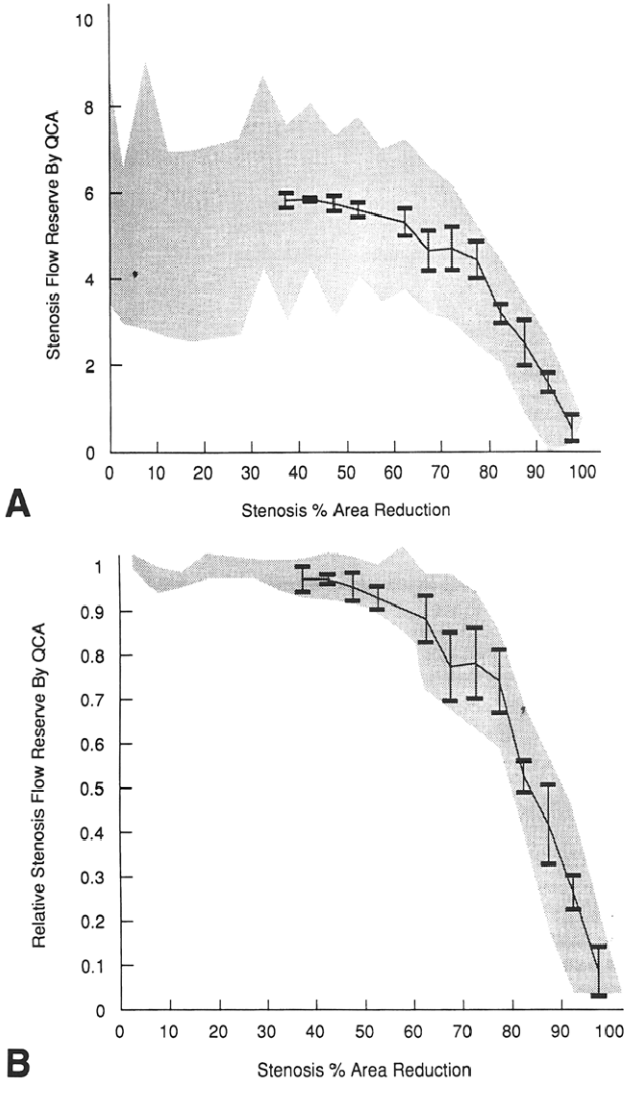


**Figure 9. A,** Arteriographic stenosis flow reserve (maximal flow/resting flow) by quantitative coronary arteriography (QCA) (**vertical axis**) derived from all geometric dimensions of percent narrowing, absolute cross-sectional luminal area and integrated length effects for those categories of progressively severe coronary stenoses shown in previous figures (**horizontal axis**). The error bars indicate ±1 SD for 52 arteriograms. The **shaded area** indicates 1 SD limits for flow meter-measured absolute and relative coronary flow reserve shown in Part I of this report. **B,** Arteriographically determined relative stenosis flow reserve by quantitative coronary arteriography (QCA) as a function of progressive stenosis severity. Display as in **A.**

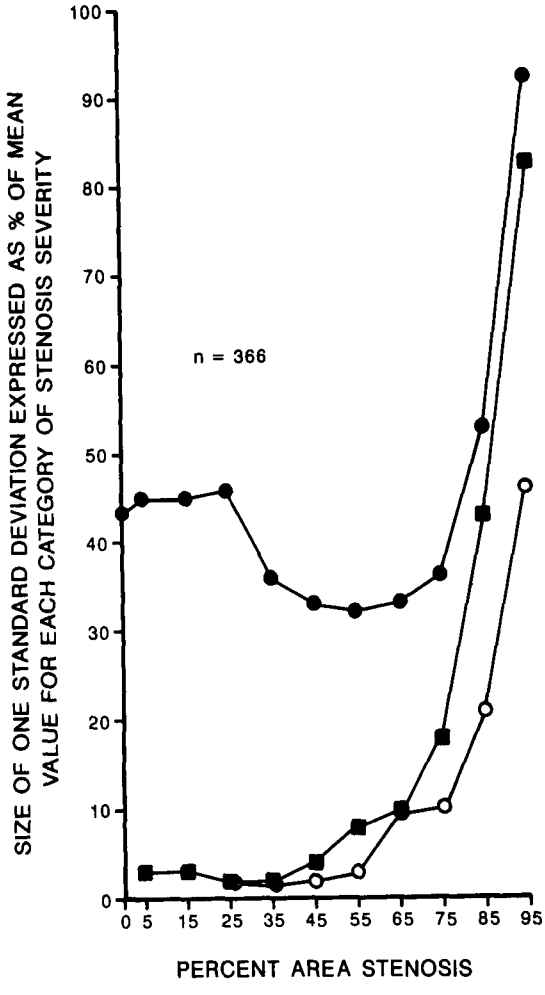


**Figure 10.** Size of 1 SD expressed as a percent of the mean value of each category of stenosis severity for directly measured absolute coronary flow reserve by flow meter (**filled circles**), for relative maximal flow reserve by flow meter (**filled squares**) and for arteriographic stenosis flow reserve and relative stenosis flow reserve by quantitative coronary arteriography (**open circles**).

conditions are more specific measures of stenosis severity than directly measured flow reserve values by flow meter under changing physiologic conditions. In Figure 9B, arteriographic relative stenosis flow reserve correlates closely with relative flow reserve by flow meter; both show little scatter, thereby indicating 1) the accuracy of arteriographic analysis for assessing physiologic severity of stenoses over a wide range of physiologic conditions, and 2) the validity and importance of "normalizing" for different physiologic conditions either by relative flow reserve using flow meters or by standardized conditions using quantitative arteriography.

**Comparison of coronary flow reserve measurements over entire range of stenosis severity under different physiologic conditions.** Figure 10 shows the relative size of 1 SD expressed as a percent of the mean value of coronary flow reserve at each category of stenosis severity for absolute coronary flow reserve measured by flow meter and quantitative arteriography over the entire range of stenosis severity and changing aortic pressures and rate-pressure products. Figure 10 demonstrates that the variability in apparent stenosis severity based on flow meter-measured coronary flow reserve at different aortic pressures is eliminated by arteriographic stenosis flow reserve using "standardized" physiologic conditions or by flow meter-determined relative flow reserve. In very severe stenoses, the percent errors for

all measurements of flow reserve are large as a result of measured values so small that the noise inherent in the measurements causes a large percent error. However, for such severe stenoses, flow reserve measurements are so low that these percent errors are of no clinical consequences because they indicate very severe stenoses.

*As a result of the large variation in directly measured coronary flow reserve by flow meter at different aortic pressures and rate-pressure products*, it is not possible to correlate the individual directly measured values of coronary flow reserve to arteriographic stenosis flow reserve. However, in Figure 11A, it is evident that arteriographic stenosis flow reserve derived from all geometric dimensions of percent narrowing, absolute cross-sectional luminal area and integrated length correlate with directly measured coronary flow reserve by flow meter. The size of the standard deviations for the arteriographic measurements is much smaller than for directly measured absolute flow reserve by flow meter over the range of aortic pressures. The correlation between relative flow reserve by flow meter and arteriographic relative stenosis flow reserve based on arteriographic geometry (Fig. 11B) is also good. The size of 1 SD is comparable for the flow meter and arteriographic measurements because the effects of changing aortic pressure and rate-pressure product have been normalized out.

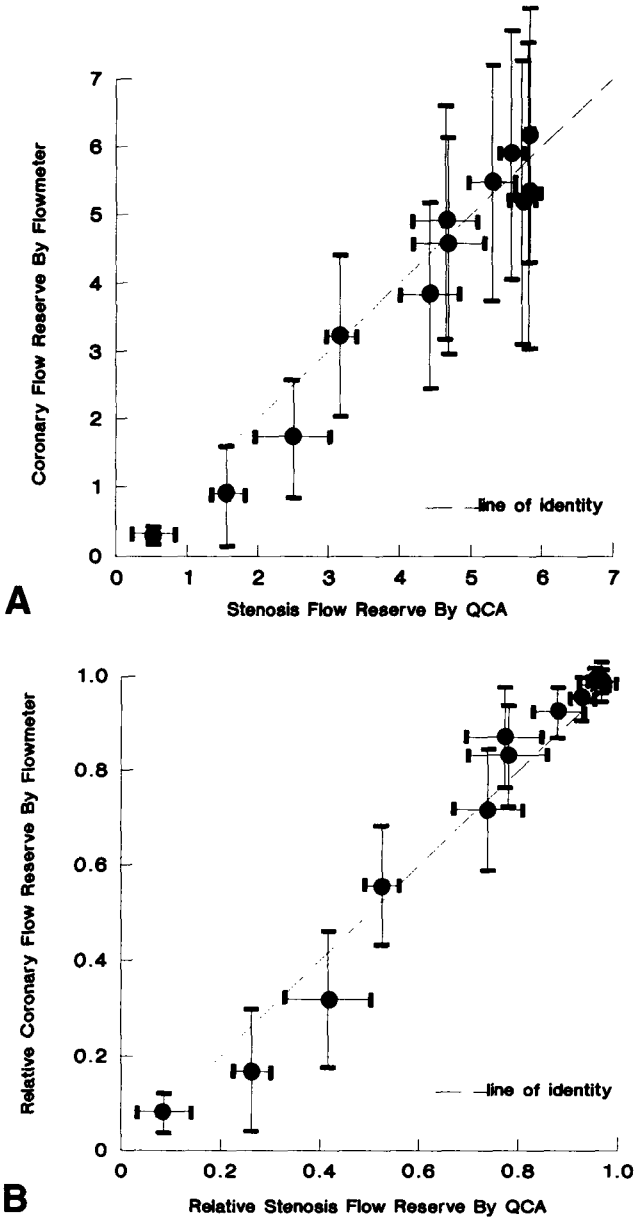


**Figure 11. A,** Correlation between directly measured coronary flow reserve by flow meter and arteriographic stenosis flow reserve by quantitative coronary arteriography (QCA). The variability for directly measured coronary flow reserve by flow meter is considerably larger than that for arteriographic stenosis flow reserve for the same stenoses from mild to severe coronary narrowing. **B,** Correlation between directly measured relative coronary flow reserve by flow meter and relative stenosis flow reserve by quantitative coronary arteriography (QCA). Error bars indicate mean values ± 1 SD.

## Discussion

This study demonstrates that stenosis flow reserve determined by coronary arteriographic analysis of all stenosis dimensions provides an accurate invasive measure of physiologic stenosis severity independent of widely varying aortic pressure and cardiac work load. Arteriographic stenosis flow reserve is a more consistent, specific functional measure of stenosis severity than direct measurement of absolute coronary flow reserve by flow meter because the effects of physiologic variables other than stenosis severity are eliminated. These findings may also explain in part why direct measurements of coronary flow reserve by invasive techniques have been of limited diagnostic benefit for assessing stenosis severity in individual patients (8–12,17–22,30–33). The variability between directly measured flow reserve and anatomic severity could perhaps be explained in part by differences in physiologic conditions not accounted for in those studies.

**Clinical relevance.** Direct measurements of absolute coronary artery flow and absolute flow reserve may be of limited value for assessing physiologic stenosis severity because they are altered by physiologic variables unrelated to stenosis severity, particularly left ventricular hypertrophy (40,42,46), small vessel disease (35,41,47), cardiomyopathy (41), sympathetic tone (36), failure to respond to vasodilatory stimuli such as dipyridamole (34) and in the immediate postangioplasty period (48). Therefore, stenosis flow reserve determined from arteriographic analysis of all stenosis dimensions may be the best available invasive approach for assessing integrated functional severity in such patients.

Rather than considering the arteriographic approach as competitive with direct flow measurements, we emphasize that these two approaches provide independent complementary data. *Directly measured coronary flow reserve by flow*

*meter* reflects the flow capacity of the coronary vascular system for whatever conditions of pressure, vasomotor tone, narrowed coronary arteries or hypertrophy are present. It reflects the cumulative summed effect of these various factors, but is not specific for cause or mechanism for reduced flow reserve and is, therefore, not specific for stenosis severity. *Stenosis flow reserve derived from arteriographic analysis of stenosis dimensions* using standardized values of pressure and normal maximal flow is a specific invasive descriptor of functional stenosis severity independent of all the physiologic conditions that may affect flow reserve. *Relative coronary flow reserve by perfusion imaging* is the most specific noninvasive measure of stenosis severity with little variability due to changing pressure or work load; however, its interpretation as a measure of stenosis severity must be conditional on some area of myocardium demonstrating normal absolute flow reserve.

*Arteriographic stenosis flow reserve may not equal the directly measured coronary flow reserve by flow meter or Doppler-tip catheter* in a given subject at a given time because the pressure and normal maximal flow for the patient at the time of direct flow measurements might not be the same as those assumed for the "standardized" arteriographic analysis. However, from another point of view, this apparent disadvantage of the arteriographic approach is also a benefit because arteriographic flow reserve allows comparison of complex lesions of different shapes in different patients without misleading effects on stenosis flow reserve due to differences in physiologic conditions among the patients separate from stenosis geometry.

**Limitations of the method.** There are some conceptual and practical problems with quantitative coronary arteriography for determining stenosis flow reserve. As currently applied, all quantitative coronary arteriography addresses only the severity of discrete segments of an artery. As currently used, it does not account for diffuse coronary artery disease because it is applied to discrete arterial segments. In addition, in diffuse disease of a coronary artery, there may be no discrete stenosis or no normal segment of that artery that serves as a normal size reference for determining percent narrowing (49). In this instance, directly measured absolute coronary flow reserve by flow meter or Doppler-tip catheter contributes important independent information not obtainable by quantitative coronary arteriographic analysis *as currently applied* to discrete segments of the involved artery. However, directly measured coronary flow reserve by flow meter or Doppler-tip catheter as a reflection of diffuse coronary artery disease will still depend on extraneous physiologic variables unrelated to the anatomic severity of the disease, such as hypertrophy, hypertension and small vessel disease. Thus, there are limitations of each approach to stenosis quantitation that must be applied with knowledge of what it means and where it is applicable (44).

*The optimal solution for the these limitations of quantitative coronary arteriography as currently applied* is to extend the angiographic method for analyzing discrete segments of the coronary artery to its entire epicardial length by integrating the geometric dimensions from the origin to distal segments. Several approaches to accomplish this look promising, but require further investigation.

**Conclusions.** Quantitative coronary arteriography has now been validated in two previous independent experimental studies (8,28) and in the current report. The diagnostic utility of quantitative coronary arteriography for routine clinical applications has also been demonstrated (9–12). However, high quality arteriographic work stations for multiview, high resolution, three-dimensional analysis of stenoses will be required to demonstrate the routine clinical applications of these concepts.

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