VISUAL interpretations of coronary arteriograms are marked by such great interobserver and intraobserver variability (Bjork et al., 1975; Detre et al., 1975; Zir et al., 1976; DeRouen et al., 1977; Meyers et al., 1978) that comparison of arteriograms from different subjects, or at different times in the same subject, are of limited value for assessing severity, changes in severity, or functional significance of coronary artery stenoses. The universal use of relative percent diameter narrowing as a clinical measure of severity ignores other geometric characteristics of stenoses such as length, absolute diameter, multiple lesions in series, or eccentric narrowings which may be worse in one view, compared with another view.

In vivo quantification of coronary stenosis is necessary for studying the pathogenesis, pathophysiology, and progression/regression of coronary artery disease. For example, what severity of coronary artery stenosis is necessary for altering ventricular function or metabolism? What degree of coronary artery narrowing can be detected by noninvasive methods? What are the quantitative effects of a variety of pharmacological agents on stenosis severity? Why do patients develop resting angina pectoris at one time but not at other times during equal supply-demand conditions? Is percent narrowing or absolute stenosis dimension the more important measurement? How do we quantify the shear forces on the endothelial wall at sites of arterial bending, branching, and/or narrowing which are important in the pathogenesis of cholesterol deposition, atheroma formation, and abnormal endothelial behavior, including platelet activation or release of substances causing arterial vasospasm?

A number of therapeutic trials of coronary atherosclerosis now utilize relatively small numbers of patients studied by specific measures of stenosis progression or regression by quantitative arteriography. This approach contrasts with larger epidemiological studies utilizing nonspecific end-points, such as mortality or new cardiac events, which may be due to factors other than progression of atheroma, e.g., arrhythmias, clotting tendencies, plaque hemorrhage, or spasm unrelated to anatomic progression.

Anatomic changes in stenoses that might be seen during a natural history study, or during therapeutic interventions for coronary disease, may be difficult to interpret due to opposing alterations in different dimensions. During such followup studies for progression or regression, what if there is progressive diffuse involvement of the arterial wall proximal and distal to a stenotic segment such that percent diameter narrowing diminishes (improves), but there is no change or a worsening in the absolute dimensions? Measurement of percent stenosis would show improvement, but measurement of absolute dimensions would show no change or worsening. What if, at a followup study, the length of the stenosis increased while the stenosis diameter became slightly greater, or some combination of the above changes occurred? Or what if one part of an irregular stenosis became less severe while another part became worse? What if the stenosis became elliptical or worse in one view but better in another, rather than demonstrating concentric changes? These possibilities have been demonstrated both experimentally and in humans, as is discussed subsequently.

The interpretation of these multidimensional changes as demonstrating progression or regression of disease is not possible by visual estimation. They can be taken into account by quantitative coronary arteriography to provide a measure of the net change or final, cumulative, functional-hemodynamic characteristics of the stenosis.

However, quantitative arteriography requires cardiac catheterization, high quality arteriograms, complex hardware and software for analysis, and tech-
nically sophisticated personnel for its application. Although suitable for study protocols in limited numbers of patients at research centers, this approach may not be appropriate as a clinical or experimental routine. Furthermore, there remain significant questions about the limits of variability of quantitative arteriography. Although improved non-invasive, functional measurements of coronary flow reserve may provide an alternative approach for assessing stenosis severity, that concept has some problems as well. Therefore, it is important to understand how functional effects of a stenosis relate to its anatomic geometry. Having established a raison d’être for quantifying the severity of coronary stenoses, what are the approaches, that is their theoretical basis, how well do they work experimentally and clinically?

We can view coronary artery stenoses in two fundamentally different ways: anatomically and functionally. The anatomic severity of a coronary lesion is measured in geometric terms, i.e., percent narrowing, absolute diameter, length, and shape. Quantitative coronary arteriography delineates these dimensions which are then used to calculate the functional or pressure flow characteristics according to theoretical fluid dynamic equations. The functional severity of a stenosis is described in physiological terms, i.e., by directly measured coronary blood flow, pressure gradient or distal perfusion pressure, and coronary flow reserve from which certain deductions about geometric severity can be made.

Both the anatomic and functional approaches to quantifying severity are derived from, or related to, fluid dynamics of flow in narrowed tubes. In theory, therefore, the two approaches should be interchangeable and equivalent, both mathematically and experimentally. The purpose here is to provide an overview of functional and anatomic approaches to quantifying severity of coronary artery stenoses, to outline their validation in the literature, and to indicate the remaining problems. Since it is basic to both approaches, a brief review of fluid dynamics in narrowed tubes is appropriate.

Principles of Fluid Dynamics in Narrowed Arteries

According to presently used fluid dynamic equations for flow in rigid tubes (Young and Tsai, 1973a, 1973b; Brown et al., 1977; Mates et al., 1978; Lipscomb and Hooten, 1978; Gould, 1978a; Gould et al., 1982), the energy or pressure losses across a coronary artery stenosis occur primarily because of two geometric characteristics: narrowness of the arterial lumen and its abrupt expansion at the distal end where it opens into the normal-sized artery. Along the narrowed lumen of the stenosis, viscous friction is generated by the layers of blood sliding against each other and against the endothelium of the artery. This same phenomenon occurs in all arteries (normal or abnormal), but because it is inversely related to the fourth power of the lumen diameter, the energy loss due to viscous friction is great in the narrowed, diseased artery. The pressure loss accompanying viscous friction is also directly proportional to the length of the narrowing, the viscosity of blood, and the flow through the stenosis.

The flow of blood out of the stenotic lumen and into the distal normal-sized artery is analogous to the flow of water from a narrow chute of rapids into a wide river. As flow emerges from the narrowing, its momentum keeps it moving forward, not allowing it to expand immediately with the enlarged flow channel. The bulk of the flow therefore separates from the channel boundaries and mixes violently with the surrounding slow-moving blood, thereby forming eddies, localized turbulence and jets, all of which dissipate energy. The energy lost in this abrupt expansion is termed an inertial loss and increases with the square of blood flow. Furthermore, this expansion loss has been considered to depend primarily on the kinetic energy of the flow at the point of flow separation (at, or just distal to, the minimal stenotic area section) which is inversely related to the minimal stenotic area squared when expressed in terms of the volumetric flow rate, Q.

The fact that coronary blood flow is pulsatile appears to be of minor importance for pressure losses across moderate to severely stenotic coronary arteries for several reasons (Young and Tsai, 1973b; Cassanova, 1978). Rapid changes in coronary flow are confined to the brief periods of isovolumetric contraction and relaxation. During the remainder of systole and diastole, time-dependent changes in flow are much smaller, and instantaneous pressure losses are dominated by the viscous and expansion losses. Progressively severe coronary stenoses increasingly dampen the coronary flow waveform, thereby reducing its pulsatile nature. Thus, at least for purposes of analyzing the mean or instantaneous diastolic pressure drops across clinically significant coronary stenoses, blood flow can be considered as quasi-steady (Young et al., 1975; Mates et al., 1978; Gould, 1978a). The total pressure drop across a stenosis is then the sum of the viscous and expansion losses, expressed in the general form of a quadratic equation relating pressure gradient, ΔP, across a given stenosis to the volumetric flow, Q, through it as follows:

\[ ΔP = fQ + sQ^2 \]

where f is the constant of pressure loss due to the viscous friction and s is the constant describing inertial pressure loss due to expansion. At resting conditions with relatively low coronary flow, the first term due to viscous friction accounts for the greatest proportion of total pressure loss with either severe or mild stenoses; however, at high-flow conditions, the second term accounts for a greater proportion of the total pressure loss because the effect of this expansion term increases as the square of blood flow (Gould, 1978a; Gould et al., 1982).
To obtain equations for predicting the viscous and expansion pressure loss coefficients from stenosis geometry, the cross-sectional velocity profiles along the stenotic lumen must be specified. Since such information cannot be measured clinically, it has been assumed by means of hydraulic studies of flow through pipes and abrupt expansions in pipes as a guide. Specifically, it has been assumed that flow from the proximal portion of the stenosis to its minimal area section is laminar and fully developed, thereby implying that flow velocities are parabolically distributed across the lumen in this segment. At the minimal area section, or slightly distal to it, the flow is assumed to separate and thereafter have as a one-dimensional flow through an abrupt expansion in a pipe (in which the velocity profiles are everywhere flat). The constants \( f \) and \( s \) are then related to stenosis geometry as follows:

\[
 f = \frac{8 \pi \mu L}{A_s^2} \quad \text{and} \quad s = \frac{\rho}{2} \left( \frac{1}{A_s} - \frac{1}{A_n} \right)^2
\]

where \( \Delta P \) = pressure loss across the stenosis, \( \mu \) = absolute blood viscosity, \( L \) = stenosis length, \( A_n \) = the cross-sectional area of the normal artery, \( A_s \) = the cross-sectional area of the stenotic segment, \( Q \) = volume flow, and \( \rho \) = blood density. The critical dimensions are stenosis length raised to the first power, and diameter of the stenotic segment and of the normal artery raised to the fourth power. Since the stenosis diameter affects flow by a fourth power term, a small decrease in stenosis diameter may cause a profound effect on pressure or flow, whereas length has a proportionately lesser effect. For tapering stenoses, the length effects are integrated as described by Brown et al. (1977) and are discussed further in the next section.

If these geometric dimensions are measured either directly or on coronary arteriograms, the functional or hemodynamic characteristics of the stenosis may theoretically be predicted by substituting those values into these equations. The result is a specific quadratic equation with known values of \( f \) and \( s \) characteristic of a given stenosis describing the relation of the pressure gradient to flow. The curves shown in Figure 1 are graphic plots of the quadratic equations for stenoses of progressive severity (Gould, 1978a). With increasing flow, the pressure gradient-flow relation curves nonlinearly upward, since the pressure gradient increases as a function of flow raised to the second power.

The basic tenets of the above theory for predicting pressure losses across coronary stenoses from arteriographic data have been validated in an extensive series of in vivo experiments (Gould et al., 1982). However, the variation in geometrically predicted pressure-flow characteristics, compared with directly measured values, was sufficient that assumptions regarding the shape of the velocity profiles along the stenosis may be questioned. This question will be discussed subsequently in more detail. From this brief overview of fluid dynamics, it is appropriate now to consider anatomic and functional approaches for describing stenosis severity.

### Anatomic Imaging of the Coronary Arteries

Quantitative coronary arteriography was originally proposed by Brown et al. (1977) and subsequently validated in vivo by Gould et al. (1982). It requires high quality coronary arteriograms taken in two views angled at 90° to each other. Significant errors appear with deviation from orthogonal views (Spears et al., 1983a, 1983b). The x-rays then may...
be processed in two different ways. In the first, the images are optically magnified onto a digitizing tablet with the borders of the artery traced by hand and thereby digitized for computer processing (Brown et al., 1977; McMahon et al., 1979; Kirkeeide et al., 1981; Gould et al., 1982). There is some subjectivity in tracing the arterial borders visually. In the second approach, the entire region of interest on the arteriogram is digitized with the borders of the artery identified automatically by computer software without visual interpretation (Sanders et al., 1979; Booman et al., 1979; Selzer and Blankenhorn, 1982; Kirkeeide et al., 1982a; Spears et al., 1983a). In our laboratory, this automated computer technique utilizes an edge-detection method, as well as analysis of the absorbance (gray scale) patterns diametrically across the artery image. The cross-sectional areas measured by both techniques are automatically compared for each segment of the artery. Disagreements between the two methods may occur, especially for eccentric lesions in which the border-recognition technique using orthogonal biplane views is not as accurate as the densitometry technique (Kirkeeide et al., 1982b), or, in cases where other optically dense structures (catheters, other vessels, etc.) are superimposed on the arterial segment of interest. In the latter circumstance, the diameter is best determined by the automated border recognition approach. An example of automated analysis is shown in Figure 2, which illustrates the arterial borders identified automatically and shown by the dashed lines superimposed on the arteriogram. Also shown are the diameters of the artery measured at increments along the long axis of the stenosis for purposes of computing the various geometric dimensions of the lesion.

After the borders of the opacified artery on the arteriogram are identified, the stenosis is analyzed by quantitatively adding the exit losses to the integrated viscous losses along the length of the stenosis. The final computer printout gives the measured dimensions and predicted pressure drop for a given coronary flow, as well as the pressure gradient-flow relation (Gould et al., 1982). It is emphasized that the quantitative arteriography described above cannot predict the actual flow or the actual gradient unless flow is measured independently. Since that is not possible in humans, it predicts the pressure gradient—flow relation, i.e., the range of gradients for a range of flows. The automated technique is accurate to 0.1 mm (Kirkeeide et al., 1982a) for absolute dimensions. By this approach, the reproducibility of any given dimension is quite remarkable, with approximately ±2%-3% variation on sequential repeated x-rays of the same stenosis (Gould et al., 1982). As demonstrated by Brown et al. (1982), such geometric accuracy allows intervention studies with relatively small numbers of patients in randomized therapeutic trials. Quantitative coronary arteriography is therefore of great value in determining progression or regression of coronary disease. However, there are problems in this approach, as discussed in the section on validation.

**Functional Analysis of Coronary Artery Stenosis**

**Pressure Gradient-Flow Relation**

The functional severity of a coronary artery narrowing may also be defined by the relation of pressure gradient to flow, measured directly by implanted instruments, and without knowledge of anatomic geometry (Gould, 1978a). Coronary artery stenosis not only reduces the maximum increase in coronary flow but also causes a reduction in distal coronary perfusion pressure due to pressure losses across the stenosis. The upper panel of Figure 3 shows a normal coronary artery with the expected increase in flow after a vasodilatory stimulus (Lipscomb and Gould, 1975). Aortic and distal coronary artery pressures show no significant difference or gradient in the absence of a stenosis. However, in the lower panel, coronary stenosis restricts the increase in coronary flow and causes a pressure loss or gradient with lowered distal coronary perfusion pressure. There is a direct correlation between the degree of flow increase and the increase in the pressure gradient across the stenosis.

Thus, coronary vascular bed vasodilation may cause only a modest increase in total arterial coronary flow, but a large fall in distal coronary perfusion pressure (Gould et al., 1975; Gould, 1978a) with attendant fall in subendocardial perfusion (Gould, 1978c; Weintraub et al., 1981; Bache and Schwartz, 1982). The quantitative relation between coronary blood flow and the pressure gradient across the stenosis during diastole is a hemodynamic measure of stenosis severity, as shown in Figure 4.
Figure 3. Recordings of coronary flow and proximal and distal coronary pressures in a normal coronary artery (panel A) and in a stenotic coronary artery (panel B). At rest, there is a pressure gradient of approximately 30 mm Hg between the aorta and the distal coronary artery caused by the stenosis. Coronary blood flow at rest is normal in both arteries. Following a vasodilatory stimulus, coronary flow increases slightly in the stenotic artery with a marked increase in the pressure gradient. Flow increases appropriately in the normal coronary artery with no pressure gradient. Thus, the small increase in coronary flow through the stenotic artery was associated with a large increase in the pressure gradient and fall in distal coronary perfusion pressure. Reproduced from Lipscomb and Gould (1975).

In the absence of a stenosis, there is a mild, (5–8 mm Hg) gradient at maximum flows following administration of a potent coronary vasodilator. In the presence of a stenosis, the pressure gradient-flow relation becomes much steeper, with a higher pressure gradient for any given flow. With severe coronary stenosis, this relation becomes very steep, with a large increase in pressure gradient for a small increase in coronary flow caused by distal arteriolar vasodilation. This pressure gradient-flow relation acquired during diastole characterizes the functional severity of coronary artery stenoses in hemodynamic terms, rather than in terms of anatomic geometry (Gould, 1978a, 1978b, 1978c, 1980; Gould et al., 1978, 1982). This approach is suitable only for experimental animals in which direct pressure-flow measurements can be made by implanted instruments.

Coronary Flow Reserve

An essential concept relating stenosis anatomy to its functional effects is that of coronary flow reserve. It is defined as the ratio of maximum coronary flow after a maximal vasodilatory stimulus to resting flow, as first described experimentally by Gould et al. (1974) and explained in fluid dynamic terms by Young et al. (1977). The concept is demonstrated in Figure 5. Under resting conditions, coronary blood flow in an artery with a relatively tight stenosis (82% diameter narrowing in this example) is the same as in a normal artery. The blood flow in the normal artery increases three to four times in response to a vasodilatory stimulus such as pharmacological coronary vasodilators, a brief coronary occlusion, or physical stress. In the presence of coro-

Figure 4. Relation between coronary flow velocity and pressure gradient due to a stenosis under resting control conditions. Panel A shows the original pressure and velocity recordings. Panel B shows the relationship between the pressure gradient, $\Delta P$, on the vertical axis and flow velocity, $V$, on the horizontal axis. The numbered points on the gradient-velocity relationship correspond to the numbered points on the original recordings and illustrate the effects of early systolic deceleration and late systolic acceleration of flow (shaded areas). Panel C shows the gradient-velocity relationship after the effects of deceleration and acceleration, unrelated to the severity of the stenosis, had been discarded. The relationship is characterized by a quadratic equation. The first or linear term gives the pressure loss due to viscous friction, and the second or nonlinear term gives the pressure loss due to flow separation. In the example shown, the coefficient of friction loss is 0.383 and the coefficient of separation loss is 0.02, both characteristic of moderate stenoses. Reproduced from Gould (1978a).
Coronary blood flow is shown for a normal artery in the upper panel and for a stenotic coronary artery in the lower panel. Resting coronary blood flow is equal in the two arteries, but the increase in flow seen after a coronary vasodilator or after stress fails to become greater in the presence of a stenosis. Normally flow will increase three to five times, demonstrating a coronary flow reserve of up to five. The coronary flow reserve of the stenotic coronary artery is greatly reduced, as shown in the lower panel. Adapted from Gould et al. (1974).

The normal 3- to 4-fold relative increase after a vasodilatory stimulus identifies a coronary flow reserve of three to four. Coronary artery narrowing limits this coronary flow reserve to an extent that is proportional to the severity of the stenosis. This approach to evaluating coronary stenoses has been shown to be practical, both experimentally and clinically (Gould, 1978a, 1978b, 1978c; Gould et al., 1978, 1979; Albro et al., 1978; Marcus et al., 1981; Schelbert et al., 1982). For a stimulus which normally increases coronary flow to five or six times baseline levels, coronary flow reserve becomes impaired with mild stenoses 3-12 mm long, and approximately 30%-40% narrowing of a 3 mm diameter artery.

To explain the maintenance of normal resting coronary flow but reduced coronary flow reserve during progressive coronary constriction, one might best consider the stenotic coronary artery as two resistances in series, i.e., a narrowed tube and a distal coronary vascular bed, represented schematically in Figure 6 (Gould, 1978c). For purposes of illustrating the importance of the normally high distal coronary bed resistance at rest, consider that the driving pressure for flow is the total pressure gradient across the stenosis and distal vascular bed, which is approximately central aortic pressure, since venous pressure is relatively small. Flow is therefore determined approximately by aortic pressure divided by the sum of the resistances of the stenosis, $R_s$, and of the distal vascular bed, $R_d$, in series. If the distal bed resistance is large compared with the stenosis resistance as normally found at rest, large changes in the stenosis resistance will have little effect on flow, which is determined primarily by distal vascular bed resistance. Therefore, a progressive stenosis up to a point will have no hemodynamic effect on resting coronary blood flow.

However, as the stenosis becomes sufficiently severe to create a resistance comparable to that of the distal vascular bed, the distal bed vasodilates, loses its ability to autoregulate, and the stenosis will cause a fall in resting coronary blood flow. When the stenosis becomes sufficiently severe that its resistance is much greater than that of the distal vascular bed, autoregulation will be lost, for the most part, and flow will be determined predominantly by the stenosis alone. At that point, changes in distal vascular bed resistance will have little effect on blood flow through the stenosis. Gould et al. (1975) have also shown that compensatory vasodilation plays little role in maintaining resting flow in response to progressive stenosis.

Thus, the coronary vascular system is normally a low-flow, high-resistance circulation at rest. Coronary vasodilators or stress convert this normally low-flow, high-resistance system into a high-flow, low-resistance system in which coronary stenoses, even mild ones, have greater effects on maximum flow. Such logic explains why imaging of regional myocardial perfusion at maximum coronary vasodilation can be used to detect even mild coronary artery narrowing, however, this increase in blood flow is limited.

![Figure 5](image-url) Coronary blood flow is shown for a normal artery in the upper panel and for a stenotic coronary artery in the lower panel. Resting coronary blood flow is equal in the two arteries, but the increase in flow seen after a coronary vasodilator or after stress fails to become greater in the presence of a stenosis. Normally flow will increase three to five times, demonstrating a coronary flow reserve of up to five. The coronary flow reserve of the stenotic coronary artery is greatly reduced, as shown in the lower panel. Adapted from Gould et al. (1974).

![Figure 6](image-url) A diagram representing the diseased coronary circulation as two resistances in series, $R_s$ is the resistance of the narrowed tube and $R_d$ is the resistance of the distal vascular bed. The effects of reducing $R_d$ with vasodilators is shown by the dashed line. The equation shows the relation between resistance and flow ($F$) for various segments of the curves. For a given total pressure gradient across the narrowed tube and distal vascular bed ($\Delta P$), flow is determined primarily by $R_d$ if $R_s$ is large. Changes in the stenotic resistance $R_s$ have little effect until the value of $R_s$ approaches that of $R_d$. Adapted from Gould (1978c).
narrowing. This discussion and the schematic in Figure 6 have to be qualified further by acknowledg-
ing that the true venular back pressure to coro-
nary flow may be considerably higher than venous pressure (Kirkede et al., 1981), for example, zero flow pressure of the coronary artery may range from 10–20 mm Hg, which is higher than venous pres-
sure. However, the conceptual explanation of why resting flow remains normal with progressive ste-
nosis remains true.

Relation between Anatomic and Functional Characteristics of Coronary Stenosis: Validation, Limitations and Problems

We have experimentally validated the basic theory and x-ray techniques of quantitative coronary arte-
riography applied in vivo to tapered, narrowed coro-
nary arteries (Gould et al., 1982). In that study, analysis of anatomic geometry on coronary arterio-
grams appropriately predicts the pressure gradient-
flow characteristics or functional effects of coronary artery stenoses with 95% confidence intervals for individual values of ±18.5 mm Hg. However, there was considerable scatter of the data about the rela-
tively good overall correlation between anatomic, x-
ray-predicted pressure gradients at a given flow, compared with those measured directly by im-
planted instruments. This scatter makes it difficult to predict accurately a given pressure gradient for an individual stenosis despite highly repeatable ge-
ometric measurements.

There are several possible explanations for the paradoxical disparity between repeatable geometric measurements and the more variable predictions of the pressure-flow characteristics derived from these dimensions. The first is that the equations used for predicting stenosis pressure drop may not have suffi-
ciently accounted for all mechanisms of pressure losses occurring in vivo. An example of this potential prob-
lem is the influence of arterial velocity profiles and their development along the stenosis upon vis-
cous and exit pressure losses. As described previ-
ously, prediction of viscous losses along the stenosis was based on the assumption of fully developed, laminar flow conditions (parabolically shaped velocity profiles) existing from the proximal end of the stenosis upon vis-
cous and exit pressure losses. As described previ-
ously, prediction of viscous losses along the stenosis was based on the assumption of fully developed, laminar flow conditions (parabolically shaped velocity profiles) existing from the proximal end of the stenosis to the minimal area section. The expansion pressure losses were predicted on the basis of a one-
dimensional flow through an abrupt expansion (the velocity profiles being flat everywhere from the minimal area section to the normal artery section distal to the stenosis). There is an obvious contradic-
tion in these two assumptions which needs to be resolved.

Theoretically, neither of the assumptions is likely to be true. Redevelopment of an initially fully de-
veloped flow following an abrupt change in flow geometry, such as the abrupt contraction, requires a finite length to occur. For flow conditions similar to those in coronary arteries, the required distance for flow development, the entrance length, is on the order of 5–25 local arterial diameters, depending on the coronary flow rate. Instrastenotic flow for most coronary stenoses is therefore likely to be underde-
veloped, with parabolically shaped velocity profiles being approached only with very long stenoses, under resting flow conditions. For such flow condi-
tions, viscous losses across coronary stenoses would be greater than that predicted by the presently used equations (Seeley and Young, 1976; Lipscomb and Hooten, 1978), as would the inertial expansion losses as previously hypothesized (Mates et al., 1978; Lipscomb and Hooten, 1978). Entrance losses, previously assumed to be negligible in quantitative arteriography, are related to the issue of flow profile effects, since entrance geometry may profoundly affect flow profiles in the stenotic segment and therefore influence exit losses as well. Thus, en-
trance effects are likely to be significant on theoretical grounds, but have not been accounted for in quantitative arteriography to date.

It is not clear at this point how sensitive the pressure drop-flow characteristics of stenoses are to variations in velocity profile shape or the range of velocity profile shapes that can occur in vivo in stenotic coronary arteries. Depending on this sensi-
tivity, variations in coronary anatomy (such as ar-
terial branching patterns, vessel curvature and taper, eccentricity), heart rate and blood properties which influence velocity profile shape could also influence pressure losses across coronary stenoses. Eccentricity of lesions has been demonstrated to cause little more pressure loss at a given flow than concentric lesions of equal area reduction and length (Seeley and Young, 1976). Mean pressure-flow characteristics are complicated further by the fact that instanta-
neous flow squared is not equal to mean flow squared, but the relation between instantaneous and mean flows squared depends on the shape of the waveform (Young and Tsai, 1973b).

Since the present equations for predicting stenosis pressure losses do not account for some of these phenomena, errors of a random or systematic nature might have resulted from their omission. It is prob-
able that flow velocity profiles do influence pressure losses for a given flow through a geometrically fixed stenosis. In a larger sense, a consequence of this probability would be that, for a given constant mean flow through a geometrically fixed stenosis, a range of pressure gradients would occur depending upon flow velocity profiles. There would be no unique pressure-flow relation characteristic of a given ge-
ometry. In that case, geometric measurements alone, no matter how accurate, could not uniquely predict pressure-flow or functional characteristics of a ste-
nosis. It might do so, however, within a certain range of ambiguity or with a certain statistical prob-
ability subject to theoretical prediction and experi-
mental testing. A definitive study of this important topic remains to be published.

The second of the major possible contributing reasons for the scatter in predicted vs. directly meas-
ured results is uncertainty in border recognition of the artery on arteriograms. The border of an opacified artery on x-ray demonstrates a penumbra or border zone of less radiodensity between the more radiodense central lumen of the artery and the radiolucent area external to the artery (Gould et al., 1982; Kirkeeide et al., 1982a, 1982b; Siebes et al., 1982; Spears et al., 1983a). This edge unsharpness or penumbra zone is due to two radiographic effects: the progressive decrease in contrast media depth as the lumen edge is approached from the lumen center (subject unsharpness) and the finite resolving capabilities of the x-ray imaging system. A satisfactory overall correlation between predicted vs. measured pressure gradients was obtained in our laboratory only when the arterial border was drawn by visual estimate in the center of this penumbral zone. Normally, with relatively round cross-section, the border zone constitutes 10–15% of a coronary artery 3 mm in diameter. However, at stenoses, particularly as eccentricity increases, this zone may become relatively large. Border recognition consequently becomes more uncertain. Since hemodynamic effects are proportional to the diameter of the stenosis raised to the fourth power, a small uncertainty in border definition may introduce a large uncertainty into the hemodynamic effects calculated from x-ray-measured dimensions. The degree of this uncertainty in border definition and the extent of associated uncertainty in resulting hemodynamic predictions has not been described by formal error analysis.

Thus, the quantitative interpretation of stenosis dimensions on arteriograms has evolved to a probabilistic expression that the true severity for a given individual stenosis lies somewhere within a range of severities defined by the range of uncertainty in border definition and flow velocity profiles. Automated border recognition programs offer a promising solution to reducing these uncertainties when combined with densitometric analysis of the arterial x-ray image. The combination of the border recognition and density techniques is particularly useful, because background-corrected radiodensity is integrated across the artery image (including the entire border zone) to yield a measure of vessel cross-sectional area independent of its sectional shape (Rutishauser, 1971; Crawford et al., 1977; Kirkeeide et al., 1984; Nichols et al., 1984; Serruys et al., 1984). They also eliminate the human error in visual interpretation of the penumbral zone. As discussed subsequently in more detail, another promising approach using quantitative arteriography expresses stenosis severity in terms of impairment of coronary flow reserve (Kirkeeide et al., 1984), rather than the pressure gradient-flow relation which is difficult to apply practically. However, the limits of uncertainty for all of these new techniques have not been systematically defined.

Another profound difficulty in interpreting quantitative arteriography in functional terms relates to the size of the distal vascular bed and the absolute arterial diameter. Even if all the dimensions of a stenosis were known, including absolute diameter, one would not know—in the absence of atherosclerosis—what the absolute diameter of the artery normally should be, or was, in order to supply that distal vascular bed with adequate flow. In other words, even if quantitative arteriography could precisely predict what coronary flow and distal coronary pressure were at a given aortic pressure, one would not know whether that blood flow was appropriate for the vascular bed size. This problem also relates to where absolute dimensions are measured. A given absolute dimension may be normal for a distal segment of coronary artery, but would indicate severe narrowing if present more proximally in that artery. However, we believe that the measurement of coronary flow reserve as a reflection of stenosis severity obviates some of these difficulties. For example, in the presence of diffuse narrowing of a coronary artery to a relatively large distal vascular bed, coronary flow reserve would be impaired. In contrast, a normal coronary artery of the same absolute diameter supplying a smaller distal vascular bed in proportion to the normal arterial size will have a normal coronary flow reserve. Thus, the measurement of coronary flow reserve takes into account this problem of diffuse disease causing diffuse narrowing, relative to the size of the distal vascular bed.

An associated interesting observation relates to the purported mechanism for energy losses at the stenosis exit. Virtually every text on fluid dynamics describes the exit loss as being due to vortex shedding or regional turbulence (eddying). However, the equations describe inertial effects only without terms reflecting the presence or degree of disordered flow. It may therefore be that disordered flow at the exit of a stenosis is not a primary mechanism for significant dissipation of energy; it may merely be a secondary, associated phenomenon, accompanying the inertial energy losses—a point of view opposite to traditional dogma. A definitive study on this point examining the effects of drag-reducing agents to reduce turbulence, for example, also remains to be done.

It is important to emphasize that, even with these limitations, quantitative arteriographic measurements, as described by Brown et al. (1977) and Gould et al. (1982; Gould and Kelley, 1982) are objective, allow statistical analysis, provide several orders of magnitude more accuracy than previous visual estimates of stenosis severity, and may also be used to predict coronary flow reserve from x-rays (Kirkeeide et al., 1984).

In addition to the above major issues that have been discussed, a number of more minor questions frequently arise. Can quantitative coronary arteriography account for diffuse coronary artery disease

*y*...
in which there is no discrete single lesion? Since the equations include absolute dimensions, they are applicable to this circumstance, with length being that of the artery or a segment of it. In that case, viscous friction, as accounted for in the first term of these equations, would cause the major pressure loss, since length would be large, and the second term, reflecting exit pressure loss, would be fairly small in the absence of a discrete lesion. As a variation of this same question, the combined effects of multiple stenoses in series can be accounted for by appropriate fluid dynamic analysis (Gould and Lipscomb, 1974; Talukder et al., 1977).

The final complication of applying quantitative arteriography results from dynamically changing stenosis, first described by Gould and co-workers (1978a, 1980; Gould et al., 1982), experimentally developed further by Walinsky et al. (1979), Schwartz et al. (1979), and Santamore and Walinsky (1980), and observed by Brown et al. (1981a, 1981b, 1982, 1984) in humans. In a significant proportion of human coronary stenoses, some part of the arterial wall is sufficiently intact and flexible that vasomotion of the stenotic segment (Logan, 1975), or of the artery on either side of the stenosis, may occur. Both types of vasomotion alter stenosis geometry sufficiently to change its functional characteristics. The appropriate fluid dynamic equations are still applicable, as long as the altered geometry is used (Gould and Kelley, 1982). A flexible-walled, very severe coronary stenosis may also behave as a pressure-dependent flow regulator, like a Starling resistor (Gould, 1982), which is a more complex problem not yet fully described.

Approximations of Stenosis Severity

Quantification of arterial stenosis in vivo is sufficiently complex and poorly understood in terms of basic theory, physiological-hemodynamic effects, experimental preparation, and imaging technology, that a number of studies have utilized indices or approximate estimates of severity. The old issue of the relative value of percent diameter narrowing vs. absolute diameter narrowing is an example of controversy based upon approximations or incomplete analysis and lack of perspective into the multiple facets of the fluid dynamics or physiology involved.

The limitations of percent diameter narrowing compared to absolute diameter was proposed as long as 20 years ago (Fiddian et al., 1964), with the discussion continuing to our own analysis integrating both approaches with fluid dynamic principles (Gould, 1980). The issue frequently resurfaces, possibly in part due to lack of considering all the aspects of the problem based on complete fluid dynamic equations. For example, Collins et al. (1982), White et al. (1984), and Harrison et al. (1984), reconfirmed previous reports on the limitations of percent diameter narrowing as a measure of stenosis severity in comparison to coronary flow reserve. They concluded that absolute diameter is a more important measure of severity. A generally applicable description of stenosis severity requires both absolute diameter and relative percent narrowing in addition to length, absolute diameter of the normal artery, and blood viscosity. In any given circumstance, one of these factors may be the dominant contributor to total pressure loss. For example, for mild diffuse narrowing with no discrete stenosis, absolute diameter and length of the diffusely involved segment might be the most important geometry. On the other hand, for a short orifice like stenosis, percent diameter narrowing might be most important. Most lesions are between these extremes. Their studies, however, do reemphasize the importance of functional assessment of stenosis severity using coronary flow reserve as we originally proposed.

Unfortunately, there are problems with coronary flow reserve, as well, as suggested by Gewirtz et al. (1983) and reviewed by Hoffman (1984). The maximum flow achievable with vasodilatory stimulus, the resting blood flow, and their ratio (coronary flow reserve) are reasonably variable between individual subjects, and perhaps in the same individual at different times, depending on a number of factors unrelated to presence or severity of stenosis, such as adrenergic tone, presence of hypertrophy, perfusion pressure, and the type of stimulus for increasing flow. Relative perfusion reserve (Mullani, 1984), as might be measured quantitatively with positron perfusion tracers (Mullani et al., 1983; Goldstein et al., 1983), may eliminate some of this variability, since part of the heart serves as an internal control area for the rest of the heart. The optimal stimulus for increasing coronary flow has also not been worked out, and probably is different for different individuals. One would anticipate that the type of stimulus for maximizing coronary flow in an unsteady 70-year-old would be different from the one required for a 40-year-old athletic individual. Thus, the type of stimulus and normal responses have to be identified.

The problem of assessing severity is hindered by the lack of a readily applied gold standard. The correlation of angiographic dimensions with postmortem measurements suggests that angiographic measurements are only qualitative (Gallagher et al., 1978; Vlodaver et al., 1973; Grondin et al., 1974; Hutchins et al., 1977), but Marcus et al. (1982) report that postmortem examination of the undistended coronary artery overestimates severity. Because of the issue of arterial distensibility and geometric changes, an important test of an angiographic system is an x-ray phantom consisting of contrast-filled tubes of varying diameters immersed in a scattering media (Kirkeeide et al., 1982a). Metal phantoms such as machined brass rods, which are commonly used, are inappropriate, because they lack the graded decrease in depth of contrast along the radius of an opacified artery (Siebes et al., 1982).
The concept of coronary flow reserve as a single integrated measure of all the geometric dimensions of a stenosis is illustrated conceptually in Figure 7. This figure is a theoretical computer simulation utilizing previously validated, standard fluid dynamic equations relating pressure gradient across the stenosis to coronary flow and stenosis dimensions. For a given aortic pressure, the distal coronary pressure can then be related, as shown by the downward curved line, to coronary flow, here expressed as a ratio to resting flow levels, i.e., in terms of coronary flow reserve (Kirkeeide et al., 1984). The rising straight line plots the normal, experimentally observed relation between coronary perfusion pressure and flow under conditions of maximal coronary vasodilation in the absence of a stenosis, as previously reported (Bache and Schwarz, 1982). It shows the maximum possible flow in the artery in the absence of a stenosis at a given perfusion pressure under conditions of maximum coronary vasodilation. The intersection of this straight line with the vertical axis gives the coronary pressure at zero flow.

Future Directions

To establish a better base of knowledge for quantifying stenosis severity, a number of problem areas need to be described further. It will be necessary to reexamine the basic assumption regarding flow velocity profiles underlying fluid dynamic equations for analyzing stenoses. Corrections of current fluid dynamic equations consistent with more appropriate assumptions probably will be necessary. It also will be necessary to carry out formal error analysis to define limits of accuracy in predicting pressure-flow characteristics based upon limits of border recognition on x-rays, automated techniques, and reasonable possible ranges of flow-velocity profiles which cannot be measured by noninvasive means.

Recent reports by Mullani (1984) and Kirkeeide et al., (1984) are important steps in that direction. Since our introduction of the concept (Gould et al., 1974) we are evolving toward the viewpoint that maximum myocardial perfusion, or coronary flow reserve, may, per se, be the best-integrated single measure of stenosis severity, reflecting all of its combined geometric and fluid dynamic characteristics. As indicated earlier, the measurement of coronary flow reserve also reflects, or is affected by, diffuse narrowing, when the entire artery is smaller than it would normally be, relative to the size of its distal vascular bed.

The schematic of Figure 7 shows theoretically, by quantitative arteriography, how coronary flow reserve is related to, or might be predicted from, stenosis dimensions. The downward-curving line, representing the distal coronary perfusion pressure-flow relation, can be predicted from stenosis dimensions (f and s discussed previously) for any measured blood pressure. The point at which the downward-curving line, showing the distal pressure-flow relation for the stenosis, intersects the rising linear line, showing the maximum normal flow at a given perfusion pressure, gives the coronary flow reserve for that stenosis. For example, for a normal, non-stenotic coronary artery with a coronary flow reserve of five, the perfusion pressure would be normal, shown as 100 mm Hg for purposes of illustration. A 40% diameter stenosis 3–12 mm long in an artery normally 3 mm in diameter would reduce this coronary flow reserve to approximately four, in association with a pressure gradient across the stenosis that reduced the distal perfusion pressure to 80 mm Hg. By reasoning, in the opposite direction, a reduction in coronary flow reserve to 1.4, compared with a normal coronary reserve of five, would predict a stenosis of 40% diameter narrowing, 3–12 mm long, with a distal perfusion pressure of 80 mm Hg under conditions of maximum vasodilation. A reduction of coronary flow reserve to 1.4, compared with a normal of five, would predict a 65% diameter narrowing in association with a distal perfusion pressure in the coronary artery of 30 mm Hg under conditions of maximal coronary vasodilation. At a lower coronary flow produced by distal arteriolar vasoconstriction, or absence of vasodilation, the pressure loss across the stenosis would be less and distal perfusion pressure would be higher than at maximum vasodilation. Thus, this figure illustrates not only the concept of coronary flow reserve, but, also, the experimentally observed fact that the gain in coronary flow with...
arteriolar vasodilation is associated with a loss of perfusion pressure due to a greater pressure gradient across the stenosis (Gould, 1978). Although it is a powerful conceptual approach with preliminary experimental support (Kirkeeide, 1984), validation of this approach will require more work in order to avoid the pitfalls of focusing on a single facet of the problem. This approach must also incorporate error analysis on the limits of variability for experimental testing or clinical application.

For understanding pathogenesis, it will be important to establish a more extensive and integrated knowledge of the interaction between the vascular endothelium and wall shear. Since the early work by Fry (1968, 1969), wall shear has been recognized as a crucial element in localization of coronary atherosclerosis. Recent studies by Friedman et al. (1981), Zarins et al. (1981, 1983), and Bharadva et al. (1982) suggest that flow separation and instability favor atherosogenesis, whereas increased flow velocity may be protective. However, Caro and Nerem (1973), Brown et al. (1982), and Fry (1968, 1969), hold the opposite point of view. The issue remains to be settled. Bomberger et al. (1981) reported that atherosclerosis propagated distal to mild arterial narrowing in association with the disturbed exit flow conditions. In either case, there is reason to believe that fluid dynamic conditions may "mold" stenoses, making them progressively longer or changed in shape, a subject of both research and clinical interest.

In addition, we first observed that elevated coronary flow per se due to arteriolar vasodilation will cause a delayed proximal large epicardial artery vasodilation (Gould and Kelley, 1982). Hintze and Vatner (1983) have elegantly expanded on this observation, and demonstrated that the mechanism is not mediated by neural reflexes but depends only on flow. The mechanism probably is a direct effect of wall shear on endothelial release of vasoactive substances locally, as demonstrated by Holtz et al. (1983). Caro and Nerem (1973) have demonstrated the sensitivity of endothelial cell transport to wall shear, whereas Furchgott (1983) has recently reviewed the complex phenomenon of vasoactive substances released by the vascular endothelium. The relation between wall shear, endothelial cell function, and vasomotion is poorly defined, however; clarification of this relation will be an important part of understanding coronary stenosis, fluid dynamics, and vascular physiology.

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