Experimental Validation of Quantitative Coronary Arteriography for Determining Pressure-Flow Characteristics of Coronary Stenosis

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SUMMARY The applicability of classic fluid dynamic equations to tapering stenoses in vasoactive, flexible coronary arteries in vivo and the validity of quantitative coronary arteriography was tested by comparing experimentally measured and x-ray-predicted pressure gradients at equal flows for left circumflex stenoses in five dogs chronically instrumented with a balloon occluder, flow probe, and proximal and distal catheters for injection of contrast medium or recording distal coronary pressure. Arterial borders on cut-film orthogonal arteriograms were digitized and computer processed into a three-dimensional reconstruction of the stenosis. The total pressure gradient was calculated from stenosis dimensions using classic fluid dynamic equations. Over the full range of flow, the correlation of x-ray-predicted and experimentally measured pressure gradient for 51 separate stenoses was $y = 1.11x + 0.75$, $r = 0.95$, $p < 0.001$, with a standard deviation about the regression line of $± 9.4$ mm Hg and with 95% of x-ray-predicted values falling within $± 18.5$ mm Hg of the experimentally measured values (95% confidence limits). Mean experimentally measured and x-ray-predicted pressure gradients were $10.1 ± 7.7$ mm Hg ($±$ sd) and 10.9 $± 5.6$ mm Hg at low flow and 48.2 $± 23.1$ mm Hg and 55.8 $± 28.8$ mm Hg at high flow, respectively. The mean difference was 3.9 $± 4.3$ mm Hg at rest flow and 11.9 $± 10.5$ mm Hg at high flow. For all data over the entire range of flows, the frequency distribution of differences between x-ray-predicted and experimentally measured gradients was a bell-shaped curve with a peak, or mean difference, of $± 4$ mm Hg, a standard deviation of $± 9.8$ mm Hg and 95% confidence limits for individual values of $± 19.6$ mm Hg. These data demonstrate the validity of applying classic fluid dynamic theory to tapering stenoses in vivo. Quantitative coronary arteriography on the average or in individual instances approximately predicts the pressure gradient-flow characteristics of coronary arterial stenoses in intact animals. However, as indicated by the above measures of variability, there is considerable scatter in x-ray predictions that limits its applicability to individual clinical cases. We believe that this scatter is a result of difficulties in visually tracing arterial borders on arteriograms and can most likely be reduced by automatic border recognition techniques.

VISUAL INTERPRETATION of coronary arteriography is so variable that its value is limited as an objective standard for measuring severity of coronary stenosis. In addition, the hemodynamic severity of a stenosis depends upon its length and absolute stenosis diameter as well as relative percent narrowing, which is the commonest clinical expression for severity. Based on classic fluid dynamic equations, Brown and co-workers developed a method of quantitative coronary arteriography that predicts the pressure gradient-flow characteristics of an arterial stenosis from x-ray measurements of the stenosis geometry. They applied the technique to patient studies. Other groups are also using quantitative coronary arteriography for clinical studies. Quantitative arteriography is important because visual interpretation of coronary arteriograms is so variable that it is essentially invalid as a scientific quantitative measure of severity. Although quantitative coronary arteriography has been applied to clinical studies in an effort to overcome the limitations of visual interpretation, the technique has never been validated experimentally. The basic fluid dynamic theory derived from rigid-tube, in vitro experiments upon which the technique is based has never been proved to apply to flexible arteries in vivo, where stenoses are irregular, eccentric, tapering, and altered by vasomotion tone. The purpose of this study was to experimentally validate the applicability of classic fluid dynamic theory to tapering coronary arterial stenoses in vivo and to determine the accuracy of quantitative coronary arteriography for determining pressure-flow characteristics of coronary stenoses by comparison to directly measured pressure-flow characteristics of stenoses in intact, awake animals. We have used an intact animal model with eccentric, irregular, tapering coronary stenoses to test the applicability of the technique to human stenoses, which are also usually eccentric, irregular and tapering.

Methods

Surgical Preparation

Five male field hounds that weighed 22–28 kg were anesthetized with i. v. sodium thiopental and a mixture of nitrous oxide and methoxyfluorane. The left circumflex coronary artery was dissected free through a sterile left thoracotomy. A small, tapered, Tygon catheter was implanted at the origin of the left circumflex artery for injection of contrast medium in order to obtain coronary arteriograms and to measure proximal coronary perfusion pressure. A Doppler flow velocity transducer was placed around the left circumflex coronary artery distal to the proximal coronary catheter tip. Two millimeters distal to the Doppler transducer, a saline-filled circumferential balloon constrictor was sutured in place. A second Tygon catheter was inserted.

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in the distal main circumflex artery before major branches to measure coronary pressure distal to the constrictor. Dogs were treated with 100 mg of dipyridamole and 600 mg of aspirin for 2 days before and 10 days after surgery to prevent formation of platelet clots on the catheters postoperatively. Catheters were flushed daily and filled with heparin.

The coronary catheter construction and implantation techniques and the conditions and characteristics of the animal model have been described in detail.\textsuperscript{18, 19}

**Instrumentation**

Instantaneous mean cross-sectional flow velocity in the circumflex artery was measured with a continuous-wave directional Doppler probe (L and M Electronics) operating at 8–9 MHz processed through a zero-crossing detector with analog output proportional to the Doppler shift. The construction and calibration of the Doppler transducer has been described.\textsuperscript{18, 19} These transducers had a linear response from zero flow velocity up to the maximum measured value of 156 cm/sec (600 ml/min through a 3-mm i.d. tube) with maximum Doppler shifts of up to 12 kHz and signal-to-noise ratios of 50:1 to 100:1 both in vitro and in vivo.

Proximal and distal coronary pressures on either side of the constrictor were measured with Bio-Tec BT-70 pressure transducers, and differential pressures were recorded simultaneously using a differential pressure gauge (National Semiconductor Corp., part Lx1701D) mounted in a plastic manifold to which the BT-70 transducers were also attached. Needle obturators, stopcocks and plastic parts were filled by immersion under sterile saline in a vacuum chamber to remove micro air bubbles and maximize frequency response. The response of the Bio Tec catheter meter system was flat (± 5%) to 15 Hz with debubbled saline and that of the differential gauge with two simultaneous pressures applied to catheters used for implantation was flat to 30 Hz. For each experiment, pressure calibrations were recorded with 100-mm Hg pressure applied by mercury column to the coronary and differential transducers at the beginning and end of each study.

ECG standard lead II, mean and instantaneous phasic flow, proximal and distal coronary pressure and differential coronary pressure were recorded on an Electronics for Medicine DR 12 with a direct writer and on a Honeywell 7600 tape recorder for analog-to-digital computer conversion and subsequent analysis. In two of the dogs, differential pressure was obtained by subtracting the proximal and distal coronary pressure outputs from the tape recorder using a differential operational amplifier circuit with zero and gain adjustment. There was no difference in differential pressure values obtained by either method within a given experiment.

Coronary arteriograms were obtained by injecting radiopaque contrast medium (Renografin-76) into the proximal coronary catheter while triggering exposure of a single-spot film from the ECG at mid-diastole. The injection/x-ray sequence was automated and precisely controlled using a timing circuit triggered by the R wave from the ECG. The contrast medium was injected using a thermodilution injector (OMP Lab Inc.) modified to inject from an energized solenoid, triggered from the ECG. The injector was powered with compressed air regulated to inject the contrast medium through the catheter at a flow rate not exceeding the dog's coronary arterial flow. With this system, less than 2 ml of contrast medium produced adequate filling for visualization of the stenotic region as well as proximal and distal normal sections of the circumflex artery. The x-rays were taken with a General Electric Maxiray 100 tube with a 0.3-mm focal spot, a 6½° target angle and a 26-inch tube-to-film distance. Exposures were at 1/60 or 1/30 second, 200 mA, at 90–116 kV using Ultra Detail, Cronex 4, DuPont 3 x-ray film and either Ultra Detail phosphor Radelain cassettes or Kodak X-Omatic cassettes with regular intensifying screens. The entire system had a resolution of 11 line pairs/mm or 215 line pairs/inch.

**Protocol**

The dogs were positioned on their right side for biplane x-rays. Some of the dogs were lightly sedated with xylazine (1 mg/kg i.m.) to facilitate a stable position during the x-rays. During a 5-minute rest period, initial flow and pressure calibrations were made and the flow response to a 10-second total occlusion was recorded. The coronary constrictor was then expanded with saline under pressures of up to 1000 mm Hg (20 psi), depending on the severity of stenosis desired. The expansion pressure was held constant at the chosen level by a water-sealed ball valve in line with an automatic pressure regulator attached to a compressed air source.

The stenosis was allowed to stabilize for 20 minutes. Four sets of data were obtained to characterize the pressure-flow relationships resulting from this stenosis.

X-rays at rest. Biplane x-rays were taken during baseline flow conditions in the left anterior oblique and left posterior oblique view. The two x-rays were taken sequentially, separated by at least 3 minutes such that flow and heart rate had returned to baseline values before the second x-ray was taken. In preliminary studies, repeated x-rays in the same plane demonstrated return of all dimensions to control baseline at 3 minutes.

**Measured pressure-flow data at rest.** The pressure and flow velocity transducers were recalibrated and baseline control recordings were made of the ECG, coronary flow velocity, and proximal, distal and differential coronary pressures.

**Measured pressure-flow data at vasodilation.** A dose of 0.4–0.8 ml of papaverine in a concentration of 2.0 mg/ml was injected as a bolus through the distal coronary catheter to produce a transient increase in flow while phasic pressures and flow velocity were recorded. Transducer calibrations were verified at the end of data collection.

X-rays at vasodilation. The same dose of papaverine was injected again and then x-rays were taken at 10
seconds and 60 seconds after the injection. The dog was repositioned for the opposing biplane view and the same hyperemia x-ray sequence was repeated. X-rays were developed with the stenosis still in place and were repeated if films were of poor quality. The entire experiment lasted 1 hour. Data were obtained over a wide range of coronary constrictions for each dog during repeated studies over 4–6 weeks.

Data Analysis

For each stenosis, the relation of instantaneous differential pressure to instantaneous flow velocity was determined for each of four to six heart cycles for flow levels ranging from resting control to peak flow during pharmacologic vasodilation. Analog voltage recordings of phasic flow velocity and phasic differential pressure (stenosis pressure gradient) from the diastolic portion of the selected cardiac cycles were converted to digital signals at 100 samples/sec with a PDP-8e computer. Data were processed by a digital filter equivalent to a low-pass filter flat to 15 Hz and with linear rolloff from 15 to 30 Hz (–40 db down at 30 Hz with no phase shift). During each cardiac cycle, the pressure gradient and flow velocity were correlated by a quadratic equation that has the general form $\Delta P = FV + SV^2$, where $\Delta P$ = pressure loss (mm Hg), $V$ = coronary flow velocity (cm/sec), $F$ = the coefficient of pressure loss due to viscous friction, and $S$ = the coefficient of pressure loss due to flow separation or localized turbulence downstream from the stenosis. For single heart cycles, we determined the constants $F$ and $S$, which best fit this general equation to the experimental data by computer, using a general-purpose curve-fitting algorithm previously described. The computer output consisted of the coefficients $F$ and $S$, the mean velocity, the average velocity, and the mean differential pressure for each heart cycle as well as a plot of the experimental values for the differential pressure vs flow velocity and the calculated best-fit curve for each heart cycle.

The quadratic relation between $\Delta P$ and $V$ for several single cardiac cycles at different flows for each stenosis were used to establish a composite relation for $\Delta P$ and $V$ over the entire range of flows for that stenosis. Five beats were selected, one at rest and four over a range of increased flow during vasodilation. Flow velocity was then converted to volume flow by multiplying velocity times the cross-sectional area of the vessel at the site of the Doppler flow probe. This cross-sectional area was determined from orthogonal arteriograms taken in each experiment. The cross-sectional area of the artery at the site of the velocity transducer from the rest x-ray was used with the hydraulic data for the rest beat and the cross-sectional area of the artery at the velocity transducer from the vasodilated x-ray was used with the hydraulic data for the high flow beats after vasodilators. We demonstrated by sequential arteriograms that this arterial cross-sectional area was relatively constant after injection of the vasodilator for the 60-second period of data collection.

The fluid dynamic equations used for predicting $\Delta P$ in terms of coronary flow velocity or volume flow have been described in detail and are as follows:

$$\Delta P = \frac{8\pi \mu L A_n}{A_s} V + \frac{p_k}{2} \left( \frac{A_s}{A_n} - 1 \right)^2 V^2$$

or

X-ray Analysis

X-ray films were prepared for computer analysis of stenosis dimensions and x-ray–predicted pressure flow relationships as follows: X-ray films were printed directly in reverse image with a 4 × 5 enlarger at three times magnification using Kodak polycontrast, lightweight paper, contrast grade 2. Exposure times were individually adjusted to maximize contrast at the vessel border. Vessel borders on the prints were outlined lightly in pencil independently by each investigator and then jointly reevaluated for consensus tracing. One copy of each x-ray was always left unmarked for visual reference. The penciled vessel outlines were traced into a PDP 11/45 computer using an x-y cursor system on a back-lighted drafting board with resolution of 250 lines/inch. The outline of a 3.18-mm stainless-steel ball surgically implanted next to the stenosis was also traced into the computer as a size reference.

Tracings of paired biplane images of coronary arteries and the steel ball as a size reference were processed by a previously described computer program using an adaptation of these equations for tapering stenoses. The program corrected for pin-cushion distortion and absolute size to produce a true-scale, three-dimensional characterization of the vessel and stenotic segment by matching center lines of the individual biplane projections and assuming the vessel cross section to be ellipsoidal. A hard-copy printout included stenosis dimensions, the cross-sectional area of the vessel at the center of the Doppler flow probe and the computer reconstruction of the digitized vessels in each view. Each x-ray print was digitized three times. Data from the most disparate trace were discarded. Data from the remaining two traces were averaged together and stored in the data base of a PDP 10 computer.

The fluid dynamic equations used for predicting $\Delta P$ in terms of coronary flow velocity or volume flow have been described in detail and are as follows:

$$\Delta P = \frac{8\pi \mu L A_n}{A_s} V + \frac{p_k}{2} \left( \frac{A_s}{A_n} - 1 \right)^2 V^2$$

or
\[
\Delta P = \frac{8\pi \mu L}{A_i} - \frac{1}{A_i} Q + \frac{\rho k}{2} \left( 1 - \frac{1}{A_i} \right)^2 Q^2
\]

or

\[
\Delta P = fQ + sQ^2
\]

where \( \Delta P \) = pressure loss across the stenosis, \( \mu \) = absolute blood viscosity, \( L \) = stenosis length, \( A_i \) = the cross-sectional area of the normal artery, \( A_n \) = the cross-sectional area of the stenotic segment, \( V \) = flow velocity, \( \rho \) = blood density, \( k \) = a constant related to entrance and exit effects here equal to 1, \( Q \) = volume flow, \( F \) and \( S \) = the coefficients of pressure loss due to viscous friction and exit separation in the velocity equation 1 and \( f \) and \( s \) = corresponding coefficients in the flow equation 2. Resistance was calculated from x-ray geometry for both Poiseuille resistance due to viscous friction (\( f \)), assuming laminar flow in the converging portion of the stenosis, and for resistance due to exit separation (\( s \)) due to vortex formation in the diverging portion of the stenosis. The total pressure drop across the stenosis was predicted by multiplying these coefficients as determined from x-ray geometry times a selected flow value according to the equation

\[
\Delta P = fQ + sQ^2.
\]

Using the measured pressure-flow data and the x-ray data, we then could compare the methods for determining the pressure gradient for a given stenosis at a given flow. For purposes of comparison (as in table 1), two flow levels were chosen for each stenosis. Resting flow was designated as either 15 or 30 ml/min and high flow was designated as either 45, 60, 75 or 90 ml/min. The choice of flow levels used for a particular stenosis was based on the range of flow actually observed in the experiment. For example, in study 11, pressure gradient comparisons between x-ray--predicted and directly measured pressure gradients were made at flow rates of 15 ml/min (resting control) and 45 ml/min (vasodilation), since the highest instantaneous flow value recorded was only 45.8 ml/min. In each stenosis, the experimental pressure gradient was determined at the selected flow level using the cubic equation coefficients from the hydraulic analysis. The pressure gradient was then also determined at the same flow using the resistance equation from the x-ray analysis.

### Statistical Analysis

For 51 stenoses the pressure gradients determined from measured hydraulic data and from x-ray--predicted data at the resting flow level were compared by regression analysis. Similar regression analyses were performed on the measured and x-ray--predicted pressure gradients at high coronary flows after intracoronary vasodilators. Data in tables 1 and 2 are reported as mean ± sd. For table 1, comparing the x-ray and experimentally measured pressure gradient, the null hypothesis states that the x-ray--predicted pressure gradient and the experimentally determined pressure gradient are samples from data from the same common source of data and their means should therefore be equal. This hypothesis is true and the mean pressure gradient of the x-ray studies is the same as the mean pressure gradient experimentally measured if there is a high probability (\( p > 0.05 \)) that they came from the same population. Paired \( t \) tests were used to determine the probability.

Reproducibility of tracing and digitizing the x-rays was evaluated in two ways. In the first, the difference between the stenosis dimensions in the two traces used was divided by 2, averaged for all stenoses and then compared with the mean resting value. Reproducibility of the stenosis x-ray system and digitizing was also assessed by taking five pairs of biplane x-rays of the same stenosis sequentially moving and repositioning the dog between each set of x-rays. Then the vessel border was outlined eight times, four each by two observers, for a total of 40 observations on a fixed stenosis. The mean ± sd of the 40 determinations of the percent stenosis were then determined. Intrinsic variability was defined as the standard deviation divided by the mean.

### Results

Measured pressure-flow data and biplane x-rays were obtained for 51 separate left circumflex stenoses at resting control conditions and at high coronary blood flow after coronary vasodilators. The measured pressure gradient at resting flows of 30 ml/min ranged from 1 to 26 mm Hg. Figure 1 illustrates orthogonal x-rays taken of each stenosis. The average diameter stenosis determined from biplane x-rays ranged from 45% to 78% (mean 68%). The reduction in cross-sectional

<table>
<thead>
<tr>
<th>Table 1. Measured and X-ray-predicted Pressure Gradient (n = 51)</th>
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<td><strong>Measured</strong> (mm Hg)</td>
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<tr>
<td><strong>Rest</strong></td>
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<tr>
<td>10.1 ± 7.7</td>
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<td><strong>Vasodilators</strong></td>
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<td>48.2 ± 23.1</td>
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Values are mean ± sd.
area of the artery at the stenosis ranged from 78% to 95% (mean 91%). The severity of the stenosis in the two orthogonal biplane views was asymmetric. The mean ratio of minimum stenosis diameter in one view to the stenosis diameter at the same point in the other orthogonal view was 0.64 ± 0.21.

After intracoronary papaverine, coronary blood flow rose to peak values within 10 seconds and gradually returned to resting values after 90 seconds. The maximum flow after papaverine in each dog depended on the severity of the stenosis and varied from 45 to 90 ml/min. The pressure gradient across the stenosis became more severe at the higher flows, as high as 70 mm Hg for the most severe stenosis.

The instantaneous pressure gradient-flow relation, ΔP-Q, measured during diastole for a single heart cycle, was curvilinear and fit a quadratic relation, ΔP = fQ + sQ², where ΔP = pressure gradient (mm Hg), Q = flow (ml/min), f = the coefficient of viscous friction loss and s = the coefficient of separation loss. For a given stenosis, the quadratic relation changed as flow increased during vasodilation. The coefficients f and s for the quadratic relation became greater at higher flow levels, indicating an increase in the resistance due to the stenosis. Thus, for each stenosis, there was a family of curves describing the ΔP-Q relation over a range of flow from rest to vasodilation (fig. 2). The combined data for beats at several flow rates for a given stenosis did not fit a simple composite quadratic relationship due to changing stenosis geometry at high flows, as previously described. An arbitrary cubic equation was fit to the combined data in the form ΔP = aQ + bQ² + cQ³ so that, with the coefficients for the best fit cubic equation, a pressure gradient at any flow for that stenosis could be calculated based on experimental data. This calculated experimental pressure gradient was a single value within the range of actual data points measured during the experiment. A sample of this analysis is shown in figure 3.

The ΔP-Q relation and total pressure gradient at a given flow for each stenosis were also predicted from angiographic determinations of vessel geometry and dimensions of the stenosis. Since vasodilation caused a change in stenosis dimensions, a second ΔP-Q relationship for each stenosis was obtained from biplane x-rays taken during vasodilation. The pressure-gradient-
flow relation from the measured pressure-flow data and from the x-ray analysis at rest and at vasodilation were plotted together. Figure 4 shows examples from four experiments. In general, there was good agreement between ΔP-Q relations derived from x-rays and those derived from direct experimental pressure-flow measurements.

For each of 51 stenoses at resting coronary flows of either 15 or 30 ml/min, the pressure gradient measured during the experiment and the pressure gradient predicted by the x-rays at the same flow rate were compared by regression analysis (fig. 5). The regression line is characterized by the equation \( \Delta P (\text{x-ray}) = 0.57 \Delta P (\text{measured}) + 5.25 (r = 0.770, p < 0.001) \). At elevated flows of either 45, 60, 75 or 90 ml/min, the measured pressure gradient and the pressure gradient predicted from x-rays at the same flow were similarly correlated. The regression line is characterized by the equation \( \Delta P (\text{x-ray}) = 1.112 \times \Delta P (\text{measured}) + 1.60 (r = 0.902, p < 0.0001) \). Over the entire range of flow using combined resting and high-flow data, the regression line correlating x-ray with experimentally determined pressure gradients was \( \Delta P (\text{x-ray}) = 1.11 \Delta P (\text{measured}) + 0.75 \) with \( r = 0.95 \), a standard deviation for the regression line of \( \pm 9.4 \text{ mm Hg} \) and a 95% confidence interval for individual values of \( \pm 18.5 \text{ mm Hg} \), i.e., 95% of the x-ray predicted values fell within \( \pm 18.5 \text{ mm Hg} \) of measured values (fig. 6).

There was no significant difference in the mean values for the pressure gradient measured at rest, \( 10.1 \pm 7.7 \text{ mm Hg} \), and the x-ray–predicted pressure gradient at rest, \( 10.9 \pm 5.6 \text{ mm Hg} \) (table 1). At high flows after coronary vasodilation, there was a slight but significant \( (p < 0.001) \) difference between the mean values of the measured pressure gradient, \( 48.2 \pm 23.1 \text{ mm Hg} \), and the x-ray–predicted pressure gradient, \( 55.8 \pm 28.8 \text{ mm Hg} \), at the same flow. Thus, on the average, the x-rays slightly overestimated the pressure gradient during vasodilation as compared to measured values. The mean value for the difference between the x-ray–predicted and the measured pressure gradient was \( 3.9 \pm 4.3 \text{ mm Hg} \) at rest and \( 11.9 \pm 10.5 \text{ mm Hg} \) during vasodilation. For all data over the entire range

![Figure 4. Pressure gradient–flow relation for four stenoses.](image)

![Figure 5. Correlation of x-ray–predicted pressure gradient and measured pressure gradient at the same coronary blood flow under resting conditions.](image)
FIGURE 6. Correlation of x-ray–predicted pressure gradient and measured pressure gradient for the entire range of coronary blood flows after coronary vasodilators. The dashed lines indicate 95% confidence limits, i.e., 95% of the predicted x-ray values fall within ± 18.5 mm Hg of experimentally measured values.

of coronary blood flows the differences between x-ray–predicted and experimentally determined pressure gradients were plotted as a frequency distribution to demonstrate the extent and type of systematic errors in the technique. The frequency distribution of errors (fig. 7) is a bell-shaped curve centering around a peak, or mean error, of +4 mm Hg, with a standard deviation of ± 9.8 mm Hg and 95% confidence limits for individual values of ± 19.6 mm Hg.

The reproducibility of digitizing the x-ray dimensions for computer analysis was evaluated for several stenosis dimensions. Variability was measured as the difference in a stenosis dimension between two traces divided by two, \( \frac{T_1 - T_2}{2} \). The mean of this measure of variability for all stenoses was compared to the mean absolute value of that dimension at rest. These data are presented in table 2. The difference in stenosis dimensions between an individual trace and the average value of two traces was less than 5% of that dimension at rest. The difference in pressure gradient between an individual trace and the average pressure gradient derived from two traces was 10% of the pressure gradient at resting coronary flow.

The overall reproducibility of the x-ray system was further evaluated by taking five sequential biplanes of the same stenosis at rest. Each pair of biplane films was outlined on four separate photographic prints and traced twice onto the digitizing tablet, for a total of 40 tracings of orthogonal x-rays of the same stenosis. The mean cross-sectional area reduction for 40 tracings of this stenosis was 88.4 ± 1.8%. For these data, the standard deviation of 1.8 is only 1.8/88.4 (2%) of the area reduction, indicating great reproducibility on sequential x-rays and tracings. The same analysis was performed for 40 traces on a second stenosis of 89.5 ± 1.9% area reduction, with an identical 2% variability.

Discussion

This study in intact, instrumented dogs validates the applicability of classic fluid dynamic equations to tapering stenoses in vasoactive, flexible coronary arteries in vivo using quantitative coronary arteriography as described by Brown et al.\(^16\),\(^17\) for predicting hemodynamic severity of coronary artery stenoses from x-ray geometry alone. At resting coronary blood flow, the mean error in x-ray–predicted pressure gradient was 3.9 ± 4.3 mm Hg, compared with the small measured pressure gradient of 10.1 ± 7.7 mm Hg. At elevated coronary blood flows, the mean error in x-ray–predicted pressure gradient was 11.9 ± 10.5 mm Hg, compared with the large measured pressure gradient of 48.2 ± 23.1 mm Hg, an error of 22%. The error at rest is proportionately larger than that at high flows because errors in visually traced arterial borders cause irreducible errors in absolute values which, in the presence of a small gradient of 10 mm Hg, is a large relative or percent error. The regression correlation between the x-ray–predicted pressure gradient and the measured gradient had an \( r \) value of 0.95, with considerable scatter; 95% of the x-ray predictions fell within ± 19 mm Hg of measured observations.

Quantitative arteriography predicts only the pressure-flow relation characteristic of stenosis severity. It cannot predict an actual pressure gradient in clinical circumstances because coronary flow is unknown. In these animal experiments, the x-ray predictions were

FIGURE 7. Frequency histogram of differences between x-ray and experimentally measured pressure gradients. On the horizontal axis is x-ray–predicted–experimentally measured pressure gradient and on the vertical axis is the frequency with which a given difference was observed.
compared to experimentally determined gradients for equal coronary blood flows.

Quantitative coronary arteriography is highly reproducible, with variations in the geometric measurements of 2–3\% on sequential repeated studies of the same stenosis. The quantitative technique therefore represents a substantial improvement over the widespread use of visual estimates of percent narrowing separate from its application for predicting pressure-flow relations characteristic of a stenosis.

In a severe stenosis, very small diameter changes of fractions of a millimeter have dramatic consequences on flow and pressure gradient because these effects of the stenosis are a function of the fourth power of the radius of the stenotic segment. Similarly, small errors in drawing the borders of the stenotic segment on the x-ray will cause large errors in the predicted pressure gradient. The greatest cause of error in these studies, therefore, is in drawing the borders of the stenotic segment and probably accounts for the significant scatter in these correlations. Stenoses in this study were particularly difficult because they were eccentric, with the ratio of the minimum diameter in one view to the other orthogonal view being 0.64. In the x-ray view with the smallest dimension, small errors in outlining the borders of the stenosis would produce large errors in the predicted gradient.

The borders of coronary arteriograms typically demonstrate a penumbra, a zone of relatively less radiodensity of the radiodense lumen of the artery and the radiolucent area external to the artery. This penumbra is due to progressively less depth of contrast media along a radial direction from the center to the edge of a round or elliptical artery. Accordingly, we randomly selected several subsets of 10–15 stenoses and traced as the boundary of the artery either the inner or the outer edge of this penumbra. Tracing the boundary of the artery as the inner edge of the penumbra caused a systematic overestimation of pressure gradient and stenosis severity. Tracing the boundary of the artery as the outer edge of the penumbra caused an underestimation of pressure gradient and stenosis severity. These subsets of stenoses were traced in “batches” with the knowledge, after the first trace, that they would generally over- or underestimate known gradients, but each specific stenosis was traced blindly without specific knowledge of hemodynamic severity for that specific stenosis. In this study, if the x-ray–predicted gradient exceeded the physiologic range or deviated from the measured hydraulic pressure gradient more than 30 mm Hg due to tracing the inner or outer border of the penumbra, the vessel border was reevaluated, a new outline was drawn, and the coronary tracing redigitized. Some adjustment in vessel border was made in almost 50\% of the x-rays used in this study in the process of defining the boundary of the artery within the penumbra. Satisfactory results were obtained consistently when we outlined the boundary of the artery as approximately halfway between the outer and inner edge of the penumbra.

We believe that the most satisfactory solution to the problem of outlining borders of the artery on the arteriogram is to obtain very high quality x-rays and apply automatic border recognition techniques in order to reduce subjectivity and improve reproducibility in border definition. We are developing techniques for obtaining background-subtracted coronary arteriograms and border recognition software that would provide complete automation of quantitative coronary arteriography, thereby avoiding the problems of drawing the stenosis borders by hand.

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