INVESTIGATIVE NUCLEAR MEDICINE

Myocardial Perfusion with Rubidium-82: III. Theory Relating Severity of Coronary Stenosis to Perfusion Deficit

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The relation between the quantitative perfusion deficit, as measured by emission computerized tomography, and the severity of coronary artery stenosis is important for the noninvasive clinical evaluation of coronary artery disease in man. Positron emission tomography allows direct noninvasive measurement of myocardial perfusion and quantification of the size of the perfusion defect. Given this important information, a mathematical model has been derived to gauge the severity of a coronary stenosis from quantitative perfusion measurements in the normal and poststenotic regions of the heart. The theoretical basis is presented for relating regional myocardial perfusion and regional perfusion resistance to total coronary blood flow and resistance at normal resting flow and during maximal coronary vasodilation. The concept of perfusion reserve is presented as a clinical measure of the severity of a stenosis.

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The effect of a stenosis on the reduction of total blood flow in an artery was first investigated by Mann et al. (*1*) as early as 1938. Working with dogs, they noted that the diameter of a carotid artery had to be reduced by more than 40% before any noticeable reduction in blood flow occurred. They also found that a 70% reduction in diameter was necessary before the blood flow was reduced by 50%. Subsequently, Shipley and Gregg (*2*) verified the foregoing findings in arteries of anesthetized dogs. They emphasized Poiseuille's law, which describes the flow through small tubes as being related to the reciprocal of the fourth power of the lumen diameter of the tube. Several other reports (*3–7*) subsequently described the effect of a stenosis on blood flow and pressure drop in intact animal models.

The mathematical relation between dimensions of the stenosis, coronary blood flow, and the pressure drop across the stenosis has been derived by Young et al. (*8*), Brown et al. (*9*), and Kirkeeide (*10*), and was experimentally validated by Gould (*4*). From these hemodynamic equations it is possible to predict the flow and pressure gradient characterizing the severity of a stenosis if the proximal normal diameter of the artery, the stenosis diameter, and the length and percent narrowing of the stenosis are measured accurately. This information is important clinically for assessing the coronary flow and flow reserve, as proposed by Gould et al. (*5*), in the region of the heart supplied by that artery.

The only current method for accurately measuring the dimensions of a stenosis is by quantitative arteriography (*9*), which requires cardiac catheterization, extremely high-quality angiograms, and sophisticated analytical techniques requiring specialized digitizing and computer hardware besides software not commercially available. Thus this technique is not used commonly and is not suitable for detecting mild coronary stenosis in asymptomatic patients for early diagnosis and treatment of the disease because such patients do not undergo cardiac catheterization.

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Nuclear cardiology, particularly thallium perfusion imaging under exercise (*11*), has been used extensively for noninvasively assessing the adequacy of myocardial perfusion as a means of identifying coronary stenoses. Whereas this technique has been of some value in detecting severe stenosis (>80%), its sensitivity and specificity in detecting disease in asymptomatic individuals is quite low (*12*), due to the noisy images obtained (*13,14*).

Positron emission tomography (PET) (*15*), on the other hand, provides a noninvasive quantitative measurement of regional myocardial perfusion (*16*), and with an appropriate design of the positron camera, it can also produce information on the size or anatomic extent of the perfusion defect, i.e., the volume of the myocardium affected. Thus PET produces a visually apparent quantitative measure of altered myocardial perfusion caused by a coronary stenosis. Although such information is very useful for the diagnosis of myocardial ischemia or detection of coronary artery disease, it would be of even greater value if the severity of a stenosis could be quantified by perfusion imaging with enough accuracy so that progression or regression of the lesion could be determined noninvasively.

In this paper, a mathematical model is derived to relate quantitative myocardial perfusion and the size of a perfusion defect, as measured by positron tomography, to the anatomic dimensions that describe severity of stenosis—i.e., normal proximal diameter of the coronary artery, actual stenosis diameter, percent narrowing, and its length. Since most stenoses are irregular in shape and size, the derivation of the hemodynamic pressure-flow relationship can become quite complicated, as demonstrated by Seeley et al. (*17*) and Brown et al. (*9*). Our derivation will therefore consider an idealized stenosis with uniform effective diameter and length. The effective diameter is then defined as the functionally equivalent uniform diameter of a real stenosis that would produce a similar pressure-flow relationship. The dimensions of the stenosis are therefore presented in terms of a functionally equivalent stenosis (FES) with uniform cylindrical geometry.

In order to simplify the mathematical relationship between coronary flow and myocardial perfusion, some reasonable simplifications and assumptions are made about the hemodynamics of the coronary circulation. These assumptions are based on the known physiological characteristics of the coronary circulation, and are justified in the Appendix. The assumptions made in the derivation of the model are as follows:

1. Myocardial perfusion, as measured by PET, is homogenous within given regions of the heart—i.e., in regions having normal arterial supply and in others supplied by a stenotic coronary artery, where the level of perfusion in the poststenotic area may be less than normal. Therefore, regional perfusion pressure and regional perfusion resistances are also considered homogenous within the different regions of the myocardium.

2. The pressure drop along a coronary artery is caused primarily by the resistances to flow through the stenosis and the vascular bed. Therefore, the pressure drop due to resistance along the length of a major coronary artery can be considered negligible compared with that across a stenosis and in the distal coronary vascular bed.

3. The regional perfusion resistance of the distal coronary vascular bed will reach a minimum during maximum vasodilation and will be equal in all normal regions of the myocardium.

Based on these assumptions, the pressure-flow relation for a stenotic artery will be formulated and then related to the perfusion defect as measured by PET. These equations will then be used to relate the severity of the perfusion defect and its size to the dimensions of the stenosis.

THEORETICAL BASIS

Relation of perfusion to pressure-flow characteristics of a single stenosis in a single artery. For this situation, and assuming no collateral circulation, the pressure drop across the stenosis can be related to coronary flow by two equations describing the arterial hemodynamics with and without a stenosis. If the vessel has no stenosis (Fig. 1, top), then the pressure drop ($P_a - P_v$) across the artery and its distal vascular bed can be described as a function

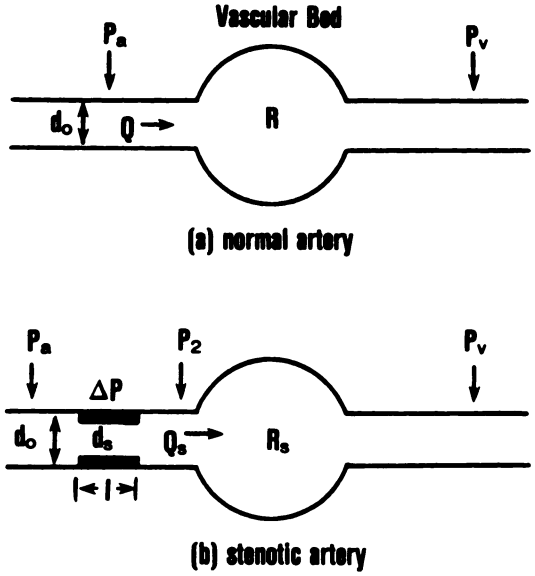

FIG. 1. Functional diagram of coronary circulation, as used in derivation of pressure-perfusion equation. Top: Normal artery supplying flow, Q, to vascular bed. Diameter of normal artery is d_o and vascular bed resistance is R. Pressure drop across vascular bed is taken as ($P_a - P_v$), where P_a is arterial pressure and P_v is venous. Bottom: Same artery with stenosis of diameter d_s and length l. Flow through stenosis is Q_s and pressure drop is ΔP for distal bed resistance of R_s.

of the total flow, Q, and the total resistance, R, of its distal vascular bed as follows:

$$P_a - P_v = QR, \quad (1)$$

where P_a is the arterial pressure and P_v is the venous pressure.

If a stenosis is placed in the same vessel proximally (Fig. 1, bottom), then the total pressure drop $P_a - P_v$ can be expressed as:

$$P_a - P_v = \Delta P + Q_s R_s, \quad (2)$$

where $\Delta P = P_a - P_2$, is the pressure drop across the stenosis, Q_s is the flow in the stenotic artery, P_2 is the coronary artery pressure distal to the stenosis, and R_s is the resistance of bed distal to the stenotic region. Dividing Eq. (2) by Eq. (1), we get Eq. (3):

$$1 = \frac{\Delta P}{QR} + \frac{Q_s R_s}{QR}. \quad (3)$$

Since $QR = P_a - P_v$, Eq. (3) can be expressed as

$$\frac{\Delta P}{P_a - P_v} = 1 - \frac{Q_s R_s}{QR}, \quad (4)$$

which states that the ratio of the pressure drop across the stenosis to the total pressure drop is related to a second ratio whose numerator is the product of the flow through the stenosis and the vascular resistance beyond it, and whose denominator is a similar product of flow and resistance for the normal part of the heart.

Since perfusion, f, is a measure of the regional blood flow per unit mass of myocardium, the total flow, Q, can be computed from the total mass, M, and the regional perfusion, f, by the following equations.

$$Q = Mf \text{ for the normal artery,}$$

and

$$Q_s = Mf_s \text{ for the stenotic artery.}$$

By substituting for Q and Q_s in Eq. (4) the pressure drop across the stenosis can be expressed as a function of perfusions, as follows:

$$\frac{\Delta P}{P_a - P_v} = 1 - \frac{f_s R_s}{fR}. \quad (5)$$

The resistances R and R_s can be expressed as a linear combination of the regional perfusion resistances r and r_s, where

$$r = MR, \text{ units } R = \frac{\text{mm Hg}}{\text{cc/min}}$$

and

$$r_s = MR_s, \text{ units } r = \frac{\text{mm Hg}}{\text{cc/min}}$$

By substituting for R and R_s in Eq. (5), the pressure drop across a stenosis can be expressed as a function of the regional perfusion and regional resistances, i.e.,

$$\frac{\Delta P}{P_a - P_v} = 1 - \frac{f_s r_s}{fr}. \quad (6)$$

During maximal pharmacologic vasodilation, the resistances reach a minimum and are all equivalent—i.e., $r_s = r_{min} = r$—and Eq. (6) reduces to

$$\frac{\Delta P}{P_a - P_v} = 1 - \frac{f_s}{f}. \quad (7)$$

Therefore, under conditions of maximum coronary vasodilation, the pressure drop across a stenosis can be obtained noninvasively if $P_a - P_v$, f_s, and f are measured. The derivation of Eq. (6) from Eq. (4) also implies that in the absence of collateral input, circulation from another artery:

$$\frac{f_s}{f} = \frac{Q_s}{Q}. \quad (8)$$

Thus the perfusion ratio for the poststenotic region to the normal region is directly related to the ratio of stenotic to normal coronary arterial flows. This relation between perfusion and total flow will become extremely important in the future application of PET for the early detection of coronary artery disease, as will be developed presently.

Relation of perfusion deficit to stenosis dimensions. The next step in this derivation is to express the perfusion-pressure relation of Eq. (6) in terms of the dimensions of the stenosis. Young (*8*) has derived the pressure-flow equation for a stenosis relating the instantaneous as well as mean pressure and flow during a cardiac cycle. These equations have been verified in experimental animals by Gould (*4*) for mean flows and mean pressure drops using the following form:

$$\Delta P = DQ_s + SQ_s^2. \quad (9)$$

Equation (9) states that the mean pressure drop across a stenosis can be represented by a quadratic equation where ΔP is the pressure drop across the stenosis, Q_s is the flow in the stenosed artery, D is the viscous drag coefficient, and S is the nonlinear separation coefficient. D and S are functions of the diameter of the normal segment of the coronary artery (d_o), the diameter of the stenosis (d_s), the length of the stenosis (l_s), the viscosity of the blood (μ), and the density of the blood (ρ). The expressions for D and S as functions of the stenosis dimensions are shown below.

$$D = \frac{128\mu l}{\pi d_s^4} \quad (10)$$

and

$$S = \frac{128\rho}{\pi^4}[d_s^{-2} - d_o^{-2}]^2 \quad (11)$$

Note that D is independent of the prestenotic diameter of the artery, and S is independent of the length of the stenosis.

By substituting the pressure drop from Eq. (9) into the perfusion-pressure Eq. (6), a relationship between perfusion ratio and the flow in a stenosed artery is obtained, as follows:

$$(P_a - P_v)\left[1 - \frac{f_s r_s}{fr}\right] = DQ_s + SQ_s^2. \quad (12)$$

Q_s has already been expressed in terms of M and f_s, and therefore by substituting $Q_s = Mf_s$ in Eq. (12), the equation relating the quantitative perfusion defect and its size to the dimensions of the stenosis is obtained:

$$(P_a - P_v)\left[1 - \frac{f_s r_s}{fr}\right] = DMf_s + SM^2f_s^2. \quad (13)$$

This general equation relates the perfusion as measured by PET to the regional perfusion resistances, D and S, which are functions of stenosis dimensions.

By rearranging the terms in Eq. (13), the final form of the equation is obtained:

$$\frac{f_s r_s}{fr} = \frac{DMf_s + SM^2f^2s}{P_a - P_v}, \quad (14)$$

In theory, the variables f_s, f, M, and $P_a - P_v$ can be measured, but r_s, r, D, and S remain unknown. Since D and S are functions of d_o, d_s, and l, we are left with several unknowns if each of the variables is to be estimated. The influence of r and r_s can be minimized by maximal vasodilatation such that $r = r_s = r_{min}$, thus leaving three unknowns that describe the dimensions of the stenosis, d_o, d_s, and l. Given a three-dimensional imaging device (PET) and perfusion images of the heart, it may be possible to estimate the proximal diameter of the stenosis, d_o, by the size of the perfusion defect (*18–20*). However, we are still left with d_s and l as unknowns that can affect the poststenotic perfusion. Kirkeeide (*21*) has simulated the affect of stenosis dimension on coronary flow. However, it may be necessary to characterize the severity of the stenosis from perfusion defects.

DISCUSSION

We have assumed in the derivation of the model that the stenosis is regular in shape, whereas most coronary stenoses have irregular geometry. Determining severity of a geometrically irregular stenosis from perfusion defects may be difficult, but it is unnecessary for clinical applications. In fact, there is no clinical or hemodynamic evidence to indicate that one stenosis shape is worse than another. For example, is a long mild stenosis better or worse than a shorter more severe one for any given pressure gradient at a given flow? Furthermore, in measuring stenosis dimensions for progression or regression, one may reasonably ask how one would classify a coronary lesion that becomes less severe but longer on reversal therapy. Would it be functionally worse or better? It may therefore be necessary to grade the severity of a stenosis by its effect on perfusion in the areas distal to it, which is a function of all the dimensions of the stenosis.

PET measures the perfusion defect directly, and can therefore be used to obtain information that may be of considerable help in a clinical situation. Gould (*20*) and Young (*6*) have shown that at resting flow the pressure drop across a stenosis remains fairly small as the narrowing becomes more severe until a critical point is reached where minimal further narrowing causes a drastic increase in pressure drop and falloff in flow. This phenomenon, termed "critical stenosis," has been studied by Young et al. (*6*), Mates et al. (*7*), and Gould et al. (*20*). A second observation made by Gould (*5*) is the concept of "coronary flow reserve" (CFR) whereby the maximum flow possible through a stenotic artery is used to measure total flow reserves available to the myocardium as a functional measure of the severity of a stenosis. Initial data, obtained with PET cameras and N-13 ammonia (*16*) for coronary stenosis in dogs, have shown that perfusion in an ischemic region is fairly normal for mild stenosis (<80%) at normal resting flow. Moreover, the ratio f_s/f becomes abnormal when flow is maximally increased even for milder stenoses.

These experimental observations can be related to the theoretical predictions in Eq. (6), which can be rearranged to represent the pressure-perfusion relationship:

$$\frac{f_s}{f} = \frac{r}{r_s}\left[1 - \frac{\Delta P}{P_a - P_v}\right]. \quad (15)$$

As flow is increased from the normal resting value to a higher rate, the pressure drop ΔP increases gradually, such that the term

$$\left[1 - \frac{\Delta P}{(P_a - P_v)}\right] \text{ becomes less than 1,}$$

and if the perfusion ratio f_s/f is equal to 1, then r/r_s must increase to compensate for the pressure drop due to the stenosis. Thus, Eq. (15) indicates that compensatory vasodilation must occur in the poststenotic regions if the perfusion levels are to be maintained.

From experimental observations, we know that, in the presence of a stenosis, the resistance of the capillary bed decreases due to autoregulation (*22,23*), and flow is maintained in the face of a fall in perfusion pressure. We also know that the ratio f_s/f, as derived from PET observations in mild stenosis, remains close to unity; therefore, the ratio r/r_s has to be greater than one in order for autoregulation to be present. This phenomenon has been documented experimentally by Gould et al. (*23*) and Schaper et al. (*24*).

As flow is increased further by coronary vasodilation,

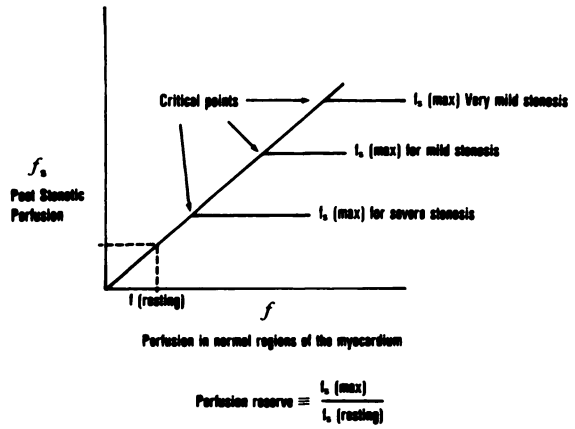

FIG. 2. Relationship between f and f_s, as expressed by Eq. (6). As vascular bed is dilated, both f and f_s will increase proportionally due to autoregulation. When resistance r_s in poststenotic area reaches minimum value, r_{min}, perfusion in poststenotic region, f_s, cannot increase any further and stenosis reaches a critical point, depending on severity of stenosis. Perfusion reserve is then defined as maximum perfusion in the region divided by normal resting perfusion.

a point will be reached when $r_s = r_{min}$ and cannot fall further. At that point, for a given perfusion pressure, the maximum possible flow to the poststenotic area is reached. As long as the driving pressure, $(P_a - P_v)$, is constant, the flow will remain at that level while flow increases further in the normal area with ongoing vasodilation. The perfusion resistance, r, in the normal area will continue to decrease until a point is reached when it also equals r_{min} and cannot decrease any more. The normal region of the myocardium then also reaches its maximum coronary flow reserve.

If the two perfusions, f_s and f, are plotted, then one would expect a straight line (Fig. 2) until $r_s = r_{min}$, at which point f_s (max) becomes constant. However, f will continue to increase with further vasodilation. The point at which perfusion in the poststenotic region becomes maximum can then be used to measure the "perfusion reserve" of that region of the myocardium by obtaining the ratio of f_s (max) to f_s (resting). That is:

$$\text{"perfusion reserve"} \equiv \frac{\text{maximum perfusion}}{\text{normal resting perfusion}},$$

$$\text{or perfusion reserve} = \frac{f_s\ (max)}{f_s\ (resting)}$$

Perfusion reserve (PR) and coronary flow reserve are identical in the absence of collateral circulation because of the relationship

$$\frac{f_s}{f} = \frac{\dot{Q}_s}{Q}.$$

In the presence of collateral circulation, however, some of the perfusion in the poststenotic area may be supplied by an adjacent artery, which would artificially elevate the coronary flow reserve for that artery. PR, on the other hand, is measured irrespective of where the flow originates, and therefore can account for the change in perfusion caused by collateral circulation in addition to, and independent of, any change in severity of the stenosis.

The concept of perfusion reserve is extremely powerful in that it allows a direct measurement of the maximum capacity of the coronary circulation for the maintenance of the tissue distal to the stenosis. For a severe stenosis, in which angina is present during mild exercise, the perfusion reserve would be depleted with minimal increase in flow, and would be close to unity.

It is possible for the perfusion reserve ratio to fall below unity. Flameng et al. (*25*) have shown that vasodilation beyond a severe obstruction can cause the pressure drop across the stenosis to increase, thus reducing the perfusion distal to it. Gould (*20*) has shown that this phenomenon is due to the dilation of the proximal and distal normal coronary artery or due to "collapse" of the stenotic segment.

Perfusion reserve is easy to measure with PET, since it requires only two measurements: one obtained at normal resting flow and another during maximum vasodilation (*3*). The normal resting perfusion for each patient is used as the control perfusion against which to rate the maximum perfusion. The requirements on the PET camera are also simplified, since the perfusion reserve can be computed from a single image plane, without requiring a multislice camera.

CONCLUSION

A simple model has been presented, which relates the severity of a myocardial perfusion defect to severity of coronary artery stenosis. The model has been derived for a single vessel, assuming a single stenosis and the absence of collateral circulation. The assumptions made in the derivation of the model are either based on known myocardial physiology or are justified by current literature. The relation between perfusion deficit and stenosis dimensions shows that predicting the stenosis dimensions may be difficult but is unnecessary for clinical applications.

The extension of the concept of coronary flow reserve and perfusion reserve to characterize the severity of a stenosis is powerful, with immediate clinical implications in man. Its application is easily achieved with positron tomography provided maximal coronary vasodilation can be implemented in man effectively.

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APPENDIX

Justification of assumptions in the derivations. In the derivation of the perfusion-pressure equations there have been some explicit and implicit assumptions made about myocardial physiology and coronary circulation, and these need to be justified. The first major assumption made in the equations is that myocardial perfusion is uniform within regions of myocardium. Several studies of myocardial perfusion, as measured with microspheres under different physiological conditions, confirm this assumption. Most of these studies have shown that there is a perfusion gradient from the endocardium to the epicardium.

Marcus et al. (*26*) measured the distribution of 7-10 μm microspheres in the dog myocardium for small (0.78-g) samples of tissue. They found that the distribution of perfusion values along the whole heart could be represented by a normal probability distribution with a mean of 88.19 ml/min-100 g and a standard deviation of 14.95 ml/min-100 g. The endo-to-epi perfusion ratio ranged from 1.2 at the base to 0.98 at the apex. Ball et al. (*27*) have studied the variability of the endo-to-epi perfusion ratio under exercise and ischemia in dog models, and found that this ratio decreases with ischemia and with exercise.

A comprehensive study by Yipinstoi et al. (*28*) compared the distribution of labeled microspheres of different sizes and labels with that of diffusible tracers such as I-125-labeled antipyrene (IAP), [^{42}K] potassium chloride, and [^{86}Rb] rubidium chloride. They found large variations in microsphere measured flow relative to IAP-measured flow. They collected extremely small samples of tissue, ranging from 0.02 to 0.48 g, and showed that the distribution of microspheres depended on the size of the microspheres and the radioactive label. RbCl and small microspheres (<10 μm) were distributed fairly uniformly in the heart but showed slightly higher perfusion in the endocardium as relative to the epicardium.

An analysis of the several perfusion studies carried out with microspheres indicates that a large portion of the variability reported in perfusion from region to region may be due to the inherent complexity and errors associated with labeled microspheres used as perfusion indicators. Yipinstoi et al. (*28*) found variability by a factor of 15 in perfusion measurements with microspheres for small tissue samples. Marcus et al. (*26*) observed a much smaller variation ($\pm$16%) for larger tissue samples.

Diffusible tracers such as [N-13] ammonia and [^{82}Rb]rubidium chloride show very little difference in distribution, as was observed by Yipinstoi et al. for IAP and RbCl, Gould et al. (*16*) observed less than 10% difference in the distribution on N-13 ammonia in dog hearts as imaged with an ECAT (*29*) positron camera. Mullani et al. (unpublished data) have also observed less than 10% variation in the distribution of [^{82}Rb]rubidium chloride in dog hearts at normal and maximal flow as observed with the TOFPET I (*30*) positron camera. Since the resolution of the present PET cameras is not sufficient to distinguish between epi and endo perfusion, it is reasonable to expect homogenity of perfusion in the myocardium as imaged with these devices. Therefore, the assumption of uniform perfusion for sample volume as observed with a PET camera is valid for the first-order model derived in this text.

The second major assumption in the model is that the pressure gradient along a major epicardial coronary artery is very small and can be neglected in comparison with the pressure drop across a stenosis or across the distal vascular bed. Kelley (*31*) in an extensive study of the pressure drop along a coronary artery, found it to be small even in the distal ($\sim$1 mm diam) arteries. Implicit in these two assumptions is the requirement that regional perfusion pressure be uniform in a normal area of the heart. If perfusion is homogenous and the pressure drop in the large vessel is negligible, then the perfusion pressure for all regions must also be uniform. These conclusions imply that the perfusion resistance must also be homogenous within a given region of myocardium.

Several other assumptions have been made in this paper, such as the ability of PET cameras to measure accurately perfusion and the sizes of perfusion defects. The model also assumes that maximal vasodilation will be possible in the heart and that a short-lived positron emitter such as Rb-82 or oxygen-15 can be used to make two or more measurements with PET sequentially.

The application of this model to man will require several experimental studies in order to determine errors in estimating severity of stenosis, caused by random noise in the data and the motion of the heart. Finally, these studies will need to be validated in man by comparison with quantitative coronary arteriography.

REFERENCES

1. MANN FC, HERRICK JF, ESSEX HE, et al: The effect on the blood flow of decreasing the lumen of a blood vessel. *Surgery* 4:249-252, 1938
2. SHIPLEY RE, GREGG DE: The effect of external constriction of a blood vessel on blood flow. *Am J Physiol* 141:289-296, 1944
3. BROWN BG, JOSEPHSON MA, PETERSON RB, et al: Intravenous dipyridamole combined with isometric handgrip for near maximal acute increase in coronary flow in patients with coronary artery disease. *Am J Cardiol* 48:1077-1085, 1981
4. GOULD KL: Pressure-flow charactertistics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. *Circ Res* 43:242-253, 1978
5. GOULD KL, LIPSCOMB K, HAMILTON GW: Physiologic basis for assessing critical coronary stenosis. *Am J Cardiol* 33:87-94, 1974
6. YOUNG DF, CHOLVIN NR, KIRKEEIDE RL, et al: Hemodynamics of arterial stenoses at elevated flow rates. *Circ Res* 41:99-107, 1977
7. MATES RE, GUPTA RL, BELL AC, et al: Fluid dynamics of coronary artery stenosis. *Circ Res* 42:152-162, 1978
8. YOUNG DF, TSAI FY: Flow characteristics in models of arterial stenoses-I. Steady flow. *J Biomech* 6:395-410, 1973
9. BROWN BG, BOLSON EL, FRIMER M, et al: Quantitative coronary arteriography: Estimation of dimensions, hemodynamic resistance, and atheroma mass of coronary artery lesions using the arteriogram and digital computation. *Circulation* 55:329-337, 1977
10. KIRKEEIDE RL: Wall vibrations induced by flow through modeled arterial stenoses. MS Thesis, Iowa State University, 1974
11. RITCHIE JL, ZARET BL, STRAUSS HW, et al: Myocardial imaging with thallium-201: A multicenter study in patients with angina pectoris or acute myocardial infarction. *Am J Cardiol* 42:345-350, 1978
12. LEPPO J, BOUCHER CA, OKADA RD, et al: Serial thallium-201 myocardial imaging after dipyridamole infusion: Diagnostic utility in detecting coronary stenoses and relationship to regional wall motion. *Circulation* 66:649-657, 1982
13. MULLANI NA, GOULD KL, GAETA JM: Tomographic imaging of the heart with thallium-201: Seven-pinhole or rotating gamma camera? *J Nucl Med* 22:925-926, 1981
14. SMALLING RW: The SPECTrum of thallium-201 imaging

in coronary artery disease. *J Nucl Med* 24:854–858, 1983
15. PHELPS ME, HOFFMAN EJ, MULLANI NA, et al: Application of annihilation coincidence detection to transaxial reconstruction tomography. *J Nucl Med* 16:210–224, 1975
16. GOULD KL, SCHELBERT HR, PHELPS ME, et al: Noninvasive assessment of coronary stenoses with myocardial perfusion imaging during pharmacologic coronary vasodilation. V. Detection of 47 percent diameter coronary stenosis with intravenous nitrogen-13 ammonia and emission-computed tomography in intact dogs. *Am J Cardiol* 43:200–208, 1979
17. SEELY BD, YOUNG DF: Effect of geometry on pressure losses across models of arterial stenoses. *J Biomech* 9:439–448, 1976
18. STACK RS, REMBERT JC, SCHRIMER B, et al: Relation of left ventricular mass to geometry of the proximal coronary arteries in the dog. *Am J Cardiol* 51:1728–1731, 1983
19. HUTCHINS GM, BULKLEY BH, MINER MM, et al: Correlation of age and heart weight with tortuosity and caliber of normal human coronary arteries. *Am Heart J* 94:196–202, 1977
20. MACALPIN RN, ABBASI AS, GROLLMAN JH, et al: Human coronary artery size during life. *Radiology* 108: 567–576, 1973
21. KIRKEEIDE RL, GOULD KL: Cardiovascular Imaging: Coronary Artery Stenosis. *Hospital Practice* 19(4):160–175, 1984
22. MOSHER P, ROSS J, MCFATE PA, et al: Control of coronary blood flow by an autoregulatory mechanism. *Circ Res* 14: 250–259, 1964
23. GOULD KL, LIPSCOMB K, CALVERT C: Compensatory changes of the distal coronary vascular bed during progressive coronary constriction. *Circulation* 51:1085–1094, 1975
24. SCHAPER W, FLAMENG W, WINKLER B, et al: Quantification of collateral resistance in acute and chronic experimental coronary occlusion in the dog. *Circ Res* 39:371–377, 1976
25. FLAMENG W, WÜSTEN B, SCHAPER W: On the distribution of myocardial flow. Part II: Effects of arterial stenosis and vasodilation. *Basic Res Cardiol* 69:435–446, 1974
26. MARCUS ML, KERBER RE, EHRHARD J, et al: Three dimensional geometry of acutely ischemic myocardium. *Circulation* 52:254–263, 1975
27. BALL RM, BACHE RJ: Distribution of myocardial blood flow in the exercising dog with restricted coronary artery inflow. *Circ Res* 38:60–66, 1976
28. YIPINSTOI T, DOBBS WA, SCANTON PD, et al: Regional distribution of diffusible tracers and carbonized microspheres in the left ventricle of isolated dog hearts. *Circ Res* 33:573–587, 1973
29. PHELPS ME, HOFFMAN EJ, HUANG SC, et al: ECAT: a new computerized tomographic imaging system for positron emitting radiopharmaceuticals. *J Nucl Med* 19:635–647, 1978
30. MULLANI NA, WONG WH, HARTZ RK, et al: Design of TOFPET: A high resolution time-of-flight positron camera. *IEEE Trans Nucl Sci*:31–36, 1982
31. KELLEY KO, FEIGL EO: Segmental α-receptor-mediated vasoconstriction in the canine coronary circulation. *Circ Res* 43:908–917, 1978