The study reported by Hess et al in this issue of Circulation presents a timely opportunity to discuss several issues that are directly relevant to use of angiographic methods for estimating myocardial perfusion. These issues are motivation for use of angiographic methods, limitations of the gold standard used, limitations of the angiographic method, limitations of the conceptual model used and importance of negative studies in this field.

Angiographic Methods

As recently as 1987, positron emission tomography was deemed to be the most accurate clinically usable method. Angiographic methods continue to be explored, however, because if they were of acceptable accuracy, the additional advantage would be that they could be performed simultaneously with the angiographic imaging used to visualize and quantify coronary artery anatomy. This capability could enhance the utility of coronary angiography, which is currently also used to estimate the physiological implications of the stenoses. However, this approach is generally acknowledged to be of insufficient accuracy for establishing whether a particular stenosis, even one of 50–70% severity, is truly responsible for causing the clinical signs and symptoms of myocardial ischemia. In addition, if flow could be measured at the time of coronary angiography, the added cost of the procedure could be small in comparison with the cost of a separate study just for flow measurement.

See p 1438

Because it has been possible to estimate coronary flow and perfusion by analog means since the mid-1960s and digital recording of video angiograms has been possible since the mid-1970s, one asks why this approach was not more fully exploited until the 1980s. One possibility is that the superposition of two opposite heart walls and the transmural layers of the heart wall made physiologically useful measurements essentially impossible. Although these limitations are largely overcome by fast computed tomography, we continue to see publication of slight modifications of angiography-based techniques. There are several plausible reasons for this—one is possibly that widely available digital recording angiography systems provide this image analysis capability. Another plausible reason is that even though flow might not be quantifiable in terms of milliliters per gram per minute, the images do provide a quantitative index of the hemodynamic implication of a coronary stenosis. In pursuit of this goal, several models, including that used by Hess et al, have been proposed for use in estimating an index of relative perfusion. Thus, if the coronary artery cannot support the normal four- or fivefold increase of flow (also known as flow reserve) that would occur during increased myocardial oxygen demand (during exercise or pacing tachycardia) or during regional vasodilatation (such as that produced with dipyridamole), a stenosis in that artery is deemed to be of hemodynamic significance. Clearly, such a study would require a coronary angiogram under control conditions and an additional one during the intervention condition.

Before discussing this approach we need to address the feasibility of evaluating the accuracy of any method of flow estimation.

Gold Standard Used

There are several potential problems with gold standards even if they are 100% accurate. First, use of the gold standard at a time other than that of the angiographic study (with potentially different perfusion) is a problem that is often experienced.

Second, different methods may measure different flows. Radiolabeled microspheres tend to measure flow of cells, whereas plasma-soluble contrast agents tend to measure flow of plasma. This may result in differences in, for instance, estimates of transmural distribution of flow.

Third, even if the microsphere method (or any other method that requires the heart to be removed at postmortem) were 100% accurate, the flow is...
expressed in milliliters per gram per minute. However, postmortem myocardium contains little blood (due to partial exsanguination) as compared with the in vivo measurement where flow is measured in milliliters per cubic centimeter per minute—a cubic centimeter of in vivo myocardium almost certainly contains more blood and less muscle than does a cubic centimeter of postmortem myocardium. As the intramyocardial blood volume may be of the order of 10–20%, and is flow dependent, underestimation of in vivo flow would occur at higher flows.

True gold standards rarely exist and, as pointed out by Marcus et al., it is unlikely that one exists for measurement of myocardial perfusion. This inaccuracy is due to imprecision as well as corrupting influences such as partial volume effects and averaging over a number of cardiac cycles. In addition, spatial and temporal heterogeneity of flow make it most unlikely that flow values obtained by two methods ever correspond exactly because measuring identical sample volumes at identical sample locations and times is generally unachievable. Nonetheless, it may be possible to normalize for heterogeneity using a fractal analysis technique such as that proposed recently by Bassingthwaighte et al.

**Angiographic Method Limitations**

Limitations of the angiographic methods are important. The radiography generation, video recording, and processing technicalities, along with the correct transformation of image data from radiographic intensity to subject density values, require techniques or corrections that are well understood but often not fully implemented. However, the limitations of the radiographic projection process are often minimized or made negligible by use of special experimental conditions. Thus, superposition of the anterior and posterior left ventricular walls can be largely overcome if a superselective injection of dye is used to opacify one wall only. However, this method still suffers from practitioners’ inability to separate the flow in transmural layers.

The use of selective coronary injection also raises the question of the artificial perfusion modulation by the injection itself. Although this problem can be minimized if nonselective injections of dye are used, this in turn results in problems for most conceptual models. In addition, if the cardiac chambers are opacified (as would be the case with a right-sided injection of dye), radiographic beam hardening and/or photon scatter may cause imaging artifacts that are particularly difficult to deal with. Selective injections can result in brief curves (which are needed to satisfy the conditions of some conceptual models for estimating flow) but this causes loss of accuracy due to the slow sampling frequency (generally one sample per cardiac cycle).

**Conceptual Model Limitations**

The most straightforward model for calculating blood flow from indicator dilution curves is the one that uses the angiographic image to calculate the myocardial intravascular blood volume (V) and the transit time (ΔT) through that volume. Flow, then, is V/ΔT. Transit time can be measured quite well with angiographic methods—indeed, most of the reports over the past decade, including the study by Hess et al., have used some index of bolus transit time. The problem lies with the determination of myocardial intravascular volume, largely because with projection images no distinction can readily be made between concentration and depth of the contrast in the heart walls. As a consequence, V is often ignored, leaving the ratio of the ΔTs (estimated during rest and stress or vasodilation) to be used as an index of flow reserve.

Unfortunately, this approach has several problems. First, it requires that V remain unchanged with flow and that is clearly not true. Second, even if this transit time ratio analysis were an accurate index of relative flow, flow reserve as an index of the hemodynamic importance of a coronary artery stenosis should be used with caution.

Another model that is commonly used is an indicator-dilution model first applied to radionuclide washout methods. This method also has several problems that were well delineated and discussed in recent correspondence between Yen and Mullani and Gould in the Journal of Nuclear Medicine. Briefly, for this method there is the need to have all the injected contrast in the region of interest after the injection has stopped. This is difficult to do, especially if nonselective injections of contrast are used.

A more basic problem with this approach, however, is that it is based on the assumption that a significant proportion of the indicator enters the extravascular space, or at best mixes freely in a mixing chamber. Most contrast agents, by design, exhibit insufficient extraction to reliably permit such an analysis. Although Mullani’s computer model suggests that this does not invalidate this model, the practical reality is that the lack of extraction results in rapid transit of the contrast, violating the basic premise of the model. In addition to these concerns, this approach requires that small volumes of tissue be sampled so that the spatial heterogeneity of flow can be accounted for. This can be done correctly with tomographic methods, but the inability of projection methods to account for the spatial heterogeneity of flow may be an important reason for its imprecision.

Despite all the above problems, however, the practical accuracy of the technique may still be acceptable. A good example of this type of situation was the widespread use of indocyanine green for calculating cardiac output even though the theoretically necessary conditions were generally not met. However, in this circumstance, the onus is on the investigators to demonstrate that their imprecise method is adequate for the clinical or research goals.
Negative Studies

Taking all the above aspects into account, it is clear that a superficially negative study such as the study of Hess et al (see Figure 5, Reference 1) should not be discarded out of hand because their results may still be adequate for population studies. It is unlikely, however, that their approach will be adequate for evaluation of an individual patient. It is to be hoped that the results of their study will indicate a need for careful, critical thought before an off-the-shelf, expensive angiographic image analysis system is purchased and employed for estimation of coronary flow or flow reserve, especially if evaluation of individual subjects is intended in the near future.

References


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