Instantaneous Hyperemic Flow-Versus-Pressure Slope Index
Microsphere Validation of an Alternative to Measures of Coronary Reserve

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Background. The instantaneous hyperemic flow-versus-pressure (i-HFVP) slope index is a new method of assessing maximal coronary conductance and can be used as an alternative to conventional measures of coronary reserve. The i-HFVP slope index is determined by measuring the slope of the linear diastolic segment of the relation between instantaneous aortic pressure and hyperemic coronary flow.

Methods and Results. To validate the i-HFVP slope index as a measure of maximal coronary conductance, we compared this method with a microsphere-derived measurement of maximal coronary conductance (m-HFVP slope index) by determining the slope of the least-squares regression line of the data points for coronary flow during maximal hyperemia and four or five steady-state alterations of aortic pressure in 43 dogs (open-chest, anesthetized preparations) with or without coronary stenoses. The i-HFVP slope index demonstrated no dependence on heart rate, left ventricular end-diastolic pressure, or mean aortic pressure and was highly reproducible within the groups studied (intraclass correlation coefficient, 0.86 for normal arteries, 0.87 for stenotic arteries, and 0.93 for combined groups; for all coefficients, \(p<0.001\)). The i-HFVP slope index was significantly decreased in the presence of a stenosis \((10.3\pm3.9\) for normal arteries versus \(3.6\pm1.6\) for stenotic arteries, \(p<0.001\)) as was the transmural m-HFVP slope index \((8.9\pm4.6\) for normal arteries versus \(5.3\pm3.1\), \(p<0.01\)). Of special importance, the i-HFVP slope index measurement for normal arteries was not significantly different from the transmural and subendocardial m-HFVP slope index measurements \((10.3\pm3.9\) versus \(8.9\pm4.6\) and \(9.2\pm5.7\), respectively). For stenotic arteries, the i-HFVP slope index measurement was also not significantly different from the transmural and subendocardial m-HFVP slope index measurements \((3.6\pm1.6\) versus \(5.3\pm3.1\) and \(4.1\pm2.3\), respectively). The i-HFVP slope index correlated best with subendocardial m-HFVP slope index measurements \((r=0.57\); \(p<0.001\)). When the 95% confidence intervals for the transmural (or subendocardial) m-HFVP slope index in normal arteries were compared with the i-HFVP slope index values, the latter demonstrated a systematic trend to overestimate the m-HFVP slope index. In the presence of a stenosis, this effect was minimized, and the slope values were nearly identical.

Conclusions. The i-HFVP slope index correlates most closely with subendocardial coronary conductance; the index is a hemodynamically independent measure of coronary reserve that is reproducible over a broad range of aortic pressures; and the methodology is applicable to an intact circulation in experimental preparations and may with future developments also prove useful in humans. (Circulation 1991;84:862–870)

The development of digital angiography and subselective Doppler flow catheters has facilitated the measurement of coronary flow reserve in humans. As recently reviewed by Hoffman and Klocke, however, there are theoretical limitations to the coronary flow reserve concept. For
example, maximum hyperemic coronary blood flow is strongly pressure dependent, and the autoregulated level of basal coronary flow varies greatly. Consequently, the ratio of hyperemic to basal coronary flow, often used as an index of stenosis severity, displays substantial inconsistencies that dilute its potential diagnostic usefulness.

Theoretical problems such as this motivated us to examine the hemodynamic dependency of various methods of determining coronary flow reserve and to propose a new index, the instantaneous hyperemic flow-versus-pressure (i-HFVP) slope index. The i-HFVP slope index is determined by measuring the slope of the linear diastolic segment of the relation between instantaneous aortic pressure and hyperemic coronary flow (Figure 1). The graphic representation of the relation inscribes a flow–pressure loop that moves in a counterclockwise direction through the phases of the cardiac cycle. Only during late diastole and under the conditions of maximal hyperemia does the relation become linear and allow measurement of a slope, which is the i-HFVP slope index.

In the intact canine model, maximal coronary flow is measured with a calibrated electromagnetic flow probe placed around the external surface of a coronary artery, and aortic pressure is measured by a high-fidelity micromanometer introduced through a carotid arterial cannula. When the i-HFVP slope index is normalized by the perfusion bed mass, it is measured in milliliters per minute per millimeters of mercury per 100 g. Thus, the i-HFVP slope index constitutes a measure of maximal coronary conductance.

Prior work has shown that the i-HFVP slope index was independent of changes in mean aortic pressure and slightly more sensitive in detecting stenoses than the traditional measure of coronary flow reserve.\(^5\) However, whether the index correlates with an actual measurement of myocardial conductance based on microsphere measurements is not known. Accordingly, the purpose of the present investigation was to
determine the relation between maximal coronary conductance measured by the i-HFVP slope index and by radiolabeled microspheres. In so doing, a reanalysis of the hemodynamic determinants of the i-HFVP slope index was also possible.

Methods

Forty-three mongrel dogs of either sex (mean weight, 21.4 kg; range, 15.3–26.6 kg) were studied. All animals were anesthetized with sodium pentobarbital (35 mg/kg), intubated, and ventilated with a Harvard respirator. A left thoracotomy was performed in the fifth intercostal space. The heart was exposed and supported in a pericardial cradle. The proximal descending aorta was dissected free and surrounded by a Blalock clamp. A left carotid arteriotomy and left jugular venotomy were performed, and sheaths were inserted for vascular access. The proximal left anterior descending and circumflex arteries were dissected free for 3–4 cm. An appropriately sized and calibrated electromagnetic blood flow probe (Carolina Medical Electronics, King, N.C.) and an elastic vessel loop were placed on each coronary artery to produce brief occlusions for zero-flow determination. A lightweight acrylic C-clamp (Poly C Co., Rochester Hills, Mich.) was placed on the left anterior descending artery (n=7) or the circumflex artery (n=6) to produce partial stenosis.

Calibrated, 5F micromanometers (Millar Instruments, Houston, Tex.) were passed through the carotid sheath into the ascending aorta and through an apical stab wound into the left ventricle. Zero pressure was established at the mid heart level after thoracotomy. Drift was assessed frequently throughout the protocol. Left ventricular pressures, differentiated left ventricular pressure (dP/dt), phasic aortic pressure, phasic coronary blood flow, and heart rate were monitored on a Gould recorder (model 2800S, Gould Electronics, Cleveland, Ohio) interfaced to an IBM AT computer modified for on-line signal digitization at 200 Hz/channel (Figure 1, left panel).

Additional preparation in these animals included placement of a withdrawal cannula through a femoral arteriotomy and insertion of a polyethylene injection line into the left atrial appendage. Commercially available microspheres (Dupont/New England Nuclear, North Billerica, Mass.) 15 μm in diameter and labeled with 113Sn, 46Sc, 50Nb, 114Ce, and 103Ru were used. Each microsphere sample (approximately 1.5×10⁵ spheres in 10 ml of 37°C saline) was ultrasonicated, vortexed, and injected over 30–60 seconds through the left atrial line during steady-state, maximal hyperemia induced by adenosine (see below).

All animals were treated with propranolol (1 mg/kg) and atropine sulfate (1 mg) before performing the protocol. Adenosine (9-D-ribofuranosyladenine) (Sigma Chemical Co., St. Louis) was dissolved in 37°C saline to produce a supersaturated solution that was infused through the jugular cannula at a rate of 1 mg/kg/min to induce maximal hyperemia. Microspheres were injected during four or five steady-state levels of aortic pressure altered in increments of 10–15 mm Hg by variable constriction of the aortic Blalock clamp. Mean aortic pressures below 60 and above 140 mm Hg were avoided. During microsphere injections, a reference arterial sample⁶ was withdrawn from the femoral artery (7.6 ml/min for 3 minutes) using a Harvard withdrawal pump. The microsphere technique used by this laboratory has been described previously.⁷

Coronary stenoses were produced by adjusting the C-clamp occluders during adenosine infusion in the subsets of animals designed to evaluate the i-HFVP slope index with coronary obstruction. The occluder was adjusted until electromagnetically measured coronary blood flow had decreased to values approximating resting flow values before adenosine infusion. As described above, different aortic pressures were produced after the coronary obstruction was produced. After reaching each steady-state pressure, microspheres were injected during each steady-state pressure level.

Pressure and flow data from two to 11 (average, eight) cardiac cycles were digitized, averaged, and stored on disk at the beginning, middle, and end of the femoral blood withdrawal periods. The experiments were concluded by the administration of an overdose of pentobarbital and potassium chloride.

Subselective intracoronary infusion with 2,3,5-triphenyltetrazolium chloride (Sigma) and Evans blue dye (Sigma) was used to determine perfusion bed mass at the conclusion of the experiments. The left anterior descending coronary and left circumflex coronary arteries were proximally cannulated with polyethylene tubing (at the level of the C-clamp in the stenosed artery). The aortic root was separately cannulated and simultaneously perfused with 37°C isotonic saline. Dye perfusion was performed at 100 mm Hg for 5 minutes. Dyed perfusion beds were then dissected free and weighed. Three to 14 (average, eight) tissue samples were obtained from each perfusion bed. Each transmural sample was dissected into subendocardial, midmyocardial, and subepicardial pieces of approximately equal thicknesses. All tissue samples were weighed on a Sartorius digital balance (Goettingen, FRG). Blood samples were hemolyzed with KOH and desiccated at 70°C for 3–5 days.

Radioactive counts were determined with a Tracor (model 1185) gamma scintillation counter, and blood flow was calculated as the following:⁸

\[ Q_m = \frac{c_m Q_t}{c_r} \]

where \( Q_m \) is myocardial blood flow (ml/min), \( c_m \) is counts in the tissue sample (counts/min), \( Q_t \) is withdrawal rate of the reference blood sample (ml/min), and \( c_r \) is counts in the reference blood sample (counts/min). Blood flow per gram of tissue was calculated by dividing \( Q_m \) by the weight of the tissue sample.⁸
Forty-three mongrel dogs were studied, but the protocol was completed in only 34 (68 arterial beds). Of these, data from 28 beds were excluded because of greater than 10% changes in electromagnetic probe blood flow measurements during microsphere injections. One dog (two beds) was excluded because of technical problems with the high-fidelity micromanometer. One arterial bed with impaired epicardial coronary flow was excluded because microsphere measurements were completely normal, suggesting profuse collateral blood flow. Eight additional arterial beds were excluded from analysis as discussed below. Therefore, this report is based on 29 arterial beds studied in 18 dogs.

Calculation of Mean Maximal Coronary Conductance From Microsphere Data

The microsphere perfusion results during each level of mean aortic pressure were analyzed by least-squares linear regression analysis to determine a slope value equal to the mean, maximal coronary conductance in the myocardium (ml/min/mm Hg/100 g). This was calculated for the entire wall (using transmural microsphere measurements) as well as for each layer (using microsphere measurements from only the endocardium, midmyocardium, or epicardium). Regression analyses that did not yield a significant ($p<0.05$) correlation coefficient for all three layers of the wall were not considered further (eight perfusion beds) because under such circumstances the validity of the microsphere measurements as a standard for comparison with the i-HFVP slope index would be questionable. Because each dog was subjected to at least four pressure levels and each perfusion bed yielded a minimum of three transmural tissue samples, the linear regression analyses were performed on a minimum of 12 data points. A maximum of 60 points were available in some instances. Statistically significant $r$ values can be no less than 0.30 when 60 points are used and no less than 0.54 when 12 points are used. The resulting, statistically significant $r$ values in the present study ranged from 0.33 to 0.96. Ninety-five percent confidence limits were calculated for the slope values. 8 Thus, each coronary bed could be characterized by a single, microsphere-derived measure of mean, maximal coronary conductance associated with a confidence interval (microsphere-derived hyperemic flow-versus-pressure [m-HFVP]) slope index.

Calculation of i-HFVP Slope Index

The i-HFVP slope index was calculated from the instantaneous flowmeter and aortic pressure measurements during diastole as previously described. 8 Figure 1 shows the process schematically. An aortic pressure tracing and a flowmeter tracing are combined to create a flow versus pressure loop. The slope of the relatively linear diastolic portion defines the i-HFVP slope index, which, after normalizing for bed weight, is an index of maximal coronary conductance (ml/min/mm Hg/100 g). Note that this was calculated at each pressure level, four or five times per coronary bed, whereas only a single transmural measurement of maximal coronary conductance could be calculated from the microsphere data for the same coronary bed. The reproducibility of the four or five values obtained for the i-HFVP slope index at different pressure levels was determined using an intraclass correlation. 9 Repeated measures analysis of covariance was used to determine hemodynamic dependency of the i-HFVP slope index measured at different pressure levels. 10 To provide a balanced model as required for this analysis, data for arteries, which were investigated at five different pressure levels, had to be adjusted to four pressure levels. This was done by averaging the data from the pair of observations obtained at the most similar mean aortic pressure levels. Comparisons between the i-HFVP and the m-HFVP slope indexes were made using repeated measures analysis of covariance and the Bonferroni simultaneous multiple comparison method. 11 Least-squares linear regression was used to correlate i-HFVP and m-HFVP slope indexes. The frequency with which the i-HFVP slope index measurements fell within or outside the 95% confidence intervals for the m-HFVP slope index derived from the microsphere data in individual dogs was also tabulated.

Beat-to-Beat Variability of i-HFVP Slope Index Measurements

Although the i-HFVP slope index is always determined by averaging several cardiac cycles (Figure 1), the index was calculated in four randomly selected studies for each cycle to demonstrate beat-to-beat variability.

Results

As previously stated, the i-HFVP slope index could be derived at each pressure level, resulting in four or five determinations per artery (or coronary bed). Therefore, the i-HFVP slope index was calculated 71 times in 16 normal arteries (five determinations in seven normal arteries and four determinations in nine normal arteries) and 60 times in 13 stenotic arteries (five determinations in eight stenotic arteries and four determinations in five stenotic arteries). These calculations were highly reproducible and yielded an intraclass correlation coefficient of 0.86 in normal arteries, 0.87 in stenotic arteries, and 0.93 when combined (all coefficients were associated with $p<0.001$).

Recall that for the microsphere technique, 12 to 15 data points were measured from each arterial bed. Radioactive counts were measured from three to 14 transmural specimens that were divided into subepicardial, midmyocardial, and subendocardial muscle layers. A data point was calculated as the average of the three to 14 values for each layer. Arterial beds were studied at four or five pressure levels, and each pressure level corresponded to a different microsphere isotope. Therefore, three data points were generated per pressure level ([3×4 or 5]=12 to 15).
Table 1. Comparison of i-HFVP and m-HFVP Slope Indexes of Maximal Coronary Conductance

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=16)</th>
<th>Stenotic (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-HFVP</td>
<td>10.3±3.9</td>
<td>3.6±1.6*</td>
</tr>
<tr>
<td>m-HFVP</td>
<td>9.2±5.7</td>
<td>4.1±2.3*</td>
</tr>
<tr>
<td>Transmural</td>
<td>8.9±4.6</td>
<td>5.3±3.1†</td>
</tr>
<tr>
<td>Subendocardial</td>
<td>10.3±5.7</td>
<td>6.0±3.4†‡</td>
</tr>
<tr>
<td>Midmyocardial</td>
<td>7.3±3.3</td>
<td>5.7±3.7</td>
</tr>
</tbody>
</table>

i-HFVP, instantaneous hyperemic flow-versus-pressure slope index; m-HFVP, microsphere-derived hyperemic flow-versus-pressure slope index.

All values are given as mean±1 SD and in ml/min/mm Hg/100g.

*p<0.001 vs. normal.

†p<0.01 vs. normal.

‡p<0.05 vs. i-HFVP.

Regression of the four or five data points that were unique for a particular muscle layer yielded a single linear regression line and a single slope value. The transmural m-HFVP slope index was derived similarly, except that the regression analysis was performed on the average value of the three muscle layers for four or five pressure levels. This analysis also yielded a single regression line and a single slope value. Therefore, the relation of arterial beds to m-HFVP indexes was 1:1. Accordingly, for the 16 normal arteries, each m-HFVP slope index was derived 16 times; for the 13 stenotic arteries, each m-HFVP slope index was derived 13 times.

Analysis of covariance showed no dependence of the i-HFVP slope index values on heart rate, left ventricular end-diastolic pressure, or mean aortic pressure. Accordingly, in comparing the i-HFVP and m-HFVP slopes indexes, the i-HFVP slope index values obtained at different pressure levels were averaged. Table 1 shows these results. The i-HFVP slope index averaged 10.3 in normal arteries and 3.6 in stenotic arteries (p<0.001).

The m-HFVP slope indexes determined from transmural, microsphere-determined myocardial blood flow data showed a similar trend for reduction in the presence of a coronary stenosis (8.9±4.6 versus 5.3±3.1, p<0.01), and these values were not significantly different from the i-HFVP slope index values. The subendocardial perfusion data displayed the most striking difference between normal (9.2±5.7) and stenotic (4.1±2.3, p<0.001) beds, the midmyocardial data showed an intermediate difference, and the subepicardial data were not significantly different between stenotic and normal beds (Table 1). The subendocardial m-HFVP slope index values were not significantly different from the i-HFVP slope index values.

Table 2 shows the results of correlating the average i-HFVP and m-HFVP slope indexes. The closest relation was between i-HFVP and m-HFVP slope indexes derived from subendocardial measurements. The i-HFVP slope index also significantly correlated with the transmural m-HFVP slope index.

Table 2. Correlation Coefficients From Least-Squares Linear Regression Comparisons of Instantaneous and Microsphere-Derived Hyperemic Flow-Versus-Pressure Slope Indexes

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=16)</th>
<th>Stenotic (n=13)</th>
<th>All (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmural</td>
<td>0.18</td>
<td>0.30</td>
<td>0.43*</td>
</tr>
<tr>
<td>Subendocardial</td>
<td>0.33</td>
<td>0.33</td>
<td>0.57†</td>
</tr>
<tr>
<td>Midmyocardial</td>
<td>0.20</td>
<td>0.35</td>
<td>0.44*</td>
</tr>
<tr>
<td>Subepicardial</td>
<td>-0.17</td>
<td>0.22</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*p<0.02, †p<0.001.

Figure 2 shows the frequency with which individual i-HFVP slope index values fell within 95% confidence intervals determined from the microsphere-derived m-HFVP slope index in individual dogs. In normal beds, approximately 60% of the i-HFVP slope index values overestimated either transmural or subendocardial m-HFVP slope index values. In the presence of a stenosis, most observations fell within the 95% confidence intervals determined from the subendocardial m-HFVP slope index. Transmural measures of m-HFVP slope index in the presence of a stenosis were accurately reflected or underestimated by the i-HFVP slope index at nearly identical frequencies.

We randomly selected four studies for beat-to-beat analysis; two were stenotic, and two were not. There were nine cycles available in two cases and eight and seven cycles in the other two. The coefficient of variation of the observations ranged between 9.5% and 12.3%. Minimum and maximum i-HFVP slope index values were 15.0 and 18.8 and 9.5 and 12.5 for

Figure 2. Bar graph showing frequency with which individual instantaneous hyperemic flow-versus-pressure (i-HFVP) slope index values fell within the 95% confidence intervals (C.I.) derived from the subendocardial microsphere data of individual dogs. Although the strongest relations were between the i-HFVP slope index and either transmural or subendocardial microsphere-derived hyperemic flow-versus-pressure (m-HFVP) slope index (see Table 2), this illustration points out systematic differences in the relation depending on the presence or absence of a stenosis. Subendocardial m-HFVP slope index was overestimated by the i-HFVP slope index in normal beds, whereas subendocardial m-HFVP slope index values in stenotic beds were more accurately reflected.
the two normal arteries and 3.3 and 4.5 and 4.7 and 6.8 ml/min/mm Hg/100 g for the two stenotic arteries.

Discussion

Results from this study establish the relation between maximal myocardial conductance as determined by the radiolabeled microsphere technique and the i-HFVP slope index. The latter index is the slope value normalized by perfusion bed weight, which is derived from the least-squares linear regression analysis between late diastolic hyperemic coronary flow and aortic pressure as measured by a coronary flowmeter and a high-fidelity micromanometer in the ascending aorta, respectively. Our new results demonstrate that the i-HFVP slope index is most closely related to subendocardial coronary conductance (derived from microsphere-determined blood flow) during hyperemia. The present findings also confirm our previous report \(^5\) on the i-HFVP slope index and support its usefulness as a hemodynamically independent method of measuring vascular reserve in the intact coronary circulation.

The relation between the i-HFVP slope index and radiolabeled microsphere measurements was strongest with the subendocardial and weakest with the subepicardial coronary perfusion data analyses. This is probably because subendocardial blood flow is largely dependent on diastolic coronary perfusion \(^12-22\) and this is the time period during which the i-HFVP slope index is derived. \(^5\) Subepicardial and midmyocardial blood flows are not as restricted to the diastolic interval as subendocardial flow; consequently, they would not be as likely to parallel changes in the i-HFVP slope index.

A systematic difference was noted in the frequency with which the individual i-HFVP slope index determinations actually fell within the 95% confidence intervals for maximal coronary conductance derived from the microsphere data (Figure 2). We propose two major factors to account for these findings. The first is the fact that microsphere measures of flow represent a mean flow over a rather prolonged period of time (minutes), whereas the i-HFVP slope index is derived from instantaneous diastolic hyperemic flow data. Accordingly, we had the a priori expectation that the absolute coronary conductance value, derived from the microsphere perfusion measurements, would be less than that derived from the flowmeter values. We also predicted that this disparity would be minimized in the presence of a coronary stenosis. This argument is represented in schematic form in Figure 3 and is in keeping with the results of this investigation. Figure 4 shows an actual example of this phenomenon.

The second important factor is the distinct difference in flows measured by the epicardial coronary flow probes and by the radiolabeled microspheres. The latter measures flow from all sources, including collateral flow, whereas the former measures only flow through the epicardial coronary artery. Disparities between such measurements would be exaggerated in the presence of a stenosis if collateral flow during hyperemia to the compromised bed is substantial. Accordingly, one would expect relative preservation of myocardial perfusion even in the face of impaired epicardial coronary blood flow if collateral flow is recruited from other sources not measured with the flow probe. This could account for the relatively high proportion of i-HFVP slope index values in stenotic beds that were below the 95% confidence intervals established from the perfusion data (i.e., the epicardial measurements tended to overestimate the actual severity of the perfusion deficit). Indeed, there was one study, which was excluded from analysis, in which collateral flow was extensive enough to maintain totally normal transmural myocardial perfusion in the presence of a stenosis that induced frank impairment of epicardial flow (see “Methods”). In the remaining studies, it is impossible to know whether collateral flow was recruited or to what degree, but the systematic underestimation of maximal, microsphere-determined myocardial conductance suggests that this may well have happened in the stenotic beds.

It should be emphasized that this limitation is not unique to the i-HFVP slope index concept but rather is a limitation of all measures of vascular reserve that depend on measurement of epicardial coronary blood flow or flow velocity. \(^23\) We have previously demonstrated that not all impairments of coronary flow reserve necessarily result in myocardial dysfunction during stress and postulated that collateral flow plays an important role in this phenomenon. \(^24-28\) For this reason, both exercise and nonexercise methods

![Figure 3](https://example.com/figure3.png)
Figure 4. Plots superimpose the diastolic relation between hyperemic coronary flow and aortic pressure used to determine the instantaneous hyperemic flow-versus-pressure (i-HFVP) slope index and the microsphere-derived flow-versus-pressure data with the associated 95% confidence intervals (C.I.). In contrast to Figure 3, these results are from an actual experiment. The data have been plotted so that both the i-HFVP and the microsphere-derived hyperemic flow-versus-pressure (m-HFVP) slope indexes have the same x intercept, thereby simplifying visual comparison of the slopes. The 95% C.I. for microsphere-derived flow are also shown. In the nonstenotic state (upper panel), the data used to derive the i-HFVP slope index inscribe a slope that is steeper than the slope of the m-HFVP slope index as well as steeper than the slope of the uppermost C.I. In contrast, in the presence of a stenosis (lower panel), the data used to derive the i-HFVP slope index inscribe a slope that is nearly identical to the m-HFVP slope index and falls well within the slope range inscribed by the two C.I.

of stress testing with positron emission tomography or thallium or radionuclide angiography, all of which assess directly or indirectly the adequacy of myocardial perfusion from all sources, may be of greater diagnostic value than simple measures of vascular reserve (including the i-HFVP slope index and other measures of coronary flow reserve) derived from epicardial coronary flow or velocity measurements alone.

Although the present study validates the conceptual basis for using the i-HFVP slope index as a measure of maximal coronary conductance, the lack of stronger correlation coefficients may at first be disturbing. There are, however, numerous technical factors that we felt would necessarily predispose to finding only a modest correlation between the microsphere-derived (m-HFVP) and flow probe-derived (i-HFVP) slope indexes. The microspheres measure perfusion from all sources (arterial flow and collateral flow), and the flowmeter measures only blood flow through large epicardial coronary arteries. The flowmeter provides instantaneous flow measurements that were analyzed only during late diastole, whereas the microspheres can only measure mean flow through the entire cardiac cycle averaged over a time course of minutes. The perfusion bed weight used for normalizing the i-HFVP slope index was determined by postmortem perfusion and differential dyeing techniques; this is likely to also have contributed to disparities. The single m-HFVP slope index value was derived from four or five separate microsphere injections, each with an inherent error of 15–20% and substantial biological variability, even within a single perfusion bed. The aortic pressure during diastole, although easy to measure and clinically applicable, may not accurately reflect the true coronary perfusion pressure, especially in the presence of a coronary stenosis. Accordingly, very high correlations between the two methods were not and should not be expected.

The preeminent importance of subendocardial flow in relation to systolic function as measured by systolic myocardial thickening has been established with a high degree of confidence in the canine model for both conscious and open-chest anesthetized preparations. It is striking that the relation of subendocardial flow to systolic myocardial thickening is exceedingly poor. In ischemic preparations and preparations in which subendocardial flow is maximally dilated and perfusion pressure is allowed to decrease below the subendocardial autoregulatory plateau, decrements in subendocardial flow are tightly and linearly coupled to decrements in systolic function as measured by systolic myocardial thickening.

From this perspective, the i-HFVP slope index may have a unique and important application in studies of the relation between subendocardial flow and systolic function. The i-HFVP slope index is constrained by definition to the specific analysis of coronary conductance determined by the relation between aortic pressure (or proximal coronary pressure) and hyperemic diastolic flow. Previous research has clearly demonstrated that subendocardial flow occurs primarily, if not exclusively, during diastole. Therefore, we hypothesized that the i-HFVP slope index would be most highly correlated with subendocardial perfusion, and the results of the present investigation support this contention. Future analyses of the relation between systolic function and subendocardial flow in humans may be more appropriately undertaken using the i-HFVP slope index that is specific to the diastolic period and subendocardial flow than by digital angiography or Doppler flow catheters. Currently, the i-HFVP slope index cannot be directly measured in humans because of the absence of a well-validated method for measuring instantaneous coronary blood flow. Current technological advances, however, suggest that human applications may eventually be feasible. The combination of endovascular echocardiography and Doppler velocity measurements have been used to measure absolute coronary flow. Quantitative arteriography in conjunction with Doppler velocity probes have also been used to measure absolute coronary blood flow. Guide wire–mounted, high-fidelity micromanometers for measuring intracoronary and perhaps postlesional
coronary perfusion pressures are being developed.\textsuperscript{37}
Myocardial perfusion bed mass measurements may soon be feasible using cine-computed tomography or perfusion echocardiography.\textsuperscript{38} Accordingly, it is worthwhile to lay the groundwork for potential human applications by studying the i-HFVP slope index concept with available techniques in animals.

In summary, the i-HFVP slope index is a hemodynamically independent measure of coronary reserve that is reproducible over a broad range of aortic pressures, is applicable to an intact circulation, and provides a measure that most closely corresponds to maximal subendocardial coronary conductance. With technological advances, this approach may be of value in humans for assessing the physiological significance of coronary lesions and documenting changes induced by interventions.

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**KEY WORDS** • hyperemic flow-versus-pressure slope index • microspheres • coronary conductance • coronary reserve • stenoses • hyperemia • micromanometer • electromagnetic flow probe
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