First-Pass Entry of Nonionic Contrast Agent Into the Myocardial Extravascular Space

Effects on Radiographic Estimates of Transit Time and Blood Volume

John M. Canty Jr., MD; Robert M. Judd, PhD; 
Alan S. Brody, MD; and Francis J. Klocke, MD

Background. Almost all x-ray–based techniques intended to assess regional myocardial perfusion from myocardial concentration–time curves following the administration of soluble contrast agents assume that these agents behave as intravascular indicators and can therefore provide measurements of intravascular transit time and intramyocardial blood volume.

Methods and Results. We tested this assumption by comparing a conventional nonionic contrast agent (ioversol) to a particulate emulsion (ethiodol) that remained in the vascular space in closed-chest dogs during pharmacological vasodilation. Using fast computed tomography (CT), pairs of myocardial CT intensity–time curves were obtained following sequential bolus aortic administration of the two contrast agents. The emulsion (particle size <3 μm) was almost completely washed out of the myocardial region of interest within a few seconds, as would be anticipated for a vascular indicator. At the onset of recirculation, CT intensity for ethiodol fell to 5±1% (SEM) of peak values in normally perfused areas and to 10±4% of peak values in an area in which flow had been reduced by 50% by a chronically implanted coronary artery occluder (p=NS). In comparison, the diffusible nonionic contrast agent ioversol showed substantial intramyocardial retention at the onset of recirculation. At the time of recirculation, CT intensities for ioversol averaged 36±2% of peak values in normally perfused nonstenotic areas and 54±4% of peak values in stenotic areas (p<0.01). Using residue function analysis for a diffusible indicator, first-pass extractions of the conventional nonionic agent averaged 33±2% in normally perfused areas and 50±3% in stenotic areas (p<0.01). Because of the significant first-pass myocardial retention of ioversol, both mean myocardial appearance time and intramyocardial blood volume were consistently overestimated.

Conclusions. Soluble radiographic contrast agents, like other small molecules, enter the interstitial space to a degree, which is important because it affects estimates of myocardial perfusion based on transit time and intramyocardial blood volume. Indicator dilution models intended to quantify myocardial perfusion with conventional radiographic contrast agents need to account for this extravascular exchange. (Circulation 1991;84:2071–2078)

A variety of approaches have been suggested for quantifying relative and/or absolute myocardial perfusion radiographically using planar digital x-ray techniques1–4 and, more recently, fast computed tomography (CT).5–8 These densitometric techniques rely on changes in the myocardial concentration–time curve of a soluble iodinated contrast agent during its first pass through the coronary circulation. A major assumption in nearly all approaches is that the myocardial density–time curve (or CT intensity–time curve) reflects the passage of a purely vascular indicator.

There is a considerable body of evidence indicating that currently available ionic and nonionic contrast agents exit the vascular space and distribute throughout the vascular and interstitial spaces in the steady state.9–12 The notion that these agents can be considered intravascular could be tenable as an approximation only if their first-pass extraction were small, with
equilibration throughout the extracellular space occurring slowly. Although the myocardial extraction of both ionic and nonionic contrast agents has not yet been defined in vivo, a preliminary study in isolated hearts demonstrated mean extractions of ionic contrast as high as 44%.12 Since all of these contrast agents are relatively small benzene-based molecules, they may freely permeate slits or pores between capillary endothelial cells in the coronary vascular bed.

We therefore decided to compare the first-pass behavior of a conventional nonionic contrast agent (ioversol) with that of a particulate emulsion of ethiodized oil (ethiodol).13 The latter had particle sizes (<3 μm) that enabled it to pass through the capillary bed freely but were too large to traverse the 100–200-Å openings between capillary endothelial cells. With fast CT, myocardial CT intensity–time curves were obtained in closed-chest dogs following injection of each contrast agent into the ascending aorta. The aortic injection circumvented the nonlinear imaging artifacts related to beam hardening and scatter common to all x-ray techniques in which contrast passes through the cardiac chambers.7 Measurements were performed during pharmacological vasodilation to avoid potential changes in coronary vasomotion due to contrast administration. Flow dependence of extraction was assessed by evaluating a normally perfused region in relation to one in which flow had been reduced by 50% by inflating a chronically implanted arterial occluder. Our findings indicate substantial first-pass retention of nonionic contrast agent, with estimates of extraction being inversely related to flow.

Methods

Studies were performed in anesthetized chronically instrumented dogs, using procedures and protocols concordant with institutional guidelines for the care and use of experimental animals.

Experimental Preparation

Mongrel dogs (n=8) were fasted and premedicated with Innovar-Vet (fentanyl 0.4 mg/ml and droperidol 20 mg/ml, 1–3 ml i.m.). After induction of general anesthesia with sodium thiamylal (20 mg/kg i.v.), a surgical plane of anesthesia was maintained using a mixture of nitrous oxide (~60%), halothane (1–2%), and oxygen (~40%) during mechanical ventilation. The details of the surgical procedure have been described previously.14 In brief, a left thoracotomy was performed under sterile conditions. Tygon catheters were inserted into the left atrium and aorta for pressure measurement. The proximal circumflex artery was dissected free and instrumented with a Transonics ultrasonic flow probe (Transonics, Inc., Ithaca, N.Y.), which uses a transit-time approach and therefore provides absolute measurements of perfusion (ml/min).15 A hydraulic occluder was placed adjacent to the flow probe to allow selected levels of circumflex flow restriction. A catheter was inserted distal to the occluder to provide measurements of circumflex perfusion pressure. The dogs were allowed to recover from the surgical procedure for at least 1 week before study.

CT Scanning Protocol

Dogs were fasted on the day of the CT study. After sedation with Innovar-Vet (1–3 ml i.m.), general anesthesia was induced with sodium pentobarbital (30 mg/kg i.v.) and maintained with supplemental doses of this agent throughout the study. Ventilation was controlled with a piston-type respirator connected to an endotracheal tube. The left carotid artery was isolated and an 8F tight-radius pigtail catheter (Bard-USC1, Inc., Tewksbury, Mass.) was positioned into the ascending aorta under fluoroscopic guidance. The dogs were then transported to the CT scanner.

Fast CT images were obtained using the Picker/Imatron FASTRAC Scanner (Picker, Inc., Cleveland, Ohio; Imatron, Inc., South San Francisco, Calif.).16 Using a fixed time delay triggered from the R wave of the ECG, we obtained nearly simultaneous end-diastolic tomograms at four contiguous levels at each or every other beat for a total of 20 cardiac cycles. In this mode, multilevel tomograms can be obtained rapidly with a scan aperture time of ~50 msec; the voxel resolution for a 35-cm field of view is ~1.4 x 1.4 mm with an 8-mm slice thickness. Dogs were scanned in the right lateral decubitus position and skewed ~30° to obtain a short-axis image of the left ventricle; respiratory artifacts were circumvented by scanning with respiration suspended at end expiration. The first tomographic level was oriented at the coronary ostia and immediately above the aortic valve leaflets. We used the fourth tomographic level, located ~3 cm below the first, to obtain regional myocardial CT intensity–time curves.

Experimental Protocol

We compared CT intensity–time curves (i.e., CT number or iodine concentration versus time) for a nonionic contrast agent (ioversol, 320 mg iodine/ml, Mallinckrodt, Inc., St. Louis, Mo., [n=7] or iohexol, 365 mg iodine/ml, Winthrop Diagnostics, New York, N.Y. [n=1]) to those for a particulate emulsion of ethiodized oil (ethiodol, 475 mg iodine/ml, Altana, Inc., Melville, N.Y.) in each dog. The originally described synthesis of the emulsion13 was modified by mixing equal volumes of ethiodol and 10% Tween-80 in normal saline. We sonicated 20 ml of the mixture at 100 W for 60 seconds and then passed it through a 3 μm Millipore filter. The resultant emulsion (237 mg iodine/ml) was considered to represent an intravascular marker since it had stable particle sizes that were expected to pass freely through the coronary microcirculation but not through openings between capillary endothelial cells (100–200 Å). When we examined emulsions 48 hours after sonication, less than 1% of the particles had coalesced to sizes greater than 3 μm. To minimize this small effect
further, all ethiodol emulsions were injected within 5 hours of the time they were sonicated.

Resting circumflex flow and hemodynamics were measured, and the coronary circulation was maximally vasodilated with carbocromen, 7.5 mg/kg i.v. Following repeat measurements of flow and hemodynamics, circumflex flow was reduced by ~50% and scanning was begun. Paired injections of each agent were performed in all of the dogs. After at least one background tomogram was obtained, ioversol was administered as a bolus through the aortic catheter (8–10 ml/sec for 2–3 seconds) with a power injector. Subsequently, scans were obtained under similar hemodynamic conditions with a bolus aortic injection of ethiodol. Neither agent affected systemic hemodynamics during the 15–20-second period required to obtain each set of 20 diastolic tomograms. However, because of the high concentration of Tween-80 in the ethiodol emulsion, systemic arterial pressure decreased abruptly 30–60 seconds after the ethiodol injection, thereby precluding variation of the sequence of administration of the two contrast agents. Dogs were killed with a lethal injection of sodium pentobarbital after ethiodol scans.

Data Analysis and Calculations

We constructed background-subtracted CT intensity–time curves for similar user-defined regions of interest for the two contrast agents. Linearity of the scanner was documented over a range of 0–1,000 Hounsfield units using a phantom filled with various iodine concentrations (CT number = 23×iodine concentration [mg/ml] + 32; n = 9, r = 0.998). Aortic input curves were obtained from the first tomographic level; myocardial curves were obtained from the fourth tomographic level. Full-thickness myocardial CT intensity–time curves were constructed for regions having both normal (anterior free wall and septum) and restricted (circumflex) perfusion. The areas under these curves and their first moments were obtained by approximating discrete data up to the point of minimum concentration (i.e., the onset of recirculation) as a Riemann sum. Although myocardial curves for ethiodol returned to near-baseline levels a few seconds after contrast injection, those for ioversol did not. The latter behavior has usually been attributed to recirculation in previous studies, with application of various curves (e.g., a gamma-variate fit)5,6 to extrapolate the data back to baseline and derive the “first-pass” curve free of recirculation. For comparative purposes with other studies, we also fit myocardial curves for ethiodol and ioversol to a gamma-variate function. We used data points that were above background up until the time at which recirculation was apparent on the regional myocardial intensity–time curves. From these curves, first moments and areas were calculated and compared with those derived from the Riemann sum.

First-pass extraction of ioversol was estimated from the uncorrected ethiodol and ioversol myocardial curves using a modification of an approach originally proposed by Guller et al18 for deriving the first-pass myocardial extraction of 24NaCl from externally measured residue curves following bolus aortic injection. Myocardial CT intensity–time curves were represented as residue functions19 with CT number changes in each region [R(t)] expressed as a fraction of curve peaks. We assumed that the amount of ethiodol present at the point of minimum concentration (i.e., the onset of recirculation) reflected the small amount of intravascular indicator not yet cleared from the region of interest. The fraction of ioversol present at a similar point in its CT intensity–time curve was taken to represent the small amount remaining in the vascular space plus the amount of indicator retained because of permeation into the extravascular space. Using the approach of Guller et al,18 first-pass extraction of ioversol was estimated as follows:

$$\text{Extraction} = \frac{R_{\text{ioversol}} - R_{\text{ethiodol}}}{1 - R_{\text{ethiodol}}}$$

For comparative purposes with previous studies, mean regional myocardial appearance times and regional blood volumes were calculated using the Riemann sum to the aortic curve and gamma variate fits to the regional myocardial curves as follows:

$$\text{Mean appearance time} = T_{\text{aorta}} - T_{\text{myocardium}}$$

where $T_{\text{aorta}}$ and $T_{\text{myocardium}}$ are the first moments of the aortic input and regional myocardial residue curves (seconds), respectively. The first moment of the CT intensity–time curves is the time where half of this indicator has opacified the region of interest (i.e., the area under the curve before and after this time are equal). Blood volume (ml/100 ml myocardium) was also estimated:

$$\text{Myocardial blood volume} = \frac{\text{area}_{\text{myocardium}} \times 100}{\text{area}_{\text{aorta}}}$$

where $\text{area}_{\text{myocardium}}$ and $\text{area}_{\text{aorta}}$ are the areas under the regional myocardial and aortic CT intensity–time curves, respectively.

Data are presented as the mean±SEM. Differences between ethiodol and ioversol curves have been assessed by a two-tailed paired $t$ test with $p<0.05$ considered significant.

Results

Following vasodilation, mean circumflex flow increased sixfold from 20±3 to 123±11 ml/min. The hemodynamic parameters corresponding to each pair of contrast injections after application of a stenosis to reduce circumflex flow are summarized in Table 1. The values for the sequential injections were similar except for a small difference in circumflex coronary flow between the contrast injections (67±12 for ioversol versus 70±12 for ethiodol, $p < 0.05$).

Figure 1 illustrates CT intensity–time curves comparing an aortic region of interest to a normally
perfused myocardial region of interest following bolus injection of ioversol. There is considerable diminution in the myocardial CT values in relation to values obtained for arterial blood in the aorta. This is because myocardial cells do not take up the contrast agent, and thus, its distribution volume in tissue represents only a fraction of the total myocardial volume imaged within the region of interest. Figure 2 compares a pair of myocardial curves for each contrast agent during vasodilation in a nonstenotic normally perfused region. Values are expressed as a fraction of the peak amount of each contrast agent residing in the tissue at any point in time [R(t)], with the peak intensity equal to 1. The myocardial curve for ethiodol rises rapidly and falls to a value near baseline before the onset of recirculation (the time indicated by the vertical arrow). In comparison, the CT intensity–time curve for ioversol at this time remains persistently elevated in relation to the peak. This indicates that a significant fraction of ioversol left the vascular space and was retained within the myocardial region of interest.

**Ioversol Retention and First-Pass Estimates of Extraction**

We quantified the relative retention of each indicator by determining the CT number before recirculation as a percent of that present at the peak (Figure 3). Data from one dog could not be analyzed because the contrast injections began late in the scanning sequence, and image acquisition ended before the onset of contrast recirculation. During vasodilation in the normally perfused region, the concentration of ethiodol before recirculation was only 5% of the

![CT Number(Hu)](image)

**TABLE 1. Systemic Hemodynamics During Ioversol and Ethiodol Contrast Injections**

<table>
<thead>
<tr>
<th></th>
<th>Ioversol</th>
<th>Ethiodol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>122±13</td>
<td>120±14</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td>102±6</td>
<td>101±7</td>
</tr>
<tr>
<td>Circumflex pressure (mm Hg)</td>
<td>46±8</td>
<td>47±8</td>
</tr>
<tr>
<td>Circumflex flow (ml/min)</td>
<td>67±12</td>
<td>70±11*</td>
</tr>
</tbody>
</table>

Values are mean±1 SEM. Circumflex pressure was operative in five of the dogs and circumflex flow in seven. *p<0.05 vs. ioversol.

![Figure 1. Comparison of background subtracted aortic (left panel) and myocardial (right panel) computed tomography (CT) intensity–time curves in a nonstenotic region following an aortic bolus of ioversol. Each point represents the CT number change above background in a selected region of interest. The shaded area under the aortic curve represents that derived using numerical analysis (Riemann sum), whereas that under the myocardial curve corresponds to a gamma-variate fit. Arrows illustrate the onset of recirculation as represented by the nadir of the respective CT intensity–time curves. Note that the gamma-variate fit underestimates the myocardial CT intensity–time curve for ioversol even before recirculation, suggesting intramyocardial retention of the nonionic contrast agent. Hu, Hounsfield units.](image)

![Figure 2. Sequential pair of myocardial computed tomography (CT) intensity–time curves for a nonstenotic myocardial region of interest. Myocardial CT values are plotted as residue curves [R(t)] depicting the fraction of the peak concentration remaining at any point in time and have been superimposed on the same time scale. The vascular agent ethiodol (closed circles) enters and exits the myocardial region of interest rapidly with tissue values approaching background levels before the onset of recirculation (arrow). In comparison, ioversol (shaded circles) remains persistently elevated before recirculation after passage of most of the vascular indicator. This demonstrates retention of the ioversol outside the vascular space on its first pass through the coronary circulation. The equation for estimating the extraction of ioversol is discussed in the text.](image)

![Figure 3. Retention of ioversol at the onset of recirculation for each of the two contrast agents. Values for the vascular indicator ethiodol were a small fraction of those for the nonionic contrast agent. Retention of each indicator increased distal to a stenosis. Only a small portion of the increase for ioversol was related to increased temporal dispersion of the vascular indicator within the stenotic region of interest.](image)
peak, whereas the concentration of ioversol averaged 36±2% of the peak. These values increased to 10±4% for ethiodol and 54±4% for ioversol in the stenotic circumflex area where flow was reduced by half.

Estimates of first-pass extraction for the diffusible agent, ioversol, are summarized in Figure 4. In the normally perfused area, the first-pass extraction averaged 33±2%. When flow was reduced by half, the retention of ioversol increased and first-pass extraction rose to 50±3% (p<0.01 versus normally perfused area). Thus, during pharmacological vasodilation, the first-pass extraction of ioversol was significant and was inversely related to flow. Furthermore, since most of the vascular agent was washed out of the myocardial regions of interest by the time recirculation began, the values for extraction shown in Figure 4 were fairly close to the measurements of ioversol retention shown in Figure 3.

**Effect of Extraction on Intramyocardial Blood Volume and Mean Appearance Time Estimates**

The retention of ioversol caused both the first moment and area under the myocardial CT intensity–time curves to be overestimated in a systematic fashion when compared with values derived from ethiodol. Parameters for curves approximated using a gamma-variate fit were not significantly different from those obtained by numerical analysis using a Riemann sum, which was truncated at the onset of recirculation. Only estimates derived from gamma-variate fits to the myocardial CT intensity–time curves will be summarized.

In normally perfused regions, the area under the myocardial CT intensity–time curve for ioversol significantly overestimated blood volume content in comparison to ethiodol (Figure 5). Vascular blood volume based on ethiodol averaged 16.4±2.7 ml/100 ml myocardium. In comparison, even though the area under the gamma-variate fit underestimated the myocardial CT intensity–time curve for ioversol (e.g., see Figure 1), blood volume was still overestimated significantly (23.1±3.6 ml/100 ml myocardium, p<0.001 versus ethiodol).

A coronary stenosis caused a reduction in estimates of intramyocardial blood volume. Results based on the gamma-variate fits are also summarized in Figure 5. Mean circumflex pressure distal to the stenosis was reduced to 46±8 mm Hg (n=5). Vasodilated flow was reduced by approximately 50% of prestenotic values but still three times the resting flow level prior to vasodilation. Using the data for ethiodol, blood volume decreased from 16.4±2.7 ml/100 ml myocardium in normally perfused areas to 12.5±1.8 ml/100 ml myocardium in stenotic regions (p<0.06). The area under the ioversol curve also decreased, resulting in estimated blood volume decreasing from 23.1±3.6 ml/100 ml myocardium in normal regions to 14.3±2.9 ml/100 ml myocardium in stenotic regions (p<0.01). Thus, distribution volumes were dependent on coronary pressure and flow even though the coronary vascular bed was pharmacologically vasodilated.

The retention of the nonionic contrast agent also affected estimates of mean myocardial appearance time based on differences in the first moment of the aortic and myocardial residue CT intensity–time curves (Figure 6). In normally perfused vasodilated regions, the mean appearance time for ethiodol was 1.1±0.2 seconds and shorter than that for ioversol which averaged 1.9±0.3 seconds (p<0.005). As anticipated, mean myocardial appearance time for both agents increased in the stenotic region, but the differences between the two agents did not achieve statistical significance.

**Discussion**

This study documents significant first-pass myocardial retention of the nonionic contrast agent, ioversol. Because of similar physical and chemical properties, a comparable magnitude of retention seems likely for other commonly used benzene-ring–based contrast agents. The magnitude of first-pass retention appears to impose an important limitation on studies that neglect extravascular exchange of contrast in attempting to quantify myocardial perfusion by assessing transit time and intramyocardial blood volume.
Methodological Considerations

Aortic root injection of contrast largely circumvents CT x-ray artifacts caused by scatter and beam hardening when ioted agents pass through the left ventricle and/or other cardiac chambers. The magnitude of these artifacts varies in time as well as with position within the tomogram. Accordingly, when contrast is injected intravenously or into the left heart, the relation between regional changes in myocardial radiographic density and contrast concentration becomes nonlinear, time variant, and quantitatively unreliable. Although aortic root injection circumvents these artifacts, it is to some extent limited by the lack of complete mixing of contrast with blood entering the aortic root from the left ventricle. This may affect estimates of intramyocardial blood volume, which depend on the area under the aortic as well as the myocardial CT intensity–time curve. We minimized heterogeneous mixing in two ways: 1) Each pair of nonionic and particulate contrast injections was made under similar hemodynamic conditions and compared carefully matched aortic and myocardial regions of interest. Assuming that aortic mixing conditions were similar for each injection pair, observed differences between the two contrast agents should be reliable. 2) Since the entire left ventricle is supplied by the left coronary artery in the dog, each region within the ventricle should have received a similar contrast input function, with the amount of contrast delivered to each region being proportional to flow. Thus, differences between ioversol and ethiodol regional contrast concentrations and mean appearance times within individual dogs are felt to have been relatively free of the methodological limitations of aortic injection. The degree of variation of blood volume estimates among dogs, however, may have been increased by this approach.

First-Pass Extraction of Ioversol

We used a method described by Guller et al.18 for estimating first-pass extraction from externally detected myocardial residue curves following an arterial bolus input. They measured first-pass extraction of $^{24}$NaCl by external detection as well as by continuous sampling of arterial and coronary venous blood in isolated hearts in which recirculation of tracer was prevented. Using measurements of residual precardial $^{24}$Na activity, they found that values of extraction derived from the myocardial residue curves tended to underestimate that measured by venous outflow curves. This reflects the fact that back-diffusion of indicator from the interstitial to the vascular space is not accounted for by this approach. Thus, even though our estimates of extraction were based on data taken fairly soon after the peak (i.e., at the onset of recirculation as defined by the nadir of the regional CT intensity–time curve), they may have underestimated extraction because of back diffusion of ioversol during its first pass through the myocardium. An additional assumption in the calculation of extraction from residue curves is that the peak of the residue concentration–time curve reflects a point at which all of the indicator is contained within the region of interest and none has washed out. Even though we used very brief aortic boluses, the peak of the myocardial CT intensity–time curve sometimes preceded return of the aortic CT intensity–time curve to baseline. This was most likely secondary to the high flow rates accompanying maximum coronary vasodilation and most noticeable in normally perfused nonstenotic areas of the heart. Such an effect would cause peak contrast concentration to be underestimated, with calculated extraction therefore overestimated. Although the magnitude of these two opposing effects is difficult to assess with certainty, the study of Guller et al.18 suggests that they are small and/or canceling.

The magnitude and inverse flow-dependency of the present first-pass ioversol extraction values (33% at full vasodilated flow and 50% when flow was reduced by half) are perhaps not surprising in light of the physical properties and systemic pharmacokinetic behavior of soluble contrast agents. Both ionic and nonionic contrast agents are small molecules. Previous studies in dogs as well as other species have clearly demonstrated that soluble contrast agents can be considered to behave as an extracellular indicator that exchanges between the vascular and interstitial spaces.9-12 The rapidity of this exchange in rats was demonstrated by Newhouse and Murphy.11 They found that approximately 80% of the myocardial content of the contrast agent iothalamate was extravascular 1 minute after an intravenous contrast bolus. The myocardial distribution between extravascular and vascular regions remained nearly constant for over 30 minutes after the initial bolus. This rapid exchange supports the notion that the single-pass extraction of soluble contrast agents is high and in a range that we have demonstrated in our study.

Effects of Contrast Extravasation on Estimates of Blood Volume and Appearance Time

The fact that soluble nonionic contrast agents leave the vascular space during their first pass
through the coronary circulation has a profound effect on estimates of myocardial appearance time and blood volume content. Our results actually underestimate the true difference between the two contrast agents because we could not follow the myocardial CT intensity–time curves for ioversol back to baseline before recirculation of the indicator. Nevertheless, even when the tail on the ioversol CT intensity–time curve was underestimated by extrapolating it back to baseline with a gamma-variate fit (or numerically truncated at the onset of recirculation using a Riemann sum), the difference between the two contrast agents was still substantial. Other types of extrapolation might provide slightly different estimates but would not influence the overall differences between ioversol and the vascular indicator. Thus, the systematically larger area under the myocardial CT intensity–time curves for ioversol causes estimates of both intramyocardial blood volume and mean myocardial appearance time to be greater than those for ethiodol.

The effect of these systematic differences on flow calculations is difficult to predict. Since flow is equal to the quotient of blood volume divided by mean transit time, the increase in each of the parameters may, to some extent, cancel out as they would for venous outflow dilution curves analyzed for long periods of time.20 This might result in a circumstance where parameters derived from nonionic contrast agents could provide a reasonable index of flow. This appears to be particularly true in the case of analyses that rely on the peak of the bolus at resting flow levels6 or the early myocardial wash-in phase following a step infusion of contrast.8,21 Each of these approaches will tend to minimize (but not eliminate) the effects related to the long tail of the washout phase following entry of contrast into the interstitial space. Nonetheless, these approaches still assume that conventional contrast agents remain intravascular on their first pass or are distributed within a single well-mixed compartment. Because of this, despite a sometimes reasonable correlation with flow, they are probably best considered as indexes of perfusion, which may be helpful in assessing relative changes in flow21 as opposed to quantifying absolute values of myocardial perfusion.5–8

**Comparison of Intramyocardial Blood Volume Estimates With Previous Studies**

The estimates of intramyocardial blood volume we obtained using the ethiodol are similar to those from previous studies in experimental animals. We found blood volume to average ~16 ml/100 g myocardium during vasodilation. Values reported in the literature using a variety of other techniques have ranged from approximately 8–18 ml/100 g,22–26 with measurements during vasodilation at the uppermost end of this range. Direct comparison of our CT data with these previous studies is problematic for several reasons. First, systematic differences may occur between in vivo measurements and those in excised hearts. Although much of the blood probably remains in the microcirculation after the heart is excised, one study has shown that in vivo blood volume measurements are somewhat larger.22 Second, the physiological determinants of intramyocardial blood volume are unlikely to be similar among these different studies. Salisbury et al22 demonstrated that heart rate, coronary pressure, and vasomotor tone are important in determining intramyocardial blood volume, and these are likely to vary among studies. Recently, Judd and Levy26 demonstrated that blood volume may also vary throughout the cardiac cycle, and thus, our end-diastolic measurements are probably higher than those averaged over the entire cardiac cycle. Finally, some studies have included large epicardial vessels22 as well as microcirculatory vessels23–26 in the measurements, and the results are not strictly comparable to small-vessel intramyocardial blood volume content measured by imaging the myocardium. The impact of these factors on CT estimates of blood volume content remains to be defined but has relevance to quantifying myocardial perfusion with CT as well as with other imaging modalities.

Our results suggest that in situ diastolic intramyocardial blood volume derived from CT varies with coronary pressure even after the coronary circulation is vasodilated pharmacologically. Variability of blood volume with changes in coronary pressure and flow is consonant with the findings of Salisbury et al22 in isolated hearts. We found that a 50% reduction in vasodilated flow was associated with a reduction in vascular volume of approximately 25% (16.4–12.5 ml/100 ml myocardium). This finding indicates that changes in flow distal to a stenosis during pharmacological vasodilation appear to be affected by changes in both transit time and blood volume content. Several laboratories have proposed relative flow indexes, based on transit-time differences between normal and stenotic regions, that assume that blood volume during vasodilation distal to a stenosis remains constant as stenosis severity varies.3,4 According to our results, relative perfusion indexes might be significantly improved if changes in blood volume during vasodilation were also taken into account. Such is the case for a relative perfusion index we have recently developed that is derived from myocardial CT intensity–time curves during vasodilation.21

**Clinical Implications**

These experiments show that a significant fraction of nonionic contrast is extracted on the first pass of an arterial bolus through the coronary circulation. While this will not affect densitometric estimates of perfusion based on the analysis of indicator dilution curves derived from the epicardial coronary arteries,27 it seriously challenges the notion that these agents can be considered to behave as intravascular indicators in the coronary circulation. Although our measurements were obtained during vasodilation, extraction is probably even higher at resting flows, as has been demon-
strated for numerous other diffuse indicators as well as the ionic contrast agent meglumine diatrizoate. While indexes of relative perfusion may still be obtained using analyses that focus on the entry of nonionic contrast into a myocardial region of interest, the retention of nonionic contrast, if not accounted for, precludes quantitative flow measurements, which assume that these agents are intravascular indicators. The magnitude of this first-pass extraction and its dependence on flow indicate that more sophisticated indicator dilution models will need to be used to quantitatively measure myocardial perfusion accurately using fast CT as well as other x-ray imaging modalities that rely on characterizing the myocardial concentration–time curve of soluble contrast agents.

Acknowledgments

We would like to express our appreciation to Paul Andreaksen, Karen Stanley, Robert Kufchak, Kathleen Harris, and Kathleen Weibel, all of whom provided the technical assistance necessary to complete this study, and to Brenda Sauka and Carol Michlin, who typed the manuscript. We would also like to thank Mallinckrodt, Inc. (ioversol) and Altana Inc. (ethiodol) for their generosity in supplying the contrast agents used in this study.

References


Key Words • computed tomography • radiographic contrast agents
First-pass entry of nonionic contrast agent into the myocardial extravascular space. 
Effects on radiographic estimates of transit time and blood volume. 
J M Canty, Jr, R M Judd, A S Brody and F J Klocke

Circulation. 1991;84:2071-2078
doi: 10.1161/01.CIR.84.5.2071

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/84/5/2071

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/