Laboratory Investigation

Mean Transit Time for the Assessment of Myocardial Perfusion by Videodensitometry

Nico H.J. Pijls, MD, Gerard J.H. Uijen, PhD, Albert Hoevelaken, MSc, Theo Arts, Wim R.M. Aengevaeren, MD, Hans S. Bos, MD, Jules H. Fast, MD, Karel L. van Leeuwen, MD, and Tjeerd van der Werf, MD

The intrinsic limitations of coronary arteriography to predict the physiological effects of coronary obstructions are well known. Therefore, more direct assessments of the functional significance of coronary stenoses are becoming increasingly important. Study of contrast passage by electrocardiogram-triggered digital radiography has been proposed as a way of assessing changes in myocardial perfusion. The main problems in this approach are the limited time for motionless image acquisition, the potential alteration of vascular volume between different states, and the changing flow pattern induced by contrast agents. This has led to empiric substitution of mean transit time (Tmn) by other time parameters and to representation of vascular volume by maximal contrast intensity (Dmax). To avoid these problems, intact dogs were studied during almost motionless image acquisition of 20–25 consecutive paced heart beats obtained with synchronous radiographic pulses. In this way, unequivocal and reproducible determination of Tmn was possible. Constant and maximal vascular volume was created by continuous infusion of dipyridamole, and it was proved that coronary flow in this model was not influenced by contrast injections. Flow in the circumflex artery was measured by a ring mounted and calibrated Doppler probe. In each dog, flow in the circumflex artery was varied by a balloon occluder in 12 small steps (range, 0–174±42 ml/min). Inverse appearance time (1/Tapp), Dmax/Tapp, inverse time of maximal intensity (1/Tmax), and 1/Tmn were calculated, and the relations of these parameters to measured flow were investigated. Tmn proved to be the most reliable parameter for this purpose (r=0.97±0.02; mean±SD), followed by Tmax (r=0.93±0.04). Dmax failed to represent vascular volume but, in fact, showed a moderate correlation with flow (r=0.78±0.22), as did Tapp (r=0.64±0.18, 0.75±0.27, and 0.59±0.26 for the three definitions of Tapp used in this study). Dmax/Tapp correlated better with flow than either component separately. Our results indicate that the mean transit time calculated by videodensitometry can be used to accurately assess changes in myocardial perfusion strictly according to the original principles of indicator dilution theory. (Circulation 1990;81:1331-1340)

Calculation of myocardial blood flow by studying contrast density in a myocardial region of interest (ROI) as a function of time was already suggested by Rutishauer et al1–3 more than 20 years ago. According to the principles of indicator dilution theory,4 this flow (F) can be calculated from the time-density curve (TDC) by:

\[ F = \frac{V}{T_{mn}} \]  

From the Department of Cardiology, St. Radboud Hospital, University of Nijmegen, Nijmegen, The Netherlands.

Supported in part by grants from Siemens AG Medical Engineering Group, Erlangen, FRG, and by grant 86,050 from The Dutch Heart Foundation, The Hague, The Netherlands.

Address for correspondence: Nico H.J. Pijls, MD, St. Radboud Hospital, University of Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

Received May 3, 1989; revision accepted November 30, 1989.

where V is the volume of the vascular bed between the injection site of the contrast agent and the measuring site and Tmn is the mean transit time of the contrast particles. Tmn is calculated from the TDC d(t) according to:

\[ T_{mn} = \int_0^{T_{mn}} d(t) \cdot \frac{d}{dt} \int_0^t d(t) \cdot dt \]  

(2)

In vivo calculation of flow in this way, however, is complicated by a number of problems. The most important problems are as follows: 1) the vascular...
traction imaging without motion artifacts during approximately 15–20 heart beats.

Several solutions for these problems have been suggested, and current approaches are commonly based on two major assumptions.  

The mean transit time $T_{mn}$ in Equation 1 is generally replaced by some other time parameter of which contrast appearance time ($T_{app}$) is the most popular, and it is hypothesized that vascular volume $V$ can be represented by the ROI-averaged maximal contrast intensity. Although this approach has empirically proved to be useful in animal and human studies, it should be emphasized that these assumptions are not supported by any physical or physiological theory. Investigation of the value of videodensitometry for myocardial flow assessment, according to the original physiological principles, would require improvement of image quality to enable determination of $T_{mn}$ from the TDC in an unequivocal and reproducible way, constant blood flow during the acquisition of the TDC itself, and a vascular volume that remains constant between different situations in which flow is compared. If all these conditions are fulfilled, flow from one situation to another should be inversely proportional to $T_{mn}$ according to Equation 1.

The aims of this study were, therefore, to achieve such an improvement of image and TDC quality, to investigate the feasibility of $T_{mn}$ for the assessment of myocardial perfusion using a dog model in which vascular volume was kept constant and flow was not influenced by contrast injection, and to analyze the validity of the two major assumptions as previously mentioned.

**Methods**

**Animal Instrumentation and Experimental Protocol**

After premedication with 0.1 mg fentanyl, 5.0 mg droperidol, and 0.5 mg atropine i.m., eight mongrel dogs (weight, 26–36 kg) were anesthetized with sodium pentobarbital 25 mg/kg i.v., a left thoracotomy was performed, and epicardial pacing electrodes were sutured on the left atrium. The proximal part of the left circumflex artery (LCx) was gently dissected free, over a distance of 1.0–1.5 cm proximal of the origin of the first large obtuse marginal branch. A ring-mounted 20-MHz pulsed Doppler probe (Crystal Biotech Inc., Holliston, Massachusetts) was placed around the artery and a circular balloon occluder (R.E. Jones, Silver Springs, Maryland) was placed just distal to the Doppler probe. The pericardium and chest were closed, and the instrumentation leads were placed in a subcutaneous pocket until the time of study.

At day 11 after instrumentation, each dog was anesthetized by nicomorphine 10 mg/hr i.v. and ethrane. The subcutaneous pocket was opened, and the wires of the Doppler probe were connected to the appropriate recording equipment (545C-4 Directional Pulsed Doppler Flowmeter, Department of Bioengineering, University of Iowa, Iowa City, Iowa). The pacing electrodes were attached to a trigger unit (Department of Bioengineering, University of Nijmegen, The Netherlands) and the occluder tube was connected to a 5-ml syringe. Both femoral arteries were dissected free. An 8F pigtail manometer catheter (Millar microtipped-catheter transducer SPC-780C) was introduced into the left femoral artery and positioned for simultaneous pressure recording in the left ventricle and the ascending aorta. A 5F left Judkins catheter was introduced into the right femoral artery and advanced into the ostium of the left main coronary artery. Electrocardiogram, left ventricular pressure and its first derivative, aortic pressure, and phasic and mean coronary blood flow velocity in the LCx were recorded on an eight-channel recorder (Hewlett-Packard).

After intravenous infusion of 5 mg propranolol during 20 minutes to prevent disproportionate increase in heart rate, an initial dose of dipyridamole (0.75 mg/kg) was administered intravenously during 4 minutes to create maximal dilation of the myocardial vascular bed, followed by 0.1 mg/kg/min for maintenance of this maximal dilated state. Presence of maximal vasodilatation was verified by the absence of any additional flow increase after 20 seconds of occlusion (Figure 1) or after intracoronary administration of 7.5 mg papaverine. Subsequently, the balloon occluder was inflated in two series of six small steps, guided by the mean Doppler signal and resulting in a step-by-step decrease of coronary flow velocity (Figure 1). In this way, 12 different flow levels at a constant (and maximal) vascular volume were achieved.

**Image Acquisition and Image Processing**

Image acquisition and processing were performed with a Siemens Bicor x-ray system connected to a Siemens Digitron-3 computer (Siemens AG, Erlangen, FRG). After stabilization of the hemodynamic parameters at every degree of stenosis, 6 ml of contrast agent (iohexol-140, Nycomed) was injected into the LAD with a power injector (Sybron Angiomat 300) at an injection rate of 4 ml/sec. Contrast injection started 5 seconds after the start of image acquisition to provide a stable baseline density level. The moment at which contrast agent appeared in the left main stem was defined as $t$ equaling 0. Voltage and current of the x-ray generator and pulse width were identical in all studies of one dog, and the automatic brightness control of the equipment was switched off after the fourth image in every series, to enable density comparison within one study and from one study to another. The radiographic projection was chosen so the parts of the myocardium corresponding with the LAD and LCx artery were well separated, usually the left anterior oblique 60° view. Meticulous care was used to not change the dog’s position during the course of the experiment or allow motion during image acquisition. Image acquisition was performed in the electrocardiogram-triggered mode using the principle of apparent cardiac arrest.
Figure 1. Recordings of example of step-by-step stenosis induction in circumflex artery during maximally dilated myocardial vascular volume achieved by continuous dipyridamole infusion. Electrocardiogram (ECG), left ventricular pressure (LVP), left ventricular dP/dt (LV dP/dt), aortic pressure (AoP), and phasic and mean Doppler shift are recorded. From left to right, step-by-step increases in stenosis correspond to step-by-step decreases in flow velocity. Contrast injection is performed at every flow level and causes artifactual short dip because of lack of ultrasound reflection by contrast agent. No increase in flow is observed after contrast injection and flow remains constant during image acquisition. Absence of breathing shortly before and during image acquisition can be recognized in pressure signals. Presence of maximal vascular volume is confirmed by absence of any additional hyperemia after 20 seconds of CX occlusion (right part of figure). This maximal flow velocity equals signal obtained in left part of figure where no stenosis is present. Note that during steady-state drug infusion, no changes in LVP and LV dP/dt are observed.
This means that the heart is stimulated slightly above its inherent frequency to provide a strictly regular heart rate, and that x-ray pulses are in phase with the cardiac cycle. To prevent motion because of breathing the muscle-relaxant drug, norcuron 0.1 mg/kg/hr was administered intravenously, artificial respiration was stopped, and the intratracheal tube was clamped during image acquisition. Thus, images without noticeable motion artifacts were acquired during 20–25 consecutive heart cycles. Images were digitized in 512×512 matrices with 1,024 density levels and subsequently stored.

**Processing of Regions of Interest and Time-Density Curves**

ROIs were chosen over the left main stem of the dogs to record the start of contrast injection and over the parts of the myocardium supplied by the LCx as well as the LAD for myocardial flow assessment (Figure 2). All ROIs over the myocardium were circular and of identical size (225–400 pixels). Close to the myocardial ROIs (CM1, CM2, LM1, and LM2), background ROIs (BCM1, BCM2, BLM1, and BLM2) were chosen outside the heart contour to analyze changes in background density (Figure 2). Once chosen, ROI position and size were kept constant in each dog.

TDCs were obtained by sampling the average pixel density within an ROI in the consecutive images and corrected by subtraction of the sampled average density in the corresponding background ROIs. The remaining TDC was fitted to a γ-function according to the Marquardt method, using all samples between t equaling 0 and the instant at which the descending part of the curve became less than 40% of the peak value. The quality of the fit was judged by the relative error E, which was defined as the square root of the ratio of the mean squares of differences between observed data and calculated data, and mean squares of the fit function. A 10% value of E was considered the upper limit for acceptance of the fit. These techniques have been described earlier.

Thereafter, T_{app} was calculated according to three different definitions, as follows: 1) T_{app(1)} was defined as the time at which the fit function exceeded a value of 0.01 multiplied by maximal contrast intensity;
2) \( T_{\text{app}}^{(2)} \), in an analogous way, as the time corresponding with 0.125 multiplied by maximal contrast intensity; and 3) \( T_{\text{app}}^{(3)} \) as the time of maximal inclination of the ascending limb of the fit function. Time of maximal contrast intensity (\( T_{\text{max}} \)) was defined as the time corresponding with the top of the fitted curve. \( T_{\text{mn}} \) was computed directly from the parameters of the \( \gamma \) function according to Equation 2. For each ROI, the ROI-averaged maximal contrast intensity was also computed and called \( D_{\text{max}} \). The relation between flow velocity and \( 1/T_{\text{app}}^{(1)} \), \( 1/T_{\text{app}}^{(2)} \), \( 1/T_{\text{app}}^{(3)} \), \( D_{\text{max}} \), \( D_{\text{max}}/T_{\text{app}}^{(1)} \), \( D_{\text{max}}/T_{\text{app}}^{(2)} \), \( D_{\text{max}}/T_{\text{app}}^{(3)} \), \( 1/T_{\text{max}} \), and \( 1/T_{\text{mn}} \) was computed for the myocardial ROIs in all dogs.

**Data Processing and Statistical Analysis**

Statistical analysis was performed using the SAS software package (SAS Institute Inc., Cary, North Carolina). Hemodynamic data are presented as mean±SD.

In testing reproducibility of calculation of \( T_{\text{mn}} \) in every dog, two arbitrary studies were performed in duplicate, coefficients of variation were calculated for every pair of studies, and the correlation coefficients between the first and the second measurement were calculated for the respective ROIs.

According to Equation 1, the relation between \( 1/T_{\text{mn}} \) and flow and between flow and volume should be linear. Therefore, the relations between the inverse time parameters and flow, between \( D_{\text{max}} \) and flow, and between \( D_{\text{max}}/T_{\text{app}} \) and flow were tested on a linear model, according to the \( F \) test. A \( p \) value of less than 0.05 was considered significant.

The results of the eight dogs will be presented in two ways. First, for the individual dogs, the median and range of correlation coefficients were evaluated for all investigated parameters and for both ROIs belonging to the LCx myocardium. Second, the data of all dogs were normalized and collected in one population. Normalization was performed in every dog by expressing the corresponding time parameter in a particular study as the ratio to the value of this parameter in the study without LCx stenosis. Flow velocity was normalized in an analogous way. The linear model was also tested for these normalized data. For the ROIs belonging to the LAD myocardium, only \( T_{\text{mn}} \) was analyzed. Because the flow in the LAD artery was not directly measured, these values for \( T_{\text{mn}} \) are corrected for changes in mean arterial pressure.

**Results**

**Hemodynamic Observations**

The dipyridamole infusion induced maximal flow velocity within 4 minutes in all dogs. Flow velocity increased to 346±39% of its resting value. Steady-state values for left ventricular pressure, left ventricular dP/dt, aortic pressure, and heart rate were reached within 10 minutes in four dogs. In the remaining four dogs, a slight gradual further decrease of arterial pressure occurred during the course of the experiment, accompanied by a similar decrease in coronary flow velocity. In this way, a constant (and maximal) vascular volume was achieved during the remaining part of the experiment.

Figure 1 shows that contrast injections were not followed by any change in flow velocity and that flow remained constant during image acquisition.

Maximal Doppler shift was 6.4±0.9 kHz. Calibration against an electromagnetic probe was performed successfully in six of the eight dogs just before killing, and an excellent correlation between both measurements was found in all cases (\( r=0.96±0.05 \)). Maximal Doppler shift corresponded with a maximal volumetric flow of 174±42 ml/min.

**Quality of Image Acquisition and Time-Density Curves**

Almost motionless image acquisition was achieved during 20–25 consecutive heart beats in 91 of 96 studies (94%). The excellent image quality is demonstrated in Figure 2. The positions of the myocardial ROIs and their corresponding background ROIs are also indicated in Figure 2.

Some examples of TDCs, the corresponding background curves, the background-corrected curves, and the corresponding fits are shown in Figure 3. After background correction, the baseline is more constant and the descending part of the curve returns to the baseline. Adequate fits could always be obtained. The
relative error $E_r$ representing the quality of the fit, was always less than 10% and averaged less than 3%.

Reproducibility of $T_{mn}$ was excellent, with mean coefficients of variation of 4.1%, 6.6%, 5.8%, and 7.6% for the four ROIs (CM1, CM2, LM1, and LM2, respectively). The correlation coefficients between the first and the second measurement were 0.98, 0.97, 0.91, and 0.96 for the respective ROIs.

**Relation Between Inverse Mean Transit Time and Flow**

In all dogs and for both ROIs over the LCx myocardium, a good linear correlation was found between inverse $T_{mn}$ and LCx flow velocity with correlation coefficients in the range of 0.92–0.99 (Table 1). The results per dog for one of the two ROIs are presented in Figure 4. The collected normalized data are presented in Figure 5 and Table 2 and show a linear relation between $1/T_{mn}$ and flow over the entire range ($r=0.94$ and 0.95, respectively, for the ROIs CM1 and CM2).

Delineation of TDCs and calculation of $T_{mn}$ was also performed for both ROIs LM1 and LM2 corresponding with the myocardium supplied by the LAD artery. The individual results of $1/T_{mn}$ for one of these ROIs in the consecutive studies are also shown in Figure 4. As expected, the corresponding values for $1/T_{mn}$ showed little variation in every dog, and the regression lines are nearly horizontal. The collected data are presented in Table 2.

**Table 1. Median and Range of Correlation Coefficients for Different Investigated Parameters for Regions of Interest CM1 and CM2 Over Myocardium Supplied by Left Circumflex Artery**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CM1</th>
<th>CM2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>m</td>
<td>r</td>
</tr>
<tr>
<td>$1/T_{app}(1)$</td>
<td>2</td>
<td>0.69</td>
</tr>
<tr>
<td>$1/T_{app}(2)$</td>
<td>6</td>
<td>0.75</td>
</tr>
<tr>
<td>$1/T_{app}(3)$</td>
<td>1</td>
<td>0.57</td>
</tr>
<tr>
<td>$D_{max}$</td>
<td>5</td>
<td>0.80</td>
</tr>
<tr>
<td>$D_{max}/T_{app}(1)$</td>
<td>5</td>
<td>0.82</td>
</tr>
<tr>
<td>$D_{max}/T_{app}(2)$</td>
<td>6</td>
<td>0.88</td>
</tr>
<tr>
<td>$D_{max}/T_{app}(3)$</td>
<td>5</td>
<td>0.67</td>
</tr>
<tr>
<td>$1/T_{mn}$</td>
<td>8</td>
<td>0.94</td>
</tr>
<tr>
<td>$1/T_{mn}$</td>
<td>8</td>
<td>0.97</td>
</tr>
</tbody>
</table>

$n=8$ number of dogs. $m$ for which linear model can be hypothetized according to $F$ test is indicated by $m$. $r$ median.

$T_{app}(1)$, time at which fit function exceeded a value of 0.01 multiplied by maximal contrast intensity; $T_{app}(2)$, time corresponding with 0.125 multiplied by maximal contrast intensity; $T_{app}(3)$, time of maximal inclination of ascending limb of fit function; $D_{max}$ region-of-interest-averaged maximal contrast intensity; $T_{mn}$, time of maximal contrast intensity, corresponding with the top of fitted curve; $T_{mn}$, computed from parameters of $y$-function according to Equation 2 (see text).

**Relation Between $1/T_{app}$, $1/T_{app}(2)$, $1/T_{app}(3)$, $D_{max}$**

The relations between $1/T_{app}(1)$, $1/T_{app}(2)$, and $1/T_{app}(3)$, respectively, and flow were studied for ROI CM1 and CM2 in an analogous way. A linear relation between $1/T_{app}$ and flow could be shown in a minority of dogs, and the correlation coefficients cover a wide range (Table 1). The collected data are presented in

**Figure 4. Scatterplots showing left circumflex (LCx) flow velocity versus inverse mean transit time ($1/T_{mn}$) during different degrees of LCx stenosis for individual dogs for one ROI over LCx myocardium and one ROI over the left anterior descending coronary artery (LAD) myocardium. (■), LCx myocardium; (○), LAD myocardium.**
Table 2. Because all time parameters in Table 2 are derived from the fit function and are related to appearance of contrast in the left main stem ROI, because of noise, some negative values for $T_{\text{app}}$ occurred that have been omitted for analysis and explain the different $n$ values in Table 2.

If $D_{\text{max}}$ adequately represented vascular volume, then this parameter would have to remain unchanged during a series of studies. This was not the case. In all dogs, $D_{\text{max}}$ decreased with decreasing flow (Table 1).

Subsequently, the relation between the $D_{\text{max}}/T_{\text{app}}$ ratio and flow was investigated for $T_{\text{app}}^{(1)}$, $T_{\text{app}}^{(2)}$, and $T_{\text{app}}^{(3)}$. The correlations obtained were better than those obtained using $1/T_{\text{app}}$ or $D_{\text{max}}$ alone but considerably less than the results obtained when using mean transit time (Figure 5 and Table 1).

Finally, the relation between $1/T_{\text{max}}$ and flow was examined. A linear relation was present in all dogs (Table 1). The correlation coefficients are better for $T_{\text{mn}}$ than for $T_{\text{max}}$ ($p<0.05$, Wilcoxon test for paired observations). The differences, however, are small; and $T_{\text{max}}$ is quite favorable as compared with $T_{\text{app}}$ (Table 2).

**Discussion**

The experimental model used in this study was devised to be as close to ideal for application of the indicator dilution theory as possible.

Flow was not influenced by contrast injection and remained constant during the acquisition of the TDC, whereas vascular volume, although unknown, remained unchanged between the different studies (Figure 1).

Image quality was enhanced considerably, and passage of contrast through the myocardium was studied reliably during 20–25 consecutive heart beats. This resulted in TDCs representing the sampled density values during consecutive heart beats on a scale of 0–1,023 density units. This scale is relative but uniform within one dog. For all ROIs, the density in corresponding background ROIs outside the left ventricular contour was also analyzed and, with time, usually showed a slight increase. After correction for these changes in background density, the time density curves almost invariably returned to the baseline.

Because TDCs in this study were constructed by sampling the average pixel density within the ROI and not on a pixel-by-pixel basis, this approach does not permit generation of parametric images but is less influenced by image noise.

After adequate fitting of the background corrected TDC, reliable and reproducible determination of mean transit time was possible. In all dogs and for both ROIs over the LCx myocardium, an excellent correlation was demonstrated between $1/T_{\text{mn}}$ and flow (Figures 4 and 5). Moreover, TDCs and $T_{\text{mn}}$ belonging to the ROIs over the LAD myocardium showed only minor changes during progressive flow reduction in the LCx artery, which argues for the intrinsic correctness of this model.

Our model also offered an ideal opportunity to study the value of other time parameters proposed for myocardial flow assessment and the value of $D_{\text{max}}$ for volume estimation. For all three definitions of contrast-appearance time used in this study, the relation with flow velocity is rather weak. A poor correlation between appearance time and flow has been documented in some previous studies. It is unlikely that the poorer results of appearance time to assess flow are because of methodological mistakes or shortcomings of this experimental dog model because the results for mean transit time were excellent and consistent with standard indicator dilution theory.

Because vascular volume remained constant in this study, one would expect $D_{\text{max}}$ to remain constant also, if this parameter reliably represents vascular volume. Instead, we found a decrease of $D_{\text{max}}$ with decreasing flow, which can be explained by the original principles of indicator dilution theory. The volume of indicator, that is, the contrast agent, will pass through the vascular compartment as a dispersed bolus; the rate of dispersion increasing with the length of time after injection. Because at low flow the moment of passage through a fixed ROI will be later than at high flow, the TDC at these low flows will be broader and have a lower peak. Justification for replacement of vascular volume by $D_{\text{max}}$ in Equation 1 has been defended by postulating that for every pixel in an ROI, all blood in the corresponding vascular space will be totally replaced by contrast agent shortly after contrast injection. Although 6–8 ml of contrast agent is generally injected, however, a considerable part of this will leak away in the aorta, whereas in the
presence of a severe stenosis in one branch, only a fraction of the injected contrast agent will enter the diseased branch and stain the corresponding myocardium. Additionally, according to pathological studies, the maximal volume of the vascular compartment of the heart is approximately 25 ml/100 mg,27-30 and although the vascular volume per unit increases from the left main coronary artery down to the capillary bed, the contrast bolus is actually dispersing. Therefore, it appears unlikely that undiluted contrast agent will pass through a myocardial ROI at sites more distal to the injection site. Whatever the explanation is, $D_{\text{max}}$ does not adequately represent vascular volume. The $D_{\text{max}}$/T$_{\text{app}}$ ratio generally showed a better correlation with flow than either component alone for all three definitions of T$_{\text{app}}$ (Figure 5 and Table 1). It must be emphasized from our results that this improvement is not because of the suitability of $D_{\text{max}}$ as an index of vascular volume but rather because $D_{\text{max}}$ is an independent parameter that reflects flow. Accordingly, $D_{\text{max}}$/T$_{\text{app}}$ shows a better correlation with flow.

**Clinical Implications and Limitations**

For clinical use, our model has some important limitations. The patient must stop breathing and remain motionless during at least 15 seconds, which requires extensive training and is only possible in select patients. If T$_{\text{mn}}$ cannot be determined reliably, use of T$_{\text{max}}$ only slightly less suitable than T$_{\text{mn}}$ in this study, could be considered.

Our model is only valid in situations of maximal vasodilation to guarantee constant vascular volume. Therefore, it should be emphasized that no information about resting flow can be obtained and that coronary flow reserve cannot be calculated. Our approach, however, does offer the ability to compare maximal myocardial blood flow before and after an appropriate intervention such as angioplasty or bypass surgery. Unlike coronary flow reserve, this maximal flow ratio is independent of resting flow and, therefore, not influenced by heart rate, left ventricular hypertrophy, previous infarction, prolonged ischemia, or by the preceding percutaneous transluminal coronary angioplasty procedure itself.21,31-36 Thus, despite potential clinical limitations, this study contributes to the understanding of the methods used to assess myocardial perfusion by studying contrast passage and shows that accurate calculation of relative myocardial perfusion by videodensitometry can

---

**Table 2. Collected Data of All Dogs, Normalized for Investigated Parameter and Flow**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>r</th>
<th>Slope ± SEM</th>
<th>Int ± SEM</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region of interest CM$_1$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/T$_{\text{app}}^{(1)}$</td>
<td>83</td>
<td>0.22</td>
<td>0.97±0.47</td>
<td>0.20±0.30</td>
<td>1.21</td>
</tr>
<tr>
<td>1/T$_{\text{app}}^{(2)}$</td>
<td>90</td>
<td>0.38</td>
<td>1.18±0.31</td>
<td>0.18±0.20</td>
<td>0.87</td>
</tr>
<tr>
<td>1/T$_{\text{app}}^{(3)}$</td>
<td>89</td>
<td>0.08</td>
<td>0.29±0.42</td>
<td>0.86±0.29</td>
<td>1.09</td>
</tr>
<tr>
<td>D$_{\text{max}}$</td>
<td>91</td>
<td>0.68</td>
<td>0.75±0.09</td>
<td>0.33±0.06</td>
<td>0.25</td>
</tr>
<tr>
<td>D$<em>{\text{max}}$/T$</em>{\text{app}}^{(1)}$</td>
<td>83</td>
<td>0.26</td>
<td>1.47±0.61</td>
<td>-0.15±0.39</td>
<td>0.56</td>
</tr>
<tr>
<td>D$<em>{\text{max}}$/T$</em>{\text{app}}^{(2)}$</td>
<td>90</td>
<td>0.56</td>
<td>1.62±0.25</td>
<td>-0.21±0.16</td>
<td>0.72</td>
</tr>
<tr>
<td>D$<em>{\text{max}}$/T$</em>{\text{app}}^{(3)}$</td>
<td>89</td>
<td>0.47</td>
<td>1.06±0.23</td>
<td>0.15±0.16</td>
<td>0.58</td>
</tr>
<tr>
<td>1/T$_{\text{max}}$</td>
<td>91</td>
<td>0.93</td>
<td>0.80±0.03</td>
<td>0.26±0.02</td>
<td>0.10</td>
</tr>
<tr>
<td>1/T$_{\text{mn}}$</td>
<td>91</td>
<td>0.94</td>
<td>0.86±0.03</td>
<td>0.13±0.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Region of interest LM$_1$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/T$_{\text{mn}}$</td>
<td>86</td>
<td>0.25</td>
<td>0.12±0.05</td>
<td>0.92±0.03</td>
<td>0.14</td>
</tr>
<tr>
<td>Region of interest CM$_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/T$_{\text{app}}^{(1)}$</td>
<td>80</td>
<td>0.22</td>
<td>0.72±0.36</td>
<td>0.12±0.22</td>
<td>0.91</td>
</tr>
<tr>
<td>1/T$_{\text{app}}^{(2)}$</td>
<td>89</td>
<td>0.41</td>
<td>1.78±0.42</td>
<td>-0.15±0.27</td>
<td>1.20</td>
</tr>
<tr>
<td>1/T$_{\text{app}}^{(3)}$</td>
<td>90</td>
<td>0.34</td>
<td>1.34±0.43</td>
<td>0.20±0.30</td>
<td>1.03</td>
</tr>
<tr>
<td>D$_{\text{max}}$</td>
<td>91</td>
<td>0.72</td>
<td>0.75±0.08</td>
<td>0.30±0.05</td>
<td>0.22</td>
</tr>
<tr>
<td>D$<em>{\text{max}}$/T$</em>{\text{app}}^{(1)}$</td>
<td>80</td>
<td>0.32</td>
<td>0.84±0.28</td>
<td>-0.10±0.17</td>
<td>0.71</td>
</tr>
<tr>
<td>D$<em>{\text{max}}$/T$</em>{\text{app}}^{(2)}$</td>
<td>89</td>
<td>0.45</td>
<td>2.04±0.43</td>
<td>-0.46±0.28</td>
<td>1.23</td>
</tr>
<tr>
<td>D$<em>{\text{max}}$/T$</em>{\text{app}}^{(3)}$</td>
<td>90</td>
<td>0.51</td>
<td>1.62±0.31</td>
<td>-0.20±0.03</td>
<td>0.74</td>
</tr>
<tr>
<td>1/T$_{\text{max}}$</td>
<td>91</td>
<td>0.90</td>
<td>0.81±0.04</td>
<td>0.26±0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>1/T$_{\text{mn}}$</td>
<td>91</td>
<td>0.95</td>
<td>0.90±0.03</td>
<td>0.17±0.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Region of interest LM$_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/T$_{\text{mn}}$</td>
<td>90</td>
<td>0.26</td>
<td>0.09±0.03</td>
<td>0.85±0.02</td>
<td>0.10</td>
</tr>
</tbody>
</table>

n = number of studies for each investigated parameter.

r, correlation coefficient; SEM, standard error of slope and intercept, respectively; SEE, standard error of estimate.

T$_{\text{app}}^{(1)}$, time at which fit function exceeded a value of 0.01 multiplied by maximal contrast intensity; T$_{\text{app}}^{(2)}$, time corresponding with 0.125 multiplied by maximal contrast intensity; T$_{\text{app}}^{(3)}$, time of maximal inclination of ascending limb of fit function; $D_{\text{max}}$, region-of-interest-averaged maximal contrast intensity; T$_{\text{max}}$, time of maximal contrast intensity, time corresponding with the top of fitted curve; T$_{\text{mn}}$, computed from parameters of γ-function according to Equation 2 (see text).
be performed in an intact organism according to the original principles of indicator dilution theory.

Acknowledgments

We wish to express our gratitude to Dr. K. Kubat for the histological examinations, to Truus Pijnenburg and Tanja van den Heuvel for their assistance in preparing this manuscript, and to G.B. John Mancini, MD (University of Michigan Medical Center), for his thoughtful review of the manuscript.

References


**KEY WORDS** • contrast appearance time • digital radiography • myocardial blood flow • time-density curve
Mean transit time for the assessment of myocardial perfusion by videodensitometry.
N H Pijls, G J Uijen, A Hoevelaken, T Arts, W R Aengevaeren, H S Bos, J H Fast, K L van Leeuwen and T van der Werf

Circulation. 1990;81:1331-1340
doi: 10.1161/01.CIR.81.4.1331

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/81/4/1331

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/