Digital Angiographic Impulse Response Analysis of Regional Myocardial Perfusion

Estimation of Coronary Flow, Flow Reserve, and Distribution Volume by Compartmental Transit Time Measurement in a Canine Model

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A system impulse response function that describes the kinetics of radiographic contrast material transit through the coronary circulation was calculated from 175 selective digital angiograms of normal and stenotic arteries in 10 dogs during rest and hyperemia. The goal of the study was to determine if the flow and distribution volume characteristics of the epicardial coronary arteries and the myocardial microcirculation could be simulated by specific mathematical compartments of a lagged normal density model impulse response function in which the flow/distribution volume ratio is the inverse of the mean transit time. The arterial compartment mean transit time correlated with flow \((r=0.75)\); however, the correlation was significantly improved in individual dogs \((r=0.83\pm0.13; p<0.005)\) and was highly dependent on the length of the conduit vessel. The microcirculation compartment mean transit time was distributed as two populations with respect to flow. There was a linear correlation during hyperemia \((r=0.87)\) and a nonlinear relation during rest, which was characteristic of an autoregulating system. Resting values of microcirculation compartment mean transit time correlated with coronary flow reserve \((r=0.84)\) and differed significantly between vessels that were normal and those with subcritical stenosis, critical stenosis, or total occlusion \((p<0.01)\) for all comparisons. The estimated microcirculation compartment distribution volume increased from a minimum of 4.0±1.5 ml/100 g myocardium in normal vessels with resting flow to 11.2±3.5 ml/100 g during hyperemia. These data suggest that the model compartments functionally describe the physiological behavior of their anatomic analogues and permit the quantification of microcirculatory autoregulation from a single measurement at rest without provoking hyperemia. (Circulation Research 1991;68:870–880)

A reliable and practical angiographic method for quantifying regional myocardial perfusion and coronary flow reserve would be useful for diagnosis and evaluating treatment strategies in patients with coronary artery disease. We have described a method called digital angiographic impulse response analysis, which uses a two-compartment linear mathematical model to simulate radiographic contrast material transit through the coronary circulation. Working with an intact coronary circulation in an open-chest canine preparation, we found that there was a close linear correlation between system mean transit time \((T_{\text{sp}})\) of the model and regional myocardial perfusion during pharmacological hyperemia but not during rest, where vasodilatory autoregulation was intact.

By definition, \(T_{\text{sp}}\) is the distribution volume of the indicator divided by flow. We propose that deviations from a linear relation between transit time and flow are due to changes in the distribution volume. Moreover, since the majority of the coronary blood volume is located in the myocardial microcirculation, autoregulatory vasodilation of these vessels may affect the distribution volume of contrast material. Thus, we...
postulate that the mean transit time may be a composite index of both the flow and autoregulatory vasodilation.

The purpose of this study was to evaluate the transit time parameters of the individual model compartments with respect to three questions: 1) Can these parameters be used to estimate coronary flow or flow reserve? 2) Can compartmental modeling be used to differentiate normal from stenotic vessels with or without hyperemic flow? 3) Do the model compartments represent discrete anatomic or physiological entities?

Materials and Methods

System Description

The coronary circulation can be thought of as a system of interconnecting pathways that transport indicator from a proximal coronary artery (the input) to the myocardial microcirculation (the output). If such a system is linear and stationary, it can be characterized by its system impulse response function, which defines the relation between any input and output. During coronary angiography, digital videodensitometry can detect the input and output signals, which are proportional to the relative concentration of contrast material within a given region of interest. This assumes that, within the region, myocardial wall thickness and the density of the vasculature within the wall are uniform. These input and output signals are used to calculate the system impulse response function.

Impulse Response Algorithm

The impulse response algorithm uses an iterative procedure to fit a two-compartment lagged normal density function (Figure 1) to model indicator dispersion in a flowing arterial system. We propose that the first compartment represents dispersion of indicator in the large epicardial coronary arteries, which may be analogous to flow through a simple conduit. This produces symmetrical dispersion of indicator about a central or mean transit time, which is approximated by a normal distribution function, h1(t):

$$h_1(t) = \frac{e^{-t^2/(2\delta^2)}}{\sqrt{2\pi}\delta} \text{ for } t > 0$$ (1)

$$h_1(t) = 0 \text{ for } t \leq 0$$

where T**art** is the arterial compartment mean transit time with standard deviation δ. Complete mixing of indicator with blood need not take place in this compartment, but it is required that blood and indicator have the same distribution of transit times.

We postulate that the second compartment describes flow through the myocardial microcirculation. Such a highly branched network may be analogous to a well-stirred mixing chamber in which dispersion is nonsymmetrical and can be modeled by a monoexponential decay function, h2(t):

$$h_2(t) = \frac{e^{-t/T_{micro}}}{T_{micro}} \text{ for } t > 0$$ (2)

$$h_2(t) = 0 \text{ for } t \leq 0$$

where T**micro** is the microcirculation compartment mean transit time.

Serial flow through the two compartments is described by the lagged normal density function, h(t), which is generated by convolution of the two compartmental functions:

$$h(t) = h_1(t) * h_2(t)$$ (3)

The system impulse response is calculated by iterative convolution. The input time–density curve is repetitively convolved with the lagged normal density model, whereas the parameters, T**art**, δ, and T**micro** are adjusted with a minimal time resolution of 0.06 second until the coefficient of variation between the convolution and the output time–density curve is minimized. The final model parameters define the system impulse response. The mean transit time for the system impulse response (T**sys**) is the sum of the individual compartment transit times:

$$T_{sys} = T_{art} + T_{micro}$$ (4)

FIGURE 1. Schematic of lagged normal density model impulse response function. Top panels: The coronary circulation is conceptualized as a two-compartment anatomic system composed of the epicardial coronary arteries and the myocardial microcirculation. Middle panels: Physical analogues that simulate the flow and distribution volume behavior of the respective anatomic compartments—a rigid conduit and a well-stirred mixing chamber. Bottom panels: Graphical representation of the mathematical model compartments: T**art**, arterial compartment mean transit time; T**micro**, microcirculation compartment mean transit time; T**sys**, total system mean transit time; t, time. Normal density curve and monoexponential decay functions, when convolved, yield the lagged normal density function.
Animal Model

The animal studies in this report conform to the guiding principles of the American Physiological Society and were approved by the institutional animal welfare committee. Ten open-chest mongrel dogs (31.8±6.4 kg; range, 24.5–48 kg) were anesthetized with morphine sulfate (1.0 mg/kg i.m.) and sodium pentobarbital (30 mg/kg i.v.). The dogs were mechanically ventilated with 50% oxygen, and anesthesia was maintained with vaporized enflurane. In the first six dogs, appropriately sized electromagnetic flow probes (Micron Instruments, Los Angeles) were placed around the proximal left circumflex coronary artery as previously described.1 In the last four dogs, a perivascular ultrasonic volume/flow probe was substituted (Transonic Systems, Inc., Ithaca, N.Y.). These ultrasonic probes do not compress the artery and can be reliably calibrated in vitro; there is negligible zero drift.10,11 Clotted blood was used to maintain acoustic coupling between the probe and artery. A pneumatic occluder (In Vivo Metric, Healdsburg, Calif.) was placed immediately distal to the flow probe. A 7F Judkins R4 catheter was introduced into the left common carotid artery and positioned in the left main coronary artery, and heparin (5,000 units i.v.) was given. The electrocardiogram, proximal coronary artery blood pressure, and coronary blood flow were continuously monitored. The coronary catheter did not restrict flow or affect proximal coronary pressure.

Hand-injected selective left coronary angiograms (n=175) were performed with 4 ml ionic contrast material, meglumine diatrizoate (370 mg iodine/ml Angiost, Berlex Laboratories, Inc., Wayne, N.J.). Coronary physiology was altered by creating variable degrees of acute proximal coronary artery stenosis and/or by pharmacological vasodilation of the microcirculation (hyperemia). Thus, there were four physiological states: normal and stenotic arteries with resting microcirculation and normal and stenotic arteries during hyperemia. Hyperemia was induced by dipyridamole infusion (0.56–1.02 mg i.v. for 5–10 minutes) in two dogs (n=16) and by intracoronary injection of 4 ml ionic contrast material in eight dogs (n=59). Injections were separated by a minimum of 4 minutes to allow contrast-induced hyperemic coronary flow to return to baseline.12–14 At the conclusion of each study, a 2.5F coronary infusion catheter was placed subselectively into the left circumflex artery, and 10 ml Monastral blue was injected, followed immediately by death with intravenous KCl. The heart was cut into 1-cm-thick short-axis sections, weighed, and photographed to determine the mass of myocardium supplied by the left circumflex artery (whole heart weights, 239±62 g; range, 175–348 g).

Imaging Procedure

Radiographic exposures were created with a Siemens Gigantos system, which consisted of a 100-kW cine generator and a 0.6-mm focal spot grid-pulsed x-ray tube with 2.8-mm aluminum equivalent filtration (Siemens, Erlangen, FRG). The imaging chain included an 8:1 antiscatter grid, a 23/18/11-cm triso mode image intensifier coupled with a low-noise (signal-to-noise ratio=1,000/1) 1-in. Plumbicon television camera operating in the 525–horizontal line interlaced scanning mode (ADAC 4110, ADAC Laboratories, Milpitas, Calif.). The x-ray technique used 60-Hz, 5-msec pulsed fluoroscopy with fixed tube potential (75 kVp) and current, resulting in typical input exposures of 8 µR/pulse. The camera black level was set at 65 mV, and the lens aperture was adjusted so that the brightest portions of the image were below target saturation (750 mV).

The dogs were positioned so that there was minimal overlap of the microvascular territories supplied by the left circumflex and left anterior descending arteries, as determined by subselective coronary injection. This was usually accomplished by placing the image intensifier directly over the left lateral thoracotomy. Two lead blockers were positioned between the x-ray source and the dog to project into the center of the cardiac silhouette and adjacent to the left main coronary artery for regional x-ray scatter and veiling glare (SVG) measurement.

The raw images were recorded on 3/4-in. U-matic video tape (model BVU-200, Sony, Tokyo) with linear fixed-gain amplification. Five seconds before injection, ventilation was suspended at end inspiration, and angiographic and physiological recording was begun to establish a baseline. Recording was continued for about 20 seconds after injection until there was no visible contrast material in the coronary sinus. Videotape images were time-base corrected (Harris Video Systems, Sunnyvale, Calif.) and digitized off-line on an ADAC 4100C cardiac angiographic image processing system in a 256×256-pixel, 256 gray level format at 6 frames/sec, and every fifth video frame was stored on disk.

Image Processing

While viewing the digitized images in a cine-loop format, the operator positioned regions of interest (ROIs) for time–density curve acquisition. A 100-pixel ROI was placed over the left main coronary artery just distal to the tip of the catheter for the input, and 100-pixel ROIs were placed over each lead blocker. A 1,600–2,000 pixel output ROI was drawn over the myocardial microcirculation blush of the left circumflex territory. Two smaller ROIs consisting of 400 pixels were placed at locations designated as proximal and distal within the large ROI. The mean digitized intensity within each ROI was determined as a function of time from unsubtracted images.

Scatter-corrected time–density curves were constructed by subtracting the nearest SVG curve frame by frame from the input and output ROIs.1,12 The resultant curves were logarithmically transformed to correct for exponential attenuation of radiation and subtracted from the preinjection background. High-
frequency variations due to cardiac motion were reduced by unweighted time domain filtration over
two cardiac cycles. A monoexponential decay function
was fitted by the least-squares method to the downslip-
ning portion of the input curve from the inflection point
after the peak to 60% of the peak value. This curve
then replaced the terminal portion of the input curve
to compensate for contrast material that exited the
coronary sinus and overlapped the input ROI late in
the angiographic acquisition. These corrected input/
output time-density curves were the data used in
conjunction with the lagged normal density model to
calculate the system impulse response.

Data Analysis

To compensate for insufficiency described myocar-
dial ROI time–density curves, two empiric crite-
ria were applied as previously described.1 If the
output function rose progressively without peaking
during the 15–20 seconds after contrast injection or
if the change in x-ray intensity was not greater than
three gray levels (the preinjection background noise
varied by two to three gray levels), Tsys and Tmicro
were assumed to be infinite. If there was less than 5
seconds of data following the peak density of the
output function, Tsys and Tmicro were assigned to be
20 seconds. These criteria were satisfied in all 11
injections in which total occlusion was present and
in an additional four other vessels with greatly
diminished resting flow. Transit time parameters
were obtained by impulse response analysis in the
other 160 injections.

Coronary blood flow was measured as the mean
flowmeter reading during the 3 seconds before con-
trast injection. Coronary flow was normalized with
respect to the mean resting coronary blood flow in
nonstenotic arteries for each dog. Coronary flow
reserve (CFR) was defined as

\[ \text{CFR} = \frac{Q_{hy}}{Q_r} \]

where the peak hyperemic flow after ionic contrast
injection (Qhy) was normalized for the prestenotic
resting flow (Qr). This definition was chosen because
1) it quantifies the maximal flow for a given hyper-
emeric stimulus and 2) interpretation of data may be
more difficult with the conventional definition of the
CFR ratio where the denominator is the stenotic
resting flow. This is because pharmacological vasodil-
itation often exceeds the maximal vasodilatation re-
sulting from ischemia.15–17

Normal vessels were characterized by the absence
of angiographic stenosis, and CFR was always greater
than 3.1. Angiographic stenoses were further subcat-
egorized: subcritical, when resting flow was main-
tained but CFR was reduced; critical, when resting
flow was reduced and CFR was 1.0 or less; and
occluded, when antegrade flow was abolished.

The reciprocal of Tsys, Tart, and Tmicro were com-
pared with normalized coronary flow by linear regres-
sion analysis. The distribution volumes of contrast
material with respect to myocardial mass (VM) were
calculated as

\[ V_{M(sys, art, micro)} = T_{sys, art, micro} \times Q_M \]

where QM was the flow normalized for each 100 g left
ventricular myocardial mass supplied by the left
circumflex coronary artery.

The model system assumes that flow in each model
compartment is the same. Thus, the ratio of the
microcirculation and total system volumes is given by

\[ \frac{V_{micro}}{V_{sys}} = \frac{T_{micro}}{T_{sys}} \]

which is computationally independent of flow.

Statistical Analysis

Data throughout the text are expressed as
mean±SD. Statistical inference testing was per-
formed using the two-tailed Student’s t test for single
and two-sample data. One-way analysis of variance
was used to compare the means of three or more
independent samples, and multiple comparisons be-
tween pairs of samples were performed using the
Bonferroni modification of the t statistic.18,19

Results

Hemodynamic and angiographic parameters for
the four physiological states are summarized in Table
1. There were no significant differences in heart rate
or mean blood pressure between the groups. Al-
though the flowmeter and angiographic parameters
were significantly different between the states, the
interrelations are better perceived in the individual
injection data scatter plots.

Figure 2 compares the inverse of Tsys, Tart, and
Tmicro (Tsys⁻¹, Tart⁻¹, and Tmicro⁻¹) with left circumflex
 coronary blood flow for each of the four physiological
states. Tsys⁻¹ is distributed as two populations, with
respect to flow, that were related to the state of
microcirculation vasodilation. There was a strong
linear correlation (r=0.89) during hyperemia over a
wide range of flow (more than sevenfold basal flow),
but during rest, there was a curvilinear relation
between Tart⁻¹ and normalized coronary flow. For
critical stenoses, where resting flow was diminished,
this relation closely paralleled the hyperemic data;
however, this distribution turned upward with sub-
critical stenosis and became essentially vertical for
normal vessels.

The correlation of Tart⁻¹ with flow was much lower
(r=0.75), with substantial scatter. Regression coeffi-
cients for individual dogs averaged significantly
higher (r=0.83±0.13; p<0.005) than when all the
dogs were combined, due primarily to large differ-
ences in regression slopes (range, 38–68). There was
no apparent difference in the linear distribution for
the resting and hyperemic states.

Tmicro⁻¹ showed an even more distinct two-popula-
tion distribution with respect to the state of micro-
circulation vasodilation. There was a linear correla-
tion during hyperemia (r=0.87) and a nonlinear
TABLE 1. Summary of Hemodynamic and Angiographic Parameters by Physiological State

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>p by ANOVA</th>
<th>p&lt;0.01 by t test*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>103±16</td>
<td>102±15</td>
<td>107±16</td>
<td>105±16</td>
<td>0.90</td>
<td>None</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>83±16</td>
<td>80±15</td>
<td>86±8</td>
<td>87±6</td>
<td>0.63</td>
<td>None</td>
</tr>
<tr>
<td>Qd (ml/min/100 g)</td>
<td>3.9±1.2</td>
<td>1.4±0.7</td>
<td>1.0±0.1</td>
<td>0.8±0.3</td>
<td>&lt;0.001</td>
<td>1 vs. 2,3,4</td>
</tr>
<tr>
<td>CFR (ml/min/100 g)</td>
<td>200±103</td>
<td>84±57</td>
<td>62±18</td>
<td>43±21</td>
<td>&lt;0.001</td>
<td>1 vs. 2,3,4</td>
</tr>
<tr>
<td>Tsysy-1 (min⁻¹)</td>
<td>17.8±7.4</td>
<td>7.6±3.8</td>
<td>11.1±2.0</td>
<td>5.3±2.8</td>
<td>&lt;0.001</td>
<td>All</td>
</tr>
<tr>
<td>Tarty-1 (min⁻¹)</td>
<td>222±147</td>
<td>80±83</td>
<td>45±23</td>
<td>42±25</td>
<td>&lt;0.001</td>
<td>1 vs. 2,3,4</td>
</tr>
<tr>
<td>Tmean-1 (min⁻¹)</td>
<td>20.7±8.8</td>
<td>8.7±4.5</td>
<td>16.5±4.0</td>
<td>6.3±3.8</td>
<td>&lt;0.001</td>
<td>All</td>
</tr>
</tbody>
</table>

Values are mean±SD. 1, Normal arteries during hyperemia; 2, stenotic arteries during hyperemia; 3, normal arteries with resting microcirculation; 4, stenotic arteries with resting microcirculation; ANOVA, analysis of variance; BP, blood pressure; Qd, preinjection flow normalized for mean prestenotic resting flow; Qn, preinjection flow normalized for left circumflex myocardial mass; CFR, coronary flow reserve; Tsysy, Tarty, and Tmean system, arterial, and microcirculation compartment mean transit times, respectively.

*Multiple comparison t tests: for example, 1 vs. 2,3,4 signifies that state 1 is different from states 2, 3, and 4 at p<0.01. No other comparisons achieved p<0.05.

Relation at rest, which was analogous to that seen with Tsysy⁻¹. Hyperemic regression coefficients for individual dogs were not significantly improved compared with the aggregate (r=0.89±0.05; p=0.30). None of the correlations between angiographic parameter and flow was improved by normalizing the data for heart rate, blood pressure, or hematocrit.

Figure 3 compares compartmental transit times from proximal and distal regions of myocardium. Although there was a linear correlation, Tarty⁻¹ was an average 1.8-fold longer in the distal compared with the proximal region, and this difference was highly significant (p<0.0001). Tmean⁻¹ was negligibly affected by the myocardial region of interest.
location. There was, however, a small but significant difference between the regression line and identity (p<0.0001).

Figure 4 compares resting state measurements of \( T_{\text{micro}}^{-1} \) with CFR for each category of stenosis severity. There was a linear correlation (\( r=0.84 \)) with the best agreement in the range of CFR associated with stenosis (for CFR<3.0, \( r=0.90 \)). Variability was greater for vessels with CFR greater than 3.0 due, in part, to differences between individual dogs. The mean regression coefficient was slightly higher for individual dogs (\( r=0.90 \pm 0.09 \); p<0.01). The mean values of \( T_{\text{micro}}^{-1} \) for each of the four stenosis categories differed significantly (p<0.01) for all possible pairwise comparisons. \( T_{\text{sys}}^{-1} \) was also linearly related to CFR; however, \( T_{\text{art}}^{-1} \) was not (\( r=0.85 \) and 0.29, respectively).

Table 2 shows the calculated compartmental distribution volumes for the four physiological states. \( V_{\text{art}} \) was similar for all physiological states, ranging from 1.2 to 1.7 ml/100 g myocardium. The microcirculation distribution volume, \( V_{\text{micro}} \), progressively increased from a minimum of 4.0 ml/100 g in normal/resting injections to 11.2 ml/100 g during hyperemia. The fraction of the contrast distribution material contained in the microcirculation, \( V_{\text{micro}}/V_{\text{sys}} \), was significantly smaller for normal/resting injections than in all other categories.

To further assess the relative contribution of \( V_{\text{micro}} \) to \( V_{\text{sys}} \), the two mean transit times that calculate this ratio are plotted in Figure 5. There was a very high linear correlation during hyperemia (\( r=0.98 \)), with \( V_{\text{micro}} \), occupying approximately 90% of \( V_{\text{sys}} \). There was a curvilinear response during rest, which was well described by a power function (\( r=0.97 \)), with the \( V_{\text{micro}} \) occupying a smaller percentage of \( V_{\text{sys}} \) in normal/resting arteries. There were significant differences (p<0.01) between normal arteries at rest and all other physiological state categories.

**Discussion**

We have described a new method called digital angiographic impulse response analysis for densitometric myocardial flow measurement. A two-com-

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**Table 2. Comparison of Compartmental Volumes for Physiological States**

<table>
<thead>
<tr>
<th>Physiological state</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>( p ) by ANOVA</th>
<th>( p&lt;0.01 ) by t test*</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{\text{art}(mi)} ) (ml/100 g)</td>
<td>12.7±3.8</td>
<td>11.0±5.0</td>
<td>5.8±2.0</td>
<td>9.1±4.6</td>
<td>&lt;0.001</td>
<td>3 vs. 1,2,4</td>
</tr>
<tr>
<td>( V_{\text{art}(mi)} ) (ml/100 g)</td>
<td>1.4±0.9</td>
<td>1.2±1.5</td>
<td>1.7±0.9</td>
<td>1.2±0.7</td>
<td>0.144</td>
<td>None</td>
</tr>
<tr>
<td>( V_{\text{art}(mi)} ) (ml/100 g)</td>
<td>11.2±3.5</td>
<td>9.8±4.5</td>
<td>4.0±1.5</td>
<td>7.9±4.4</td>
<td>&lt;0.001</td>
<td>3 vs. 1,2,4</td>
</tr>
<tr>
<td>( V_{\text{art}(mi)}/V_{\text{art}(mi)} )</td>
<td>0.93±0.08</td>
<td>0.90±0.07</td>
<td>0.69±0.11</td>
<td>0.87±0.08</td>
<td>&lt;0.001</td>
<td>3 vs. 1,2,4</td>
</tr>
</tbody>
</table>

Values are mean±SD. 1, Normal arteries during hyperemia; 2, stenotic arteries during hyperemia; 3, normal arteries with resting microcirculation; 4, stenotic arteries with resting microcirculation; ANOVA, analysis of variance; \( V_{\text{art}} \), compartmental distribution volume normalized for myocardial mass; sys, system; art, arterial; micro, microcirculation.

*Multiple comparison t tests: for example, 3 vs. 1,2,4 signifies that state 3 is different from states 1, 2, and 4 at \( p<0.01 \). No other comparisons achieved \( p<0.05 \).
A. **Coronary Flow Reserve**

**Figure 4.** Graphs comparing the resting state inverse microcirculation compartment mean transit time \( T_{\text{micro}}^{-1} \) with coronary flow reserve (CFR) grouped by four categories of stenosis severity. Panel A: ■, total occlusion; ●, critical stenosis; ▲, subcritical stenosis; ○, normal artery. Panel B: Mean±SD for four categories defined in panel A.

B. **Coronary Flow Reserve**

A compartment mathematical model, the lagged normal density function, was used to quantify the passage of radiographic contrast material through the coronary circulation from an input region at the site of injection in a proximal coronary artery to an output region in the myocardial microcirculation. Working with an intact coronary circulation in an open-chest canine preparation, we previously demonstrated that the model accurately and reproducibly simulated the behavior of the system under a variety of conditions and that the coronary passage of contrast material could be modeled as a linear system. Specifically, the method was not affected by the type of contrast agent used (ionic versus nonionic), the shape of the contrast bolus injection, or the type of stimulus used to provoke hyperemic flow. \( T_{\text{res}}^{-1} \) was linearly correlated with regional myocardial blood flow when the microcirculation was vasodilated. Moreover, the model more closely predicted regional myocardial perfusion than did traditional indicator dilution curve parameters, including time-to-peak concentration and exponential washout rate. The present study extends these observations by examining the individual model compartment transit times with respect to regional coronary flow, CFR, and distribution volume in normal and stenotic arteries during rest and hyperemia.

**Choice of Model**

We chose the lagged normal density curve to model the coronary circulation for three reasons: 1) There are only three parameters to adjust, which permits rapid computation and minimizes the variability of individual parameters to system noise. 2) The model permits the assumption that there are two transport zones; mixing need only take place in one of these zones, thus, relaxing the classic as-

A. **Hyperemia**

**Figure 5.** Graphs showing relation of microcirculation compartment and total system mean transit times \( T_{\text{micro}} \) and \( T_{\text{res}} \), respectively) for hyperemic vessels and resting vessels.

B. **Rest**

\[ T_{\text{res}}^{-1} = 0.83 T_{\text{micro}}^{-1} + 0.5 \]

\[ T_{\text{res}}^{-1} = 1.33 T_{\text{micro}}^{-1} \]
Assumption of indicator dilution that mixing is complete and instantaneous. 3) The model tests the hypothesis that the two model compartments approximate discrete anatomic or physiological entities, that is, the epicardial coronary arteries and the coronary microcirculation.

Although many mathematical model types (e.g., gamma-variate, random walk, and parallel axial tube) would permit accurate calculation of the system impulse response function and its mean transit time, they do not satisfy the above criteria. For example, even though the distributed parallel axial tube model described by Turner closely resembles the coronary circulation, it does not account for capillary branching, and it implies that mixing is uniformly distributed throughout the system. Moreover, in the absence of radial transport to the extravascular space, such a system is equally well described by the lagged normal density curve.

**Relation of Compartmental Transit Times to Regional Myocardial Blood Flow**

This report extends our earlier observation that T\textsubscript{sys} distributes as two distinct populations with respect to flow and that the distributions depend on the physiological state of the microcirculation. T\textsubscript{sys} was a linear function of flow over a wide range (zero to sevenfold baseline flow) during hyperemia, when vasodilatation of the microcirculation was maximal, and a nonlinear function of flow when autoregulatory mechanisms were intact. T\textsubscript{at} correlated only modestly with regional myocardial blood flow, and the data distributed as a single population. However, this parameter was closely associated with flow in individual dogs and was dependent on the location of the output ROI; the more distal the ROI, the longer the arterial mean transit time.

The microcirculation compartment had the most exaggerated two-population distribution relation with regional flow, which was highly dependent on the physiological state of the microcirculation and was unvarying within the output region of the circumflex-supplied myocardium. The dependency of the relation between T\textsubscript{micro} and flow on the reactivity of microcirculation resistance vessels is analogous to the well-described relation between coronary driving pressure and blood flow. There was a highly linear relation between T\textsubscript{micro} and flow during hyperemia, when vasodilatory capacity was exhausted. When the microcirculation was at rest, with vasodilatory capacity intact, flow was autoregulated until critical stenosis produced maximal vasodilatation and there was once again a linear relation between T\textsubscript{micro} and flow. Thus, T\textsubscript{micro} appears to be reflective of the state of autoregulatory vasodilatation.

**Proposed Mechanisms for Two-Population Distribution**

There are two hypotheses that may explain the observed dual population distributions. The nonlinear car relation at rest may have resulted from the transient hyperemic flow induced by contrast media in normal vessels, which was blunted or absent in stenotic vessels. Hyperemia typically reached a maximum at 10–14 seconds after injection and thus occurred simultaneously with time–density curve acquisition. This disturbance in the steady-state flow would be expected to shorten the mean transit time in normal, compared with subcritically stenotic, vessels, where preinjection flow was the same.

Our previous study showed that injections into normal/resting arteries with ionic and nonionic contrast media resulted in nearly equivalent mean transit times even though ionic contrast media produced 90% greater transient flow. Therefore, it is unlikely that this proposed mechanism has a significant effect on the mean transit time.

An alternative mechanism is required that, in addition to explaining the nonlinear relation during the resting state, also explains why the large difference in peak hyperemic flow with ionic and nonionic contrast does not affect mean transit time. We postulate that the process that creates hyperemic flow, that is, microcirculatory vasodilatation, also simultaneously increases contrast distribution volume. Thus, the flow/distribution volume ratio and, hence, mean transit time, remains relatively stationary during contrast-induced hyperemia. Moreover, this hypothesis suggests that differences in the mean transit time for a given resting flow result from differences in distribution volume. This mechanism is supported by two experimental results in the present study: 1) In normal arteries where the microcirculation was vasocostricted, the calculated distribution volume was small. 2) As proximal stenosis increased in severity, there was progressive vasodilatation and enlarging distribution volume. Figure 6 is a schematic diagram illustrating this proposed mechanism.

**Relation to Coronary Flow Reserve and Stenosis Severity**

Our study demonstrated that both T\textsubscript{sys} and T\textsubscript{micro} were linearly related to CFR. CFR is traditionally
computed as the ratio of two measurements of flow, one taken at rest and one taken after a hyperemic stimulus. The angiographic mean transit times, however, estimate CFR with a single measurement taken at rest. Furthermore, the mean transit time can be used to differentiate normal vessels from those in which stenosis was subcritical and resting flow was unchanged. Once again, we explain these findings by recalling that the mean transit time is also a ratio, and if flow is constant, distribution volume must be changing in proportion to CFR. This lends further credence to the argument that changes in distribution volume are a direct consequence of microcirculation vasodilation. When the microcirculation dilates, there is an increase in vascular cross-sectional area. The increase in $V_{micro}$ may be approximately proportional to the change in cross-sectional area and, thus, inversely proportional to microcirculation resistance.

Additionally, single resting-state measurements of $T_{sys}$ and $T_{micro}$ discriminated discrete grades of stenosis (critical stenosis or total occlusion) from subcritical stenosis. In these instances, vasodilation and distribution volume were already maximized; therefore, the flow/distribution volume ratio and CFR were directly related to changes in resting flow.

**Contrast Material Distribution Volume**

The arterial compartment had a smaller calculated contrast material distribution volume that did not change significantly with stenosis or hyperemia. $V_{micro}$ however, was closely related to the state of microcirculation vasodilation, ranging from 69% of $V_{sys}$ in the nonstenotic resting state to approximately 90% of $V_{sys}$ during stenosis or hyperemia.

Our hypothesis is that the contrast distribution volume during a first pass through the coronary circulation can be approximated by the plasma volume. This is based on the previous observations that 1) contrast material does not appreciably enter red blood cells and 2) there is minimal extravascular accumulation of contrast material during the first 15–20 seconds after injection. We have corrected the literature values for blood volume by the red blood cell volumes stated in the same references for the appropriate vessel size. Thus, the cited literature values are plasma volumes.

The observed compartmental distribution volumes are in close agreement with estimates of the coronary circulation plasma volume reconstructed from previously reported radionuclide measurements of small- and large-vessel blood volume and hematocrit. These studies showed that the large coronary arteries (>300 mm) have a plasma volume of 1–2 ml/100 g myocardium at rest, which is not affected by hyperemia. The microcirculation plasma volume is typically 3.5–5 ml/100 g at rest, which increases to a range of 7–12 ml/100 g during hyperemia. Moreover, Crystal et al have observed that the microcirculation occupies approximately 70% of the plasma volume in normal arteries at rest and that this proportion increases to 90% during hyperemia.

One problem with applying angiographic mean transit time to estimate the severity of arterial obstruction or CFR is knowing whether the microcirculation's vasodilatory capacity has been attenuated by a process other than proximal artery stenosis. For example, it is apparent in Figure 2C that a value of $T_{micro}^{-1}$, which is associated with a normal artery in the resting state, could also describe a stenotic but hyperemic vessel. Although in clinical practice one may assume that the microcirculation reactivity is normal, there may be unknown limitations on small-vessel vasodilation due to disease, or there may be hidden hyperemic stimuli such as left ventricular hypertrophy.

The $T_{micro}/T_{sys}$ ratio is equivalent to the relative compartmental distribution volume ratio, $V_{micro}/V_{sys}$ and is computationally independent of flow. This ratio differentiated normal arteries at rest, when $V_{micro}$ was small, from hyperemic and or stenotic vessels. These data suggest that relative compartmental volume ratios are related to the vasodilatory state of the microcirculation. This approach may also be useful for validating impulse response analysis in humans, where simultaneous direct measurement of regional coronary flow and CFR is more difficult. Also, a high ratio in the absence of epicardial coronary artery disease may suggest occult microcirculation vasodilation due to drugs, contrast material, or left ventricular hypertrophy.

**Correspondence of Model Compartments to Physiological Parameters**

There are four lines of evidence that suggest that the model compartments simulate arterial and microvascular portions of the coronary circulation, as hypothesized in Figure 1. 1) Classic autoregulatory behavior was observed in the microcirculation compartment but not in the arterial portion of the model. 2) Resting values of $T_{micro}$ correlated with CFR and differentiated normally from subcritical stenosis on the basis of changing distribution volume associated with adjustments of vascular resistance, whereas $T_{art}$ did not. 3) $T_{art}$ increased with the length of the conduit vessel and was highly variable between individual dogs. In contrast, $T_{micro}$ was not affected by conduit vessel length, and similar responses were seen in each animal. 4) The arterial and microcirculation compartment contrast material distribution volumes were precisely within the range expected for the plasma volume of these two portions of the coronary vasculature, and these volumes behaved appropriately in response to small-vessel vasodilators; that is, the microcirculation distribution volume increased and the arterial volume remained relatively fixed. Therefore, these data suggest that the two-compartment lagged normal density model is a good approximation both in terms of anatomic and physiological behavior of the coronary arteries and the myocardial microcirculation. Aside from the physiological information that may be made accessible by this model, its primary utility may be that it removes the effects of...
differing conduit length and size and, thus, allows a more specific assessment of myocardial perfusion.

Limitations

For each model compartment, there was a progressive increase in variability of the mean transit time with increasing flow. Our data suggest that a major source of variability for $T_{\text{mean}}$ was differences in the transit time versus flow relation between animals. This was demonstrated by the variability of individual dog regression slopes and further suggested by the observation that the mean correlation coefficient for individual dogs was significantly higher than when the data from all experiments were analyzed as a single regression. This may have been due to differences in large-vessel volume or conduit length between dogs. Differences in small-vessel hematocrit as well as the known limitations of planar imaging with respect to isolating a desired segment of myocardium from overlying large vessels, ventricles, and nonadjacent myocardium could have also contributed to the observed scatter between dogs.

Another source of variability was the fixed temporal precision of the iterative convolution algorithm with respect to each parameter. This was a substantial source of variability for the arterial compartment, where the error for the shortest transit times could be as large as 27%, resulting in the quantized appearance for the values of this parameter. Temporal precision errors did not exceed 4% for $T_{\text{micro}}$.

The inhaled anesthetic, enflurane, may have introduced a systematic error because this agent has been shown to reduce resting coronary blood flow by as much as 30%. This effect is suggested by the mean resting myocardial flow of 62 ml/100 g/min (Table 1), which is lower than values typically reported with barbiturate anesthesia (65–96 ml/100 g/min). It is unlikely that this had a major effect on the relative relation of transit time to myocardial perfusion or CFR, because enflurane causes an even greater reduction in oxygen consumption and an increased cardiac extraction of lactate. Furthermore, the reactivity of the microcirculation was not impaired, as demonstrated by the normal fourfold hyperemic response to contrast material and dipyridamole.

The efficacy of the model in the presence of multiple stenoses, branch stenoses, collaterals, hypertrophy, and myocardial fibrosis remains to be tested. Application of impulse response analysis in humans may be further complicated by breathing artifacts that can severely interfere with densitometric measurements of relative iodine concentration. Determining the perfusion field of a specific coronary artery from planar projection images will be another source of error because of overlapping vascular territories. This may be minimized by isolating myocardium near the border of the cardiac shadow in projections where there is clear delineation of the arterial supply to the region. Moreover, impulse response analysis should be applicable to tomographic imaging modalities, such as contrast echocardiography and cine computed tomography, where the ability to isolate myocardial regions is greatly enhanced.

Clinical Applications

Densitometric assessment of regional myocardial perfusion offers functional information that is complementary to quantitative stenosis analysis. This may be particularly helpful in situations in which the hemodynamic effects of stenosis anatomy are poorly quantified by current quantitative angiographic algorithms, such as diffusely diseased segments, serial stenoses, or lesions with eccentric or complex morphology, including thrombus and dissection. Additionally, adequate orthogonal views for quantitative angiography of a given stenosis are not obtainable in 15–50% of patients.

Application of impulse response analysis for clinical evaluation of coronary artery disease will depend, in part, on determining solutions to the limiting problems described above and demonstrating improved predictive accuracy with respect to other reported densitometric perfusion indexes. We have previously demonstrated that impulse response analysis is more highly correlated with coronary flow than conventional indicator dilution curve parameters, time to peak, and exponential washout rate.

Another potential advantage of impulse response analysis is the ability to discriminate the functional severity of proximal coronary stenosis during resting flow conditions. No hyperemic stimulus is needed. This may be important clinically because it reduces the number of coronary injections by 50% and eliminates the small but real risk of hyperemic agent–associated ischemia and hypotension. Furthermore, the capability of a hyperemic ratio to assess the hemodynamic effects of stenosis may be confounded if the hyperemic agent also affects coronary driving pressure and myocardial metabolism or if maximal hyperemia is not achieved.

Conclusions

The data presented suggest that compartmental analysis of regional angiographic time–density curves can be used to estimate coronary flow or CFR. The methods developed can differentiate normal from stenotic vessels with a single contrast injection in the absence of hyperemia. Finally, the two-compartment lagged normal density model simulates the anatomic and physiological properties of the large epicardial coronary arteries and the small myocardial vessels in the intact canine circulation.

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