Digital angiographic impulse response analysis of regional myocardial perfusion: linearity, reproducibility, accuracy, and comparison with conventional indicator dilution curve parameters in phantom and canine models.

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Digital coronary cineangiography produces high spatial and temporal resolution images of contrast material transit through the coronary microcirculation from which the regional density of iodine as a function of time can be quantified and, in theory, allows regional perfusion to be calculated. Although conventional indicator dilution parameter analysis of these time-density curves (e.g., time of appearance, time to peak concentration, washout rate, and curve area) have correlated with stenosis severity, coronary blood flow, hyperemic flow ratios, and transstenotic pressure gradients, these data are not sufficiently precise to reliably quantify regional myocardial blood flow.

If the coronary passage of contrast material behaves as a linear system that can be described by its impulse response function, then a number of limitations of conventional indicator dilution analysis may be overcome, including the requirement for instantaneous complete mixing of contrast with blood and the necessity for power or subselective...
coronary injections. The purposes of this study were to 1) document the linearity of digital angiographic densitometry and impulse response analysis in a phantom model where system flow and volume can be controlled; 2) determine the linearity, reproducibility, and accuracy of impulse response analysis in a canine model by direct measurements of regional myocardial flow during altered states of coronary physiology, where flow and volume may be changing; and 3) compare impulse response analysis with conventional indicator dilution curve parameters in both the phantom and canine models.

Materials and Methods

System Description

The coronary circulation can be thought of as a system for transporting contrast material from a proximal coronary artery (the input) to the myocardium (the output). Digital angiography is used to measure the time-density functions of contrast material at the input and output. The system consists of multiple pathways interconnecting the input and output which disperse contrast material as a function of blood flow and distribution volume. The total system under consideration consists of the anatomic system being measured and the digital angiographic measurement system itself.

This system is said to be linear if it obeys the principle of superposition. If the response to the input, \( x(t) \), is the output, \( y(t) \), then the response to the more complicated input constructed by adding together two simple input curves \( a x_1(t) + b x_2(t) \), where \( a \) and \( b \) are constants, will be the arithmetic sum of the simpler output curves \( a y_1(t) + b y_2(t) \). This means that any input/output curve pair relation completely describes the transport properties of the system (as long as it does not change with time; that is, the system is stationary). If so, the response to any input is described by the convolution integral

\[
y(t) = x(t) * h(t) = \int_{0}^{\infty} x(T) h(t-T) dT
\]

where \( * \) is the symbol for convolution, \( T \) is a dummy variable of integration, and \( h(t) \) is the impulse response, which is the output to a perfect bolus input whose mass is delivered to the system instantaneously.

Impulse Response Algorithm

Impulse response analysis consists of numerical determination of the impulse response function of a system given measured input and output functions. We used the algorithm developed and validated by Bassingthwaighte et al.\(^7\) to fit a two-compartment lagged normal density function as a model of contrast material transport in the coronary circulation. The first compartment is represented by a normal distribution curve, \( h_1(t) \):

\[
h_1(t) = \left(\frac{1}{\sqrt{2\pi} \sigma} \right) \cdot \exp(-0.5 \cdot \left(\frac{t-T_c}{\sigma}\right)^2) \quad \text{for} \ t > 0
\]

which models the temporal dispersion of transit times through a conduit as a symmetric random distribution about a central, or mean time \( (T_c) \) with standard deviation \( \sigma \). We postulate that this type of dispersion occurs, for the most part, in the large coronary arteries and at the tip of the injecting catheter. Complete mixing of indicator with blood is not required for this type of compartmental function, but it is required that blood and indicator should have the same distribution of transit times.

The second compartment, \( h_2(t) \), is a monoeponential decay function that represents dispersion due to complete mixing as in a highly branched network such as the coronary microcirculation.

\[
h_2(t) = \left(\frac{1}{\tau} \right) \cdot \exp(-t/\tau) \quad \text{for} \ t > 0
\]

where \( \tau \) is the time constant.

The lagged normal density curve, \( h(t) \), is generated by convolution of the two compartmental functions:

\[
h(t) = h_1(t) * h_2(t)
\]

The impulse response is not effected by the order of compartmental flow. Thus, the conduit could be proximal or distal to the mixing chamber or both.

The best fit, lagged normal density model for the corresponding system impulse response was calculated by iterative convolution as previously described.\(^7\) In brief, the input time-density curve was repetitively convolved with the lagged normal density model while the parameters \( T_c, \sigma \), and \( \tau \) were serially adjusted with a temporal precision of 0.06 seconds until the error between the convolution and the output time-density curve, as measured by the coefficient of variation, was minimized. The final model parameters thus define the system impulse response function. The mean transit time for the system impulse response, \( T_{sys} \), was calculated as the sum of the individual compartment transit times, \( T_c + \tau \).

Phantom Model

We developed a linear x-ray phantom model with flow and volume characteristics similar to the coronary circulation to determine the linearity of the digital angiographic measurement system and the potential accuracy of our linear model (Figure 1). The phantom consisted of polyethylene inflow and outflow conduits (3.0 mm i.d.) connected to a cylindrical mixing chamber (48 mm long, 20 mm diameter). The chamber contained a baffle near the inflow to create turbulence, and the remaining volume was filled with 2.0-mm diameter glass beads to provide multiple interconnected path lengths to simulate a branched vascular network. The phantom was perfused with normal saline by a constant-flow syringe pump (Harvard Apparatus, South Natick, Massachusetts) at rates from 10 to 450 ml/min ± 1.0%, while phantom volume was fixed at 11.2 ± 0.10 ml.

Imaging procedure. The phantom was immersed in 20 cm water to simulate tissue scattering, and a
lead blocker (2 mm thick, 5 mm diameter) was positioned adjacent to the inflow and outflow regions for scatter and veiling glare (SVG) measurement (see "Appendix"). Digital x-ray image acquisition was performed during 46 injections of ionic contrast material (sodium meglumine diatrizoate, 370 mg I/ml; E.R. Squibb & Sons Inc, Princeton, New Jersey) delivered by a power injector (Medrad Mark IV, Pittsburgh, Pennsylvania) connected to the inflow tubing. To determine if the phantom and our method of acquiring and processing digital images were linear, the input bolus injection was manipulated as follows: injection volume was maintained constant while flow rate was varied (4.0 ml at 1.0, 2.0, and 3.0 ml/sec), flow rate was held constant while volume was varied (2.0, 4.0, 6.0, and 8.0 ml at 2.0 ml/sec), and bolus shape was altered with a double-peaked injection (2.0 ml at 2.0 ml/sec injected twice separated by 1 second).

The x-ray imaging was performed in the clinical cardiac catheterization laboratory using a Philips Maximus II generator (Eindhoven, Netherlands), an Eimac (Salt Lake City, Utah) rotating anode x-ray tube (0.6 mm nominal focal spot with 3.0 mm Al equivalent filtration), and a Thomson-Houston trimode image intensifier using the 15-cm intensifier field size. The automatic exposure control system was disabled to provide stable 6-msec x-ray pulses at 70 kVp and 300 mA. Images were acquired with a progressive-readout Plumbicon video camera, and directly digitized on an AD AC 4100C cardiac digital angiography system (Milpitas, California), and stored on an IBM 4133 677 Mbyte real-time disk in a 512^2 pixel, 256 gray level format at six frames per second. Before acquisition, the video gain was adjusted so that target saturation produced an output of 900 mV. The A/D converter was then calibrated at grey level 0-5 for black and gray level 255 at 715 mV, thus avoiding time and temperature dependent nonlinear response of the Plumbicon target near saturation. During highly collimated imaging (1 cm^2 field size), the x-ray/video/digital chain was highly linear with respect to input exposure (γ>0.99).

**Animal Model**

Six mongrel dogs (27-48 kg) were premedicated with morphine sulfate (1.0 mg/kg i.m.), and then anesthetized with sodium pentobarbital (30 mg/kg i.v.) and vaporized enflurane while respiration was supported mechanically (Harvard Apparatus). Following left lateral thoracotomy, a 2.5-4.0-mm square-wave 400 Hz perivascular electromagnetic flow probe (Micron Instruments, Los Angeles, California) was placed around the dissected left circumflex coronary artery in the left atrioventricular sulcus. Care was taken to eliminate stenosis caused by torsion of the artery by the probe. A snare occluder was positioned 0.5-1.0 cm proximal to the flow probe and isolated from the probe by an undissected bridge of perivascular connective tissue. This preparation produced variable degrees of proximal circumflex stenosis, confirmed by angiography, without affecting the electrical contact between flow probe and artery. Total occlusion was produced several times during each experiment to document flowmeter zero drift. The left femoral vein and artery and the left common carotid artery were cannulated by cutdown for intravenous infusion, arterial pressure monitoring, and coronary catheter placement, respectively. A 7F Judkins R4 catheter was positioned in the left main coronary artery and heparin (5,000 units i.v.) was given. ECG, arterial pressure, and coronary blood flow were continuously monitored on a physiological recorder (Honeywell VR-12, Pleasantville, New York).

Hand-injected selective left coronary angiograms (n=102) with simultaneous flowmeter tracings were recorded during four coronary flow states: normal arteries under resting flow conditions (31 injections), stenotic arteries with or without reduction in resting flow (29 injections), normal arteries with hyperemic flow (23 injections), and stenotic arteries...
during hyperemia (19 injections). The presence ofstenosis was confirmed angiographically and in 11
injections the artery was totally occluded.

To evaluate the presence of superposition and
stationarity, several types of coronary contrast injec-
tion and hyperemic stimuli were administered. Nor-
mal and stenotic arteries with resting flow were
hand-injected with a single-peaked, 4-ml bolus of
undiluted ionic contrast material (44 injections), a
double-peaked bolus of ionic contrast (2 ml twice
separated by approximately 1–2 seconds) (nine injec-
tions), or a single 4-ml bolus of nonionic contrast
(Iohexol, Omnipaque 350 mg I/ml; Sterling-
Hyperemia was induced by four methods: dipyri-
damole infusion (0.56–1.02 mg i.v. over 5–10 minutes),
dipyridamole plus norepinephrine infusion (titrated
to raise mean blood pressure to 90–150 mm Hg),
20-second coronary occlusion, or following intra-
coronary contrast injection with 4 ml ionic contrast
(16, 8, 4, and 13 injections respectively). Injections
were separated by a minimum of 4 minutes to allow
contrast induced hyperemic coronary flow to return
to baseline. At the conclusion of each study, 5 ml
Monastral blue was injected subselectively into the
left circumflex artery, immediately followed by death
with potassium chloride (50 meq i.v.). The heart
was cut into 1-cm thick short axis sections, weighed,
and photographed. The flow probe was then cali-

Imaging procedure. Two lead blockers were posi-
tioned 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 SVG
measurement. Imaging was performed in the left
circumflex artery, immediately followed by death
with potassium chloride (50 meq i.v.). The heart
was cut into 1-cm thick short axis sections, weighed,
and photographed. The flow probe was then cali-

Videotape images were time-base corrected
(Microtime 1600, Bloomfield, Connecticut), and
the black level and gain were again optimized before
off-line digitization. This method of tape record-
ing, playback, and image digitization was linear
for the entire gray scale (n = 18, r >0.999, SEE = 1.0
gray levels).

Postacquisition Image Processing

Densitometric analysis for both phantom and
animal studies was performed on the ADAC image
processing system. While viewing the digitized
images in a cine-loop format, the operator positioned
rectangular or irregularly shaped regions of
interest (ROIs). For the phantom studies, rectangu-
lar 200-pixel ROIs were placed over the inflow and
outflow tubing (Figure 1) and a 100-pixel ROI was
positioned over the intervening lead blocker for
SVG measurement. Figure 2 shows the locations of
the ROIs for the animal experiments. A 225-pixel

FIGURE 2. Schematic of open chest canine
model: 1. catheter, 2. snare occluder, 3. flow-
meter, 4. and 5. lead blockers. Regions of interest
for densitometry: A, left main (LAD); B, large left
circumflex (LCX) territory; C, proximal; D, mid;
E, distal; F, inner; G, outer; and H, apex.
ROI (A) 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 large 9,000–10,000 pixel output ROI (B) was drawn over the myocardium supplied by the left circumflex artery. Sensitivity to ROI positioning was assessed by dividing this output ROI into five smaller adjacent regions, each containing 1,600 pixels, located at positions designated C, D, E, F, or G. An additional 1,600-pixel ROI (H) was placed near the apex, which was supplied by both the left circumflex and left anterior descending coronary arteries. The mean digitized intensity within each ROI was determined as a function of time from un subtracted images.

Impulse response analysis requires that the input and output signals be proportional to regional projected contrast density without distortion by the detection system. Corrected time-density curves were constructed by subtracting the SVG curve frame-by-frame from the input and output ROIs (see “Appendix”). 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 least-squares fitted monoe xponential decay function replaced the terminal portion of the input curve to compensate for overlapping contrast material exiting the coronary sinus. 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 insufficiently described myocardial ROI time-density curves, two empiric criteria were developed and prospectively applied. If the output function rose progressively without peaking during the 15 to 20 seconds after contrast injection or the change in x-ray intensity was not greater than three gray levels (the preinjection background noise varied by two to three gray levels), $T_{sys}$ was assumed to be infinite. If there were less than 3 seconds of data after the peak density of the output function, $T_{sys}$ was assigned to be 20 seconds. These criteria were satisfied in all 11 injections where total occlusion was present and in an additional four other vessels with greatly diminished resting flow. $T_{sys}$ was obtained by impulse response analysis in the other 87 injections.

Conventional indicator dilution curve parameters, time to peak concentration (TPC) and monoe xponential washout rate ($k$) were calculated as previously described. TPC was defined as the time from injection measured at the input ROI, to the peak in the myocardial curve. Washout rate, $k$, was the inverse of the monoe xponential time constant determined by linear least-squares fitting of the logarithm of the washout portion of the myocardial time-density curve. Similar empiric criteria were applied to determine TPC and $k$ when myocardial time-density curve description was incomplete at the end of acquisition. These parameters were not evaluated for double-peaked bolus injections or when nonionic contrast material was used.

The mass of the left circumflex-supplied myocardium was calculated from the sum of the mass of each myocardial section multiplied by the proportion of stained myocardium. The left circumflex territory myocardial mass varied widely (36–85 g). Regional left circumflex myocardial perfusion ($Q_M$) was calculated as the mean electromagnetic flow ($Q$) during the 3 seconds before injection, normalized for each 100 g of left circumflex myocardial mass. Coronary flow reserve was defined by the ratio of peak to resting flow following injection of ionic contrast material.

The inverse of each mean transit time parameter was assumed to equal system flow ($Q$) divided by its volume ($V$), thus

$$T_{sys}^{-1}, TPC^{-1}, k = \frac{Q_M}{V_M}$$

where $V_M$ is the distribution volume of the indicator normalized for myocardial mass. These transit times

![Figure 3](http://circres.ahajournals.org/) Panel A: Two compartment functions which yield the lagged-normal density model impulse response. Panel B: The processed phantom input and output time-density curves and the convolution of the input curve with the fitted impulse response. The coefficient of variation (coeff) compares the convolution with the observed output.
were compared with myocardial perfusion by linear regression analysis. Regressions were performed both including and excluding arteries with total occlusion to evaluate the effects of data near the origin.

Data throughout the text are expressed as mean±SD. Statistical significance was calculated with the two-tailed Student's t test for paired and nonpaired data where appropriate.

Results

Phantom Studies

Figure 3 shows typical time-density curves acquired with the phantom, the derived impulse response, and its individual mathematical compartments. The input curve was produced by a single-peaked bolus injection while the output curve had a skewed configuration typical of indicator dilution curves. The convolution of the input and impulse response closely simulated the output (mean coefficient of variation 0.017±0.009; n=46) with the largest errors occurring near the end of the washout phase of the output curve.

Figure 4 compares the inverse of the system mean transit time, $T_{sys}^{-1}$, with calibrated flow-to-volume ratios in the phantom. Impulse response analysis accurately and reproducibly predicted flow/volume over the full range of phantom flow rates (15–450 ml/min) with the linear regression equation nearly identical to the line of identity ($T_{sys}^{-1}=0.99$ flow/volume+0.24; n=46, r=0.99, SEE=1.6). Variations of contrast bolus injection rate, injection volume, and double-peaked bolus injections had no apparent effect on the relation between $T_{sys}^{-1}$ and flow/volume.

Figure 5 compares conventional indicator dilution curve parameters TPC$^{-1}$ and k with phantom flow-to-volume ratios. The relation for TPC$^{-1}$ was curvilinear, progressively underestimated the flow-to-volume ratio and was injection rate dependent; the more rapid the injection, the larger the value of TPC$^{-1}$. Washout rate, k, had a linear relation with flow-to-volume ratios, but flow-to-volume ratios were consistently overestimated.

Animal Studies

The convolution of the input and the model impulse response also closely simulated the observed output during hand-injected coronary angiography in vivo (mean coefficient of variation 0.015±0.007). This
A. SINGLE-PEAKED BOLUS INJECTION

\[
\text{Normalized Density} \quad \text{TIME (sec)}
\]

B. DUAL-PEAKED BOLUS INJECTION

\[
\text{Normalized Density} \quad \text{TIME (sec)}
\]

C. IMPULSE RESPONSE FUNCTIONS

\[
\text{Normalized Density} \quad \text{TIME (sec)}
\]

Figure 6. Canine study demonstrating the superposition principle with a normal artery at resting flow. Panel A: Processed input/output time-density curves and convolution after a single-peaked bolus injection. Panel B: Double-peaked bolus injection. Panel C: Comparison of calculated impulse responses derived from panels A and B.

The transient biphasic flow response after injections of ionic contrast material in normal arteries produced a decrease to 0.58±0.11 of baseline flow at 2–4 seconds followed by a maximum transient 4.0±0.5-fold increase at 10–14 seconds. Nonionic contrast caused a similar initial fall in coronary flow (0.54±0.10); however, maximum hyperemic flow was significantly less (2.1±0.3-fold) compared with baseline (p<0.001).

Figure 7 demonstrates the effects of injection bolus shape (single- versus double-peaked) and type of contrast agent (ionic or nonionic) on \(T_{\text{sys}}^{-1}\) for paired injections in normal and stenotic arteries at resting flow conditions. There were close linear correlations between double- and single-peaked injections of ionic contrast material \((r=0.90)\), between single-peaked injections of nonionic and ionic contrast material \((r=0.95)\), and when double-peaked ionic and single-peaked nonionic injections were compared with standard single-peaked ionic contrast injections \((r=0.94)\). In each case, the regression slope did not differ significantly from identity.

Figure 8 compares \(T_{\text{sys}}^{-1}\) with myocardial perfusion during the four different hyperemic stimuli. Whether coronary blood flow was augmented by dipyridamole, dipyridamole plus norepinephrine, a 20-second coronary occlusion, or ionic contrast, there was a strong linear relation between \(T_{\text{sys}}^{-1}\) and \(Q_M\) \((r=0.90)\) with an effective distribution volume.
$V_M=15.2 \text{ ml/100 g}$. Although the correlation coefficients and effective distribution volumes for individual stimuli showed wide variability ($r=0.67-0.99$, $V_M=12.4-21.0$), the number of observations and the narrow range of myocardial perfusion over which each stimulus was measured were insufficient to determine if these differences in $V_M$ were significant. Variability was greater at the highest flows and when hyperemia was induced by ionic contrast material.

The effect of ROI position on the reproducibility of $T_{sys}^{-1}$ is demonstrated in Figure 9. For the 10 combinations of linear regression between the multiple 1,600-pixel circumflex territory ROIs, reproducibility was very high ($r_{\text{mean}}=0.98\pm0.01$), there were no significant deviations from identity, and no apparent differences related to flow state. In comparison, the correlations between each of the five small left circumflex myocardial ROIs and the apex were less reproducible ($r_{\text{mean}}=0.82\pm0.01$), and $T_{sys}^{-1}$ was systematically smaller at the apex for all four flow states.

Figure 10 compares $T_{sys}^{-1}$ with myocardial perfusion for each of the four flow states. There was a close linear correlation between $T_{sys}^{-1}$ and flowmeter perfusion ($r=0.90$) over a wide range—from 0 to 514 ml/min/100 g myocardium. Inspection of these data, however, revealed a bimodal distribution of $T_{sys}^{-1}$ with respect to flow. When injections under normal resting conditions were excluded, an even stronger correlation was seen ($r=0.94$), with the effective distribution volume, $V_M=14.9 \text{ ml/100 g}$. There were no significant differences between dogs, with $V_M$ ranging from 14.4 to 17.3 ml/100 g for individual dogs. The bimodal data distribution resulted in values of $T_{sys}^{-1}$ that were significantly greater ($10.6\pm1.3$ vs. $6.8\pm1.7 \text{ min}^{-1}$; $p<0.001$) for normal arteries at rest compared with stenotic vessels where resting flow was the same but coronary flow reserve was diminished (Table 1). $V_M$ was smaller for normal compared with stenotic arteries at rest ($7.1\pm1.1 \text{ vs. } 11.5\pm3.6 \text{ ml/100 g} ; p<0.001$). Exclusion of data at the origin had no effect on the relation between $T_{sys}^{-1}$ and myocardial perfusion ($T_{sys}^{-1}=0.965Q_M+0.88$; $n=60$, $r=0.93$, SEE=3.4).
There was a modest correlation of the conventional indicator-dilution parameters, TPC\(^{-1}\) and k, with the corresponding values of \( T_{sys}^{-1} \) (r = 0.76 for each regression). The relations of TPC\(^{-1}\) and k with myocardial perfusion are displayed in Figure 11. TPC\(^{-1}\) was a highly variable but curvilinear function of myocardial perfusion reaching a plateau at flow rates greater than 200 ml/min/100 g. The washout rate k also showed a flow-state dependent bimodal distribution: there was a linear relation during stenosis and/or hyperemia (r = 0.84), while normal arteries at rest systematically had larger values of k compared with stenotic arteries at the same flows (22.0±6.4 vs. 11.0±5.0; p<0.001).

Discussion

This study describes a new method, digital angiographic impulse response analysis, for densitometric measurement of contrast material transit through the coronary circulation. We adapted a previously described linear mathematical model of arterial flow, distribution volume, and indicator dispersion, to analyze digital coronary angiographic images. Impulse response analysis was validated in an x-ray phantom and in the coronary circulation by demonstrating system linearity. Our method was not sensitive to the variability of hand-injected coronary angiography, the type of contrast agent used, or the choice of stimulus for provoking hyperemic flow. Furthermore, impulse response analysis was a more accurate descriptor of regional myocardial blood flow than conventional indicator dilution parameters, TPC or k.

### Digital Angiographic System Linearity

Impulse response analysis requires that both the system being measured and the detection system be linear; that is, the processed detector signal must be linearly proportional to contrast density. Individual sources of densitometric error such as x-ray technique instability, SVG, and video/digital system nonlinearity were quantified and corrected. The linearity of the entire angiographic detection and measurement systems, was tested by imaging a known linear system, the dynamic flow x-ray phantom, which simulated the flow, volume, contrast concentration, and scatter conditions expected in vivo. The configuration of serial compartments resembles an artery-microcirculation-vein system to facilitate imaging. This same phantom, however, also simulates an artery-microcirculation system where the length of the artery is the sum of the lengths of the inflow and outflow tubing. Both representations are computationally equivalent. Contrast injection rate, volume, and bolus shape were widely varied as a test of the superposition principle, while stationary flow and volume were maintained. We demonstrated linearity by showing that the mean transit time of the impulse response was highly accurate and reproducible for determining phantom flow-to-volume ratios over the expected physiological range of flow rates, from 15 to 450 ml/min, and was independent of the method of contrast injection. From these data we concluded that our method for acquiring and analyzing digital images satisfies the requirements of linear systems.

### Table 1. Comparison of Hemodynamic and Angiographic Parameters for Normal and Non-Flow-Limiting Stenoses Measured at Resting Flow

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Stenosis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>117±14</td>
<td>111±16</td>
<td>NS</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>87±13</td>
<td>86±16</td>
<td>NS</td>
</tr>
<tr>
<td>QLD(ml/min/100 g)</td>
<td>77±12</td>
<td>74±12</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary flow reserve ratio</td>
<td>4.0±0.6</td>
<td>2.1±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( T_{sys}^{-1}(\text{min}^{-1}))</td>
<td>10.0±1.3</td>
<td>6.8±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( V_M ) (ml/100 g)</td>
<td>7.1±1.1</td>
<td>11.5±3.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

QLD, regional left circumflex myocardial perfusion; \( T_{sys}^{-1} \), inverse of system mean transit time; \( V_M \), distribution volume of indicator normalized for myocardial mass.
Impulse Response Analysis

We chose an iterative, model-based method for calculating the impulse response rather than a Fourier or other type of transform for the following reasons: 1) It is less sensitive to noise because all the data points from the input and output curves are used in an integrative process with the model serving as a smooth template for the impulse response. 2) The impulse response can be calculated when the output signal has not returned to baseline at the end of image acquisition. 3) It permits analysis of compartmental models.

Although many mathematical models (gamma-variate, log normal, and random walk) would permit accurate calculation of the impulse response and mean transit time,13 the lagged normal density curve was chosen because of its ease of computation and its previous performance as a model for the central and peripheral circulations with indocyanine green dye, and because it is based in part on a physical analogy.

Clearly, our system definition is an oversimplification of the underlying complex anatomy that is further complicated by overlap from other regional systems as a consequence of planar imaging. Despite these problems, we found that the lagged normal density model closely predicted the observed input/output relations (coefficient of variation 0.015±0.007) over a wide range of physiological conditions. The largest errors tended to occur during the later stages of contrast washout and were probably due to differing proportions of arteries and veins within the output ROI. For the purpose of measuring the mean transit time, however, the lagged normal density model appears to be an adequate description of contrast material transit in the canine coronary circulation.

Coronary Circulation System Linearity

A dual-peaked input where the individual peaks are so closely spaced that the system must respond to a complex polyphasic input rather than two separated simple inputs has been recognized as a rigorous test of superposition.7 We showed that changing the complexity of the input from a single- to a double-peaked injection had no effect on T^-1 in normal and stenotic arteries at resting or reduced flows.

System nonstationarity caused by the transient hyperemic effects of contrast media during densitometric data acquisition were evaluated by examining the effects of ionic and nonionic contrast media on the impulse response. While both contrast media caused a similar early reduction in coronary blood flow, the secondary hyperemic increase in flow differed markedly (4 times baseline with ionic
versus 2.1 times with nonionic) in normal arteries. We found, however, that the type of contrast agent did not affect $T_{\gamma}^{-1}$ in either normal or stenotic arteries at resting or reduced flow.

How can the system appear stationary when flow is changing markedly? We hypothesize that the impulse response is relatively insensitive to the transient increase in flow because there is a simultaneous increase in contrast distribution volume, and therefore the mean transit time is minimally affected. Since the model's parameters are compartmental mean transit times and not flow per se, this might explain why the system would appear to be stationary when flow is clearly nonstationary. Zierler has defined stationarity in exactly these terms, namely, that the distribution of transit times for indicator particles does not change during the time of measurement. From these data we concluded that the transit of contrast material can be modeled by as a linear system in normal and stenotic coronary arteries under resting flow conditions.

Testing system linearity during preexisting hyperemia is also problematic because there may be hyperemic stimulus specific changes in distribution volume which alter the relation of $T_{\gamma}^{-1}$ with flow. We examined the effects of four hyperemic stimuli: dipyridamole, dipyridamole plus norepinephrine, 20-second total coronary occlusion, and intracoronary injection of ionic contrast on the relation between $T_{\gamma}^{-1}$ and myocardial perfusion. Our data show that when all stimuli are considered together, the relation was highly linear. Variability was greatest for ionic contrast media where the preinjection coronary blood flow was the least stationary. Further investigation is required to determine if individual stimuli are associated with characteristic distribution volumes.

The strict criteria of linearity are never achieved in any physical or biological system. Certainly the selective injection of large volumes of full strength, viscous contrast media produced time-dependent changes in blood flow and volume in our system. Based on our data, however, the deviations from linearity and stationarity are not sufficient to preclude extraction of myocardial flow and volume information, even when ionic contrast material is injected.

Spatial Reproducibility of Impulse Response

Myocardial ROI positioning is the major subjective task that could induce variability in the computed impulse response function. We tested the reproducibility of the impulse response function in multiple ROIs within the left circumflex territory and between these regions and the cardiac apex. Our data show that for nonoverlapping 1,600-pixel ROIs centered 60–100 pixels apart within the same vascular territory, the impulse response algorithm was highly reproducible regardless of the direction of ROI displacement or the coronary flow state being measured. In contradistinction, when we compared the left circumflex regions with the cardiac apex, which had a dual arterial supply, variability was significantly greater and $T_{\gamma}^{-1}$ was systematically less (27%) at the apex. Although apical myocardial flow was not measured, these findings are consistent with previous determinations of small vessel blood volume with $^{59}$Fe-siderophilin labeled plasma which showed that small vessel blood volume progressively increases from base to apex.

Measurement of Regional Myocardial Perfusion

Our studies demonstrated a flow-state dependent, bimodal relation between angiographic mean transit time, $T_{\gamma}^{-1}$, and regional myocardial flow in the dog. There was a strong linear correlation ($r=0.94$) over the entire physiological range of myocardial perfusion (0–514 ml/min/100 g) in the presence of stenosis and/or hyperemic stimuli. Under these conditions, it can be inferred that the effective distribution volume remained relatively constant (14.9 ml/100 g). There was, however, too much variability to permit estimation of absolute myocardial flow from a single value of $T_{\gamma}^{-1}$. This variability was more apparent at higher flows and cannot be accounted for by differences in distribution volume between individual dogs (range, 14.4–17.3 ml/100 g). Variability may instead be due to other factors such as the fixed temporal precision of $T_{\gamma}^{-1}$, inadequate image acquisition rate (the timing of injection with respect to pulsatile coronary artery blood flow), instability of preinjection flow/volume after a hyperemic stimulus, and the well-described variability of flowmeter measurements.

Normal arteries at resting flow rates were characterized by a different distribution of $T_{\gamma}^{-1}$ compared with stenotic and/or hyperemic vessels. $T_{\gamma}^{-1}$ was consistently and significantly greater in normal compared with stenotic vessels where preinjection resting flow was identical but coronary flow reserve measured by the hyperemic response to ionic contrast was diminished by almost 50%. Assuming that these differences are explained by flow-state dependent changes in effective contrast distribution volume, the volume would have to increase from 7.1±1.1 ml/100 g in normal vessels with resting flow to 11.5±3.6 ml/100 g in response to non-flow-limiting stenosis.

These derived distribution volumes are in close agreement with previous determinations of the coronary circulation volume at rest and after hyperemic stimuli. Crystal et al showed that canine coronary blood volume increased from 7.3 to 12.8 ml/100 g in response to adenosine. Asphyxia also has been shown to increase coronary small vessel blood volume by 40–160%.

Although contrast material does not enter normal erythrocytes or muscle, it does eventually diffuse into the extravascular space with a volume of distribution nearly twice the intravascular volume. Our data suggest that contrast material is largely confined to the plasma volume during a first pass through the coronary circulation. Consequently, we
are measuring the flow per plasma volume of the regional system contained between the input and output ROIs rather than true myocardial perfusion, which requires an indicator that freely diffuses into myocardial tissue such as xenon-133.8,20

We hypothesize that the observed flow dependent changes in distribution volume are part of the normal mechanism that regulates coronary flow. As the myocardial microcirculation vasodilates to decrease vascular resistance and thus maintain flow in the presence of stenosis or to augment flow following a hyperemic stimulus, vascular capacitance simultaneously increases as reflected by the distribution volume of contrast material. This sensitivity of the mean transit time to autoregulatory vasodilatation represents a new finding which may differentiate normal and stenotic arteries at resting flow rates without requiring a prior hyperemic stimulus.

Comparisons With Conventional Time-Density Curve Parameters

We compared impulse response analysis with conventional time-density curve parameters $T_{\text{PC}}^{-1}$ and $k$ in the dynamic x-ray phantom under optimal measurement conditions of precisely controlled volume, nonpulsatile flow, and reproducible power injection. $T_{\text{PC}}^{-1}$ was highly injection-rate dependent and progressively underestimated phantom flow-to-volume ratios such that the relation was curvilinear. Although $k$ was not injection-rate dependent, it consistently overestimated flow-to-volume and thus underestimated distribution volume. This is because $k$ only applies to that portion of the system that acts as a well-mixed chamber and neglects the conduit portions where more symmetrical dispersion occurs. Thus, for flowing systems with input-to-output relations similar to our phantom, $T_{\text{PC}}^{-1}$ and $k$ are inadequate descriptors of flow-to-volume ratios. $T_{\text{mV}}^{-1}$, however, accurately predicted flow/volume ratios and was insensitive to injection technique.

Time to peak concentration exhibited similar behavior in vivo. $T_{\text{PC}}^{-1}$ was nonlinear with respect to myocardial blood flow reaching a plateau when flow exceeded 200 ml/min/100 g and predicted smaller flow-to-volume ratios than $T_{\text{mV}}^{-1}$. The greater variability of $T_{\text{PC}}^{-1}$ in the animal experiments may reflect the variability of hand-injection on the rate of contrast material input. The curvilinear relation may occur because $T_{\text{PC}}$ measured from the leading edge of the input function to the peak of the output function, must be longer than the time to peak of the input function. The finite width of the input function establishes a minimum $T_{\text{PC}}$, and therefore a maximum value of $T_{\text{PC}}^{-1}$.

The washout rate $k$ showed a linear correlation with flow during stenosis or hyperemia, however, the predicted flow-to-volume ratios were higher than $T_{\text{mV}}^{-1}$ thereby suggesting a smaller distribution volume. We observed that the relation of $k$ with myocardial perfusion also distributed as two separate populations with significantly larger values of $k$ for normal arteries at resting flow.

This bimodal distribution was not seen in our previous animal experiments and may be explained by the presence of unrecognized stenosis produced by the electromagnetic flowmeter. This is supported by the blunted transient flow response to ionic contrast media, which did not exceed 2.5-fold in 'normal' vessels (authors' unpublished data) compared with a mean increment of fourfold in this report. The same study also suggested a more linear relation of $T_{\text{PC}}^{-1}$ with respect to flow. These observations were made over a much narrower range of flows: only five data points were obtained at the highest flow rates, and these did not exceed threefold above resting flow compared with the 6.7-fold increment in flow achieved in the present study.

From these data comparing the behavior of $T_{\text{mV}}^{-1}$, $T_{\text{PC}}^{-1}$, and $k$ in the phantom model and in vivo, we conclude that the vasodilated coronary circulation closely approximates a conduit/mixing chamber model. Moreover, impulse response analysis using the lagged normal density model is superior to the conventional indicator dilution parameters $T_{\text{PC}}^{-1}$ or $k$ for the assessment of regional myocardial flow from hand-injected coronary angiograms.

Limitations

Several unresolved problems may impede the application of digital angiographic impulse response analysis in humans. Reliable densitometry is highly dependent on sustained breath holding for 15 to 20 seconds, which may be difficult in ill or uncooperative patients. The accuracy of this technique in other animal species, in the left anterior descending and right coronary artery distributions, and the effects of more chronic or more distal stenoses have not been determined. Maximal hyperemic flow may not have been achieved using ionic contrast media as the stimulus for vasodilatory reserve (mean fivefold increment with 20-second occlusion compared with fourfold increase with ionic contrast). The scatter of data, particularly at high flow rates, limits the prediction of absolute myocardial perfusion for a given injection. Planar projection imaging yields transmyocardial average perfusion and cannot separate superimposed coronary vascular beds, or overlapping left ventricular walls, without multiple projections. Furthermore, differentiation of subendocardial versus subepicardial perfusion is not possible. One solution would be to apply impulse response analysis to rapid computed tomography after selective coronary or aortic root injection.

In conclusion, both digital coronary angiography and coronary contrast transit behave as linear systems, thus legitimizing impulse response analysis. Impulse response analysis eliminates the need for standardized intracoronary injections and can be used with either ionic or nonionic contrast media and a variety of hyperemic stimuli. Finally, impulse response analysis correlates more closely with
regional coronary blood flow in dogs than conventional indicator dilution curve parameters time to peak concentration and washout rate. These data suggest that impulse response analysis may offer distinct advantages over other available angiographic methods for assessing regional myocardial perfusion and the physiological effects of coronary stenosis.

Appendix

According to the Lambert-Beer relation, the intensity of monoenergetic x-rays decreases exponentially with increasing thickness of an absorbing media. This provides the basis for measuring projected iodine thickness ($x_i$) from regional image intensities as follows:

$$x_i (mg/cm^2) = \frac{\ln(I_0/I_1) \times 1,000 mg/g}{\mu_i (cm^2/g)}$$  \hspace{1cm} (6)

where $I_1$ and $I_0$ are the intensities with and without iodine present respectively, and $\mu_i$ is the mass attenuation coefficient for iodine.

Conventional x-rays, however, are polychromatic, and there is preferential absorption of low energy x-rays known as "beam hardening." Because $\mu_i$ is sensitive to changes in mean x-ray energy, it will decrease with increasing iodine and patient thickness. Beam hardening errors can be measured under highly collimated imaging geometry to minimize scatter (field size 1 x 1 cm). We found that measured versus true iodine concentration is highly linear ($r>0.995$) for contrast densities ranging from 0 to 200 mg/cm$^2$ as expected during coronary angiography and that iodine beam hardening error is less than 5%. Tissue beam hardening produces larger errors that must be corrected for absolute measurements of iodine density because tissue thickness may vary substantially between nonadjacent regions. Since $\mu_i$ and $k$ require only relative densitometric accuracy, beam hardening errors are negligible.$^{21}$

Scattered radiation is the predominant source of error for densitometric measurement$^{22-26}$ and exists as two major components: 1) compton scatter within the patient, and 2) light dispersion within the phosphors of the image intensifier known as "veiling glare." SVG is a much larger source of error than beam hardening, and failure to remove the SVG component before logarithmic transformation results in significant loss of contrast and a strongly nonlinear response.$^{24,25}$

We have developed a SVG correction method based on the intensity measured beneath a lead disk in close proximity to the region. The lead disk absorbs greater than 99% of the primary beam and therefore the intensity measured over it reflects SVG from adjacent regions$^{28}$ and additional contributions from off-focus radiation within the electronics of the image intensifier, and lens scatter within the optics of the light distributor and video camera. These are spatially variant phenomena that act as additive components to the primary beam. Calculation of the primary x-ray intensity, and therefore the true iodine thickness, may be accomplished by subtracting this estimate of SVG before logarithmic transformation as follows:

$$x_i = \frac{\ln(I_0 - SVG)}{\ln(I_1 - SVG)}$$  \hspace{1cm} (7)

$$x_i = \frac{\ln(I_0 - SVG_d)}{\ln(I_1 - SVG_d)}$$  \hspace{1cm} (8)

where $\mu_i$ is the mass attenuation coefficient for iodine.
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