Digital Angiographic Impulse Response Analysis of Regional Myocardial Perfusion

Detection of Autoregulatory Changes in Nonstenotic Coronary Arteries Induced by Collateral Flow to Adjacent Stenotic Arteries

Helmut Schühlen, MD; Neal L. Eigler, MD; James S. Whiting, PhD

Background Our study compares the effect of acute proximal stenosis of a coronary artery supplying a myocardial perfusion bed with that of stenosis of an adjacent artery resulting in collateral flow diversion supplied by the same perfusion bed. These alterations in coronary physiology were quantified by digital angiographic impulse response analysis of contrast material mean transit time for the coronary microcirculation, Tmicro, and by flowmeter and microsphere assessment of flow and regional flow distribution.

Methods and Results In 25 open-chest, anesthetized dogs, progressive circumflex coronary artery stenosis led to a concordant decrease of circumflex artery resting and hyperemic flow, coronary flow reserve, and inverse angiographic mean transit time Tmicro⁻¹ (P<.01). Progressive left anterior descending artery stenosis led to no or only minor changes of circumflex artery resting or hyperemic flow or flow reserve; only occlusion induced a significant decrease of coronary flow reserve (from 4.0±0.7 to 3.2±0.5, P<.05), whereas resting flow was increased by +8.6±5.9%. In contrast, circumflex artery Tmicro⁻¹ diminished significantly with critical left anterior descending artery stenosis and occlusion (from 16.7±4.2 to 12.6±2.2 [P<.05] and 12.0±3.0 min⁻¹ [P<.01], respectively). In 8 dogs, collateral flow induced by left anterior descending artery occlusion was quantified by microsphere injections. The decrease of circumflex artery Tmicro⁻¹ correlated with the magnitude of collateral flow (r=.76) and was associated with the angiographic extent of collateral filling.

Conclusions Digital angiographic impulse response analysis is a sensitive method to detect the influence of proximal artery stenosis on an artery’s myocardial perfusion bed as well as the changes induced by an adjacent artery stenosis inducing collateral flow diversion from the supplying myocardial perfusion zone. (Circulation. 1994;89:1004-1012.)

Key Words • angiography • stenosis • perfusion • collateral circulation

The hemodynamic severity of a proximal coronary stenosis can be quantified by direct measurements of maximal hyperemic flow or the ratio of hyperemic to resting flow known as coronary flow reserve (CFR).¹ These parameters characterize the ability of the vessel to conduct flow when the vasodilatory capacity of the microcirculatory resistance vessels has been exhausted.²³ We have developed a digital angiographic analytical method that uses the coronary circulation system impulse response to contrast material injection to determine the vasodilatory capacity of a regional myocardial perfusion zone. In the setting of proximal stenosis, this method accurately and reproducibly correlated with maximal hyperemic flow and CFR.⁴⁵

If severe stenosis or occlusion of an adjacent coronary artery induces shunting of blood through epicardial collaterals away from a regional myocardial perfusion zone, compensatory vasodilation of the microcirculation of that zone would be expected to maintain nutrient flow. The present study uses angiographic, flowmeter, and microsphere measurements in the intact canine circulation to characterize the microcirculatory response of a perfusion bed to acutely created proximal stenosis of its own primary supply artery or of an adjacent artery that normally supplies a contiguous but different myocardial bed.

Methods

Animal Model

Animal studies conformed to the “Position of the American Heart Association on Research Animal Use” and were approved by the Cedars-Sinai Medical Center Institutional Animal Care and Use Committee. Twenty-five open-chest mongrel dogs (21.3 to 40.8 kg) were anesthetized with morphine sulfate (1.0 mg/kg IM) and sodium pentobarbital (30 mg/kg IV). The animals were mechanically ventilated, and anesthesia was maintained with vaporized enflurane (1 to 2.5 minimal alveolar concentration) and 50% oxygen.

After the heart was exposed by lateral thoracotomy, 2.0- or 3.0-mm perivascular ultrasonic flow probes (Transonics Systems, Ithaca, NY) were placed on the proximal left circumflex (LCx) and left anterior descending (LAD) coronary arteries (Fig 1A). Clotted blood was used as an acoustic coupler. Flow-probe gain settings were chosen to accurately assess resting and hyperemic flow; this range limited the precision of flow measurements to 1 mL/min. Stenoses were created by pneumatic vascular occluders (In Vivo Metric, Healdsburg, Calif) positioned directly distal to the probes. Both flow probe and occluder on the LAD were immediately distal to the large first septal perforating branch. This placement was found to

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minimize hemodynamic instability by limiting the amount of ischemic myocardium with LAD occlusion.

A 7F Judkins R4 catheter was introduced into the left common carotid artery and positioned in the left main coronary artery, and heparin (5000 U IV) was given. ECG, proximal coronary artery blood pressure, and coronary blood flow of both arteries were continuously monitored.

For conceptual purposes based on the direction of collateral flow from the LCx to the stenotic LAD artery, the LCx will be referred to as the primary or supplying artery and the LAD as the adjacent or receiving artery throughout the text.

Graded severities of stenosis were created either on the LCx or the LAD artery. After stable flow probe measurements had been observed for 2 minutes, hand-injected selective left coronary angiograms (n=206) were performed with 4 mL of ionic contrast material (meglumine diatrizoate, Angiovist, 370 mg iodine/mL, Berlex Laboratories, Wayne, NJ). After each injection the stenosis was released, and a minimum of 4 minutes was allowed for contrast-induced hyperemic flow to return to baseline.

To delineate the distinct perfusion territories of the LCx and LAD arteries at the conclusion of a study, a 2.5F endhole coronary infusion catheter (ACS, Temecula, Calif) was placed subselectively into the LCx artery, and 10 mL of monastral blue was injected, immediately followed by death (KCl IV) under anesthesia. The heart was excised and cut into 1-cm-thick short-axis sections, weighed, and photographed to determine the mass of the left ventricular myocardium supplied by the LCx (stained part) and LAD artery (unstained part).

In the last eight dogs, the protocol was modified to examine in more detail the effect of total occlusion of a collateral receiving artery on the collateral supplying artery microcirculation, as illustrated in Fig 1B. Contrast injections were made through a 7F JR4 percutaneous transluminal coronary angioplasty (PTCA) guiding catheter positioned in the left main coronary artery. A 2.5F infusion catheter was advanced over a 0.014-in PTCA guide wire into the LCx artery, with its tip just proximal to the flow probe. After the guide wire was withdrawn, intermittent occlusion of the (collateral receiving) LAD was created and proximal (supplying) LCx flow allowed to stabilize for 2 minutes. Left coronary angiograms were alternated with injections of approximately 250 000 colored latex microspheres (15±0.45 μm; E-Z Trac, Los Angeles, Calif), subselectively delivered into the LCx via the infusion catheter (n=45). The supplied colors allowed up to six microsphere injections per dog. Colored microspheres have been validated in comparison to radioactive spheres for the range of coronary flow encountered in our study.6,7

Image Acquisition

Digital coronary angiography was performed as previously described.4 The image intensifier was positioned to obtain a projection that minimized the overlap of the LCx and LAD artery myocardial perfusion zones. A lead blocker was placed between the x-ray source and the thorax to project in the center of the cardiac silhouette for x-ray scatter and veiling glare correction. Aluminum wedge filters were positioned to minimize saturation over the lung fields.

X-ray exposures were created at 60 Hz with the system fixed at 75 kV (peak) with an input exposure of 0.08 μGy per pulse. The image intensifier (15-cm field) was coupled with a 525-line, 1000:1 signal-to-noise ratio video camera (ADAC, Milpitas, Calif) operating in the interlaced field mode. The camera aperture was adjusted so that the output video signal did not exceed 750 mV.

Images were recorded on 3/4-in. U-matic videotape (Sony, Tokyo, Japan) with linear fixed-gain amplification. Five seconds before injection, ventilation was suspended at end inspiration and angiographic and physiological recording began 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 10 frames per second and stored on disk.

Image Analysis

While viewing the digitized images in a cine-loop format, the operator positioned regions of interest (ROIs) for time-density curve acquisition. An 80-pixel ROI was placed over the left main coronary artery just distal to the tip of the catheter for the input function, and a 25-pixel region was placed over the lead blocker. A 400- to 900-pixel output ROI was placed over a proximal and a second one over a distal area of the myocardial microcirculation blush supplied by the LCx (Fig 1A). 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 scatter and veiling glare curve frame by frame from the input and output ROIs.8 The resultant curves were logarithmically transformed to correct for exponential attenuation of radiation and subtracted from the preinjection background. High-frequency variations caused by cardiac motion were smoothed by unweighted time domain filtration over two...
cardiac cycles. A least-squares fitted monoeponential decay function replaced the terminal portion of the input curve to compensate for the late artifact produced by contrast material exiting the coronary sinus, which overlapped this ROI.

The transit of contrast material in the coronary circulation from the proximal left main coronary artery (the input) to the myocardial microcirculation (the output) has been shown to be accurately characterized by its system impulse response function calculated from a two-compartment lagged-normal density model of indicator dispersion.\(^5\) The input and output signals are the regional time-density curves, which are proportional to the relative concentration of contrast material.

The first and second compartments accurately characterize flow and indicator distribution volume of the epicardial coronary arteries and the myocardial microcirculation, respectively (Fig 2A): The epicardial coronary arteries are modeled as a simple conduit in which dispersion is symmetrical about a mean transit time (\(T_{\text{art}}\)). The highly branched myocardial microcirculation is modeled as a well-stirred mixing chamber that produces nonsymmetrical dispersion. This is described by a monoeponential decay function with a mean transit time \(T_{\text{micro}}\). The lagged normal density function is generated by convolution of the two compartmental functions.

The compartmental transit times were determined by iterative convolution of the model (expressed as a difference equation) with the input function, using a fast Fourier transform algorithm and serially adjusting the parameters \((T_{\text{mean}}, T_{\text{art}}, \text{and } \sigma)\) by a gradient descending method until the best \(\chi^2\) fit with the observed output curve was obtained.

Unlike measurements of flow, resting measurements of \(T_{\text{micro}}\) are sensitive to vasodilatory changes induced by progressively severe coronary stenosis,\(^3,4\) the mechanisms of which are summarized in Fig 2B. By definition, \(T_{\text{micro}}\) is the distribution volume, \(V_{\text{micro}}\), divided by the flow, \(Q\). \(V_{\text{micro}}\) increases as the vasodilatory capacity is exhausted.\(^6\) Thus, for normal arteries at resting flow, distribution volume is small, since full vasodilatory capacity is maintained. With increasing stenosis, \(T_{\text{micro}}\) is prolonged. At first, basal flow is maintained by compensatory vasodilation, manifest by an increase in \(V_{\text{micro}}\). With critical stenosis, \(V_{\text{micro}}\) is at a maximum and resting flow progressively diminishes.

In previous work, \(T_{\text{mean}}\) was shown to best correlate with flow regulations, whereas the arterial compartment transit time was more closely related to coronary artery length and cross-sectional dimensions.\(^5\) For these reasons, we report only the results for microcirculatory mean transit times expressed as their inverse, \(T_{\text{mean}}^{-1}\), which is the calculated mean of the respective transit times of the two output regions of interest.

Angiographic images were also semiquantitatively graded for the extent of visible collateral circulation similar to the scale described by Rentrop et al:\(^7\) 0, no visible collaterals; 1, retrograde filling of side branches without visualization of the epicardial segment; 2, partial retrograde filling of the epicardial segment; and 3, complete retrograde filling of the epicardial segment. Grading was by consensus of two experienced angiographers unaware of related measurements.

### Analysis of Direct Flow Measurements

Supplying (ie, LCx) coronary artery resting flow \((Q)\) was measured as the mean flow over 3 seconds before contrast injection. Since resting flow varied substantially between dogs (range, 10 to 58 mL/min), \(Q\) was normalized \((Q_{\text{rel}})\) with respect to the mean prestenotic resting flow in each dog \((Q_{\text{pre-mean}})\):

\[
Q_{\text{rel}} = \frac{Q}{Q_{\text{pre-mean}}}
\]

Two measurements of vasodilatory capacity were recorded. CFR was calculated as the ratio of maximum hyperemic flow induced by ion contrast material \((Q)\) to mean immediate preinjection resting flow \((Q)\):

\[
\text{CFR} = \frac{Q}{Q_{\text{pre-mean}}}
\]

\(Q\) was normalized to the \(Q_{\text{pre-mean}}\) in each dog, similar to resting flow \((Q_{\text{rel}})\):

\[
Q_{\text{rel}} = \frac{Q}{Q_{\text{pre-mean}}}
\]

The absolute change in supplying (ie, LCx) artery resting flow \((\Delta Q)\) caused by receiving (ie, LAD) artery occlusion was measured (in milliliters per minute) as
TABLE 1. Hemodynamic and Angiographic Parameters

<table>
<thead>
<tr>
<th>Seven Physiological States</th>
<th>Normal</th>
<th>Subcritical</th>
<th>Critical</th>
<th>Occlusion</th>
<th>Subcritical</th>
<th>Critical</th>
<th>Occlusion</th>
<th>t Test Within ANOVA</th>
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<tr>
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<td>14</td>
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<td>HR, bpm</td>
<td>103±19</td>
<td>98±19</td>
<td>102±20</td>
<td>105±20</td>
<td>97±21</td>
<td>95±10</td>
<td>102±20</td>
<td>NS</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>91±11</td>
<td>88±8</td>
<td>87±9</td>
<td>84±9</td>
<td>92±6</td>
<td>92±12</td>
<td>92±10</td>
<td>NS</td>
</tr>
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<td>Qh,rel</td>
<td>1.01±0.09</td>
<td>0.94±0.09</td>
<td>0.72±0.22</td>
<td>±0.15</td>
<td>1.06±0.16</td>
<td>1.06±0.13</td>
<td>1.09±0.09</td>
<td>1-3,4,7</td>
</tr>
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<td>CFR</td>
<td>4.0±0.7</td>
<td>1.8±0.4</td>
<td>1.1±0.3</td>
<td>0.4±0.6</td>
<td>3.5±0.7</td>
<td>3.6±0.4</td>
<td>3.2±0.5</td>
<td>1-2,3,4,7</td>
</tr>
<tr>
<td>Qh-rel</td>
<td>4.0±0.7</td>
<td>1.7±0.4</td>
<td>0.7±0.3</td>
<td>0.0±0.0</td>
<td>3.7±0.6</td>
<td>3.8±0.5</td>
<td>3.5±0.5</td>
<td>1-2,3,4</td>
</tr>
<tr>
<td>T_micro⁻¹, min⁻¹</td>
<td>16.7±4.2</td>
<td>8.9±1.9</td>
<td>5.3±2.5</td>
<td>0.7±1.1</td>
<td>16.2±3.9</td>
<td>12.6±2.2</td>
<td>12.0±3.0</td>
<td>1-2,3,4,6,7</td>
</tr>
</tbody>
</table>

n indicates number of data points for each group; HR, heart rate; bpm, beats per minute; MAP, mean arterial blood pressure; Qh,rel, normalized resting flow; CFR, coronary flow reserve; Qh-rel, normalized hyperemic flow; and T_micro,⁻¹, inverse of microcirculatory mean transit time. Qh-rel, CFR, Qh-rel, and T_micro⁻¹ are all data for the supplying artery; t test within ANOVA: "1-2,3," for example, denotes a significant difference between groups 1 and 2 and between 1 and 3 (P<.05).

\[
\Delta Q = Q_{pos} - Q_{pre}
\]

where \( Q_{pos} \) was the supplying arterial resting flow measured 2 minutes after establishing receiving artery stenosis or occlusion (immediately before contrast injection) and \( Q_{pre} \) was the supplying arterial flow before stenosis or occlusion. \( \Delta Q \) has been validated as an indirect means of quantifying collateral flow.\(^{16-18} \) provided that hemodynamics remained stable after acute occlusion. In addition, a relative change in supplying arterial resting flow was calculated (in percent) as

\[
\Delta Q_{rel} = \Delta Q / Q_{pre}
\]

Supplying and receiving artery stenoses were categorized by prospective hemodynamic and angiographic criteria. Normal vessels were defined by the absence of angiographic stenosis and CFR ≥3.0. A subcritical stenosis was defined when angiographically visible stenosis did not affect resting flow but CFR was reduced below 3.0. Critical stenosis was when resting flow was reduced by more than 20%. An occlusion was documented when antegrade flow was abolished. These definitions established seven physiological flow states: 1, both arteries normal; 2, subcritical stenosis of the supplying artery; 3, critical stenosis of the supplying artery; 4, occlusion of the supplying artery; 5, subcritical stenosis of the receiving artery (with normal supplying artery); 6, critical stenosis of the receiving artery; and 7, occlusion of the receiving artery.

**Microsphere Processing and Analysis**

Two transmural left ventricular myocardial samples of a proximal and two samples from a distal part of the perfusion territory of both supplying (LCx) and receiving (LAD) arteries were excised for microsphere counting (ie, eight samples per dog; average tissue sample mass, 2.59±1.09 g). To ensure precise sampling of collateralized segments, the excised heart was aligned in the same projection as used for angiography, and samples were removed at least 1 cm from the border of the perfusion zone. Tissue was digested and microspheres were extracted as previously described.\(^6 \) Aliquots of microspheres were counted at ×200 magnification in a Fuchs-Rosenthal hemocytometer.

The microsphere count per gram of tissue (\( C_n \)) was calculated for each color and tissue sample as

\[
C_n = (N \times 1000 \text{ mm}^3 \text{ ml}^{-1} \times n \times 3.2 \text{ mm}^3) \times (V/M)
\]

where \( N \) is the total number of microspheres counted, \( n \) the number of hemocytometer chambers counted (chamber volume, 3.2 mm\(^3\)), and \( V \) the volume of the final solution extracted from a tissue sample with the original weight \( M \). The mean value of the four tissue samples from each artery was used for subsequent calculations. The respective microsphere counts per gram tissue were multiplied by the mass of the total perfusion territory for the supplying artery and by the mass of the territory distal to the occluder for the receiving artery to yield an estimate for the total number of microspheres in the respective territory (\( C_{m-sup} \) and \( C_{m-rec} \)).

The proportion of supplying artery flow collateralizing to the receiving artery territory, \( Q_{coll-rel} \) (in percent), was

\[
Q_{coll-rel} = C_{m-rec} / (C_{m-rec} + C_{m-sup}) \times 100
\]

Absolute collateral flow, \( Q_{coll} \), was calculated (in milliliters per minute) as

\[
Q_{coll} = (Q_{coll-rel} / 100) \times Q_r
\]

**Statistical Analysis**

Data throughout the text are expressed as the mean±SD. Comparison between the seven physiological states was by one-way ANOVA, and intergroup comparisons were evaluated by the adjusted \( t \) test within ANOVA (Bonferroni/least significant difference). Where applicable, the following tests were applied: two-tailed Student’s \( t \) test for paired or nonpaired data, one-sample \( t \) test, Mann-Whitney \( U \) test for nonparametric data, and linear regression analysis. Statistical significance was defined as \( P<.05 \).

**Results**

The hemodynamic and digital angiographic parameters for the seven physiological states are summarized in Table 1. There were no significant differences in heart rate or mean blood pressure. There was a progressive decrease in supplying artery resting flow (\( Q_{rel} \)) with increasing grades of supplying artery stenosis as expected from the prospective definitions of stenosis severity. Receiving coronary artery stenosis was associated with a small but consistent increase in supplying artery flow, which achieved statistical significance when the receiving artery was totally occluded (flow increase, +8%; \( P<.05 \)). Angiographic filling of collaterals was seen in all injections after coronary artery occlusion of either the supplying or receiving artery. Collaterals were visualized less frequently (13 of 30 injections) with
critical stenosis and not at all with subcritical stenosis or normal arteries. Although the flow-probe and angiographic parameters listed in Table 1 were significantly different between states, the interrelations are better perceived in the individual injection data scatterplots.

Fig 3 demonstrates the effects of graded supplying and receiving artery stenosis on the inverse of microcirculatory mean transit time, $T_{\text{micro}}^{-1}$, determined in the supplying artery myocardial region. $T_{\text{micro}}^{-1}$ declined progressively and significantly with increasing severity of supplying artery stenosis (Fig 3A). $T_{\text{micro}}^{-1}$ of the same supplying region also diminished significantly with critical stenosis or total occlusion of the receiving coronary artery (Fig 3B), although to a lesser extent than with supplying artery stenosis of equivalent severity. These effects were consistent within individual dogs and were observed in all dogs studied.

Fig 4 compares angiographic $T_{\text{micro}}^{-1}$ with flowmeter-derived measurements of CFR and normalized hyperemic flow ($Q_{\text{rel}}$), all determined in the supplying artery region. For supplying artery stenosis, $T_{\text{micro}}^{-1}$ correlates with CFR (Fig 4A) and $Q_{\text{rel}}$ (Fig 4C). There were significant differences between each of the stenosis grades for all three indices. With increasing severity of receiving artery stenosis, there was a trend for a decrease in maximal hyperemic flow (Fig 4D) and a significant fall in supplying artery flow reserve only when the receiving artery was occluded ($P<.05$; Fig 4B). This trend was more pronounced for $T_{\text{micro}}^{-1}$, for which it achieved statistical significance for critical stenosis or total occlusion of the receiving artery.

Table 2 summarizes the last eight dogs with microsphere studies. Receiving artery occlusion had no effect on heart rate and blood pressure. As in Table 1, supplying artery $Q_{\text{rel}},\text{CFR}$, and $T_{\text{micro}}^{-1}$ fell significantly with receiving artery occlusion. Receiving artery occlusion was associated with an increase of supplying artery flow ($\Delta Q; 2.3 \pm 1.5 \text{ mL/min};$ range, 0 to 5 mL/min). This represented an $8.6 \pm 5.9\%$ increase relative to the flow before the occlusion was created ($\Delta Q_{\text{rel}}$). Collateral flow ($Q_{\text{coll}}$) varied likewise with receiving artery occlusion (2.6 $\pm$ 2.3 mL/min; range, 0 to 8.5 mL/min) and was negligible when the receiving artery was normally patent. Relative collateral flow, $Q_{\text{coll-rel}}$, represented $8.5 \pm 6.8\%$ of supplying artery flow diverted to the receiving myocardial bed. Fig 5 shows that there was a close linear correlation between these two methods of quantifying collateral flow.

Receiving artery occlusion was associated with a $>25\%$ decrease of supplying artery $T_{\text{micro}}^{-1}$. Moreover, Fig 6 shows that there was a linear relation between the decrease of $T_{\text{micro}}^{-1}$ after receiving artery occlusion and the absolute value of collateral flow ($Q_{\text{coll}}$). Further evidence of the effect of collateral flow diversion to receiving myocardium on supplying perfusion zone transit time is illustrated in Fig 7, which shows that $\Delta T_{\text{micro}}$ in the supplying artery was associated with the extent of collateral filling resulting from receiving artery occlusion.

**Discussion**

**Observations With Primary or Supplying Artery Stenosis**

The present study reconfirms previous observations that there is a close concordance between resting values of the microcirculation transit time of angiographic contrast material, $T_{\text{micro}}$, and flowmeter measurements of the vasodilatory capacity of a regional myocardial perfusion zone, including CFR and maximal hyperemic flow (Fig 4). Moreover, this digital imaging technique was sensitive enough to differentiate normal vessels from those in which stenosis was subcritical and resting flow was unchanged or to discriminate discrete grades of stenoses in which resting flow was diminished (critical stenosis or total occlusion) from subcritical stenosis.

$T_{\text{micro}}^{-1}$ measured under resting flow conditions predicts vasodilatory capacity because microcirculation blood volume varies with the conductance of the resistance vessels. In relative terms, the calculated microcirculation distribution volume increased by 74% with subcritical stenosis, 124% with critical stenosis, and 136% with total occlusion. This observation has been verified with direct measurements by several investigators. It is the codependence of the mean transit time on volume and inversely on flow that explains why a single angiographic measurement taken in the absence of a pharmacological hyperemic stimulus can quantify the severity of proximal stenosis by its effect on the microcirculation (Fig 2B).

**Observations With Adjacent or Receiving Artery Stenosis**

Our second objective was to evaluate whether stenosis of an adjacent or receiving coronary artery has
angiographically demonstrable effects on flow or the magnitude of vasodilation of the supplying myocardial bed by diverting collateral flow from the supplying to the receiving vascular bed. Supplying artery CFR and maximal hyperemic response, $Q_{\text{rel}}$, were not diminished until the receiving artery was totally occluded and collateral filling was uniformly observed. Even then, the decrements in these parameters were modest, averaging 20% and 12.5%, respectively. Supplying artery $T_{\text{micro}}^{-1}$ measured at rest was more sensitive to the severity of receiving artery stenosis than direct flow measurements during hyperemia. $T_{\text{micro}}^{-1}$ was significantly diminished with receiving artery critical stenosis, by an average of 25%, and decreased further with total occlusion.

Effect of Receiving Coronary Artery Occlusion on Collateral and Regional Flow

Collateral perfusion was quantified by subselective injections of colored microspheres. Receiving artery occlusion was associated with a small but significant increase in supplying artery flow ($Q_{\text{rel}}$), averaging 2.3 mL/min, or 8.6%. The observation that supplying artery proximal flow increases and CFR decreases has been described previously in animals and humans. Collateral flow to the receiving artery, $Q_{\text{coll}}$, was negligible with a patent receiving artery but significantly increased to an average of 2.6 mL/min, or 8.5% of supplying artery flow, with receiving artery occlusion. Thus, whether measured in absolute or relative terms, there was a striking equivalency between the increment in proximal supplying artery flow and collateral flow with receiving artery occlusion (Fig 5). That the fall in supplying myocardial inverse transit time resulted from collateral drafting to the receiving arterial bed is suggested by the association between the change in $T_{\text{micro}}^{-1}$ and the magnitude of collateral flow and the extent of collateral filling (Figs 6 and 7).

Proposed Mechanisms

We propose the following explanation for the mechanism explaining the prolongation of supplying bed microcirculatory mean transit time with receiving artery occlusion. Collateral flow induces an increase in proximal supplying artery flow with negligible steal of transmural flow from the supplying myocardial perfusion zone. Increased proximal flow results in a small drop in perfusion pressure of the supplying microcirculation bed, causing autoregulatory vasodilation to maintain flow. This is suggested by the observation of a small but significant fall in maximal hyperemic flow, since...
perfusion pressure is the main determinant of maximal hyperemic flow.

Fig 8 conceptualizes these changes in terms of supplying microcirculation distribution volume and flow to explain the decrease of $T_{\text{micro}}^{-1}$ in response to receiving artery stenosis. Assuming that the flow reaching the supplying myocardial bed does not change, the microcirculation distribution volume increased by an average of 32% with receiving artery critical stenosis and by 39% with total occlusion. Although these changes in volume were modest compared with the effects of supplying artery stenosis, they are consistent within the same animal and between animals and demonstrate the importance of distribution volume in determining the angiographic impulse response.

**TABLE 2. Measurements in Microsphere Studies**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Receiving Artery Occlusion</th>
<th>t Test (P)</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>32</td>
<td>...</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>99±15</td>
<td>98±17</td>
<td>NS</td>
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<tr>
<td>MAP, mm Hg</td>
<td>95±13</td>
<td>96±11</td>
<td>NS</td>
</tr>
<tr>
<td>$Q_{rel}$</td>
<td>1.01±0.09</td>
<td>1.09±0.09</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CFR</td>
<td>4.2±0.8</td>
<td>3.6±0.5</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>$T_{\text{micro}}^{-1}$, min$^{-1}$</td>
<td>17.0±5.2</td>
<td>13.5±3.7</td>
<td>&lt;.02</td>
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<tr>
<td>$\Delta Q$, mL/min</td>
<td>...</td>
<td>2.3±1.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>$\Delta Q_{rel}$, %</td>
<td>...</td>
<td>8.6±5.9</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>$Q_{col}$, mL/min</td>
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<td>&lt;.001</td>
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<tr>
<td>$Q_{col-rel}$, %</td>
<td>0.6±0.9</td>
<td>8.5±6.8</td>
<td>&lt;.001</td>
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</tbody>
</table>

HR indicates heart rate; bpm, beats per minute; MAP, mean arterial pressure; $Q_{rel}$, normalized resting supplying artery flow; CFR, coronary flow reserve of the supplying artery; $T_{\text{micro}}^{-1}$, inverse of digital angiographically determined mean transit time of the microcirculation of the supplying artery; $\Delta Q$, change of supplying artery resting flow induced by receiving artery occlusion; $\Delta Q_{rel}$, relative change of proximal resting supplying artery flow with receiving artery occlusion; $Q_{col}$, microsphere-derived collateral flow; and $Q_{col-rel}$, ratio of microsphere counts, i.e., the relative portion of proximal supplying artery flow collateralizing to the receiving artery.

**Limitations**

Interpretation of the results of this study should be limited to the context of acute coronary stenosis in dogs. Canine hearts have preexisting, well-developed collaterals\(^\text{32,33}\) that can easily be recruited by a small pressure gradient between perfusion beds.\(^\text{32,34}\) Furthermore, physiological and anatomic changes in the native vessels and the collaterals can occur when coronary occlusions are chronic,\(^\text{29,35,36}\) and vasomotor changes caused by atherosclerosis limit further interpretation of this single-vessel stenosis model. Broad inferences to the human coronary circulation should thus be qualified by these differences.

The proposed autoregulatory mechanisms have been oversimplified because they do not account for differences between subepicardial and subendocardial perfusion. This is an inherent limitation of planar projection angiographic imaging and flowmeter measurement of proximal coronary artery flow. Theoretically, impulse response analysis would be applicable to tomographic imaging methods, such as contrast echocardiography.
changes in the two parameters that compose it, flow and volume. There should be no important impact of collateral flow on $T_{\text{micro}}^{-1}$, since collateral flow is usually only a small fraction of normal antegrade flow. In our study, collateral flow was approximately 15% of normal antegrade flow. However, further research will be needed to validate the effect of significant unvisualized collaterals.

We did not quantify global or regional oxygen consumption or wall motion abnormalities. It has been suggested that regional ischemic asynergy is associated with a compensatory hypercontractility of nonischemic segments. As such, receiving artery occlusion should have created an increase in proximal supplying artery blood flow that exceeded the portion shunted to collateral flow to satisfy the increased demand of the supplying myocardial perfusion zone. Since the increase in proximal supplying artery flow was precisely balanced by the contribution of collateral flow, it may be surmised that compensatory hypercontractility did not play an important role in these experiments.

Although there were no significant changes in systemic blood pressure or heart rate, we did not measure or control left ventricular filling pressure, which is an important determinant of coronary blood flow. Finally, the applicability of the model in the presence of multiple stenoses, branch stenoses, hypertrophy, myocardial fibrosis, and extremes of heart rate and blood pressure remains to be tested.

**Implications**

Taken in the context of these limitations, the present study suggests that impulse response analysis can provide quantitative insight into regional flow distribution and autoregulation of the intact coronary circulation. This technique is reliable for quantifying regional transmural perfusion that is impaired by proximal stenosis of its own supplying artery and to detect the influence of adjacent or receiving artery stenosis on the resistance vessels of the supplying myocardial perfusion zone by collateral shunting. This may have implications for the clinical determination of the adequacy of collateral perfusion. For example, the hemodynamic significance of a stenosis labeled as moderate by dimensional quantitative angiographic parameters may be modulated if that vessel is the source of collateral flow to a receiving region.

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