Concept of Maximal Flow Ratio for Immediate Evaluation of Percutaneous Transluminal Coronary Angioplasty Result by Videodensitometry

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Background. In the setting of percutaneous transluminal coronary angioplasty (PTCA), immediate information about the result of the intervention is important, whereas morphological parameters are often less reliable than in diagnostic coronary arteriography. Recently, a new videodensitometric method was introduced and validated in animal experiments, which allows accurate comparison of maximal myocardial perfusion between situations with different degrees of stenosis. This method uses mean transit time (Tmn) of the contrast agent at maximal hyperemia as a parameter for maximal flow and is strictly in accordance with indicated dilation theory.

Methods and Results. In 40 patients with angina pectoris, single-vessel disease, and a positive exercise test at the time of acceptance for PTCA, this approach was applied for evaluation of the improvement of maximal flow achieved by the PTCA. Maximal vasodilation was induced immediately before and 15 minutes after PTCA by intracoronary administration of papaverine, and digital angiographic studies were performed. By special breath-holding instruction, almost motionless, triggered image acquisition was possible during 15–20 heartbeats. Excellent subtraction images could be obtained, and reliable determination of Tmn at maximal hyperemia was possible in 33 patients both before and after PTCA. The ratio between maximal flow after and before PTCA, called maximal flow ratio (MFR), was represented by the ratio between Tmn before and after the intervention and compared with the results of exercise testing 24–48 hours before and 7–10 days after the procedure. After correction for pressure changes, MFR was 2.2 ± 1.5 for the 33 dilated vessels and 1.0 ± 0.2 for 25 normal vessels serving as a control. In 94% of all patients, an MFR value of more than 1.6 or less than 1.6 discriminated between presence or absence of reversal of exercise test result from positive to negative. If on-line judgment of success was based upon angiographic parameters or measurement of trans-stenotic pressure gradient, the relation with noninvasive functional improvement was present only in 66% and 74% of all patients, respectively. A definite range of what can be called normal Tmn at maximal hyperemia could be distinguished, and post-PTCA values for successfully dilated arteries returned completely to this normal range.

Conclusions. Accurate comparison of maximal myocardial perfusion before and after PTCA is possible in man, improvement of maximal flow is highly related to functional improvement as indicated by exercise test results, and, therefore, this method provides a straightforward way for on-line evaluation of the result of the intervention. (Circulation 1991;83:854–865)

For many years, it has been widely recognized that the best way to evaluate the functional result of a coronary angioplasty is to investigate its effect on coronary flow or myocardial perfusion.1–3 One method for flow measurement used in clinical practice nowadays is electrocardiogram-triggered digital radiography. Most approaches in this
field, however, have at least three important limitations, namely, 1) the influence of the indicator (contrast agent) on flow, 2) the changes in vascular volume between different situations in which flow is compared, and 3) the limited time available for motionless image acquisition. To avoid these problems, different adjusted versions of the original theory have been proposed with somewhat disappointing results.\textsuperscript{4-11} In fact, most problems are related to the inability to determine resting flow accurately, which implies unreliable assessment of coronary flow reserve.\textsuperscript{9,12-14}

Recently, we developed and validated a videodensitometric method for comparison of merely maximal myocardial perfusion between different situations (e.g., different degrees of coronary artery stenosis).\textsuperscript{15}

In this approach, the influence of indicator on flow and changes in vascular volume is circumvented; although no data about resting flow or coronary flow reserve can be obtained, maximal flow could be determined very accurately in animal validation studies. This method uses mean transit time (T\textsubscript{mn}) as a single parameter that is inversely proportional to maximal flow and is strictly in accordance with the mathematical principles of indicator dilution theory. Considering the fact that in the majority of patients anginal complaints are not caused by inadequate resting flow but rather by impaired maximal flow, it seems to be plausible that the increase in maximal flow after an intervention will be a straightforward parameter to reflect functional improvement of the patient.\textsuperscript{14,16}

The aims of this study were to test the applicability of this method in humans during percutaneous transluminal coronary angioplasty (PTCA), to relate the relative increase in maximal flow immediately after PTCA to functional improvement at noninvasive exercise testing 7-10 days later, and to investigate values for T\textsubscript{mn} during maximal hyperemia in normal coronary arteries.

**Methods**

**Patient Population and Study Design**

Forty consecutive patients referred for elective PTCA were included in this study. They met the criteria of presence of the combination of angina pectoris of New York Heart Association functional class III, a positive exercise test, and one-vessel disease at coronary arteriography at the time of acceptance for PTCA less than 6 weeks before the actual date of the intervention; presence of sinus rhythm; absence of previous bypass surgery or myocardial infarction causing more than mild hypokinesia of one of the segments on the left ventriculogram; and absence of visible collateral circulation. These patients were seen in the outpatient department 24-48 hours before the intervention. At that time, the aim of the study was explained to the patient, and another exercise test was performed. When preexisting electrocardiogram abnormalities interfered with regular evaluation of the stress electrocardiogram, the test was combined with thallium scintigraphy. This was the case in only two patients. This exercise test was followed by extensive training to hold breath, using a nose clamp, at maximal inspiration for 15-20 seconds. Patients were asked to repeat this training at night and the next day, lying in the same position as during the catheterization. Careful attention was paid to avoid moving the head, neck, shoulders, or thorax during breath holding.

Exercise testing was repeated 7-10 days after the PTCA. All exercise tests were performed on a bicycle ergometer in upright position according to local routine, starting at a load of 50 W with stepwise increases of 10 W/min. A 12-lead electrocardiogram was recorded every minute. Exercise test results were classified as negative or mildly, moderately, or strongly positive according to Selzer et al.\textsuperscript{17} Thallium scintigraphy was classified as positive, if evident filling defects were present by visual interpretation in at least two segments immediately after exercise and had disappeared 4 hours later.\textsuperscript{18}

All patients used aspirin 160 mg daily and dipyriramole 75 mg q.i.d. from at least 2 days before until 10 days after the procedure. No further restrictions were made concerning concomitant medication.

At the time of PTCA, a 6F stimulation catheter was positioned in the right atrium, and then the following protocol was performed. In case of a stenosis in one of the large branches of the left coronary artery (LCA), a 7F diagnostic right Judkins catheter was advanced into the right coronary artery (RCA) and an electrocardiogram-triggered digital study was performed in the 30° right anterior oblique projection during maximal vasodilation of the myocardial vascular bed. After changing the coronary catheter, this was followed by a similar study of the LCA in the 60° left anterior oblique projection, sometimes with slight cranial angulation depending on the patient’s anatomy. After removal of the diagnostic catheter, an appropriate 8F guiding catheter was advanced into the LCA. Thereafter, the regular PTCA procedure was performed, preferably using an over-the-wire balloon (USCI Simplus, C.R. Bard Ireland Ltd., Galway, Ireland) to enable measurement of stenotonic pressure gradients before the first balloon inflation, 5 minutes after the final balloon inflation, and at least 2 minutes after intracoronary injection of contrast medium. Fifteen minutes after the last balloon inflation, another electrocardiogram-triggered digital study of the LCA during maximal vasodilation was performed using the left Judkins diagnostic catheter. In case of an RCA stenosis, RCA and LCA were interchanged in this protocol. During image acquisition, arterial pressure was recorded continuously through the side channel of the arterial sheath. The stimulated heart rate remained constant in all studies in one patient. By following this protocol, not only could data about maximal flow in the diseased artery before and after PTCA be compared, but also reference data for apparently normal coronary arteries could be collected.
Image Acquisition and Processing

Image acquisition and processing were performed using a Siemens Bicor radiograph system connected to a Siemens Digitron-3 computer for digital subtraction angiography (Siemens AG, Erlangen, FRG). For all studies, 6 ml of nonionic contrast agent Iohexol-350 (Nycomed AS, Oslo, Norway) was injected, using a power injector at a speed of 4 ml/sec. Image acquisition was performed during breath holding at maximal inspiration as described above using the principle of apparent cardiac arrest. This means not only that the heart is triggered slightly above its inherent frequency to provide a strictly regular heart rhythm, but also that the radiographic pulses are in synchrony with the paced heartbeats. One image was obtained per heart cycle just before the onset of the QRS complex. Image acquisition started exactly 25 seconds after intracoronary administration of 8 mg papaverine in the RCA or 12 mg in the LCA to provide maximal vasodilation of the myocardial vascular bed. Contrast injection started 5 seconds after the onset of image acquisition to provide a stable baseline density level. The moment at which 50% of the contrast agent was injected was defined as \( t=0 \). Voltage and current of the radiograph generator and pulse width were identical in all studies within one patient, and the automatic brightness control of the radiograph equipment was switched off after the fourth image in every study to enable density comparison within one study. All studies were performed using a 7-in. image intensifier. Meticulous care was taken to avoid changes in the patient’s position between the different studies. After logarithmic transformation, images were digitized in a 512x512 matrix with 1,024 density levels using a 10-byte ADC at a rate of 22 MHz and subsequently stored.

Stenosis severity before and after the PTCA was assessed by quantitative coronary arteriography by calculation of the reduction of cross-sectional area compared with a nearby normal arterial segment (DIGITRON STENOSIS program, Siemens AG, Erlangen, FRG).

Processing of the Regions of Interest and Time–Density Curves

Regions of interest (ROIs) were chosen over the tip of the coronary catheter to record the start of contrast injection and over the myocardium supplied by the respective arteries. For the left anterior descending coronary artery (LAD), the myocardial ROI was preferably chosen over the anteroapical region; for the left circumflex (LCx) artery, the myocardial ROI was preferably chosen over the posterolateral area at the level of the posteromedian papillary muscle; and for the RCA, the myocardial ROI was preferably chosen over the central portion of the posterior septum. All myocardial ROIs were circular and of identical size (225–600 pixels) in one patient. ROIs were chosen so that overlap of LAD and LCx myocardium was avoided and care was taken to avoid overprojection of the large epicardial arteries and veins. Close to the myocardial ROIs, background ROIs were chosen for analysis of changes in background density. This analysis is performed because the background always shows slight variations in density over time, predominantly a slight increase. This is caused by instability of the radiograph chain, small motion artifacts, and sometimes overlap of extramyocardial structures such as the descending aorta or the right atrium, which are faintly stained by contrast agent during the latter phase of image acquisition. Once chosen, position and size of the ROIs were kept constant in each patient. Time–density curves were obtained by sampling the average pixel density within an ROI in the consecutive images and corrected by subtraction of the sampled average density in the corresponding background ROI. The remaining data were fitted by a gamma function according to the Marquardt method, using all samples between \( t=0 \) and the instant at which the descending part of the curve became less than 40% of the peak value. In this fit procedure, the time–density curve is presented as a sampled dilution curve superposed on a baseline density \( a_0 \) and beginning to be different from \( a_0 \) at \( t=t_0 \). The fit function \( c(t) \) is defined as:

\[
c(t)=a_0+D_{\text{max}} \cdot \Theta \cdot e^{-b(t-t_0)} \quad t \geq t_0
\]

\[
c(t)=a_0 \quad t < t_0
\]

where \( D_{\text{max}} \) is maximal contrast density of the sampled data, \( t_{\text{max}} \) is time of maximal contrast density, \( \Theta \) is \( (t-t_0)/(t-t_{\text{max}}) \), and \( b \) is shaping factor.

These parameters are determined in an iterative way such that the relative error between the fit function and the observed data is minimized. The quality of the fit is judged by the relative error \( E_r \), which is defined as the square root of the ratio of the mean squares of differences between observed data and calculated data to the mean squares of the fit function. A 10% value of \( E_r \) was considered as the upper limit for acceptance of the fit as being representative for the sampled data. This is analogous with the former animal validation study. \( T_{mn} \) was calculated from the fit function \( c(t) \) according to theory by the following:

\[
T_{mn} = \int_0^z t \cdot c(t) \, dt
\]

By solving Equation 2, \( T_{mn} \) can be expressed in the parameters of the gamma fit \( c(t) \) as follows:

\[
T_{mn} = \frac{(b+1)}{b} \cdot (t_{\text{max}}-t_0)+t_0
\]
**Data Processing and Statistical Analysis**

The ratio between maximal myocardial flow after and before the PTCA was called the maximal flow ratio (MFR) for the respective ROI and calculated as:

\[
\text{MFR} = \frac{T_{mn} \text{ before PTCA}}{T_{mn} \text{ after PTCA}}
\]  

(4)

Because of the pressure dependency of flow during maximal vasodilation, MFR was corrected for changes in mean arterial pressure in the studies before and after PTCA. This was performed by multiplying MFR by the ratio Pa(1)/Pa(2) where Pa(1) and Pa(2) represent the mean arterial pressures in the studies before and after PTCA, respectively. The corrected value was called MFRc.

In testing reproducibility of calculation of \(T_{mn}\), in two sets of 10 patients one study of either the LCA or the RCA was performed twice during maximal vasodilation under identical circumstances with an interval of 10 minutes. In these paired studies, image processing and ROI processing were automatically performed in an identical way. Correction for possible pressure changes between the paired studies was performed by multiplying \(T_{mn}\) at the second measurement by the ratio Pa(2)/Pa(1) where Pa(1) and Pa(2) represent the mean arterial pressures at the first and the second of the paired studies, respectively. Linear regression plots were drawn, and the correlation coefficients between the first and second measurements were calculated for the ROIs corresponding with the LAD, LCx, and RCA, respectively. Also, the coefficients of variation for \(T_{mn}\) were calculated for every pair of studies and for each ROI. Angiographic success of PTCA was defined as a reduction of the area stenosis of at least 20% of the diameter of a nearby normal segment and a residual area stenosis of less than 50%.\(^{26}\) Success according to pressure measurements was considered to be present if the mean trans-stenotic pressure gradient after the PTCA was 15 mm Hg or less.\(^{26,27}\) To determine separation between MFR, values indicative for successful or unsuccessful PTCA according to exercise test results, linear discriminant analysis was performed on the logarithmic data. The performances of the angiographic criterion, trans-stenotic pressure gradient, and MFR, for classification of PTCA results are expressed as percentages of correct classification. Furthermore, the relations between the result of exercise testing and results of the PTCA according to angiographic stenosis reduction, trans-stenotic pressure gradient, or MFR, were evaluated by \(\chi^2\) tests. Statistical analysis was performed using the SAS software package (SAS Institute Inc., Cary, N.C.). Hemodynamic data are given as mean±SD.

**Results**

**Clinical and Hemodynamic Data**

The clinical characteristics of the study population and the data on exercise testing, stenosis severity, pressure gradients, \(T_{mn}\) before and after PTCA, MFR, and MFRc are tabulated in Table 1. The mean±SD values for these parameters are mentioned in Table 2. MFR could not be determined in seven patients. In one patient, atrial fibrillation occurred during positioning of the stimulation catheter; this was the only complication related to this study. In three patients, overall image quality was insufficient because of motion artifacts. In one patient, an RCA stenosis could not be passed successfully; in one patient, a previously narrowed LCx artery was totally occluded at the time of the PTCA; and in one patient, emergency surgery was necessary after a large dissection at the site of an LAD stenosis—this was the only complication related to the PTCA procedure itself in this study population. Trans-stenotic pressure gradients were not measured in 13 patients because the balloon catheter deemed necessary in these patients by the interventional cardiologist did not permit pressure measurements.

The frequency of atrial pacing in the study population was 82±10 (range, 71–107, but always the same in all studies belonging to one patient). Mean arterial pressure was 82±14 mm Hg during the study of the affected artery before PTCA and 77±14 mm Hg thereafter.

PTCA was successful according to eyeball assessment by the interventional cardiologist immediately after the procedure in 36 of 40 patients, and reversal of the exercise test from positive to negative occurred in 30 patients, including both patients in whom thallium scintigraphy was performed. After an average follow-up of 6 months (range, 1–13 months), recurrent angina pectoris occurred in seven patients, necessitating re-PTCA in four of them.

**Quality and Reproducibility of Image Acquisition and Time–Density Curves**

The average image quality was surprisingly good. Adequate fits to the sampled time–density curves could be obtained in 91% of all studies, the relative error \(E_r\) being less than 10%. Some representative examples of images are shown in Figures 1 and 2. Some examples of background-corrected time–density curves and the corresponding fits are also presented in Figure 2. Reproducibility of \(T_{mn}\) obtained from two identical studies with an interval of 10 minutes was excellent (Figure 3). After correction for the small changes in mean arterial pressure in the paired studies as outlined in “Methods,” the correlation coefficients between the first and second measurements were 0.97, 0.91, and 0.98 for the LAD, LCx, and RCA, respectively. Mean coefficients of variation were 5.8%, 5.7%, and 5.3% for the respective arteries.

**Relation Between Maximal Flow Ratio and Exercise Test Results**

\(T_{mn}\) was 6.9±2.1 seconds before and 3.4±1.4 seconds after PTCA. After correction for pressure changes as
**TABLE 1. Clinical Characteristics of Study Population and Data on Exercise Testing, Densitometric Area Stenosis Severity, Trans-stenotic Pressure Gradient, and Mean Transit Time at Maximal Hyperemia Before and After Percutaneous Transluminal Coronary Angioplasty**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Affected artery</th>
<th>Exercise time (sec)</th>
<th>Stenosis (%)</th>
<th>Trans-stenotic Δ P (mm Hg)</th>
<th>$T_{max}$ at maximal hyperemia (sec)</th>
<th>Maximal flow ratio</th>
<th>MFR$_x$</th>
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<td>69</td>
<td>M</td>
<td>LAD ++ -</td>
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<td>12 10</td>
<td>79 32</td>
<td>-</td>
<td>12.2 5.8</td>
<td>2.2 2.2</td>
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<tr>
<td>33</td>
<td>77</td>
<td>F</td>
<td>LAD + + +</td>
<td>1 5</td>
<td>95 39</td>
<td>30 20</td>
<td>7.6 6.3</td>
<td>1.2 1.3</td>
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<tr>
<td>34</td>
<td>48</td>
<td>M</td>
<td>LAD ++ -</td>
<td>5 12</td>
<td>86 19</td>
<td>39 8</td>
<td>8.1 4.7</td>
<td>1.7 1.8</td>
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<tr>
<td>35</td>
<td>64</td>
<td>M</td>
<td>RCA ++ -</td>
<td>7 9</td>
<td>92 65</td>
<td>55 9</td>
<td>8.3 7.8</td>
<td>1.1 1.1</td>
<td></td>
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<tr>
<td>36</td>
<td>52</td>
<td>M</td>
<td>RCA +++ -</td>
<td>6 7</td>
<td>91 77</td>
<td>-</td>
<td>7.3 3.6</td>
<td>2.0 2.0</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>55</td>
<td>M</td>
<td>RCA + + -</td>
<td>9 9</td>
<td>74 60</td>
<td>40 10</td>
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<tr>
<td>38</td>
<td>61</td>
<td>M</td>
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<td>7 5</td>
<td>77 46</td>
<td>45 9</td>
<td>6.3 2.2</td>
<td>2.9 2.9</td>
<td></td>
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<tr>
<td>39</td>
<td>54</td>
<td>M</td>
<td>RCA + + +</td>
<td>8 9</td>
<td>84 48</td>
<td>52 34</td>
<td>4.9 6.8</td>
<td>0.7 0.8</td>
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<tr>
<td>40</td>
<td>47</td>
<td>M</td>
<td>LCX + -</td>
<td>12 16</td>
<td>81 26</td>
<td>54 13</td>
<td>5.1 2.3</td>
<td>2.2 2.4</td>
<td></td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; PTCA, percutaneous transluminal coronary angioplasty; Δ P, trans-stenotic pressure gradient; $T_{max}$, mean transit time; MFR$_x$, maximal flow ratio after correction for pressure changes.

- -, +, +++, and +++ refer to exercise test results according to Selzer et al.\textsuperscript{17}

*Corresponding value could not be determined (see text).

indicated above, this corresponded with a relative increase in maximal myocardial perfusion of $224\pm149\%$ (range, 80–420%). If only patients with a successful PTCA according to exercise test results were considered, the pressure-corrected increase in maximal flow was $249\pm73\%$. MFR$_x$ was correlated to presence or
abuse of reversal of exercise test result from positive to negative. By linear discriminant analysis, maximal separation was yielded by an MFR, value of 1.6. Therefore, MFR, of more than 1.6 or less than 1.6 was chosen for further evaluation (Table 3).

MFR, was more than 1.6 in 26 patients. In 25 of these patients, a positive exercise test 1–2 days before the intervention became negative 7 days thereafter. In the remaining patient (patient 28), a severe stenosis in a posterolateral branch of the LCx artery had been present 24 days before PTCA; at that time, this patient had severe anginal complaints and a positive exercise test. After prolonged nocturnal pain 2 weeks before the PTCA, anginal complaints disappeared. The exercise pain 24 hours before PTCA was negative and remained so after successful dilation of the LCx stenosis with an MFR, of 2.1. This course suggests that a small infarction had occurred at the time of prolonged nocturnal pain and that PTCA had been unnecessary.

MFR, was less than 1.6 in seven patients; in six of these seven patients, no reversal of exercise test result was observed. In three of these patients (patients 6, 7, and 25), anginal complaints and a positive exercise test had been present 2–6 weeks earlier; a significant stenosis was found at that time. Two days before the PTCA, however, a maximal exercise test was performed without anginal complaints or electrocardiogram abnormalities. At PTCA, the stenosis was still present and apparently unchanged in all of these patients. Tm, however, was already rather short before PTCA and remained so thereafter, resulting in MFR, values of 1.2, 0.9, and 1.4, respectively. This strongly suggests that between the time of acceptance and actual performance of the PTCA, the functional significance of the stenosis had diminished in these patients, and the necessity of these three PTCA.s can be considered doubtful. In the remaining three patients without reversal of exercise test result (patients 22, 33, and 39), PTCA was not successful and a positive exercise test remained positive. In all of these patients, Tm, remained almost unchanged, resulting in MFR, values of 1.0, 1.3, and 0.8, respectively. In only one patient (patient 35), a previously positive exercise test became negative after PTCA despite absence of decrease of Tm, over the myocardium of the dilated artery. No explanation is available in this case.
In Table 3 it can be seen that MFR, of more or less than 1.6, determined from studies immediately before and 15 minutes after PTCA, is highly predictive for functional success or failure as indicated by exercise testing (correct classification in 94%, $\chi^2=21.9, p<0.001$). If, on the contrary, on-line evaluation of the PTCA result was based on angiographic criteria or on measurement of trans-stenotic pressure gradient, the relation with exercise testing result was significantly worse (correct classification of 66% and 74%, respectively; $\chi^2=1.20$ and 2.64, respectively).

**Comparison of $T_{mn}$ Belonging to Apparently Normal Arteries and to Stenotic Arteries Before and After Successful Percutaneous Transluminal Coronary Angioplasty**

In this population of 40 patients with one-vessel disease, 64 values of $T_{mn}$ of apparently normal coronary arteries could be obtained. The 16 “missing values” are due to the reasons mentioned in one of the former sections ($n=9$), to presence of a rudimentary LCA ($n=2$), and to presence of wall irregularities of more than 20% as judged by an independent reviewer ($n=5$).

A definite range of time could be distinguished for $T_{mn}$ at maximal hyperemia corresponding with these apparently normal vessels (Figure 4). These values were compared with measurements of $T_{mn}$ of the affected artery before and after PTCA. Before PTCA, $T_{mn}$ is long and covers a wide range, as expected. After successful PTCA, $T_{mn}$ returns to the “normal” range. Some overlap between normal and affected arteries is present in case of the RCA.

In 25 of 30 patients in whom a stenotic LAD or LCx artery was dilated, $T_{mn}$ of the normal branch of the LCA could be compared before and after PTCA. MFR, for these control vessels was 1.0±0.2. 

Finally, the ratio of $T_{mn}$ of the diseased branch of the LCA to $T_{mn}$ of the normal branch of the LCA was calculated in this group. This ratio is not dependent on pressure and decreased from 1.9±0.3 before PTCA to 0.9±0.3 after PTCA.

**Discussion**

The videodensitometric approach for flow measurement as used in this clinical study was very similar to the method previously validated in animal experiments. In that validation study, it was shown that comparison of maximal myocardial flow between situations with different degrees of stenosis can be accurately performed by calculating ratios of $T_{mn}$.

In this clinical study, after extensive breath-holding training and use of synchronous radiographic pulses, image quality was so good that passage of the contrast agent through the myocardium could be studied long enough to allow reliable determination of $T_{mn}$ in about 90% of the patients. Reproducibility of $T_{mn}$ in paired studies under identical circumstances was excellent. Therefore, it can be concluded that this videodensitometric approach is applicable in clinical practice, at least in stable patients, and the first aim of this study has been achieved by that.

A difference between the previously mentioned experimental study and this clinical study is the different method used to induce maximal hyperemia. In the validation study, continuous infusion of dipyridamole was applied for this purpose. For practical reasons, such as short time of activity, intracoronary papaverine was used in the clinical study. It has been shown by former investigators that from approximately 25 to 60 seconds after intracoronary administration of 8-12 mg papaverine, maximal dilation of the myocardial vascular bed is achieved. Therefore, we assumed that during acquisition of the time–density curve, the vascular volume remained constant and flow was not influenced by contrast injection.

In this clinical study, exercise testing 24–48 hours before and 7–10 days after the PTCA was the method of choice for noninvasive functional evaluation of the result of the procedure. Because in all patients the combination of anginal complaints of NYHA class III, a positive exercise test, and proved one-vessel disease had been present less than 6 weeks before the PTCA, exercise testing can discriminate accurately between presence or absence of (residual) ischemia in this particular group of patients. Moreover, because of the presence of just one-vessel disease, it is justified to assume that ischemia, if present at exercise testing, is actually caused by the affected artery. Therefore, exercise test results could be used in this study as the gold standard for PTCA success. MFR, angiographic result, and final trans-stenotic pressure gradient were correlated to this gold standard.

Because exercise testing after the PTCA was performed several days after the flow measurements, changes in coronary anatomy and physiology could have occurred in the meantime. The 94% agreement between MFR, and exercise testing seems to be very high in this respect. If, however, PTCA results in this study were judged by classic anatomical criteria, a previously positive exercise test remained positive despite an angiographically successful intervention in three patients (patients 22, 33, and 39), leading to a

### Table 2. Area Stenosis Severity (Determined by Quantitative Densitometry), Trans-stenotic Pressure Gradient, Mean Transit Time at Maximal Hyperemia, and Exercise Time Before and After Percutaneous Transluminal Coronary Angioplasty

<table>
<thead>
<tr>
<th></th>
<th>Pre-PTCA</th>
<th>Post-PTCA</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area stenosis (%)</td>
<td>83±10</td>
<td>42±18</td>
<td>38</td>
</tr>
<tr>
<td>Trans-stenotic $\Delta$ P (mm Hg)</td>
<td>45±10</td>
<td>14±9</td>
<td>27</td>
</tr>
<tr>
<td>$T_{mn}$ at maximal hyperemia (sec)</td>
<td>6.9±2.1</td>
<td>3.4±1.3</td>
<td>33</td>
</tr>
<tr>
<td>Exercise time (sec)</td>
<td>350±191</td>
<td>520±76</td>
<td>38</td>
</tr>
</tbody>
</table>

**PTCA**, percutaneous transluminal coronary angioplasty; $\Delta$ P, trans-stenotic pressure gradient; $T_{mn}$, mean transit time at maximal hyperemia.

Values are given as mean±SD.
Figure 2. Images of left anterior descending coronary artery of a 57-year-old man before percutaneous transluminal coronary angioplasty (PTCA) (left) and after PTCA (right) and corresponding background-corrected time–density curves. Functional effect of the stenosis is pronounced, and these images enable clear detection of the perfusion defect. After PTCA, coronary anatomy has moderately improved, but a dissection is present at the site of balloon inflation. However, rapid and complete filling of the apex occurs this time. Time–density curves, derived from a region of interest over the apex (circle), are presented in lower part of figure. Mean transit time was 8.7 seconds before and 2.9 seconds after PTCA, corresponding with an increase in maximal flow of 300%. Arrows indicate moment of start of contrast injection.
The approach used in this study for calculation of flow is only valid in situations of maximal vasodilation to guarantee constant vascular volume. It should be emphasized that no information about resting flow can be obtained, and therefore no coronary flow reserve can be calculated. This approach, however, offers the possibility of comparing maximal myocardial flow before and after an appropriate intervention, such as angioplasty in this study, but possibly also long-lasting lipid-lowering therapy. Unlike coronary flow reserve, this MFR is independent of resting flow, which in turn is influenced by heart rate, left ventricular hypertrophy, previous infarction, prolonged ischemia, and the PTCA procedure itself. At maximal vasodilation, flow is only dependent on pressure, which can easily be measured and corrected for as was done in this study. In fact, MFR, as defined in this study can be considered as the improvement of relative coronary flow reserve, as recently defined by Gould et al. It should be realized in this context that anginal complaints in the majority of patients are due to inadequate maximal flow. Therefore, increase in maximal flow is a clinically relevant parameter and is expected to reflect improved exercise tolerance. In the practice of interventional cardiology, parameters for on-line evaluation of the result of the intervention are essential. Because $T_{mn}$ can be calculated within minutes after image acquisition and decrease of this value correlates well with the functional result of the PTCA, determination of MFR, can be used for this purpose.

Despite their limitations, some other methods have been used for on-line evaluation of the PTCA, such as assessment of angiographic stenosis severity or measurement of trans-stenotic pressure gradients. Therefore, we also investigated the relation between these on-line parameters and exercise test results 7–10 days after the procedure. Both parameters were significantly less reliable than the use of MFR,. In most former videodensitometric approaches, flow has been represented by contrast density divided by a certain time parameter such as appearance time. Because contrast density, expressed in arbitrary units, is dependent on many factors not related to flow and differs more than 1,000% among different patients, it has been regarded as impossible to indicate normal values in these studies. Because in the present study merely a time parameter is used as an index of flow, it makes sense to determine whether a range of normal values for $T_{mn}$ at maximal hyperemia exists. Most of the patients in this study provided two apparently normal coronary arteries, and a definite range for $T_{mn}$ of these normal vessels during maximal hyperemia could be distinguished. Moreover, after successful PTCA according to exercise testing, $T_{mn}$ returned to the normal range except in one case (patient 35) (Figure 4).

In previous studies using digital radiography for evaluation of coronary flow reserve improvement after PTCA, it was observed that coronary flow reserve immediately after the intervention did not return to normal. It has been hypothesized that this phenomenon could be caused by the fact that resting flow after PTCA would still be elevated due to prolonged ischemia and to the procedure itself. Our results are in favor of this explanation because $T_{mn}$ at maximal flow in the dilated vessel was lower than in the normal vessel.

**Table 3. Relations Among Maximal Flow Ratio After Correction for Pressure Changes, Angiographic Success, and Trans-stenotic Pressure Gradient as Measured 5 Minutes After the Last Balloon Inflation and Presence or Absence of Reversal of Exercise Test Result**

| ET   | MFR,  | MFR,  | Angioplasty | Angioplasty | ET | $\Delta P \leq 15$ | $\Delta P > 15$
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>&gt;1.6</td>
<td>&lt;1.6</td>
<td>successful</td>
<td>unsuccessful</td>
<td></td>
<td>mm Hg</td>
<td>mm Hg</td>
</tr>
<tr>
<td>+→→</td>
<td>25</td>
<td>1</td>
<td>21</td>
<td>9</td>
<td>+→</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>+→→</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>+→</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

ET, exercise test; +, positive ET; –, negative ET; MFR, maximal flow ratio after correction for pressure changes; $\Delta P$, trans-stenotic pressure gradient as measured 5 minutes after the last balloon inflation.

Angiographic success was defined as $\geq 20\%$ area stenosis reduction and residual area stenosis $<50\%$, calculated by quantitative coronary arteriography.
not longer than $T_{mn}$ at maximal flow in apparently normal coronary arteries. Furthermore, in those 30 patients with one diseased and one normal branch of the LCA, the ratio of $T_{mn}$ diseased artery to $T_{mn}$ normal artery decreased from 1.9±0.3 before PTCA to 0.9±0.3 after PTCA, which gives further support to that explanation. This last observation also suggests that the ratio of $T_{mn}$ of a stenotic to $T_{mn}$ of a normal branch can help to assess the functional significance of the stenosis. Finally, it was observed in this group that the MFR, of normal control vessels was 1.0±0.2, which argues for the intrinsic correctness of this method.

**Limitations**

For the time being, the approach suggested in this study provides only an index for the maximal flow achievable for a certain vascular bed before and after an intervention. Although a certain range of normal values could be distinguished in this special group of patients, it is still too early to judge its value for diagnostic catheterization. More data about normal coronary arteries are necessary. It should be noted in this context that inadequate MFR can mean either that the PTCA failed or that the situation before the PTCA was already (nearly) normal and that PTCA had not been necessary, as was probably the case in three of our patients (patients 6, 7, and 25). This ambiguity between an unsuccessful intervention and an anatomically successful intervention in a distribution without baseline flow abnormality could restrict the clinical usefulness of this approach. As can be observed in Figure 4, however, knowledge of normal values for $T_{mn}$ during maximal hyperemia can help to discriminate between these possibilities. In case of the LAD and LCx, an excellent partition between pathological and normal values is present. In case of the RCA, there is some overlap. In case of a stenosis in one branch of the LCA, the ratio of $T_{mn}$ diseased branch to $T_{mn}$ normal branch can also be helpful in this respect. A further limitation is that acquisition of well- interpretable time-density curves is highly dependent on sufficient image quality. In this study, adequate image acquisition before as well as after PTCA was possible in approximately 90% of patients. In emergency situations, there is no chance for previous breath-holding training. In that case, motion artifacts serious enough to interfere with reliable image processing will probably be present more often. The study population was a selected homogeneous group of patients with one-vessel disease. Although from a theoretical point of view there is no reason why this approach would not be valid in multivessel disease, caution is warranted in extrapolation of these results to other groups of patients. It is well known that a number of other methods for blood flow evaluation, although physiologically valid and validated in one-vessel disease, are difficult to use in multivessel disease and more complex pathological states. The reason to confine this study to patients with one-vessel disease was to be sure of an unambiguous functional test to determine success or failure of the intervention. As explained above, exercise testing could be used for this purpose in this particular group of patients. On the contrary, in multivessel disease, a positive exercise test is hard to relate to a particular stenosis even if combined with thallium scintigraphy.

Another factor that may restrict the clinical value of the MFR is the presence of collateral circulation, which is excluded in this study. In that case, transport of the contrast agent injected into the vessel itself can be slowed down by collateral blood supply. This also holds true for patients with bypass grafts in whom the native vessel is not completely occluded.

Next, it is necessary that overprojection of the myocardium supplied by the analyzed artery can be avoided, although its thickness in the chosen projection should be large enough to ensure sufficient staining after contrast injection. This can be hard to
obtain for diagonal and intermediate branches of the LAD artery and for posterolateral branches of the LCx artery.

Finally, it should be remarked that in case of serial lesions within one vessel, $T_{\text{max}}$ at maximal hyperemia for the supplied vascular bed tells something about the summed effect of all abnormalities and nothing about the significance of the individual lesions. Despite these limitations, this study shows that comparison of maximal flow before and after PTCA is possible in at least a large part of patients and enables reliable, on-line evaluation of the functional improvement achieved by the intervention.

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KEY WORDS • digital radiography • myocardial perfusion • coronary blood flow • mean transit time
Concept of maximal flow ratio for immediate evaluation of percutaneous transluminal coronary angioplasty result by videodensitometry.

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