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Validation of videodensitometric myocardial perfusion assessment

Research Article

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Abstract: Introduction. Invasive methods for assessment of coronary microcirculatory function are time- and instrumentation-consuming tools. Recently, novel computer-assisted videodensitometric methods have been demonstrated to provide quantitative information on myocardial (re)perfusion. The aim of the present prospective study was to evaluate the accuracy of videodensitometry-derived perfusion parameters in patients with stable angina undergoing elective coronary angiography. Methods. The study comprised 13 patients with borderline epicardial coronary artery stenosis (40-70%). Coronary flow reserve and index of microcirculatory resistance were measured by using an intracoronary pressure and temperature sensor-tipped guidewire. A videodensitometric quantitative parameter of myocardial perfusion was calculated by the ratio of maximal density (G_{max}) and the time to reach maximum density (T_{max}) of the time–density curves in regions of interest on conventional coronary angiograms. Myocardium perfusion reserve was calculated as a ratio of hyperemic and baseline G_{max}/T_{max}. Results. At hyperemia a significant increase in G_{max}/T_{max}could be observed ($p < 0.0001$). Significant correlations were found between myocardium perfusion reserve and coronary flow reserve ($r = 0.82$, $p = 0.0008$) and between hyperemic G_{max}/T_{max} and hyperemic index of microcirculatory resistance ($r = -0.72$, $p = 0.0058$). Conclusions. Videodensitometric G_{max}/T_{max} assessment seems to be a promising method to assess the myocardial microcirculatory state.

Keywords: *Fractional flow reserve • Coronary flow reserve • Index of microcirculatory resistance • Videodensitometry*

1. Introduction

Traditionally, the diagnosis and treatment of myocardial ischemia has focused on flow-limiting stenosis of the epicardial arteries. However, over the past two decades it has become evident that coronary microvascular dysfunction also plays a significant role in a number of disease states. Although in some instances merely an epiphenomenon, in others it has proven to be a powerful indicator of adverse outcome and a potential therapeutic target [1]. Owing to the growing awareness of the importance of coronary microvascular dysfunction, a number of noninvasive and invasive techniques have been developed to provide functional assessment of the coronary microcirculation [2].

The time-honored invasive method for measurement of microvascular function in the catheter laboratory is coronary flow reserve (CFR), representing the magnitude of the increase of coronary flow that can be achieved at maximum hyperemia [3]. The index of microcirculatory resistance (IMR), a novel invasive method for assessing the status of coronary microcirculation is independent of epicardial artery stenosis [4,5]. It is derived from the distal hyperemic mean coronary pressure and hyperemic mean transit time, and shows superior reproducibility and less hemodynamic dependence then

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CFR [6]. The above techniques however have proven to be too time-, instrumentation- and expense-consuming for everyday use in the catheter laboratory.

Simple angiographic methods such as myocardial blush grade [7] and TIMI (thrombolysis in myocardial infarction) myocardial perfusion grade [8] have also been developed for direct angiographic assessment of coronary microvascular dysfunction in acute myocardial infarction. However, these methods are limited inherently by their subjective nature and categorical values. Recently, novel computer-assisted videodensitometric methods have been introduced for the quantitative assessment of myocardial (re)perfusion in acute myocardial infarction [9-11]. Alongside others, we have quantified myocardial perfusion by the ratio of maximal density (G_{max}) and the time to reach maximal density (T_{max}) of the time–density curves in regions of interest on X-ray coronary angiograms [9,12]. Sensitized by a vessel masking technique, it supplies easily obtainable, objective and quantitative information on short-term outcomes in acute myocardial infarction [12,13].

The aim of the present prospective study was to evaluate the correlations between videodensitometry-derived myocardial perfusion parameters and thermodilution-derived CFR and IMR in patients with stable angina pectoris.

2. Materials and methods

2.1. Patient population

The present study comprised thirteen patients with borderline coronary artery stenosis (40% to 70% diameter stenosis by visual assessment). All of them were admitted for elective coronarography after a positive stress test showing inducible ischemia. Borderline stenosis served as an indication for fractional flow reserve (FFR) measurement in all cases for functional evaluation of stenosis. For the main risk factors of the patients, see Table 1. Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a prior approval by the institution's Human Research Committee.

Table 1. Clinical and demographic parameters of patients

	Patients
Sample size (n)	13
Male gender (%)	8 (62)
Age (years)	60.1 ± 8.7
Diabetes mellitus (%)	4 (31)
Hypercholesterolemia (%)	9 (70)
Hypertension (%)	9 (70)
Smoking (%)	4 (31)

2.2. Measurement of CFR, IMR and FFR

CFR [14], IMR [4], and FFR [14] were measured according to methods described previously. Briefly, after conventional diagnostic coronary angiography, a 6F coronary guiding catheter was used to engage the coronary artery. Heparin (5000 IU) and intracoronary nitroglycerin (200 µg) were administered. After equalization, an intracoronary pressure and temperature sensor-tipped guide wire (Certus-pressure wire, Radi Medical Systems, Uppsala, Sweden) was inserted into the target coronary artery past the borderline stenosis and used to record thermodilution curves and distal coronary pressure. Thermodilution curves were obtained in triplicate from a hand-held, 3 ml brisk (<0.25 s) injection of room temperature saline at baseline and at maximal hyperemia. Mean transit time at baseline and maximal hyperemia were derived from thermodilution curves. Simultaneous measurements of mean aortic pressure (P_a, by guiding catheter) and mean distal coronary pressure (P_d, by pressure wire) were also made in resting and maximal hyperemic states. Maximal hyperemia was achieved by a 140 µg/kg/min intravenous infusion of adenosine. CFR was calculated from the ratio of baseline to hyperemic mean transit time. IMR was calculated from the ratio of the mean distal coronary pressure at maximal hyperemia divided by the inverse of the hyperemic mean transit time. FFR was calculated by the ratio of P_d/P_a at maximal hyperemia.

2.3. Myocardium selective videodensitometry

Angiograms for densitometric analysis at baseline and maximal hyperemia were recorded on an Innova 2000™ system (GE Healthcare, Chalfont St. Giles, Buckinghamshire, United Kingdom) in a way that phase-matched digital subtraction angiography could be performed on them. This required the following criteria: (1) motion of patient and table should be avoided; (2) patient should hold breath for the time of recording; (3) one contrast-free heart cycle should be recorded before injection of contrast material; (4) field of view is to be set to contain the whole supplied area of the vessel of interest. Standardized projections were chosen to minimize the superimposition of coronary arteries, veins and the aorta with the myocardium of interest. The left anterior

descending coronary artery and left circumflex coronary artery were recorded in lateral, while the right coronary artery was recorded in a left anterior oblique 15° projection. A constant quantity of nonionic contrast material (6 ml) was injected for all angiograms by an automatic injector (Acist Medical Systems, Bracco, Milan) at a rate of 3 ml/sec in order to standardize the density of angiograms.

Time-density curves were recorded in polygonal regions of interest for the relevant coronary artery, as selected by a cardiologist experienced in the analysis of coronary angiograms. Phase-matched digital subtraction angiography images were used with standard image acquisition parameters. Visible vessels were automatically masked from the regions of measurements to eliminate their effect in the densitometric signal [13]. Time-density curves were analyzed to obtain G_{max}/T_{max} values, as described previously, at baseline as at hyperemia [12]. Maximal hyperemia, as per CFR, IMR and FFR protocols, was achieved by a 140 μg/kg/min intravenous infusion of adenosine. Two angiograms were taken with identical parameters in both baseline and hyperemic state, and videodensitometric myocardium perfusion reserve was calculated from the ratio of hyperemic to baseline G_{max}/T_{max}.

3. Statistical methods

Data are reported as means ± standard deviation. Data analyses were performed using the statistical software Medcalc (Medcalc 11.3, Mariakerke, Belgium). A paired sample *t*-test was used to compare baseline and hyperemic values of G_{max}/T_{max}. Correlations between thermodilution-derived CFR and videodensitometric myocardium perfusion reserve, hyperemic IMR and hyperemic $G_{max}/T_{max,}$ as well as other corresponding datasets were assessed by Pearson's correlation coefficients. A $p < 0.05$ was considered to be statistically significant.

4. Results

4.1. Relationship between FFR and G_{max}/T_{max}

Of the 13 patients enrolled in the study videodensitometric and pressure wire measurements were conducted in 13 coronary arteries: 10 left anterior descending, 2 right coronary arteries and 1 circumflex artery with borderline coronary angiographic stenosis. The mean degree of diametric stenosis by visual assessment was 55 ± 12 %. The corresponding mean FFR was found to be 0.86 ± 0.12 (Table 2). Of the 13 coronary arteries, 5 (all left anterior descending coronary arteries) showed a FFR <0.8 – in these patients successful stenting was performed. Measurements were not repeated after stenting. FFR showed no correlation with hyperemic G_{max}/T_{max} ($r = -0.14$, $p = 0.66$) or videodensitometric myocardium perfusion reserve ($r = -0.37$, $p = 0.22$).

Table 2. Parameters of coronary microvascular function and epicardial flow

	At baseline	At hyperemia
Blood pressure, systolic (mm Hg)	125 ± 18	108 ± 20
Blood pressure, diastolic (mm Hg)	64 ± 8	52 ± 16
Mean transit time (sec)	0.89 ± 0.44	0.29 ± 0.18
Index of microcirculatory resistance (U)	78.06 ± 44.03	18.86 ± 11.00
G_{max}/T_{max} (1/sec)	3.76 ± 1.28	5.77 ± 1.68
Fractional flow reserve	0.86 ± 0.12	
Coronary flow reserve	3.53 ± 1.84	
Myocardium perfusion reserve	1.60± 0.42	

4.2. Relationship between mean transit time and G_{max}/T_{max}.

At baseline conditions mean transit time was 0.89 ± 0.44 sec, and G_{max}/T_{max} was 3.76 ± 1.28 /sec (Table 2). During maximal hyperemia, mean transit time decreased to 0.29±0.18 sec and G_{max}/T_{max} increased to 5.77 ± 1.68 / sec (Table 2). The improvement of G_{max}/T_{max} at hyperemia proved to be significant compared to baseline ($p < 0.0001$) (Figure 1). A significant correlation could be demonstrated between baseline mean transit time and baseline G_{max}/T_{max} ($r = -0.70$ $p = 0.0076$), and a trend could be demonstrated between hyperemic mean transit time and hyperemic G_{max}/T_{max} ($r = -0.53$, $p = 0.0628$,).

4.3. Relationship between IMR and G_{max}/T_{max}

Baseline and hyperemic IMRs were found to be 78.06 ± 44.03 U and 18.86 ± 11.00 U, respectively (Table 2). A significant correlation was found between baseline IMR and baseline G_{max}/T_{max} ($r = -0.71$, $p = 0.0069$), as well as between hyperemic IMR and hyperemic G_{max}/T_{max} ($r = -0.72$, $p = 0.0058$) (Figure 2).

4.4. Relationship between CFR and G_{max}/T_{max}

The mean thermodilution-derived CFR was 3.53 ± 1.84 and the videodensitometric myocardium perfusion

Figure 1. Left sided coronary angiographic frames taken from the same patient at baseline and at maximal hyperemia achieved by intravenous adenosine infusion. Dashed white polygons are regions of interest. Corresponding time-density curves (gray) and frequency filtered curves (black) shown on the right are used to obtain Gmax/Tmax values descriptive of myocardial perfusion. At maximal hyperemia a reduction of Tmax and an increase in Gmax could be appreciated leading to rise in G_{max}/T_{max} value.

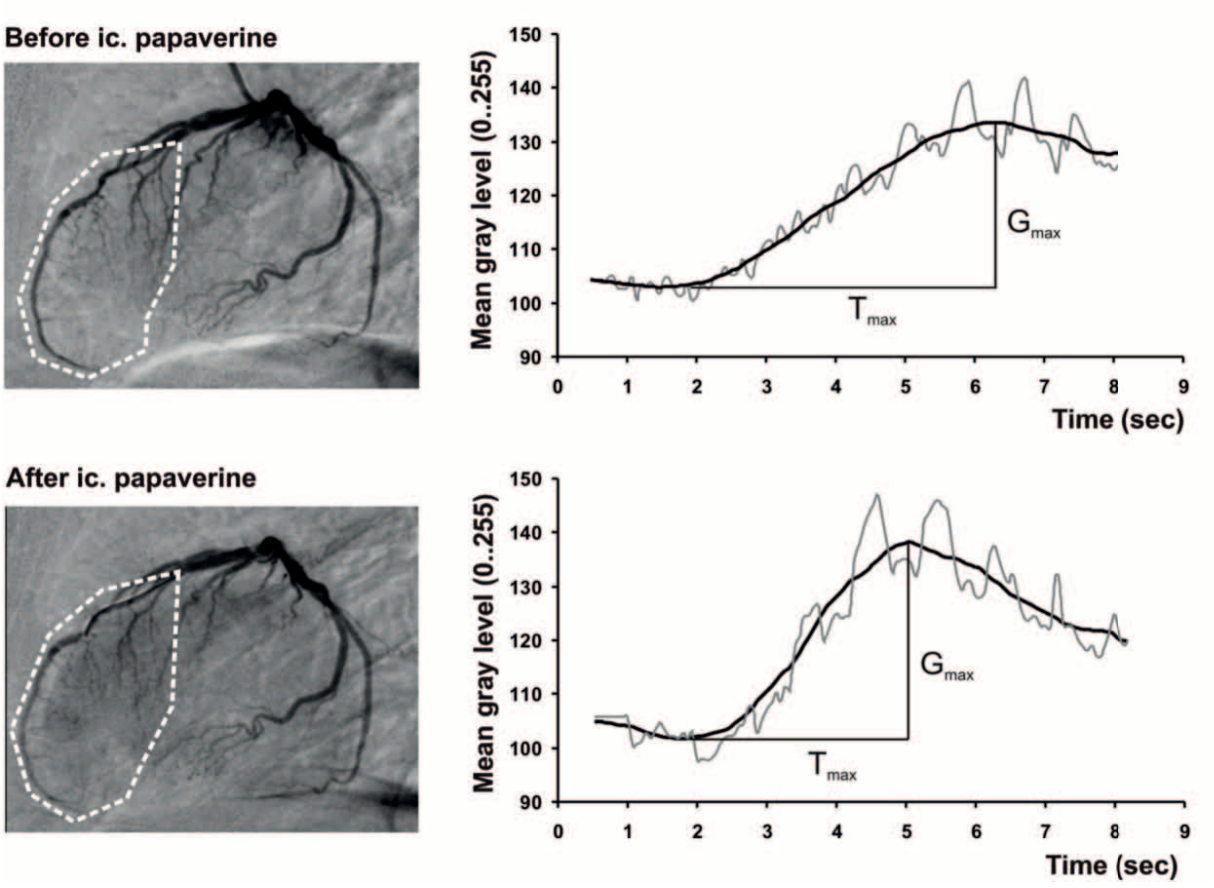


Figure 2. Correlation between hyperemic Gmax/Tmax and hyperemic index of microcirculatory resistance. Dotted lines represent 95% confidence intervals.

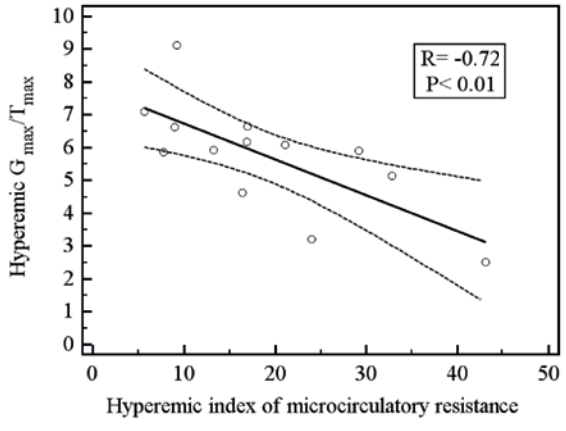
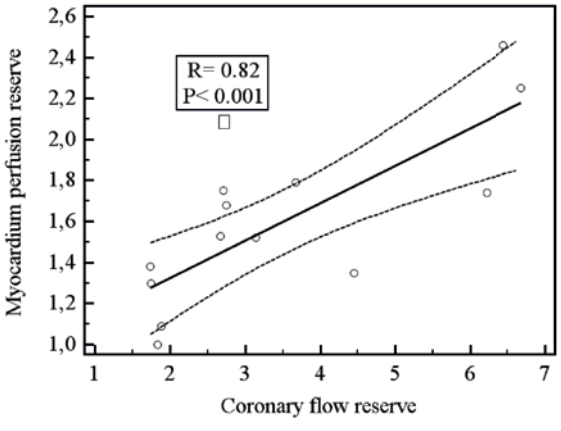


Figure 3. Correlation between thermodilution-derived coronary flow reserve and videodensitometric myocardium perfusion reserve. Dotted lines represent 95% confidence intervals.



reserve was 1.60 ± 0.42 (Table 2). A significant correlation was found between videodensitometric myocardium perfusion reserve and thermodilution-derived CFR (r =0.82, p =0.0008) (Figure 3).

5. Discussion

In the present study significant correlations could be demonstrated between videodensitometric myocardium perfusion reserve and thermodilution-derived CFR, as well as between hyperemic videodensitometric G_{max}/T_{max} and hyperemic IMR in stable angina patients. These findings suggest that computer-assisted myocardium selective videodensitometry may be applied in the cardiac catheterization laboratory as a means of interrogating and quantifying the microcirculatory function of coronary arteries.

5.1. The need for assessment of coronary microvascular dysfunction in the catheterization laboratory and current available techniques

Despite the rapid evolvement of noninvasive techniques for investigating coronary microcirculatory disorders, such as as contrast echocardiography [15], cardiac magnetic resonance imaging [16], multislice computed tomography [16], myocardial perfusion scintigraphy [17], positron emission tomography [18] and combined techniques [19], the quantitative assessment of the coronary microcirculation in the catheterization laboratory remains desirable. The reasons for this are as follows: (1) angiography remains the gold standard for ruling out epicardial stenosis [20]; (2) a large proportion of patients still present without adequately interpretable prior functional noninvasive testing [21]; (3) reperfusion therapy in acute myocardial infarction has shifted to the catheterization laboratory, where the immediate evaluation of therapeutic success and further outcomes is an advantage [11].

Current available techniques include invasive measurement by CFR and IMR, which can prove to be time-, expense- and instrumentation-consuming. Angiographic visual assessment by myocardial blush grade and TIMI myocardial perfusion grade on the other hand is only routinely applied to study the microcirculation during reperfusion in acute myocardial infarction. Myocardium selective videodensitometric assessment of perfusion in a similar fashion to the aforementioned methods utilizes the indicator dilution principle where the input function is an intracoronary injection of X-ray contrast and the output observation is opacification of the myocardium supplied [22]. Perfusion is numerically assessed by the ratio of maximal density and the time to reach maximal density of the time-density curves in regions of interest on X-ray coronary angiograms [9,12]. This method allows for objective and quantitative assessment, is cost-effective and has no need for further coronary instrumentation. It could be interpretable in specific non-acute coronary syndrome settings as well with more sensitivity and specificity than the myocardial blush grade and TIMI myocardial perfusion grade [23].

5.2. Relationship between G_{max}/T_{max} and CFR

CFR is defined as the ratio of peak hyperemic to baseline flow. A drop in CFR may indicate a loss of response to hyperemic stimuli secondary to either coronary microvascular dysfunction in the absence of significant coronary artery disease, or a decreased resting microcirculatory resistance as a consequence of a flow-limiting epicardial coronary artery stenosis. At hyperemia, a rise in epicardial coronary flow is accompanied by an increase in myocardial perfusion, which theoretically can be observed as a rise in (G_{max}/T_{max}) compared to baseline. This theory was justified in our experiment as we found a significant elevation of hyperemic G_{max}/T_{max} values compared to baseline G_{max}/T_{max} in all patients (Figure 1). The ratio of hyperemic to resting perfusion (G_{max}/T_{max}) could be interpreted as the videodensitometric myocardium perfusion reserve, similar to the concept of CFR creating an index representing the state of the microcirculation. Underlining this concept, others before us found a decline of videodensitometric myocardium perfusion reserve in hypertensive patients known to suffer from coronary microvascular dysfunction compared to controls. However they did not attempt to study a possible correlation between myocardium perfusion reserve and other validated methods [24]. In the current publication we go further by reporting a significant correlation between the validated method of thermodilution-derived CFR and myocardium perfusion reserve, suggesting comparable clinical benefits (Figure 3).

5.3. Relationship between G_{max}/T_{max} and IMR

Recently IMR, a novel marker of coronary microvascular function, has been introduced, showing superior reproducibility and less hemodynamic dependence than CFR [6]. It is derived from the directly-measured distal coronary pressure and mean transit time at hyperemia, and is validated in animal models to correlate with true microvascular resistance [4]. Theoretically, coronary microvascular dysfunction detected by IMR as rise of microvascular resistance at maximum hyperemia can also

be assessed by hyperemic G_{max}/T_{max} as an impediment of contrast penetration into the myocardium leading to a flattened rise slope of the hyperemic time-density curve and decreased values of $G_{max}/T_{max.}$ Indeed, in the current study we report a significant correlation between hyperemic G_{max}/T_{max} and hyperemic IMR (Figure 2).

5.4. Possible independence of G_{max}/T_{max} from epicardial stenosis

Severe epicardial stenosis leads to a drop in distal pressure and flow (observed as a rise in mean transit time) distal to the lesion. In the current study population with borderline lesions this phenomenon is prominent at hyperemia only [25]. The rise in hyperemic mean transit time will lower the CFR value independently and additionally to the underlying coronary microvascular dysfunction obscuring data interpretation [22]. In the case of hyperemic IMR (calculated as hyperemic distal pressure x hyperemic mean transit time) the drop in distal pressure caused by epicardial stenosis is hypothesized to counterbalance the rise of mean transit time, leaving IMR unchanged [5]. In this study, as expected, we found no significant correlations between FFR, solely dependent on epicardial stenosis severity, and any of the videodensitometry-derived parameters representing myocardial perfusion. A significant correlation observed between mean transit time and G_{max}/T_{max} at baseline was found to be a non-significant trend at hyperemia, whereas the significant correlation observed at baseline between IMR and G_{max}/T_{max} was also significant at hyperemia. The correlation of hyperemic G_{max}/T_{max} to hyperemic IMR, rather than to hyperemic mean transit time, in this special patient subset suggests that hyperemic G_{max}/T_{max} like IMR may be unaffected by epicardial stenosis. This does not contradict previous findings of correlation between videodensitometric myocardium perfusion reserve and CFR which in this specific population seems to be mainly driven by a significant correlation between baseline G_{max}/T_{max} and mean transit time. To clarify this matter further, prospective investigations are warranted in larger groups of patients with clearly significant epicardial disease affecting baseline flow, as well as in groups entirely free of epicardial coronary artery disease.

5.5. Limitations

Computer-assisted myocardium selective videodensitometric perfusion assessment has been under constant improvement as technological progress permitted. Further investigations however are needed to solve the remaining problem of static region of interest areas. Large areas can result in variable results due to inhomogeneous distribution of contrast material. On the other hand, small static area selection is difficult for the whole image sequence because of the cyclic motion of the myocardium caused by the heart beating. A possible improvement to tackle this problem and improve precision could be motion tracking of myocardial regions. All procedures were done by a single operator using automatic contrast injector using a standardized flow rate and volume. Timing of injection however was not synchronized to the phase of the heart cycle, which may contribute to the limited level of correlation in our results [26]. This problem can be eliminated by the use of an electrocardiogram triggered injector. Further inherent limitations include current commercial unavailability of the method which renders large scale clinical use difficult.

6. Conclusions

Videodensitometric G_{max}/T_{max} measurement seems to be a promising method to assess the myocardial microcirculatory state in patients with stable angina referred for coronary angiography. It may prove to be a low-cost, easily obtainable alternative method to the thermodilution-derived CFR and IMR measurements. Additional studies are warranted for further validation of this method and to study possible independence from epicardial stenosis severity.

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