Myocardium selective densitometric perfusion assessment after acute myocardial infarction☆

Tamás Ungi, Imre Ungi, Zsuzsanna Jónás, Viktor Sas, András Lassó, Zsolt Zimmermann, Tamás Forster, András Palkó, Attila Nemes,⁎

a Department of Radiology, Medical Faculty, Albert Szent-Györgyi Clinical Centre, University of Szeged, Szeged, Hungary
b Second Department of Medicine and Cardiology Centre, Medical Faculty, Albert Szent-Györgyi Clinical Centre, University of Szeged, Szeged, Hungary
c General Electric Healthcare, Budaörs, Hungary

Received 11 August 2008; received in revised form 14 October 2008; accepted 23 October 2008

Abstract Background: Myocardial perfusion is an important prognostic factor after recanalisation in acute myocardial infarction patients. We present a computerized, densitometric measurement method to assess myocardial perfusion on phase-matched digitally subtracted coronary angiograms.

Methods and materials: Quantitative myocardial perfusion was assessed by the $G_{\text{max}}/T_{\text{max}}$ parameter of the time–density curves (TDCs) in infarct-related myocardial regions on X-ray coronary angiograms. Arteries were masked out from regions of measurement. This novel method has been compared with enzymatic infarct size, ST-segment resolution, and ejection fraction after successful revascularization of 62 patients with acute myocardial infarction.

Results: Significant correlations were found between $G_{\text{max}}/T_{\text{max}}$ and enzymatic infarct size ($R=-0.445, P<.001$), ST-segment resolution ($R=0.364, P=.004$), and ejection fraction ($R=0.278, P=.029$). Bland and Altman plot of $G_{\text{max}}/T_{\text{max}}$ reveals good interobserver agreement.

Conclusions: $G_{\text{max}}/T_{\text{max}}$ of the TDC measured in the infarct-related myocardial area is a reliable parameter to assess clinical indicators of myocardial reperfusion. Therefore, results suggest that it could be used to immediately assess the success of recanalisation at the tissue perfusion level during coronary intervention, and as an objective end point in clinical trials of new interventional devices and drugs.

© 2009 Elsevier Inc. All rights reserved.

Keywords: Acute myocardial infarction; Cineangiography; Myocardial viability

1. Introduction

The primary objective of treatment for acute myocardial infarction (AMI) is to restore normal blood flow in the epicardial infarct-related artery and to obtain reperfusion of the myocardium at risk. Assessment of myocardial perfusion on coronary angiograms is performed by visual estimation in the current clinical practice. Two visual grading scales proved to be informative in assessing the viability of the infarct-related myocardium: Myocardial Blush Grade [1] and TIMI Myocardial Perfusion Grade [2]. Both grades have four

☆ This study was partially supported by the Regional Cooperative Research Center of Life and Material Sciences of the University of Szeged together with industrial partner General Electric Healthcare Hungary.

⁎ Corresponding author. Medical Faculty, Second Department of Medicine and Cardiology Centre, University of Szeged, Korányi fasor 6, P.O. Box 427, H-6720 Szeged, Hungary. Tel.: +36 62 545220; fax: +36 62 544568.

E-mail address: nemes@in2nd.szote.u-szeged.hu (A. Nemes).
levels: 0 and 1 representing no or minimal contrast signal in the infarct related myocardium and 2 and 3 representing impaired and normal states. The interobserver and intraobserver variabilities associated with subjective angiographic assessments are limitations of these visual grades.

Methods for computerized videodensitometric analysis of digital subtraction coronary angiograms have been reported to be under study for a long time both in animal models and in human subjects. The primary goal of these studies was to develop an operator-independent and quantitative way of myocardial perfusion assessment based on X-ray coronary angiograms, which is the only imaging modality widely available during coronary interventions. Pijls et al. [3] demonstrated in a canine model that mean transit time calculated by videodensitometry can be used to assess myocardial perfusion. Haude et al. [4] also proved an excellent correlation of a similar method with myocardial perfusion using colored microspheres. More recent reports proved that even volumetric blood flow measurements are feasible by densitometry [5,6].

Despite the promising results, none of these methods has yet been shifted to the clinical practice or became a standard end point of clinical trials in place of the four-graded visual assessment. Clinical environment, especially in case of AMI patients, does not allow the direct application of methods developed for experimental studies. Korosoglou et al. [7] recently published the results of a study of AMI patients proving that the computerized method for myocardial perfusion assessment is clinically feasible. Their results suggest that this low-cost measurement provides incremental prognostic value compared to the semi-quantitative visual assessment. However, the software used is not yet available and also has other limitations [8], e.g., coronary arteries should be excluded from the region of measurement, which severely limits the myocardial area where the method is applicable.

The objective of the present study was to evaluate regional myocardial perfusion assessed by a novel computerized videodensitometric method, and its relation to electrocardiographic, echocardiographic, and enzymatic indicators of myocardial damage in AMI patients after coronary intervention.

2. Materials and methods

2.1. Study populations

The study comprised 62 patients with AMI, who underwent primary percutaneous coronary intervention (PCI) at the Invasive Cardiology Division of the University of Szeged. Patients with the following inclusion criteria were enrolled into the present study: (1) acute ST-elevation on 12-lead ECG; (2) pain-to-balloon time <12 h; (3) total occlusion of the proximal segment in one of the three main coronary arteries; and (4) ability of the patient to cooperate.

Demographic and clinical data of the patients are shown in Table 1. Patients who were unconscious or showed signs of cardiogenic shock or had visible collateral circulation in the infarct-related myocardial region were excluded from the study. 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 priori approval by the institution’s human research committee.

2.2. Technical features of coronary angiography

Angiograms for densitometric analysis were recorded in a way that phase-matched digital subtraction angiography (DSA) can be performed on them. This required the following criteria: (1) motion of the patient or the table should be avoided, (2) patient should hold their breath during the period of the 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. All coronary angiograms met these criteria. Patients who were not able to hold their breath during the period of the recording were excluded from the study, which occurred in 11 (15%) of 73 cases. Projections were chosen to minimize the superpositioning of non–infarct-related myocardium and edge of the diaphragm, which usually gives motion artifacts on DSA images. Left anterior descending coronary artery and left circumflex artery were recorded in lateral (LAO 90°), while the right coronary artery was recorded in antero–posterior projection. The same nonionic contrast material (Visipaque, 320 mg/ml iodine) was used for all angiograms injected by a manual injector; contrast quantity was 6.84±0.97 ml (mean±S.D.); injection rate was 3.04±0.34 ml/s. Angiograms were recorded on an Innova 2000 system (GE Healthcare, Chalfont St. Giles, Buckinghamshire, UK); images were stored in 512×512-size, 8-bit, grayscale, uncompressed format.

2.3. Echocardiographic, electrocardiographic, and enzymatic measurements

Echocardiographic measurements were performed 3 days after the primary PCI to assess left ventricular ejection fraction.

Table 1
Clinical features of the patients

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Sample size (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (n)</td>
<td>62</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>43 (70)</td>
</tr>
<tr>
<td>Age (years+S.D.)</td>
<td>60±6</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>45 (73)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>37 (60)</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>31 (50)</td>
</tr>
<tr>
<td>Left circumflex coronary artery (%)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Right coronary artery (%)</td>
<td>20 (33)</td>
</tr>
</tbody>
</table>
LV-EF. Twelve-lead electrocardiograms were recorded at the beginning of PCI and 90 min later. ST-resolution was defined as a decrease of ST-segment at 90 min compared to the first measurement in the lead with highest ST-segment elevation, expressed as percentage of initial ST elevation. Blood creatine kinase (CK) enzyme levels were measured 6, 12, 24, and 48 h after the PCI. These four measurements were summed up to assess total enzymatic infarct size.

2.4. Densitometric analysis

Phase-matched DSA angiograms were recorded with constant contrast, brightness, and stabilized acquisition parameters of the X-ray imaging system. The computerized method for myocardial perfusion assessment was based on the analysis of time–density curves (TDCs) measured over the infarct-related myocardial region of interest (ROI). Polygonal-shaped ROIs were selected by an experienced interventional cardiologist and covered the whole myocardial area at risk. Vesselness probability maps were calculated for each image frame according to Frangi et al. [9]. Typical ROI selections and related TDCs are shown in Fig. 1. Time–density curves were calculated as average pixel value in the ROI, excluding pixels having a vesselness probability value >0.8. Frequencies higher than 0.6 Hz have been removed from the TDC to eliminate artifacts from cyclic heart contractions, and noise in image acquisition and digital subtraction. Myocardial perfusion has a single-wave density signal around 0.1 Hz; therefore it is still present on the filtered curve. Frequency filtering was performed using the Matlab 7.0 mathematical software. Maximal density of the TDC ($G_{max}$) and time to reach maximal density ($T_{max}$) were measured on the filtered curve. To get more reliable results and to assess interobserver variability of this new measurement method, two independent physicians were required to select the myocardial area at risk and draw a polygonal ROI. Two $G_{max}/T_{max}$ values calculated with the two different ROIs were averaged, and these results were used to analyze correlation with other clinical parameters. Cardiologists were blinded to all other clinical data.

2.5. Statistical methods

All statistical tests were performed with MedCalc software (MedCalc Software, Mariakerke, Belgium). A
value of \( P < 0.05 \) was considered to be statistically significant. Correlation of \( G_{\text{max}}/T_{\text{max}} \) with clinical parameters was assessed by Pearson correlation coefficient. Interobserver variability was analyzed by the Bland-Altman method.

3. Results

All patients underwent a successful recanalisation of the occluded vessel and achieved \(<50\% \) residual stenosis within 12 h from the onset of symptoms. Plotting the \( G_{\text{max}}/T_{\text{max}} \) values on Bland-Altman plot and scatter diagram obtained by two independent observers reveals a reliable interobserver agreement (Fig. 2) of our method.

Enzymatic infarct size as expressed by sum of CK release had a significant negative correlation (\( R = -0.445, P < 0.001 \)) with \( G_{\text{max}}/T_{\text{max}} \). Scatter plot and regression line along with 95\% predictive boundary are shown in Fig. 3. Additionally, a positive significant (\( R = 0.364, P = 0.004 \)) correlation was found between \( G_{\text{max}}/T_{\text{max}} \) and ST-segment resolution as % decrease of initial ST elevation (Fig. 4). A milder, but still significant relationship was found between \( G_{\text{max}}/T_{\text{max}} \) and echocardiographic LV-EF measured 3 days after PCI (\( R = 0.278, P = 0.029 \)) (Fig. 5).

4. Discussion

Results of the present study show that the demonstrated computerized videodensitometric method for regional myocardial perfusion assessment can be used in clinical circumstances to get immediate information on the viability and functionality of the revascularised myocardium. Moreover, measurements correlate with clinical indicators of myocardial damage suggesting it as an end point for studies on the success of recanalisation in AMI.

There is an abundance of evidence from several techniques, such as intracoronary contrast echo [10,11], magnetic resonance imaging (MRI) [12], and radionuclide studies [13], showing that many patients have inadequate flow at myocardial tissue level despite a reopened epicardial coronary artery. Low microcirculatory perfusion after angioplasty results in larger enzymatic infarct size, lower residual ejection fraction, higher mortality, and higher incidence of major adverse cardiac events in a long-term follow-up [14]. In daily practice, coronary angiography is the most used technique during recanalisation procedure to study the effectiveness of reperfusion therapy. Assessment of microcirculatory perfusion in the myocardium is therefore necessary even if the recanalisation of occluded epicardial artery is successful (TIMI 3 flow grade). The demonstrated

Fig. 3. Correlation between \( G_{\text{max}}/T_{\text{max}} \) and enzymatic infarct size as sum of four creatine kinase blood levels (measured 6, 12, 24, and 48 h after coronary intervention). Thick line indicates regression line; thin lines indicate 95\% prediction.

Fig. 4. Correlation between \( G_{\text{max}}/T_{\text{max}} \) and ST-resolution measured as a relative decrease in ST elevation between PCI and 90 min after coronary intervention. There is a significant positive correlation between these two parameters. Thick line indicates regression line; thin lines indicate 95\% prediction.

Fig. 5. Correlation between \( G_{\text{max}}/T_{\text{max}} \) and echocardiographic left ventricular ejection fraction 3 days after coronary intervention. Thick line indicates regression line; thin lines indicate 95\% prediction.
method provides direct information on the flow of contrast agent through myocardial areas, where vessel patency cannot be visually assessed due to small vessel diameters and limited imaging resolution.

In most previous studies [3,7], myocardial ROI was smaller than in our method. We have chosen to include the whole distribution bed of the infarct-related vessel in the ROI because the distribution of contrast material in the myocardium is generally not homogeneous. During our previous investigations, smaller ROIs resulted in greater interobserver variability, because measurement values varied much if the ROI was placed at different locations inside the infarct-related area by different observers. To our knowledge, the present study is the first to combine vessel masking with perfusion assessment on X-ray coronary angiograms. This allowed us to define ROIs including the whole myocardial area at risk, while arterial contrast density still did not interfere with myocardial density signal analysis. Overcoming the problem of positioning small ROIs in the myocardial area, we have reached an almost observer-independent densitometric method, as reflected by our interobserver agreement ($R^2=0.97$).

In most animal studies, the method of TDC analysis involves fitting of an ideal curve to measurement data. Pijls et al. [3] used least squares minimization with gamma function. A two-compartment mathematical model was also proven to be useful for regional perfusion assessment in a canine model [15] and later in humans [16]. Haude et al. [4] used a lognormal curve fitting method to compute densitometric parameters of contrast perfusion. We have chosen a more simple curve smoothing method because multiparameter curve fitting can be a source of numerical errors and algorithmical variability. Our previous investigations show that the parameters of the fitted curve depend strongly on the size of the window that we use for fitting on the original curve. In cases of AMI, the wash-out phase is often missing from the acquisition, and motion artifacts cause temporary noise on the measurement curves. $G_{\text{max}}/T_{\text{max}}$ calculation needs only two points of the filtered curve, and frequency filtering is enough to accurately locate these points; therefore this method is simple, robust, and can be applied in most of the cases.

4.1. Study limitations

As already mentioned, distribution of contrast material in infarct-related myocardium is not homogeneous. Division of this area and analysis of smaller regions have not been performed in the framework of this study. The problem with small ROI areas is that a static ROI was used during the whole image sequence, and cyclic motion of myocardium due to heart beating increases relatively to the size of ROI. A possible improvement of our method could be the motion tracking of myocardial regions. This could enable us to perform measurements in smaller regions and could give a more precise localisation of the myocardial injury.

Another limitation of our method is that it requires a meaningful cooperation of the patient while recording images for phase-matched DSA conversion. Patients with AMI are often unable to hold their breath during the period of image acquisition. During the enrollment period of this study, 11 (15%) of 73 patients could not be enrolled because of lack of cooperation. Since the breathing of the patient makes densitometric measurements extremely difficult, in such cases other myocardial perfusion assessment methods must be used; myocardial contrast echocardiography may be an alternative.

Contrast material quantity somewhat differed between image acquisitions (6.84±0.97 ml), and injection rate also had 11% standard deviation (compared to mean value) (3.04±0.34 ml/s). It was hypothesized that variability in total contrast quantity and injection rate did not affect the rise in the slope of the TDC, because contrast material completely filled the coronary arteries at the point of injection, in each image acquisition.

Measurement of CK release, LV-EF, and ST resolution are only indirect indicators of reperfusion. Validation of this novel videodensitometric method could be more valuable if it is compared to other imaging modalities that directly assess regional myocardial perfusion. A comparison with myocardial contrast echocardiography, MRI, or positron emission tomography measurements could provide stronger evidence or valuable information on this method. However, videodensitometry for myocardial perfusion assessment is strongly supported by previous animal experiments and human studies as well. The weak correlation compared to echocardiographic LV-EF may be explained by myocardial stunning that can still be present 3 days after the infarction. Follow-up studies may reveal stronger correlation between $G_{\text{max}}/T_{\text{max}}$ and left ventricular function.

4.2. Clinical implications

A good quality DSA coronary angiography can be acquired in the majority of AMI patients. Based on the results of the present study, it can be stated that videodensitometric measurements on coronary angiograms can be developed and used in cardiac catheterization laboratories. Videodensitometry proves to be a low-cost alternative to other imaging modalities like myocardial contrast echocardiography or MRI to immediately assess success of PCI, but further validation studies are warranted.

References


