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Estimation of infarct size using transthoracic Doppler echocardiographic measurement of coronary flow reserve in infarct related and reference coronary artery

Vojislav Giga [a,*], Milan Dobric [a], Branko Beleslin [a,c], Dragana Sobic-Saranovic [b,c], Milorad Tesic [a], Ana Djordjevic-Dikic [a,c], Jelena Stepanovic [a,c], Ivana Nedeljkovic [a,c], Vera Artiko [b,c], Vladimir Obradovic [b,c], Petar M. Seferovic [a,c], Miodrag Ostojic [a,c]

[a] Clinic for Cardiology, Clinical Center of Serbia, 26 Visegradska, 11000 Belgrade, Serbia
[b] Institute for Nuclear Medicine, Clinical Center of Serbia, 26 Visegradska, 11000 Belgrade, Serbia
[c] School of Medicine, University of Belgrade, 8 Dr Subotica, 11000 Belgrade, Serbia

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ABSTRACT

Background: Patients in chronic phase of myocardial infarction (MI) have decreased coronary flow reserve (CFR) in infarct related artery (IRA) that is proportional to the extent of microvascular/myocardial damage. We proposed a novel model for the assessment of microvascular damage and infarct size using Doppler echocardiography evaluation of CFRs of the IRA (LAD) and reference artery (RCA).

Methods: Our study included 34 consecutive patients (28 men, mean age 50 ± 11 years) with first anterior STEMI and single vessel disease successfully treated with primary PCI. All patients underwent SPECT MPI for the assessment of infarct size (expressed as a percentage of myocardium with fixed perfusion abnormalities) and CFR evaluation of LAD and RCA. CFR derived percentage of microvascular damage (CFR PMD) was calculated as: CFR PMD = (CFR RCA − CFR LAD) / (CFR RCA − 1) × 100 (%).

Results: CFR PMD correlated significantly with all parameters evaluating the severity of myocardial damage including: peak CK activity ($r = 0.632$, $p < 0.001$), WMSI ($r = 0.857$, $p < 0.001$), ejection fraction ($r = -0.820$, $p < 0.001$), left ventricular end diastolic ($r = 0.757$, $p < 0.001$) and end systolic volume ($r = 0.794$, $p < 0.001$). Most importantly, CFR PMD (22 ± 17%) correlated significantly with infarct size by SPECT MPI (21 ± 17%) ($r = 0.874$, $p < 0.001$).

Conclusions: CFR PMD derived from the proposed model was significantly related to echocardiographic and enzymatic parameters of infarct size, as well as to myocardial damage assessed by SPECT MPI in patients with successfully reperfused first anterior STEMI.

1. Introduction

Coronary flow reserve (CFR) in patients without epicardial stenoses reflects both structural and functional integrity of microvasculature in the myocardium. Microvascular function is impaired in several pathological conditions such as myocardial hypertrophy, diabetes, smoking, and coronary vasospasm [1], as well as in acute and chronic phases of myocardial infarction (MI). CFR measured early after successful reperfusion of infarct related artery (IRA) (24–72 h) may be impaired in significant number of patients due to reperfusion microvascular injury [2]. The microvascular injury in acute phase of MI is multifactorial and includes distal embolization, cellular swelling, impaired endothelial function and activation of different blood cells apart from direct microvascular damage. This decreased vasodilatatory response is predictive of adverse left ventricular (LV) remodeling and extent of viable myocardium in mid-term follow-up [3–7].

On the other hand, the decreased CFR in IRA (assessed by Doppler wire technique) in the chronic phase of ST elevation MI (STEMI) treated with successful PCI without residual stenosis, seems to exclusively reflect the final extent of microvascular damage and infarct size [8,9]. This view is further supported by the fact that the observed improvement of invasively assessed CFR in IRA over time is related to the reduction of infarct size, suggesting that CFR may reflect infarct size in the absence of epicardial stenosis in convalescent phase of MI [10].

Abbreviations: CFR, coronary flow reserve; CK, creatine kinase; EDV, end-diastolic volume of the left ventricle; ESV, end-systolic volume of the left ventricle; IRA, infarct related artery; LAD, left anterior descending artery; LV, left ventricle; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SPECT, single photon emission computed tomography; MPI, myocardial perfusion imaging; SRS, summed rest score; STEMI, ST segment elevation myocardial infarction; WMSI, wall motion score index.

* Corresponding author. Tel./fax: +381 11 3613653.
E-mail address: voja2011@yahoo.com (V. Giga).

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Importantly, it has been demonstrated that perfusion defect at myocardial contrast echocardiography in the subacute phase of STEMI represents an area of both microvascular and myocardial necrosis as proven by cardiac magnetic resonance imaging [11].

We hypothesized that patients in convalescent phase of first anterior MI treated by primary PCI have decreased CFR in IRA in comparison to reference coronary artery and that this decrease in CFR is proportional to the extent of microvascular/myocardial damage. Therefore, we proposed a novel, pathophysiologically based, model of microvascular damage estimation using transthoracic Doppler echocardiography derived CFRs of the IRA (LAD) and reference artery (RCA) for the final infarct size estimation.

2. Materials and methods

2.1. Study population

Thirty eight consecutive patients with first anterior STEMI, successfully treated with primary percutaneous coronary intervention (PCI) and single vessel disease were included in the study. Exclusion criteria were the presence of any but treated coronary lesion, atrial fibrillation (due to beat-to-beat variability of coronary flow velocity that might affect CFR measurement), high-degree atrioventricular block, and severe chronic obstructive pulmonary disease (respiratory compromise may occur during adenosine infusion).

Four patients had poor acoustic windows and suboptimal Doppler signals during the evaluation of coronary flow (3 in RCA region and 1 in LAD region) and therefore, were excluded from further analysis — so the final number of studied patients was 34 (28 (82%) men, mean age 50 ± 11 years). The study protocol was approved by our institution's medical ethical committee. All patients were informed about the procedure and provided informed consent prior to the enrollment. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Study protocol

All patients underwent resting two-dimensional echocardiography and adenosine stress echocardiography (0.14 mg/kg/min) with CFR evaluation of the left anterior descending artery (infarct related artery) and right coronary artery (reference artery), 30 ± 3 days after primary PCI. The intake of xanthine-containing foods or beverages was discontinued the day before the examination. At the time of testing, all the patients were treated with beta blockers, aspirin, and clopidogrel; 30 patients (88%) were on statins, whereas 29 (85%) received ACE-inhibitors. Transthoracic echocardiography was performed using a commercially available digital ultrasound system (Acuson Sequoia C256; Siemens Medical Solutions USA, Inc., Mountain View, CA) with a 3V2C multifrequency transducer using second-harmonic technology. All standard echocardiographic views were obtained. The volumes of the left ventricle were measured from the dimension and area obtained from orthogonal apical views (four and two chambers), and then the ejection fraction was calculated using the modified Simpson's method. A 17-segment model was used to determine systolic LV function [12]. Segmental wall motion was graded as follows: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. The wall motion score index (WMSI) was obtained by dividing the sum of individual visualized segment scores by the number of visualized segments.

2.3. Transthoracic Doppler echocardiographic evaluation of CFR

Transthoracic Doppler echocardiography was performed using the same ultrasound unit. After standard examination, distal left anterior descending coronary artery and right coronary artery flow were evaluated using a 4-MHz transducer. In color Doppler flow mapping, the velocity range was set from 16 to 24 cm/s. For distal left anterior descending coronary artery examination, the acoustic window was around the midclavicular line in the fourth and fifth intercostal spaces in the left lateral decubitus position. For posterior descending coronary artery examination, the left ventricle was imaged in a standard apical two-chamber view. From this position, the transducer was slightly rotated anticlockwise and tilted anteriorly, until coronary blood flow in the posterior interventricular groove was identified by color Doppler. A sample volume (3–5 mm wide) was positioned on the color signal of the distal arterial segment. The spectral Doppler of the coronary artery flow showed a characteristic biphasic flow pattern with a larger diastolic component and a small systolic one. Flow velocity recordings were performed with the stable transducer position at rest and maximal hyperemia, which was induced by the administration of intravenous adenosine (0.14 mg/kg/min). All studies of stop frames and clips were digitally recorded and stored on magneto-optical disks for offline analysis. CFR was calculated as the ratio of hyperemic to basal peak diastolic flow velocities. At each time point, three optimal diastolic flow profiles were measured and the results averaged.

2.4. CFR derived percentage of microvascular damage

Basically, CFR has the same value in all three coronary arteries supplying normal myocardium [13,14]. An area of an old myocardial infarction typically contains two histological/functional compartments: 1. islands of fibrotic scar tissue mixed with 2. areas of normal viable myocardial cells. Both compartments have their own microcirculation that could be regarded as a parallel circuit, meaning that both have the same pressures on the arterial side and the same pressures on the venous side of the microcirculation (Fig. 1). However, these two compartments have entirely different properties after myocardial infarction. However, the areas of normal viable cells have the same properties, including microvascular resistance and flow in basal conditions and exhibit the same increase in flow after hyperemic stimulus as remote unaffected myocardium [15]. On the other hand, scar tissue has an enormously high microvascular resistance in basal conditions and virtually exhibits no vasodilation and no increase in flow with hyperemia [16].

There are two main assumptions of our model:

1. Pure scar tissue (or areas of scar tissue) does not have coronary flow reserve (i.e. cannot increase blood flow after hyperemic stimulus; $CFR_{scar} = 1$) [16],
2. The areas of normal viable myocardium (those mixed with scar tissue) have the same coronary flow reserve as a territory of myocardium supplied by normal coronary artery (without previous infarction), so $CFR_{viab} = CFR_{RCA}$ and these two can be used interchangeably.

In our population, LAD artery was the infarct related artery (with areas of scar and viable tissues that are, from a hemodynamic point of view, connected in parallel circuit), and RCA was a normal epicardial artery supplying myocardial territory without previous infarction. Therefore, total blood flow through LAD artery is the sum of blood flows through scar (Q_{scar}) and viable myocardial compartments (Q_{viab}). Percentage of blood that flows through scar tissue in basal conditions is expressed in Eq. (1), and this ratio will be named 'percentage of microvascular damage' (PMD).

$$PMD = \frac{Q_{scar}^{bas}}{Q_{scar}^{bas} + Q_{viab}^{bas}} \cdot 100, \tag{1}$$

where superscript bas denotes basal state.

By definition, coronary flow reserve (CFR) is the ratio of hyperemic and basal blood flows. In our model, we may define CFR of the LAD artery as follows:

$$CFR_{LAD} = \frac{Q_{scar}^{hyp} + Q_{viab}^{hyp}}{Q_{scar}^{bas} + Q_{viab}^{bas}} \tag{2}$$

where superscript hyp denotes hyperemic state.

First assumption of our model ($CFR_{scar} = 1$) could be expressed as follows:

$$Q_{scar}^{hyp} = Q_{scar}^{bas}. \tag{3}$$

Furthermore, second assumption of our model could be presented as follows:

$$CFR_{RCA} = CFR_{viab} = \frac{Q_{viab}^{hyp}}{Q_{viab}^{bas}}. \tag{4}$$

After substituting Eqs. (3) and (4) into Eq. (2) we have the following relation:

$$CFR_{LAD} = \frac{Q_{scar}^{bas} + CFR_{RCA} \cdot Q_{viab}^{bas}}{Q_{scar}^{bas} + Q_{viab}^{bas}}. \tag{5}$$

Eq. (5) could be rearranged and expressed as follows:

$$Q_{viab}^{bas} = Q_{scar}^{bas} \cdot \frac{CFR_{RCA} - 1}{CFR_{RCA} - CFR_{LAD}}. \tag{6}$$

After substituting Q_{viab}^{bas} in Eq.(1) with Eq.(6), the rearrangement gives the following equation:

$$PMD = \frac{Q_{scar}^{bas}}{Q_{scar}^{bas} + Q_{scar}^{bas} \frac{CFR_{RCA} - 1}{CFR_{RCA} - CFR_{LAD}}} \cdot 100. \tag{7}$$

After dividing the nominator and denominator with Q_{scar}^{bas} and simple rearrangement, we have the final equation:

$$PMD = \frac{CFR_{RCA} - CFR_{LAD}}{CFR_{RCA} - 1} \cdot 100. \tag{8}$$

2.5. SPECT MPI

All patients underwent gated SPECT MPI the next day after echocardiographic examination with the investigator unaware of the results of previous measurements. 740 MBq of 99mTc-MIBI was injected 10–15 min after sublingual administration of 0.5 mg nitroglycerin coinciding with the peak hemodynamic response, as previously reported [17]. The