Serial transthoracic coronary Doppler shows complete reversibility of microvascular obstruction pattern at one month after reperfused acute myocardial infarction.

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Abstract

“No reflow” phenomenon is a common complication with significant prognostic repercussions after reperfused acute myocardial infarction. Previous studies have shown the feasibility and prognostic significance of coronary microcirculation assessment by transthoracic Doppler of left anterior descending artery (LAD). **The aim** of the study was to evaluate the time course of the coronary microcirculation status after acute anterior myocardial infarction reperfused by primary angioplasty with stent on LAD. **Material and methods:** Twenty-three patients underwent transthoracic echocardiography at 3 days (M0) and one month (M1) after reperfusion, with LAD flow analysis (peak systolic and diastolic velocities, diastolic deceleration time and systolic flow reversal). The patients were divided into two groups, of good reperfusion and “no reflow”, by a 600 ms cut-off of the M0 diastolic deceleration time, previously shown to best discriminate between the two microvascular reperfusion states. **Results:** Of all patients, 21 survived to M1 and were included in analysis. Microvascular obstruction, as defined, was present in 50% of patients at M0 and it was associated with significantly worse ejection fraction both at M0 and M1 ($p=0.01$ and 0.04 , respectively). Killip class at admission was the only independent predictor of “no reflow”. DDT increased from 661.9 ± 339.3 at M0 to 948.2 ± 201.8 at M1 ($p=0.0003$). In patients with initial “no reflow”, DDT increased to normal values at M1 (876.2 ± 167.7 vs. 346.3 ± 133.9 at M0, $p<0.0001$). In these patients, the PDV/PSV ratio decreased at one month (1.91 ± 0.37 vs. 2.70 ± 1.22 , $p=0.06$), by decrease of PDV (0.29 ± 0.06 vs. 0.40 ± 0.19 , $p=0.03$). **Conclusions:** The parameters of coronary microcirculatory impedance improve significantly at one month after infarction, suggesting delayed full reversibility of the microvascular obstruction.

Keywords: “no reflow” reversibility; microvascular obstruction reversibility; coronary Doppler flow; acute myocardial infarction; primary angioplasty

Introduction

“No reflow” phenomenon is a frequent complication of acute myocardial infarction (AMI) reperfused either by pharmacological or by interventional means. It consists of persistent microvascular obstruction, despite permeable epicardial coronary artery, leading to further necrosis in the infarct territory [1-2].

Previous studies showed that “no reflow” phenomenon is present in about half of the patients with AMI reperfused by primary percutaneous intervention (pPCI), and it has prognostic significance, by a larger extent of necrosis, maladaptive left ventricular remodelling, and, consequently, higher incidence of mechanical complications and clinical events [3-5].

There are multiple mechanisms [2,6] involved in the genesis of this phenomenon, but the final, common pathway of these is the microvascular obstruction (MVO), with consequent increase of the microcirculatory impedance. This can be assessed either by intracoronary flow wire [7,8] or by transthoracic Doppler examination [9-11] of coronary arteries, especially of the left anterior descending artery (LAD), which is the most accessible. Previous studies showed the feasibility and the prognostic utility of transthoracic Doppler of LAD in the setting of reperfused AMI [9-11].

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Various Doppler parameters were proven to correlate with “no reflow” phenomenon [7-11], predicting the lack of myocardial recovery after reperfusion. The increase in microvascular impedance secondary to microcirculatory obstruction is associated with a specific Doppler pattern, which includes an increase of the deceleration slope of the coronary diastolic flow, with consequent shortening of the diastolic deceleration time (DDT) [7-9], increase of the peak diastolic velocity (PDV), and decrease of peak systolic velocity (PSV), up to a systolic flow reversal (SFR) [10], leading to an increase of the ratio of peak diastolic over peak systolic velocities (PDV/PSV) [11].

The most utilised of these parameters is DDT, with a very well validated cut-off of 600ms [7-9, 12-15], significant for MVO with prognostic relevance. However, as shown by Okamura et al [12], “no reflow” is not an “all or nothing” phenomenon and there are markers of more severe MVO, as the presence of SFR [12] or shorter DDT, with a threshold of 190ms that seems to predict totally non-viable myocardium [16,17].

However, there are less data concerning the time course of the MVO after the acute phase of the infarction, thus **the aim** of the present study was to assess the time course of Doppler parameters of microvascular resistance at one month, in patients with a first anterior AMI, reperfused by pPCI with stent.

Material and methods

This is a prospective, observational, longitudinal, single blinded study, which included 23 consecutive patients with a first anterior AMI, reperfused by pPCI with stent on the LAD, admitted at the Heart Institute Cluj-Napoca, between April and September 2010. The study was approved by the local Ethics Committee. All patients signed an informed consent before the index pPCI. This was an exploratory research, conducted before the randomised phase of our previously published work [18], following the same examination protocols. The diagnosis and treatment of STEMI were made according to the current practice guidelines at the time of the study [19], as decided by the attending physician. All patients were pre-treated with aspirin 325mg and clopidogrel 600mg, orally, at the first hospital contact. In all patients, unfractionated heparin 100ui/kg was given intravenously in the catheterisation laboratory, before pPCI.

Electrocardiogram was analysed by the attending physician, independent of the present study, at admission and at 90 minutes post pPCI, in order to estimate the ST-segment resolution (STR); STR > 70% in the worst initial lead was taken into account.

Blood samples were obtained on admission; of these, glycaemia (mg/dl), leukocyte count, and creatinine clearance (ml/min) were evaluated as potential predictors of MVO. Serial blood samples were also drawn in order to get the peak of creatin-kinase-MB isoform (CK-MB, U/L), as an estimation of the extent of necrosis.

Coronary angiography after pPCI was analysed by the operator, independent of the present study, by visual estimation, with respect to TIMI flow grading and myocardial blush grading (MBG), as described by TIMI study group [20] and van't Hof et al [21], respectively, in order to estimate perfusion at myocardial level.

Echocardiography was performed at three days (M0) and one month (M1) post-procedure, using a GE Vivid 7 ultrasound system (General Electric, Milwaukee, WI, USA). Standard echocardiographic parameters were recorded, including those regarding left ventricle function as an ejection fraction (EF), end-diastolic volume (EDV), and end-systolic volume (ESV), measured by biplane Simpson's method. Since diastolic function might influence coronary flow, trans-mitral flow and mitral annulus tissue Doppler were analysed as predictors of MVO. Annular E' wave was measured at septal and anterior points of the annulus, and an average of these values was recorded, as a marker of regional diastolic function in the infarct territory. Ratio of mitral E wave velocity and average E' velocity was also calculated, as an estimate of global diastolic function. In addition, the flow velocity profile in the mid-distal LAD was recorded by transthoracic Doppler echocardiography, as previously described [22], in order to determine the parameters associated with MVO, by an experienced operator (C.D.O.), blinded to the angiographic and clinical data. Briefly, in order to record the LAD flow, the transducer was set on the midclavicular line, in an intermediate position between parasternal long axis and apical two-chamber view, and the LAD colour Doppler signal was searched by slight rotation and angulation of the transducer, using the built-in coronary examination preset. After locating the artery, the spectral curve of pulsed-wave Doppler was recorded and analysed. The pulsed-wave Doppler gate length was set to 1 to 3 mm, according to the estimated vessel size.

Consequently, the LAD Doppler flow pattern was recorded, taking into account the parameters correlated with MVO: DDT, PDV, PSV, PDV/PSV, and early SFR. DDT was measured as below shown, on the slope of deceleration of coronary flow, from the diastolic peak to the intersection with the horizontal axis. All parameters were measured on three to five cardiac cycles with the best definition of the velocity curve, and the average of the measurements was recorded.

The patients were divided by the result of DDT at M0, with a cut-off value of 600ms, into a “no reflow” Group (NR, DDT<600ms) and a ‘Good Reperfusion’ Group (GR, DDT>600ms). Figure 1 shows the method of measurement of DDT, with typical patterns of good reperfusion (fig 1a) and “no reflow” (fig 1b).

Fig 1. Method of measurement of diastolic deceleration time (DDT), with typical patterns of normal flow (a) and “no reflow” (b).

Statistical analysis

Statistical analysis was performed in Microsoft Excel 2003 and Epi Info 6.04 (Center for Disease Control, Atlanta, USA). A p value <0.05 was interpreted as significant. Continuous variables were expressed as mean $\pm$ standard deviation and they were compared using Student's t test (paired for the comparisons M1 vs. M0, unpaired for other comparisons). Discrete variables are expressed as number (percentage) and they were compared using the χ^2 test or Fischer exact test, as appropriate; univariate analysis results are expressed as a relative risk (RR) with Taylor series 95% confidence limits. Similarly, known markers of myocardial perfusion (TIMI flow, MBG, and STR) were analysed as predictors of the tissue perfusion status. Non-binary variables (Killip class and MBG) were compared by χ^2 test with the appropriate degrees of liberty.

Table I. Baseline features both for all patients and divided by reperfusion status (univariate predictors of microvascular obstruction).

	All (n=23)	NR Group (n=11)	GR Group (n=11)	p	RR (95% CI)
Age (years)	59.7 $\pm$ 13.2	61.5 $\pm$ 14.2	57.0 $\pm$ 11.9	0.43	
Gender (female)	8 (34.8%)	3 (27.3%)	4 (36.4%)	1	0.80 (0.30-2.14)
Smoking	12 (52.2%)	4 (36.4%)	8 (72.7%)	0.09	0.48 (0.19-1.17)
Hypertension	14 (60.9%)	7 (63.6%)	6 (54.5%)	1	1.21 (0.50-2.94)
Diabetes Mellitus	6 (26.1%)	2 (18.2%)	3 (27.3%)	1	0.76 (0.24-2.42)
Previous Angina	11 (47.8%)	5 (45.5%)	5 (45.5%)	1	1.00 (0.43-2.31)
Killip Class > 1	8 (34.7%)	7 (63.6%)	1 (9.1%)	0.024	3.06 (1.28-7.30)
Killip 1	15	4	10	0.02*	
Killip 2	6	5	1		
Killip 3	2	2	0		
TIMI flow pre PCI > 1	9 (39.1%)	3 (27.3%)	6 (54.5%)	0.38	0.54 (0.20-1.50)
TIMI 2	9	3	6		
TIMI 0	14	8	5		
Pre-dilatation	7 (30.4%)	5 (45.5%)	2 (18.2%)	0.36	1.79 (0.82-3.88)
Body mass index	27.0 $\pm$ 3.9	28.8 $\pm$ 4.5	26.0 $\pm$ 2.7	0.09	
Leukocyte count (x103/mm3)	13.0 $\pm$ 4.8	13.5 $\pm$ 4.3	11.6 $\pm$ 5.1	0.35	
Glycaemia (mg/dl)	158 $\pm$ 79.1	144.3 $\pm$ 48.2	145.7 $\pm$ 53.3	0.95	
Creatinine clearance (ml/min)	87.0 $\pm$ 29.9	86.4 $\pm$ 29.2	90.3 $\pm$ 32.7	0.76	
Peak CK-MB (U/L)	215.0 $\pm$ 143.0	264.6 $\pm$ 116.4	179.2 $\pm$ 159.0	0.17	
Total ischemic time (min)	352 $\pm$ 181.5	369.1 $\pm$ 195.4	323.6 $\pm$ 177.3	0.57	
Stent length (mm)	20.8 $\pm$ 3.9	20.9 $\pm$ 3.8	20.5 $\pm$ 4.4	0.80	
Stent diameter (mm)	3.04 $\pm$ 0.2	3.1 $\pm$ 0.2	3.0 $\pm$ 0.2	0.09	
E' velocity (m/s)	0.059 $\pm$ 0.018	0.050 $\pm$ 0.015	0.067 $\pm$ 0.017	0.028	
E/E' ratio	14.2 $\pm$ 5.8	15.9 $\pm$ 6.9	12.5 $\pm$ 6.9	0.17	
TIMI flow					
TIMI 3	20 (86.9%)	8 (72.7%)	11 (100%)	0.21	0.42 (0.25-0.71)
TIMI 2	3	3	0		
MBG (3 vs. < 3)	4 (17.4%)	1 (9.1%)	3 (27.3%)	0.59	0.45 (0.08-2.58)
MBG 0	6	4	2	0.57*	
MBG 1	7	4	3		
MBG 2	6	2	3		
MBG 3	4	1	3		
STR > 70%	7 (30.4%)	1 (9.1%)	6 (54.5%)	0.06	0.21 (0.03-1.36)

RR – relative risk, CI – Taylor series 95% confidence interval; * χ^2 test with 2 and 3 degrees of liberty, respectively; TIMI – “Thrombolysis in Myocardial Infarction”, MBG – myocardial blush grade, STR – ST segment resolution

The variables with $p < 0.1$ at univariate analysis were tested in a stepwise multivariate logistic regression analysis model to identify independent predictors for “no reflow”. In addition, the markers of myocardial reperfusion (TIMI 3 flow, MBG 3, and STR) were analysed in a similar stepwise multivariate logistic model as predictors for “no reflow”. The results of the multivariate analysis are expressed as odds ratio (OR) with 95% confidence interval (95% CI), coefficients (b), standard error (SE), for the variables included in the model, and the χ^2 and p values for the overall model. Logistic regression analysis was performed using Medcalc Software (www.medcalc.org, Ostend, Belgium).

Results

Of the 23 patients who entered the study, one patient died before M0 examination and other (in the NR group) before M1 (mortality at one month of 8.70%), therefore they were excluded from the longitudinal analysis.

Table I shows the demographic data and the baseline features, both for all patients, and divided by DDT at M0, as univariate predictors of microvascular obstruction.

LAD flow was analysable in all patients at both examinations. MVO was present in 11 (50%) of the 22 patients with reperfused anterior AMI, who underwent the M0 echocardiography. Two patients (9.1%) showed markers of severe MVO; one patient had DDT < 190ms and SFR, and another had SFR only. No significant difference of peak CK-MB was noted between the two groups. Of the analysed variables, only lower E' wave velocity and higher Killip class at admission ($p = 0.028$ and 0.024 , respectively) were significant predictors for “no reflow”. Higher body mass index, larger stent diameter, and non-smoking status showed also a trend to predict MVO, that did not reach statistical significance ($p = 0.09$, each). These five variables were tested in a stepwise multivariate logistic regression analysis model. Only Killip class > 1 at

admission remained an independent predictor for MVO, OR=17.5 (95% CI:1.6-191.9), $b = 2.86$, $SE = 1.22$, $p = 0.02$, with an overall model fit $\chi^2 = 7.72$ and $p = 0.0055$.

There was no significant correlation between angiographic markers of MVO (TIMI flow, MBG) and DDT group, but an almost significant correlation with ST-segment resolution was noticed ($p = 0.06$). At the multivariate logistic regression analysis, STR appeared as the only significant independent predictor for MVO, OR=0.08 (95% CI:0.0078-0.8947), $b = -2.48$, $SE = 1.21$, $p = 0.04$, with an overall model fit $\chi^2 = 5.7$ and $p = 0.017$.

The whole group analysis at one month (Table II) showed a significant increase of the left ventricular systolic function, expressed by EF, especially by left ventricle dilatation (significant increase of EDV, without ESV change).

DDT increased significantly at one month, reaching the ‘good reperfusion’ threshold of 600ms in all patients (fig 2a). The PDV/PSV ratio decreased significantly, by a significant decrease of PDV; PSV did not change at M1 vs. M0.

The sub-group analysis (Table III) revealed a significantly greater EF in the GR group, both at M0 and M1. There was a trend towards increased EF in both groups at M1 vs. M0, significant for the NR group, but non-significant for the GR group. This was based on a significant

Table II. Echocardiographic parameters for the patients followed to M1 ($n = 21$); paired comparison between M0 and M1.

	M0	M1	p
EF (%)	50.0 ± 11.1	55.1 ± 11.3	0.007
EDV (ml)	98.2 ± 29.2	106.4 ± 33.2	0.03
ESV (ml)	48.9 ± 18.2	48.5 ± 21.4	0.87
DDT (ms)	661.9 ± 339.3	948.2 ± 201.8	0.0003
PDV/PSV	2.25 ± 0.97	1.83 ± 0.32	0.02
PDV (m/s)	0.35 ± 0.16	0.28 ± 0.06	0.03
PSV (m/s)	0.16 ± 0.07	0.16 ± 0.03	0.67

EF – ejection fraction, EDV – end systolic volume, ESV – end systolic volume, DDT – diastolic deceleration time, PDV – peak diastolic velocity, PSV – peak systolic velocity

Table III. Echocardiographic parameters by the initial status of reperfusion; paired comparison intra-group between M1 and M0 and unpaired comparison between groups at M0 and M1, respectively.

	NR Group ($n = 10$)			GR Group ($n = 11$)			p* M0	p* M1
	M0	M1	p†	M0	M1	p†		
EF (%)	42.9 ± 11.7	49.9 ± 11.2	0.04	55.2 ± 8.1	59.8 ± 9.4	0.10	0.01	0.04
EDV (ml)	97.2 ± 22.9	113.2 ± 30.2	0.002	100.2 ± 34.9	100.2 ± 35.9	1	0.81	0.38
ESV (ml)	54.5 ± 15.2	57.7 ± 22.3	0.16	45.6 ± 21.3	40.1 ± 17.5	0.049	0.27	0.06
DDT (ms)	346.3 ± 133.9	876.2 ± 167.7	< 0.0001	948.8 ± 154.7	1013.7 ± 215.1	0.34	NA	0.12
PDV/PSV	2.70 ± 1.22	1.91 ± 0.37	0.06	1.93 ± 0.40	1.75 ± 0.26	0.20	0.09	0.27
PDV (m/s)	0.40 ± 0.19	0.29 ± 0.06	0.03	0.30 ± 0.07	0.28 ± 0.05	0.58	0.07	0.93
PSV (m/s)	0.20 ± 0.09	0.15 ± 0.02	0.46	0.16 ± 0.04	0.16 ± 0.03	0.69	0.69	0.30

† intra-group, M0 vs. M1; * between groups; NA – not applicable, EF – ejection fraction, EDV – end systolic volume, ESV – end systolic volume, DDT – diastolic deceleration time, PDV – peak diastolic velocity, PSV – peak systolic velocity

Fig 2. Evolution of DDT from M0 to M1, for the whole population (a) and for the “no reflow” group (b); in red, average evolution, respectively.

increase of EDV in the NR group ($p=0.002$), but on a significant decrease of ESV in GR group ($p=0.049$), leading to a divergent change of the ESV between the two groups, with a trend to smaller ESV at M1 in GR group ($p=0.06$).

In addition, we noted a highly significant increase of DDT at M1 and a decrease of PDV and PDV/PSV ratio in the NR group (fig 2b), with no significant change in the GR group, leading to “normal” microcirculatory resistance parameters in all patients (including those with severe MVO), with no difference between groups at one month. Of note, SFR was absent in all patients at M1.

Discussions

Our study shows that the “no reflow” phenomenon, as assessed by transthoracic coronary Doppler echocardiography, is a frequent occurrence after reperfused anterior AMI and it is associated with worse functional recovery. In addition, serial recordings at one month show significant improvement of the coronary Doppler parameters, with complete “normalisation” in the “no reflow” group.

The only independent predictor of microvascular obstruction was Killip class at admission, but the cause-effect relationship is unclear. A possible explanation might be that MVO would be present before reperfusion and it would be associated with worse ventricular function (especially diastolic, as suggested by the lower E' velocity in the MVO group).

Another important finding of our study was the lack of correlation between angiographic markers of MVO (TIMI flow, MBG) and the actual diagnosis of “no reflow” by coronary Doppler; this makes the diagnostic of MVO difficult for the operator in the catheterisation laboratory and it precludes timely intervention against it. Better correlation was shown with ST-segment resolution at 90 minutes, which might be of more help in diagnosis, but usually its assessment is delayed until the exit of the catheterisation laboratory.

There are a few studies showing delayed improvement of microcirculation after “no reflow” phenomenon by coronary Doppler [14,23], cardiac magnetic resonance

[24,25] or contrast echocardiography [26]. However, to the best of our knowledge, this is the first study to show such complete reversal of the Doppler pattern of the MVO associated with “no reflow” phenomenon, at one month.

The proof of reversibility of MVO, even delayed, would be of great conceptual importance, as it would be an incentive to search new means and to use current ones [1,2,5,6] to accelerate this reversal in the acute phase, in order to maximise myocardial salvage. Therefore, given that MVO is a very frequent occurrence and it seems poorly correlated with angiographic markers, it is important to keep in mind the possibility of “no reflow” in all patients with reperfused AMI and to make every effort to revert it as soon as possible with current therapies. However, the fact that MVO might be present before reperfusion could suggest that “no reflow” phenomenon is not a cause, but an effect of more extensive myocardial damage, and it could explain the current relative lack of success of myocardial salvage by MVO-targeted means.

In addition, there could be a practical impact of the demonstration MVO reversibility, as some therapies (e.g. cell therapy) require a permeable microcirculation in order to be effective.

Inherently, there are some limitations in our study. Firstly, the small number of patients; however, the accuracy is increased by the longitudinal design, with self-controlled comparisons. Secondly, the coronary Doppler pattern is a surrogate marker of MVO, but, as shown above, it is well correlated with other methods of diagnosis and it has a prognostic value. Nevertheless, we cannot exclude other mechanisms of decrease of coronary impedance (e.g. collateral development with shunting of microcirculation). Thirdly, because of the difficulty of examination of other arteries, we took into account only anterior infarcts, with LAD lesions; however, the LAD occlusion has the most important prognostic impact and the results may be probably generalised at the concept level.

In **conclusion**, transthoracic Doppler parameters indicating microvascular obstruction after “no reflow” phenomenon improve significantly at one month, reaching values similar to those recorded in patients with good reperfusion.

Conflict of interest: none

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