

The use of myocardial contrast echocardiography in the assessment of left ventricular function recovery after primary percutaneous coronary intervention in the setting of acute myocardial infarction

Krystian Wita, Artur Filipecki, Agnieszka Drzewiecka-Gerber, Maciej Turski, Anna Rybicka-Musialik, Zbigniew Tabor, Mariola Nowak, Wojciech Wróbel, Jolanta Krauze, Jan Szczogiel, Maria Trusz-Gluza

1st Department of Cardiology, Medical Academy of Silesia, Katowice, Poland

Abstract

Background: Despite successful reperfusion therapy of acute myocardial infarction and complete restoration of infarct-related artery patency, the improvement of systolic function in long-term outcome depends on preserved microvasculature integrity. Myocardial contrast echocardiography (MCE) is a useful technique for identification of viable myocardium.

Aim: To assess the value of real-time myocardial contrast echocardiography (rt-MCE) in prediction of left ventricular function improvement in patients with anterior wall acute myocardial infarction as well as selection of the optimal cut-off value for the number of dysfunctional segments with preserved complete perfusion, in order to predict the global left ventricular function improvement during one-month observation.

Methods: Rt-MCE was performed in 74 patients (50 men, aged 58±11 years) with anterior wall myocardial infarction, treated with primary percutaneous coronary intervention (PCI) within 12 hours from the onset of symptoms. After estimation of regional contractility disturbances and global systolic function of the left ventricle, rt-MCE was performed with contrast assessment of dysfunctional segments (normal contrast pattern=2, heterogeneous=1, lack of contrast=0). Regional perfusion score index (RPSI) was calculated by adding the perfusion indices and dividing by the number of dysfunctional segments.

Results: Of a total of 1184 visualised segments, 344 (29.1%) were dysfunctional (189 hypokinetic, 155 akinetic). Contractility improvement was observed in 192 segments (preserved viability in 105 hypokinetic and 37 akinetic segments). In a group of 44 patients with systolic function improvement, 34 of them had preserved viability, and in a group of 30 patients without LVEF improvement, in 22 of them myocardium viability was not observed. Sensitivity, specificity and accuracy of rt-MCE in prediction of left ventricular global improvement were 72.7%, 73.3% and 73%, respectively, whereas in prediction of regional function improvement these values were 73.9%, 77% and 75.5%, respectively.

Conclusion: Rt-MCE performed in the early phase of myocardial infarction enables the prediction of left ventricular regional and global function improvement in patients treated with primary PCI.

Key words: myocardial contrast echocardiography, systolic function, myocardial infarction

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Introduction

Despite reperfusion therapy assisted by intensive pharmacological treatment, coronary artery disease still remains the leading cause of death, and the

subpopulation of patients after myocardial infarction (MI) is considered to be at the highest risk [1].

It is generally known that depressed left ventricular ejection fraction (LVEF) is an independent predictor of

Address for correspondence:

Prof. Maria Trusz-Gluza, I Klinika Kardiologii, Śląska Akademia Medyczna, Samodzielny Publiczny Szpital Kliniczny, ul. Ziołowa 45/47, 40-635 Katowice, Poland, tel.: +48 32 359 88 90, fax: +48 32 252 36 58, e-mail: trusz@cathlab.katowice.pl

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death in patients after MI, and the annual mortality rate increases with heart failure progression. It equals 5-15% in patients with NYHA class II and exceeds 50% in those with NYHA class IV [2]. Arrhythmia and LV dysfunction are caused by unfavourable LV remodelling. For that reason, survival after MI depends on preserved LV function and its ability to gain functional improvement, which is determined by the presence of viable myocardium in the infarct zone. Unfortunately, no improvement of systolic function in the infarct area is often observed, despite an open infarct-related artery with preserved TIMI III flow. This is a result of the absence of tissue perfusion and myocardial necrosis [3]. The absence of perfusion in coronary microvasculature may be caused by microembolisation, oedema, or intramural haemorrhage. This is the so-called *no reflow phenomenon*, which means a lack of perfusion of ischaemic myocardium despite the patent epicardial infarct-related artery [4].

Myocardial Contrast Echocardiography (MCE), particularly in adequately selected scanning modes (real-time perfusion, rt-MCE), with the use of second generation contrast agents, combines the advantages of various non-invasive techniques of visualisation of viable segments with improper contractility in the infarct area. This technique is also used by Polish clinicians [5-8].

The aim of the study was to assess the diagnostic value of rt-MCE in prediction of regional and global LV function improvement in patients with anterior acute MI treated with primary percutaneous coronary intervention (PCI). Another important objective was to identify the optimal cut-off number of dysfunctional segments with preserved complete perfusion, which predicts global LV function improvement during one-month follow-up. It has not been reliably established so far as suggested by medical reading.

Methods

Study population

Eighty-six patients were initially enrolled in the study. All of them were admitted to the hospital within 12 hours from the onset of chest pain with a diagnosis of first anterior acute MI and were treated with primary PCI due to occlusion of the left anterior descending artery. In all these patients TIMI III flow was restored.

Exclusion criteria were as follows: hypertrophic cardiomyopathy, electric instability, implanted cardioverter-defibrillator or pacemaker, lack of TIMI III flow after PCI, residual stenosis >50%, inability to identify infarct-related artery, significant valve disease, child-bearing age in women. All of the patients gave their informed consent and the study protocol was approved by the Local Ethics Committee.

Conventional echocardiography

Resting echocardiography was performed two days after PCI, directly before contrast echocardiography and at one month. The Vivid 7 (GE Vingmed Norway) ultrasound system was used and three typical apical views were obtained. The LV echo image was divided into 16 segments [9]. Each segment was assessed as normo-, hypo-, a- or dyskinetic, according to a four-point scale (from 1 to 4), based on subjective estimation of LV wall motion amplitude and myocardium thickening during systole. A wall motion score index (WMSI) was calculated by adding individual segment motion scores and dividing the result by the number of visualised segments. LVEF was assessed as the percent change in LV volume from end diastole to end systole [9].

The improvement of segment contractility at one month after MI was defined as an improvement of at least of one degree, whereas LVEF improvement was defined as LVEF increase of more than 5% as compared to the baseline value.

Real-time perfusion Myocardial Contrast Echocardiography (rt-MCE)

The examination was performed using the second generation contrast agent *Optison*, manufactured by Mallinckrodt. A dose of 0.3-0.5 ml per each of three apical views was given intravenously in slow bolus followed by an infusion of physiologic saline solution (3-5 ml). The infusion rate and dose of contrast agent were individually modified depending on the presence of particular artefacts. Infusion of contrast agent was not associated with any adverse side effects.

Real-time assessment of myocardial perfusion was performed using a new visualisation mode with a low mechanical index (0.10-0.16), eliminating destruction of contrast bubbles. Gain and depth of the projection were individually optimised and remained constant during the whole examination.

As the cavity of LV and walls were filled up with the contrast and steady state was achieved, contrast microbubbles localized in the myocardium were destroyed using the Flash method [10]. This involves a series of ultrasound impulses of high mechanical index, resulting in destruction of all microbubbles in the visualisation area. The sequence following this measurement was acquired in real time and consisted of 15 cardiac cycles with low mechanical index. From these sequences, the estimation of degree of LV segmental contrast filling was performed.

Semiquantitative analysis of myocardial perfusion was based on visual evaluation of colour intensity (Figure 1) in

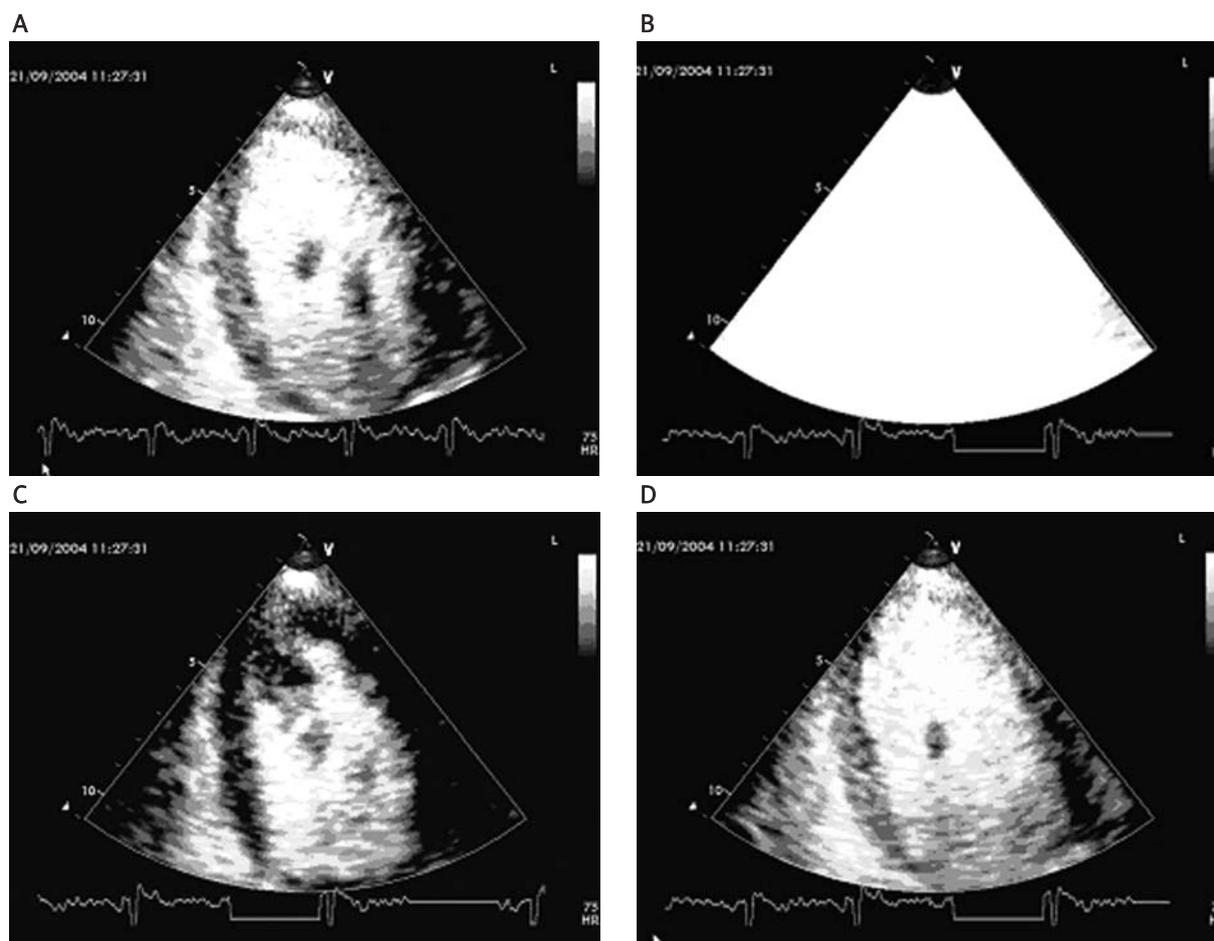


Figure 1. Real time contrast echocardiograms, four chamber view, 60-year old patient 2 days after anterior wall acute MI with normal perfusion in the infarct area. **A.** Complete LV opacification after a bolus of 0.3 ml Optison. **B.** Ultrasound beam of high Mechanical Index – flash. **C.** Imaging directly after flash: complete contrasting of LV, all bubbles in myocardium destroyed. **D.** Imaging after a few heart cycles later: complete contrasting of interventricular septum and LV apex

each segment of impaired contractility localised in the area of interest (risk area, RA) [11]. Contrastated myocardium reflected the degree of each dysfunctional segment perfusion, which was described as: normal perfusion – 2, partial perfusion – 1 and lack of perfusion – 0. A regional perfusion score index (RPSI) was calculated by adding the perfusion indicators and dividing by the number of dysfunctional segments [11]. If homogeneous contrasting (score=2) was noted, a segment was diagnosed as viable, whereas global microvasculature integrity was detected when at least 50% of dysfunctional segments were completely contrasted.

Coronary angiography and PCI

In all patients coronary angiography with the assessment of flow in the infarct-related artery (IRA) according to the TIMI scale [12] was carried out and

followed by PCI. After successful PCI of the occluded left anterior descending artery responsible for anterior MI, the assessment of blood flow was repeated and angiographic analysis of perfusion based on the MBG scale was performed. Restoration of TIMI 3 flow with less than 30% of residual narrowing was accepted as the optimum angiographic result.

Statistical analysis

Statistical calculations were performed using Statistica 6 software. Continuous variables are given as the mean value and standard deviation (\pm SD) and were analysed using Student's t-test or ANOVA. Categorical data are presented in absolute or percentage values proportional data and compared using Fisher's test. Sensitivity and specificity of rt-MCE for prediction of LV global function improvement was assessed based on

Table I. Study population characteristics

Parameter	Value
Number [n]	74
Men [%]	73
Diabetes* [%]	10
Arterial hypertension* [%]	40
Hypercholesterolaemia* [%]	45
Reperfusion time [min]	364±322
Troponin max [µg/l]	34±19
CKMB max [U/l]	262±201
LVEF 0 [%]	41.9±7.7
LVEF 30 [%]	49.4±15.4
WMSI 0	1.42±0.23
WMSI 30	1.30±0.31
LVEDV 0 [ml]	105±33
LVEDV 30 [ml]	119±39
RPSI	1.26±0.55
MBG 0-1 [%]	44.6
MBG 2-3 [%]	55.4
NYHA I 30 [%]	70
NYHA II-IV 30 [%]	30
Beta-blocker [%]	92
Nitrate [%]	24
Angiotensin converting enzyme inhibitor [%]	89
Statin [%]	86
Aspirin [%]	100

*Diagnostic criteria: **diabetes** – casual glycaemia >199 mg% with typical hyperglycaemic symptoms or fasting plasma glucose >125 mg%, **arterial hypertension** – SBP>140 or DBP >90, **hypercholesterolaemia** – TCh>200 mg% or LDL>130 mg%

Abbreviations: LVEF – left ventricular ejection fraction, WMSI – wall motion score index, EDV – left ventricular end-diastolic volume, RPSI – regional perfusion score index, MBG – myocardial blush grade, 0 – initial examination, 30 – examination at 30 days

the ROC curve, which determined the cut-off number or percentage of dysfunctional segments with normal perfusion, identifying patients with improvement of LVEF. Sensitivity, specificity and accuracy were compared using the McNemar test.

Results

Two patients of the study population of initially 86 patients died due to haemodynamically significant ventricular tachycardia and ventricular fibrillation during the first twenty-four hours before echocardiography was performed. In the next ten consecutive patients visualisation of all 16 segments was impossible, or the images recorded in the area of interest were difficult to

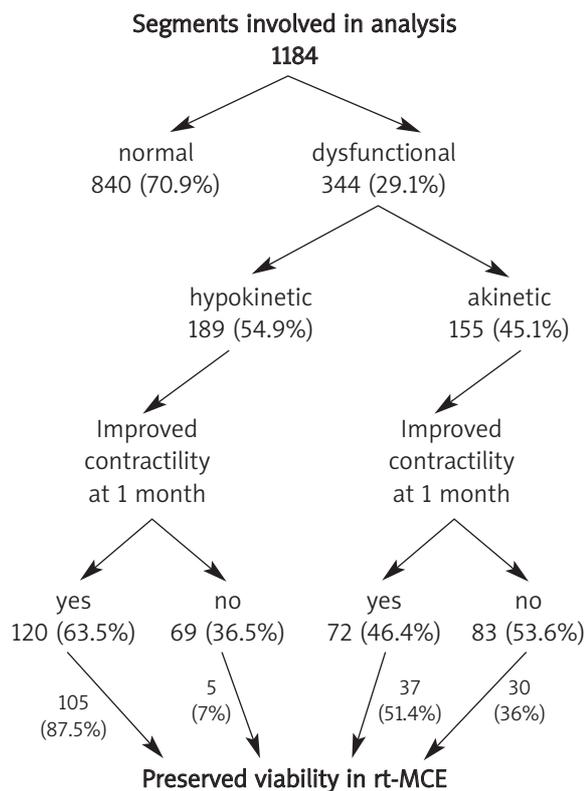


Figure 2. Segmental analysis

interpret. Finally, 74 persons were enrolled in the study; their characteristics are given in Table I.

1. Diagnostic value of rt-MCE in prediction of LV regional function improvement Among a total number of 1184 visualised segments, 344 (29.1%) were dysfunctional, and their improvement of contractility and maintenance of perfusion are given in Figure 2. In hypokinetic segments a significantly higher contractility improvement after one month (63.5%) was observed than in akinetic segments (46.4%, $p=0.001$). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of rt-MCE in prediction of LV segmental improvement were 73.9%, 77%, 80%, 70% and 75.5%, respectively.

2. Diagnostic value of rt-MCE in prediction of LV global function improvement Based on whole study population analysis, a close correlation ($r=0.79$, $p < 0.001$) between regional perfusion score index (RPSI) and LV systolic function estimated based on LVEF measured at 30 days (Figure 3) was found. According to the results of LVEF measurements at 30 days, the study population was divided into Group A with LVEF improvement, and Group B without. Analysed parameters in both groups are shown in

Table II. Characteristics of groups of patients. Group A –LVEF improvement; Group B – no LVEF improvement at 30 days

Parameter	Group A	Group B	p
Number [n]	44	30	
Men [%]	68	20	NS
Diabetes* [%]	9	10	NS
Arterial hypertension* [%]	52	23	NS
Hypercholesterolaemia* [%]	45	43	NS
Reperfusion time [min]	350±273	383±408	NS
Troponin max [µg/l]	28±21	43±13	p <0.05
CKMB max [U/l]	183±135	379±226	p <0.05
LVEF 0 [%]	42.9±7.8	40.4±7.4	ns
LVEF 30 [%]	58.2±11.8	36.3±9.5	p <0.001
WMSI 0	2.33±0.30	2.48±0.30	ns
WMSI 30	1.65±0.6	2.60±0.31	p <0.01
LVEDV 0 [ml]	95.1±30.3	120.5±30.4	p <0.01
LVEDV 30 [ml]	104.2±27.9	141.5±41.4	p <0.05
RPSI	1.54±0.41	0.86±0.48	p <0.05
MBG 0-1 [%]	66	43	p <0.05
MBG 2-3 [%]	34	57	p <0.05
NYHA I 30 [%]	36	57	p <0.05
NYHA II-IV 30 [%]	64	43	p <0.05
β-blockers [%]	90	93	NS
Nitrate [%]	23	27	NS
Angiotensin-converting enzyme Inhibitors [%]	92	85	NS s
Statin [%]	88	83	NS
Aspirin [%]	100	100	NS

Abbreviations: see Table I

Table II. Rt-MCE enabled prediction of the improvement of systolic function in 32 patients. Among 30 patients without improvement of global systolic function, in 22 rt-MCE did not reveal the presence of viable myocardium. Sensitivity, specificity, PPV, NPV and accuracy of rt-MCE in prediction of LV global improvement were 72.7%, 73.3%, 80%, 64.7% and 73%, respectively.

3. Selection of optimal cut-off number of dysfunctional segments with complete perfusion in order to predict LV global function improvement Two ROC curves were traced – the first one to assess the cut-off number of dysfunctional segments with preserved adequate perfusion, the second one to estimate the cut-off percentage of dysfunctional segments with preserved full perfusion – determining the improvement of

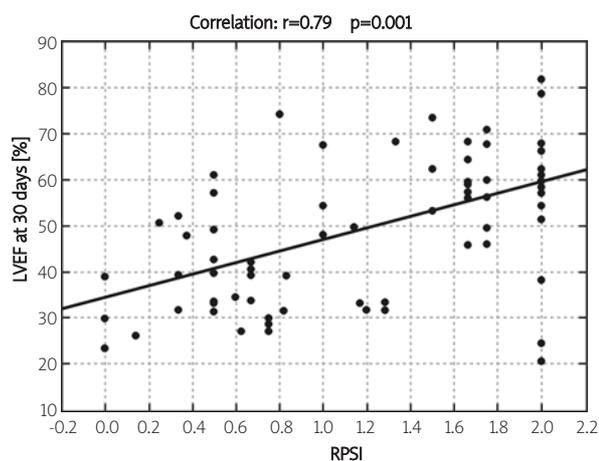


Figure 3. Pearson's correlation test for the relationship between regional perfusion score index (RPSI) LVEF at 30 days

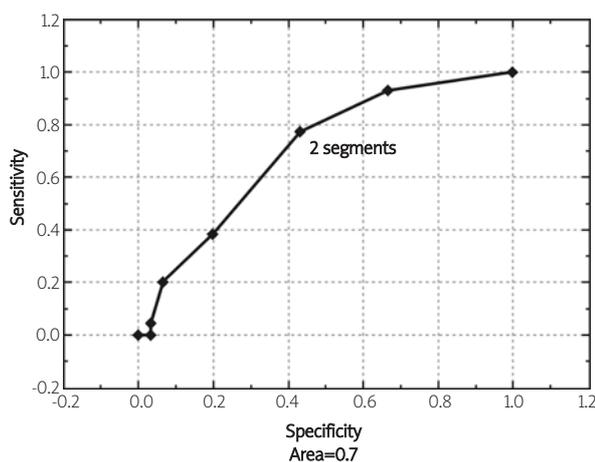


Figure 4. ROC curve for selection of cut-off for the number of dysfunctional segments with preserved complete perfusion, predicting LVEF improvement at 30 days

systolic function. The optimum differentiating number of dysfunctional segments (Figure 4) in groups with vs without improvement of LV systolic function was two. Sensitivity, specificity, PPV, NPV and accuracy were 77.2%, 56.6%, 72%, 62.7% and 68%, respectively. The ROC curve determining the percentage of dysfunctional segments was characterised by a large area under the curve (0.78). This suggests that the cut-off value of 35% viable segments among dysfunctional ones is highly predictive (Figure 5). Such analysis provided higher sensitivity, specificity, PPV and NPV as well as accuracy, which were estimated to

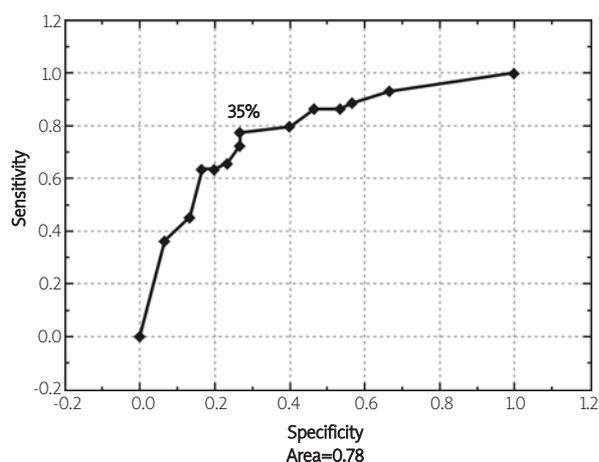


Figure 5. ROC curve for selection of cut-off percentage of dysfunctional segments with preserved complete perfusion, predicting LVEF improvement at 30 days

be 77.3%, 73.3%, 81%, 69% and 75.7%, respectively.

Discussion

The *no reflow* phenomenon, described for the first time by Kloner et al. [4] in an experimental animal model, was confirmed in humans at the beginning of the nineties by Ito et al. They showed by the use of MCE that patent infarct-related artery may not be directly related to preserved microvasculature and tissue perfusion [4, 13, 14]. Prolonged occlusion of a large epicardial artery leads to disturbances in microvasculature in each fourth patient, which in turn has a negative impact on LV systolic function and long-term outcome [15].

Myocardial Contrast Echocardiography, particularly in adequately selected scanning modes, combines the advantages of various non-invasive techniques in visualisation of viable segments with impaired contractility in the infarcted area [16]. In the mid-nineties, the availability of second generation contrast agents and modern projection techniques, which use a nonlinear response range from stimulated bubbles, enabled the development of MCE [17].

In the present study, the results of baseline echocardiography performed two days after successful PCI showed the presence of hypokinetic and akinetic segments only in the infarcted area. In long-term follow-up the improvement of systolic function was reported significantly more often in hypokinetic segments, consistently with other reports [18], and a homogeneous perfusion pattern in segments without contractility improvement was observed in MCE more

frequently in primary akinetic segments. These observations are consistent with the idea, supported by MCE findings, that preserved perfusion may be associated with the absence of systolic reserve in akinetic segments [19].

Balcells et al., in a study [20] enrolling 58 patients with MI, revealed a close relationship between WMSI-RA and RPSI in one-month follow-up ($r=0.82$). A similar relationship was confirmed in the population analysed in this study, which included 74 patients ($r=0.78$, $p < 0.001$). These results confirm the high value of rt-MCE in identifying preserved viable segments in the infarct area and are similar to the results reported by other investigators [11, 20]. Although definitely lower sensitivity (59%) and PPV (47%), with similar specificity (76%) and NPV (82%) in Swinburn's research [18] are difficult to explain, they may have resulted from the different detection method used, requiring high mechanical index and triggered imaging mode. The selection of patients may be the second, but presumably more important reason – the population of our study consists of patients with MI anterior wall only, and the area supplied by the left anterior descending artery is the easiest heart region to be visualised with contrast echocardiography.

In terms of prognosis and long-term survival, the prediction of LV global function improvement is more essential than prediction of regional function improvement. From a clinical point of view, it is important to realise how large an improvement of LVEF is needed to result in significant functional improvement of the patient. In the majority of published studies [21, 22], a LVEF increase of at least 5% was considered predictive. Reproducibility of LVEF measurements between the tests, not the empirical knowledge about the clinical significance of its growth, was crucial for the estimation of this value. The second important question is the assessment of the area of hibernated myocardium that would guarantee an improvement of LVEF in long-term follow-up. This cut-off area of hibernated myocardium predictive of an improvement in systolic function varies from 8% to 53%, depending on the imaging technique [21]. Only in one study was the ROC curve used to estimate the minimum area of hibernated myocardium necessary to provide an improvement in global function. It was estimated to be 25% [22].

In the present study, the patients with LVEF improvement presented with a lower index of necrosis, expressed by lower levels of troponin and CK-MB, which is consistent with results of other studies [18]. The high correlation index between RSCI value and LVEF estimated at 30 days reflects a significant improvement of LVEF in Group A. Left ventricular function after MI

depends on the infarct area, reflecting the percentage of myocardium without perfusion and destruction of microvasculature integrity [15, 20].

In this study, based on ROC curves, the optimum differentiating value for the number of dysfunctional segments with preserved perfusion in rt-MCE was estimated to be at least 2 or, in the case of percentage analysis, at least 35% of dysfunctional myocardium. Higher values predict an improvement in LV function in long-term outcome. Sensitivity, specificity and accuracy of prediction of LV global function are high and similar in both methods.

It is difficult to refer the results of the present study to published data, because the number of papers dealing with this problem in a similar manner is very limited. In the mentioned paper by Bax et al., published in 1999 [22], the best value based on the ROC curve was achieved for 4 dysfunctional segments. However, in this study a dobutamine stress test was used to assess contractility reserve, and the study population consisted of patients with chronic ischaemic heart failure with significantly worse LV function (LFEF=28%) than in the population in the present study. Besides, due to early PCI, in patients analysed in the present study, the number of dysfunctional segments (4, 7) was lower than in Bax et al. study, which included patients with large dysfunction after MI, frequently without any reperfusion treatment used, with a long history of heart failure, and thus with a definitely higher number of dysfunctional segments.

Rocchi et al. in a study published in 2001 [23] postulated a limited value of perfusion echocardiography performed immediately after PCI in the first twenty-four hours of MI. The assessment of perfusion on the second day seems to be not only more comfortable but also more reliable. This is a result of reactive hyperaemia [24], which may lead to underestimation of the necrotic area in rt-MCE examination performed in the very early period. In the present study, the accuracy of intravenous rt-MCE in detection of perfusion defect, with documented IRA occlusion and successful PCI, turned out to be very high and satisfactory.

Limitations of the study

The most important limitation of the study is the lack of standardisation of contrast echocardiography image assessment, despite the 10-year history of its development.

The semi-quantitative analysis used here is operator-dependent and poses an essential limitation of the study. Nevertheless, quantitative analysis demands the use of an infusion pump and additional software, and is much more time-consuming.

Conclusion

Contrast echocardiography is a useful and safe bedside method of perfusion assessment in patients with acute anterior MI. Rt-MCE examination performed in the early infarct phase allows one to predict the improvement of regional and global function in patients treated with primary PCI. Improvement is observed in patients with homogeneous perfusion images, when it is present in at least 2 or 35% of initially dysfunctional segments.

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Zastosowanie kontrastowej echokardiografii perfuzyjnej do przewidywania powrotu funkcji lewej komory po pierwotnej interwencji wewnątrzświeńcowej w ostrym zawale serca

Krystian Wita, Artur Filipecki, Agnieszka Drzewiecka-Gerber, Maciej Turski, Anna Rybicka-Musialik, Zbigniew Tabor, Mariola Nowak, Wojciech Wróbel, Jolanta Krauze, Jan Szczogiel, Maria Trusz-Gluza

I Klinika Kardiologii, Śląska Akademia Medyczna, Katowice

Streszczenie

Wstęp: Pomimo skutecznego leczenia reperfuzyjnego zawału serca i pełnego powrotu przepływu w tętnicy pozawałowej, o poprawie funkcji skurczowej w obserwacji odległej decyduje przede wszystkim zachowana integralność mikrokrążenia. Perfuzyjna echokardiografia kontrastowa (*myocardial contrast echocardiography*, MCE) stanowi użyteczną metodę identyfikacji żywotnego mięśnia sercowego.

Cel: Określenie wartości MCE w trybie obrazowania *real-time perfusion* (rt-MCE) dla przewidywania poprawy funkcji lewej komory u chorych z zawałem serca ściany przedniej, a także dobór optymalnego punktu odcięcia liczby dysfunkcyjnych segmentów z zachowaną pełną perfuzją dla przewidywania poprawy globalnej funkcji skurczowej lewej komory w obserwacji miesięcznej.

Metody: U 74 pacjentów (50 mężczyzn w wieku 58 ± 11 lat), z przednim zawałem mięśnia sercowego, leczonych pierwotną interwencją wewnątrzświeńcową (*percutaneous coronary intervention*, PCI) do 12 godz. od początku objawów wykonano rt-MCE. Po ocenie odcinkowych zaburzeń kurczliwości i globalnej funkcji skurczowej lewej komory wykonywano rt-MCE z oceną kontrastowania segmentów dysfunkcyjnych (prawidłowe zakontraktowanie – 2, heterogenne – 1, brak kontrastowania – 0), a regionalny wskaźnik perfuzji (RSCI) stanowił iloraz sumy wskaźników perfuzji i liczby dysfunkcyjnych segmentów.

Wyniki: Wśród 1184 segmentów 344 miały zaburzoną kurczliwość (189 hipokinetyczne, 155 akinetyczne). Poprawę kurczliwości stwierdzono w 192 segmentach (zachowana żywotność dotyczyła 105 segmentów hipokinetycznych i 37 akinetycznych). W grupie 44 pacjentów z poprawą funkcji skurczowej 34 pacjentów miało zachowaną żywotność, a w grupie 30 bez poprawy LVEF u 22 chorych nie stwierdzono zachowanej żywotności. Czułość, swoistość i dokładność rt-MCE dla przewidywania poprawy globalnej funkcji skurczowej wynosiły odpowiednio 72,7%, 73,3% i 73%, a dla przewidywania funkcji regionalnej 73,9%, 77%, 75,5%.

Wniosek: Echokardiografia rt-MCE we wczesnej fazie zawału pozwala przewidywać poprawę funkcji regionalnej i globalnej lewej komory u chorych leczonych pierwotną PCI.

Słowa kluczowe: echokardiografia perfuzyjna, funkcja skurczowa, zawał serca

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Adres do korespondencji:

prof. Maria Trusz-Gluza, I Klinika Kardiologii, Śląska Akademia Medyczna, Samodzielny Publiczny Szpital Kliniczny, ul. Złotowa 45/47, 40-635 Katowice, tel.: +48 252 36 58, faks: +48 32 252 36 58, e-mail: trusz@cathlab.katowice.pl

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