The prognostic significance of early dobutamine echocardiography in patients with acute myocardial infarction treated with primary coronary angioplasty

Anna Tomaszuk-Kazberuk[1], Włodzimierz J. Musiał[1], Sławomir Dobrzycki[2], Janusz Korecki[1]

[1]Clinic of Cardiology, Medical Academy, Białystok, Poland
[2]Invasive Cardiology Department, Medical Academy, Białystok, Poland

Abstract

Background: The prognostic significance of early dobutamine echocardiography (DE) after successfully treated acute myocardial infarction (AMI) with primary coronary angioplasty (PTCA) is still unclear. Patients who respond to DE may have better left ventricular function improvement and possibly a better clinical outcome.

Aim: To assess whether early DE can predict spontaneous functional recovery in patients treated successfully with primary PTCA and whether responders to DE have a better clinical outcome.

Methods: DE (5 and 10 ug/kg/min) was performed in 110 consecutive patients (61±10 years) 4±1 days after successful primary PTCA (TIMI 3, stenosis <30%). Left ventricular ejection fraction (LVEF) and wall motion index (WMSI) were measured. Patients underwent clinical assessment and two-dimensional echocardiography at 3 and 6 months.

Results: In the DE responders (76 pts), LVEF increased significantly from 41%±9% at baseline to 47%±10% at 6 months ($p<0.0001$), whereas the improvement found in nonresponders (34 pts) was insignificant (from 36.3%±9% at baseline to 38.8%±10% at 6 months, $p=0.4$). The nonresponders to DE had a higher incidence of subsequent revascularisation (4/34 (11.8%) vs 3/76 (3.9%) $p=0.12$), reinfarction (5/34 (14.7%) vs 2/76 (2.6%), $p=0.28$) and death (3/34 (9%) vs 0/76 (0%), $p=0.0086$). The incidence of combined end-point (revascularisation, reinfarction and death) was significantly lower in the group of responders to early DE ($p=0.03$).

Conclusions: Early DE can precisely predict functional recovery and the extent of irreversibly damaged myocardium in patients with AMI in whom anterograde flow is fully restored. A positive response to early DE is associated with a better clinical outcome and prognosis.

Key words: acute myocardial infarction, primary coronary angioplasty, echocardiographic dobutamine test

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Introduction

Early restoration of coronary flow (with fibrinolysis or angioplasty) in patients with acute myocardial infarction (MI) limits necrosis, results in recovery of systolic function of the stunned myocardium and improves prognosis [1].

Left ventricular (LV) function may change over weeks and months after MI due to remodelling or gradual recovery of the stunned myocardium [2]. For this reason, it is essential to establish whether this improvement occurs and to what extent if any. This is especially important since LV systolic function remains one of the major prognostic factors in patients after MI [3].

Dobutamine infusion during the echocardiographic dobutamine test identifies irreversibly damaged myocardium. The prognostic significance of early dobutamine echocardiography (DE) after primary coronary angioplasty (PTCA) in patients after MI is still

Address for correspondence:
Dr Anna Tomaszuk-Kazberuk, Klinika Kardiologii, Akademia Medyczna, ul. M. Skłodowskiej-Curie 24A, 15-276 Białystok, Poland,
tel.: + 48 85 746 85 65, fax: + 48 85 746 86 04, e-mail: walkaz@poczta.fm
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unclear [4]. Moreover, data on LV systolic function within the first 6 months after the procedure are limited. Patients responding to dobutamine infusion with an improvement of systolic function may have better contractility in a longer perspective and a more favourable prognosis.

The aim of the study was to assess whether early DE can predict spontaneous LV systolic function recovery in patients after successful primary PTCA during 6-month follow-up and whether a positive response to dobutamine infusion allows identification of patients with a better long-term prognosis.

Methods

Patients

The study involved 110 consecutive patients (33 females and 77 males, mean age 59.2 years) with acute MI treated with primary PTCA in the Department of Cardiology of the Medical Academy in Białystok in 2000.

Inclusion criteria were as follows: 1) first, acute ST segment elevation MI meeting standard criteria, 2) successful primary PTCA (flow in the infarct-related artery of TIMI 3, residual stenosis of <30%) performed within 12 hours after the onset of pain, 3) patient's informed consent. The approval of the local Ethicks Committee was obtained.

Exclusion criteria: 1. non-ST segment elevation MI, 2. fibrinolytics used, 3. unsuccessful primary PTCA, 4. cardiogenic shock, 5. mechanical MI complications, 6. severe disease with poor prognosis and 7. lack of patient's consent.

Patients were divided into two groups with respect to the response type to dobutamine infusion during early dobutamine echocardiographic test:

Group DE (+) – 76 subjects aged 34 to 81 years (mean 57±10 years), with a positive response to dobutamine infusion.

Group DE (-) – 34 subjects aged 37 to 77 years (mean 62±10 years), with no response to dobutamine infusion.

Demographics and clinical characteristics of the two groups are presented in Table I.

The groups did not differ significantly with respect to clinical and haemodynamical data. In the acute phase of MI all patients received pharmacotherapy according to the guidelines of the Polish Cardiac Society. Prior to angioplasty, patients received a standard dose of aspirin and heparin, and ticlopidine 500 mg daily over four weeks was given after stent implantation.

Resting echocardiography and dobutamine echocardiographic test

Transthoracic echocardiography and dobutamine echocardiography were performed with Hewlett-Packard SONOS 5500 equipment using the S-3 transducer (frequency range: 1-3 MHz, ULTRABAND), and Frequency Fusion and Harmonic Fusion technologies.

The dobutamine test was performed with a low-dose dobutamine infusion (5-10 µg/kg/min) on day 4/5 of hospitalisation in patients receiving optimum pharmacotherapy. Intravenous dobutamine infusion was administered at 5 µg/kg/min over 3 minutes, followed by 10 µg/kg/min over the next

Table I. Patient demographics and clinical characteristics

Parameters	Dobutamine infusion responders N=76	Dobutamine infusion nonresponders N=34	p
mean age (years±SD)	62 (±10)	57 (±10)	0.29
weight (kg±SD)	78 (±11)	80 (±14.2)	**0.46**
height (cm±SD)	169 (±6)	167 (±8)	**0.99**
BMI (kg/m^2±SD)	26 (±3)	27 (±4)	**0.34**
arterial hypertension [%]	55	62	**0.52**
diabetes mellitus [%]	20	18	**0.79**
dyslipidemia [%]	65	55	**0.35**
smoking [%]	55	38	**0.98**
family history of coronary artery disease [%]	32	21	**0.23**
Killip class	1.43	1.47	0.79
Peak CK [UI/L]	3207	4809	**0.0026**
Peak CK-MB [UI/L]	354	451	0.068
Reinfarction, n [%]	2 (2)	5 (15)	0.28
Additional PTCA, n [%]	3 (4)	4 (12)	0.12
Cardiac arrest after infarction, n [%]	3 (4)	1 (3)	0.79

3 minutes. The administration rate was 0.01 ml/kg/min over the initial 3 minutes, and subsequently 0.02 ml/kg/min. Interruption criteria included a fall in blood pressure >10% of baseline level, angina, increasing dyspnoea, and significant ventricular or supraventricular arrhythmias.

LV systolic function was assessed by the analysis of systolic thickening of the myocardium in 16 segments according to the recommendations of the American Society of Echocardiography. The Wall Motion Score Index was calculated and included a four-step contractility scale, where: normokinesia (normal contractility) = 1, hypokinesia (systolic thickening of the myocardium decreased) = 2, akinesia (no systolic thickening) = 3, dyskinesia (paradoxical motion) = 4. The index was calculated by dividing the sum of scores by the number of segments analysed.

The ejection fraction was determined as a percentage using the Simpson method modified by Chapman. Both parameters were evaluated during all resting echocardiographic examinations and both stages of DE. Myocardial viability was defined as an improvement of the systolic function by one degree on a four-degree contractility scale in at least two segments within the MI region in comparison to the baseline. The systolic function improvement was found significant if WMSI increased by at least 0.22 within MI segments.

Resting echocardiography was performed on the first day of hospitalisation, on the fourth or fifth day prior to low-dose dobutamine infusion, and at 3 and 6 months after MI. Low-dose dobutamine echocardiography was carried out on day 4/5 of hospitalisation in all 110 patients.

Coronary angiography and primary percutaneous transluminal coronary angioplasty

Coronary angiography and PTCA were performed with standard techniques in the Invasive Cardiology Department of the Medical Academy in Białystok using TOSHIBA model DFP-60A. Angiograms were evaluated by two experienced physicians. Coronary artery stenosis of >70% or 50% stenosis of the left main coronary artery were considered significant.

Statistical analysis

The statistical significance of the differences between normally distributed mean variables was assessed using Student's t test. For the analysis of data not following a normal distribution, the Mann-Whitney U test was used. Categorical independent data were analysed using the χ^2 test, whereas dependent data were assessed using the McNemara test. The results were found significant if the p value was lower than 0.05. Calculations were performed using the Statistica for Windows package, version 5.0 (2000).

Results

Characteristics of the selected clinical and angiographic parameters of the two groups of patients are detailed in Table II.

A positive response to dobutamine infusion during early DE was observed in 76 (69%) patients [group DE (+)]. The mean time from the onset of angina to coronary intervention was 4 hours 28 min in this group and 5 hours 17 min in the DE (-) group (p=0.11).

Slightly more than half of DE (+) patients had anterior wall MI (51.3%), whereas in group DE (-) the vast majority of patients experienced anterior MI (88.2%), p=0.00022.

The two groups did not differ significantly with respect to pharmacotherapy used in the acute phase of MI or in the postinfarction period.

Echocardiographic evaluation of contractility deficits

All echocardiographic examinations listed in the 'Methods' section were performed at specified intervals in all patients excluding exams at 3 and 6 months in three patients who died and in seven patients who had another MI between the DE visit and the sixth month of follow-up.

After coronary angioplasty, left ventricular systolic dysfunction was significantly more frequent in dobutamine infusion nonresponders [group DE (-)]. This was expressed as a significant decrease in EF and higher WMSI (41.9% vs 36.3%, p=0.002 and 1.65 vs 1.82, p=0.019, respectively).

Table II. Selected haemodynamic parameters of dobutamine infusion in responders and nonresponders

Parameters	Dobutamine infusion responders N=76	Dobutamine infusion nonresponders N=34	p
Number of significantly stenosed arteries	1.69	1.91	0.18
TIMI in the target artery prior to PTCA	0.31	0.32	0.93
Post-PTCA residual stenosis	0.037	0.034	0.86
Number of stents in the target artery	0.48	0.50	0.90

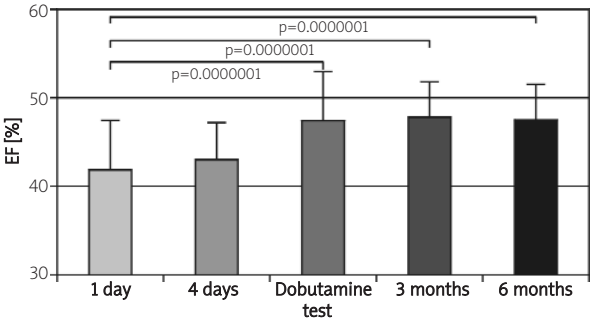

Figure 1. Changes of EF in dobutamine infusion responders over 6-month follow-up. EF was assessed after 1 and 4 days and 3 and 6 months with resting echocardiography

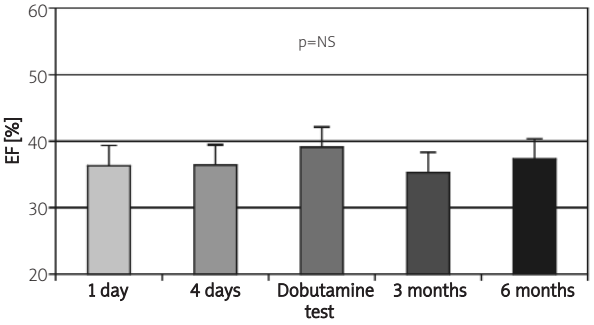

Figure 2. Changes of EF in dobutamine infusion nonresponders over 6-month follow-up

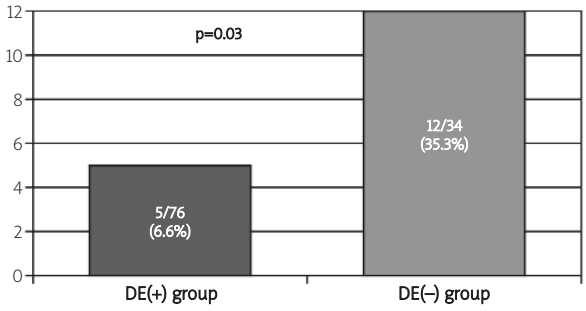

Figure 3. Combined endpoint (death, reinfarction and revascularisation need) in dobutamine infusion responders [DE(+)] and nonresponders [DE(-)]

The low-dose dobutamine test in the DE (-) group did not result in a significant increase of EF (36.3% after first day of MI and 38.8% at DE, p=NS). These patients were not found to have WMSI improved as well, which was 1.8 on the first day of MI and 1.7 on DE day (p=NS). The impaired systolic function persisted after 3 months, as well as over 6-month follow-up, and this pattern was absolutely different than in group DE (+).

Both EF and WMSI improved significantly in the DE (+) group over 3- and 6-month follow-up in comparison to baseline values. Ejection fraction increased significantly from 41%±9% on the first day of hospitalisation to 47%±10% after 6 months (p=0.0001) whereas WMSI significantly decreased (p=0.0001). EF and WMSI at peak dopamine infusion closely correlated with values obtained at 3 and 6 months.

Changes in the left ventricular ejection fraction over 6-month follow-up are shown in Figures 1 and 2.

Clinical course

No deaths were observed in the DE (+) group over 6-month follow-up, whereas 3 deaths occurred in group DE (-) (p=0.0086). Additionally, in the DE (+) group 2 MIs were recorded, whereas in the DE (-) group 5 patients experienced another MI over 6 months (p=0.03).

Another PTCA was required in 3 (3.9%) patients from the DE (+) group and in 4 (11.8%) dobutamine nonresponders (p=0.12, Table III).

At 6 months the combined endpoint of death, reinfarction and revascularisation need differed significantly in favour of the DE (+) group (p=0.03, Figure 3).

Discussion

The role of dobutamine echocardiography in identifying stunned myocardium

Dobutamine stress echocardiography has become an important technique that enables the detection of viable myocardium. It is used not only in patients with suspected hibernated myocardium but also with postinfarction stunned myocardium [5]. The assumption of presence of viable myocardium within the MI-affected segments is supported by the improvement of segmental LV systolic function after

Table III. Clinical outcomes: 6-month follow-up

	Dobutamine infusion responders (n=76)	Dobutamine infusion nonresponders (n=34)	p
Death	0 (0%)	3 (10%)	0.008
Reinfarction	2 (2.6%)	5 (14.7%)	0.03
Additional PTCA	3 (3.9%)	4 (11.8%)	0.12

low-dose dobutamine [6]. Pierard et al. found, in patients with recent MI, 79% consistency between myocardium performance during low-dose dobutamine and the results of positron emission tomography (PET), which was the reference method in that study [7].

The diagnostic value of DE has been evaluated in numerous patient groups representing a wide spectrum of coronary heart disease: in patients with chronic coronary heart disease without a history of MI, in subjects after MI, in symptomatic patients with intact LV function, and in fibrinolysed patients with acute MI [8-10]. Jeremy et al. demonstrated a high consistency of PET and DE in the identification of stunned myocardium [11]. Other authors confirmed similar outcomes regarding the studied method in comparison to thallium scintigraphy or other isotope methods [12]. Most reported studies involved patients with MI treated with fibrinolysis. Few data on patients treated with primary coronary angioplasty are available so far and come from studies involving a small number of patients. Thus, we decided to carry out our own investigation in this field.

Stress echocardiography is strongly predictive with respect to recovery of viable myocardium function after delayed revascularisation in patients with the first Q-wave MI. Monin et al. determined the sensitivity of the method to be 83%, and specificity 82% [13]. Roxy et al. studied the relationship between myocardium viability during low-dose dobutamine infusion and long-term prognosis in patients with postinfarction heart failure. They revealed that the smallest group of subjects with preserved LV viable myocardium, who underwent subsequent revascularisation, had the lowest risk of death [14, 15].

Pierard et al. [7] used DE for identification of stunned myocardium. Two months after acute MI in patients treated with fibrinolysis the recovery of normal systolic function in impaired segments resulted in improved systolic function after low-dose dobutamine. Watada et al. performed pioneer studies in patients treated with primary PTCA. They found high sensitivity and specificity (83% and 86%, respectively) as well as safety of very early low-dose DE (third day post MI) [16]. The high predictive value of DE may be partially explained by no residual stenosis of the coronary artery after coronary angioplasty.

The present study confirms the usefulness and safety of this test. No serious complications of early DE (on day 4 or 5 of MI) were observed in 110 patients. Our study involved patients with anterior MI and with MI of other locations. Smart et al. showed that low-dose DE is sensitive and specific in detecting stunned myocardium regardless of the MI location [17].

Bolognese et al. studied the prognostic value of DE in 197 patients with acute MI treated with PTCA [18]. They observed that WMSI at peak low-dose dobutamine infusion correlated well with spontaneous recovery of systolic function in long-term follow-up. In our study not only WMSI but also EF at peak low-dose dobutamine infusion (10 µg/kg/min) closely correlated with a later improvement of LV contractility. This is consistent with findings of Watad et al., Gall et al. [16, 19], and Leclercq et al. [20]. Dobutamine stress echocardiography allows very precise assessment of systolic performance of stunned myocardium in short-and long-term follow-up. Furthermore, our study demonstrated that at 6 months the combined endpoint of death, reinfarction and additional revascularisation need differed significantly in favour of the responding group (p=0.03).

Cardiac contractile reserve after myocardial infarction

Prediction of LV function recovery in patients after MI has significant prognostic value and therapeutic implications; however, relevant data regarding patients undergoing PTCA are limited. Reduced EF is associated with a high risk of death, and therefore identification of subjects in whom mechanical reperfusion (reopening of the target MI artery) translates into later EF improvement [18] is essential. In our series, LV systolic disturbances assessed immediately after primary PTCA were significantly higher in patients not responding to dobutamine infusion; this group was found to have mainly extensive anterior wall myocardial infarctions. Impaired systolic function persisted in these patients for the entire follow-up. However, EF and WMSI significantly improved in comparison with baseline values in responders to dobutamine, i.e. in patients with mainly less extensive non-anterior MIs. This seems to be the major conclusion-generating finding of our study.

In about 30% of the studied patients no improvement of LV function was observed between the first and third month after MI. This might result from relief of hyperkinesia of unaffected segments, further deterioration of systolic function, or both of them. Worsening of LV systolic function over 6 months may be caused by restenosis, although the percentage of restenoses after primary PTCA, particularly with stents, is usually low. This could not be excluded and atherosclerosis progression could not be assessed due to the lack of control coronary angiography. This represents a major limitation of these types of studies. Bolognese et al. [18] performed control coronary angiography at 1 and 6 months post MI. A low percentage of occlusions and restenoses was found.

Study limitations

1. Dobutamine test was performed *a priori* in patients without residual stenosis of the infarct related artery.

Therefore, the study results cannot be related to clinical situations where significant stenosis of the epicardial artery is present.
2. Control coronary angiography was not performed after 6 months of follow-up. Thus, the occurrence of restenosis after primary PTCA and atherosclerosis progression was not precisely assessed.
3. There was no opportunity to assess the effects of medications in detail, particularly angiotensin converting enzyme inhibitors.

Conclusions

1. Early dobutamine echocardiography can precisely predict left ventricular systolic function recovery in patients undergoing primary coronary angioplasty.
2. Dobutamine echocardiography performed after successful coronary angioplasty allows selection of a group of patients showing particular benefits of reopening of the infarct-related artery and a better long-term prognosis.

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Wartość rokownicza wczesnej próby dobutaminowej u pacjentów ze świeżym zawałem serca leczonych pierwotną angioplastyką wieńcową

Anna Tomaszuk-Kazberuk[1], Włodzimierz J. Musiał[1], Sławomir Dobrzycki[2], Janusz Korecki[1]

[1]Klinika Kardiologii, Akademia Medyczna, Białystok
[2]Zakład Kardiologii Inwazyjnej, Akademia Medyczna, Białystok

Streszczenie

Wstęp: Wartość rokownicza wczesnej próby dobutaminowej (DE) u pacjentów ze świeżym zawałem serca (AMI) leczonych pierwotną angioplastyką wieńcową (PTCA) pozostaje nieustalona. Chorzy wykazujący poprawę kurczliwości lewej komory w trakcie wlewu dobutaminy mają potencjalnie większe szanse nie tylko na spontaniczny powrót kurczliwości, ale także na lepsze rokowanie.

Cel: Celem pracy była ocena czy wczesna DE po pierwotnej PTCA pozwala przewidzieć spontaniczny powrót funkcji skurczowej lewej komory, a także czy pozytywna reakcja na wlew dobutaminy umożliwia wyodrębnienie chorych o lepszym rokowaniu odległym.

Metody: DE (5 i 10 ug/kg/min) wykonano u 110 kolejnych pacjentów (61±10 lat) ze świeżym zawałem serca 4±1 dni po skutecznej pierwotnej PTCA (TIMI 3, zwężenie <30%). Oceniano frakcję wyrzutową (LVEF) oraz indeks kurczliwości ścian lewej komory (WMSI) po zabiegu, w czasie wczesnej DE oraz po 3 i 6 miesiącach.

Wyniki: U 76 pacjentów wystąpiła istotna statystycznie poprawa kurczliwości na szczycie wlewu dobutaminy. Wartości EF i WMSI w czasie DE w tej grupie chorych korelowały ściśle z EF i WMSI po 6 miesiącach (p=0,0001). Poprawa u osób niereagujących na wlew dobutaminy nie wystąpiła (p=0,4). W grupie z pozytywną reakcją na wlew dobutaminy mniej było zgonów (p=0,0086), ponownych zawałów (p=0,03) oraz powtórnych rewaskularyzacji (p=0,12). Złożony punkt końcowy (zgony, zawały, potrzeba rewaskularyzacji) występował istotnie statystycznie częściej (p=0,03) u osób bez reakcji na dobutaminę.

Wnioski: 1. Wczesna echokardiograficzna próba dobutaminowa u chorych po zawale serca posiada wysoką wartość w prognozowaniu powrotu funkcji skurczowej lewej komory u pacjentów leczonych pierwotną angioplastyką. 2. Próba dobutaminowa po skutecznej plastyce pozwala na wyodrębnienie grupy chorych, którzy odnoszą szczególne korzyści z udrożnienia tętnicy odpowiedzialnej za zawał oraz charakteryzują się lepszym rokowaniem odległym.

Słowa kluczowe: zawał serca, pierwotna plastyka wieńcowa, echokardiograficzna próba dobutaminowa

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Adres do korespondencji:
dr n. med. Anna Tomaszuk-Kazberuk, Klinika Kardiologii, Akademia Medyczna, ul. M. Skłodowskiej-Curie 24A, 15-276 Białystok,
tel.: +48 85 746 85 65, faks: +48 85 746 86 04, e-mail: walkaz@poczta.fm
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