The Relationship Between Left Ventricular Filling Shortly After an Uncomplicated Myocardial Infarction and Subsequent Exercise Capacity

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ABSTRACT

Resting measurement of only left ventricular systolic function, is not enough sufficient parameter that predicts exercise capacity in patients with cardiac disease. Therefore, left ventricular filling shortly after an acute myocardial infarction (AMI) was prospectively studied to determine whether it could predict subsequent exercise time. Consecutive AMI patients underwent Doppler and two-dimensional echocardiography within 48 hours of infarction. The study group consisted of 63 participants: 33 patients with an uncomplicated AMI who had undergone symptom-limited stress testing during recovery and 30 healthy subjects. Systolic function was evaluated by wall motion score index (WMSI), and diastolic one was assessed by the peak transmitral Doppler velocity in early diastole (E)and atrial systole (A), then by their ratio (E/A), normalized E/A ratio, and by diastolic filling period (DFP). Myocardial infarction (MI) size was measured electrocardiographically, using Selvester's QRS scoring system (QRSSI) and then expressed in percentages. Healthy participants and patients were compared, through common parameters. The patients receiving BB treatment at the time of exercise testing, had a lower resting pulse, and achieved a lower maximal pulse, yet their exercise time was similar incomparison to that of the group not receiving BB therapy. Our results have shown a strong positive correlation between exercise time and WMSI (r = 0.77, p < 0.001) DFP (r = 0.56, p < 0.001), respectively weak negative correlation with QRSSI (r = -0.17, p < 0.001) and better negative correlation with normalized E/A ratio (r = -0.56, p < 0.001). This correlation was not influenced by beta-blokers (BB) at the time of stress testing. Normalized E/A ratio and DFP are the only diastolic function parameters, which predict exercise capacity during recovery, measured soon after an uncomplicated AMI.

Received for publication December 4, 1999.

Introduction

The acute myocardial infarction (AMI) is an evolutive process, in which the early spreading of the infarction zone is followed by the thinning of the wall, and the scar formation, i.e. the histomorphological transformation, resulting in the change of left ventricle characteristics. This remodeling process is also characterized by the changed size and form of the left ventricle, and it is dependent on the size of the infarction, its treatment, and the characteristics of the endured stress¹. Ups to now, experiments have shown that AMI leads to abnormal stunning of the left ventricular myocardium, which can decrease in time².

In comparison with hemodynamic, angiographic and radioisotopic methods³, transmitral Doppler-echocardiography has been proved, as a reliable method for studying left ventricular filling in coronary heart disease patients. Numerous parameters of the transmitral Doppler-echocardiographic blood flow^{2,4-10} were used to study the diastolic function in AMI patients. The Doppler transmitral indices of the left ventricular diastolic filling are indirect. They are influenced not only by the relaxation and left ventricular compliance factors, but also by age, heart frequency, left ventricular systolic function, mitral ring displacement, drug therapy, i.e. preload and afterload¹¹. Left ventricular diastolic dysfunction plays a great role in creating the indications and symptoms of cardiac deficiency in the case of myocardial disease, with the final result of higher left ventricular pressure per volume unit of incoming blood. This higher pressure of the left ventricular filling also makes the left atrium blood pressure higher, which reflects back to the pulmonary circulation causing short breath, and pulmonary congestion symptoms. Although the ejection fraction (EF) of the left ventricle predicts long-term survival, it does not necessarily predict the heart exercise capacity too. Similarly, EF doesnot show any correlation with the duration of the endured stress: the left ventricular diastolic dimensions, the myofibril reduction fraction, the relation of the pre-ejection period, respectively the moment of left ventricular ejection, and the cardial index. Analyses of the transmitral flow in the early AMI phase, with the later one, and the MI size, or the left ventricular WMSI, and the duration of the stress testing, could show a lot about the prognostic value of early transmitral flow in assessing the heart exercise capacity in the recovery phase¹². The current knowledge supports the hypothesis stating that the abnormality of the left ventricular diastolic function considerably contributes to the inability to endure stress testing. The prognostic value of post-AMI maximum stress testing is a valuable fact in respect to cardiac ischaemia, and left ventricular function, i.e. two major pathophysiological parameters which indicate the outcome of AMI^{13,14}.

Patients and Methods

The study involved 63 examinees, (age 45-57), then 33 patients (average age X SD 51.0 5.9) with anamnestically, electrocardiographically and enzymatically verified acute uncomplicated Q-AMI were examined. The patients underwent the Doppler and two-dimensional echocardiography within 48 hours from the beginning of the anginous pain, then between 14th and 21st day of recovery, when they also underwent symptom-limited, and sub-maximum frequency-limited maximum stress testing. Echocardiographic scoring system was used to assess the patients' left ventricular WMSI, while the size of the AMI was assessed electrocardiographically¹⁵.

The following criteria had to be met for the participation in the study: sinus rhythm showing no left or right block with hemiblock, absence of pre-excitation or left or right ventricle hypertrophy, adequate echocardiographic measurement, absence of valvular defects (confirmed by Doppler-echocardiographic test), thrombolytics-free therapy, lack of information on previous MI and diabetes. The control group consisted of 30 examinees (average age X SD 50.0 4.9) with no anamnestic data of cardiovascular disease, with normal resting electrocardiogram, i.e. normal maximum stress testing results for the given age, normal Doppler-echocardiographic test results, and the absence of higher blood pressure readings (140/90 mm Hg limit) and diabetes. The following anthropometric data were applied: blood pressure (mm Hg), pulse rate (bpm), patients' weight (kg), height (cm), body surface calculation (m²), static electrocardiogram at the speed of 25 mm/s and the gauging impulse of 1 mV = 10mm, using a 6-channel, 12 conductor Siemens machine.

In the study, according to their electrocardiographic data, only the Q-AMI was included. All patients were divided into two groups: the first one with anterior infarctions (anteroseptal, anterolateral, anteroseptolateral) and the other one with inferior infarctions (inferior, inferoposterior, inferolateral). Electrocardiographic determination of the infarction size was given by well established scoring system (QRSSI)¹⁵. Doppler, one- and two-dimensional echocardiography were performed transthoracally on a computerized *Hitachi* machine, model EUB 165 with 2.5 performed and 3.5 MHz probes.

The following parameters were measured: early (E) and late atrial (A) left ventricular diastolic filling peak velocity, E/A ratio, left ventricular diastolic filling period (DFP) (measured from the start to the end of mitral flow), normalized E/Aratio (i.e. (E/A) / DFP) – to eliminate the influence of heart frequency on the E/Aratio, in order to avoid incorrect interpretation¹⁶. Left ventricular systolic function is given in WMSI. The wall contractility

was examined in 16 left ventricle segments¹⁷⁻¹⁹. Two experienced echocardiography technicians assessed the segmental myocardial contractility by mutual co-ordination. The stress testing was on a bicycle-ergometer; continual, multi-degree and progressive, between the 14th and the 21st day of recovery, according to the standard criteria²⁰. The study was completed along with the usual drug therapy, which was divided into drug groups, and taken into account during the results interpretation. The peroral beta blocker (BB) therapy was started immediately after the admittance to the hospital, for non-bradycardic patients (pulse > 60/min), and for patients who showed no signs of arterial hypotension (systolic pressure < 100 mm Hg), disrupted atrioventricular flow, left ventricle failure or obstructive pulmonary disease. The study excluded the patients who were already on BB therapy or calcium channels antagonists therapy. Comparison was done between the group of patients on standard therapy with the addition of BB, and the other one without BB. The influence of BB on Doppler-echocardiographic and ergometric parameters was examined, as well as their correlation too.

Descriptive statistics has been used to present the results of the study, which are given tabularly, with the average figures, and standard deviations for each examined variable. Since the values of the examined variables followed the regular distribution for testing the differences between the studied groups, the Student t-test (t) was used. The correlation between the individual parameters was proved by Pearson's correlation test (r).

Results

A total of 63 examinees were included in the study: 33 AMI patients and 30 healthy controls. All the patients had undergone Q-AMI; 9 of them, anterior wall, and 24 ones inferior wall. During the course of treatment, 15 of 33 patients were treated with BB (45%), calcium channel blocker 4 (12%), nitrates 29 (87%) and ACE inchibitor 16 (48%) at the time of A total of 63 examinees were included in the study; 33 AMI patients and 30 echo/Doppler. At the time of stress testing the 15 (45%) AMI patients were attending BB therapy, 5 (15%) calcium channel blocker, nitrates 28 (84%) and ACE inchibitor 16 (46%). The patients' characteristics are given in Table 1.

The comparison between the Doppler / ergometric characteristics of AMI patients and healthy controls showed higher BSA 0.13 vs. 1.77 0.25, p < 0.05), low-(2.0)er resting pulse (70.0 14 vs. 73.0 11, p < 0.05), lower maximum pulse during the stress testing (120.0 19 vs. 165.0 17, p < 0.05), and significantly shorter stress period (10.0 3.7 vs. 15.8 5.6, p < 0.05) in AMI patients group (Table 2). All the patients had undergone the uncomplicated (Killip 1) Q-AMI and none of them had echocardiographic i.e. clinical indicators of the right ventricular dysfunction at the time of Doppler-echocardiographic test. This measurement was performed in the interval of 8-48 hours from the occurrence of the symptoms, as well as at the time of the stress testing, 14-21 days.

Out of the total of 33 patients, 15 (45%) ones underwent cardioselective BB therapy. The characteristics of the patients treated with BB, when compared to the ones without BB therapy, did not show statistically significant differences in respect to age, infarction localization or the rest of the drug therapy (calcium channel blockers, ACE-inhibitors, nitrates), both at the time of Doppler-echocardiographic test, and the stress testing. Doppler-echocardiographic parameters (< 48 hours), mean X SD DFP (449 170) and WMSI $(3.78 \quad 0.16, p < 0.05)$ data were statistically significant in AMI patients group on BB therapy, in comparison to healthy controls without BB therapy, for the same parameters (395 87, 3.62 0.21, p < 0.05) respectively. WMSI and DFP were significantly higher in patients at the beginning of BB therapy, while E (m/s), A (m/s), E/A ratio, pulse rate and (E/A) / DFP showed no statistically significant differences between the groups (Table 3).

Repeated Doppler-echocardiographic measurements in both groups, in respect to the presence or absence of BB therapy, at the time of the stress testing, presents Table 4. There were statistically significant higher mean value of the left ventricule for E/A ratio X SD (1.41 0.42.p < 0.05), DFP (609 194, p < 0.001) and 0.21, p < 0.005) in the AMI WMSI (3.79 patients on BB therapy, and lower pulse rate $(60.0 \quad 12, p < 0.01)$ in comparison to the AMI patients without BB therapy, as following for the same parameters (E/A 0.47, DFP 395 ratio 1.04 87, pulse rate 79.0 14 and WMSI 3.62 0.21). The stress testing period ranged from 4–15 minutes, with the average value (X

SD 10.0 3.7) indicating a normal aerobic functional capacity. Patients who were on BB therapy, at the time of the stress testing, had a significantly lower resting pulse (X SD 60.0 12, p < 0.01) and

 TABLE 1

 PATIENT CHARACTERISTICS (N = 33)

	51.0	59
Age (years)	(range	45-57)
Infarction localization (EKG)	N %	
- anterior	9	27
- inferior	24	73
Drugs therapy		
a) at the time of echo/Doppler		
- beta-blocker	15	45
- calcium channel blocker	4	12
- nitrates	29	87
- ACE inhibitor	16	48
b) at the time of stress testing		
- beta-blocker	15	45
- calcium channel blocker	5	15
- nitrates	28	84
- ACE inhibitors	16	46

	AMI (N = 3)	33) X S	D	Controls (N =	= 30) X	SD	р
Age (years)	51.0	5.9		50.0	4.9		ns
SBP (mm Hg)	130.0	16		130.0	15		ns
DBP (mm Hg)	85.0	8		84.0	16		ns
E (m/s)	0.61	0.15		0.61	0.13		ns
A (m/s)	0.54	0.17		0.52	0.12		ns
E/A ratio	1.23	0.49		1.23	0.33		ns
DFP (ms)	411.0	153		421.0	126		ns
$BSA(m^2)$	2.00	0.13		1.77	0.25		0.05
(E/A) / DFP	0.002	0.001		0.002	0.001		ns
Pulse (bpm)	85.0	26		73.0	11		0.05
Maximum pulse (n/min)	120.0	19		165.0	17		0.05
Maximum SBP (mm Hg)	171.0	26		187.0	26		0.05
Maximum DBP (mm Hg)	89.0	9		90.0	11		ns
Stress period (min)	10.0	3.7		15.8	5.6		0.05

 TABLE 2

 COMPARASION OF DOPPLER/ERGOMETRIC CHARACTERISTICS OF AMI PATIENTS AND HEALTHY CONTROLS

*p < 0.05;

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Preasure, E = Early diastole filling peak velocity, A = Atrial systole filling peak velocity, DFP = Diastolic Filling Period; BSA = Body Surface Area.

 TABLE 3

 DOPPLER-ECHOCARDIOGRAPHIC PARAMETERS (< 48 HOURS) IN AMI PATIENTS WITH AND</td>

 WITHOUT BETA-BLOCKERS THERAPY

Beta-blockers therapy (N = 15) X SD	No beta-blockers therapy (N = 18) X SD	р
0.62 0.12	0.55 0.16	ns
0.57 0.15	0.58 0.19	ns
1.11 0.23	1.04 0.47	ns
449 170	395 87	0.05
73.0 13	79.0 14	ns
0.002 0.001	0.002 0.002	ns
3.78 0.16	3.62 0.21	0.05
	$\begin{array}{c c} Beta-blockers therapy \\ (N = 15) X & SD \\ \hline 0.62 & 0.12 \\ 0.57 & 0.15 \\ 1.11 & 0.23 \\ 449 & 170 \\ 73.0 & 13 \\ 0.002 & 0.001 \\ 3.78 & 0.16 \\ \end{array}$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

p < 0.05;

WMSI = Wall Motion Score Index.

lower stress testing maximum pulse (X SD 104.0 12, p < 0.001), when compared to the patients without BB therapy (78.0 12, 131 15) for the same parameters. The duration of the stress period for the patients on BB therapy was somewhat longer in relation to the patients, who did not receive that therapy. There were no statistically significant differ-

ences for SBP, DBP, maximal SBP nor for maximal DBP under stress (Table 5). Correlation between the stress period duration, and the other stress testing parameters, in respect to the presence or absence of BB therapy, points at a great significance of resting pulse (r = -0.54, p < 0.001); one can observe a positive correlation between the duration of the stress period,

Total (N = 33)	Beta-blockers therapy (N = 15) X SD	No beta-blockers therapy $(N = 18) X SD p$
E (m/s)	0.67 0.21	0.55 0.16 ns
A(m/s)	0.48 0.11	0.58 0.19 ns
E/A	1.41 0.42	1.04 0.47 0.05
DFP (ms)	609 194	395 87 0.001
PULSE (bpm)	60.0 12	79.0 14 0.01
(E/A) / DFP	0.0002 0.001	0.002 0.002 ns
WMSI	3.79 0.21	3.62 0.21 0.005

 TABLE 4

 DOPPLER-ECHOCARDIOGRAPHIC PARAMETERS IN AMI PATIENTS WITH AND WITHOUT

 BETA-BLOCKERS THERAPY AT THE TIME OF STRESS TESTING

 TABLE 5

 STRESS TESTING OF AMI PATIENTS ACCORDING TO BETA-BLOCKER THERAPY

	Beta-blocker therapy N = 15 X SD	No beta-blocker therapy N = 18 X SD	р
Stress period (min)	11.53 2.60	9.44 3.71	ns
Resting pulse (bpm)	60.0 12	78.0 12	0.01
Maximal pulse under stress (bpm)	104.0 12	131.0 15 0	.001
Resting SBP(mm Hg)	127.0 15	133.0 16	ns
Resting DBP (mm Hg)	83 7	88.0 8	ns
Maximal SBP under stress (mm Hg)	164.0 28	178.0 24	ns
Maximal DBP under stress (mm Hg)	88.0 9	90.0 11	ns

and the resting diastolic pressure (r = 0.76, r = 0.76)p < 0.01) and the stress testing maximum pulse (r = 0.73, p < 0.01) in patients whose therapy included BB, and a negative correlation with the resting pulse (r = -0.57, p < 0.01) in those ones without BB therapy. We tried to assess the correlation between the left ventricular function parameters, QRSSI and the duration of the stress period. The duration of the stress testing is not dependent neither on the E or A wave velocity, nor on their ratio, if heart frequency is not taken into account. The only ventricular function parameters influencing upon the duration of the stress period are WMSI (r = 0.77, p < 0.001), left ventricular DFP (r = 0.56, p < 0.001), normalized E/A (r = -0.56, p < 0.001) and QRSSI (r = -0.17, p < 0.01). A positive correlation, that is, a direct interrelation, exists between the duration of the stress period WMSI and DFP, and a negative correlation with normalized E/A and QRSSI. The correlation is not dependent on BB therapy.

Discussion

The AMI patients' prognosis depends on many risk factors, including the infarction size, left ventricular function, the remaining myocardial ischaemia, and the presence of arrhythmia, at the time of the discharge from the hospital^{8,13,19,21,22}. Our study has shown that out of several measurements of the left ventricular function, by Doppler-echocardiography, this testing can be easily accomplished through daily routine during monitoring an acute uncomplicated Q-MI. The parameters of the left ventricular function like WMSI, DFP, normalized DFP and QRSSI strongly correlate with the duration of

the stress period during recovery. It is important to emphasize that this relation is not influenced by BB therapy. The left ventricular WMSI represents a semi--quantitative data, which have so far proved to be highly congruent with left ventricular EF^{23-25} . In the absence of very early revascularization, serial measurements of the left ventricular post-AMI EF have shown, minor changes during the recovery, regardless of different drug therapies^{18,19,26-28}. Thus, Flamen et al.²⁹ have found that global left ventricular EF, WMSI and myocardial perfusion score are markedly related to the seriousness of the coronary heart disease, both while resting and during sub-maximum stress testing.

Our study also has shown a significant positive correlation between WMSI, and the duration of the stress period. For that reason, patients with less damage of the left ventricular contractile ability, achieve longer stress periods, and have greater exercise capacity independently of the BB therapy. The average WMSI value was 3.68 0.22 out of the maximum 4.0, which exceeds the 2.0 limit, that Kathinka et al.¹⁹ have presented as an indicator of the left ventricular dilatation and mortality. This study has shown that WMSI and the average stress period of 10.0 3 minutes point out the relatively small degree of myocardial mass affection at mean QRSSI 12.96 5.82%with the uncomplicated course of disease, and they actually represent independent post-MI prognostic information²⁷.

There is a significant correlation at the time of stress testing between the E/A ratio, pulse rate, DFP and WMSI (Table 4) partly caused by BB therapy, which can't be seen at the beginning of BB therapy (Table 3). DFP is causing normal heart frequency effects, so the so called normalized E/A ratio ((E/A) / DFP) does not correlate with heart frequency, but it correlates with $EF^{30,31}$. The stress period negatively correlates with the normalized E/A ratio, and positively with DFP; it is to be expected, since a higher filling pressure can develop under stress, due to the shortening of DFP³. That correlation is not influenced by BB. Investigating the influence of BB on AMI, Basu et al.³² have also found a considerable reduction of: pulse, resting blood pressure, »double product« under endured stress, and a considerably higher E/A ratio prior to the discharge from the hospital, but only in AMI patients, treated with BB. The increase of the E/A ratio, which is a diastolic functional parameter, is explained by the improvement of the left ventricular filling.

The size of the scar after the MI is essential to the future clinical development, and is probably the most important prognostic factor in patients who underwent MI. The occurrence, and the degree of heart failure, respectively life-threatening arrhythmia, mostly depend on the size of the infarction. Bergovec et al.^{33,34} have proved that the size of MI, determined by QRSSI, correlates well with the global EF and WMSI. Their study has also shown the negative correlation between the QRSSI figures and the stress period, and reciprocal to MI size and the stress period. In our study, taking into account the differences between the AMI group and healthy controls (Table 2), the causes may be found in the well known greater incidence of AMI among the patients, who have higher risk factors (in this case, greater body mass, i.e. BSA).

The differences in functional parameters during the stress testing could be the results of a newly developed cardiac disease (reduction of the systolic-diastolic function) and the BB therapy effect. The expected significant differences in the Doppler indicators of diastolic left ventricular filling omitted, probably due to the very restrictive participants criteria; a group of less seriously ill was selected, that is, the patients with smaller MI and

with a relatively large active myocardial mass preserved. The other various cardiac therapy (calcium channel blockers, ACE-inhibitors, nitrates) different than BB may be also partly responsible for such results. It was started before applying the Doppler testing, which may be influenced by therapy on the myocardium, the preload and afterload, pressures and pulse^{26,35,36}. Another one reason is probably the fact that the patients did not have systolic dysfunction. To determine the presence and degree of serious diastolic dysfunction only from mitral flow velocity, and in normal EF patients is much more difficult than in other ones. The hemodynamic studies have shown that in such patients, the diastolic dysfunction plays a major role in determining the post-AMI exercise capacity³⁷.

Until the reliable method of differentiating normal and »pseudonormal« left ventricular filling characteristics is found, the use of only transmitral velocities in investigating of diastolic function in patients with normal, or almost normal, left ventricular systolic function remains limited¹¹. More recent studies of the subject of »diastole« are directed towards that particular problem, and some new methods that should be applied in this very scope, are necessary^{38–41}.

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ODNOS IZMEĐU RANOG TRANSMITRALNOG PROTOKA KRVI I FUNKCIONALNE SPOSOBNOSTI SRCA U BOLESNIKA S AKUTNIM NEKOMPLICIRANIM INFARKTOM MIOKARDA

SAŽETAK

Kod srčanih bolesnika samo mjerenje sistoličke funkcije lijeve klijetke nedostatno je za prikaz funkcionalne sposobnosti srca. Stoga su parametri punjenja lijeve klijetke u ranoj fazi akutnog miokardnog infarkta (AMI), praćeni prospektivno s ciljem prepoznavanja da li neki od njih predskazuje funkcionalnu sposobnost srca, izraženu vremenom opterećenja. Bolesnicima s AMI izvršena su mjerenja s Doppler i dvo-dimenzionalnom ehokardiografijom unutar 48 sati od početka AMI. Istraživanje je provedeno kod ukupno 63 ispitanika. Ispitivanu skupinu činilo je 33 bolesnika s nekompliciranim AMI, koji su tijekom oporavka bili podvrgnuti testu opterećenja ograničenom simptomima, te 30 zdravih dobrovoljaca. Sistolička funkcija procjenjivana je sustavom bodovanja pokretljivosti stjenke lijeve klijetke (WMSI), a dijastolička funkcija putem maksimalnih transmitralnih Dopplerskih brzina protoka u ranoj dijastoli (E) i atrijskoj sistoli (A), njihovom omjeru (E/A), normaliziranim E/A omjerom i dijastoličkim periodom punjenja (DFP). Veličina AMI određivana je elektrokardiografski Selvestrovim QRS sustavom bodovanja (QRSSI), a prikazana u postocima. Zdravi ispitanici i bolesnici međusobno su uspoređivani u zajedničkim parametrima. Bolesnici koji su primali beta-blokator (BB) u terapiji u vrijeme testa opterećenja, imali su niži puls u mirovanju, te su postigli niži maksimalni puls u testu opterećenja, dok se dužina opterećenja nije bitno razlikovala od onih koji nisu primali BB u terapiji. Naši rezultati pokazuju snažnu pozitivnu korelaciju vremena opterećenja s WMSI (r = 0.77, p < 0.001) i DFP (r = 0.56, p < 0.001) te negativnu korelaciju s QRSSI (r = -0.17, p < 0.001) i s normaliziranim E/A omjerom (r = -0.56, p < 0.001). Ta međuovisnost nije pod utjecajem BB u vrijeme testa opterećenja. U zaključku, jedini parametri dijastoličke funkcije koji predskazuju funkcionalnu sposobnost tijekom oporavka, mjereni ubrzo nakon nekompliciranog AMI su normalizirani E/A omjer i DFP.