

Wall motion changes in myocardial infarction in relation to the time elapsed from symptoms until revascularization

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ABSTRACT

Objective: Wall motion abnormalities during acute ST-segment elevation myocardial infarction (STEMI) and the improvement after recanalization depend on the conditions of the coronary occlusion.

Methods: Fifty-seven patients with first-ever STEMI due to one-artery occlusion, treated with primary PCI, were evaluated. Area at risk and left ventricular wall motion abnormalities were localized with coronary angiography and echocardiography and then compared in relation to the time elapsed from the onset of symptoms at the time of infarction and at 3 months. Left ventricular diameters and ejection fractions were evaluated in relation to the ischemic time.

Results: Three hundred forty-one affected left ventricular segments were detected with angiography, while echocardiography showed 206 segments with motion abnormality. No correlation was found between the regional wall motion index in the area at risk and the time elapsed from the beginning of symptoms. However, the improvement in wall motion abnormalities at the follow-up was dependent on the ischemic time ($r=-0.29$, $p<0.03$). The early subgroup showed significant improvement in left ventricular ejection fraction at follow-up ($p=0.03$), whereas in the late subgroup, a significant increase in left ventricle diameters was observed.

Conclusion: Our results first demonstrate in humans that in the early hours from the occlusion of the coronary artery, the extent and severity of the wall motion abnormalities inside the area at risk show large variability without relation to the elapsed time since the onset of symptoms. On the other hand, the results of follow-up echocardiography proved that the wall motion improvement was highly dependent on the ischemic time. (*Anadolu Kardiyol Derg 2015; 15(0): 000-000*)

Key words: myocardial infarction, echocardiography, angiography, remodeling

Introduction

During acute ST-segment elevation myocardial infarction (STEMI), an occlusive thrombus causes complete ischemia and subsequent necrosis in the region supplied by the occluded artery (1, 2).

Rapid recanalization decreases the myocardial damage, whereas the probability of permanent myocardial dysfunction and cell death increases with the duration of the delay. Experimental observations have demonstrated a lateral advance of necrosis in the endocardium for approximately 40 min, followed by a transmural characteristic, as defined in the wave-front theory, while the wall motion abnormality advances gradually after the occlusion, evolving 1 h after an artificial occlusion, and subsequently does not change significantly up to 6 h (3, 4).

During treatment, the primary goal must be the immediate restoration of circulation in the coronary artery responsible for the STEMI, with or without postconditioning (5). The diagnosis of STEMI is primarily based on the electrocardiogram, but echocardiography that reveals the regional wall motion abnormalities also furnishes important information for the evaluation of the actual state of the patient. Invasive coronary angiography should be performed to shed light on the features of the revascularization (1, 6).

Numerous investigations have provided evidence that primary percutaneous coronary intervention (PCI) improves left ventricular function and inhibits post-infarction dilation and remodeling (7, 8). Left ventricle (LV) dilation that results in marked remodeling starts 7 days after myocardial infarction (MI) (9). However, little data are available concerning the correlation

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between the time elapsed from the onset of pain until revascularization (pain-to-treatment) and the extent of the wall motion abnormality-i.e., the final magnitude of the necrosis. Uslu et al. (10) described that significant recovery in end-systolic volume (ESV), end-diastolic volume (EDV), and increase in left ventricular ejection fraction (LVEF)-the substantial part of the remodeling process after the infarction-is completed in 2 months. With regards to the time and volumetric definition of remodeling, there are different ways to characterize the measures of the process. Masci et al. (11) have defined remodeling as a 15% increase in the left ventricular end-systolic diameter at the 4-month follow-up. We decided not to apply cut-off values for characterizing the remodeling process; rather, we investigated the diameter changes due to the remodeling between the early and late managed groups. Inflammatory and genetic factors may also play role in remodeling (12).

The aims of our investigation were to examine the correlation between the left ventricular wall motion abnormality and the localization of the occlusion of the coronary artery in STEMI patients and to clarify the effect of the duration of ischemia on the extent and improvement of the wall motion abnormality at admission and after revascularization

Methods

The study was conducted ethically according to the Declaration of Helsinki. All of the patients gave written approval for the collection of their clinical data. Data collection and handling were approved by the institutional review boards of the Institute of Cardiology and Ethic Committee of the University of Debrecen, Hungary, and the Hungarian National Ambulance Service.

Inclusion was restricted to patients with first-ever STEMI due to a single coronary artery with total occlusion treated by successful primary PCI in our department. This study was conducted from June 2011-June 2012. Only patients without an adverse event in the follow-up period were involved in our retrospective analysis. Further inclusion criteria were: 1. lack of macroembolization in the distal part of the affected epicardial coronary vessel; and 2. TIMI III flow after the stenting (13). Exclusion criteria were: 1. angina after the PCI; 2. further myocardial event in the next 6-month period; and 3. more than 50% stenosis in non-culprit coronary vessels.

Fifty-seven patients (43 men, 14 women, mean age 55.8±10.6 years) met these criteria during the investigated 12-month period. Cardiovascular risk factors, such as obesity (calculated BMI), smoking, hyperlipidemia, hypertension, diabetes mellitus, and co-morbidities, including stroke/TIA and peripheral artery diseases, were recorded (Table 1). Troponin I, CK, and CK-MB; serum cholesterol; LDL-cholesterol; and HDL-cholesterol levels were measured.

All patients underwent an echocardiographic examination before the intervention and at 2.8±0.2 months using an Acuson-Sequoia device with a 3.5 MHz harmonic imaging transducer

Table 1. Occurrence of risk factors and co-morbidities at the time of hospital admission

Risk factors/co-morbidity	Overall (n=57)	Male (n=43)	Female (n=14)
Obesity (BMI>25)	21	13	8
Smoking	23	19	4
Hypercholesterolaemia	33	21	11
Hypertension	27	16	11
Diabetes mellitus	4	3	1
Stroke/TIA	3	2	1
Peripheral artery disease	5	3	2

Data are presented as n and as proportion (percentage). Significance levels were used according to international standards-e.g., BMI>25, serum total cholesterol level >5.2 mmol/L, hypertension and diabetes mellitus, and requiring medical therapy at least within the last 6 months prior to hospitalization.
BMI - body mass index

(Siemens Medical Solutions of Siemens AG, Erlangen, Germany). The patients were examined in the left lateral position. The end-diastolic (EDD) and end-systolic (ESD) left ventricular diameters were measured from the parasternal M-mode view. The apical 4- and 2-chamber views were chosen to estimate left ventricular parameters, and care was taken to obtain the maximal left ventricular dimensions and adequate left ventricular borders. As already standardized by others, the echocardiography images were considered to be acceptable for analysis when at least 75% of the endocardial border was clearly visualized (14). The endocardial border was manually drawn around the left ventricular cavity at end-diastole and end-systole, and LVEF was performed by the Simpson's formula integrated in the software. The data were obtained by averaging 3 consecutive measurements. The wall motion alterations were defined with the 16-segment model, as recommended by the American Society of Echocardiography (15). All segments of the left ventricle were scored with the usual method-1-normokinesis, 2- hypokinesis, 3- akinesis, 4- dyskinesis, and 5- aneurysm-using the 2-D mode, through the short axis projections and apical 2-, 3-, and 4-chamber visualization. The wall motion of all 16 left ventricular was scored according to the listed parameters (1-5). The sum of wall motion score was divided by the 16 results of the value of wall motion score index (WMSI), which is 1.0 if normokinesis is detected in all segments. The regional wall motion score index (rWMSI) was derived in the same way with respect to the affected left ventricular wall segments. Left ventricular measurements and wall motion abnormalities of the 57 selected patients were reviewed by 2 independent cardiologists, and the average score value was used for further analysis.

The admission examination was performed 1-9 h (on average 3.5 h) from the onset of the symptoms. The follow-up echocardiography was performed after 2.8±0.2 months.

Holistic Coronary Care (HCC) software, based on Microsoft Access 2000 (Coronart Ltd., Debrecen, Hungary), was used for the comparison of the cardiac images and clinical data. This

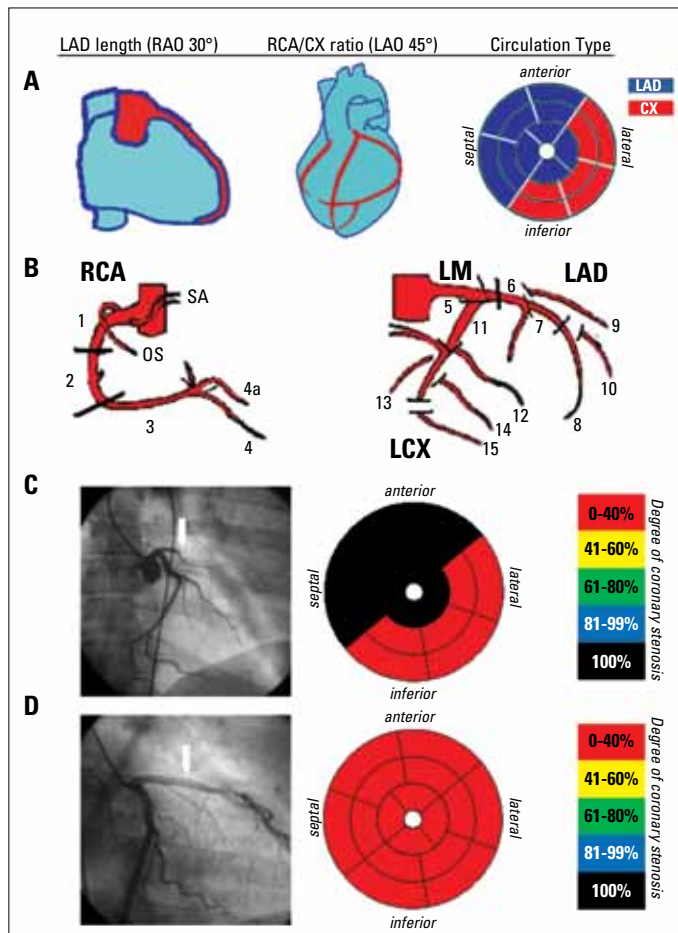


Figure 1. Coronary circulation types, coronary tree segments, angiograms, and polar maps in the HCC software

Coronary circulation types (A) and coronary tree segments (B) are shown as they are identified in HCC software. Angiograms and polar maps at the bottom indicate the area at risk before and after PCI (panel C and D, respectively). The scales of these panels represent the degree of stenosis of the supplying epicardial artery (e.g., in panel C, black segments represent the corresponding left ventricle segments of the occluded LAD). In this case, proximal LAD occlusion is indicated by an arrow. By giving the exact site of the occlusion, the 10 regions with endangered perfusion areas are presented in the polar map (C). The segments with high possibility of a wall motion abnormality are highlighted. After revascularization of the occluded artery, the perfusion is restored, and no endangered segments remain in the polar map (D). CX/LCX - circumflex artery; HCC - holistic coronary care; LAD - left anterior descending artery; LAO - left anterior oblique; LM - left main coronary artery; OS - conic branch; RAO - right anterior oblique; RCA - right coronary artery; SA - sinoatrial branch

program, which integrates the 16 segments of the left ventricle model, was designed in our institute (16). With an appropriate algorithm, the supplied left ventricular segments can be transferred into a 16-segment polar map projection used in nuclear cardiology in relation to the 12 coronary circulation types. The previous medical history (sex, age, risk factors, history of illnesses, etc.), physical findings, and laboratory parameters (with emphasis on necroenzymes and troponin values) are recorded, together with the time of onset of the symptoms and the medication administered. The 16-segment polar map (representing the left ventricle) was applied for the analysis of the results: apex,

septum, lateral, anterior, and inferior walls are presented in the middle, left, right, lower, and top part of the map, respectively (17). With the 12 different coronary circulations taken into consideration, the following individual circulation types can be differentiated in the HCC. From a right anterior oblique (RAO) projection, the left anterior descending artery (LAD) can be visualized in its entire length (reaching, extending past, or ending before the apex). From the left anterior oblique (LAO) projection, the border of the areas supplied by the right coronary/circumflex artery (RCA/Cx) can be defined. Based on the latter, four types of predominant coronary circulation can be differentiated: super-right, right, balanced, or left dominant. In all cases, the coronary tree type is a combination of these two characters supporting 12 (3x4) unique coronary circulations. After defining the circulation type, the software automatically assigns the left ventricular segments to the occluded artery. The coronary tree can be divided into 15+1 segments (Fig. 1B) (18). By giving an accurate localization and grade (%) of the stenosis, the area at risk can be visualized on the polar map with color coding. For a better result of the comparability, the wall motion abnormalities detected in the 16-segment model were projected to the polar map with color coding. Good-quality comparison was performed regarding the segments at risk identified in the coronary angiogram and the wall motion abnormalities detected by echocardiography (19). A pathological validation of the HCC program as an angiographic area-at-risk predictor has been recently published (20). In this paper, we found a significant correlation between the HCC method and autopsy findings with regard to the area at risk of the culprit coronary lesions.

The follow-up echocardiographic data were also registered in the HCC software. The grade of improvement was measured by comparison of the regional wall motion score index (rWMSSI) at admission and at follow-up. Figures 1 and 2 represent the data uploaded from a patient. From the RAO projection, the LAD reaches over the apex (Fig. 1A). From the LAO, it is possible to detect the border between regions supplied by the RCA and Cx (Fig. 1B). Based on the data above, the software projects each coronary branch and the left ventricular segments in the polar map (Fig. 1C, D). Echocardiography images at admission and at the follow-up examination were compared to evaluate the improvement in wall motion (Fig. 2A, B).

Statistical considerations

Sample size calculation was performed with an assumption that a 5% change in the EF during the follow-up with a 10% SD in the average of the values can be detected with 0.90 power of the test. We aimed to include 43 patients into the study to achieve this power with a 0.05 probability of making a type I error.

Categorical variables are reported as counts (percentages), and continuous variables are reported as mean and standard deviation (SD). Kolmogorov-Smirnov test was performed to examine the normality of parameter distribution. All variables showed a normal distribution. Results are expressed as mean (95% confidence interval, CI). The p value threshold for signifi-

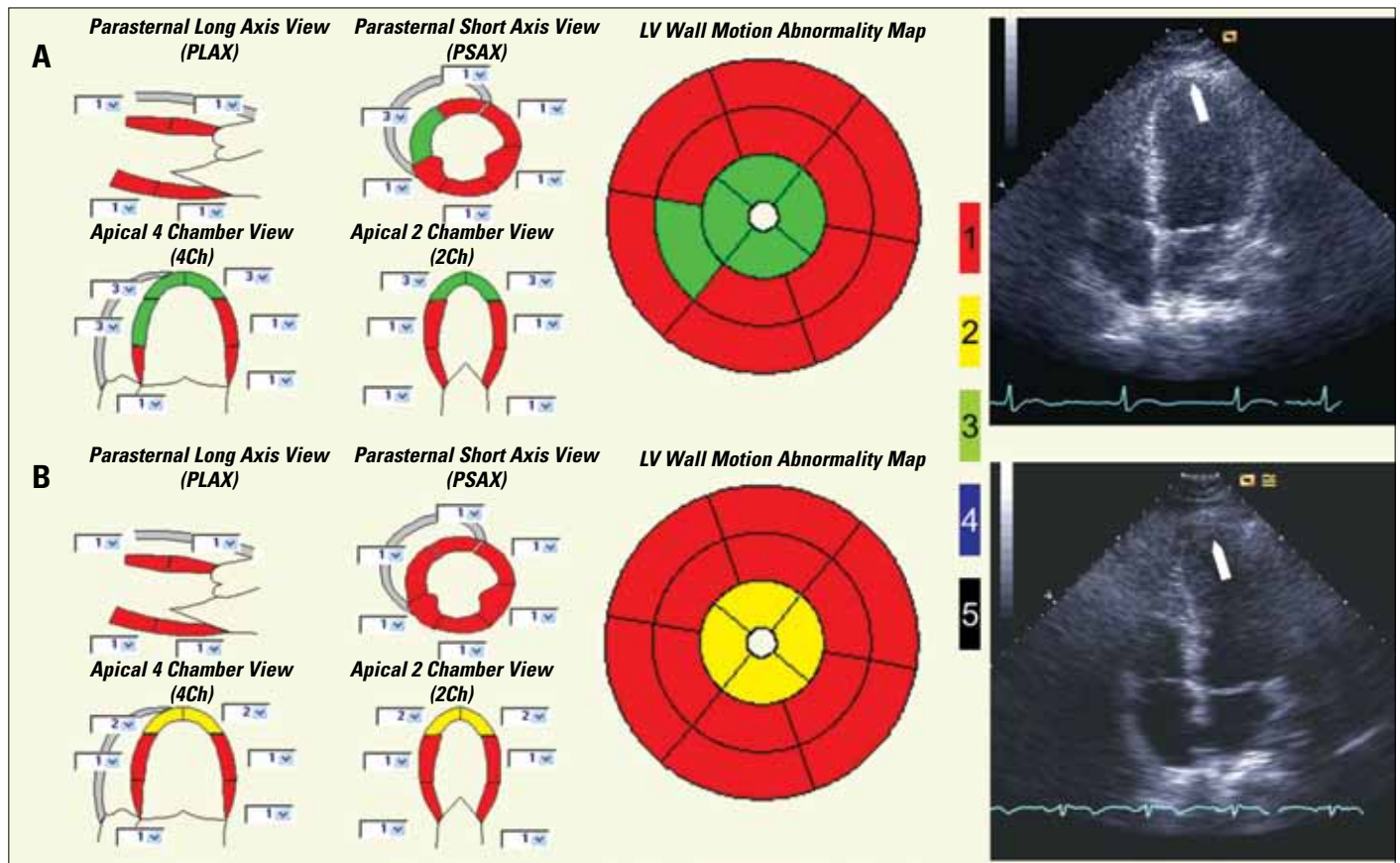


Figure 2. Wall motion abnormalities detected by echocardiography and registration on polar maps in the HCC software
Segmental wall motion abnormality at admission (A) and follow-up (B). Colors reflect different severities of segmental wall movement disorders: 1 - normokinesis, 2 - hypokinesis, 3 - akinesia, 4 - dyskinesis, and 5 - aneurysm. By registration of the results from standard echocardiographic slices, the software revealed 5 left ventricular wall segments with akinesia (A). At the follow-up, the 4-segment akinesia improved to hypokinesis, and the midseptal region became normokinetic (B). Arrows on the right side of the picture show apical akinesia at admission and hypokinesis in the same area in the control examination.
2Ch - apical 2-chamber view; 4Ch - apical 4-chamber view; LV - left ventricle; PLAX - parasternal long-axis view; PSAX - parasternal short-axis view

cance was a two-sided value of 0.05. Positive and negative predictive values were calculated by standard methods. Within-subject differences between follow-up and admission parameters were tested using student's paired t-tests separately in the early and late groups. Late versus early group comparisons were evaluated using student's two-sample t-tests separately at admission and follow-up. Regression analysis was used to determine the relation between the change in regional wall motion and the elapsed time from the symptoms. All statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistics v20.0.0, USA).

Results

All subjects participating in this study received bare-metal stents during PCI with an average diameter and length of 3.33 ± 0.68 and 22.63 ± 8.86 mm, respectively. A total number of 64 stents were used for recanalization of the LAD (26), CX (10), and RCA (21). During angiography, significant collateral circulation was not detected in any case (collateral grade was 0-1 according to the Rentrop classification) (21).

From the 57x16 (912) segments analyzed, the data from the angiography performed at admission indicated that 341 left ventricular segments were areas at risk of the epicardial artery, while echocardiography detected wall motion abnormalities in 206 segments. According to our definition, as echocardiography is the gold standard for the detection of wall motion abnormalities using the 16-segmental model, 149 segments proved to be true-positive, because echocardiography detected the wall motion abnormality that was indicated by angiography as the area at risk. Only 57 segments with a wall motion abnormality outside the area at risk were considered false-negatives, while a further 193 segments that showed no wall motion abnormalities but were in the region supplied by the occluded artery were characterized as false-positives. All of the other 513 segments were true-negatives.

Evaluation of the overlap between the area at risk by angiography and the echocardiography findings revealed that angiography predicted the left ventricular segments with wall motion abnormalities with a positive predictive value of 0.47. The negative predictive value of angiography in predicting a wall motion abnormality was 0.9, demonstrating that echocardiography

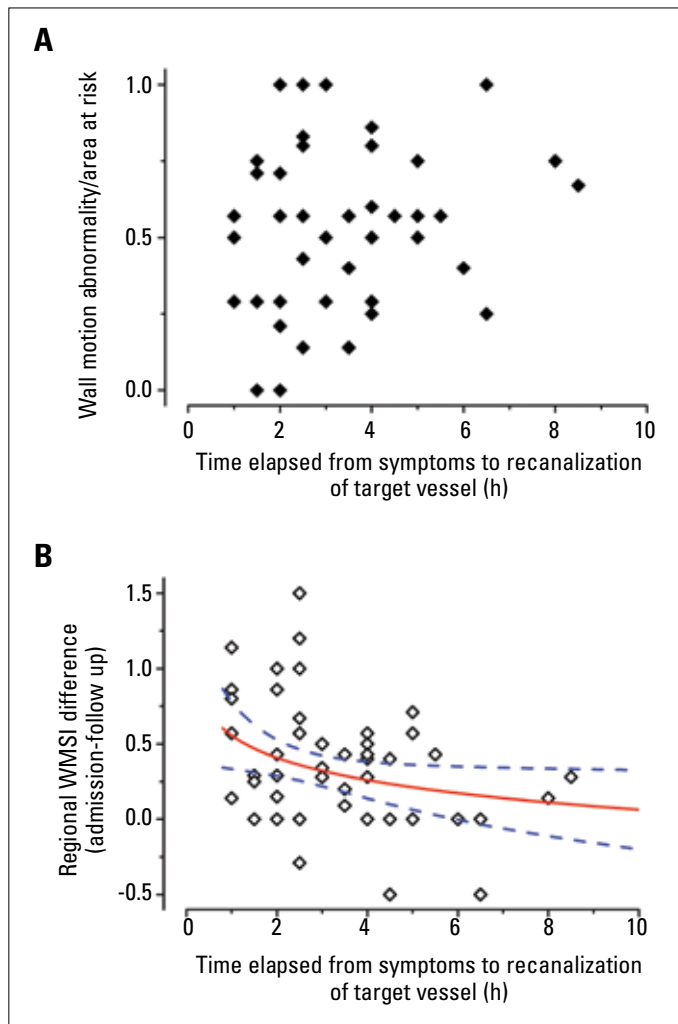


Figure 3. Data relating to the wall motion abnormality at admission and the rate of improvement in relation with the time elapsed from the onset of symptoms

Panel A represents the number of segments with wall motion abnormality/area at risk ratio in relation to the time from the beginning of the symptoms. The "x" axis denotes the time elapsed from the occlusion in hours-i.e., the time from the onset of the symptoms. The "y" axis represents the ratio between the number of segments with wall motion abnormalities detected by echocardiography and the number of segments endangered by perfusion defects diagnosed by angiography. Panel B shows the correlation between the difference of the regional WMSI between the admission and the follow-up values and the time elapsed until recanalization of the target vessel. The continuous line indicates the regression fit for the displayed data ($r=-0.29$; $p<0.03$); dashed curves indicate the upper and lower 95% confidence limits. WMSI - wall motion score index

detected segmental wall motion abnormalities only in a few cases outside the angiographically defined area at risk. We have to emphasize that the relatively low value of the positive predictive value is not the measure of a diagnostic tool of the HCC program. In our approach, the occlusion-associated segments were defined by the angiogram, and the relation with the detected wall motion abnormalities was evaluated by the predictive values. The low positive predictive value in this case means that wall motion abnormalities can be detected only in a part of the

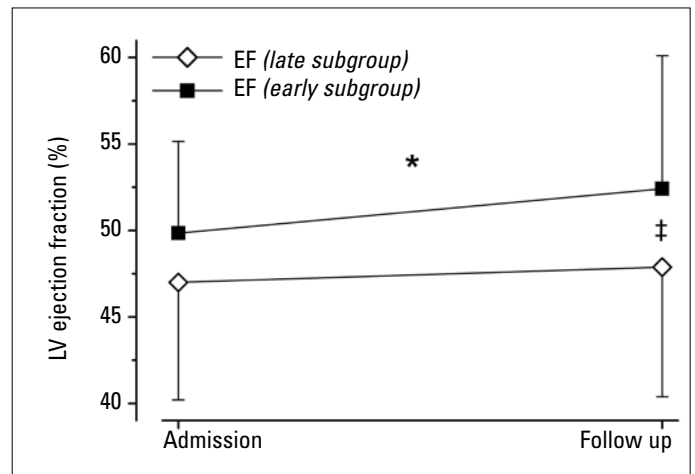


Figure 4. Changes in LV ejection fraction during the follow-up time in the two subgroups

The improvement of LV ejection fraction from hospital admission to follow-up was significant (asterisk, $p=0.04$) in those patients who arrived within 3 hours from the beginning of chest pain (closed square), while late-comers did not demonstrate a significant improvement (open diamond). There was no significant difference in LVEF at admission between the two subgroups; however, the difference became significant at the follow-up (double cross, $p=0.03$).

EF - ejection fraction; LV - left ventricle

occlusion-associated regions. This phenomenon can be explained mainly by the function of collaterals.

Figure 3A illustrates data relating to the wall motion abnormality at admission in relation to the time elapsed from the onset of symptoms until the time of revascularization. The x-axis denotes the time elapsed from the occlusion-i.e., the time from the onset of the symptoms, in hours. According to the regression analysis, it can be concluded that the evaluation of the admission echocardiography results did not reveal a significant correlation between the time elapsed from the onset of pain until the revascularization and the ratio of the size of the wall motion abnormality at risk.

Figure 3B depicts the rate of improvement of the wall motion abnormality with regard to the time elapsed from the onset of pain until revascularization (x-axis). The "y" axis represents the improvement in wall motion, calculated from the difference between the admission and follow-up rWMSI. A significant correlation is clearly seen ($r=-0.29$, $p<0.03$) between the wall motion improvement and ischemic time.

Analyzing all patient data, the left ventricular EDD and ESD were measured by cardiac ultrasound at the hospital admission and at follow-up. Then, the patients were divided into two subgroups, based on the time elapsed from the beginning of the symptoms until revascularization: 33 patients were within 3 hours, and 24 were later. Patients undergoing PCI within 3 hours from the onset of pain (early subgroup) showed significant improvement in LVEF at the follow-up (49.85 ± 5.3 vs. $52.41\pm 7.7\%$, $p=0.04$) (Fig. 4) but no significant change in EDD (51.66 ± 4.9 vs. 52.91 ± 6.0 mm, $p=0.24$) and ESD (34.56 ± 4.7 vs. 35.72 ± 6.1 mm, $p=0.29$) (Fig. 5).

However, if PCI was performed later than 3 hours from the beginning of chest pain (late subgroup), a significant increase in

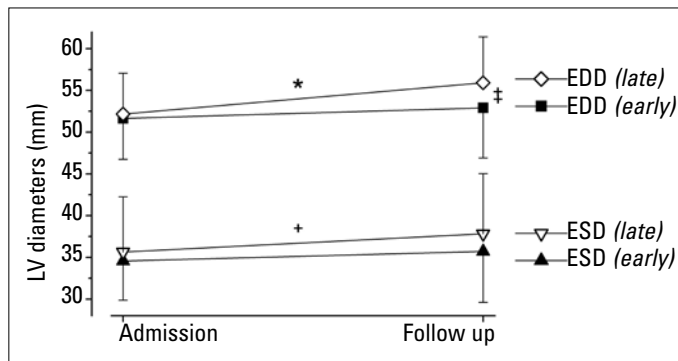


Figure 5. Changes in LV diameters at follow-up in the two subgroups
Diagram indicating the left ventricular end-diastolic and end-systolic diameters (EDD and ESD) at admission and follow-up. In the early subgroup, these parameters did not change significantly (closed symbols), whereas in the late subgroup, a significant increase was observed (open symbols; asterisk, $p < 0.01$, single cross, $p = 0.04$), resulting in a significant difference in EDD between the two subgroups at the follow-up (double cross, $p = 0.03$).

EDD - end-diastolic diameter; ESD - end-systolic diameter; LV - left ventricle

EDD (52.17 ± 4.9 vs. 55.91 ± 5.5 mm, $p < 0.01$) and ESD (35.65 ± 6.6 vs. 37.83 ± 7.2 mm, $p = 0.04$) was observed (Fig. 5), while no significant improvement of LVEF (47.0 ± 6.8 vs. 47.88 ± 7.5 %, $p = 0.53$) was detected (Fig. 4).

Figure 4 also shows that at admission, there was no significant difference in LVEF between the two subgroups (early vs. late: 49.85 ± 5.3 vs. 47.0 ± 6.8 , $p = 0.07$, respectively), whereas a significant difference evolved for the benefit of the early subgroup at follow-up with regard to final LVEF (early vs. late: 52.41 ± 7.7 vs. 47.88 ± 7.5 , $p = 0.03$, respectively).

Figure 5 indicates the left ventricular end-diastolic and end-systolic diameters (EDD and ESD) in both groups, measured by echocardiography at hospital admission and at follow-up. At hospital admission, EDD and ESD did not differ significantly in the two subgroups (51.66 ± 4.9 vs. 52.17 ± 4.9 mm, $p = 0.70$ and 34.56 ± 4.7 vs. 35.65 ± 6.6 mm, $p = 0.46$, respectively). At the follow-up, EDD changed significantly, while ESD did not (52.91 ± 6.0 vs. 55.91 ± 5.5 mm, $p = 0.03$ and 35.72 ± 6.1 vs. 37.83 ± 7.2 mm, $p = 0.25$, respectively).

Discussion

Our investigations indicate that in the first couple of hours of occlusion, the extent and severity of the wall motion abnormality related to the occluded coronary artery are not affected by the pain-to-balloon time.

By means of contrast-MRI examinations (using the BARI and modified APPROACH scores), Ortiz-Pérez et al. (22) demonstrated that the lateral advance of the endangered area in STEMI evolves almost completely in the first hour, after which the direction becomes transmural. Gerber suggested that those score systems were easy to apply but lacked reference examinations (23). In patients with a similar medical history, the wall motion abnormalities detected by 2-D echocardiography differed significantly in some instances. It is probable that the considerable

individual differences were due to the presence and maturity of collaterals and differences in the ischemic tolerance or metabolic characteristics of the myocardium involved.

Our results, which have not been reported yet in human settings, were compared with those of the experimental models mentioned previously. Gillam et al. (4) performed single canine coronary ligation and evaluated the severity of wall motion abnormalities sequentially every 10 min in the first 90 min and then every 30 min up to a total of 6 h. These investigations revealed that the wall motion abnormality evolved almost completely in the first 10 min and did not change significantly in the remaining hours.

In our clinical investigation, the onset of pain was taken as the time of the occlusion, while the ischemic time was considered the time until revascularization. The results of the follow-up echocardiography approximately 3 months after the episode suggested that following the PCI, the future wall motion improvement was highly dependent on how quickly it was possible to reinstate perfusion in the occluded artery. In patients whose perfusion was restored earlier with PCI, the follow-up echocardiography reflected a significantly better improvement.

The significant improvement of LVEF and no significant change of left ventricular diameters in the early PCI group can be explained by successful timely revascularization, showing that there was no substantial remodeling in the myocardium. In late-comer patients, the delay in the intervention caused possible global remodeling, resulting in a significant increase of the left ventricle diameters but no improvement in LVEF. The earlier the patient underwent primary PCI, the better the results were during the follow-up, from the aspect of improvement in the regional wall motion in the area affected by the occlusion. The presence of remodeling in the late revascularization group resulted in significant difference between the two subgroups with regards to EDD and LVEF at the follow-up.

Definition of the area at risk in clinical practice has considerable importance, because it is an independent predictor of the extent of the myocardial infarction and also correlates with mortality (24). Moreover, in evaluations of the efficacy of additional treatment regimens accompanying PCI (e.g., glycoprotein IIb/IIIa inhibitor, thrombus aspiration, stem cell treatment, etc.), it is necessary to compare the area at risk and the final size of the necrosis. Our investigation has demonstrated that in an evaluation of the time relation of the effect of revascularization in myocardial infarction, it is important to see the results in an integrated form. Only such a complex comparison of the results can serve as an exact performance indicator of the treatment.

Study limitations

The number of patients enrolled into the study seems to be low in comparison to the general occurrence of ischemic heart disease. The relatively low number of enrolled patients is primarily due to the rigorous inclusion and exclusion criteria, focusing on patients with first STEMI and single vessel disease.

In our study, the follow-up duration of the patients for the investigation of improvement of the wall motion abnormality after recanalization of the coronary artery was relatively short. Although the improvement in left ventricular function and in left ventricular remodeling continues for years (25), the ample publications in this field indicate that the improvement can be completed in this time period (26, 27). During the follow-up, repeat coronary angiography was not performed; therefore, only the clinical evaluation formed the basis for the exclusion of any ischemic event. In this way, a silent angiographic restenotic process could not be ruled out; however, in this relatively short observation period, this is quite unlikely.

The assessment of wall motion abnormalities by echocardiography was hampered by some subjectivity; however, the sensitivity of the echocardiography evaluation in our approach was improved by continuous recording and an off-line analysis by two independent investigators who were blinded to the PCI result.

Conclusion

According to our best knowledge, our results first demonstrated in humans that in the first hours from the occlusion of the coronary artery, the extent and severity of the wall motion abnormality detected on echocardiography are not affected by the elapsed time from the onset of the occlusion. We found considerable individual differences in the ratio of the segments with wall motion abnormalities in the area at risk, which were presumably due to the function of collaterals or differences in the ischemic tolerance of the myocardium involved. The results of follow-up echocardiography, in concordance with previous studies, showed that the wall motion improvement was highly dependent on ischemic time, underlying the significance of the elapsed time until recanalization.

In our opinion, our integrated approach of the evaluation of the area at risk derived by coronary angiography and the contraction pattern on the echocardiography both in the acute phase and during the follow-up provides an exact measure of different treatment methods of acute myocardial infarction.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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