

Echocardiographic Predictors of Ventricular Remodeling After Acute Myocardial Infarction in Rats

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Abstract

Background: The prediction of the ventricular remodeling process after acute myocardial infarction (AMI) may have important clinical implications.

Objective: To analyze echocardiographic variables predictors of remodeling in the infarction model in rats.

Methods: The animals underwent echocardiography in two moments, five days and three months after infarction (AMI group) or sham surgery (control group). Linear regression was used to identify the echocardiographic variables on the fifth day after the infarction, which were predictive of remodeling after three months of coronary occlusion. We considered as a criterion of remodeling in this study, the values of left ventricular diastolic diameter (LVDD) after three months of infarction.

Results: The infarction induced increase in the left chambers, associated with changes in systolic and diastolic functions. The variables body weight, left ventricular wall stress index (LVWSI), systolic area (SA), diastolic area (DA), LVDD, left ventricular systolic diameter (LVSD), fractional area change (FAC), ejection fraction (EF), fractional shortening (%Short), posterior wall shortening velocity (PWSV) and infarct size assessed five days after infarction were predictors of LVDD after three months. At the multivariate regression analysis, we included the size of infarction, the LVWSI and PWSV. The LVWSI (coefficient: 4.402, standard error: 2.221, $p = 0.05$), but not the size of infarction and PWSV, was a predictor of remodeling after three months of infarction.

Conclusion: LVPSI was an independent predictor of remodeling three months after the myocardial infarction and could be included in the clinical stratification after the coronary occlusion. (Arq Bras Cardiol 2011;97(6):502-506)

Keywords: Ventricular remodeling, myocardial infarction, rats, echocardiography.

Introduction

After an acute myocardial infarction (AMI), changes can occur in ventricular architecture involving both infarcted and the non-infarcted region. These morphological alterations are the result of genetic, cellular and molecular cardiac alterations that occur in response to certain injury. All these adaptations, which are clinically detected by changes in the ventricular composition, mass, volume and geometry, is called “cardiac remodeling”¹⁻⁴.

The presence and intensity of remodeling are directly associated with worse prognosis, as this process results in a higher prevalence of ventricular rupture, aneurysms and malignant arrhythmias. Additionally, remodeling is related to the onset and progression of ventricular dysfunction after the infarction¹⁻⁶. Therefore, early identification of variables

that could determine the evolution of remodeling after infarction may have important clinical implications.

Another relevant aspect refers to the fact that one of the most frequently used strategies for the study of remodeling due to coronary occlusion is the experimental infarction model in rats. Among other factors, the use of this model is due to the similarity between the pathophysiological changes that occur in rats and humans after the infarction^{7,8}.

In recent years, echocardiography has been used for the assessment of secondary ventricular remodeling in different etiologies, including the one in the experimental infarction model in rats. Thus, the objective of this study was to identify possible predictors of the ventricular remodeling process assessed by echocardiography in infarcted rats.

Methods

The experimental protocol of the present study was approved by the Ethics Committee on Animal Experimentation of our institution, and complies with the Ethical Principles in Animal Research adopted by Brazilian College of Animal Experimentation (COBEA).

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Experimental infarction

Male Wistar rats, weighing 200-250 grams, were evaluated in the study. Acute myocardial infarction was produced according to the previously described method⁹. In brief, the rats were anesthetized with ketamine hydrochloride (50 mg/kg) and submitted to left thoracotomy. After exteriorization of the heart, the left atrium was pushed aside, and the left coronary artery was ligated with a 5.00 mononylon thread between the emergence of the pulmonary artery and the left atrium. The heart was then returned to the thorax, the lungs were inflated with positive pressure and the surgical wound was closed by sutures with cotton 10. Coronary occlusion was not performed in 15 animals (control group).

The animals were kept in cages for recovery, were fed standard commercial rodent chow and had free access to water, with light control - 12-hour cycles, temperature of about 25 ° C and controlled humidity.

Echocardiographic study

Echocardiography was performed at two different moments, five days and three months after the infarction. The surviving animals were anesthetized with ketamine hydrochloride (50 mg/kg) and xylazine (1 mg/kg) intramuscularly, for the echocardiographic study. After trichotomy of the anterior chest region, the animals were placed supine on specially designed holder, which allows slight rotation to the left for the examination to be carried out, using a Philips equipment (model HDI 5000), equipped with a multifrequency electronic transducer of up to 12 MHz. All measurements were carried out in accordance with the recommendations of the American Society of Echocardiography and the European Association of Echocardiography¹⁰, which have been described in the infarcted rat model^{11,12}.

The image of the left ventricular cavity was obtained by positioning the M mode cursor between the papillary muscles, just below the mitral valve plane. The left ventricular diastolic diameter (LVDD) and left ventricular septal thickness (LVST) were measured at the time corresponding to the maximum cavity diameter. The left ventricular systolic diameter (LVSD) was measured at the maximum systolic excursion of the cavity posterior wall. The left ventricular (LV) diastolic area (DA) and systolic area (AS) were measured in two-dimensional mode, using planimetry in the parasternal short-axis plane. We considered as a criterion of remodeling in this study, the values of LVDD after three months of infarction.

The left ventricular wall stress index (LVWSI) was determined by the formula: $(\text{diastolic area} / 2 \times \text{LVST})^{13}$. The LV systolic function was assessed by calculating the fractional area change (FAC), posterior wall shortening velocity (PWSV), ejection fraction (EF) and endocardial fractional shortening (%Short). Diastolic function was assessed by E/A ratio, the E wave deceleration time (EDT) and the isovolumetric relaxation time adjusted by heart rate (IVRT/HR).

To estimate the infarction size, endocardial circumferences of the akinetic or dyskinetic regions and

non-infarcted segments were determined, as previously described^{14,15}. The infarct size was calculated by dividing the ventricular endocardial circumferences of the infarcted region by the total endocardial circumferences.

The parameter used to characterize cardiac remodeling was the LVDD.

Statistical analysis

Comparisons between the groups after three months were carried out with Student's *t* test when the data showed normal distribution. However, when the distribution was not normal, comparisons between groups were carried out using Mann-Whitney U test. Data were expressed as mean \pm standard deviation or median with 25th and 75th percentiles. Predictive values were analyzed by univariate and multivariate linear regression. The significance level was set at 5%. Statistical analysis was performed with the SigmaStat for Windows v3.5 (SPSS Inc., Chicago, IL).

Results

Five days after the infarction, several potential echocardiographic parameters that could predict the remodeling process after three months were assessed in infarcted animals ($n = 39$), including infarct size, left atrial diameter, LVDD, LVSD, LVST, LVWSI, DA, SA, FAC, PWSV, EF, %Short, heart failure (HF), E/A, EDT and IVRT/HR (Table 1).

After three months, no differences were found between the groups regarding body weight (control group = 467 ± 51 g, AMI = 351 ± 51 g, $p = 0.345$) and heart rate (control = 267 ± 19 bpm, AMI = 266 ± 27 bpm, $p = 0.956$).

The results of the echocardiographic study after three months are shown in Table 2. In the AMI group, the infarct sizes were $41 \pm 9\%$. As expected, infarcted animals ($n = 32$) had greater left atrial diameters and increased LV cavity in diastole and systole, as compared to control animals ($n = 15$). Likewise, infarcted animals had lower levels of FAC, PWSV, EF and %Short. Regarding diastolic function, myocardial infarction resulted in higher values of E wave and IVRT / HR, with lower values of the EDT. The LVWSI was statistically higher in infarcted animals when compared to the control group.

The factors predictive of remodeling in the univariate analysis are shown in Table 3. The variables body weight, LVPSI, DA, SA, LVDD, LVSD, FAC, PWSV, EF, % Short and infarct size were predictors of LVDD after three months. On the other hand, the variables of diastolic function and left atrial diameter adjusted for body weight were not predictors of remodeling.

In the multivariate linear regression analysis, our model included infarct size, the LVWSI and PWSV. The LVWSI (coefficient: 4.402, standard error: 2.221, $p = 0.05$), but not infarct size (coefficient: -0.005, standard error: 0.0221, $p = 0.80$) and PWSV (coefficient: - 0.041, standard error: 0.029, $p = 0.17$) was a predictor of remodeling three months after the infarction.

Discussion

The aim of this study was to identify possible predictors of the ventricular remodeling process assessed by echocardiography in infarcted rats. Our results suggest that the morphological variables, systolic function, infarct size and LV wall stress, evaluated five days after the infarction, are predictors of remodeling after three months of coronary occlusion. However, at the multivariate analysis, only the LV wall stress was a predictor of remodeling three months after the AMI.

Although the process is extremely complex, after the myocardial infarction, remodeling is clinically characterized by an increased ventricular cavity. In the acute phase, ventricular dilation is a consequence of the infarction expansion process, whereas late cavity dilation is a result of eccentric hypertrophy¹⁻⁴. Thus, the diagnosis of remodeling after infarction is clinically based on the detection of an increased LV cavity. For this reason, in our study, the chosen parameter of remodeling was LVDD. Hence, we observe that the infarcted animals showed significantly higher values of LVDD than the control group animals, confirming that the infarction induced remodeling three months after the coronary occlusion.

Currently, the most important aspects to be considered in myocardial infarction treatment are prevention and

remodeling process attenuation. Consequently, the early identification of factors associated with remodeling can be extremely relevant, as high-risk situations can be treated more aggressively.

Regarding the determinants of the remodeling process after the infarction, it is accepted that a key modulator of progressive ventricular dilatation is the infarction size. Although the remodeling occurs with different sizes of ischemic injury, its predominance is observed in larger infarctions. Similarly, a minimum lesion size (16%-20%) seems to be necessary, as a prerequisite, for the remodeling to occur^{1,16,17}. In our study, the results are in agreement with this concept, as the size of infarction was a predictor of the ventricular cavity diameter. Interesting, however, was the fact that the infarct size did not remain a determinant of remodeling in the multivariate analysis, suggesting that in the rat model, other factors may be more important the cause of this process.

Another factor that can potentially determine the frequency and intensity of remodeling after infarction is the ventricular function. However, the available data in clinical trials on the role of systolic dysfunction as a predictor of remodeling are controversial^{6,18,19}. A possible explanation for this conflict was given by the Heart study²⁰. In that study, 20% of the patients undergoing reperfusion therapy showed complete recovery, and approximately 50% of the patients showed

Table 1 - Echocardiographic study after five-day observation

| Variables | Control (n = 15) | AMI (n = 32) | p |
|-----------------------|------------------|------------------|--------|
| LA (mm) | 4.9 ± 0.45 | 6.3 ± 0.88 | <0.001 |
| LVDD (mm) | 7.48 (7.15-7.64) | 8.64 (7.98-9.41) | <0.001 |
| LVSD (mm) | 3.64 (3.29-4.10) | 6.51 (5.87-7.38) | <0.001 |
| E (cm/s) | 87 (84-89) | 110 (96-125) | <0.001 |
| A (cm/s) | 53 (48-59) | 42 (23-90) | 0.639 |
| E/A | 1.65 (1.49-1.78) | 2.44 (1.13-5.56) | 0.393 |
| IVRT/HR | 54.1 (44.2-58.0) | 59.8 (51.4-65.6) | 0.025 |
| EDT (ms) | 47.1 ± 6.6 | 34.6 ± 6.9 | <0.001 |
| DA (cm ²) | 0.40 (0.36-0.42) | 0.59 (0.51-0.66) | <0.001 |
| SA (cm ²) | 0.11 (0.10-0.13) | 0.38 (0.27-0.44) | <0.001 |
| FAC (%) | 71 (70-73) | 37 (31-46) | <0.001 |
| PWSV (mm/s) | 33.7 (31.5-35.5) | 25.5 (19.9-30.8) | <0.001 |
| EF | 0.87 (0.85-0.91) | 0.56 (0.44-0.63) | <0.001 |
| % Short (%) | 50 ± 4.9 | 24 ± 8.3 | <0.001 |
| LVPSI | 0.24 (0.22-0.26) | 0.41 (0.31-0.46) | <0.001 |

AMI – acute myocardial infarction; LA – left atrium diameter; LVDD – left ventricular diastolic diameter; LVSD – left ventricular systolic diameter; IVRT/HR – isovolumetric relaxation time, adjusted by heart rate; EDT – E-wave deceleration time; DA – diastolic area; SA – systolic area; FAC – fractional area change; PWSV – posterior wall shortening velocity; EF – ejection fraction; %Short – percent of endocardial shortening; LVPSI – left ventricular wall stress index. Data are expressed as means ± standard deviation (for parametric distribution) or median with 25th and 75th percentiles (for non-parametric distribution).

Table 2 - Echocardiographic study after three-month observation

| Variables | Control (n = 15) | AMI (n = 32) | p |
|-----------------------|------------------|------------------|--------|
| LA (mm) | 6.2 (5.6-6.4) | 7.1 (6.7-8.2) | <0.001 |
| LVDD (mm) | 8.52 (8.32-8.87) | 10.6 (9.83-11.2) | <0.001 |
| LVSD (mm) | 4.1 (3.99-4.56) | 8.44 (7.23-9.32) | <0.001 |
| E (cm/s) | 87 (80-93) | 100 (82-120) | 0.017 |
| A (cm/s) | 60 (53-65) | 38 (19-75) | 0.201 |
| E/A | 1.45 (1.28-1.58) | 1.91 (1.14-5.94) | 0.141 |
| IVRT/HR (ms) | 57 ± 9.4 | 66 ± 11.3 | 0.017 |
| EDT (ms) | 49 ± 6.3 | 42 ± 8.6 | 0.003 |
| DA (cm ²) | 0.48 (0.44-0.49) | 0.88 (0.81-0.95) | <0.001 |
| SA (cm ²) | 0.15 (0.14-0.16) | 0.60 (0.52-0.69) | <0.001 |
| FAC (%) | 68 ± 4.4 | 32 ± 8.7 | <0.001 |
| PWSV (mm/s) | 35 ± 4.1 | 24 ± 7.1 | <0.001 |
| EF | 0.88 (0.87-0.90) | 0.50 (0.40-0.63) | <0.001 |
| % Short (%) | 50 ± 4.9 | 21 ± 8.1 | <0.001 |
| LVPSI | 0.33 (0.30-0.35) | 0.71 (0.63-0.80) | <0.001 |

AMI – acute myocardial infarction; LA – left atrium diameter; LVDD – left ventricular diastolic diameter; LVSD – left ventricular systolic diameter; IVRT/HR – isovolumetric relaxation time, adjusted by heart rate; EDT – E-wave deceleration time; DA – diastolic area; SA – systolic area; FAC – fractional area change; PWSV – posterior wall shortening velocity; EF – ejection fraction; %Short – percent of endocardial shortening; LVPSI – left ventricular wall stress index. Data are expressed as means ± standard deviation (for parametric distribution) or median with 25th and 75th percentiles (for non-parametric distribution).

Table 3 - Predicting factors of remodeling after three months of coronary occlusion, evaluated five days after the infarction

| Variables | Coefficient | Standard Error | p |
|-----------------------|-------------|----------------|--------|
| Body weight | 0.016 | 0.006 | 0.01 |
| Size of infarction | 0.005 | 0.002 | 0.028 |
| LA (mm) | 1.430 | 0.512 | 0.009 |
| LVDD (mm) | 0.471 | 0.193 | 0.021 |
| LVSD (mm) | 0.384 | 0.127 | 0.005 |
| E/A | 0.123 | 0.069 | 0.084 |
| IVRT/HR | -0.025 | 0.014 | 0.087 |
| EDT (ms) | -0.024 | 0.028 | 0.382 |
| DA (cm ²) | 5.138 | 1.302 | <0.001 |
| SA (cm ²) | 4.800 | 1.162 | <0.001 |
| FAC (%) | -0.0469 | 0.012 | <0.001 |
| PWSV (mm/s) | -0.072 | 0.023 | 0.005 |
| EF | -3.176 | 1.142 | 0.009 |
| % Short (%) | -0.049 | 0.018 | 0.010 |
| LVPSI | 5.419 | 1.456 | <0.001 |

LA – left atrium diameter; LVDD – left ventricular diastolic diameter; LVSD – left ventricular systolic diameter; IVRT/HR – isovolumetric relaxation time, adjusted by heart rate; EDT – E-wave deceleration time; DA – diastolic area; SA – systolic area; FAC – fractional area change; PWSV – posterior wall shortening velocity; EF – ejection fraction; % Short – percent of endocardial shortening; LVPSI – left ventricular wall stress index.

partial recovery of systolic function during the first two weeks after infarction. This fact suggests that, due to the stunned myocardium phenomenon, the predictive value of systolic function variables in reperfused patients in the early phase after the infarction may be limited.

In our experimental model, with no reperfusion strategy, systolic function, assessed by four variables, was predictive of remodeling in the univariate, but not in the multivariate analysis, suggesting dependence on other factors as determinants of remodeling. The presence of diastolic dysfunction was associated with the remodeling process in some studies²¹, but not all²². In our study, diastolic function was not a determinant of ventricular dilatation in this model.

Another important aspect to consider is the participation

of wall stress as a determinant of the remodeling process. One of the pathophysiological explanations for the progressive cavity dilatation in the chronic phase of infarction is the wall stress. In infarcted hearts, the normal elliptical configuration of the heart can be lost and a more spherical shape can appear. Consequently, there is a significantly greater increase in wall tension during diastole than in systole. It is believed that the increase in stress would stimulate sarcomere replication, preferably in series^{23,24}. Therefore, the wall stress can be considered a stimulus for the remodeling process progression in the chronic phase of infarction.

In spite of the conceptual importance of this stress, we are not aware of previous studies that have evaluated this variable through echocardiography as a determinant of remodeling in this model. In our study, wall stress, measured noninvasively in the early phase of infarction, was an independent predictor of ventricular remodeling three months after coronary occlusion. Therefore, we believe that our study adds important data to the association of wall stress with left ventricular dilatation, suggesting that this variable could be used as a marker of the remodeling process.

Conclusion

The LVWSI, evaluated five days after the coronary occlusion by echocardiography, was an independent predictor of remodeling three months after the infarction in rats and could be incorporated as a tool for clinical stratification in this model.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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