

The beneficial effect of revascularization on patients with severe left ventricular dysfunction and viable myocardium: reverse remodeling and prognosis

Benefício da revascularização do miocárdio em pacientes com disfunção ventricular e músculo viável: remodelamento ventricular reverso e prognóstico

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Abstract

Objectives: To evaluate the integration of both viability and clinical parameters on the improvement in systolic performance, symptoms and prognosis, with post-revascularization reverse remodeling.

Method: One hundred and fifteen patients underwent thallium-201 imaging before myocardial revascularization. Left ventricular ejection fraction, left ventricular end-systolic volume index and left ventricular end-diastolic volume index were determined before and at each 6 months post-revascularization for 3 years.

Results: Patients with ≥ 4 viable segments evidenced by thallium-201 imaging demonstrated an improvement in the left ventricular ejection fraction of from 34 ± 6 to $44 \pm 4\%$, $p < 0.001$, left ventricular end-systolic volume decreased from 78.3 ± 11 to 57 ± 17 mL/m², $p < 0.001$; left ventricle end-diastolic volume decreased from 113 ± 31 to 91 ± 22 mL/m², $p < 0.001$. Patients with < 4 viable segments failed to demonstrate an improvement of the left ventricle ejection fraction, 33.4 ± 4

vs. $35.1 \pm 5\%$ ($p = 0.19$), and exhibited ongoing left ventricle end-systolic remodeling, 72 ± 23 vs. 73 ± 12 mL/m² ($p = 0.81$) and the left ventricle end-diastolic volume increased from 112 ± 24 to 118 ± 16 mL/m² ($p = 0.34$), without improvement in the NYHA functional class and worse long-term prognosis (event; log rank test, $p = 0.0053$). The multivariable analysis demonstrated clinical variables related to the unfavorable evolution showed diabetes, more than one myocardial infarction and a long time interval between myocardial infarction and surgery were associated with worse prognosis.

Conclusion: The benefits of myocardium revascularization in patients with viable muscle, as well as an improvement in the left ventricular ejection fraction, provide reverse remodeling, improvement in functional class and favorable long-term prognosis.

Descriptors: Myocardial revascularization. Ventricular remodeling. Heart failure, congestive.

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Resumo

Objetivo: Analisar a importância da viabilidade do miocárdio e parâmetros clínicos na melhora da função ventricular, sintomas e prognóstico, como reversão do remodelamento.

Método: Cento e quinze pacientes submetidos a revascularização do miocárdio com análise prévia da viabilidade do miocárdio com thallium-201. Fração de ejeção, volumes sistólicos e diastólicos do ventrículo esquerdo e classe funcional foram determinados, antes da cirurgia e a cada seis meses por 3 anos.

Resultados: Pacientes com ≥ 4 segmentos viáveis demonstraram melhora da fração de ejeção de 34 ± 6 para $44 \pm 4\%$ ($p < 0,001$), o volume diastólico foi de 113 ± 31 para 91 ± 22 ml/m² ($p < 0,001$) e o volume sistólico foi $78,3 \pm 11$ para 57 ± 17 ml/m² ($p < 0,001$). No grupo com < 4 segmentos viáveis, foi de

$33,4 \pm 4$ vs. $35,1 \pm 5\%$ ($p = 0,19$), o volume diastólico foi de 112 ± 24 para 118 ± 16 ml/m² ($p = 0,34$), volume sistólico de 72 ± 23 para 73 ± 12 ml/m² ($p = 0,81$). Análise multivariada apontou fatores clínicos relacionados com evolução desfavorável (diabetes mellitus, mais que um infarto e longo intervalo de tempo entre infarto e operação). Melhora da classe funcional (NYHA) no grupo com mais segmentos viáveis e menor quantidade de eventos (log rank test, $p = 0,0053$).

Conclusão: O benefício da revascularização, em pacientes com músculo viável, além da melhora função ventricular, proporciona remodelamento reverso, atenua a dilatação e reduz eventos.

Descritores: Revascularização miocárdica. Remodelação ventricular. Insuficiência cardíaca congestiva.

INTRODUCTION

The left ventricular (LV) function is a potent predictor of prognosis in patients with coronary arterial disease. In ischemic heart disease, coronary artery bypass grafting is the best therapeutic option to increase the LV function [1-2]. However, the viability of the myocardium should be verified in the preoperative period to predict the reversal of the remodeling and the long-term prognosis in respect to the final outcome of the revascularization, the improvement of the LV function. With a greater access to methods that identify viable areas, there was a necessity to define criteria for the selection of patients who would benefit from coronary artery bypass grafting. A substantial quantity of dysfunctional, but viable (hibernating), muscle has a high probability of improving the ventricular function, reducing the symptoms giving a better prognosis [3]. The restoration of an adequate flow to the viable myocardium can prevent enlargement of the LV and remodeling and consequently, thereby preventing the deterioration of the heart insufficiency evolving to death, mainly with recent infarctions with remaining viability [4-5]. The correlation between viability and clinical parameters can be useful in the therapeutic definition of patients with LV dysfunction.

In this study, we analyzed the importance of the myocardium viability and the clinical parameters on the improvement of the ventricular function, symptoms and prognosis. By using thallium-201, the presence and absence of viable tissue and clinical data were analyzed: improvement of the ejection fraction (LVEF %), the final systolic volume (FSV), the final diastolic volume (FDV) and the improvement of the symptoms of heart insufficiency.

METHOD

This study included 115 patients (82 men, mean age 61 ± 10 years), from January 1998 to December 2000, with ischemic heart disease and symptoms of heart insufficiency, on a waiting list for coronary artery bypass grafting. The following inclusion criteria were considered: 1) stable coronary arterial disease; 2) ventricular dysfunction (LVEF $< 40\%$); 3) without associated valve disease (patients with 3 to 4+ mitral valve regurgitation were excluded); 4) without prior heart surgery; 5) without recent myocardial infarction (< 4 weeks of the study).

All patients presented with sinus rhythm. One hundred and twelve (97.5%) patients had a history of acute myocardial infarction which occurred more than 6 months previous to entering in the study. The outcome of the thallium-201 study did not influence the decision of the revascularization. To decision to perform coronary artery bypass grafting depended on the following aspects: symptoms and clinical data, exercise stress testing, echocardiogram and angiogram. The indication for surgery was heart insufficiency in all cases.

Protocol of the study

Patients with ischemic heart disease were prospectively studied for LV remodeling analysis, LVEF, cardiac events in the follow-up period (three years) and the relation of myocardial viability. Before the surgery, bidimensional echocardiogram (2D) was performed to analyze the myocardial function (regional and global) and the geometry of the LV. Myocardial viability was evaluated using thallium-201. After the surgery, a 2D echocardiogram was repeated every 6 months for 3 years. Examinations and clinical

interviews were also performed at 6-month intervals. Cardiac events were reported during the 3 years of evolution. The Ethics Commission approved the protocol and the patients were informed and agreed to participate.

Echocardiographic study

All echocardiograms were performed using a Vivid 3 apparatus (General Electric) with second harmonic and transducers of from 1.8 to 3.6 MHz. Standard images of the LV were obtained at rest (before and sequentially after the surgery). All measurements were performed by the same professional. The volumes of the LV were measured using Simpson's rule biplanar method. The LV systolic and final diastolic volumes (FSV and FDV, respectively) were indexed to the body surface area (FSVI and FDVI). An increase of 5% in the LVEF was considered an improvement in the ventricular function.

201-Thallium

The patients were submitted to a pharmacological test with the infusion of dipyridamol. Thallium-201 chloride (111 MBq) was injected intravenously and images were obtained. Redistribution images were made at 3 - 4 hours. Twenty-four hours after, further images at rest and after re-injection were made. The heart was divided into 20 myocardial segments: six basal segments, six medium-ventricular segments and six apical segments, while the apex represented two segments. Both ischemia and viability were analyzed. Segments at the peak of exercising (stress), 3 - 4 hours redistribution, 24 hours later were classified as being normal levels of Thallium-201 (> 75% of the highest level), moderately reduced levels (50 - 75% of the highest level) or severely reduced levels (< 50% of the highest level).

The segments were classified as ischemic when the perfusion defect was present during stress testing and with significant redistribution occurring at 3 - 4 hours from the redistribution (> 10% increase in activity). Segments were classified as viable when the activity in the 24-hour image was normal (> 75% of the highest level), moderately reduced (50 - 75% of the highest level) or when significant redistribution was greater than 10% of the increase in the activity from the 3 - 4 hour redistribution to the late imaging. For the evolution after revascularization, ischemia and viability are important. Additionally, the segments were classified as ischemic or viable. Segments with a fixed perfusion defect and activity greater than 50% were classified as scarred (fibrotic). The patient was classified as having viable myocardium when four or more segments (representing > 20% of the LV) were at risk. The patients were divided into two groups: Group A, four or more viable segments; and Group B, non-viable, less than 4 viable segments.

Symptoms and evolution

The heart insufficiency was measured by the functional class according to the criteria of the New York Heart Association (NYHA). For each patient, the functional class was determined before the surgery and at 3, 6, 12, 18, 24, 30 and 36 months after surgery, through interviews and clinical examinations. Events included death (cardiac and non-cardiac related), myocardial infarction, hospitalization for heart insufficiency and the necessity of new therapy such as pacemaker implantation for resynchronization or implantable defibrillator.

Statistical analysis

Continuous data were expressed as means \pm standard deviation and compared using the paired and non-paired Student t-test. Univariable analysis for categorical variables was achieved with the chi-squared test. Multivariable analysis correlating hospital mortality, recurrence of heart insufficiency, recurrence of angina and improvement in the functional class (NYHA) was achieved with logistic regression. The variables analyzed were: age, gender, heart insufficiency, hypertension, mellitus diabetes, more than one myocardial infarction, time interval between infarction and surgery (at 6-month intervals), numbers of grafts, myocardial viability and LVEF. Event-free survival rate of the two groups of patients was compared using the Kaplan-Meier curve. Differences in the event-free survival rates were analyzed with log-rank chi-square.

RESULTS

Initially 115 patients were included in the study, 31 (27%) of whom did not complete the protocol. Twenty-one patients did not complete the clinical follow-up because they desisted or contact was lost with them.

In the follow-up period, 10 (8.9%) patients died, 5 related to heart disease. The hospital mortality rate was 2.6%. Mortality related to heart disease occurred in three of these patients in the first postoperative months, one patient due to evolution of the heart insufficiency 6 months after the intervention and one patient due to sudden death fifteen months after. These patients were included in the analysis of the follow up.

Thallium-201

Of the 115 patients, a total of 2,300 segments was analyzed using thallium-201 and classified as: 777 normal segments (>75% of the highest level during stress testing); 431 segments were ischemic; 576 segments were viable and 516 segments were scarred. Based on the data of the thallium-201, the patients were divided into two groups. Group A consisted of 71 patients with ≥ 4 viable segments and Group

B consisted of 44 patients with < 4 viable segments. Both groups presented the same distribution of the types of segments, except for the scarred (fibrotic) segments; group A, 196 (13.08%) segments versus group B, 320 (36.6%) segments; $p=0.008$.

Evolution versus thallium-201

The clinical characteristics did not present significant differences between the groups, except for diabetes, time between the infarction and the surgery and more than one myocardial infarction (Table 1). The LVEF in the preoperative period was similar in both groups. In Group A, the LVEF increased significantly from $34 \pm 6\%$ to $44 \pm 4\%$ ($p<0.001$), whereas there was no significant change in the LVEF of Group B (33.4 ± 4 versus $35.1 \pm 5\%$, $p=0.19$). In the preoperative period, the FDV was similar between the groups. In the postoperative period in Group A, the FDV reduced significantly from 113 ± 31 to 91 ± 22 mL/m² ($p<0.001$). On the contrary, the FDV of Group B increased from 112 ± 24 to 118 ± 16 mL/m² ($p=0.34$). The same was seen for the FSV in the preoperative period which was similar in both groups. In Group A, the FSV increased from 72 ± 23 to 73 ± 12 mL/m² ($p=0.81$) but in Group B the FDV reduced from 78.3 ± 11 to 57 ± 17 mL/m² ($p<0.001$). Variations in the parameters of function and volumes are shown in Table 2 showing opposite directions for the evolution: reverse remodeling in Group A and continued remodeling in Group B. Multivariable analysis identified some factors related with the occurrence of events (Table 3).

Table 1. Clinical characteristics of the patients

Clinical characteristic	Group A n=71	Group B n=44	p-value
Age	66±7	63 ±9	ns
Gender (m/f)	49/22	33/11	ns
SAH	32	19	ns
Diabetes	24	36	0.001
COPD	8	5	ns
Δt MI-surgery(months)	12	27	0.002
Previous MI	68	44	ns
> 1 MI	13	17	0.03
ca. stenosis	2.7±0.6	2.8±0.2	ns
NYHA	2.9±1.1	3.1±0.8	ns
CCS	2.2±1.2	2.0±0.9	ns

SAH: Systemic arterial hypertension; COPD: Chronic obstructive pulmonary disease; Δt MI: Time from myocardial infarction to surgery; MI: myocardial infarction; CCS: Canadian Cardiovascular Society; NYHA: New York Heart Association functional class; ca stenosis: stenosis of the coronary arteries;

Table 2. Variation of the ejection fraction and ventricular volumes after revascularization in Groups A and B

Ventricular Function	Group A n=59	Group B n=25	p-value
Variation of LVEF	9.4±2.9	-0.8±3.1	<0.001
Variation of FSVI	-21±9.8	0.8±6	<0.001
Variation of FDVI	-22±6.1	6±9.2	<0.001

EF: Ejection fraction (%); FSVI: Final systolic volume index; FDVI: Final diastolic volume index

Table 3. Factors related to events

Variable	β factor	p-value
Diabetes	0.04	0.012
MI-surgery(>18m)	0.02	0.03
> 1 MI	0.69	0.02

myocardial infarction - surgery: interval of time. Analyzed from 6 to 6 months. > myocardial infarction: patients with more than one myocardial infarction; MI: myocardial infarction;

However, in Group A, eight patients did not present any improvement in the LVEF. These patients had a FSV greater than those who had improvement in the heart function (68 ± 22 versus 92 ± 5 mL/m², $p=0.003$). Additionally, in Group B, six patients had an improvement in the heart function (LVEF). These patients had changes in volumes less than those who did not present any improvement in the LVEF.

Evolution and functional class

The functional class (NYHA) in the preoperative period was comparable in Groups A and B (2.9 ± 0.7 versus 3.1 ± 0.5 respectively). In Group A, the mean functional class improved from 2.9 ± 0.7 to 2.1 ± 0.6 in the three postoperative months ($p<0.001$) and continued to improve in the evolution to 1.6 ± 0.6 ($p<0.001$) over the long-term. In contrast, in Group B, the mean functional class (NYHA) did not significantly change in the first three postoperative months or over the long-term (2.7 ± 0.6 versus 2.5 ± 0.7 versus 2.7 ± 0.7 , NS). The heart events were less common in the group of viable patients (log-rank test, $p=0.0053$) – Figure 1.

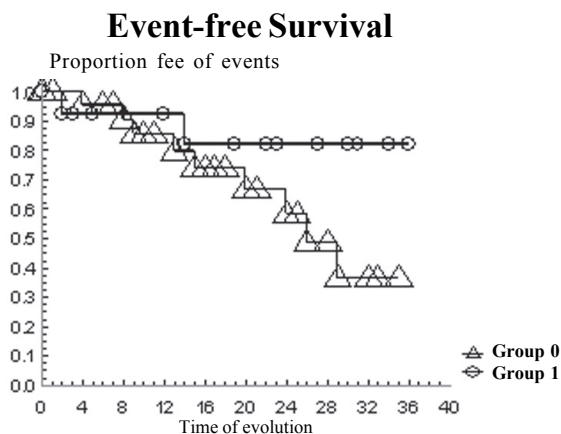


Fig. 1 - Kaplan-Meier curve for events

COMMENTS

Patients with ischemic heart disease and hibernating myocardium present improvement in the ventricular function, relief of symptoms and a better prognosis when they are submitted to coronary artery bypass grafting [1,3,6]. Maybe, the benefit of the coronary artery bypass grafting surgery in patients with viable muscle goes far beyond the simple prevention of recurrent ischemia and directly involves the global ventricular function. The data of the present study indicate that these patients, with a reasonable quantity of hibernating myocardium, present a regression and prevention of the remodeling process installed after the surgery, which is associated with improvement in the symptoms and a good prognosis over the long-term. They also reveal that the time between surgery and infarction is an important factor, as was demonstrated by the multivariable analysis, as well as the presence of diabetes and recurrent infarctions. These data corroborate with the findings of Haas et al. [7], who found a greater normalization of the ventricular function in stunned myocardium compared to hibernating myocardium. Different degrees of myocardial lesions coexist in the same patient and the better recovery after revascularization is time-dependent.

Studies have demonstrated that revascularization of patients with ischemic heart disease and viable areas improves the regional and global function of the ventricle [8]. A substantial quantity ($\geq 25\%$ of the LV) of viable myocardium is necessary to result in an increase of the LVEF and thus an improvement of the ventricular function [2,4-6]. However, in some patients with < 4 viable segments, an increase in the LVEF was observed. These patients had intense angina and, as was seen by echocardiography, small ventricular volumes. In these patients with severe anginal symptoms and preserved ventricular geometry, Di Carli et al. [2] suggested that the myocardial viability is relatively

less important. Recent data suggest that in patients with ischemic heart disease, the preservation of the ventricular geometry and the restraint of the remodeling process after revascularization are important additional objectives [5]. According to this study, the revascularization resulted in an improvement of the LVEF ($> 5\%$ increase in the LVEF from the preoperative evaluation) in only 79.6% of the patients with > 4 viable segments, while reverse remodeling of the ventricle occurred in 89% of these "viable" patients. Six patients of this group did not present improvement of the remodeling process. These patients presented higher ventricular volumes than those who showed regression of the remodeling. Yamaguchi et al. [9] have already shown that a high final systolic volume in the preoperative period ($> 100 \text{ mL/m}^2$) and the absence of heart insufficiency are predictive factors for recurrent heart insufficiency in 39 revascularized patients accompanied over 3.6 years. For this reason, after revascularization some patients with hibernating muscle present with improvement of the remodeling process, although without increases in the ejection fraction.

It is well known that remodeling after acute myocardial infarction is the best determinant of unfavorable prognosis [10]. Mule et al. [5] showed that the reduction of the ventricular volumes three months after surgery only occurred in patients with much hibernating muscle as seen by using Thallium-201 and they simultaneously observed increases in the ventricular volume in 24 patients without viable myocardium after revascularization. A large number of patients were included in this study, and more importantly, the evaluation of the ventricular volumes was sequentially made over a period of time. This showed us that the changes in these volumes occurred in opposite directions in respect to the presence or not of viable segments. In patients with absence of viability and in those with few viable segments, the volumes (FSV and FDV) of the ventricle continued to increase, indicating continuation of the remodeling process, contrary to patients with more viable segments who presented with reversal of the ventricular enlargement. The benefit of revascularization to the hibernating myocardium and the alteration of the remodeling process have important prognostic implications. In this study, patients with several viable segments of myocardium, together with improvement of the ventricular geometry, have persistent improvement in the symptoms of heart insufficiency and few events over the long term.

CONCLUSION

Patients with viable myocardium who undergo coronary artery bypass grafting surgery show improvements in the ventricular function, with a reduction of the systolic and

diastolic volumes, indicating reversal of the remodeling process. Also, there is improvement of the symptoms of heart insufficiency and the patients present with a better prognosis. The benefit of revascularization in viable myocardium extends beyond an improvement in the ventricular function.

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