Original Article

Endomyocardial Biopsy Foretells Ventricular Function Recovery After Coronary Artery Bypass Grafting

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Objective

Patients with ischemic heart failure may benefit from coronary artery bypass grafting. The histopathological variables associated with improvement in ejection fraction 6 months after surgery were assessed.

Methods

This study comprised 24 patients indicated for coronary artery bypass grafting, ejection fraction < 35%, functional class II-IV heart failure, and mean age 59 ± 9 years. Endomyocardial biopsies were performed during and 6 months after surgery. Extension of the fibrosis, number of cells with myocytolysis, and hypertrophy of the muscle fiber were quantified by using a system of image analysis. Clinical and functional review was repeated within 6 months.

Results

A significant improvement in heart failure functional class was observed in 16 patients after 6 months of follow-up (from NYHA functional class 2.8±0.7 to 1.7±0.6; P <0.001), but the ejection fraction did not change (25±6 % vs. 26±10%). Hypertrophy of the muscle fiber was similar in the specimens biopsied in the pre- and postoperative periods (21±4 vs. 22± 4 μm), but the extension of fibrosis (8±8 vs. 21±15% area) and the number of cells with myocytolysis (9±11 vs. 21±15% cell) significantly increased. However, the composition of a histological score combining those 3 variables indicated a greater increase in the ventricular function of those with a lower degree of preoperative histopathological alterations.

Conclusion

Patients with ischemic cardiomyopathy undergoing coronary artery bypass grafting improved their ventricular function when the preoperative adverse histopathological alterations were of a lower degree.

Key words

heart failure, ischemic cardiomyopathy, endomyocardial biopsy, coronary artery bypass grafting

Coronary artery disease is the major cause of heart failure in countries worldwide. After acute myocardial infarction, a pathological process, known as ventricular remodeling, installs and contributes to progression of the heart failure syndrome [1]. Several factors are associated with left ventricular remodeling, including neurohormone mediators, such as the activators of the renin-angiotensin-aldosterone system (RAAS) and the increase in the sympathetic tonus. These hormones induce ventricular alterations, such as ventricular dilation and changes in shape, leading to mechanical dysfunction in the process of contraction and relaxation [2].

In this process, the following histopathological alterations are observed: increase in fibrosis; hypertrophy and distortion of the myocyte; myocytolysis; alteration in the type I/type III collagen ratio; and some degree of inflammatory activity associated with an increase in the break down of the extracellular matrix [3-5]. This process is believed to be continuous and to self-perpetuate due to the progressive mechanical stress and activation of the renin-angiotensin-aldosterone and sympathetic systems [2].

Despite the improvement in the clinical treatment of heart failure with the introduction of angiotensin-converting enzyme inhibitors and beta-blockers, reducing ventricular remodeling, the prognosis of the patients with advanced ischemic cardiomyopathy still continues to be poor [6,7]. In past years, coronary artery bypass grafting has been indicated to improve the ventricular function and prognosis of those patients [8-10]. Although no definitive clinical assay exists in this context, a recent meta-analysis has suggested that myocardial viability in this type of patient is associated with a better postoperative outcome [11]. Therefore, the identification of the patient who can benefit from that surgery continues to be a challenge.

In this study, the changes in ejection fraction occurring in patients with severe ventricular dysfunction secondary to ischemic heart disease undergoing coronary artery bypass grafting were assessed, and the histopathological alterations in endomyocardial biopsies acquired in the pre- and postoperative periods were analyzed.

Methods

This study selected patients with ventricular dysfunction secondary to ischemic heart disease, with ejection fraction < 35%, NYHA functional class II to IV heart failure, and coronary artery bed appropriate for coronary artery bypass grafting. Patients with the following characteristics were excluded from the study: left ventricular aneurysm; postinfarction ventricular septal defect (VSD); significant valvular heart disease; ascending aorta diseases; and other cardiomyopathies, such as amyloidosis, sarcoidosis, and

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hypertrophic cardiomyopathy. Surgical indication was always discussed with the attending physician based on clinical data, presence or absence of viable myocardium, and/or presence of angina or of anginal equivalent. The study was performed at the Hospital de Clínicas de Porto Alegre and the Instituto de Cardiologia of the Fundação Universitária de Cardiologia do Rio Grande do Sul. The study protocol was approved by the committees on ethics of both institutions, and all patients signed the written informed consent to participate in the study.

The left ventricular ejection fraction was assessed by use of radionuclide ventriculography in the preoperative period and 6 months after surgery. The procedure was performed by labeling the red blood cells of the patient with 99^m Technetium pertechnetate. The images were acquired in 3 planar angles (left anterior oblique, anterior, and lateral) using a camera equipped with a collimator. The ejection fraction was automatically determined using a specific computing program.

All patients underwent coronary artery bypass grafting according to the standardized techniques [12]. With the patient under total extracorporeal circulation and moderate hypothermia, myocardial protection was provided by anterograde infusion of a crystalloid cardioplegic solution (St. Thomas II) between 4 and 10°, repeated every 20 minutes, and cold topic saline solution. After finishing all anastomoses, rewarming was initiated. After a reperfusion of at least 10 minutes and the patient's temperature reaching 37°, the extracorporeal circulation was progressively discontinued. All patients were operated upon by the same surgeons.

The endomyocardial biopsies were performed according to the standard technique [13]. The first biopsy was performed during surgery with an incision in the right atrium and, through the tricuspid valve, the middle portion of the right ventricular septum was accessed, and 4 to 5 specimens were obtained before starting revascularization. The second biopsy was performed 6 months after surgery, through puncture of the internal jugular vein, using a 9 French sheath and a Stanford bioptome, under fluoroscopy, and 4 to 5 specimens were obtained in the same septal site previously biopsied. After the second procedure, the patients remained under observation for 2 hours before being discharged home. The specimens were immediately fixed in 10% formalin for subsequent histological study. All biopsies were performed by the same surgeon.

The specimens, fixed in 10% formalin immediately after acquisition, were then embedded in paraffin, and histological sections between 5 and 7μm were performed. To define the presence of hypertrophy and myocytolysis, the slides were stained with hematoxylin-eosin. Fibrosis was assessed by using the Masson's trichrome. All histopathological analyses were performed with an Olympus Bx40 microscope coupled to the digital image analysis system (Leica Q 500MC, Image Analysis System).

For determining the degree of hypertrophy, the diameter of the myocardial cells that had a central nucleus was measured, taking their shorter axis as a reference. By using the optical microscope and a 400X magnification, a minimum of 4 and a maximum of 24 fields were analyzed. For determining the degree of myocytolysis per field, between 3 and 18 fields were examined using a 400X magnification. The degree of fibrosis, identified by the blue color of the Masson's trichrome, was delimited and measured in 10 fields of 10.500 squ, with a 100X magnification.

The results are expressed as mean ± standard deviation (SD) or standard error of the mean (SEM) for continuous variables, and as proportions for categorical variables. The Student t test was performed for comparison involving continuous variables, and the Fisher exact test was used for categorical variables. A score was built encompassing histological findings for studying the association with ejection fraction in the pre- and postoperative periods. The score of fibrosis was as follows: 0 (zero) point, for fibrosis =1% of the area; 1 point, for fibrosis between 1 and 5% of the area; 2 points, between 5 and 20% of the area; and 3 points, for fibrosis > 20% of the area. The score of myocytolysis was as follows: 0 (zero) point, for myocytolysis =5 cells per field; 1 point, for myocytolysis between 5 and 10 cells per field; 2 points, between 10 and 20 cells per field; and 3 points, for myocytolysis >20 cells per field. For the score of hypertrophy, a cut-off point was established, defining as 0 (zero) point, for a diameter of the fiber =18 μm; and 1 point, for a diameter of the fiber >18 μm. The patients were divided according to the value of the score: whether =2 or >2. Differences were considered significant when P < 0.05.

Results

From January 1999 to August 2000, 24 patients were selected for this study. The mean ejection fraction was 24 ± 6 % (range from 9 to 34), the male sex predominated, and the mean age was 59.5 ± 9.8 years (range from 39 to 75). The New York Heart Association functional class for heart failure distribution was as follows: 5 patients in class II, 11 in class III, and 8 in class IV. All patients had angina or an anginal equivalent in the preoperative period. The clinical characteristics are shown in table I.

Except for one patient, all the others were revascularized exclusively with the saphenous vein, and 96% received a graft to the anterior descending artery. The mean number of grafts was 2.9 ± 0.8 (range from 1 to 4). The mean time of extracorporeal circulation was 86 ± 19 minutes (range from 42 to 132 minutes), and the mean time of ischemia was 42 ± 10 minutes (range from 21 to 65 minutes). The intra-aortic balloon was used in 5 patients, only one in the preoperative period, and the mean time of use was 2.8 ± 0.8 days (range from 2 to 4).

Considering a period of 30 days, the operative mortality was 2 patients. One of them died in the operating room, right after

Table I - Demographic profile of the population studied	
Age, mean ± SD	59.5±9.8
Sex, men/womem	22/2
NYHA FC, mean ± SD	2.8± 0.7
NYHA FC IV	8 (33%)
III	11 (45%)
II	5 (20%)
LV ejection fraction (%)	25±6
Diabetes Mellitus	7 (29%)
SAH	14 (58%)
Smoking	18 (75%)
Dyslipidemia	8 (33%)
Renal failure	1 (4%)
Previous AMI	23 (95%)

NYHA - New York Heart Association; FC - functional class; EF - ejection fraction; SAH - systemic arterial hypertension; AMI - acute myocardial infarction; SD - standard deviation.

withdrawal of the extracorporeal circulation, and the other died due to respiratory failure in the early postoperative period, within the first 30 days. During surgery, 2 patients experienced stroke as follows: one had it in association with acute myocardial infarction, and partial recovery of the neurological deficit was observed; the other died on the 71st postoperative day. Other complications were as follows: one reintervention due to bleeding; one dehiscence of the sternum, which was managed with rotation of the greater pectoral; and one patient with arterial embolism to the right upper limb, who underwent embolectomy.

Five other patients died within the first 6 months of follow-up. One of them due to stroke and the others due to presumed sudden death, without confirmation on necropsy. The 17 surviving patients had a significant improvement in the NYHA functional class of heart failure from 2.8 ± 0.7 to 1.7 ± 0.9, P <0.0001. Although the left ventricular ejection fraction had no significant improvement (25 ± 6 to $26\pm10\%$) in the group as a whole, the ventricular function had a significant increase in 8 patients, improving from 24 ± 6 to $33\pm2\%$, P < 0.002. (fig. 1).

Initially, the histopathological variables of the surviving patients (n = 17) and of those who died (n = 7) were compared. In that analysis, the survivors had more myocytolysis (11 ± 12 vs $4\pm3\%$; P = 0.05); however, fibrosis (25 ± 5 vs $22\pm8\%$; P = 0.32), and hypertrophy (21.5 ± 4 vs $21.4\pm5\mu m$; P = 0.97) were similar in both groups.

Of the 17 patients alive 6 months after surgery, one refused to undergo the second biopsy; therefore, pre- and postoperative data were available for comparison in 16 patients. Comparing pre- and postoperative data, while the degree of hypertrophy in the specimens did not change (21 ± 4 vs 22 ± 4 μm), a significant increase was observed both in the number of cells with myocytolysis (9 ± 11 vs $21\pm15\%$ of cells, P < 0.001) and in the extension of fibrosis (8 ± 8 vs $21\pm15\%$/area, P < 0.001). Stratifying the patients into a subgroup with maintained left ventricular ejection fraction (n=8) and another with patients who got worse (n=8), individually, none of the histological variables analyzed in the pre- and postoperative period was different between the 2 groups (tab. II). Ho-

wever, when a score composed by the histological variables was used for analyzing the changes in the ejection fraction after surgery, lower scores in the preoperative period were associated with an improvement in the postoperative ventricular function (fig. 2). Microphotographs of the different histopathological characteristics are shown in figures 3 and 4.

Discussion

Patients with coronary artery disease and severe left ventricular dysfunction may benefit from coronary artery bypass grafting. The appropriate selection of patients who should undergo the procedure is still debatable. Our study showed that the individual analysis of 3 histopathological variables acquired through endomyocardial biopsies during surgery and in the late postoperative period of coronary artery bypass grafting of patients with severe ventricular dysfunction was insufficient to predict who would benefit with an increase in left ventricular ejection fraction after the procedure. However, the combination of histological alterations indicating a lower degree of remodeling was associated with an improvement in ventricular function in the postoperative period.

Our population is a typical cohort of patients with advanced cardiomyopathy, characterized by severe left ventricular dysfunction and significant functional limitation due to congestive heart failure. For these patients, despite the development of the medicamentous therapy, the prognosis continues to be poor [6,7]. Thus, the revascularization surgery has gained importance as a therapeutical option, due to the progress of the surgery and myocardial protection techniques [14]. Luciani et al [15], in a study with 143 patients with ejection fraction < 30%, compared the results according to the treatment performed (coronary artery bypass grafting, cardiac transplantation, or medicamentous treatment). Despite the relatively high surgical mortality (20%), the prognosis was significantly better in patients undergoing revascularization and cardiac transplantation as compared with those undergoing medicamentous treatment. In the present study, perioperative mortality, up to 30 days after surgery, was 8.3% (2 patients).

Our study showed no overall increase in the ejection fraction in the 17 patients who returned for reassessment after surgery. In fact, worsening of the ejection fraction > 1% occurred in 5 patients. However, 8 of the 17 patients showed a significant increase in their ejection fraction, which could be explained by the short time period for the recovery of contractility (6 months), because, according to some authors, in 2 to 6 months, only 35% of the expected recovery in ventricular function is noted [16]. On the other hand, independently of the success of myocardial revascularization, the impairment in contractility may lead to an overall progressive dilation, because the pathophysiological base, which may result in severely dilated ventricles, may depend not only on ischemia: the stress in the dilated ventricular wall perpetuates remodeling [17]. Finally, variable quantities of viable myocardium might exist in the patients, perhaps with areas of mixed fibrosis and muscle, which could justify the different degrees of ejection fraction improvement [10,18].

After a cardiac lesion, such as acute myocardial infarction, a series of events occur at the genomic, molecular, cellular, and interstitial levels leading to alterations in the cardiac size, form,
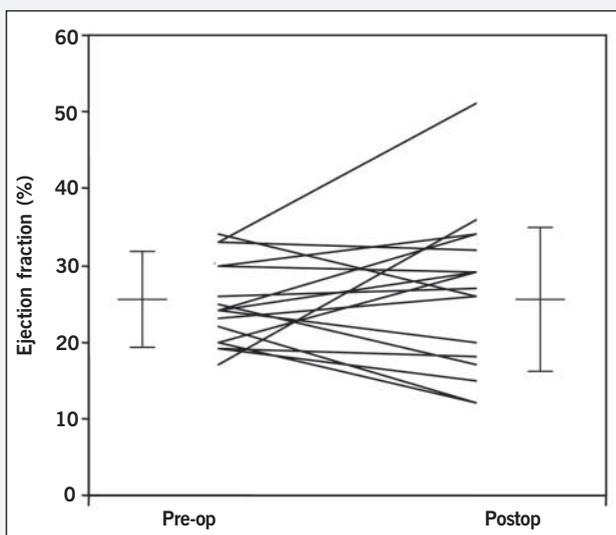

Fig. 1 - Comparison of ejection fraction (individual and mean ± SD) in all patients studied in the pre- and postoperative periods of coronary artery bupass grafting.

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Table II - Pre- and postoperative histological variables according to the decrease or increase in ejection fraction after coronary artery bypass grafting						
	Preoperative			Postoperative		
	EF decrease n=8	EF increase n=8	P	EF decrease n=8	EF increase n=8	P
Fibrosis (% area)	11.4 ±3.5	6±2.6	0.31	21.8±3.9	19.8±3.8	0.7
Myocytolysis (cells/fiels)	14.5±4	9±2.8	0.41	21±3.9	19.8±3.8	0.8
Diameter of the fiber (μm)	22.7±1.6	20.5±2.1	0.27	21.9±2	21.3±1.9	0.8

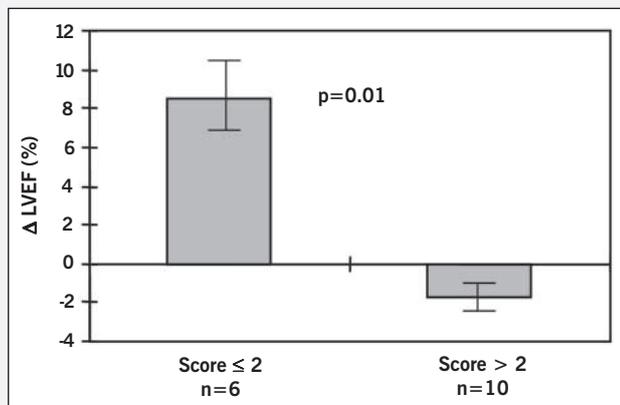* The values are expressed as mean ± standard error of the mean; EF - efection fraction.

Fig. 2 - Graph representing the variation in ejection fraction between the pre- and postoperative periods of coronary artery bypass grafting in 16 patients studied according to the combined score of the 3 histopathological variables obtained in preoperative endomyocardial biopsies.

Fig. 4 - Microphotograph of endomyocardial biopsy from specimens obtained during surgery, showing important histopathological alterations. A) moderate hypertrophy of myocytes; B) moderate degree of interstitial fibrosis (hematoxylin and eosin: A, 400X; Masson's trichrome: B, 100x). The ejection fraction was 17% in the preoperative period and passed to 36% in the postoperative period.
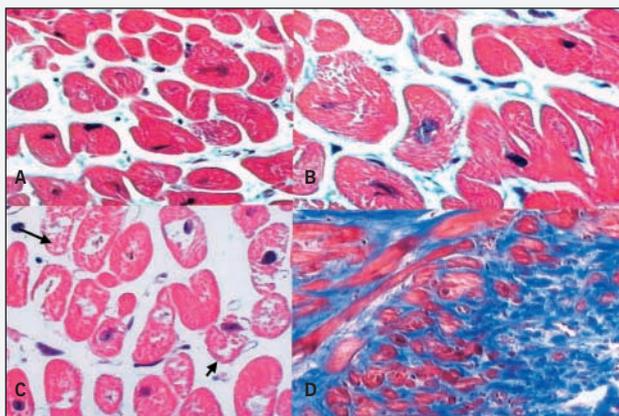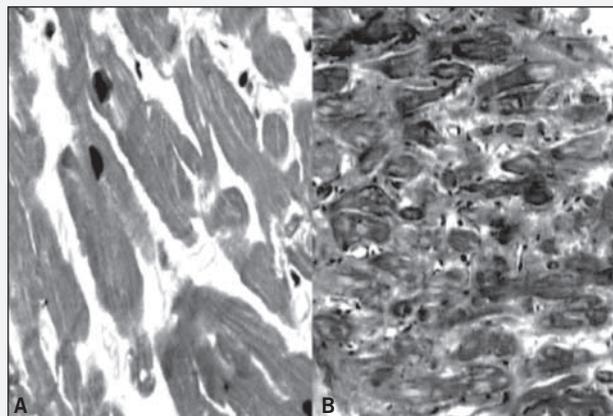

Fig. 3 - Microphotograph of endomyocardial biopsy from specimens obtained during surgery, showing important histopathological alterations. A) size variation of the myocyte fiber; B) hypertrophy of myocytes; C) loss of myofibrils (arrows); D) extensive interstitial fibrosis (hematoxylin and eosin: A and C, 200x, and B, 400x; Masson's trichrome: D, 100x). The ejection fraction was 25% in the preoperative period and passed to 17% in the postoperative period.

and function. At the histopathological level, the following may occur: hypertrophy of myocytes, necrosis, apoptosis, increase in fibrosis, fibrillary proliferation of collagen and fibroblasts [19]. The progression of the process of remodeling in several levels seems to be mediated by neurohormonal activation [20-22]. On the other hand, persistence of dilation leads to an increase in tension and overall stress, which lead to activation of several deleterious mechanisms in a vicious cycle, perpetuating remodeling [23,24]. This process is the basis for understanding that a regional defect in contractility, after acute myocardial infarction, may later lead to the development of an overall cardiac dysfunction.

In our study, the 3 following important histological alterations

that characterize remodeling were analyzed: extension of the fibrosis, degree of myocytic hypertrophy, and number of cells with myocytolysis. All 3 characteristics were clearly abnormal in the specimens examined in the preoperative period, because a mean amount of fibrosis of 8% was observed, as was the presence of cells with cytoplasmic vacuolization (myocytolysis) and hypertrophy. These findings are comparable to those reported by other investigators, who assessed the regional contractile function and histological findings in patients with ischemic cardiomyopathy [25,26]. It is worth noting that, these 2 studies that correlate histopathological characteristics and postoperative functional reversibility were very careful to perform the biopsies in the myocardial segment with an alteration in regional motility, which had been previously detected through imaging techniques. Therefore, despite the fact that in the present study the biopsies were performed only in the right ventricle, our findings suggest that, independently of the area initially injured, the process of overall remodeling may lead to alterations distant from the myocardial area. Our results may suggest a different and safer approach for studying the histological alterations in patients with advanced cardiomyopathy.

If on the one hand, the histopathological alterations observed in the preoperative period of this study characterize cardiac remodeling, on the other, the histological findings after myocardial revascularization are at least intriguing. It is worth noting that, to our knowledge, this is the first study that tried to perform histopathological comparisons in patients with severe ischemic left ventricular dysfunction before and after coronary artery bypass grafting. Despite the notion that restoration of blood flow necessarily leads to a benefit, we found no histological evidence indicating

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reversion of remodeling after revascularization. In fact, 2 of the 3 histopathological characteristics worsened after surgery: a greater number of cells had myocytolysis, and fibrosis increased. Hypertrophy did not change when comparing the pre- and postoperative specimens. Based on these observations, some speculative hypotheses may be elaborated: 1) the time elapsed after surgery for histological analysis was not sufficient for showing the reversion of remodeling at the tissue level; 2) restoration of blood flow was not sufficient to promote the beneficial effect at the tissue level; and 3) as no previous publication had focused on studying ventricular remodeling before and after coronary artery bypass grafting, our observations may have simply reflected the progressive natural history of remodeling, independently of reversion of the ischemic injury.

Considering that histological evidence of improvement was not observed after surgery, we tried to study the morphological characteristics that could predict which patients would benefit with the procedure. Other authors identified an improvement in myocardial function after revascularization, when only a small amount of fibrosis was observed in biopsies performed during surgery [25,26]. In this study, the degree of fibrosis alone was not sufficient to predict functional recovery of the myocardium. Other authors have not systematically studied other histopathological characteristics, such as myocytolysis and hypertrophy, but we observed no association between these variables and postoperative functional changes. However, because remodeling is a dynamic and multifactorial process, we developed a score with a combination of different histological characteristics, and observed that a smaller degree of fibrosis, myocytolysis, and hypertrophy in the preoperative period was associated with a significant increase in left ventricular ejection fraction after surgery. Thus, the simultaneous analysis of 3 histopathological characteristics, all indicating adverse remodeling, may constitute a better and more reliable tool to qualify the degree of structural alterations, and, therefore, better represent the amount of potentially recoverable myocardium.

Our results should be interpreted considering the specific limitations of the study. First, the specimens were collected from the right interventricular septum, which may account, at least partially, for the lack of correlation between the histological variables and the functional clinical results. On the other hand, as a second biopsy was planned in the postoperative period, this approach was considered ethically more appropriate than biopsying the left ventricle in patients followed up on an outpatient care basis. In addition, the site of biopsy could not represent the specific segment of abnormal motility, although left ventricular remodeling is assumed to be an overall and diffuse process, especially considering the severity of the cases studied. This study did not aim at assessing the association of histological variables with the presence or absence of viable myocardium. This information should be explored in the future, as myocardial viability has been used for selecting patients with a greater potential of postoperative recovery. Finally, our data should be seen as generators of hypotheses to be tested in larger studies.

Our study demonstrated that: 1) patients with severe ischemic left ventricular dysfunction undergoing coronary artery bypass surgery had an improvement in the functional class of heart failure, although this is a subjective parameter, but without an increase in left ventricular ejection fraction; 2) no improvement in the histopathological characteristics was observed; on the contrary, the degree of fibrosis and myocytolysis worsened; 3) the individual analysis of the preoperative histological characteristics was not able to predict which patients might improve their postoperative ejection fraction. However, the composition of a histological score showed that a lower degree of remodeling was present in the preoperative biopsies of patients, who had an increase in the ejection fraction after surgery. Thus, our results suggest that, despite the improvement in the functional class of heart failure in the whole group and in the left ventricular ejection fraction in a subgroup of patients, evidence of histological improvement, at least in the short run (6 months), after coronary artery bypass grafting in patients with advanced left ventricular ischemic dysfunction should not be expected. Finally, although evidence of moderate histological abnormalities may indicate a potential for ventricular function improvement, the characteristics of remodeling may require more time to evidence signs of reversion.

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