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Research Article

Does the Myocardial Viability Influence the Long-Term Survival after Coronary Surgery in Ischemic Cardiomyopathy?

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Abstract

Background: The relationship between myocardial viability and the long-term treatment effect of CABG in patients with ischemic cardiomyopathy remains uncertain. The current study was conducted to determine the relationship between the presence of myocardial viability and changes in left ventricular ejection fraction during the early stages of follow-up after CABG and their effects on the long-term prognosis of the patients.

Methods: The study group consisted of a consecutive series of 126 patients who met four criteria: (1) an angiographic resting left ventricular ejection fraction (LVEF) less than 0.40, (2) preoperative radionuclide investigations with thallium SPECT and planar evaluation of LVEF, (3) an isolated CABG procedure and (4) a prospective assessment of myocardial function and perfusion using same SPECT analysis in survivors 1 year after surgery. The survival was obtained in 2019 with a postoperative follow-up of 10.6 ± 7.4 years and 94% complete.

Results: Early and 1-year mortality were respectively 3.2% and 5.7%. At 1-year, the mean LVEF increase from 31 ± 9% to 34 ± 10% ($p = 0.01$) and the mean LV end-diastolic (LVED) volume decreased from 317 ± 112 to 285 ± 108 ml ($p = 0.023$). There was a significant correlation between the changes in LVEF, the changes in LVED volume and preoperative hibernating myocardium defined as improvement in redistribution thallium defects. The 10-year and 15-year survival were respectively 48 ± 8% and 27 ± 8%. Only age, preoperative LVEF and complete revascularization were identified as independent prognosis factors of survival. The overall incidence of death was not influenced by preoperative hibernating myocardium or postoperative improvement in LV function.

Conclusion: The postoperative improvement in left ventricular function, more likely to occur among patients with myocardial viability, is not an important mechanism for the long-term survival of patients with ischemic cardiomyopathy treated surgically. Complete revascularization appears to be more effective to stabilize the underlying cardiomyopathy and to reduce the incidence of late mortality.

Keywords: *Coronary Bypass Surgery; Left Ventricular Dysfunction; Myocardial Viability; Myocardial Hibernation; SPECT Assessment*

Introduction

It is well established that myocardial revascularization improves the life expectancy in coronary patients with left ventricular (LV) dysfunction [1]. It is clear from multiple clinical series that there is a significant subset of patients with chronic coronary artery disease and LV dysfunction who show substantial improvement in LV function after myocardial revascularization [2,3]. However, the relationship between myocardial viability and the long-term treatment effect of CABG in patients with ischemic cardiomyopathy remains uncertain [4,5]. Accordingly, the current study was conducted in patients with ischemic cardiomyopathy defined by a LV ejection fraction less than 40% to determine the relationship between the presence of myocardial viability and changes in left ventricular ejection fraction during the early stages of follow-up after CABG and their effects on the subsequent long-term prognosis of the patients. In this study, myocardial function and perfusion were determined by radionuclide investigations performed before surgery and one year after revascularization, with qualitative and quantitative analysis of thallium single photon emission computed tomography (SPECT) images; the long-term outcome was assessed using all causes of mortality with a 10-year follow-up.

Materials and Methods

The study group consisted of a consecutive series of 126 patients who met four criteria: (1) an angiographic resting left ventricular ejection fraction (LVEF) less than 0.40, (2) preoperative radionuclide investigations using the classical combination of stress/reinjection thallium SPECT and planar evaluation of LVEF, (3) an isolated CABG procedure and (4) a prospective assessment of myocardial function and perfusion using the same radionuclide investigations in surviving patients 1 year after surgery. The study was approved by the local ethical committee and received individual patient consent. The last survival status of the patients was obtained in 2019 from the National Institute of Statistics and Economic Studies (INSEE); the common closing date for follow-up was December 01, 2019. The primary endpoint was overall mortality from any cause and was analyzed according to the potential risk factors, the surgical configuration and the results of the 1-year SPECT assessment.

Surgical technique

All procedures were performed by the same surgeon. Standard cardiopulmonary bypass techniques were applied and combined antegrade/retrograde crystalloid cardioplegia solution was used for myocardial protection. Two surgical techniques were performed: (1) in multiple arterial grafting, exclusive use was made of *in situ* arterial grafts, internal thoracic arteries (ITA) and gastroepiploic artery (GEA), according to the distribution of coronary lesions; most often both ITAs were used on the left side with sequential grafts if required, and GEA on the right side, (2) in single arterial grafting, the left ITA was used to bypass the left anterior descending coronary artery (LAD) in all cases and it was associated with a sequential vein graft for the other coronary arteries. There was no randomization. The surgical technique was individually chosen in each case according to the state of the patient and the habits of the surgeon. As arterial grafting is technically more demanding, particularly in patients with LV dysfunction, the main idea was no increase in mortality and morbidity. Eventually vein grafts were most often used in the worse cases with heart dilation, severe LV dysfunction or heart failure signs, when immediate and maximal blood flow in the grafts seemed to be necessary. Complete myocardial revascularization was defined as bypass of all significant lesions defined as more than 70% stenosis. All patients received aspirin antiplatelet therapy postoperatively. Postoperative statin and beta-blockers became common practice over the years.

Radionuclide investigations

Radionuclide studies were based on the combination of stress/reinjection thallium SPECT and planar evaluation of LVEF. Both the pre- and postoperative perfusion/viability studies were performed using a stress technique for the early thallium imaging followed by thallium reinjection and redistribution imaging. In all cases the stress was bicycle exercise, consisting of 2-min stages increments of 20W. Thallium-201 injections were 111 MBq at maximal exercise and 37 MBq 3h later as an additional injection. Stress SPECT were acquired starting less than 15 min after completion of the stress test and 1h after the reinjection. After 3D reconstruction of the myocardium volume, tracer uptake was quantified and by comparison with a normal database, the size of the scintigraphic defect was quantified as a percentage of the total myocardium volume. After completion of the perfusion/viability part of the study, the patient received an injection of technetium-99m for LVEF measurement.

Statistical analysis

Descriptive statistics for categorical variables are reported as number and percentage; continuous variables are reported as mean ± standard deviation. Continuous variables were compared using Student't-test and ANOVA; categorical variables were compared using χ^2 or Fisher's exact test. Linear regression analysis was used for correlation between continuous variables with Pearson correlation coefficient. Overall survival was estimated using the Kaplan-Meier method and reported as percentage (95% confidence interval). The stratified log rank test was applied to compare the equality of the survival curves. Univariate analyses of predictors of all-cause death were done with binary logistic regression. Multivariate Cox regression analysis was used to identify independent predictors of all-cause death. A 2-tailed P value < 0.05 was always considered to indicate statistical significance. All statistical analyses were performed using IBM-SPSS Statistics software version 25.0 (IBM-SPSS Inv, Armonk, NY).

Results

Study subjects

The preoperative clinical characteristics of the 126 patients are summarized in table 1. As might be expected in a cohort of patients with severe coronary disease and abnormal LV function, the prevalence of male sex, prior myocardial infarction, three-vessel disease and heart failure signs was high. A preoperative significant ischemia was detected in 88% of patients by SPECT assessment. A complete revascularization was done in 56% of patients and a multiple arterial grafting was used in 51%. The 30-day mortality was 3.2%, higher in patients with significant heart failure NYHA class 3 - 4 (9% vs. 0%, p = 0.001). Seven patients died during the first postoperative year (7/122, 5.7%).

Preoperative data	All patients (n = 126)
Age (years)	61 ± 11
Male gender (%)	89
Previous infarction (%)	90
Three-vessel disease (%)	89
NYHA class ≥ 3 (%)	35
CCS class ≥ 3 (%)	68
Mean Pulmonary pressure (mmHg)	22 ± 7
Cardiac index (l/min/m^2)	2.2 ± 0.7
LV ejection fraction (%)	31 ± 6
LV end-diastolic pressure (mmHg)	19 ± 7
Ischemic thallium defect (%)	89
Rd LV ejection fraction (%)	30 ± 10
Rd LV end-diastolic volume (ml)	322 ± 117
Multiple arterial grafting (%)	51
Number anastomoses	3.3 ± 0.8
Complete revascularization (%)	56

Table 1: *Preoperative data.*

NYHA: New York Heart Association; CCS: Canadian Cardiovascular Society; LV: Left Ventricular; Rd: Radionuclide.

1-year assessment

One year after surgery, in the 115 surviving patients, the rate of clinical improvement was 51% in heart failure and 99% in angina. During exercise testing, 18% of patients exhibited moderate ischemic thallium defects reversible after redistribution, vs. 88% preoperatively (p = 0.01). The size of the stress thallium defects in % of the total myocardium volume, decreased from 35 ± 15 to 27 ± 10% (p = 0.023) and there was no change in the size of redistribution/reinjection thallium defects (Table 2). In mean, the significant preoperative ischemia defined as the difference between stress defects and redistribution/reinjection defects (35 ± 13 vs. 27 ± 11%, P = 0.01), disappeared after surgery: 27 ± 11 vs. 26 ± 10%, (p = 0.45). There was a significant improvement of the LV function with an increase in radionuclide LVEF and a significant reverse remodeling of the left ventricle with a decrease in end-diastolic volume (Table 2). Changes in LVEF were significantly correlated with the preoperative LVEF (Pearson = 0.433, p = 0.01) and with the changes in LV end-diastolic volume (Pearson = 0.545, p = 0.01) (Figure 1). There was no correlation between the changes in LVEF and the preoperative ischemia (Pearson = 0.08, p = 0.622) or the changes in ischemic defects (Pearson = 0.184, p = 0.282). Changes in redistribution defects were significantly correlated with LVEF changes (Pearson = 0.640, p-0.01) and changes in LV end-diastolic volume (Pearson = 0.636, p = 0.01), (Figure 2). In other words, (1) the postoperative improvement in LVEF was correlated to the reverse remodeling of the LV defined by a decrease in LV volume, (2) the improvement of the LV function (LVEF, p = 0.001 and LV end-diastolic volume, p = 0.02) was correlated to the recruitment of the hibernating myocardium defined by a positive difference between preoperative and postoperative redistribution defects, observed in 56% of patients. Interestingly, lower was the preoperative LVEF, higher was its postoperative improvement; nevertheless, the postoperative improvement in LVEF was not correlated to the preoperative level of ischemia and its postoperative improvement.

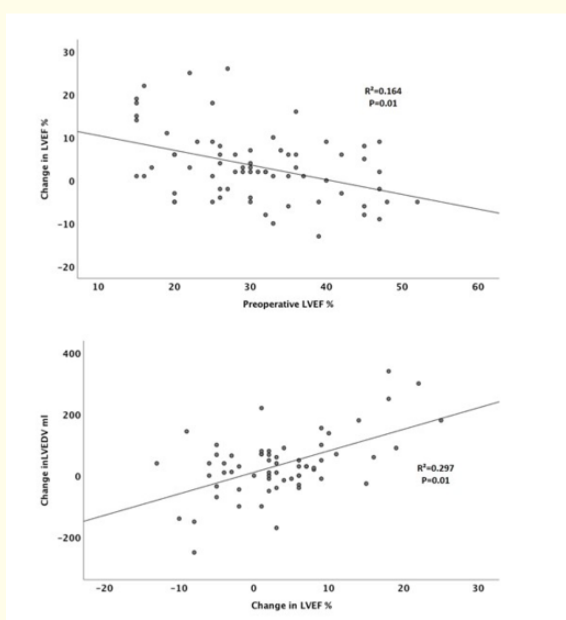

Figure 1: *Correlation of the postoperative improvement in radionuclide left ventricular ejection fraction (LVEF) defined as the difference between post- and preoperative values with the preoperative radionuclide LVEF and with the improvement in left ventricular end-diastolic volumes (LVEDV) defined as the difference between pre- and postoperative values.*

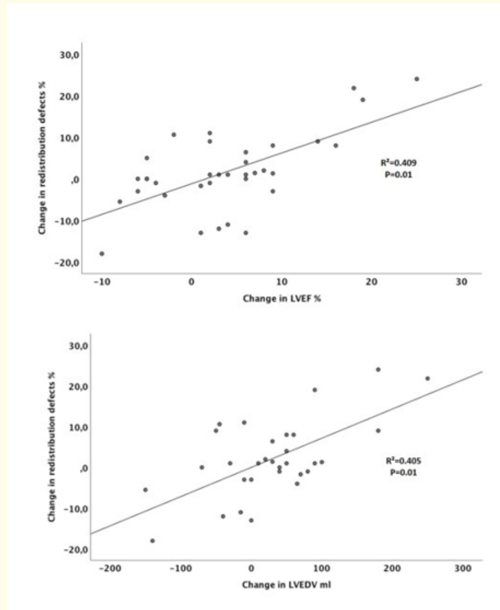

Figure 2: *Correlation of the postoperative improvement in redistribution defects defined as the difference between pre- and postoperative values with the improvement in radionuclide left ventricular ejection fraction (LVEF) defined as the difference between post- and preoperative values and with the changes in left ventricular end-diastolic volumes (LVEDV) defined as the difference between pre- and postoperative values.*

	Preoperative	Postoperative	p
Stress defects (%)	35 ± 15	27 ± 10	0.023
Redistribution defects (%)	27 ± 11	26 ± 10	0.208
Rd LV ejection fraction (%)	31 ± 9	34 ± 10	0.001
Rd LV end-diastolic volume (ml)	317 ± 112	285 ± 89	0.023

Table 2: *Comparison of radionuclide tests.*
Defects are expressed in % of the total myocardium volume. Rd: Radionuclide, LV: Left Ventricular.

Survival

The mean postoperative follow-up was 10.6 ± 7.4 years and 94% complete. There were 97 late deaths occurring within a mean delay of 9.6 ± 6.6 years. The 10-year and 15-year survival were respectively 48 ± 8% and 27 ± 8% (Figure 3). All predictive factors of late mortality established from univariate analysis were introduced in the Cox model multivariate regression analysis; finally only age, preoperative LVEF and complete revascularization were identified as independent prognosis factors of mortality (Table 3). Unlike complete revascularization, the technique of revascularization (multiple or single arterial) did not influence the survival (Figure 4). The overall incidence of death did not differ significantly between patients with hibernating myocardium and those without hibernating myocardium, and between patients who had improvement in LV function and those who did not have such improvement (Figure 5).

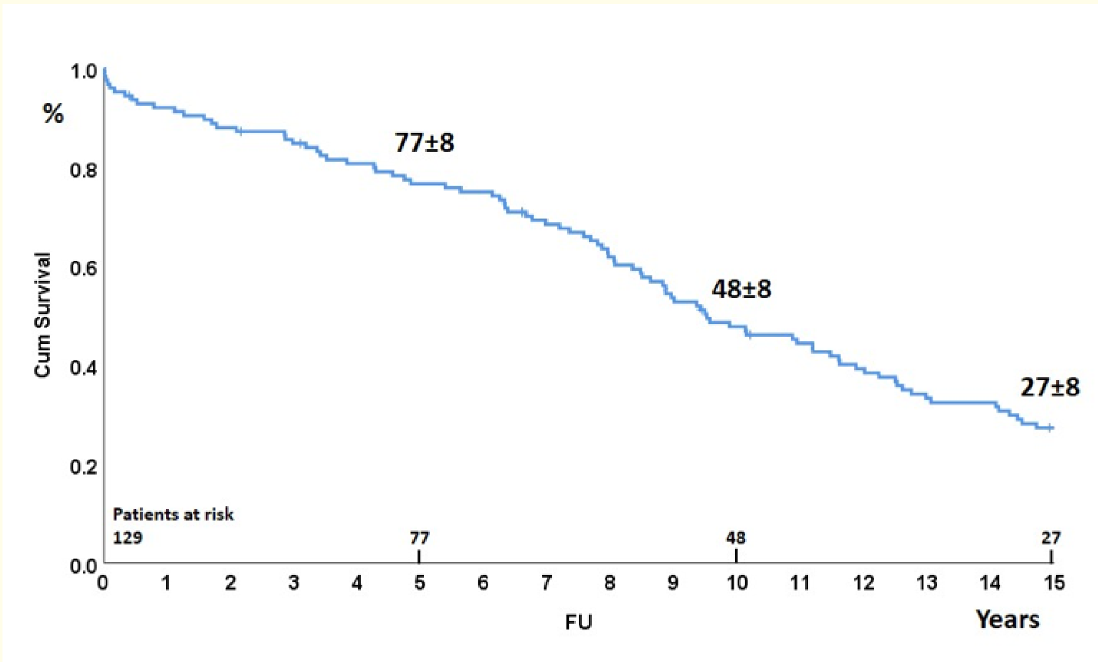

Figure 3: *Survival of patients according to Kaplan-Meier analysis.*

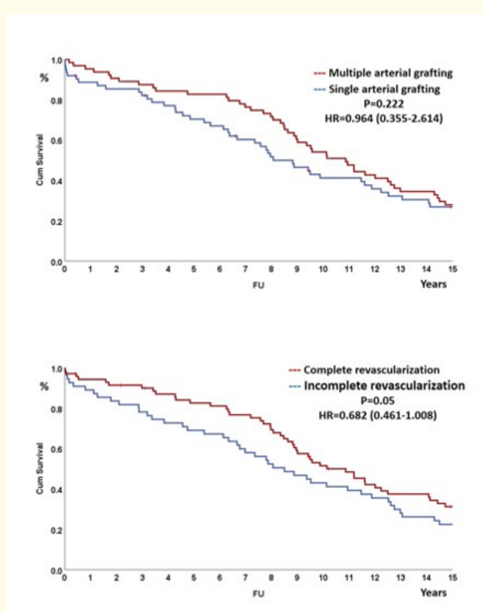

Figure 4: *Kaplan-Meier survival curves according to the technique and the completeness of the myocardial revascularization performed.*

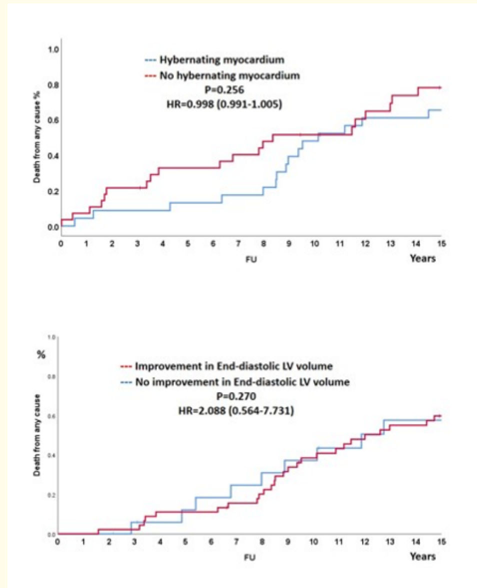

Figure 5: *Kaplan-Meier analyses of the incidence of death from any cause according to the preoperative myocardial hibernation and the postoperative reverse remodeling with improvement of the left ventricular volume.*

Predictors	HR (95% CI)	P value
Age	1.033 (1.013 - 1.054)	0.002
Male gender	1.418 (0.711 - 2.829)	0.322
NYHA ≥ 2	1.024 (0.758 - 1.382)	0.879
LV ejection fraction	0.915 (0.841 - 0.995)	0.038
Arterial grafting	0.566 (0.178 - 1.802)	0.336
Complete revascularization	0.269 (0.075 - 0.964)	0.044
Change in LV ejection fraction	0.965 (0.888 - 1.049)	0.401
Change in LV end-diastolic Volume	0.998 (0.989 - 1.006)	0.561
Preoperative ischemia	0.979 (0.921 - 1.040)	0.488
Preoperative hibernation	1.056 (0.981 - 1.136)	0.148

Table 3: *Multivariate cox regression analysis of variables influencing long-term mortality.*
HR: Hazard Ratio; CI: Confidence Interval; NYHA: New York Heart Association; LV: Left Ventricular.

Discussion

The current study was conducted to assess the relationship between myocardial viability and the long-term treatment effect of CABG in patients with ischemic cardiomyopathy. The concept of myocardial viability is based on the difference between reversible and irreversible ischemic injury and is defined as the possibility of ischemic myocardial territories to recover their contractility function when their perfusion is improved. Although the exact pathophysiology remains controversial, viability tests are used to predict which segments are likely to resume function after coronary revascularization to obtain an improvement of the systolic function which is one of the therapeutic goals of revascularization in patients with severely depressed left ventricular function: these include an increased glucose uptake detectable with positron emission tomography, the presence of partially or completely reversible exercise-induced thallium defect at delayed imaging or reinjection, a preserved wall thickness at magnetic resonance imaging and the maintenance of significant inotropic reserve during the infusion of low dose of dobutamine. However, improvement in LV function is not a universal finding after revascularization but it is not uncommon. The reversibility of LV dysfunction depends on factors including the presence and extent of stunned and hibernating myocardium, the surgeon's ability to completely revascularize hibernating tissue, perioperative myocardial infarction, and postoperative graft complications [6,7]. In this series the more depressed the LVEF was, the higher the LVEF improvement was, and the LV function improvement was significantly correlated with the decrease in LVED volume and the improvement in redistribution/reinjection thallium uptake. It confirms that improvement in mechanical contraction is the result of recovery of hibernating myocardium due to increase in myocardial perfusion.

A putative mechanism that mediates the benefit of CABG among patients with myocardial viability is the improvement in left ventricular systolic function that results from revascularization [8]. In the current study, there was no association between improvement in left ventricular ejection fraction at 1 year and subsequent survival, nor was there a significant interaction between myocardial viability and changes in left ventricular ejection fraction with regard to death from any cause. Overall, these findings are consistent with previous observations [9,10] and deemphasize the relevance of changes in left ventricular ejection fraction as a determinant of long-term prognosis in patients with ischemic cardiomyopathy. Thus, our results suggest that abatement or reversal of left ventricular systolic dysfunction is not a critical mechanism involved in mediating the beneficial effect of CABG in these patients. The findings of the current study do not support the concept that assessment of myocardial viability determines the likelihood of long-term benefit from surgical revascularization in patients with ischemic cardiomyopathy. The tests of interaction between myocardial viability and treatment effect of CABG were not significant for any of the three parameters: preoperative level of ischemia, preoperative hibernating myocardium and postoperative improvement in LV function with reverse remodeling. Therefore, we must conclude that there is no statistical evidence of association between myocardial viability and benefit from CABG.

A number of various possibilities, alone or in combination, may account for the negative results of our study. It is certainly possible that a true biologic interaction exists between myocardial viability and the benefit of revascularization and that we were unable to unveil it because of the relatively small number of patients. A complementary explanation is that the physiological complexity underpinning the potential therapeutic benefit of surgical revascularization cannot be surmised from the results of a single test of myocardial viability.

Certain limitations of this study must be acknowledged. The assessment of left ventricular ejection fraction was made at a relatively early point (i.e. after 1 year of follow-up) during the 15-year follow-up period. Our findings were based on the assessment of myocardial viability with either SPECT and did not include the routine performance of cardiac magnetic resonance imaging, which has become an accepted technique for the assessment of myocardial scarring [11], with a possibility of underestimation of the myocardial viability. Finally, the survival end-point was based on death from all causes without information regarding cardiovascular causes and other major adverse events.

Conclusion

This study confirms that in patients with coronary artery disease and LV dysfunction, CABG can be performed relatively safety, quality of life is improved and improvement in LV function can be documented objectively after surgery and is correlated with reperfusion of hibernating myocardium. However, the improvement in left ventricular function, more likely to occur among patients with myocardial viability, is not an important mechanism for the long-term survival of patients with ischemic cardiomyopathy treated surgically; complete revascularization appears to be more effective to stabilize the underlying cardiomyopathy and to reduce the incidence of late mortality.

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