Clinical Relevance of the Evaluation of Myocardial Viability in Patients with Left Ventricular Dysfunction [11]

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SUMMARY

Key-Words
Viability; Myocardial function; Nuclear cardiology

RESUMO

Relevância Clínica da Avaliação da Viabilidade Miocárdica em Doentes com Disfunção Ventricular Esquerda

Palavras-Chave
Viabilidade; Função miocárdica; Cardiologia nuclear

The Coronary Artery Surgery Study (CASS) showed that the survival rate of patients with chronic ischemic cardiopathy submitted to medical therapy, in a 4-year follow-up, was lower if the degree of left ventricular (LV) dysfunction was greater [1]. On the other hand, in more recent observations of the same population [2], with a follow-up which lasted 14 years, it was verified that the survival rate for patients with an ejection fraction (EF) below 35 % was lower if the severity of the subjacent coronary disease was greater, with 73 % for normal EF, 54 % for EF between 50 % and 35 % and lowering to 21 % for EF below 34 %.

Actually, there is more rise for coronary bypass surgery in this population, with an Odds ratio of 4.06, when EF is below 20 %. The existence of a disease of the common trunk, myocardial infarction with less than 7 days of evolution and associated cardiac insufficiency are also additional risk factors for coronary surgery, with an Odds ratio of nearly 2.0.

Alderman and col. [3] also showed that, in patients with an EF < 25 %, the survival rate in a 10-year follow-up was 60 % for the patients submitted to surgery while it was no more than 40 % in the patients who received medical therapy.

From these observations made by the CASS registry, we may therefore conclude that, despite a significant increase in risk when submitted to coronary surgery, patients with LV dysfunction and advanced stages of atherosclerotic coronary disease benefit in terms of survival (as well as quality of life) when submitted to surgery.

It is, therefore, important to define which patients with LV dysfunction benefit more from coronary surgery, that is, those in which it is possible to predict a significant improvement in LV function. This article will demonstrate that these patients are the ones who present extensive areas of viable myocardium susceptible to recovery, by revascularization, to normal contractile function.

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WHICH PATIENTS REQUIRE VIABILITY ASSESSMENT?

Several clinical standards indicate the existence of myocardial viability in a patient with chronic ischemic cardiopathy (*Table I*).

The history of angina pectoris, particularly when associated to cardiac insufficiency; the existence of non Q infarction with maximum CK relatively low; the discordance between motility alterations by echocardiography; and the existence of pathological Q waves in the ECG or small CK elevations also evoke the possibility of a viable myocardium.

Sanjiv Kaul [4] presents three models of coronary artery disease (CAD) in which myocardial viability is assumed relevant: the so-called «stunned myocardium», corresponding to the post infarction/ischemic situation in which the anterograde blood flow has been restored but the function is still low; the «hibernating myocardium», in which a persistent reduction in blood flow leads to a concordant reduction in contractile function; and, finally, infarction related persistent occlusion of the artery, but with perfusion maintained by the collateral arteries. To sum up, it may be stated [5] that there are two groups of patients in which myocardial viability assessment is indicated: those with overall severe LV dysfunction due to CAD; and, more importantly, those who exhibit regional dysfunction after acute myocardial infarction. It becomes pointless to indicate that viability assessment is not required in patients with normal, or almost normal, ventricular function.

Patients with LV dysfunction, particularly those with EF <35%, may be symptomatic or asymptomatic. The symptoms may be cardiac insufficiency or angina pectoris. In the latter, coronary revascularization is indicated even without viability studies.

Table I

Viable myocardium in CAD patients

1. History of angina in particular if associated with heart failure.
2. Peak CK<1000 Un. In AMI
3. Non-Q-wave infarction
4. Large areas of wall motion abnormalities with small increase of CK.
5. Mismatch of extensive wall motion abnormalities by echo and Q waves in EKG.
6. Ventricular wall thickness and echo density.

It is in the subgroup of patients with LV dysfunction due to ischemic cardiomyopathy that viability studies are indicated: the patients with reversible LV dysfunction, when correctly identified, improve significantly after coronary surgery, contrary to what occurs in patients with irreversible LV dysfunction due to a scarred myocardium, in which the functional class and the prognosis are identical with medical therapy or surgery.

The second group of patients is comprised of those who present a significant LV dysfunction after myocardial infarction. This subject is particularly pertinent due to the more widespread use of thrombolytic therapy, in which the patients present a residual stenosis which limits the blood flow.

It may, therefore, be concluded that the objective of myocardial viability assessment is to identify the patients with a «hibernating myocardium» in the hope that they will benefit more from myocardial revascularization.

HIBERNATING MYOCARDIUM

In an article published in the American Heart Journal in 1978 [6], Diamond and col. employed the term «hibernation» for the first time, stating that: «Reports of sometimes dramatic improvement in segmental left ventricular function following coronary bypass surgery, although not universal, leaves the clear implication that ischemic non-infarcted myocardium can exist in a state of functional hibernation». The significance of this statement was not understood in all its scope at that time, and only ten years later was the term hibernating myocardium employed and disseminated by Rahimtoola, curiously, in the same publication [7]: «A state of persistent LV dysfunction that results from chronically reduced blood flow but preserved viability. This chronic down-regulation in contractile function at rest is thought to represent a protective mechanism whereby the heart reduces its oxygen requirements to ensure myocyte survival».

The concept of down-regulation, establishing a balance between the reduction in blood flow and a corresponding reduction in LV function, leading to a new steady state, has been put in question by recent investigations.

Elsässer and col., of the Max Plank Institute tested the hypothesis [8] that the hibernating myocardium represents an incomplete

adaptation to the reduction in the oxygen supply. In 38 patients, areas of hibernating myocardium were identified by angiography, radionuclide ventriculography, thallium scintigraphy with reinjection and low dose dobutamine echocardiography. During coronary bypass surgery to which these patients were submitted, transmural biopsies were made of the centre of the area previously identified as hibernating myocardium. The histological assessment allowed the classification of tissue deterioration in three stages: slight; moderate; and severe (*Table II*). It was concluded that there was a continuous process of degeneration. Radionuclide angiography showed an improvement of regional function at 3 months postoperatively, compared to preoperative values (23.5% and 48%, respectively) and the echocardiographic wall motion score index decreased from 3.4 to 1.8. The degree of severity of the morphological changes correlated well with the extent of postoperative functional recovery: more advanced clinical improvement was observed in patients with slight and moderate morphological degeneration (stages 1 and 2), but recovery was only partial in severe degeneration (stage 3). The authors concluded that cellular degeneration rather than adaptation is present in hibernating myocardium. The consequence is «progressing diminution of the chance for complete structural and functional recovery after restoration of blood flow». The clinical implications of this notable work imply revascularization as early as possible in patients presenting areas of hibernating myocardium.

Table II

Histological changes in hibernating myocardium

Stage 1	Slight degeneration: beggining of loss of contractile material; slight fibrosis; normal mRNA distribution; no apoptosis.
Stage 2	Moderate degeneration: loss of myofilaments and cytoskeletal proteins; moderate fibrosis, decrease mRNA for myosin and actin.
Stage 3	Severe degeneration: significant loss of contractible and cytoskeletal proteins; significant fibrosis; marked decrease in mRNA for myosin and actin; apoptosis of myocytes.

Conclusion: Continuous degeneration takes place.

Adapted from. Elsasser, A. et al. (ref. 8) Circulation 1997;96:2920-31.

The authors present a new «flow chart» relating structure and function in the hibernating myocardium and their pathophysiological consequences (*Fig. 1*).

METHODS TO DETECT VIABILITY

The methods available for the assessment of myocardial viability include the demonstration of functional integrity by echocardiography, magnetic resonance imaging and contrast angiography or the demonstration of metabolic integrity by myocardial scintigraphy. From among these methods, the following have gained particular relevance in recent years[9]: perfusion imaging with thallium -201, which also assesses the integrity of cellular membrane; stress echocardiography with dobutamine, which assesses the contractile reserve of the myocardium; and, finally, positron emission to-

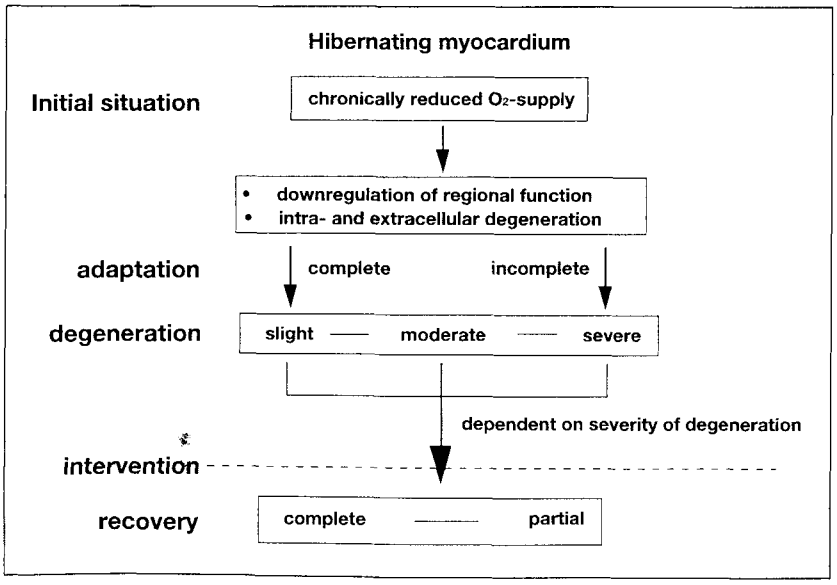

Fig. 1 Pathomechanism of Hybernating myocardium. Reproduced from Elsasser, et al. (ref. 8) with permission of the editor.

mography (PET), which assesses the metabolic activity of the myocardium.

PET was, in the 80's, considered the choice method for the demonstration of the existence of a viable myocardium, showing the preservation of metabolic activity in areas with contractile dysfunction [10-16]. Bonow, in a recent review [17] involving six studies of patients with LV dysfunction submitted to myocardial revascularization, found a «positive predictive accuracy» of 82 % and a «negative predictive accuracy» of 83 % for this test in predicting regional function recovery after revascularization.

The study of myocardial perfusion with Tl-201 is the most common imaging method for viability assessment, employing planar or tomographic images (SPECT). The initial uptake of thallium, after IV injection, is proportional to regional myocardial blood flow, whereas the poor redistribution after 4 hours reflects the integrity of the cellular membrane. Several protocols have been employed for viability assessment with Tl-201 [18], the most common being stress-redistribution and the protocols which resort to reinjection. The protocol of rest-redistribution, specifically considered when the only objective is to record ischemia, also deserves to be reviewed.

The reinjection technique, which consists of the administration of a second dose of Tl-201 after the acquisition of redistribution images, was first described by Dilsizian and Bonow [19]. These authors demonstrated that 87 % of the myocardial regions which showed reversibility after reinjection of Tl-201 had an improvement in contractile function after angioplasty. The authors concluded that the reinjection of thallium improves the detection of viable myocardium. The same group demonstrated an 88% agreement between Tl-201 imaging after reinjection and a PET metabolic image with FDG [20].

The rest-redistribution protocol is, according to Beller [18], the most useful for myocardial viability assessment in patients with CAD and LV dysfunction. The first images are recorded 10 minutes after Tl-201 injection at rest. A second acquisition is made after 4 hours. Ragosta and col. [21] showed that 73 % of the «severely asynergic» segments in 21 patients with CAD and 0.27 LVEF showed preserved myocardial viability by quantitative thallium criteria. Udelson and col. [22] employed a threshold of 60 % or more, compared to the «peak uptake», and observed that 75 % of the segments with Tl-201 activity equal to or above that value improved parietal contractility after revascularization.

Bonow, in the already mentioned review [17], selected nine studies which had employed the stress-redistribution-reinjection protocols, involving a total of 295 patients, and found a cumulative positive predictive accuracy of 69 % and negative predictive accuracy of 89 % in what concerns the improvement of regional function after revascularization. Bonow also analysed four studies of SPECT rest-redistribution imaging, with a total of 83 patients, and found comparable values of positive and negative predictive accuracies, 69 % and 92 % respectively. The combined results of these two methodologies show that Tl-201 tomographic imaging presents a higher negative predictive value due to its greater sensitivity and a lower positive predictive value due to its lower specificity, as documented in *Fig. 2*, reproduced from Bonow's review.

Perrone-Filardi and col. [23], on comparing rest-redistribution to dobutamine echo for myocardial viability assessment, demonstrated that there is a linear relation between thallium activity at a segmental level and the probability of recovery of regional function after revascularization: in 83 % of the segments with thallium activity >80 % showed functional recovery after revascularization.

Low dose dobutamine echo developed during the 90's, with a methodology capable of showing the myocardium contractile reserve, in patients with LV dysfunction. Bonow [17] selected 15 studies which included 402 patients with chronic CAD and LV dysfunction submitted to viability studies with dobutamine echo before revascularization. The overall assessment attributed a positive predictive value of 83 % and a negative predictive value of 81 % to dobutamine echocardiography. In the already mentioned Perrone-Filardi study [23], the concordance between Tl-201 and dobutamine was 82 % in the hypokinetic segments, but 43 % in the akinetic segments. In 109 revascularized segments, the positive accuracy for functional recovery was 72 % for Tl-201 and 92 % for dobutamine, whereas the negative accuracy was 100 % and 65 %, respectively. Thallium has greater sensitivity (100 % *versus* 79 %), but dobutamine has greater sensitivity.

The myocardial uptake of technetium 99m sestamibi is proportional to regional perfusion and provides adequate information for the de-

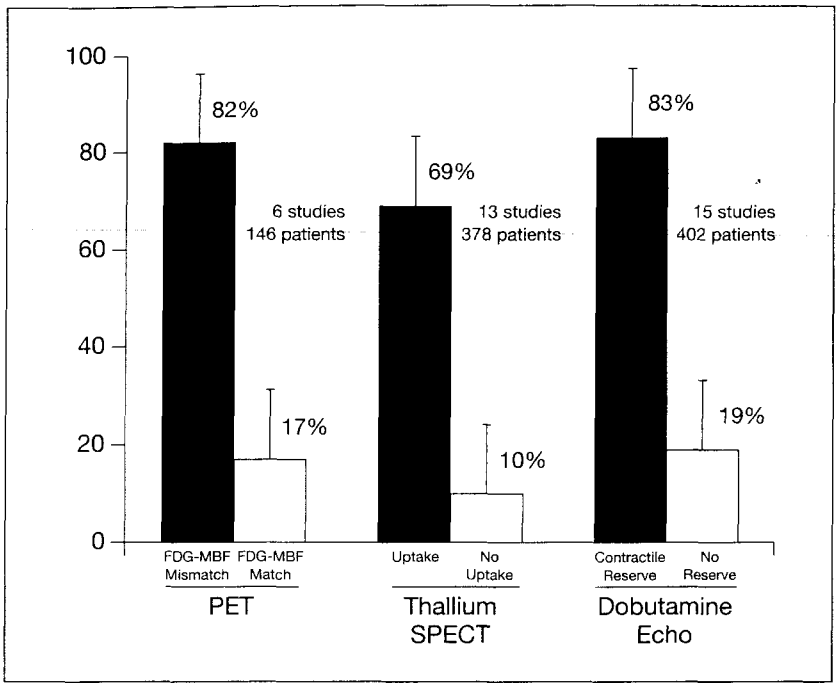

Fig. 2 Likewood of improved regional LV function after revascularization based on non invasive methods to detect viable myocardium. Reproduced from Bonow (ref. 20) with permission of the editor.

tection of ischemic cardiopathy. The uptake of sestamibi also depends on the integrity of cellular membrane and may, therefore, reflect cellular viability. However, the role of sestamibi in the detection of viable myocardium, in hibernation, remains controversial [24]. Dilsizian and col. studied 54 patients with Tl-201 stress-redistribution-reinjection and rest-stress sestamibi and observed a 70% concordance. In this study it was also observed that the cut-off level of 50% thallium-201 activity is also applicable to Tc 99m sestamibi.

Myocardial perfusion with Tc 99m sestamibi has been compared to other imaging techniques, namely thallium-201 [25, 26] and PET [27]. The comparison with Tl-201 showed an excellent concordance between the two methods, particularly when a 50% cut-off level is used. Udleson and col. [22] demonstrated a high sensitivity (94%) and specificity (86%) for the detection of functional recovery after revascularization.

Bax and col. [28] made a comparative study of different techniques used for the assessment of improved contractile function of the myocardium after coronary revascularization in patients with LV dysfunction. Five techniques were considered: Tl-201 rest-redistribution; Tl-201 stress-redistribution-reinjection; FDG-PET; Tc 99m sestamibi; and low dose dobutamine echocardiography (LDDE). This meta-analysis included 37 papers published between 1980 and 1997, which fulfilled the inclusion criteria. The sensitivity in predicting regional function recovery after revascularization was high for all the techniques (*Fig. 3*). The specificity of both thallium-201 protocols was lower ($p < 0.05$) and that of LDDE was significantly higher ($p < 0.01$) than the other techniques. This study concluded that dobutamine echo has the highest predictive accuracy.

The D. Berman group, in California, was the first to point out and validate the simultaneous study of parietal motility and ejection fraction with ECG gated SPECT myocardial perfusion imaging, in comparison with radionuclide ventriculography and echocardiography [30]. Levine and col., of the G. Heller group [31] used this methodology to study myocardial viability in 50 patients with coronary disease and LV dysfunction. The patients were assessed by Tc 99m sestamibi ECG gated SPECT imaging preoperatively and one week after revascularization; 36 patients (72%) repeated the exam 6 weeks after revascularization. Isolated perfusion predicted 87 to be viable and 18 non-viable (sensitivity 86%, specificity 55%, positive predictive value 95%, negative predictive value 28%, overall accuracy 85%). Perfusion and parietal motility combined identified 95 territories to be viable; sensitivity rose to 95% ($p < 0.05$); negative predictive value to 50% and overall accuracy to 91% ($p < 0.05$) (*Fig. 4*). Therefore, this study recorded a significant increase ($p < 0.05$) in sensitivity and overall accuracy in comparison to isolated perfusion.

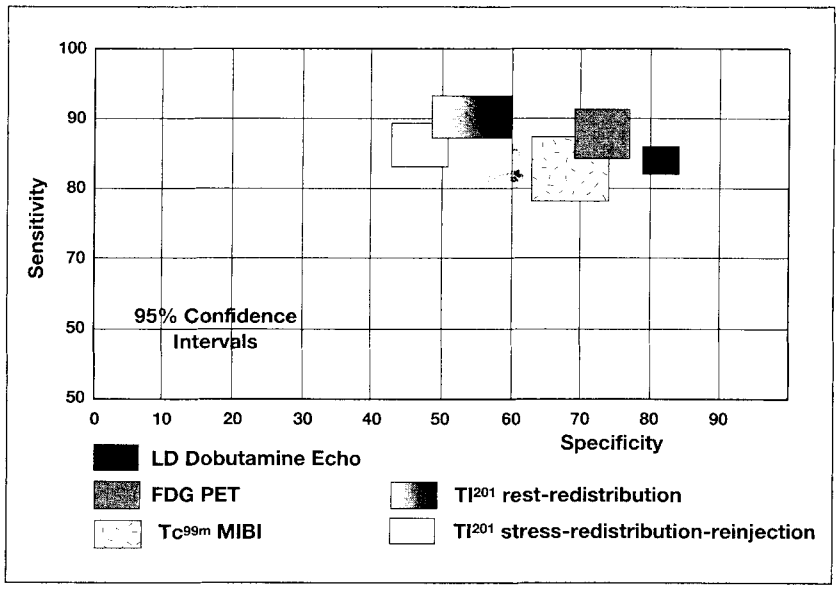

Fig. 3 Receiver operating characteristics display, indicating 95% confidence intervals for each technique. The most effective modalities are located closer to the upper corner of the graph. In this display, the smaller the square, the better the technique. A square (as opposed to a rectangle) indicates a good balance between sensitivity and specificity. A small symbol reflects narrow confidence intervals.
LD=low dose.
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CLINICAL DECISION MAKING

The last part of this presentation is to refer to a few studies which employed the various techniques already mentioned and documented, in an undeniable way, the importance of myocardial viability assessment in clinical decision making.

Gioia and col. of the Iskandrian group studied the relation between the presence of viable myocardium and the prognosis by using the rest-redistribution thallium imaging protocol [32]. Patients with CAD and LV dysfunction were divided in two groups: 47 patients received medical therapy and 38 were revascularized. Viable myocardium vas identified in 14±4 segments/patient in the first group and 15±5 segments/patient in the second group (p=NS) in a total of 20 segments/patient. In a follow-up averaging 31 months, there were 16 (34%) deaths in the first group and 6 (16%) in the second group. The authors therefore concluded that revascularization improves the prognosis of these patients.

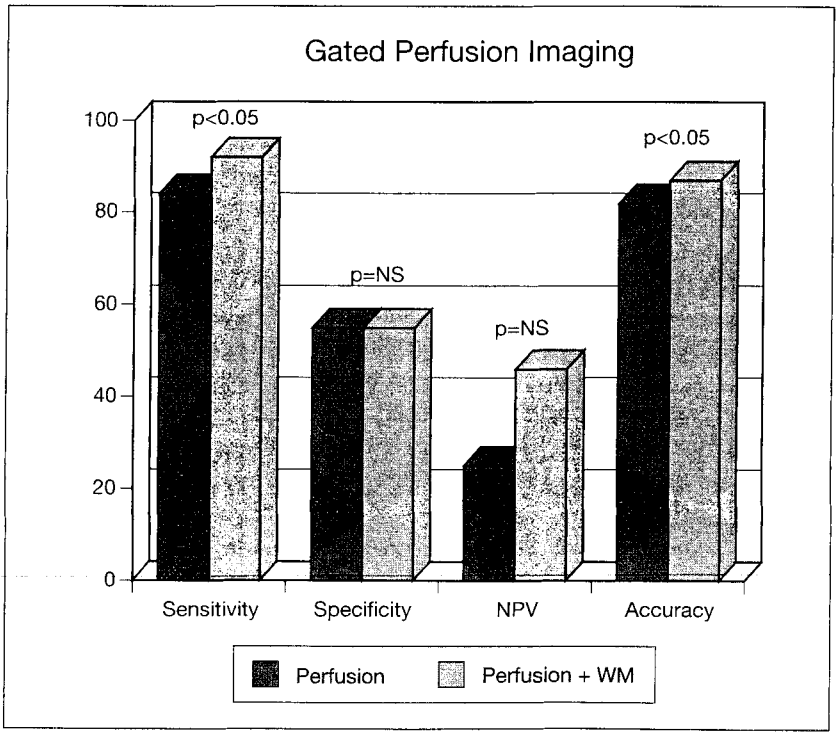

Fig. 4 Comparison of perfusion alone with perfusion + wall motion: the addition of ECG gating significantly improved sensitivity. Reproduced from Levine MG, et al. (ref. 31) with permission of the editor.

Pagley and col. also resorted to Tl-201 with a rest-redistribution protocol to characterise areas of myocardial viability. Seventy patients with multivessel CAD and LV ejection fraction < 40 % who were submitted to preoperative quantitative Tl-201 scintigraphy before coronary bypass surgery were analysed. Each segment was attributed a score according to the size of the defect. A viability index was established based on the score of the different segments. The viability index related significantly to event-free survival in a three-year follow-up. The patients with greater viability (viability index > 0.67; n = 33) were comparable in what concerns clinical and angiographic parameters to those of group 2, with less viability (viability index < 0.67; n = 37). Six cardiac deaths and no transplantations occurred in group 1 and 15 deaths and 2 transplantations occurred in group 2. The Kaplan-Meyer statistical method provided a value of p = 0.018. The value of scintigraphy with Tl-201 using rest-redistribution protocols for the stratification of patients who would benefit most from surgical revascularization was thus demonstrated.

In a recent study, Afridi et al.[34] used dobutamine echocardiography (DSE) to assess myocardial viability in patients with CAD and LV dysfunction. The study included 318 patients with a follow-up of 18 ± 10 months. The patients were classified in four groups: group I (n = 85) presenting myocardial viability and who were submitted to revascularization; group II (n = 119) with myocardial viability, but not submitted to revascularization; group III (n = 30) without myocardial viability, but with revascularization; group IV (n = 84) without myocardial viability and without revascularization. During the already mentioned follow-up, 51 patients (16 %) died: mortality was 6 % in group I; 20 % in group II, 17 % in group III; and 20 % in group IV. The difference between group I and the other groups was statistically significant. This study demonstrated that in patients with CAD and LV dysfunction, with myocardial viability shown by DSE, revascularization improves survival when compared to medical therapy. On the contrary, in the absence of viability, mortality is the same with either medical or surgical therapy.

Bax and col.[35] studied 68 patients with the use of DSE before revascularization. Sixty-two patients had an echocardiogram at rest or a radionuclide angiography before and 3 months after revascularization. In a 2-year follow-up, angina classification (CCS), cardiac insufficiency (NYHA) and major events were considered end-points. The results demonstrated that the patients with 4 or more viable segments in DSE improved LV function after 3 months (*Fig. 5*), as well as the NYHA functional class (from 3.2 ± 0.7 to 1.6 ± 0.5, p < 0.01) and CCS classification (from 2.9 to 1.2, p < 0.01). In the patients with less than 4 viable segments, LVEF and the NYHA functional class did not improve significantly, whereas the angina score (CCS) improved. The percentage of events was higher in the groups with < 4 viable segments (47 % *vs* 17 %, p < 0.05). In this study, DSE showed a high sensitivity and specificity for the prediction of regional LV function improvement.

Di Carli et al.[36] assessed the long term benefit of the determination of myocardial viability for the risk stratification and selection of patients with poor LV function for coronary bypass surgery. The study involved 93 conse-

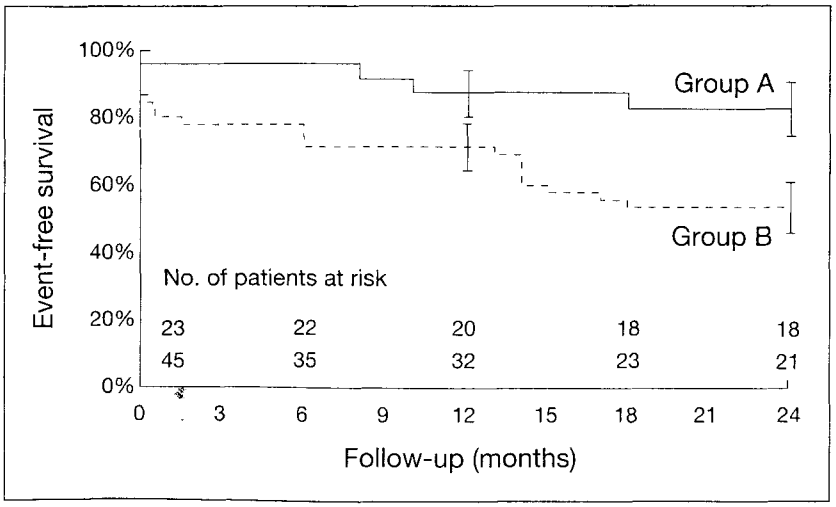

Fig. 5 Events free survival curves of the patients in the two groups. The event rate was higher in group B (p=0.02 *vs* group A). Reproduced from Bax JJ, et al (ref. 35) with permission of the editor.

cutive patients with severe CAD and low ejection fraction (mean 25%) who were submitted to positron emission tomography to calculate the extent of the perfusion metabolism mismatch (reflecting hibernating myocardium) for potential myocardial revascularization. The mean follow-up was 4 years; 50 patients were submitted to medical therapy and 43 to bypass surgery. Univariate analysis allowed the definition of previous myocardial infarction, cardiac insufficiency class and the extent of PET mismatch as significant prognostic factors. After adjustment for these important prognostic factors, survival was significantly improved over time in the group submitted to medical therapy. The estimated survival for the group submitted to medical therapy was 77%, 46% and 33% after 1, 3 and 5 years of follow-up, respectively. For the 43 patients submitted to surgery, the estimated survival was 95%, 84% and 78% after the same periods of time ($p = 0.0002$) (*Fig. 6*). In the group of patients with PET mismatch, those who were submitted to revascularization had a greater probability of survival after 4 years than those who received medical therapy (75% *versus* 30%, $p = 0.007$). In the patients without PET mismatch, revascularization only improved the probability of survival of patients with severe angina pectoris (100% *versus* 60%, $p = 0.085$). It is legitimate to conclude, from this important study, that patients with reduced ejection fraction and myocardial viability, demonstrated by appropriate methodology, present prolonged survival and improvement of the quality of life when submitted to coronary bypass surgery in comparison to those who receive medical therapy.

The assessment of myocardial viability and the extension of the area involved may interfere in the decision of cardiac transplantation. This aspect is well documented in a study by Duong Tit et al. of the UCLA School of Medicine. By using PET imaging, these authors identified a sub-group of patients on a waiting list with myocardial perfusion-metabolism mismatch who would benefit if they were referred to cardiac surgery. The study included 112 patients with ischemic cardiopathy and cardiac insufficiency (FEj <35%) referred to that Institution for cardiac transplantation. Thirty-eight patients presented PET mismatch in 2 or more areas and 30 were submitted to coronary surgery. Of the remaining 74 patients with a low viability index, 33 were submitted to cardiac transplantation and 41 remained under medical therapy. After 5 years, survival was 80% for the 30 patients submitted to coronary bypass surgery, 71.4% for the transplantation group and only 42% for the 41 patients who remained under medical therapy. The difference between the two groups treated surgically was not statistically significant. The au-

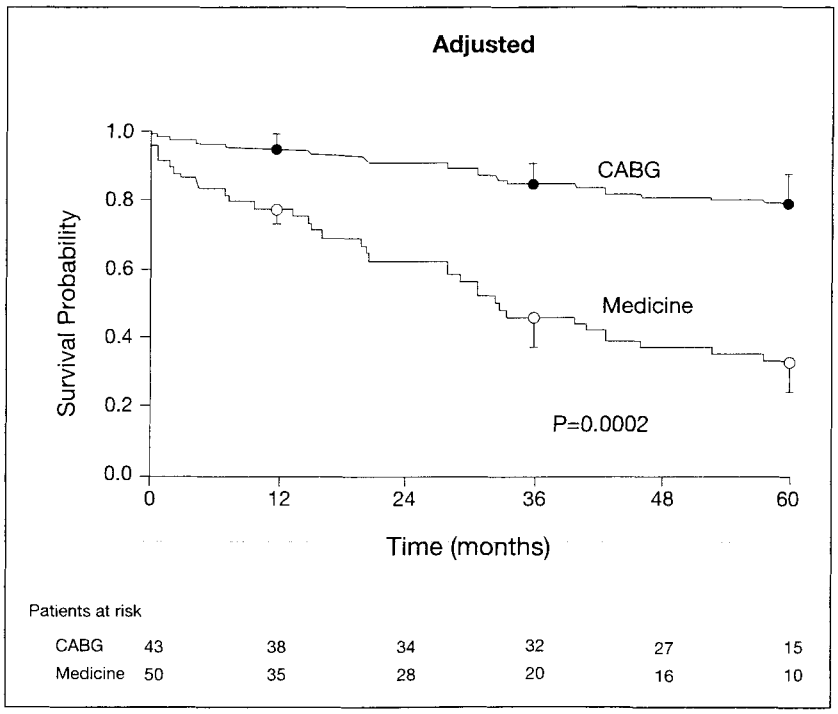

Fig. 6 Plot shows Kaplan-Meyer estimated survival probabilities for patients with left ventricular ejection fraction less than 40% treated medically and with CABG. Data are adjusted for baseline prognostic factors.
Reproduced from Di Carli, et al. (ref. 36) with permission of the editor.

thors present an economic and financial study by which they show a better cost-benefit relation of the PET-CABG algorithm versus cardiac transplantation, with identical peri-operative and survival results after 5 years.

Other studies could be mentioned to point out the benefit of valorising myocardial viability in clinical decision making in patients with significant LV dysfunction. G. Beller presented at a recent AHA meeting an analysis of 10 studies published in the 90's, indicated a 38% mortality rate for patients under medical therapy *versus* 7% for those indicated for revascularization (*Table III*).

It is, therefore, legitimate to conclude that in patients with ischemic cardiopathy and LV dysfunction who have viable myocardium, shown by any of the methods mentioned, when correctly applied, coronary revascularization, whenever technically feasible, constitutes a correct option. Despite the greater surgical risk, these patients present better results in terms of long term survival and quality of life. Medical treatment in the follow-up of these patients is easier and cheaper, with less admissions to the emergency room and hospitalizations.

Table III

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Mortality Rate After Medical Therapy of Revascularization for Hibernating Myocardium

		Viable Myocardium	
Author	**Yr.**	**Med Rx**	**Revasc**
Eitzman	1992	33	4
Schwaiger	1992	50	12
Lee	1994	48	8
Di Carli	1994	50	12
Gioia	1995	34	16
Pasquet	1995	23	8
Knickelbine	1995	58	0
Vom Dahl	1997	22	0
Pasquet	1997	24	5
Average		**38%**	**7%**

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