Review

Clinical Benefit of Noninvasive Viability Studies of Patients with Severe Ischemic Left Ventricular Dysfunction

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Summary: The population of patients who have congestive heart failure of ischemic origin is large and growing. It imposes a heavy burden on human suffering and economic costs such as the chronic use of costly medications, recurrent hospital admissions, and, eventually, death or the necessity of heart transplantation. Therefore, the development of methods for detecting viable myocardium may allow the accurate selection of those patients with coronary artery disease with severe left ventricular dysfunction who are most likely to benefit from revascularization, but also excludes patients who are unlikely to obtain any improvement with revascularization techniques. The presence of reversible dysfunctional myocardium that may improve after revascularization implies the concepts of stunned and hibernating myocardium. Recent evidence suggests that hibernation may not be a stable condition since it might evolve toward an irreversible dysfunction if it is not revascularized at the right moment. The techniques available for viability studies are single-photon emission computed tomography using thallium-201 or compounds labeled with technetium-99m, positron emission tomography, and dobutamine stress echocardiography. Newer and promising techniques are magnetic resonance imaging and contrast echocardiography, whose definitive roles are not clear yet. There is abundant evidence from several important studies showing that patients with a significant amount of viable myocardium have a poor outcome if they are treated medically. Conversely, if these patients are revascularized, their outcomes improve and their symptoms significantly decrease, with less necessity of medication, fewer admissions to the hospital, and even in

some cases avoiding heart transplantation. On the other hand, patients with poor or no viability who are revascularized do not obtain significant benefit.

Key words: coronary artery disease, left ventricular dysfunction, myocardial perfusion imaging, myocardial viability, radionuclide imaging, technetium-99m, thallium-201

Introduction

The heart failure syndrome is quite prevalent in Western society, and it is expected that its prevalence will increase even more in the future because of the aging process of the population.¹

The two most important causes of heart failure are systemic hypertension and coronary artery disease (CAD).^{1,2} It has been recognized that left ventricular (LV) dysfunction in CAD is not always irreversible. On the contrary, an improvement in regional and global function can be observed in many patients undergoing successful revascularization.³ Several multicenter studies performed in the 1970s have shown that surgery improves survival mainly in patients with extensive CAD with impaired LV function.^{4–6} However, such patients, often with previous myocardial infarction and with poor LV function, are at higher risk for perioperative mortality and complications. Thus, adequate selection of those patients most likely to improve with surgery is of paramount clinical importance.⁷ For this reason, the detection of myocardial viability with noninvasive techniques is becoming increasingly more important since they are able to distinguish viable myocardium (hibernating or stunned) from scar tissue. Patients with LV dysfunction and viable myocardium are those who seem to have the greatest benefit with revascularization.⁸

Currently, there is also evidence that the cardiac mortality rate in patients with CAD and LV dysfunction and presence of viability who are treated medically is higher than that in patients with a similar extent of viability who are revascularized. Some patients with severe heart failure of ischemic origin waiting for heart transplantation could be revascularized instead if they have a significant amount of viable myocardium and vessels suitable for revascularization.⁸

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In this review, we present the available evidence regarding the clinical benefit of performing a preoperative myocardial viability assessment in patients with CAD and severe reduction in LV function, and briefly review the concepts of stunned and hibernating myocardium and the most useful methods for detecting them.

Stunned and Hibernating Myocardium

Myocardial stunning refers to postischemic dysfunction in which the resting flow has been normalized after an ischemic insult but the contractile function remains reduced during a variable period of time (i.e., there is a mismatch between a normal flow but a reduced LV function) in the absence of myocardial necrosis.⁹ Traditionally, it has been thought that hibernation corresponds pathophysiologically to a flow-function match in which contractile function is reduced as an adaptive response to match reduced resting myocardial blood flow.^{10–12} With enhanced flow after coronary revascularization, resting function will improve in zones of hibernation.^{9, 13, 14}

The differentiation between repetitive stunning and hibernation is difficult in the clinical context. Both conditions have several essential aspects in common, such as contractile dysfunction at rest caused by CAD that improves after coronary revascularization. Both have intact sarcolemma with a preserved potassium gradient, and both conditions may show improved contractility under the effect of catecholamines. Finally, in both states the main metabolic substrate for being oxidized changes from fatty acids to glucose.⁹

Hibernation may represent an adaptive response necessary for myocardial survival in conditions of resting low myocardial blood flow, and such a state might persist indefinitely ("smart heart" hypothesis). Related to this concept, there is morphologic evidence of dedifferentiation of hibernating cardiac myocytes to an embryonic phenotype.¹⁴ Other evidence suggests that the process of hibernation might be degenerative in nature and progressive over time. The morphologic features that are described include loss of contractile material and accumulation of glycogen. Furthermore, some cardiac myocytes show nucleolar condensations suggestive of apoptosis.^{9, 14} If hibernation is indeed a progressive degenerative process, it would mean that revascularization should be performed as soon as possible; if not, the morphologic changes could become irreversible. Supporting this is the study of Beanlands *et al.*¹⁵ showing that a long waiting time for revascularization is associated with a high mortality rate and suggesting that early revascularization would yield better outcomes after the detection of hibernating myocardium (Fig. 1). The study by Shivalkar *et al.*¹⁶ also gives support to this supposition.

When morphologic changes are advanced, the functional recovery after revascularization will be slower (6 months or more). Functional recovery might not occur if a significant degree of fibrosis had occurred. Therefore, it underlines the importance of an early revascularization after hibernation is detected.^{14–16}

Methods for Detecting Viable Myocardium

The stunned and hibernating myocardium have important features in common, such as preserved cell membrane integrity, inotropic reserve, and conserved glucose metabolism. Methods for detecting one or more of these features include scintigraphic imaging with single-photon emission computed tomography (SPECT) and positron emission tomography (PET), dobutamine stress echocardiography (DSE), contrast echocardiography,¹³ and magnetic resonance imaging.¹⁷ The SPECT, PET, and DSE methods are summarized below.

Single-photon emission computed tomography (SPECT): Thallium-201 (²⁰¹Tl) has been the most commonly employed imaging agent used with SPECT for detecting myocardial viability. The predominant imaging protocols are stress-redistribution-reinjection and rest-redistribution.¹⁸

The stress-redistribution-reinjection protocol is used for detecting both viability and inducible ischemia. Redistribution images are usually acquired 3 to 4 h following stress imaging, after which a second dose of ²⁰¹Tl is injected at rest and repeat images are obtained. Using this approach allows that approximately 20–30% of the defects appearing as fixed in the 4-h redistribution images show reversibility after reinjection. Most of these defects improve function after revascularization.¹⁸

The rest-redistribution protocol is useful when presence and extent of myocardial viability constitute the variable required. Thallium-201 is injected in the resting state and images are acquired 20 min later. Images are obtained again 4 h after tracer injection, and the initial and delayed images are compared for detecting regions of rest-redistribution or mild versus severe persistent defects. It has been shown that ²⁰¹Tl uptake of $\geq 50\%$ of normal predicts functional recovery after revascularization with a high degree of accuracy. The segments with the highest probability of recovering are those that show rest redistribution. The segments showing a fixed mild to moderate defect ($\geq 50\%$ of normal) have an intermediate chance of improving function.¹⁸ Severe nonreversible defects

FIG. 1 Left ventricular function at baseline and 3-month follow-up for early and late revascularization (Revasc) groups ($p < 0.001$). Ventricular function was assessed by radionuclide angiography. Modified with permission of Lippincott, Williams & Wilkins from Beanlands *et al.*: Delay in revascularization is associated with increased mortality rate in patients with severe left ventricular dysfunction and viable myocardium on fluorine 18-fluorodeoxyglucose positron emission tomography imaging. *Circulation* 1998;98:II-51–II-56 (Ref. 15). American Heart Association, Inc. □ = Baseline, ■ = follow-up.

will most often not show improvement of contractile function after revascularization.¹⁹ Other authors have suggested a cut-off point situated in $\geq 60\%$ of normal uptake to obtain the best balance between sensitivity and specificity.^{20,21} It is important to emphasize that regional ²⁰¹Tl activity must be analyzed quantitatively, rather than by a visual analysis.¹⁸

It has been considered that technetium-99m (^{99m}Tc)-labeled agents, principally ^{99m}Tc-sestamibi, are inadequate for assessing myocardial viability. However, the current evidence supports its use for this purpose. Several studies^{22–24} have shown comparable results between resting ^{99m}Tc-sestamibi and delayed resting ²⁰¹Tl uptake, with similar accuracy for detecting viable myocardium. In addition, to increase the detection of viability by ^{99m}Tc-sestamibi, it is useful to perform quantitative analysis of the images and to administer nitrates before ^{99m}Tc-sestamibi injection. Gated SPECT for assessment of systolic thickening also enhances detection of viable myocardium.^{24,25} Two studies^{26,27} comparing resting ^{99m}Tc-tetrofosmin SPECT with ²⁰¹Tl SPECT showed that both agents provide similar accuracy for detecting viability. An underestimation of viability with ^{99m}Tc-labeled perfusion agents has been reported for the inferior wall region, probably due to attenuation.²⁵ Since ^{99m}Tc has better physical properties than ²⁰¹Tl for gamma-camera imaging, it is an attractive alternative for performing viability studies, having an accuracy comparable to ²⁰¹Tl.²⁵

Finally, the advent of high-energy gamma-camera collimators (511 keV) for SPECT has allowed the use of fluorine-18-fluorodeoxyglucose (FDG) for identifying myocardial viability with good results.^{28,29} Srinivasan *et al.*³⁰ reported that FDG SPECT enhances the sensitivity for detection of viable myocardium compared with ²⁰¹Tl imaging alone.^{30,31}

Positron emission tomography (PET): Positron emission tomography uses FDG as a metabolic tracer since this compound is a glucose analog that follows the same metabolic pathway. It is trapped within the cardiac cells after being phosphorylated. The utilization of glucose or its analog FDG is increased in the hibernating and stunned myocardium because the known change in these conditions of the oxidative metabolism from fatty acids to glucose. For assessing regional myocardial blood flow, nitrogen-13-ammonia is most often used.³² Therefore, three scan patterns may be seen, namely, (1) normal regional blood flow and normal glucose uptake and metabolism, which indicates viable myocardium; (2) a regional reduction in perfusion and a proportional reduction in glucose metabolism (match pattern), which denotes nonviability; (3) a decreased regional blood flow associated with a relative or absolute increase in FDG uptake indicative of viability. This “mismatch” pattern is typical, as the cause of systolic dysfunction, of patients with chronic CAD, poor LV function, and myocardial hibernation.^{18,32}

Positron emission tomography imaging is considered the standard of reference for detecting myocardial viability, having positive and negative predictive values both at about 80%, as to which asynergic segments will improve or will not improve their function after revascularization.³³

Dobutamine stress echocardiography (DSE): This method detects the inotropic reserve that is present in viable but non-

contracting myocardial segments.³⁴ Four different responses can be observed, during low-dose dobutamine infusion, in the segments that are dysfunctional in the resting state:

1. Biphasic: Improvement of wall motion during low-dose dobutamine followed by worsening wall motion at higher dose. The decrease of wall motion is caused by ischemia evoked at higher doses of dobutamine, when coronary flow reserve is exhausted. This pattern is an accurate predictor of viability.

2. Sustained improvement: Permanent improvement of wall motion, without deterioration, even at high dobutamine dose. This pattern is indicative of viability but without concomitant ischemia.

3. Worsening: Deterioration of wall motion during the infusion. This response can be observed in areas of myocardium where the coronary flow reserve is minimal or absent, such as zones of hibernation with resting hypoperfusion. This pattern also suggests viability.

4. No change: Absence of improvement or worsening during the test. This response is associated with the absence of myocardial viability.^{9,13}

Dobutamine stress echocardiography has good accuracy for predicting the presence of viable myocardium, comparable with SPECT (with ²⁰¹Tl or ^{99m}Tc), but DSE has less sensitivity for identifying it than scintigraphic techniques. It is, however, more specific than nuclear techniques for detecting viable tissue when functional recovery after revascularization is the criterion used for defining viability.^{35,36}

Evidence Showing Clinical Benefit of Noninvasive Viability Assessment

The patients who need diagnostic testing for hibernating myocardium are those who have significant CAD associated with severe LV dysfunction and are being considered for revascularization. Patients with CAD, low ejection fraction and showing only symptoms of heart failure without or with minimal angina may also benefit from viability testing.^{37,38}

Since the beginning of this decade, several studies have been published that showed improved outcome in patients with CAD, severe LV dysfunction, and hibernating myocardium, who are revascularized compared with those patients with similar clinical characteristics treated medically.^{39–52} Patients with predominantly nonviable myocardium treated with coronary revascularization have worse outcomes than those with viable myocardium who undergo revascularization.^{7,39,41,42,45,47–49}

Eitzman *et al.*³⁹ using PET, studied 82 patients with severe CAD and impaired LV function to evaluate myocardial viability before coronary revascularization. Of these, 40 patients underwent revascularization. Patients with evidence of viability (decreased blood flow with preserved metabolism) who were not revascularized had more events (myocardial infarction, death, cardiac arrest, or late revascularization) than the other patient groups. In addition, those with myocardial viability who underwent coronary revascularization had less events and were more likely to have improvement in functional class than all the other groups. The patients with poor viability had the same outcome with or without coronary revascularization.

In the study by Ragosta *et al.*,⁵³ 21 patients with depressed LV function and CAD were studied with quantitative planar rest-redistribution ²⁰¹Tl imaging for detecting viable myocardium and predicting improved regional and global function after revascularization. They showed that patients who had > 7 viable asynergic segments (15-segment model) in the preoperative study experienced a significant improvement in global ventricular function when studied with radionuclide ventriculography 8 weeks after surgery. In contrast, the group with ≤ 7 viable asynergic segments had no improvement in global ventricular function postoperatively. In the study by Pagley *et al.*,⁷ from the same group, 70 patients with severe CAD and an LV ejection fraction of < 40% were studied preoperatively by quantitative planar rest-redistribution ²⁰¹Tl imaging. All patients underwent coronary artery bypass graft (CABG) surgery. Patients were divided into two groups based on a quantitative viability index. One group had "greater" viability, and the other was judged to have "lesser" viability. Both groups were comparable with respect to age, comorbidities, and severity of CAD. There were 6 deaths of cardiac origin and no heart transplants in the first group and 15 cardiac deaths and 2 transplants during follow-up in the second group. The extent of viability was the only significant predictor of outcome after revascularization. Figure 2 shows the survival curves for both groups of patients in this study.

Lee *et al.*⁴⁰ studied 129 patients who underwent PET; four groups were defined, namely: (1) patients with FDG-positive dysfunctional myocardium who were revascularized (n = 49), (2) patients with FDG-positive dysfunctional myocardium who were treated conservatively (n = 21), (3) patients with FDG-negative myocardium who were revascularized (n = 19), and (4) patients with FDG-negative myocardium who were treated medically (n = 40). Nonfatal ischemic events occurred in 48% of medically treated patients with viability (FDG positive) compared with 8% of revascularized patients with viability and 5% of patients with nonviable tissue (Fig. 3). In this

FIG. 2 Survival analysis (Kaplan-Meier), showing survival free from cardiac events (cardiovascular death or heart transplantation). The solid line indicates the group of patients with more amount of viability (viability index [VI] > 0.67) and the broken line denotes patients having less myocardial viability (VI ≤ 0.67). The difference between the groups was significant ($p = 0.019$). Modified with permission of Lippincott, Williams & Wilkins from Pagley *et al.*: Improved outcome after coronary bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. *Circulation* 1997; 96:793–800 (Ref. 7).

study, only the presence of viable myocardium that had not been revascularized independently predicted ischemic events, whereas only age and ejection fraction, but not presence of viability, were predictive of death. The follow-up period was an average of 9 months.

In the studies by Di Carli *et al.*,^{41,42} 93 patients with angiographic CAD and depressed LV function (ejection fraction = 25%) were studied by PET. Median follow-up was 4 years. The patients were revascularized (n = 43) or treated medically (n = 50). Patients with PET showing myocardial viability ("mismatch") pattern and who were revascularized by CABG had an improved 4-year survival compared with those treated conservatively (75 vs. 30%) and an important improvement in angina and heart failure symptoms. In patients without viability by PET, CABG tended to improve survival, with symptoms only in those with severe angina.

Gioia *et al.*⁴³ studied 85 patients with ischemic cardiomyopathy using rest-redistribution ²⁰¹Tl SPECT. Forty-seven patients were treated medically (Group 1) and 38 patients underwent coronary revascularization (Group 2). The extent of CAD, the extent of LV ejection fraction, and the amount of viable myocardium per patient were comparable in both groups. During an average follow-up of 31 months, there were 16 deaths in Group 1 (34%) and 6 in Group 2 (16%).

In the study by vom Dahl *et al.*,⁴⁴ 135 patients were studied using FDG by PET for evaluating metabolic activity, and ^{99m}Tc-sestamibi by SPECT as a perfusion tracer. Of these patients, 36 had viable myocardium and were treated with coronary revascularization, and they had the best outcome. Functional heart failure class improved in 31% of these patients, and ejection fraction went up from 46 to 54%.

Petretta *et al.*⁵⁴ studied 82 patients who were treated medically with previous, but not a recent myocardial infarction. All had LV dysfunction by echocardiography, and ²⁰¹Tl rest-redistribution SPECT was performed in all. During the fol-

FIG. 3 Study performed using positron emission tomography, showing that patients with metabolically active (FDG+) myocardium who underwent medical therapy (MED) had more ischemic events than revascularized (RVS) FDG+ patients ($p < 0.001$), and than FDG- (metabolically inactive myocardium) who were revascularized ($p = 0.008$) or were treated medically ($p < 0.001$). FDG indicates ¹⁸F-fluorodeoxyglucose. Modified with permission of Lippincott, Williams & Wilkins from Lee *et al.*: Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction. Relative efficacy of medical therapy and revascularization. *Circulation* 1994;90:2687–2694 (Ref. 40).

low-up (mean 25 months), there were 18 cardiac events (14 deaths and 4 nonfatal events). The number of dysfunctional segments by echocardiography with preserved ^{201}Tl uptake ($\geq 50\%$ of peak uptake) and age were variables predictive of an increased number of cardiac events during follow-up with medical therapy.

Morse *et al.*⁴⁵ studied 37 patients with ischemic LV dysfunction by rest-redistribution ^{201}Tl SPECT. Fifteen patients underwent CABG and 22 were treated medically. Among patients with a large amount of myocardium showing viability who underwent CABG, the 48-month actuarial event-free survival was 89%. However, all patients who were treated medically had events. Patients with low viability had an intermediate event-free survival rate, without difference between patients receiving either surgical or medical therapy.

Haas *et al.*⁴⁶ evaluated 76 patients with severe CAD and LV dysfunction who underwent CABG. Thirty-five patients were selected for CABG using only clinical and angiographic data, whereas the second group was selected for CABG on the basis of myocardial viability by PET in addition to clinical and angiographic data. The first group had four in-hospital deaths compared with no deaths in the second group. The survival rate was 79% in the first group and 97% in the second group after a follow-up of 12 months. Finally, the group in whom a preoperative viability study was done had an immediate better postoperative course, with less necessity of catecholamine support and less incidence of low output syndrome.

Recently, two multicenter studies using DSE have been published, with follow-up of the patients included.^{47, 48} Afridi *et al.*⁴⁷ studied 318 patients with CAD and LV ejection fraction $\leq 35\%$ who were followed for a mean of 18 months. It was considered that viability was present if ≥ 4 segments of the left ventricle demonstrated improvement, worsening, or a biphasic response during DSE (the left ventricle was divided into a 16-segment model). Within 3 months after DSE, 115 patients underwent coronary revascularization; the remaining were treated medically. This study design did not entail randomization. Patients were divided into four groups according to the presence or absence of myocardial viability and revascularization status. The group of patients with myocardial viability who were revascularized had a significantly better survival than the other three groups during follow-up. The second of these studies, by Meluzin *et al.*,⁴⁸ included 274 patients with CAD and LV ejection fraction $\leq 40\%$ studied by DSE, of whom 133 were revascularized on clinical criteria and entered in the study. Revascularized patients were followed for a mean of 20 months and classified into three groups according to the amount of viable myocardium that they had. Patients with ≥ 6 segments showing viability (16-segment model of the left ventricle) had the greatest increase in global LV function and had a lower rate of cardiac events during follow-up than the other two groups. The group with an intermediate amount of viable tissue (2 to 5 segments) showed also a significant increase in LV ejection fraction, although less than the group with more viability. The group without viability showed no improvement in LV function and had a relatively high number of cardiac events, similar to the group with an intermediate

amount of viability. This study demonstrated no significant differences regarding survival among groups.

Four other studies using DSE have been published that confirm the findings reported in the studies cited above.⁴⁹⁻⁵⁴ Among them, Senior *et al.*⁴⁹ studied 87 patients with ischemic cardiomyopathy whose main clinical presentation was congestive heart failure. Patients who had ≥ 5 segments of the LV demonstrating viability (12-segment model) had improvement in New York Heart Association functional class and in global LV function. In contrast, patients with < 5 segments showing viability who were revascularized and those with 5 or more segments demonstrating viability who were treated conservatively, had a higher mortality. Thus, this study emphasizes the important benefits that may be obtained in patients with CAD and severe LV dysfunction whose main symptoms are derived from congestive heart failure, with the condition that they must have sufficient viable myocardium.

To summarize, these clinical outcomes studies that are observational in nature show that patients with extensive viability and hibernating myocardium do well following coronary revascularization, whereas such patients appear to have a higher mortality when treated medically. All the noninvasive techniques are useful with respect to predicting outcomes.

Decision-Making Algorithm

A decision-making algorithm is proposed (Fig. 4) for use of noninvasive viability testing. First, most patients with an

Fig. 4 Decision-making algorithm. (See text for details.) SPECT = single-photon emission computed tomography, PET = positron emission tomography, DSE = dobutamine stress echocardiography, CABG = coronary artery bypass grafting, PTCA = percutaneous transluminal coronary angioplasty, ^{201}Tl = thallium-201, $^{99\text{m}}\text{Tc}$ = technetium-99m, ^{18}F -FDG = fluorine-18-fluorodeoxyglucose.

ischemic cardiomyopathy with a severe reduction in LV function should undergo coronary angiography for determining whether their coronary vessels are suitable for revascularization. If diffuse CAD is detected (e.g., disease in the distal coronary bed), patients should benefit more with medical treatment than revascularization or, in certain cases, be referred for cardiac transplantation. On the other hand, if suitable target vessels are delineated, patients should undergo viability testing by SPECT (using ^{201}Tl or $^{99\text{m}}\text{Tc}$ -labeled agents) or DSE. If available, this assessment can be performed by PET. If a significant amount of viable myocardium is not demonstrated, then patients should be treated conservatively or, alternatively, undergo heart transplantation. Finally, if substantial viability is shown to be present by any of these techniques, patients should be strongly considered for myocardial revascularization.⁵⁵

Conclusion

As has been shown, there is an important body of evidence supporting the clinical benefit of viability studies in patients with ischemic cardiomyopathy. However, caution is advised regarding definitive conclusions that can be made because randomized prospective studies are not available comparing coronary revascularization with maximal current medical therapy for ischemic cardiomyopathy and myocardial hibernation.

Nevertheless, the observational studies summarized in this review suggest that the greater the extent of myocardial viability in patients with CAD and LV dysfunction, the greater the probability of enhanced survival, improved LV function, and improved heart failure symptoms after revascularization. Patients with extensive viability seem to have a worse outcome with medical therapy than with revascularization.

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