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Identification of Therapeutic Benefit from Revascularization in Patients With Left Ventricular Systolic Dysfunction

Inducible Ischemia Versus Hibernating Myocardium

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***Background*—**Although the recent surgical treatment of ischemic heart failure substudy reported that revascularization of viable myocardium did not improve survival, these results were limited by the viability imaging technique used and the lack of inducible ischemia information. We examined the relative impact of stress-rest rubidium-82/F-18 fluorodeoxyglucose positron emission tomography identified ischemia, scar, and hibernating myocardium on the survival benefit associated with revascularization in patients with systolic dysfunction.

***Methods and Results*—**The extent of perfusion defects and metabolism-perfusion mismatch was measured with an automated quantitative method in 648 consecutive patients (age, 65±12 years; 23% women; mean left ventricular ejection fraction, 31±12%) undergoing positron emission tomography. Follow-up time began at 92 days (to avoid waiting-time bias); deaths before 92 days were excluded from the analysis. During a mean follow-up of 2.8±1.2 years, 165 deaths (27.5%) occurred. Cox proportional hazards modeling was used to adjust for potential confounders, including a propensity score to adjust for nonrandomized treatment allocation. Early revascularization was performed within 92 days of positron emission tomography in 199 patients (33%). Hibernating myocardium, ischemic myocardium, and scarred myocardium were associated with all-cause death (P=0.0015, 0.0038, and 0.0010, respectively). An interaction between treatment and hibernating myocardium was present such that early revascularization in the setting of significant hibernating myocardium was associated with improved survival compared with medical therapy, especially when the extent of viability exceeded 10% of the myocardium.

***Conclusions*—**Among patients with ischemic cardiomyopathy, hibernating, but not ischemic, myocardium identifies which patients may accrue a survival benefit with revascularization versus medical therapy. ***(Circ Cardiovasc Imaging.* 2013;6:363-372)**

Key Words: ischemia ■ positron emission tomography ■ prognosis ■ revascularization ■ viability

The optimal management strategy for patients with left ventricular (LV) dysfunction secondary to coronary artery disease remains unclear. Small, nonrandomized observational studies examining a variety of imaging approaches have generally reported superior survival with a revascularization strategy in patients found to have hibernating myocardium, although many of these studies reported a worsened survival with the use of revascularization compared with medical therapy in the absence of hibernating myocardium.[1–4] These findings have been confirmed by meta-analyses.[1,3,5] However, many of these studies have also been limited by underuse of cardioprotective medication and inadequate adjustment for baseline risk.[6] The only prospective trial to randomize patients with LV dysfunction to a strategy of viability imaging with positron emission tomography (PET)-fluorodeoxyglucose (FDG) versus standard care failed to demonstrate improved outcomes with a PET-augmented strategy.[7] More recently, the nonrandomized Surgical Treatment of Ischemic Heart Failure (STICH) viability substudy reported that the presence of myocardial viability (defined by single-photon emission computed tomography and low-dose dobutamine echocardiography) did not identify patients with a survival benefit from coronary artery bypass grafting (CABG) compared with aggressive medical therapy alone.[8]

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The identification of patients who may accrue a prognostic benefit from revascularization in ischemic LV dysfunction is a complex multifactorial process in which not only viability, but also other potentially confounding processes, such as ischemia, scar, and remodeling, are substrates. The above studies are limited in that imaging was restricted to assessment

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of hibernation, and the total myocardium in jeopardy was not determined (jeopardized myocardium defined as the sum of hibernating and ischemic myocardium). A previous study using combined stress-rest perfusion plus FDG PET indicated that revascularization in the setting of severe LV dysfunction seemed to improve survival across the entire range of at-risk myocardium.[9] However, a subsequent study using stress single-photon emission computed tomography techniques revealed that the extent of jeopardized myocardium could identify which patients manifested improved survival with revascularization versus medical therapy only in the absence of extensive scar (<10% myocardium scar).[10] However, that study was limited in that many patients did not undergo viability imaging. Furthermore, in both studies, the impact of potential confounders, ventricular remodeling, and use of optimal medical treatment were not addressed.

Thus, we sought to examine whether measures of inducible ischemia and hibernation could identify optimal postimaging therapeutic strategies in patients with ischemic LV dysfunction after risk-adjustment for other imaging and clinical information.

Methods

Study Population

Between March 2006 and May 2009, a total of 1376 consecutive patients with known or suspected coronary artery disease were referred for cardiovascular PET with either regional or global systolic dysfunction by gated PET imaging. We identified 735 of these patients (53% of total) referred for combined assessment of viability and ischemia who underwent rest/vasodilator stress rubidium (Rb)-82 and F-18 FDG PET, with the remaining patients having undergone rest Rb-82 and F-18–FDG PET (641 patients). Patients with missing data (8; 1%), and without a valid US Social Security number (44; 5.9%) were excluded. In addition, to focus on the question of ischemia and hibernation, patients without ≤5% myocardium ischemic and hibernating by quantitative analysis were excluded from analyses (35; 4.8%), leaving a final study cohort of 648 patients (88% of initial cohort). The Institutional Review Board of Cleveland Clinic approved this study.

Before stress testing, all patients underwent a structured interview and chart review. Clinical data on symptoms, cardiac risk factors, medical history, medication therapy, and prior cardiac procedures were prospectively collected and entered into a computerized stress test database.[9,11,12] The study cohort was initially identified from a search of the Cleveland Clinic Nuclear Cardiology Database for all patients undergoing stress/rest/viability PET studies. Data on CABG and percutaneous coronary intervention were retrieved from the prospective Cleveland Clinic Cardiovascular Information Registry[13] and the interventional database, respectively. European System for Cardiac Operative Risk Evaluation a validated score predicting mortality for patients undergoing cardiac surgery was calculated for each patient to account for baseline comorbidities.[14] The relevant parameters of the European System for Cardiac Operative Risk Evaluation in our population include patient-related factors (age, sex, chronic pulmonary disease, extracardiac arteriopathy, neurological dysfunction, previous cardiac surgery, and renal failure), cardiac-related factors (LV dysfunction, pulmonary hypertension, unstable angina, and recent myocardial infarction), and operative factors (concomitant cardiac procedures in addition to CABG).

Positron Emission Tomography

Rb-82 PET perfusion-gated rest and dipyridamole-gated stress imaging and FDG metabolic imaging was acquired using a standard protocol according to the American Society of Nuclear Cardiology guidelines.[15,16] Attenuation correction was routinely used for all studies. Data were reconstructed as static and gated images for perfusion imaging and as static images for metabolic imaging. PET FDG image analysis was performed using an automated program (Corridor4DM; Invia, Ann Arbor, MI). Polar maps were derived and displayed using the standardized 17-segment model (Figure 1).[17,18]

Mismatch was quantified directly. The FDG metabolism map was normalized to the area of peak resting activity. Scoring was based on relative uptake with a score of 0 to 4. Hibernation score, an index of amount of hibernating myocardium, was automatically computed from the positive difference between the rest perfusion and FDG scores (summed rest score–FDG score), segment by segment, and setting any negative difference to zero. Scar score, an index of amount of scarred myocardium, was determined from the positive difference between the rest perfusion and viability scores (summed rest score–hibernation score).

The ischemic, hibernating, and scar scores were automatically derived. The total percentage of the myocardium having ischemia, hibernation, or scarring was computed by normalizing the ischemia, hibernation, or scar score with the maximum potential score (scores/[17×4]×100%).[19] Details of the imaging protocol and image interpretation are provided in the Appendix in the online-only Data Supplement.[16–21]

In our analysis, we defined total jeopardized myocardium as the sum of the percent of the myocardium classed as ischemic and as hibernating. Rest and peak stress LV volumes and ejection fractions (EFs) were calculated from gated perfusion images using standard 4DM software.[21] Quantification was performed by an observer who was blinded to patient clinical information.

Follow-up

The primary end point was all-cause death as derived from the Social Security Death Index.[22] All-cause death, defined as death from any cause substantiated by the Social Security Death Index, is more objective and clinically useful end point compared with cause-specific cardiac death.[21,23] The censoring date was February 25, 2011. In the subset of patients from Ohio, cause of death was sought from the Ohio Death Registry.

Early Post-PET Treatment and Waiting Time Bias

In the setting of a randomized clinical trial, treatment assignment was made at the time of randomization and given intent to treat principles; follow-up time can begin at that point. However, in the current study, definitive treatment assignment was certain only at 90 days. Thus, patients intended for revascularization who died before treatment was given were categorized as medical therapy deaths irrespective of therapeutic plans. Although several approaches have been used to address this issue, we chose to only begin follow-up at 92 days after the index PET study (90 days plus time for delayed intervention). Patients who died before this time point were removed from the Cox proportional hazards (CPH) analysis. Thus, for purposes of this study, follow-up time began at 92 days after the index PET study.

Statistical Analysis

Patients were categorized by revascularization status at 92 days; patients revascularized between the index PET study and 92 days were considered to be in the early revascularization group, and the remaining patients to be in the medical therapy group. Baseline characteristics of the overall cohort and the comparison with patients undergoing medical therapy or early revascularization were described in terms of mean±1 SD for continuous variables and frequency for categorical variables. The former were compared using an unpaired t test and the latter using a χ^2 test. A $P<0.05$ was considered statistically significant. To adjust for potential confounders, especially related to nonrandomized treatment assignment, we pursued a 2-step analytic approach.

Initially, a propensity score[24] was developed to adjust for potential biases introduced by the nonrandomized referral patterns to revascularization in practice. Because this propensity score was to represent these predictors as accurately as possible, all measured factors

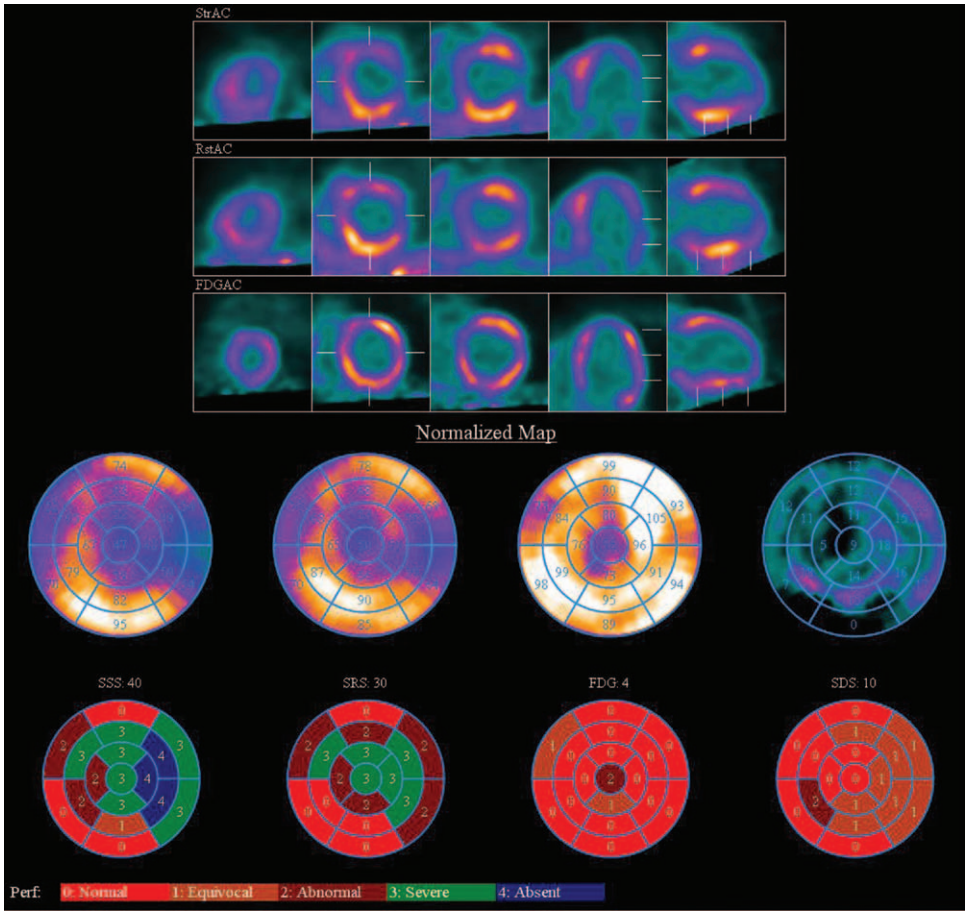

Figure 1. Output of quantitative program used for determining percent myocardium scar, ischemic, and hibernating. Polar maps along the bottom of the image represent summed stress score (SSS), summed rest score (SRS), fluorodeoxyglucose (FDG) score, and summed difference score (SDS) on the basis of automatic 5 point/17-segment segmental scoring. SDS was determined as the difference between SSS and SRS (SSS–SRS). Hibernation score, an index of amount of hibernating myocardium, was the positive difference between the SRS and FDG scores (SRS–FDG score), segment by segment, and setting any negative difference to zero. Scar score, an index of amount of scarred myocardium, was determined from the positive difference between the rest perfusion and viability scores (SRS–hibernation score). The total percentage of the myocardium having ischemia, hibernation, or scarring was computed by normalizing the ischemia, hibernation, or scar score with the maximum potential score (scores/[17×4]×100%).[18]

known to influence this referral decision to early revascularization were considered (within the constraints of overfitting). This approach modeled a decision node referral to early revascularization; use of early revascularization versus medical therapy as defined by patient revascularization status at 92 days after the index PET study using a logistic regression model to summarize measured covariates into a single composite representing a probability of patient assignment to 1 therapy versus another. This score was included in the survival analysis to allow adjustment for the determinants of therapy.

Subsequently, a CPH was used to examine the association of post-PET treatment with survival-time free of all cause death (ACD) after adjusting for baseline covariates and a propensity score.

A set of clinical, historical, and imaging variables were preselected for model entry. These were identified on the basis of previous experience, published data, and clinical judgment. These included patient clinical characteristics/demographics (diabetes mellitus, patient sex, race, and age, use of angiotensin-converting enzyme/angiotensin-receptor blocker, prior myocardial infarction, and revascularization), stress test data (change in heart rate and ischemic ECG response), and imaging data (% myocardium ischemic, scar, hibernating, LVEF, and volumes), and post-test treatment. Final covariate selection was tempered by the presence of collinearity and overfitting. To avoid overfitting, when possible, composite variables were incorporated in the model to replace individual covariates. Interactions found not to be significant by partial likelihood ratio test were not retained in the model.

Whether specific baseline variables impact the survival benefit associated with revascularization was addressed formally with the Cox model by testing for treatment–covariate interactions. Specifically, our primary hypothesis was addressed by testing the interaction between the use of early revascularization and (1) the extent and severity of ischemic myocardium, (2) the extent and severity of hibernating myocardium, and (3) the extent and severity of scar. Secondary analyses examined LVEF and volumes in this manner.

To satisfy model assumptions, we also examined the interaction of diabetes mellitus on these primary interactions and interactions among race, sex, and diabetes mellitus. Care was given to examination of model assumptions, including proportional hazards, linearity, and the additive value of the terms. The proportional hazards assumption was examined using a z test of Schoenfeld residuals after initial graphical inspection of Schoenfeld residuals for each covariate versus log(Time). To assess multicollinearity, we examined variance inflation factors (values >4 considered concerning for multicollinearity) and inspecting correlation coefficients between the covariates of the final CPH model.

The survival impact of early revascularization versus medical therapy was assessed at specific levels of ischemia and hibernating myocardium (0%–40%) and was examined by multivariable hazard ratios on the basis of CPH. The S-PLUS 2000 (Release 2) software package (Insightful Corp, Seattle, WA) was used for all analyses.

Results

Patient Characteristics

Overall, half to two thirds of our patients presented without symptoms. About half of these patients had prior myocardial infarction, with smaller numbers having prior CABG or percutaneous coronary intervention and fewer having prior implantable cardiac defibrillator (ICD) placement. Most of these patients were taking cardioprotective medications (Table 1).

Compared with patients treated medically, those referred to early revascularization did not differ with respect to clinical characteristics, but more frequently presented with typical angina and less frequently without symptoms. Patients

Table 1. Patient Characteristics

	All (n=648)	Medical Therapy (n=432)	Early Revascularization (n=216)	*P* Value
Clinical characteristics				
Age	65.4±11.6	65.1±11.8	65.9±11.2	0.3995
Female	22.5%	21.5%	24.5%	0.4445
Diabetes mellitus	44.8%	42.1%	50.0%	0.0694
Hypercholesterolemia	80.4%	79.6%	81.9%	0.552
White	80.0%	78.7%	81.9%	0.3873
Black	10.3%	11.3%	8.3%	0.2941
Other race	9.9%	10.0%	9.7%	0.9629
Smoking	52.8%	54.4%	49.5%	0.2780
Family Hx CAD	12.5%	15.7%	13.6%	0.3171
EuroSCORE	6.3±3.1	6.4±3.2	6.1±2.9	0.2564
Any chest pain	27.9%	24.8%	34.3%	0.0111
Dyspnea	13.4%	12.7%	14.8%	0.4642
No reported symptoms	62.5%	66.2%	55.1%	0.008
Historical data				
Prior MI	55.1%	55.6%	54.2%	0.7380
Prior CABG	39.4%	44.2%	29.6%	0.0003
Prior PCI	30.6%	34.3%	23.1%	0.0038
Prior ICD	16.5%	21.1%	7.4%	<0.0001
Medication use				
β-Blocker	76.7%	73.8%	82.4%	0.0150
HMG-CoA RI	59.4%	58.3%	61.6%	0.4292
ACE/ARB	59.4%	58.3%	61.6%	0.3471
Antiplatelet	74.8%	76.6%	71.3%	0.1413

Continuous variables presented as mean±1 SD; categorical variables presented as frequency (%). CE/ARB indicates angiotensin-converting enzyme inhibitor and angiotensin-receptor blocker; CABG, coronary artery bypass surgery; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HMG-CoA RI, HMG-CoA reductase inhibitors; ICD; CAD, coronary artery disease; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

undergoing early revascularization less frequently had prior ICD or revascularization.

Compared with those revascularized >92 days after the index PET study, early revascularization patients less commonly had prior revascularization or ICD placement, and more likely to be taking β-blockers at the time of testing.

Stress and Rest PET Results and Hemodynamics

Patients' rest heart rate was normal with low normal systolic and diastolic blood pressures. Heart rate increased during stress by 11.9±12.2 bpm. The patients in this study had extensive perfusion defect size, with approximately half of their defect size consisting of hibernating myocardium. Smaller amounts of scar and ischemic myocardium were present. LV dilatation was present on rest and peak stress images. Rest and peak stress EF was markedly reduced, with little increase during stress. The frequency of rest gated PET LVEF<25% was equally low in the 2 groups (medical therapy, 35.7% versus early revascularization, 36.1%; Table 2).

Compared with patients treated medically, those referred to early revascularization had similar hemodynamic characteristics, but had significantly greater perfusion defect size, with less scar and more ischemia, but similar amounts of hibernating myocardium. Interestingly, early revascularization patients also had relatively reduced EF reserve.

Patients with prior ICD had similar amounts of ischemia compared with patients without ICDs (% myocardium ischemic, 13.5±12.9 versus 14.0±9.7, respectively). However, total defect size was greater in the former compared with the latter (35.0±14.8 versus 29.8±16.0; *P*=0.002, respectively), as was the amount of scar (% myocardium fixed, 9.6±8.0 versus 5.5±9.8; *P*<0.001, respectively) and the LV volumes (resting end-systolic volume index, 67.4±39.7 versus 57.7±33.3; *P*<0.05, respectively).

Outcome

During a mean follow-up of 2.8±1.2 years, there were 213 (33%) all-cause deaths. After excluding 47 deaths occurring within the first 92 days (22% of total), 165 deaths remained (27.5%). Of these, 43 deaths occurred in the revascularization group (21.6%) and 122 in the medical therapy group (30.4%; *P*=0.030). In addition, 22 patients underwent late revascularization (5.1%) among whom 4 deaths occurred (18.0%).

Statistical Modeling

Propensity Score Development

Logistic regression identified multiple factors as predictive of referral to early revascularization (use of revascularization

Table 2. Stress and Rest PET Results and Hemodynamics

	All (n=648)	Medical Therapy (n=432)	Early Revascularization (n=216)	*P* Value
Hemodynamics				
Rest heart rate, bpm	71.3±13.4	71.3±13.6	71.1±13.2	0.8722
Rest systolic pressure, mm Hg	113.3±18.7	112.6±18.9	114.7±18.5	0.1824
Rest diastolic pressure, mm Hg	55.5±13.7	55.0±13.9	56.4±13.4	0.2514
Peak heart rate, bpm	79.1±14.4	79.0±14.5	79.2±14.3	0.8317
Peak systolic pressure, mm Hg	107.2±20.7	107.1±21.1	107.3±19.8	0.9063
Peak diastolic pressure, mm Hg	50.7±13.3	51.0±13.8	50.2±12.2	0.5120
Change in heart rate	11.9±12.2	11.7±12.4	12.2±12.0	0.6440
PET results				
% myocardium abnormal	30.6±16.0	29.5±16.1	33.0±15.5	0.0085
% myocardium scar	6.1±8.1	7.3±8.8	3.8±5.9	<0.0001
% myocardium hibernation	15.0±11.4	14.9±11.4	15.2±11.3	0.8099
% myocardium ischemic	9.5±8.5	7.2±6.6	14.0±9.9	<0.0001
% myocardium jeopardized	24.5±14.1	22.2±13.2	29.1±14.9	<0.0001
Rest ESVI, mL/m^2	59.4±34.8	59.6+34.3	59.1+35.7	0.8751
Peak stress ESVI, mL/m^2	63.4±37.6	62.8±36.3	64.4±40.1	0.6298
Rest left ventricular EF, %	31.2±12.0	31.3±12.3	31.0±11.4	0.9080
Peak stress left ventricular EF, %	32.8±14.9	33.1±16.0	32.2±12.5	0.4635
Left ventricular EF reserve	2.1±7.0	2.6±6.8	1.3±7.1	0.0238

Continuous variables presented as mean±1 SD; categorical variables presented as frequency (%). ESVI indicates end-systolic volume index; EJ, ejection fraction; and PET, positron emission tomography.

rather than medical therapy within 92 days of the index PET study) after PET (Table 3; global χ^2 94; *c*-index, 0.79; *P*<0.0001). The extent and severity of ischemia were the predominant covariate in this model. Prior CABG, extent and severity of scar, and age were the other major components of this model. Importantly, the extent and severity of hibernating myocardium were not significantly associated with referral to early revascularization. The predicted likelihood of referral to revascularization for each individual patient determined from this model was entered into the survival model as a propensity score to adjust for the lack of randomization.

Survival Analysis

CPHs modeling identified multiple independent correlates of mortality (Table 4; global χ^2, 165.4; *c*-index, 0.72; *P*<0.0001). Clinical factors included European System for Cardiac Operative Risk Evaluation, race, and diabetes mellitus, whereas significant imaging covariates included % myocardium ischemic, % myocardium scar, and % myocardium hibernating, as well as the heart rate response to vasodilator stress and LVEF reserve (the change in LVEF with stress).

A series of interaction models were examined to determine the differential benefit of revascularization versus medical therapy at varying levels of ischemia, hibernation, and scar. No significant interaction was present between the use of early revascularization and either proportions of ischemic and nonviable myocardium. A significant interaction was found between percent myocardium showing hibernation and early revascularization (interaction *P*<0.0009) as part of a 3-way interaction with diabetes mellitus. The net effect of these interactions indicates that with medical therapy, risk increases proportionally with the proportion of hibernating myocardium. However, patients treated with early revascularization seem to have a relationship between the proportion of hibernating myocardium and risk, suggesting that the use of early revascularization in these patients reduced the risk associated with increasing amounts of hibernating myocardium (Figure 2). Equipoise occurred at ≈10% myocardium hibernating; medical therapy has superior survival at 5% myocardium hibernating (Figure 3A), the survival curves overlap at 10% myocardium hibernating (Figure 3B), and early revascularization has superior survival as percent myocardium hibernating further increases (Figure 3C and 3D).

The net effect of the above interactions with respect to diabetes mellitus indicates that the survival benefit associated with the use of early revascularization in the setting of larger amounts of hibernating myocardium is limited to patients with non–diabetes mellitus. This finding is present in both men and women, although the absolute risk with and extent of hibernating myocardium is greater in patients with than those without diabetes mellitus.

Discussion

The results of the current study report an association between the extent and severity of hibernating myocardium, posttest treatment, and subsequent patient survival, suggesting the possibility that this imaging approach may identify which patients with LV dysfunction may benefit from early revascularization as opposed to medical therapy. Although patients with limited hibernating myocardium benefit from the latter, those with extensive hibernating myocardium (>10%)

Table 3. Results of Logistic Regression Modeling of Referral to Early Revascularization

Covariate	β	SE of β	χ^2	*P* Value
Intercept	−15.2901	…	…	0.0003
Age	0.2139	0.0831	7.5	0.0232
Age^2	−0.0016	0.0006	6.0	0.0145
Female	0.0271	0.2661	0.1	0.9007
Body mass index	0.0034	0.0165	0.1	0.8300
Black	−0.8920	0.3842	5.3	0.0217
In-state resident	−0.3132	0.2180	2.2	0.1376
Any chest pain	0.3500	0.2292	2.4	0.1222
Insulin use	0.0164	0.2652	0.1	0.9136
β-Blocker use	0.3445	0.2698	1.7	0.1921
Hx MI	0.3891	0.2327	2.9	0.0892
Hx CABG	−1.0176	0.2350	18.3	<0.0001
Hx PCI	−0.4843	0.2529	2.7	0.1013
% myocardium scar	−0.0618	0.0160	14.6	<0.0001
% myocardium ischemic	0.0999	0.0135	54.4	<0.0001
% myocardium hibernating	−0.0009	0.0094	0.1	0.9309
Rest end-diastolic volume index	0.0039	0.0034	1.3	0.2530

Global χ^2, 94 using 16 degrees of freedom. *C*-index, 0.79; *P*<0.0001. CABG indicates coronary artery bypass grafting; Hx, history; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

may benefit from the former. Overall, revascularization seems to reduce the risk associated with hibernating myocardium. However, the presence of diabetes mellitus seems to eliminate the survival benefit otherwise accrued with early revascularization in these patients.

Comparison With STICH and Other Previous Studies

The current results contrast with the recently published observational substudy of the STICH trial, which found no association of nonscar tissue with outcome.[8] However, there are some important differences between these studies; our study population seemed to be sicker, as the patients were older, and more had diabetes mellitus, prior revascularization, and ICD. Most importantly, they had considerably greater perfusion abnormalities and, most importantly, far more hibernating myocardium. Interestingly, the benefit of revascularization in the setting of extensive hibernation was found, despite the greater use of implantable defibrillators in the medical therapy subgroup.

In a sense, this group could be considered to be a more appropriate and clinically relevant population for viability testing than the patients in STICH, who were already identified as being candidates for revascularization. The assessment of viability testing in STICH was not standardized, including 4 different SPECT protocols and dobutamine stress echocardiography. Of note, 1 of the techniques used (rest redistribution thallium imaging) often fails to differentiate hibernating from scarred myocardium in many patients with LV dysfunction.[15] The definition of viability with SPECT in STICH also did not distinguish actual myocardium at risk (ie, ischemia and hibernation) versus the normal myocardium. Finally, in contrast to the current study, the STICH protocol was limited to assessment of hibernation without consideration of stress-induced ischemia.

In the current study, we found that a threshold of ≈10% myocardium hibernating defined equipoise between the alternative interventions, a threshold lower than the ≈25.8% previously reported in a meta-analysis.[3] Our results are also consistent with previous results from a multicenter registry suggesting improved patient outcomes with revascularization performed in the setting of more extensive PET mismatch.[25] Our results did not attribute a role to scarred myocardium in the identification of the revascularization candidate, in contradistinction to a previous reports showing <15% nonviable myocardium was associated with better outcome with revascularization than medical therapy[26] and lack of revascularization benefit if >10% myocardium scar.[19]

Viability Criteria

There are no standard criteria for the definition of viability, and wide variations between studies have been reported, even within the same imaging modality. Many studies, including the STICH viability study, have used criteria (such as tracer uptake above a particular threshold or augmentation with dobutamine) which may include normal and dysfunctional but viable segments.[8] Most prior studies with PET/FDG used the number of segments with perfusion-metabolism mismatch to assess the total extent of viable myocardium (but at various arbitrarily selected dichotomous cut points).[4] Current heart failure guidelines recommended consideration of noninvasive imaging for the assessment of both inducible ischemia and viable myocardium in the heart failure population.[27] This assessment of total myocardium at risk is clinically relevant in patients with ischemic cardiomyopathy.

Table 4. Cox Proportional Hazards Model for All-Cause Death

Factor	β	SE of β	χ^2	*P* Value
Diabetes mellitus	1.1424	0.33304	23.8	0.0001
EuroSCORE	0.1967	0.03153	38.9	0.0001
Black	0.6738	0.24168	7.8	0.0053
ACE/ARB use	–0.5872	0.16653	12.4	0.0004
Female	–0.5061	0.20863	5.9	0.0153
Hx REV	–0.3013	0.21354	2.0	0.1582
Change in heart rate with stress	–0.0292	0.00852	11.8	0.0006
EF Reserve (peak stress EF-rest EF)	–0.0327	0.01353	5.9	0.0155
% myocardium scar	0.0386	0.01173	10.8	0.0010
% myocardium ischemic	–0.0585	0.02024	8.4	0.0038
% myocardium hibernating	0.0313	0.01223	17.5	0.0016
Use of early revascularization	0.2036	0.52600	9.2	0.0569
Propensity score	1.7948	0.87305	4.2	0.0398
Diabetes mellitus×% myocardium hibernating	–0.0290	0.01614	6.7	0.0355
Diabetes mellitus×early revascularization	–1.2146	0.66983	6.6	0.0376
Early revascularization×% myocardium hibernating	–0.0232	0.02433	8.6	0.0134
Early revascularization×diabetes mellitus×% myocardium hibernating	0.0796	0.03167	6.3	0.0119
Total	…	…	113.2	<0.0001

ACE/ARB indicates angiotensin enzyme inhibitor/angiotensin receptor blocker; EF, ejection fraction; EuroSCORE, European System for Cardiac Operative Risk Evaluation; Hx: history of prior; and REV, revascularization.

The current study found the prognostic impact of revascularization to differ in patients with versus without diabetes mellitus. It is possible that the identification of which patients with diabetes mellitus may manifest a survival benefit with revascularization is more complex than patients with non–diabetes mellitus and the current study has insufficiently addressed this. However, this result may be related to diabetes mellitus adversely affecting the PET methodology for measuring metabolism because FDG imaging only reflects glucose uptake and not its actual metabolism, which requires dynamic image acquisition and the use of radiolabeled glucose. Although manipulation of glucose/FDG in patients with diabetes mellitus is entirely straightforward, the results of a similar study using flow and viability from an alternative modality (eg, cardiac MR) would address this issue.

Postimaging Referral Bias and Assessment of Risk

In the current study, we found that referring physicians depended heavily on the results of ischemia imaging and, to a lesser extent, identification of fixed defects in the decision to refer to subsequent revascularization. However, the results of the viability study seem to be less strongly incorporated in this decision. Although the current study was not designed to

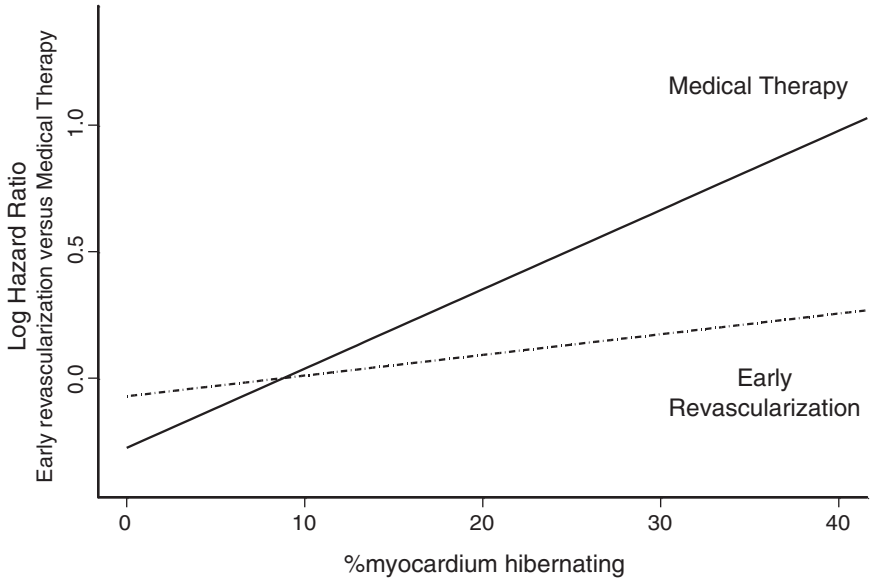

Figure 2. Relationship between percent myocardium hibernation and adjusted hazard ratio for patients treated with early revascularization vs. medical therapy. Risk increases as a function of percent myocardium hibernation in medically treated patients. In patients referred to early revascularization risk seems to be relatively unchanged across the range of values. Percent myocardium hibernation–treatment interaction; *P*=0.0009.

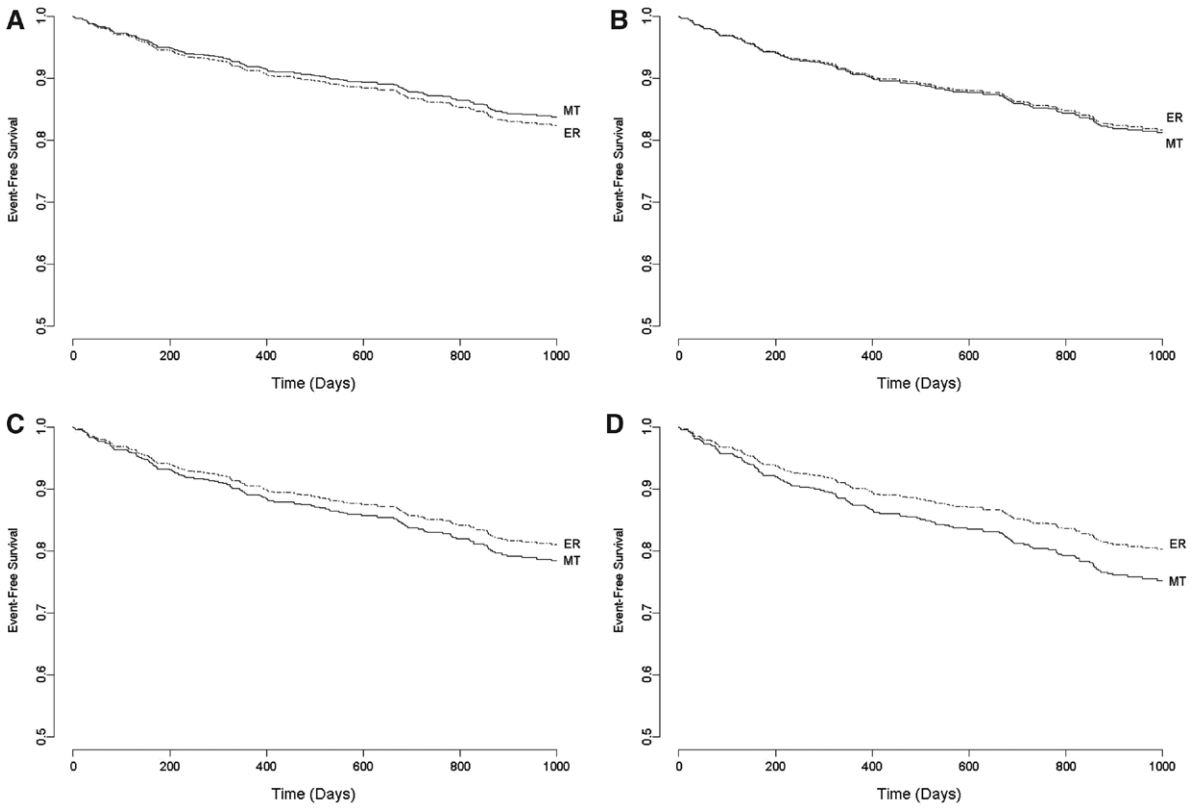

Figure 3. Adjusted Kaplan–Meier survival analysis of all-cause death with early revascularization (ER) vs. medical therapy (MT). Survival times adjusted to percent myocardium hibernation of 5% (**A**), 10% (**B**), 15% (**C**), and 20% (**D**). Event-free survival is superior with MT over ER in the setting of 5% myocardium hibernating (**A**), but equipoise is present at 10% myocardium hibernating (**B**). With further increases in and myocardium hibernating (15% and 20%), an increasing survival benefit is present with ER over MT (**C** and **D**). Interaction term; *P*=0.0014. All survival estimates based on Cox proportional hazards model are shown in Table 4.

address the question of why this occurred, the implications of this referral bias are significant. The failure to revascularize on the basis of the viability information effectively debiases the prognostic assessment of hibernation information, as has been previously described.[28] However as the revascularization referral was largely based on the ischemia information, the association between ischemia imaging results and subsequent outcomes has been altered.

Limitations

There are several limitations in our study. First, this is an observational and nonrandomized study from a single large volume tertiary referral center. The high event rates and extensive jeopardized myocardium reflect the underlying referral pattern of highly selected patients with high underlying risk. However, this represents the population among whom clinical concerns are often expressed on the risk and benefit of intervention, and is a difficult one to recruit to a randomized trial. These observational data are complementary to trial data, as they represent patients seen in clinical practice and can account for changes in therapy over time. Second, although propensity scoring was used to reduce selection bias, there might be important unmeasured confounders. However, propensity scoring is an accepted and widely used statistical method to adjust for potential biases introduced by the nonrandomized trial to balance the covariates in those groups. Third, our study did not consider anatomic information, such as the status of coronary targets, the extent of diffuse distal disease, and the suitability of the revascularization, as well as availability of suitable grafts. However, the underlying hypothesis was to examine the impact of the extent of hibernating myocardium and the therapeutic benefit associated with revascularization. Although the suitability of coronary anatomy may affect medical decision making, we do not think that this would affect the primary outcome (ie, the interaction between the hibernation myocardium and the treatment will be preserved). Fourth, by study design, our cohort was limited to patients with jeopardized myocardium, and we are unable to evaluate the impact of intervention in patients without jeopardized myocardium. Fifth, not all patients in the medically treated group underwent coronary angiography at the time of PET imaging. However, 90% in the medically treated group has documented coronary artery disease, and the mean jeopardized myocardium of 22% in this group makes it highly likely that their cardiomyopathy is ischemic in pathogenesis.

Likewise, although we anticipate that the majority of these patients with late-stage ischemic heart disease would undergo revascularization at our facility, and examination of the charts did not identify patients who underwent revascularization elsewhere, it is possible that some of the medically managed group were revascularized without our awareness. Our study examined all-cause death as the primary end point, rather than cardiac death. Although cardiac death is more specific to this

group of patients, all-cause death is more objective and can limit potential misclassification bias.

Our study population also differed from the STICH cohort and other previous studies in that a significant proportion of patients were without symptoms at the time of testing. Virtually all patients in the current study were referred to PET imaging after initial evaluation and management in our Advanced Ischemic Heart Disease Center to rule out an ischemic pathogenesis for their LV dysfunction before referral for consideration for heart transplantation candidacy. Thus, before PET imaging, these patients had already undergone aggressive therapeutic management, resulting in amelioration of symptoms in many patients.

We used quantitative scoring of image data to enhance the generalizability of our results and minimize the impact of inter-reader variability on our results. This approach included discrete scores for scared, ischemic, and hibernating myocardium using a fixed-sum scale (eg, segmental scores attributed to a myocardial state cannot be scored to a second myocardial state to prevent double counting).

Conclusions

Among patients with ischemic cardiomyopathy, a strategy of early revascularization may be superior to medical therapy in patients with >20% myocardium hibernating, and medical therapy may be superior in patients with less hibernation.

Disclosures

Dr Cerqueira is a consultant for GE Healthcare, Astellas Pharma USA, and FluoroPharma. The other authors have no conflict to report.

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CLINICAL PERSPECTIVE

Although previous observational studies have suggested that revascularization rather than medical therapy offers survival benefit in the setting of significant hibernating myocardium, the recent nonrandomized, nuclear substudy of the Surgical Treatment of Ischemic Heart Failure trial reported no difference in survival. However, these results were limited by the viability imaging technique used and the lack of information about inducible ischemia. We examined the relative impact of stress-rest rubidium-82/F-18 fluorodeoxyglucose positron emission tomography identified ischemia, scar, and hibernating myocardium on the survival benefit associated with revascularization in patients with systolic dysfunction. We identified 648 consecutive patients (age, 65±12 years; 23% women; mean LVEF, 31±12%) who underwent this protocol and were followed up for a mean of 2.8±1.2 years during which 165 deaths (27.5%) occurred. Early revascularization was performed within 92 days of positron emission tomography in 199 patients (33%). The extent of perfusion defects and metabolism-perfusion mismatch was measured with an automated quantitative method. After adjusting for patient characteristics and potential confounders using a Cox proportional hazards model, including a propensity score to adjust for nonrandomized treatment allocation, an interaction between treatment and hibernating myocardium was identified, such that early revascularization in the setting of significant hibernating myocardium was associated with improved survival compared with medical therapy, especially when the extent of viability exceeded 10% of the myocardium. Among patients with ischemic cardiomyopathy, hibernating, but not ischemic, myocardium identifies which patients may accrue a survival benefit with revascularization versus medical therapy. These results suggest that the results of the Surgical Treatment of Ischemic Heart Failure study may not be generalizable to the efficacy of revascularization decisions in patients with left ventricular systolic dysfunction after viability imaging with advanced cardiovascular imaging techniques such as stress-rest Rb-82/F-18 fluorodeoxyglucose positron emission tomography.