Relationship of non-invasive quantification of myocardial blood flow to arrhythmic events in patients with implantable cardiac defibrillators

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Background. **Ischemia contributes to arrhythmogenesis though its role is incompletely understood. Abnormal myocardial perfusion measured by PET imaging may predict ventricular arrhythmias (VAs) in a high-risk population.**

Methods. **Patients with implantable cardiac defibrillators who had undergone rubidium-82 cardiac PET imaging were identified. Patients were stratified by median MBF and MFR values for analysis. The Cox proportional hazards model was used to assess the impact of myocardial perfusion on survival free of VT independent of critical covariates.**

Results. **A total of 159 patients (124 (78%) males, median age 65.9 years, IQR [56.76-72.63]) were followed for 1.43 years IQR [0.83-2.21]. VA occurred in 29 patients (23.7%). After adjustment for ejection fraction, age, and sex, impaired stress MBF was associated with an increased risk of VA (adjusted HR per ml/min/g 1.52, 95% CI (1.01-2.31), $P = 0.04$). Summed rest and stress scores were not predictive of VA. Among patients with severe LV dysfunction, stress MBF remained an independent predictor of VA (adjusted HR per 1 ml/min/g HR 1.69, 95% CI (1.03-11.36), $P = 0.03$), while residual EF, summed rest, and summed stress scores were not ($P > 0.05$).**

Conclusions. **Impaired stress myocardial blood flow was associated with less survival free of ventricular arrhythmias. (J Nucl Cardiol 2019;26:417–27.)**

Key Words: Myocardial perfusion imaging • coronary blood flow • heart failure • diagnostic and prognostic application

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Abbreviations

EF	Ejection fraction
ICD	Implantable cardiac defibrillator
IQR	Intra-quartile range
MACE	Major adverse cardiac events
MBF	Myocardial blood flow
PET	Positron emission tomography
SCD	Sudden cardiac death
SRS	Summed rest score
SSS	Summed stress score
VA	Ventricular arrhythmia

INTRODUCTION

Left ventricular ejection fraction (EF) is the most studied variable for determination of benefit for primary prevention of sudden cardiac death (SCD) with an implantable cardiac defibrillator (ICD). Nevertheless, most SCD occurs in patients without severe left ventricular dysfunction,[1] who would not qualify for an ICD under current guidelines.[2] Additionally, many patients with ICDs implanted on the basis of EF never receive an appropriate life-saving therapy.[3]

Because of the limitations of EF criteria for ICD risk stratification, there has been growing interest in use of other non-invasive markers of arrhythmia risk including scar size and morphology and sympathetic denervation. Although myocardial ischemia increases arrhythmogenicity by multiple mechanisms,[4] including QT dispersion, increased myocyte automaticity and excitability,[5] impaired autonomic innervation, and scar-related reentry circuits,[6] the association between epicardial coronary stenosis and SCD has not been established in controlled trials. Observational studies suggest that revascularization does not change the inducibility of ventricular arrhythmias or outcomes.[7,8] This may in part be due to the complex relationship between epicardial stenosis severity and myocardial ischemia.[9] Quantitative assessment of myocardial perfusion with positron emission tomography (PET) has been established as an independent predictor of cardiac mortality,[10] even in the absence of overt coronary artery disease by angiography. Because PET-based measures more accurately and completely define the hemodynamic consequences of epicardial stenosis, diffuse atherosclerosis, and microvascular dysfunction, this method may better define ischemic contributions to electrical instability.[11] We sought to determine whether quantitative measures of myocardial perfusion by PET imaging are independently related to ventricular arrhythmias in patients with ICDs.

METHODS

Study Population

All patients referred for rest/stress cardiac PET imaging at the University of Michigan (Ann Arbor, MI) between 12/01/2007 and 2/1/2016 were identified using relevant CPT codes. Patients who had undergone placement of an ICD prior to imaging were then identified and included in the study cohort. Patients whose images were missing or uninterpretable owing to poor image quality were excluded, as were patients who did not have adequate documentation of follow-up including device interrogation reports. Patients with a history of heart transplant, ventricular assist devices, cardiac sarcoidosis, hypertrophic obstructive cardiomyopathy, or congenital arrhythmia syndromes such as inherited long QT syndrome or channelopathies were also excluded from analysis. This study was approved by the University of Michigan Institutional Review Board and conducted in accordance with institutional guidelines.

PET Imaging

Patients were studied with a whole-body PET-computed tomography scanner (Siemens Biograph mCT, Knoxville, TN) after an overnight fast. Patients refrained from caffeine- and methylxanthine-containing substances and drugs for 24 hour before their scans. Myocardial blood flow (MBF) was measured during rest and peak stress with rubidium-82 as a perfusion tracer, as described previously.[11] Briefly, after transmission imaging and beginning with the intravenous bolus administration of rubidium-82 (13-45 mCi), list mode images were acquired for 7 minutes. Then, a standard intravenous bolus of 0.4 mg of regadenoson was given. At peak stress, a second dose of rubidium-82 was injected, and images were recorded in the same manner. Heart rate, blood pressure, and 12-lead ECG were recorded at baseline and every minute during and after pharmacological stress. In the event of multiple stress tests occurring over the study period, the earliest test was selected for analysis.

Image Analysis

Semiquantitative analysis of myocardial perfusion. Semiquantitative 17-segment visual interpretation of the gated myocardial perfusion images was performed by experienced observers using a standard 5-point scoring system.[12,13] Summed rest (SRS) and summed stress (SSS) scores were calculated as the sum of individual segmental scores on the respective images, and their difference was recorded as summed difference score. For each of these variables, higher scores reflect larger areas of myocardial ischemia and/or scar. Summed rest, stress, and difference scores were converted into percentages of total myocardium by division of the maximum possible score.

LV systolic function. Rest and stress LV ejection fractions (EFs) were calculated from gated myocardial perfusion images with commercially available software (Corridor4DM; Ann Arbor, MI). LVEF reserve was considered present when LVEF increased from rest to stress.

Quantitative MBF and Flow Reserve

Absolute myocardial blood flow (MBF) (in $ml \cdot g^{-1} \cdot min^{-1}$) was computed from the dynamic rest and stress

imaging series with commercially available software (Corridor4DM; Ann Arbor, MI) and previously validated methods.[12,14] Factor analysis was used to generate blood pool (arterial input function) and tissue time-activity curves.[15] Regional and global rest and peak stress MBFs were calculated by fitting the rubidium-82 time-activity curves to a 2-compartment tracer kinetic model, as described previously.[12] Per-patient global myocardial flow reserve (MFR) was calculated as the ratio of absolute MBF at stress over rest for the entire left ventricle. Quantification of MBF was performed by one author (MG).

Patient Information and Assessment of Outcomes

Medical records were reviewed to obtain information on patient demographics, medical history, medication use, device type and indication, and the occurrence of arrhythmic events. Information on the date and cause of death was ascertained through integrating information from the medical records, the Social Security Death Index, and the National Death Index. Dates of arrhythmic events were ascertained by integrating information from the medical records, clinical device interrogation reports, and home-monitoring reports. When available, primary device interrogation data were reviewed for confirmation of arrhythmic events. In the case of disagreement, a consensus opinion was obtained from three authors (MG, KM, RC). Arrhythmic events were classified using standard definitions found in international guidelines.[16,17] Follow-up data were collected for a maximum of three years after the index PET imaging. Ventricular arrhythmia (VA) was defined as the composite occurrence of ventricular tachycardia or ventricular fibrillation. Major adverse cardiac events (MACE) were defined as a composite of ventricular tachycardia, ventricular fibrillation, or cardiac death. The primary endpoint was survival free of VA.

Statistical Analysis

Continuous variables are presented as medians and intraquartile ranges and categorical data are summarized as frequencies and percentages. Mann–Whitney-Wilcoxon testing and *Chi* square tests were used to compare patient characteristics and stress data. Patients with severe left ventricular dysfunction (defined by a resting EF of less than 35%) were stratified for pre-specified analysis. Cox proportional hazards models were used to assess the impact of various PET imaging parameters on survival free of ventricular arrhythmias independent of critical covariates. Variables were entered into Cox proportional hazard models in a continuous fashion when applicable. Kaplan–Meier survival curves for the primary study outcome (survival free of VA) were created and analyzed using the log-rank test. Covariates in the general study population included ejection fraction, age, gender, and Caucasian race. Two-sided values of $P < 0.05$ were considered significant. All statistical analyses were performed using R version 3.3.1 (The R Foundation).

RESULTS

Patient and Stress Test Characteristics

A total of 159 patients met the inclusion criteria (Figure 1) during the study period and were followed for a median of 1.43 years [0.83-2.21]. Baseline characteristics are shown in Table 1 and Supplementary Appendix (SA1). The median time from ICD implantation to PET study was 2.73 years [0.82-18.67]. Median patient age was 65.9 years IQR [56.76-72.63], and the majority of patients were Caucasian (78%) and male (78%). The most common causes of cardiomyopathy were ischemic (65%) followed by idiopathic (22%). The majority of implanted devices were dual-chamber ICDs (40%) followed by CRT-D (35%), and the most common indication for device placement was primary prevention of sudden cardiac death (73%).

Median values of PET stress parameters are displayed in Table 1. The median ejection fraction was 28.0% IQR [21.50-37.00]. Median rest MBF, stress MBF, and myocardial flow reserve (MFR) were 1.00 $ml \cdot min^{-1} \cdot g^{-1}$ IQR [0.76-1.23], 1.90 $ml \cdot min^{-1} \cdot g^{-1}$ IQR [1.19-2.43], and 1.79 IQR [1.26-2.36], respectively. Myocardial scar as assessed by SRS was common in the group, with only 7% (12/159) of patients displaying no evidence of scar (SRS of zero) with a median SRS for the study group of 11.0 IQR [4.00-20.50]. The majority of patients (108/159) had evidence of reversible perfusion defects as defined by a summed difference score (SDS) greater than zero. A minority of patients (10%, 16/159) underwent a revascularization procedure or underwent a catheter-based ventricular ablation procedure (9%, 10/159) during the follow-up period.

Patient Outcomes

Death from any cause occurred in 32 patients (20%), of which 19 deaths (59%) were due to a cardiac cause (Table 2) and five deaths were due to SCD. The occurrence of any ventricular arrhythmia was reported in 44 patients (27%), with ventricular tachycardia being the more common event (86%). There were no episodes of polymorphic ventricular tachycardia. MACE occurred in 53 patients (33%) and inappropriate device therapies occurred in 8 patients (5%). Appropriate device therapies included defibrillation in 35 patients and anti-tachycardia pacing in 32 patients. Arrhythmias terminated without device treatment in 4 patients. External cardioversion was required in 1 patient after their ICD failed to terminate the arrhythmia. Ablation for treatment of ventricular arrhythmias occurred in 4 patients between the time of stress testing and the occurrence of VA.

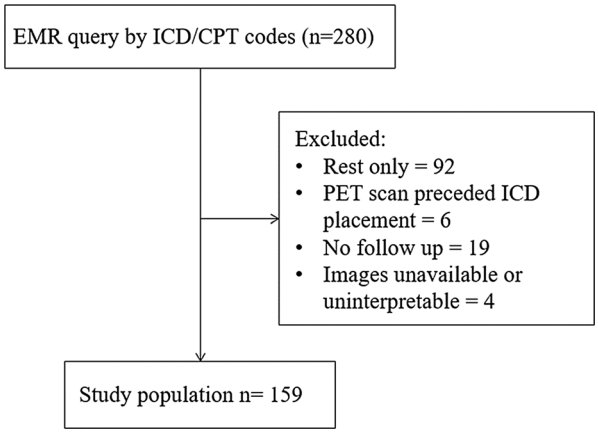

Figure 1. Patient discovery and reasons for exclusion.

Predictors of Ventricular Arrhythmias or MACE

Univariate and multivariate analyses on MBF PET parameters and the occurrence of adverse events are summarized in Table 2. On unadjusted analyses, lower resting and stress MBF values were associated with an elevated risk for VA and MACE. After adjustment for EF, age, sex, and gender, stress MBF was independently associated with an increased risk of VA (adjusted HR per ml/min/g 1.52, 95% CI (1.01-2.31), $P = 0.04$). Survival plots stratified by stress MBF are shown in Figure 2A.

Importantly, summed rest scores and summed stress scores were not predictive of VA or MACE on either unadjusted or adjusted analysis ($P > 0.05$ for all). Resting ejection fraction was a strong independent predictor of both VA and MACE (adjusted HR per 1% EF, 0.96, 95% CI (0.93-0.98), $P = 0.008$, and adjusted HR per 1% EF, 0.95, 95% CI (0.92-0.977), $P = 0.0004$). MFR assessment was not found to be predictive of adverse events on unadjusted or adjusted models (Table 3).

Patients with Severely Decreased EF

A subset of 110 patients (69% of the total study population) with severe left ventricular systolic dysfunction was identified (defined as LVEF <35%). Median patient age was 65.9 years IQR [56.6-72.0], and most patients were Caucasian (76%) and male (82%). The most common causes of cardiomyopathy were ischemic (70%) followed by idiopathic (19%). The occurrence of any ventricular arrhythmia was reported in 37 patients (34%), with ventricular tachycardia being the more common event (86%). Death from any cause occurred in 30 patients (27%), of which 18 deaths (60%) were due to a cardiac cause. Critical covariates incorporated into the adjustment model included age, gender, and Caucasian race. When evaluated as a continuous variable, resting EF was not predictive of ventricular arrhythmias among patients with severe left ventricular dysfunction (adjusted HR per 1% EF 0.96, 95% CI (0.92-1.04), p = 0.10). Summed rest scores and summed stress scores were not predictive of VA or MACE on either unadjusted or adjusted analysis ($P > 0.05$ for all). Among other myocardial blood flow parameters, only sMBF was independently predictive of VA (adjusted HR per 1 ml/min/g HR 1.71, 95% CI (1.08-2.72), $P = 0.02$). Survival plots stratified by stress MBF among this subset are shown in Figure 2B.

DISCUSSION

The aim of this study was to assess the association between quantified myocardial blood flow and the occurrence of VA among a high-risk population who had undergone ICD implantation. Preserved stress myocardial blood flow was found to be an independent predictor of survival free of VA. Among a subset of patients with severe left ventricular dysfunction, assessment of stress myocardial blood flow yielded prognostic information on survival free of VA, while assessment of residual ejection fraction did not. Assessment of myocardial scar and ischemia burden, as measured by summed rest scores and summed stress scores was not predictive of survival free of VA or MACE in either study group.

We sought to examine the potential applicability of myocardial perfusion imaging in arrhythmia risk assessment in a real-world patient population. Accordingly, patients with both ischemic and non-ischemic cardiomyopathy as well as ICD placement for both primary and secondary prevention of SCD were included. By focusing on the myocardial substrate defined by PET stress parameters rather than etiology or device indication, we hoped to explore the mechanistic explanation for arrhythmia risk. Current guidelines on the prevention of SCD include ICD implantation for select patients with an ejection fraction ≤35% irrespective of the cause of cardiomyopathy.[16] Despite adjustments for critical covariates, impaired stress myocardial blood flow was associated with increased arrhythmic risk in the cohort of patients with severe ventricular dysfunction. These results suggest the potential clinical utility of PET imaging in risk stratification of VA.

The interplay between myocardial ischemia, myocardial scaring, and the development of VA is complex and incompletely understood. Ischemic heart disease can induce myocardial substrates favorable for VA such as scar tissue, hibernating myocardium, perfusion abnormalities, and cardiac denervation.[4,18–20] Scar is also known to play an important role in non-

Table 1. Baseline demographics and stress test characteristics

	All patients (159)	sMBF ≥ 1.9 ml·min^{-1}·g^{-1} (78)	sMBF < 1.9 ml·min^{-1}·g^{-1} (81)	*P* value
Age	65.9 [56.76-72.63]	62.12 [53.71-83.32]	67.06 [62.45-75.04]	$P = 0.004$
Gender				
Male	124 (78%)	54 (69%)	70 (86%)	$P = 0.01$
Female	35 (22%)	24 (31%)	11 (14%)	-
Race				
Caucasian	124 (78%)	61 (78%)	63 (78%)	$P = 1.0$
Black	22 (14%)	13 (17%)	9 (11%)	$P = 0.43$
Hispanic	4 (2%)	3 (4%)	1 (1%)	$P = 0.58$
Other/unknown	9 (5%)	3 (4%)	6 (7%)	$P = 0.53$
Comorbidities				
BMI	29.5 [26.45-33.95]	30.1 [27.02-35.35]	29.10 [25.70-33.10]	$P = 0.14$
Hypertension	124 (78%)	60 (77%)	64 (79%)	$P = 0.89$
Dyslipidemia	113 (71%)	50 (64%)	63 (78%)	$P = 0.06$
Diabetes	78 (49%)	36 (46%)	42 (52%)	$P = 0.52$
Peripheral vascular disease	35 (22%)	13 (17%)	22 (27%)	$P = 0.16$
CVA or TIA	25 (15%)	15 (19%)	10 (12%)	$P = 0.33$
Congestive heart failure	147 (93%)	73 (94%)	74 (91%)	$P = 0.81$
Ischemic cardiomyopathy	103 (65%)	37 (47%)	66 (81%)	$P < 0.001$
Idiopathic cardiomyopathy	36 (22%)	25 (32%)	11 (14%)	$P < 0.001$
Other cardiomyopathy	18 (11%)	14 (18%)	4 (5%)	$P = 0.01$
ICD indication				
Primary Prevention	116(73%)	54 (69%)	62 (77%)	$P = 0.46$
Secondary prevention	41 (26%)	22 (28%)	19 (23%)	$P = 0.52$
Unknown	2 (1%)	2 (2%)	0 (0%)	-
ICD device				
Single chamber	34 (21%)	15 (19%)	19 (23%)	$P = 0.68$
Dual chamber	63 (40%)	36 (46%)	27 (33%)	$P = 0.24$
CRT-D	55 (35%)	22 (28%)	33 (41%)	$P = 0.14$
Subcutaneous ICD	7 (4%)	5 (6%)	2 (2%)	$P = 0.39$
Stress test parameters				
Ejection fraction (%)	28.0 [21.50-37.00]	32 [22.25-40.00]	26.00 [19.00-33.00]	$P = 0.002$
SRS	11.0 [4.00-20.5]	7.00 [2.25-18.75]	16.00 [7.00-22.00]	$P < 0.001$
SDS	3.00 [0.00-7.00]	2.00 [0.00-4.75]	5.00 [1.00-9.00]	$P < 0.001$
SSS	17.00 [7.00-25.00]	9.00 [4.00-21.75]	22.00 [14.00-28.00]	$P < 0.001$
rMBF (ml·min^{-1}·g^{-1})	1.00 [0.76-1.23]	1.12 [0.90-1.59]	0.90 [0.67-1.05]	$P < 0.001$
sMBF (ml·min^{-1}·g^{-1})	1.90 [1.19-2.43]	2.46 [2.09-2.99]	1.21 [0.95-1.59]	$P < 0.001$

Table 1 continued

	All patients (159)	sMBF ≥ 1.9 ml·min^{-1}·g^{-1} (78)	sMBF < 1.9 ml·min^{-1}·g^{-1} (81)	*P* value
MFR	1.79 [1.26–2.36]	2.25 [1.75–2.84]	1.31 [1.11–1.84]	$P < 0.001$
Medication				
ASA	114 (72%)	51 (65%)	63 (78%)	$P = 0.12$
Statin	121 (76%)	52 (67%)	69 (85%)	$P = 0.01$
Insulin	32 (20%)	13 (17%)	19 (23%)	$P = 0.38$
Calcium channel blocker	17 (11%)	11 (14%)	6 (7%)	$P = 0.25$
Beta blocker	134 (84%)	62 (79%)	72 (89%)	$P = 0.16$
Aldactone	58 (36%)	28 (36%)	30 (37%)	$P = 0.99$
ACE/ARB	108 (68%)	50 (64%)	58 (72%)	$P = 0.39$
Amiodarone	22 (14%)	5 (4%)	17 (21%)	$P = 0.01$
Sotalol	13 (8%)	7 (9%)	6 (7%)	$P = 0.96$
Dofetilide	4 (2%)	3 (4%)	1 (1%)	$P = 0.59$
Mexiletine	10 (6%)	4 (5%)	6(7%)	$P = 0.79$

Baseline demographics and stress test characteristics. *P* values reflect testing between sMBF ≥ 1.9 ml·min^{-1}·g^{-1} and sMBF < 1.9 ml·min^{-1}·g^{-1} (78)
rMBF, rest myocardial blood flow; *sMBF*, stress myocardial blood flow; *MFR*, myocardial flow reserve; *BMI*, body mass index; *CVA*, cerebral vascular accident; *TIA*, transient ischemic attack; *CRT-D*, cardiac resynchronization therapy defibrillator; *ICD*, implantable cardiac defibrillator; *LV*, left ventricle; *SRS*, summed rest score; *SSS*, summed stress score; *ASA*, aspirin; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker

Table 2. Adverse events

Events	All patients (159)	sMBF ≥ 1.9 ml·min^{-1}·g^{-1} (78)	sMBF < 1.9 ml·min^{-1}·g^{-1} (81)
Ventricular tachycardia	38	12	26
Ventricular fibrillation	15	4	11
Any ventricular arrhythmia	44	13	31
Cardiac death	19	8	11
All cause death	32	11	21
MACE	53	18	35
Inappropriate Shock	8	4	4

MACE is defined as combined cardiac death, ventricular tachycardia, or ventricular fibrillation
sMBF, stress myocardial blood flow; *MACE*, major adverse cardiac events

ischemic cardiomyopathy, where fibrosis assessed by magnetic resonance has been associated with arrhythmogenicity.[21] Scar heterogeneity and border-zone size may be more predictive of arrhythmogenicity than total scar burden[22] which may in part explain why systolic dysfunction alone lacks adequate sensitivity and specificity for determining arrhythmic risk. Translating this knowledge into clinically applicable risk stratification tools remains a challenge.

Piccini et al. examined SCD rates in a large cohort (n = 6383) of patients with coronary artery disease confirmed with invasive angiography who also underwent cardiac stress testing with single-photon emission computed tomography (SPECT) imaging. Despite adjustment for multiple clinical and imaging parameters, SSS as a marker of combined scarred, hibernating, and ischemic myocardium was independently associated with SCD and provided incremental prognostic information as compared to EF and clinical information alone.[20] Similar results were reported in patients with an EF >35% and presumably at low risk for SCD.[23]

Semiquantitative parameters may not independently predict arrhythmias in a higher risk population who already carry a substantial burden of an arrhythmic substrate. Rijnierse and colleagues used multimodality imaging including cardiac MRI and [^{15}O]H_20 PET to study patients with ischemic cardiomyopathy and an EF <35%. They reported that among previously validated markers of arrhythmic substrate (including infarct size, sympathetic denervation, systolic function, and LV volume) only impaired hyperemic blood flow was independently associated with VA inducibility at an electrophysiology study (EPS).[11] We report similar findings that abnormal perfusion as assessed by quantifying myocardial blood flow may better reflect the risk of VA or MACE compared to semiquantitative methods.

The mechanism of impaired MBF leading to VA is not completely accounted for in the current model. Impaired MBF can be observed in scarred myocardium as well as remote sites seemingly unaffected by epicardial stenosis or fibrosis,[10,11] though both phenotypes have been linked to adverse cardiac events. Impaired rest and stress myocardial perfusion may be reflective of an underlying fibrotic, arrhythmogenic substrate or the risk may be derived from microvascular dysfunction and an inability to adequately compensate during periods of hyperemia. sMBF is inversely related to epicardial coronary stenosis[24] but can also be reflective of microvascular remodeling or dysfunction and in this way may better indicate the tissue-level effects of malperfusion than markers of epicardial stenosis alone.[25] Interestingly, we did not find impaired MFR to be associated with arrhythmia risk in this population. This may be due to limitations of MFR measurements in patients with low resting MBF who may also have low stress MBF (and presumably are at an elevated risk) despite a normal or high MFR.[11]

Strengths of this study include the long-term follow-up on an inclusive population of patients at risk for arrhythmic events who were referred in clinical practice for non-invasive imaging. The cause of death in SCD is often presumed to be tachyarrhythmic in nature but may arise from bradyarrhythmias, asystole, or acute myocardial infarction.[26] By examining patients with implantable cardiac defibrillators, we were able to ensure the presence of a malignant ventricular arrhythmia as well as better characterize the nature of the rhythm and exclude inappropriate device therapies from our endpoint.

Study Limitations

This was an observational study which carries the potential for selection bias among other limitations. We

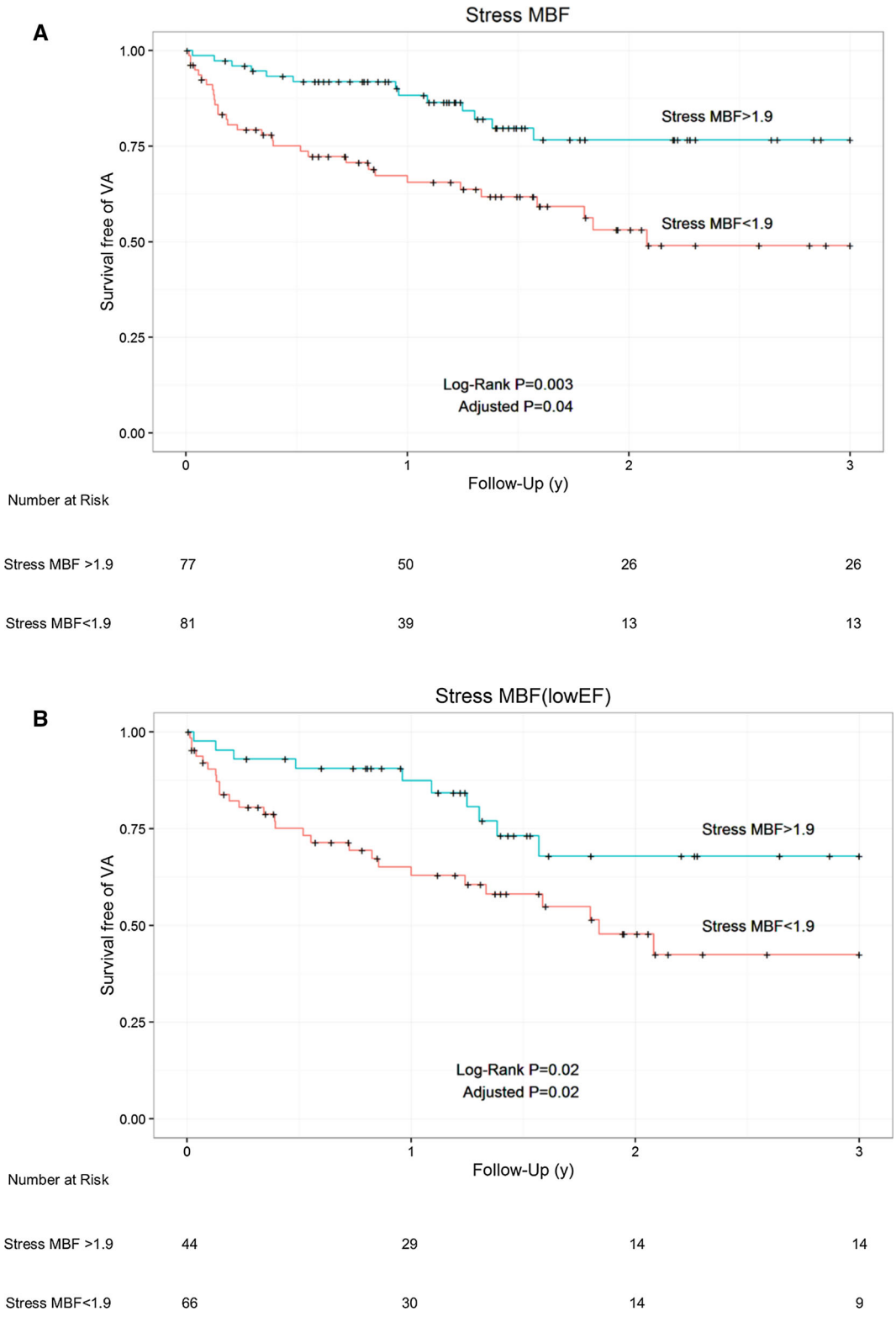

Figure 2. Survival free of ventricular arrhythmias. Survival free of ventricular arrhythmias (VAs) is shown in patients stratified by median stress myocardial blood flow. Results are shown for the total cohort (**A**) and in a subset of patients with severe left ventricular systolic dysfunction (**B**). *MBF*, myocardial blood flow; *EF*, ejection fraction.

Table 3. Myocardial blood flow and adverse events

rMBF	sMBF	MFR
Unadjusted HR		
VF		
HR 2.24, 95% CI (0.54–2.24), $P = 0.13$	HR 2.96 95% CI (0.94–9.32), $P = 0.06$	HR 1.56, 95% CI (0.55–4.40), $P = 0.39$
VT		
HR 2.69, 95% CI (1.35–5.33), $P = 0.004$	HR 2.43, 95% CI (1.22–4.82), $P = 0.011$	HR 1.27 95% CI (0.67–2.42), $P = 0.45$
VA		
HR 2.12, 95% CI (0.313–2.40), $P = 0.01$	HR 2.75, 95% CI (1.44–5.26), $P = 0.022$	HR 1.54 95% CI (0.84–2.82), $P = 0.15$
MACE		
HR 2.01, 95% CI (1.15–3.52), $P = 0.01$	HR 2.28, 95% CI (1.29–4.03), $P = 0.004$	HR 1.30, 95% CI (0.76–2.23), $P = 0.339$
Adjusted HR		
VF		
HR 1.95, 95% CI (0.51–7.41), $P = 0.32$	HR 1.98, 95% CI (1.01–3.85), $P = 0.04$	HR 1.49, 95% CI (0.77–2.88), $P = 0.23$
VT		
HR 3.22 95% CI 1.34–7.72), $P = 0.008$	HR 1.79 95% CI (1.16–2.77), $P = 0.008$	HR 1.09 95% CI (0.76–1.57), $P = 0.61$
VA		
HR 2.38 95% CI (1.09–5.19), $P = 0.029$	HR 1.52 95% CI (1.002–2.31), $P = 0.04$	HR 1.18, 95% CI (0.83–1.67), $P = 0.34$
MACE		
HR 2.03, 95% CI (1.01–4.16), $P = 0.04$	HR 1.54, 95% CI (1.09–2.19), $P = 0.01$	HR 1.13, 95% CI (0.83–1.54), $P = 0.42$

Univariate and multivariate models are shown. Covariates for adjustment include ejection fraction, age, gender, and race
rMBF, rest myocardial blood flow; *sMBF*, stress myocardial blood flow; *MFR* myocardial flow reserve; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia; *VA*, ventricular arrhythmia; *MACE*, major adverse cardiac events

did not assess the indication or appropriateness of stress testing which may introduce referral bias. This study included patients with non-ischemic cardiomyopathy who may have a different risk profile and mechanism of arrhythmia than patients with ischemic cardiomyopathy[26] and separate analysis of these groups should be considered for future studies. Due to the relatively small number of patient events, extensive multivariate analysis on potential confounders could not be performed. The occurrence of revascularization and ablation procedures likely influenced future arrhythmic events; however, due to the small numbers of patients undergoing these procedures we were unable to account for this effect in the final analyses. Lastly, while there was a significant difference in the risk profiles as stratified by myocardial blood flow assessment, event rates remained high and it is unlikely that a single imaging parameter in isolation will provide enough discriminatory power to change the clinical decision to implant an ICD. Future studies should focus on incorporating myocardial blood flow into comprehensive assessment of arrhythmic risk.

CONCLUSION

Among patients at high risk for the development of sudden cardiac death, impaired stress myocardial blood flow was associated with less survival free of ventricular arrhythmias. Markers of myocardial scar and ischemia were not predictive of arrhythmia-free survival in this population. Among patients with severe left ventricular systolic dysfunction, assessment of stress myocardial blood flow yielded additional prognostic information, while assessment of residual ejection fraction did not. Future studies should focus on incorporating myocardial blood flow into comprehensive assessment of arrhythmic risk.

NEW KNOWLEDGE GAINED

Impaired stress myocardial blood flow assessed on PET cardiac imaging is independently associated with the occurrence of ventricular arrhythmias in a high-risk cohort. Clinical risk stratification for ventricular arrhythmias is imprecise, and future methods will likely incorporate traditional and novel factors to improve performance. This study supports a possible role for stress myocardial blood flow in future models of ventricular arrhythmia risk assessment.

Disclosure

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