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Coronary vasomotor dysfunction portends worse outcomes in patients with breast cancer

Sanjay Divakaran, MD[a,b], **Jesse P. Caron, BA**[b], **Wunan Zhou, MD, MPH**[a], **Jon Hainer, BS**[a], **Courtney F. Bibbo, MSc**[a], **Hicham Skali, MD, MSc, FASNC**[a,b], **Viviany R. Taqueti, MD, MPH, FASNC**[a], **Sharmila Dorbala, MD, MPH, MASNC**[a], **Ron Blankstein, MD, FASNC**[a,b], **John D. Groarke, MD, MPH**[b], **Anju Nohria, MD**[b], **Marcelo F. Di Carli, MD, MASNC**[a,b]

[a]Cardiovascular Imaging Program, Departments of Medicine and Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[b]Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Abstract

Background.—Impaired MFR in the absence of flow-limiting CAD is associated with adverse events. Cardiovascular disease is an important cause of morbidity and mortality in patients with breast cancer. We sought to test the utility of MFR to predict outcomes in a cohort of patients with breast cancer.

Methods.—We retrospectively studied consecutive patients with breast cancer or breast cancer survivors who underwent cardiac stress PET imaging from 2006 to 2017 at Brigham and Women's Hospital. Patients with a history of clinically overt CAD, LVEF < 45%, or abnormal myocardial perfusion were excluded. Subjects were followed from time of PET to the occurrence of a first major adverse cardiovascular event (MACE) and all-cause death.

Results.—The final cohort included 87 patients (median age 69.0 years, 98.9% female, mean MFR 2.05). Over a median follow-up of 7.6 years after PET, the lowest MFR tertile was associated with higher cumulative incidence of MACE (adjusted subdistribution hazard ratio 4.91; 95% CI 1.68–14.38; $p = 0.004$) when compared with the highest MFR tertile.

Conclusions.—In patients with breast cancer, coronary vasomotor dysfunction was associated with incident cardiovascular events. MFR may have potential as a risk stratification biomarker among patients with/survivors of breast cancer.

Reprint requests: Marcelo F. Di Carli, MD, MASNC, Cardiovascular Imaging Program, Departments of Medicine and Radiology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, ASB-L1 037C, Boston, MA 02115; mdicarli@bwh.harvard.edu.

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Keywords

Cancer survivorship; Cardio-oncology; Coronary artery calcium; Myocardial flow reserve; Coronary microvascular disease; Positron emission tomography

INTRODUCTION

Coronary vasomotor dysfunction is a manifestation of atherosclerosis affecting the large and small coronary vasculature, which can be present even in the absence of flow-limiting, obstructive epicardial coronary artery disease (CAD).[1] Patients with coronary vasomotor dysfunction often present with chest pain, exertional dyspnea, and/or reduced exercise tolerance.[2–8] Cardiac stress positron emission tomography (PET) can be used to measure myocardial flow reserve (MFR), defined as the ratio of global stress over rest myocardial blood flow (MBF). In the absence of obstructive epicardial CAD, MFR is a measure of the hemodynamic abnormalities resulting from diffuse nonobstructive atherosclerosis and microcirculatory dysfunction and can therefore be used to identify patients with subclinical coronary vasomotor dysfunction. Independent of other risk factors, coronary vasomotor dysfunction has been shown to be associated with adverse cardiovascular outcomes.[3,8–14] However, these studies excluded patients with malignancy.

Patients with breast cancer can have concomitant risk factors for cardiovascular disease and may have been exposed to cardiotoxic therapies including anthracyclines, trastuzumab, and thoracic irradiation, which increases their risk of cardiovascular events.[15–18] Both macrovascular and microvascular injury to the endothelium are implicated in cardiotoxicity of cancer therapies, particularly radiation therapy to the chest. Radiation therapy is associated with accelerated atherosclerosis,[19] results in vascular endothelial cell damage, and has been linked to reduction in capillary density.[20–22] Cardiopulmonary symptoms are common in patients with breast cancer, and survivors are at increased risk of cardiovascular morbidity and mortality.[23–26] Therefore, many patients with breast cancer are referred for cardiac stress testing to help guide management decisions.[16,27]

In this study, we aimed to study if coronary vasomotor dysfunction was a marker of risk even in the absence of clinically overt CAD or left ventricular systolic dysfunction in patients with active or prior breast cancer referred for cardiac PET. We hypothesized that MFR is a biomarker of general vascular health in this population and abnormal MFR would be associated with adverse cardiovascular outcomes.

METHODS

Study Population

The study population included consecutive patients with a diagnosis of breast cancer (prior or currently active at the time of PET) who underwent cardiac PET, including MFR assessment, for evaluation of symptoms (chest pain/dyspnea/syncope/palpitations) or pre-operative assessment between 2006 and 2017 at our center. The cohort was identified using our cardiac PET database and by using ICD-9 and ICD-10 codes to identify patients with breast cancer prior to the date of PET. Patients with a history of clinically overt CAD

(defined as a history of myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery), history of end-stage renal disease on dialysis, left ventricular ejection fraction (LVEF) < 45%, or abnormal myocardial perfusion on PET (summed stress score > 2) were excluded. After detailed review of each patient's longitudinal electronic health record (EHR) (blinded to PET results) to confirm a diagnosis of breast cancer, the final cohort consisted of 87 patients.

Patient demographics, clinical history, and indications for testing were collected prospectively at the time of PET. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and anemia was defined as a hematocrit of less than 36%. History of valvular heart disease was defined as at least moderate valvular stenosis or regurgitation, or a history of valve repair or replacement. Detailed review of each patient's longitudinal EHR was performed retrospectively to obtain breast cancer-related characteristics blinded to PET results. The Mass General Brigham Institutional Review Board approved this study.

Assessment of Coronary Vasomotor Function

Coronary vasomotor function was assessed with quantitative PET imaging, which was performed on a standard hybrid whole-body PET-computed tomography (CT) scanner (Discovery RX or STE LightSpeed 64, GE Healthcare, Milwaukee, Wisconsin) with ^{13}N-ammonia or ^{82}Rubidium as flow tracers. Myocardial perfusion images were obtained at rest and in response to vasodilator-stress, as previously described.[28] Summed rest, stress, and difference scores were computed.[29] Rest LVEF was calculated from gated myocardial perfusion images with commercially available software (Corridor4DM, INVIA Medical Imaging Solutions, Ann Arbor, Michigan). Absolute global MBF (in $mL \cdot min^{-1} \cdot g^{-1}$ of tissue) was quantified at rest and peak hyperemia using commercial software, as previously described.[28] Global MFR was calculated as the ratio of stress to rest MBF. Corrected rest MBF was calculated by normalizing rest MBF by the rate pressure product [(rest MBF/(rest heart rate × rest systolic blood pressure)) × 10,000]. Corrected MFR was calculated as stress MBF/corrected rest MBF.

Coronary Artery Calcium Assessment

The presence and extent of coronary artery calcium (CAC) was assessed using semi-quantitative visual analysis of the low-dose, non-contrast, non-electrocardiogram-gated CT scan obtained for attenuation correction of the PET images.[30] Semi-quantitative assessment of CAC was performed by a cardiologist with advanced cardiovascular imaging training for each of the 87 PET/CT scans in a blinded fashion (SD). The degree of CAC was determined to be none, mild, moderate, or severe as previously described by the National Lung Screening Trial investigators.[31] This approach was previously deemed comparable to Agatston scoring and strongly associated with cardiovascular death.[31]

Outcomes

Patients were followed from the time of PET to the occurrence of a first major adverse cardiovascular event (MACE), defined as a composite of cardiovascular death or hospitalization for heart failure, nonfatal MI, or coronary revascularization. Ascertainment

of nonfatal MI or heart failure required a discharge note with a primary hospitalization diagnosis of MI and/or heart failure. In addition, only events meeting the 2018 Fourth Universal Definition of MI or defined clinical criteria for the presence of symptoms, signs, and escalation of therapy for heart failure, were classified as such.[32] Ascertainment of clinical endpoints was determined by blinded adjudication of the EHR, Mass General Brigham Research Patient Data Registry, and the National Death Index. Patient were also followed from the time of PET to all-cause death.

Statistical Analysis

Categorical variables are reported as frequencies with percentage (%). Continuous variables are expressed as mean (± standard deviation) or median (interquartile range (IQR)). We used chi-square and one-way analysis of variance or Kruskal-Wallis to evaluate for differences in categorical and continuous baseline characteristics, respectively, across MFR tertiles. To study the effect of baseline MFR and MFR tertile on incident MACE and account for competing risk of death, univariable Fine and Gray competing risks regression modeling was performed using available covariates. To avoid overfitting the model, demographic and medical history variables (age, sex, symptoms, hypertension, diabetes, hyperlipidemia, smoking history, family history of premature CAD, body mass index (BMI), and estrogen status) were incorporated into the validated Morise clinical risk score for estimating the pre-test probability of CAD (with scores of 0–8, 9–15, and 16–24 indicating low, intermediate, and high pre-test probability of CAD).[33] Multivariable adjustment was performed using the Morise score and any covariates not included in the Morise score that had significant univariable association with the outcome. We constructed cumulative incidence curves by MFR tertiles to illustrate time-to-MACE. Differences were tested with the Wald test. Fine and Gray competing risk-adjusted subdistribution hazard functions, with multivariable adjustment using the previously identified covariates, were used to examine the association between cardiovascular events and MFR tertiles.

To study the effect of baseline MFR on all-cause mortality, univariable Cox proportional hazards modeling was performed for adverse event-free survival using available covariates. Multivariable adjustment was not performed as MFR did not have significant univariable association with the outcome. We constructed Kaplan-Meier curves by MFR tertiles to illustrate all-cause survival. Differences were tested with the log-rank test. Graphical methods and Schoenfeld residuals were used to verify that proportional hazards assumptions were met. All tests were 2-sided, and a value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed with the use of Stata version 15.0 (Statacorp, College Station, Texas).

RESULTS

Characteristics of the Study Cohort

Among the 87 patients in the cohort (median age 69.0 years (IQR 59.0–75.8), 98.9% female), 82.8% (n = 72) had cardiovascular symptoms at the time of PET, 63.2% (n = 55) had hypertension, 56.3% (n = 49) had dyslipidemia, 16.1% (n = 14) had diabetes, and 14.9% (n = 13) had chronic kidney disease (Table 1). Additionally, 14.7% (n = 11) of patients had

metastatic disease at the time of their breast cancer diagnosis, 21.7% (n = 18) had recurrence of their breast cancer at some point during their course, 94.1% (n = 80) underwent surgery, 65.5% (n = 57) received chest irradiation, 31.0% (n = 27) received chemotherapy, and 46.0% (n = 40) received hormonal therapy. Further baseline and PET characteristics are listed in Table 1.

Coronary Vasomotor Dysfunction and Coronary Artery Calcification

The median time interval between breast cancer diagnosis and PET was 7.9 years (IQR 3.8–14.9). The characteristics of patients by MFR tertile are listed in Table 2. Patients in the lowest MFR tertile had the highest mean BMI (33.0 $kg \cdot m^{-2} \pm 9.9$), and a greater proportion of patients with hypertension (86%), diabetes (34%), and anemia (41%).

To account for the effect of diffuse atherosclerosis on measurements of coronary vasomotor dysfunction, we reviewed the attenuation correction CT images for CAC. The presence of CAC did not differ significantly between treatment groups (Supplemental Table 1). The severity of CAC also did not differ significantly between MFR tertiles (Table 3). Of note, 45%, 48%, and 55% of patients in the lowest, middle, and highest MFR tertiles, respectively, had no evidence of CAC. Conversely, severe CAC was present in only 3%, 10%, and 0% of patients in the lowest, middle, and highest MFR tertiles, respectively (Table 3). There was no relationship between tracer or pharmacologic stress agent used and MFR tertile (Supplemental Table 2).

Coronary Vasomotor Dysfunction, Major Adverse Cardiovascular Events, and All-Cause Mortality

Over a median follow-up of 7.6 years (IQR 3.14–9.41) after PET, there were 15 major adverse cardiovascular events: 12 cardiovascular hospitalizations (8 heart failure, 3 non-fatal MI, and 1 coronary revascularization) and 3 cardiovascular deaths (which were not preceded by a cardiovascular hospitalization). MFR was significantly associated with incident MACE after accounting for competing risk of death (subdistribution hazard ratio (SHR) 0.18, 95% CI 0.05–0.67; $p = 0.01$), and this association persisted after multivariable adjustment (which adjusted for Morise score and chronic kidney disease) (SHR 0.28; 95% CI 0.10–0.76; $p = 0.013$). MFR tertile was also significantly associated with incident MACE (SHR 2.06; 95% CI 1.10–3.84; $p = 0.023$), and this association also persisted after multivariable adjustment (SHR 1.14; 95% CI 1.14–3.15; $p = 0.013$) (Supplemental Table 3). Rest MBF (SHR 0.62; 95% CI 0.19–1.97; $p = 0.416$) was not significantly associated with incident MACE. Stress MBF was associated with incident MACE (SHR 0.37; 95% CI 0.17–0.81; $p = 0.013$), but this association did not persist after multivariable adjustment (SHR 0.45; 95% CI 0.20–1.02; $p = 0.057$).

Compared with patients in the highest MFR tertile, those in the lowest MFR tertile had a higher incidence of MACE during the follow-up period on a univariable basis (SHR 4.85; 95% CI 1.12–21.14; $p = 0.035$) and after multivariable adjustment (adjusted SHR 4.91; 95% CI 1.68–14.38; $p = 0.004$) (Figure 1). Compared with patients in the highest MFR tertile, those in the middle tertile did not have a statistically significant higher incidence of MACE during the follow-up period on a univariable basis (SHR 2.96; 95% CI 0.60–14.51;

$p = 0.181$). There were 23 deaths during the follow-up period: 5 cardiovascular and 18 non-cardiovascular (11 cancer-related deaths, 3 non-cancer related deaths, 4 unknown cause of death). Neither MFR (HR 0.49, 95% CI 0.22–1.09; $p = 0.079$) nor MFR tertile ($p = 0.081$) were significantly associated with all-cause mortality (Figure 2).

DISCUSSION

The results from our study support the hypothesis that MFR, a marker of coronary vasomotor dysfunction that is associated with adverse outcomes in patients without cancer, is also associated incident major adverse cardiovascular events in this cohort of patients with breast cancer. These results advance our understanding of the prognostic implications of abnormal MFR and may provide the basis for further evaluation of MFR as a biomarker of general vascular health and clinical risk in this population.

It is well-established that cardiovascular disease and breast cancer have overlapping risk factors, such as obesity and tobacco use.[34] The data from our study provide further evidence of this overlap as patients in the lowest MFR tertile had the highest BMI. Additionally, in older women diagnosed with breast cancer, cardiovascular disease is the leading cause of death.[35] The hypothesis-generating data from our study point to coronary vasomotor dysfunction as a potential biomarker, and possible therapeutic target, in breast cancer patients/survivors who are at increased risk of adverse cardiovascular events, even in the absence of clinically overt obstructive CAD and/or left ventricular systolic dysfunction, and in some cases even in the absence of coronary artery calcifications/non-obstructive CAD. It is notable that the lowest MFR tertile had significant coronary vasomotor dysfunction as MFR values in this group (<1.71) were much lower than the mean for the entire cohort (2.56).

We hypothesize that MFR may be a surrogate marker of underlying cardiovascular risk in patients with breast cancer, and that cancer therapies may affect MFR in this population. Recent pre-clinical work studying human ex-vivo microvascular responses identified impaired coronary arteriolar function after anthracycline treatment.[36] Atherosclerotic disease after radiation therapy has also been shown to be partly due to microvascular injury associated with reduced capillary density, fibrosis, and abnormal vascular reactivity.[19,22,37] The absence of CAC in 49% of our total study cohort and 45% of those in the lowest MFR tertile is consistent with a contribution of microvascular dysfunction to increased risk in this population. While it is possible that a portion of these patients may have had noncalcified atherosclerosis, it is unlikely that all did. Additionally, we have previously shown an inverse correlation between mean cardiac radiation dose and coronary vasomotor function in 35 patients referred for clinical stress PET following radiation therapy for a variety of malignancies.[38] Finally, though neither MFR nor MFR tertile were significantly associated with all-cause mortality, there was a trend toward significance for both. These data suggest that the inability to significantly augment MBF in response to a vasodilator-stress in patients without clinically overt obstructive CAD or left ventricular systolic dysfunction may be a surrogate marker for overall reserve and/or fitness. Additional study is needed with larger sample sizes to further test this hypothesis.

Study limitations

Our study has important limitations. It is a single-center, observational study in which the population consisted of patients referred clinically for cardiac PET. Given the retrospective nature of the study, we did not have PET data pre- and post-diagnosis nor pre- and posttreatment. This limited our ability to assess if cancer therapy affected MFR, and to what degree cardiovascular risk factors alone were responsible for abnormalities in MFR. One of the aims of the now-enrolling Cardiotoxicity in Locally Advanced Lung Cancer Patients Treated With Chemoradiation Therapy (CLARITY) study (ClinicalTrials.gov Identifier: NCT04305613) is to measure baseline MFR, and the effect of cancer therapy on MFR in patients with a new diagnosis of lung cancer. To focus on the prognostic implications of coronary vasomotor dysfunction, we excluded patients with known clinically overt CAD, left ventricular systolic dysfunction, or abnormal myocardial perfusion. Though it is possible that some patients with multivessel, obstructive CAD without perfusion abnormalities on PET were included, we have previously demonstrated that this is unlikely.[39] We did not evaluate the effect of baseline medications on MFR nor on outcomes. Finally, CAC was assessed qualitatively and not via formal calcium scoring. However, this approach is supported by societal guidelines [40] and we followed previously published methods.[30,31] Understanding these important limitations, our data still suggest potential clinical value for abnormal MFR as a biomarker of cardiovascular risk in this population.

CONCLUSIONS

In patients with breast cancer or survivors of breast cancer referred for cardiac stress PET, coronary vasomotor dysfunction was associated with higher incidence of cardiovascular events. The data from our study suggest that MFR may have value as a biomarker of cardiovascular risk in patients with breast cancer. Further investigation with larger sample sizes may provide more supportive data for the use of MFR as a general biomarker of vascular health/fitness in this population.

NEW KNOWLEDGE GAINED

In a retrospective analysis of a cohort of 87 consecutive patients with breast cancer or survivors of breast cancer clinically referred for a cardiac stress PET, coronary vasomotor dysfunction (via myocardial flow reserve (MFR)) was associated with incident major adverse cardiovascular events. MFR may have potential in risk stratification among patients with/survivors of breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

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Abbreviations

CAC	Coronary artery calcium
CAD	Coronary artery disease
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular event
MFR	Myocardial flow reserve
PET	Positron emission tomography

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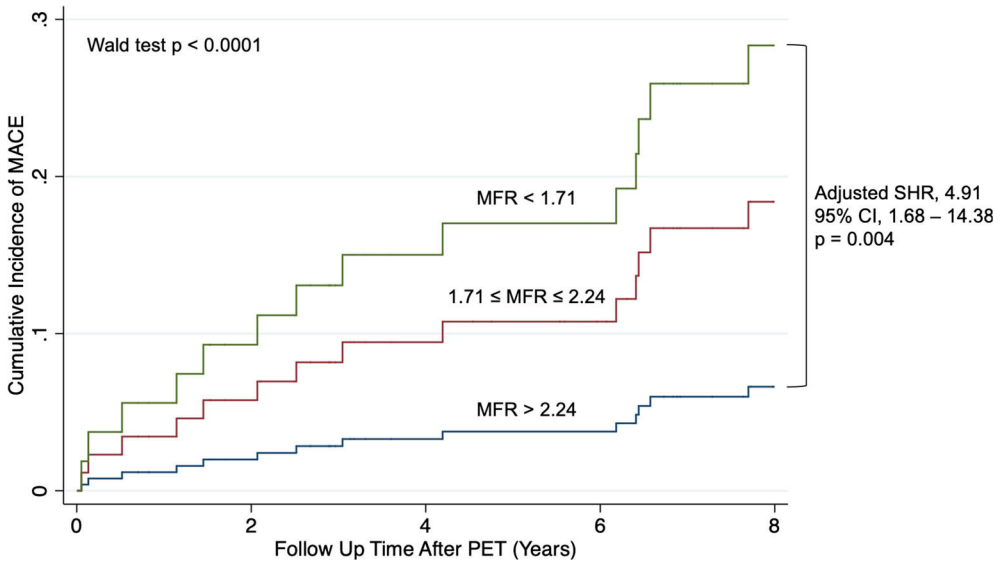

Figure 1.

Time to incident major adverse cardiovascular event by MFR tertile. Cumulative incidence of MACE for the cohort is presented stratified by MFR tertile. Multivariable analysis (considering competing risk of death) adjusted for Morise score and chronic kidney disease. *CI*, confidence interval, *MACE*, major adverse cardiovascular event; *MFR*, myocardial flow reserve; *PET*, positron emission tomography; *SHR*, subdistribution hazard ratio.

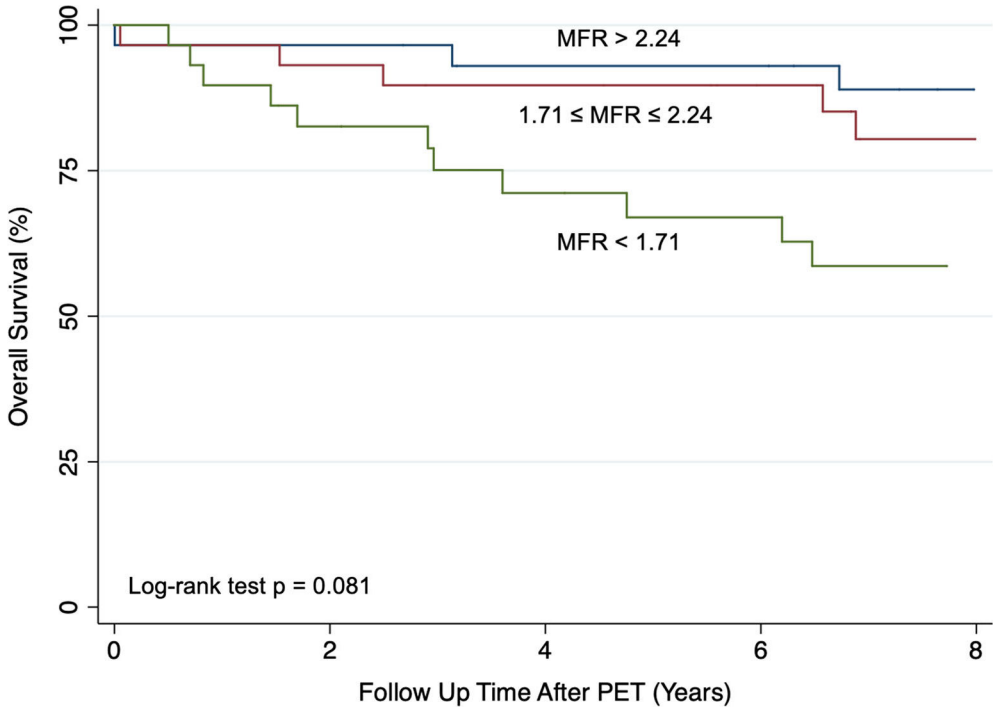

Figure 2.

Kaplan-Meier estimate of overall survival by MFR tertile. Overall survival for the cohort is presented stratified by MFR tertile. *MFR*, myocardial flow reserve; *PET*, positron emission tomography.

Table 1.

Baseline and cardiac stress positron emission tomography/computed tomography characteristics of the study cohort

	Total cohort (n = 87)
Age at PET, median (IQR) (years)	69.0 (59.0–75.8)
Cardiovascular symptoms present at time of PET	72 (82.8%)
Female	86 (98.9%)
BMI, mean (SD) ($kg \cdot m^{-2}$)	29.8 (8.3)
Hypertension	55 (63.2%)
Dyslipidemia	49 (56.3%)
Diabetes	14 (16.1%)
Family history of CAD	15 (17.2%)
Chronic kidney disease	13 (14.9%)
Anemia	20 (23.3%)
History of valvular heart disease	2 (2.3%)
History of prior heart failure admission	2 (2.3%)
Current tobacco use	5 (5.8%)
Any tobacco use	26 (29.9%)
Morise score, mean (SD)	14.3 (3.4)
Pre-test probability of CAD by Morise score	
Low (0–8 points)	5 (5.8%)
Intermediate (9–15 points)	46 (52.9%)
High (16–24 points)	36 (41.4%)
Breast cancer treatment	
Surgery	80 (94.1%)
Thoracic irradiation	57 (65.5%)
Left chest irradiation	34 (39.1%)
Chemotherapy	27 (31.0%)
Anthracyclines	16 (18.4%)
Trastuzumab	5 (5.8%)
Hormonal therapy	40 (46.0%)
Metastatic disease at breast cancer diagnosis	11 (14.7%)

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	Total cohort (n = 87)
Breast cancer recurrence after initial therapy	18 (21.7%)
Years between breast cancer diagnosis and PET, median (IQR)	7.9 (3.8–14.9)
Coronary artery calcium present	44 (50.6%)
Mild coronary artery calcium present	24 (27.6%)
Moderate or severe coronary artery calcium present	20 (23.0%)
PET tracer	
^{82}Rubidium	66 (75.9%)
^{13}N-ammonia	21 (24.1%)
Pharmacologic stress agent	
Regadenoson	51 (58.6%)
Dipyridamole	22 (25.3%)
Adenosine	10 (11.5%)
Dobutamine	4 (4.6%)
Rest LVEF, mean (SD) (%)	64.1 (7.5)
Stress MBF, mean (SD) (mL·min^{-1}·g^{-1})	2.56 (0.96)
Rest MBF, mean (SD) (mL·min^{-1}·g^{-1})	1.29 (0.48)
MFR, mean (SD)	2.05 (0.57)
Corrected rest MBF, mean (SD) (mL·min^{-1}·g^{-1})	1.21 (0.45)
Corrected MFR, mean (SD)	2.18 (0.65)

BMI, body mass index; *CAD*, coronary artery disease; *IQR*, interquartile range; *LVEF*, left ventricular ejection fraction; *MBF*, myocardial blood flow; *MFR*, myocardial flow reserve; *PET*, positron emission tomography; *SD*, standard deviation.

Table 2.

Characteristics of patients by myocardial flow reserve tertile

	MFR < 1.71 (n = 29)	1.71 ≤ MFR ≤ 2.24 (n = 29)	MFR > 2.24 (n = 29)	p value
Age at PET, median (IQR) (years)	70.5 (63.1–75.0)	71.0 (64.0–76.7)	62.0 (58.2–71.5)	0.14
Cardiovascular symptoms present at time of PET	24 (83%)	24 (93%)	24 (83%)	1.00
Female	28 (97%)	29 (100%)	29 (100%)	1.00
BMI, mean (SD) ($kg \cdot m^{-2}$)	33.0 (9.9)	27.8 (8.2)	28.5 (5.4)	0.034
Hypertension	25 (86%)	17 (59%)	13 (45%)	0.003
Dyslipidemia	20 (69%)	13 (45%)	16 (55%)	0.20
Diabetes	10 (34%)	2 (7%)	2 (7%)	0.01
Current tobacco use	0 (0%)	1 (3%)	4 (14%)	0.12
Any tobacco use	10 (34%)	4 (14%)	12 (41%)	0.058
Family History of CAD	3 (10%)	3 (10%)	9 (31%)	0.082
Chronic kidney disease	4 (14%)	4 (14%)	5 (17%)	1.00
Anemia	12 (41%)	4 (14%)	4 (14%)	0.026
History of valvular heart disease	1 (3%)	0 (0%)	1 (3%)	1.00
History of prior heart failure admission	2 (7%)	0 (0%)	0 (0%)	0.33
Morise score, mean (SD)	15.2 (2.9)	14.2 (3.4)	13.4 (3.7)	0.12
Pre-test probability of CAD by Morise score				0.50
Low (0–8 points)	1 (3%)	1 (3%)	3 (10%)	
Intermediate (9–15 points)	13 (45%)	16 (55%)	17 (59%)	
High (16–24 points)	15 (52%)	12 (41%)	9 (31%)	
Years between cancer diagnosis and PET, median (IQR)	8.7 (3.1–19.8)	6.7 (2.8–13.2)	8.5 (3.8–16.8)	0.60
Metastatic disease at breast cancer diagnosis	4 (16%)	2 (8%)	5 (19%)	0.60
Breast cancer recurrence	9 (32%)	5 (18%)	4 (15%)	0.33
Treatment with chemotherapy	9 (31%)	7 (24%)	11 (38%)	0.57
Treatment with anthracyclines	3 (10%)	5 (17%)	8 (28%)	0.27
Treatment with trastuzumab	1 (3%)	1 (3%)	3 (10%)	0.61
Treatment with hormonal therapy	13 (45%)	17 (59%)	10 (34%)	0.20
Treatment with chest irradiation	18 (62%)	20 (69%)	19 (66%)	0.96
Treatment with left chest irradiation	14 (78%)	10 (50%)	10 (53%)	0.17

	MFR < 1.71 (n = 29)	1.71 ≤ MFR ≤ 2.24 (n = 29)	MFR > 2.24 (n = 29)	p value
Treatment with surgery	28 (97%)	25 (93%)	27 (93%)	0.86
Rest LVEF, mean (SD) (%)	64.8 (7.4)	62.9 (7.3)	64.6 (8.1)	0.57
Stress MBF, mean (SD) ($mL \cdot min^{-1} \cdot g^{-1}$)	2.14 (0.86)	2.40 (0.73)	3.15 (1.00)	<0.001
Rest MBF, mean (SD) ($mL \cdot min^{-1} \cdot g^{-1}$)	1.45 (0.57)	1.24 (0.42)	1.17 (0.41)	0.079
MFR, mean (SD)	1.48 (0.18)	1.96 (0.14)	2.72 (0.36)	<0.001
Corrected rest MBF, Mean (SD) ($mL \cdot min^{-1} \cdot g^{-1}$)	1.26 (0.55)	1.17 (0.43)	1.21 (0.36)	0.75
Corrected MFR, mean (SD)	1.72 (0.34)	2.16 (0.58)	2.67 (0.60)	<0.001

BMI, body mass index; *CAD*, coronary artery disease; *LVEF*, left ventricular ejection fraction; *MBF*, myocardial blood flow; *MFR*, myocardial flow reserve; *PET*, positron emission tomography; *SD*, standard deviation.

Table 3.

Degree of coronary artery calcification by myocardial flow reserve tertile in patients with normal myocardial perfusion imaging

	MFR < 1.71 (n = 29)	1.71 ≤ MFR ≤ 2.24 (n = 29)	MFR > 2.24 (n = 29)	*p* value
No CAC	13 (45%)	14 (48%)	16 (55%)	0.80
Mild CAC	8 (28%)	8 (28%)	8 (28%)	1.00
Moderate CAC	7 (24%)	4 (14%)	5 (17%)	0.69
Severe CAC	1 (3%)	3 (10%)	0 (0%)	0.32

There were no statistically significant differences in either the overall presence or severity of coronary artery calcification seen on transmission computed tomography scans between the myocardial flow reserve tertiles.

CAC, coronary artery calcium; *MFR*, myocardial flow reserve.