Prognostic significance of blood pressure response during vasodilator stress Rb-82 positron emission tomography myocardial perfusion imaging

Bradley Witbrodt, MD,[a] Abhinav Goyal, MD, MHS,[a] Anita A. Kelkar, MD,[a] Sharmila Dorbala, MD, MPH,[b] Benjamin J. W. Chow, MD,[c] Marcelo F. Di Carli, MD,[b] Brent A. Williams, PhD,[d] Michael E. Merhige, MD,[e] Daniel S. Berman, MD,[f] Guido Germano, PhD,[f] Robert S. Beanlands, MD,[c] James K. Min, MD,[g] Punitha Arasaratnam, MD,[c] Masoud Sadreddini, MD,[c] Marjolein Lidwine van Velthuijsen, MD,[c] and Leslee J. Shaw, PhD[a]

[a] Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA
[b] Brigham and Women's Hospital, Boston, MA
[c] Department of Medicine, University of Ottawa Heart Institute, Ottawa, ON
[d] Geisinger Medical Center, Danville, PA
[e] Niagara Falls Memorial Medical Center, Buffalo, NY
[f] Cedars-Sinai Medical Center, Los Angeles, CA
[g] Weill Cornell Medical College New York, New York, NY

Received Dec 11, 2015; accepted May 4, 2016
doi:10.1007/s12350-016-0569-1

Background. **A drop in blood pressure (BP) or blunted BP response is an established high-risk marker during exercise myocardial perfusion imaging (MPI); however, data are sparse regarding the prognostic value of BP response in patients undergoing vasodilator stress rubidium-82 (Rb-82) Positron Emission Tomography (PET) MPI.**

Methods and Results. **From the PET Prognosis Multicenter Registry, a cohort of 3413 patients underwent vasodilator stress Rb-82 PET MPI with dipyridamole or adenosine. We used multivariable Cox proportional hazard regression to analyze the association with mortality of four BP variables: stress minus rest systolic BP (ΔSBP), stress minus rest diastolic BP (ΔDBP), resting systolic BP (rSBP), and resting diastolic BP (rDBP). Covariates that had univariate *P* values <.10 were entered into the multivariable model. After median 1.7 years follow-up, 270 patients died. In univariate analyses, ΔSBP (*P* = .082), rSBP (*P* = .008), and rDBP (*P* < .001) were of potential prognostic value (*P* < .10), but ΔDBP was not (*P* = .96). After adjustment for other clinical and MPI variables, ΔSBP no longer independently predicted mortality (*P* = .082); only lower rSBP (*P* = .026) and lower rDBP (*P* = .045) remained independently prognostic.**

Conclusions. **In patients undergoing vasodilator stress MPI, only lower resting BP is an independent predictor of mortality along with other clinical and MPI variables; BP response does not appear to add to risk stratification in these patients. (J Nucl Cardiol 2017;24:1966–75.)**

Key Words: Blood pressure response • myocardial perfusion imaging (MPI) • positron emission tomography (PET) • prognosis • vasodilator stress

Electronic supplementary material The online version of this article (doi:10.1007/s12350-016-0569-1) contains supplementary material, which is available to authorized users.

Reprint requests: Bradley Witbrodt, MD, Division of Cardiology, Department of Medicine, Emory University School of Medicine, 1462 Clifton Rd., Room 503, Atlanta, GA 30322; *bwitbro@emory.edu*

1071-3581/$34.00

Abbreviations	
BP	Blood pressure
CAD	Coronary artery disease
ΔDBP	Stress minus rest diastolic blood pressure
ΔSBP	Stress minus rest systolic blood pressure
MPI	Myocardial perfusion imaging
PET	Positron emission tomography
Rb-82	Rubidium-82
rDBP	Resting diastolic blood pressure
rSBP	Resting systolic blood pressure
SPECT	Single photon emission computed tomography

See related editorial, pp. 1976–1978

INTRODUCTION

In patients undergoing both exercise treadmill testing (ETT) and exercise stress single photon emission computed tomography (SPECT), myocardial perfusion imaging (MPI), blood pressure (BP) response (the difference between peak stress and resting BP) have prognostic value, independent of other clinical and MPI variables.[1,2] In contemporary practice, a large proportion of patients are unable to exercise, and in these patients, pharmacologic vasodilator SPECT or positron emission tomography (PET) MPI provides a useful alternative for risk stratification and for diagnosis of coronary artery disease (CAD).[3] However, there is a scarcity of literature describing whether BP response has the same independent prognostic value in patients undergoing vasodilator PET MPI as it has in patients undergoing ETT or exercise SPECT MPI.[4–6] A prior study has previously demonstrated that heart rate response is a significant independent predictor of cardiac death in patients undergoing vasodilator PET MPI,[7] but blood pressure response was not studied.

We utilized data from the Positron Emission Tomography (PET) Prognosis registry in order to address this gap in knowledge. The PET Prognosis Registry is a prospective, multicenter registry that has reported prognostic variables in a large set of patients that underwent vasodilator rubidium (Rb)-82 stress PET MPI for the evaluation of suspected myocardial ischemia. We sought to achieve the following objectives: (1) Examine the relationship between mortality and BP response, i.e., peak stress minus resting systolic blood pressure (ΔSBP), and peak stress minus resting diastolic blood pressure (ΔDBP); (2) Examine the relationship between mortality and both resting systolic blood pressure (rSBP) and resting diastolic blood pressure (rDBP); and (3) Determine the prognostic value of BP response (ΔSBP and ΔDBP) and resting BP (rSBP and rDBP) after adjusting for both clinical and MPI factors. We hypothesized that BP response would have added prognostic value independent of resting BP, clinical factors, and MPI findings in patients undergoing vasodilator stress Rb-82 PET MPI.

METHODS

PET Prognosis Registry

The main results from the PET Prognosis Registry have been previously published.[8] The PET Prognosis Registry enrolled 7061 consecutive patients undergoing pharmacologic stress Rb-82 PET MPI with either dobutamine or vasodilator stress. This analysis included the subset of 3413 patients who were documented to have undergone vasodilator stress with adenosine or dipyridamole (those stressed by dobutamine or by an undocumented stressor were excluded), as previously described.[4] All participating centers obtained institutional review board approval for the stress imaging procedures and follow-up methods.

Collection of Past Medical History Data

Data collection for relevant clinical history variables was conducted in a standardized fashion among all centers.[8] Study staff collected data on demographic and clinical factors including gender, age, height, weight, diabetes, hypertension, dyslipidemia, smoking, prior coronary revascularization procedures, and history of myocardial infarction. Ongoing uses of medications including beta blockers, calcium channel blockers, nitrates, ACE inhibitors, and diuretics were also recorded in the database.[9–11]

MPI Protocol and Interpretation

Study participants underwent standardized PET MPI protocols as per the guidelines of the American Society of Nuclear Cardiology.[12] Patients were instructed to fast for 6 hours and withhold caffeine-containing beverages (24 hours before the test) and antianginal medications (beta blockers, calcium blockers, and nitrates) on the morning of the test.[9] Patients underwent Rb-82 MPI PET using dedicated PET (ECAT ART; Siemens-CTI, Knoxville, TN; Posicam HZL/R, Positron Corporation, Houston, TX) or hybrid PET/CT cameras (Discovery Rx or STE Light Speed (16, 64 slice CT), GE Healthcare, Milwaukee, WI; Biograph 64, Siemens, Knoxville, TN). Infusion of 20-60 mCi Rb-82 occurred during both rest and stress. Vasodilator stress was induced by either intravenous dipyridamole (142 mcg·kg·minutes for 4-5 minutes) or adenosine (140 mcg·kg·minutes). Peak stress blood pressure measurements were obtained at or around the time of Rb-82 injection depending on site-specific protocols. This was approximately around the 7-minute mark for patients receiving dipyridamole and at the mid-point of the infusion for patients receiving adenosine.[7,8] Myocardial perfusion images were

interpreted using a standardized approach, including the 17 segmental scoring system. Based on the 17-segment scores, the summed rest and stress scores were calculated and categorized into <5%, 5-9.9%, and ≥10% abnormal myocardium.[12,13]

Blood Pressure Protocol and Blood Pressure Response

Resting and peak stress systolic and diastolic BP were measured in millimeters of mercury (mmHg) per study protocol using an automatic BP cuff with digital display or manual cuff. BP measurements were obtained at baseline and every 2 minutes during pharmacologic stress and recovery. Manual or automatic monitoring continued until the end of stress image acquisition, at which point the patient was removed from the PET gantry. A final BP with a 12-lead ECG was obtained before the patient left the imaging suite. For each patient, we defined ΔSBP as peak stress minus resting systolic BP, and ΔDBP as peak stress minus resting diastolic BP. Resting and maximum heart rate measurements were also recorded before and following intravenous vasodilator stress.

Follow-Up Methods

Detailed descriptions of the follow-up methodologies have been previously reported.[8] The primary endpoint for this analysis was all-cause mortality for an average follow-up of 1.9 years with a maximum of 5.1 years. The timing of all-cause mortality was documented for all patients. We chose all-cause mortality (instead of cause-specific death) as a primary endpoint because cause of death may not have been classified correctly in all patients, and using all-cause death would potentially avoid misclassification bias.[14] Prior studies have also demonstrated that the majority of deaths in patients with suspected coronary artery disease (such as those that might be referred for vasodilator stress Rb-82 PET MPI) are actually cardiovascular in nature, hence we considered all-cause death a reasonable endpoint.[15–17]

Each institution arranged a scripted telephone interview with the patient or family member. This was supplemented with review of patient's electronic medical record or by confirmation by the patient's primary care physician. For US centers, in order to confirm patient's survival status during the study time period, the national death index was queried. The follow-up time period was, on average, 1.9 ± 0.9 years. Survival analysis was performed by documenting the number of patients at risk during each year of follow-up.[7,8]

Statistical Methods

Descriptive statistics were used to generate histograms of our four blood pressure variables: ΔSBP, ΔDBP, rSBP, and rDBP. Even though the focus of this analysis was on BP response (ΔSBP and ΔDBP), we also evaluated the association of resting BP (rSBP and rDBP) with mortality to provide context to the BP response variables. We then created categories for ΔSBP (≤−20, >−20 to ≤−10, >−10 to ≤0, and >0 mmHg); ΔDBP (≤−10, >−10 to ≤0, and >0 mmHg); rSBP (<90, ≥90 to <120, ≥120 to <140, ≥140 to <160, and ≥160 mmHg); and for rDBP (<60, ≥60 to <90, and ≥90 mmHg). These categories were chosen because they were clinically relevant and easy to remember, while also providing for a sufficient number of patients in each category for statistical analysis. We then described baseline characteristics among the four groups of ΔSBP, and separately among the three groups ΔDBP, using ANOVA to compare continuous variables and Chi-square tests to compare categorical variables across groups.

We plotted all-cause mortality rates by categories of each BP variable: ΔSBP, ΔDBP, rSBP, and rDBP. For each plot, we showed both crude mortality by BP cut points, as well as the predicted mean mortality calculated from univariate Cox models. We then generated univariate and multivariate models using Cox regression analysis. Covariates that had univariable P values <.10 were entered into the multivariable model. Covariates included in the final multivariable analysis were as follows: age, sex, history of diabetes, history of hypertension, home use of beta blocker, home use of diuretics, home use of lipid-lowering agents, history of prior MI, history of prior revascularization, resting heart rate, heart rate response (HRR), percent abnormal myocardium at rest, percent ischemic myocardium, systolic blood pressure response (ΔSBP), resting systolic blood pressure (rSBP), and resting diastolic blood pressure (rDBP). Diastolic blood pressure response (ΔDBP) was not included in the final multivariable model because it did not predict mortality in univariate analysis ($P = .96$). Unadjusted and adjusted hazard ratios and 95% confidence intervals were presented for each blood pressure group. The proportional hazards assumption was checked both visually and through the use of residuals. We then repeated the univariate and multivariate Cox models using continuous (instead of categorical) variables for each of the four BP variables, and found no meaningful difference in the results. We used SPSS 21 statistical software for most of the statistical analyses. SAS® statistical software was used to generate Martingale residuals to confirm the linear fit of the BP variables. We also examined all our variables for co-linearity utilizing variance inflation factors, which indicated no significant co-linearity of any of the variables entered into our Cox models. An alpha of 0.05 was used to designate statistical significance for covariates entered in the multivariable model.

RESULTS

Baseline Characteristics

We examined baseline characteristics of this cohort both by categories of ΔSBP (Table 1) and ΔDBP (Table 2). Patients with the greatest drop in systolic BP with stress (ΔSBP ≤ −20 mmHg) tended to be older than patients with a less marked drop in systolic BP ($P < .001$, Table 1). This relationship was also seen by categories of ΔDBP, i.e., patients with the greatest drop in diastolic BP with stress (ΔDBP ≤ −10 mmHg) also tended to be older ($P < .001$, Table 2). Patients who had the greatest drop in systolic BP and diastolic BP also had

higher prevalence of hypertension ($P < .001$ across both ΔSBP and ΔDBP categories). Those with the greatest drop in systolic BP and diastolic BP also had a lower prevalence of smoking history ($P < .001$ across both ΔSBP and ΔDBP categories). As expected, patients with the greatest drop in systolic BP (ΔSBP ≤ −20 mmHg) had higher resting systolic and diastolic BP values, and lower stress systolic and diastolic BP values, compared with patients in the ΔSBP > 0 mmHg group ($P < .001$, Table 1). A similar relationship for resting and stress systolic and diastolic BP values was seen across the groups of ΔDBP ($P < .001$, Table 2). There was no significant association between either ΔSBP or ΔDBP and percent abnormal resting myocardium. Patients with a greater drop in systolic BP did have a higher percent of ischemic myocardium compared with patients with a lesser drop in systolic BP ($P < .001$, Table 1). However, there was no association between ΔDBP and percent ischemic myocardium ($P = .296$, Table 2).

Baseline characteristics across categories of rSBP and rDBP are also presented (Supplementary Table 1 and Supplementary Table 2). With increasing rSBP, age and the proportion of female patients tended to increase ($P < .001$ for both variables, Supplementary Table 1). In contrast, with increasing rDBP, age and the proportion of female patients tended to decrease (Supplementary Table 2). Increasing categories of rSBP and rDBP were both associated with lesser degrees of abnormal myocardium at rest ($P < .001$ for both rSBP and rDBP). However, only increasing categories of rDBP were associated with percent ischemic myocardium ($P = .049$), whereas rSBP was not ($P = .983$).

Mortality and Blood Pressure Response

We plotted crude mortality and mean predicted mortality from the Cox survival functions by groups of both change in systolic BP (ΔSBP) and change in diastolic BP (ΔDBP) (Figure 1). Both the crude mortality and predicted mortality curves were similar. For ΔSBP, mortality was highest in the first group (≤−20 mmHg) but lower in the subsequent three groups. For ΔDBP, there was no appreciable difference in mortality across the groups.

Mortality and Resting Blood Pressure

Figure 2 shows plots of both crude mortality and mean predicted mortality from the Cox survival functions by categories of rSBP and rDBP. For rSBP, crude rates of mortality were 9.1% in <90 mmHg group, 9.1% in the ≥90 to <120 mmHg group, 8.3% in the ≥120 to <140 mmHg group, 5.3% in the ≥140 to <160 mmHg group, and 9.3% in the ≥160 mmHg group. For rDBP categories, crude mortality rates were 11.9% in the <60 mmHg group, 7.0% for the ≥60 to <90 mmHg group, and 7.2% for the ≥90 mmHg group. Similar to BP response, the crude and mean predicted mortality curves were similar in shape for the rSBP and rDBP curves. Only the lowest category of diastolic blood pressure was associated with an increase in mortality.

Univariable and Multivariable Cox Models for Mortality by Blood Pressure Response and Resting Blood Pressure Categories

After median 1.9 years follow-up, 270 deaths from any cause were observed. In univariable analyses, ΔSBP ($P = .082$), rSBP ($P = .008$), and rDBP ($P < .001$) were of potential prognostic value (using $P < .10$ as the cutoff for entry into multivariable analysis), but ΔDBP was not ($P = .96$) (Table 3). After adjustment for other clinical and MPI variables, ΔSBP was no longer an independent predictor ($P = .287$), while rSBP ($P = .026$) and rDBP ($P = .045$) remained independent predictors of mortality (Table 3). In the adjusted models, the hazard ratios for categories of rDBP were consistent with the shape of the crude and predicted mean mortality curves. The rDBP group of <60 mmHg observed a hazard ratio of 1.77 (95% CI 1.35-2.32, $p = <.001$) for all-cause mortality compared with the reference group of ≥60 to <90 mmHg. There was no difference in mortality for the ≥90 mmHg group of rDBP (adjusted HR 1.00, 95% CI 0.63-1.59, $P = .99$) compared with the reference group (Table 3). For rSBP, compared with the reference group of ≥120 to <140 mmHg, most BP categories were associated with adjusted hazard ratios >1.0, although these were not significant ($P > .005$). However, those with rSBP ≥ 140 to < 160 demonstrated an adjusted HR of 0.60 (95% CI 0.42-0.86, $P = .005$). We also evaluated rDBP, rSBP, and ΔSBP in the multivariable model as continuous variables and our results were similar, in which ΔSBP was not a significant multivariate predictor of mortality; only rSBP and rDBP remained significant predictors (Table 3).

DISCUSSION

In this cohort study of 3413 consecutive patients undergoing vasodilator Rb-82 PET MPI, we hypothesized that BP response (ΔSBP and ΔDBP) during pharmacologic stress would be an independent predictor of all-cause mortality. We found that rDBP, rSBP, and ΔSBP predicted mortality in univariable analysis, and ΔDBP did not. However, when entered into a multivariable mortality model along with other clinical, hemodynamic, and MPI variables, only lower rDBP and rSBP remained independently prognostic, whereas

Table 1. Clinical descriptors of the 3413 patients referred for stress myocardial perfusion Rb-82 PET by peak stress minus resting systolic blood pressure categories

	ΔSBP ≤−20 mmHg (*n* = 22)	ΔSBP >−20 to ≤−10 mmHg (*n* = 760)	ΔSBP >−10 to ≤0 mmHg (*n* = 1967)	ΔSBP >0 mmHg (*n* = 664)	*P* value
Age	68.2 ± 12.8	65.0 ± 12.8	62.9 ± 12.4	61.5 ± 12.1	<.001
Female	49.0%	43.8%	46.1%	50.8%	.024
Cardiac risk factors					
Diabetes mellitus	33.6%	30.9%	29.1%	27.9%	.050
Hypertension	77.7%	74.4%	74.1%	69.2%	.001
Dyslipidemia	62.5%	62.6%	63.8%	65.3%	.587
Known CAD	33.9%	35.6%	36.8%	38.7%	.190
History of smoking	19.6%	25.9%	27.9%	35.5%	<.001
History of revascularization	29.9%	29.7%	32.0%	32.5%	.505
History of prior MI	23.3%	25.4%	25.2%	28.3%	.117
Heart rate					
Rest	68.4 ± 13	68.9 ± 13	69.2 ± 13	67.5 ± 13	.058
Peak stress	82.7 ± 15	83.6 ± 15	83.8 ± 15	83.6 ± 15	.373
Heart rate response					
>4 bpm	18.1%	20.9%	20.6%	15.7%	.055
5-14 bpm	34.9%	33.7%	32.1%	32.8%	
>15 bpm	47.0%	45.5%	47.3%	51.5%	
Systolic blood pressure					
Rest	150.0 ± 24	137.3 ± 23	134.5 ± 22	130.9 ± 24	<.001
Stress	116.8 ± 22	123.0 ± 23	129.8 ± 22	141.4 ± 24	<.001
Diastolic blood pressure					
Rest	73.2 ± 14	70.5 ± 13	70.7 ± 12	70.1 ± 13	<.001
Peak stress	55.7 ± 13	60.9 ± 13	65.6 ± 13	70.6 ± 13	<.001
% Abnormal myocardium at Rest (SRS)					.902
<5%	82.8%	83.6%	81.7%	83.7%	
5.0-9.9%	6.9%	6.3%	6.5%	6.3%	
≥10%	10.3%	10.1%	11.8%	10.0%	
% Ischemic myocardium (SDS)					<.001
<5%	70.1%	76.2%	77.9%	79.2%	
5.0-9.9%	13.0%	11.4%	9.8%	11.5%	
≥10%	16.9%	12.4%	12.3%	9.3%	
Medications					
Beta blockers	53.8%	54.2%	57.2%	51.8%	.178
Diuretics	29.2%	31.1%	31.8%	29.5%	.618
Lipid-lowering drugs	59.4%	60.7%	59.8%	59.1%	.921
ACE Inhibitors	32.7%	38.3%	39.9%	40.4%	.002
Calcium channel blockers	23.6%	25.4%	20.6%	20.6%	.053
Aspirin	57.3%	51.6%	53.4%	54.3%	.186

neither BP response variables (ΔSBP nor ΔDBP) were prognostic. These findings are in contrast to results from studies of exercise SPECT MPI and exercise treadmill stress testing, in which BP response has been shown to be a predictor of mortality independent of resting BP.[1–3]

Multiple prior studies have found that both resting BP and BP response are associated with mortality in patients undergoing EET or exercise SPECT MPI. However, little is published describing whether these associations hold in patients undergoing vasodilator PET

Table 2. Clinical descriptors of the 3413 patients referred for stress myocardial perfusion Rb-82 PET by peak stress minus resting diastolic blood pressure categories

	ΔDBP ≤−10 mmHg (*n* = 1467[a])	ΔDBP >−10 to ≤0 mmHg (*n* = 1199[a])	ΔDBP >0 mmHg (*n* = 719[a])	*P* value
Age	66.4 ± 12.7	63.9 ± 12.8	61.8 ± 12.5	<.001
Female	45.4%	48.5%	50.2%	.073
Cardiac risk factors				
Diabetes mellitus	32.6%	28.9%	28.7%	.058
Hypertension	76.5%	74.9%	67.6%	<.001
Dyslipidemia	63.0%	63.4%	64.8%	.702
Known CAD	32.5%	35.6%	44.4%	<.001
History of smoking	20.6%	28.4%	37.6%	<.001
History of revascularization	28.2%	30.5%	37.4%	<.001
History of prior MI	23.3%	24.8%	30.9%	.001
Heart rate				
Rest	69.3 ± 13	68.2 ± 13	67.3 ± 13	.002
Peak stress	83.9 ± 15	83.0 ± 15	82.9 ± 15	.212
Heart rate response				
> 4 bpm	19.2%	18.4%	18.2%	.782
5-14 bpm	33.9%	33.8%	32.0%	
>15 bpm	46.9%	47.8%	49.8%	
Systolic blood pressure				
Rest	142.6 ± 24	136.5 ± 24	134.4 ± 25	<.001
Stress	121.3 ± 24	129.7 ± 24	136.8 ± 25	<.001
Diastolic blood pressure				
Rest	75.4 ± 13	69.6 ± 12	65.6 ± 13	<.001
Peak Stress	56.4 ± 13	65.0 ± 12	73.1 ± 12	<.001
% Abnormal myocardium at rest				.452
<5%	83.4%	83.6%	81.4%	
5.0-9.9%	6.9%	5.8%	7.0%	
≥ 10%	9.7%	10.7%	11.7%	
% Ischemic myocardium (SDS)				.296
<5%	75.1%	77.6%	73.9%	
5.0-9.9%	11.3%	10.8%	12.9%	
≥10%	13.6%	11.7%	13.2%	
Medications				
Beta blockers	53.4%	54.0%	56.2%	.458
Diuretics	30.4%	31.0%	29.1%	.680
Lipid-lowering drugs	59.9%	58.8%	60.6%	.724
ACE Inhibitors	34.5%	39.6%	40.8%	.004
Calcium channel blockers	23.2%	21.5%	23.1%	.558
Aspirin	53.8%	54.0%	57.4%	.444

[a] 28 cases of missing data. Explains total *n* not adding up to 3413

MPI. In these patients, our study demonstrated that only resting BP but not BP response was associated with mortality. There are potential explanations for this discrepancy in the prognostic value of BP response in patients undergoing exercise versus vasodilator stress.

First, the expected BP response is inherently different between these two stress modalities: SBP is expected to rise during exercise testing, whereas it may not rise (and often decreases) during vasodilator stress. Second, patients referred for vasodilator MPI tend to

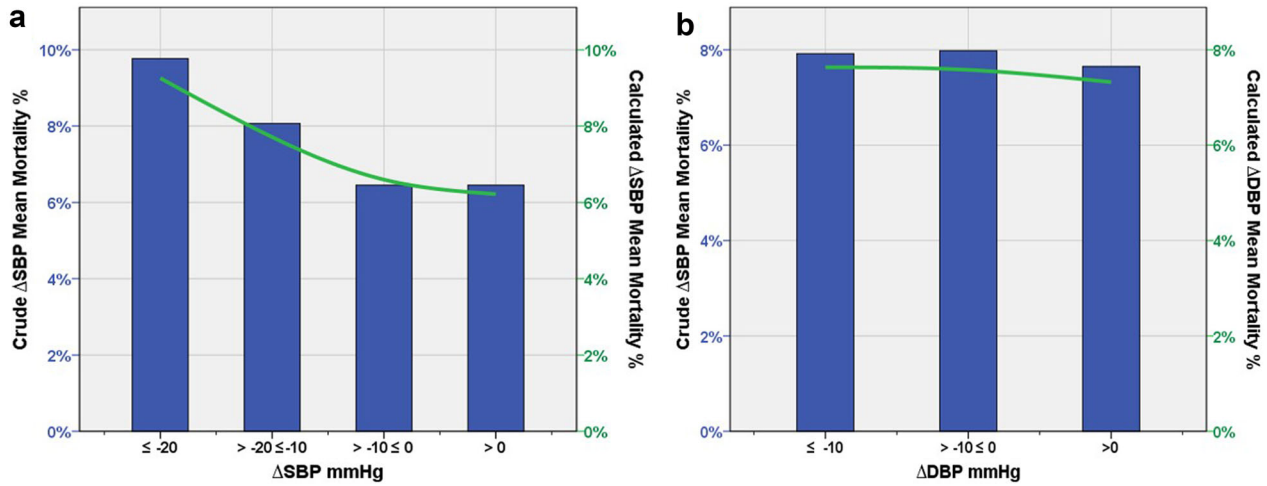

Figure 1. Peak stress minus resting blood pressure mortality curves. Crude mortality (*blue bars*) and mean predicted mortality from the Cox survival function (*green line*) for systolic blood pressure response (ΔSBP) (**A**) and diastolic blood pressure response (ΔDBP) (**B**). Blood pressure response is calculated as the peak stress minus the resting (pre-vasodilator infusion) blood pressure.

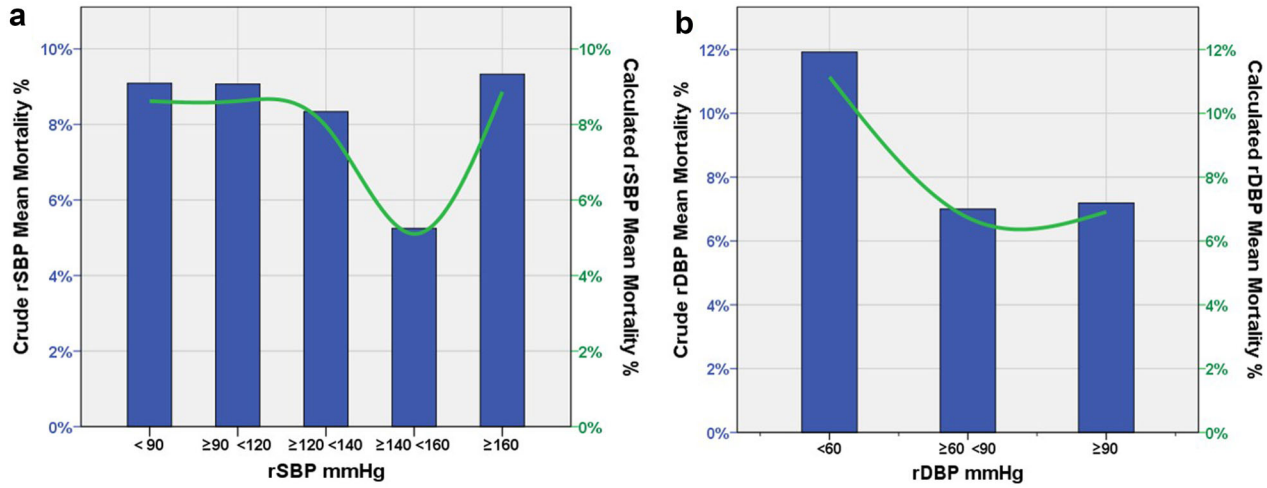

Figure 2. Resting systolic blood pressure mortality curves. Crude (*blue bars*) and predicted (*green line*) mortality curves for resting systolic blood pressure (rSBP) (**A**) and resting diastolic blood pressure (rDBP) (**B**), i.e., prior to vasodilator infusion.

have a greater burden of comorbidities that either preclude or limit exercise, or are more deconditioned and unlikely to achieve an adequate heart rate response during exercise. In these ''sicker'' patients referred for vasodilator stress MPI, there may be diminishing prognostic value of hemodynamic variables that are known to be prognostic in exercise testing, including BP response. Third, as previously shown by our group, heart rate response has been shown to be prognostic in vasodilator stress PET MPI.[7] Compared with the reference group of ≤4 beats per minute (bpm) heart rate increase with vasodilator stress, patients with a 5-14 bpm increase had an adjusted HR for CAD mortality of 0.58 (95% CI 0.44-0.77; $P < .001$), and patients with a ≥ 15 bpm increase had an adjusted HR of 0.30 (95% CI 0.21-0.43; $P < .001$). This association between heart rate response and mortality perhaps leaves little room for other hemodynamic response variables (such as BP response) to confer any additional prognostic information, given that changes in heart rate and blood pressure tend to be strongly inversely linked during vasodilator stress and therefore statistically collinear.

This relationship between heart rate response and vasodilators has been studied extensively in the diabetic population, a population that is prone to blunting of their hemodynamic responses.[18–20] These prior studies

Table 3. Predictors of mortality in patients undergoing vasodilator stress Rb-82 PET MPI

	Unadjusted hazard ratio (95% confidence interval)	Unadjusted *P* value	Adjusted hazard ratio (95% confidence interval)	Adjusted *P* value
Age (per 1 year increase)	1.04 (1.03–1.05)	<.001	1.03 (1.02–1.04)	<.001
Female sex	0.64 (0.50–0.82)	<.001	0.79 (0.61–1.04)	.097
Diabetes mellitus	1.67 (1.31–2.12)	<.001	1.33 (1.03–1.73)	.028
History of Hypertension	1.58 (1.16–2.14)	.003	1.25 (0.90–1.74)	.189
Home use of beta blocker	1.62 (1.26–2.07)	<.001	1.39 (1.06–1.82)	.018
Home use of diuretics	1.50 (1.17–1.91)	.001	0.98 (0.75–1.27)	.859
Home use of lipid-lowering drugs	0.80 (0.63–1.02)	.070	0.66 (0.51–0.85)	.002
History of Prior MI	2.03 (1.59–2.59)	<.001	1.30 (0.98–1.74)	.074
History of Revascularization	1.42 (1.11–1.82)	.005	0.96 (0.72–1.28)	.781
Resting heart rate (per 1 beat per minute increase)	1.03 (1.02–1.04)	<.001	1.03 (1.02–1.04)	<.001
Peak stress minus resting heart rate (beats per minute)	–	<.001*	–	<.001*
≤4	Reference	Reference	Reference	Reference
5 to 14	0.41 (0.31–0.53)	<.001	0.58 (0.44–0.77)	<.001
≥15	0.15 (0.11–0.20)	<.001	0.30 (0.21–0.43)	<.001
MPI findings				
% abnormal myocardium at rest (per 1% increase)	1.04 (1.03–1.05)	<.001	1.01 (1.00–1.03)	.055
% ischemic myocardium (per 1% increase)	1.04 (1.03–1.06)	<.001	1.02 (1.01–1.04)	.003
Resting DBP (mmHg)	–	<.001*	–	.045*
<60	1.77 (1.35–2.32)	<.001	1.45 (1.08–1.96)	.013
≥60 to <90	Reference	Reference	Reference	Reference
≥90	1.00 (0.63–1.59)	.99	0.97 (0.59–1.59)	.894
Resting SBP (mmHg)	–	.008*	–	.026*
<90	1.38 (0.34–5.62)	.650	1.52 (0.36–6.41)	.572
≥90 to <120	1.17 (0.86–1.61)	.307	1.35 (0.97–1.89)	.075
≥120 to <140	Reference	Reference	Reference	Reference
≥140 to <160	0.60 (0.42–0.86)	.005	0.70 (0.49–1.01)	.58
≥160	1.07 (0.77–1.47)	.696	1.10 (0.77–1.58)	.602
Stress minus rest SBP (ΔSBP) (mmHg)	–	.082*	–	.287*
≤−20	1.39 (0.996–1.95)	.053	1.38 (0.97–1.96)	.070
>−20 to ≤−10	1.15 (0.80–1.66)	.45	1.10 (0.76–1.59)	.61
>−10 to ≤0	Reference	Reference	Reference	Reference
>0	0.94 (0.65–1.37)	.75	1.15 (0.78–1.68)	.48

Shown below are only those covariates with univariate *P* value ≤ .10 that were subsequently entered into the multivariable model. In the multivariable model, an alpha of 0.05 was used to designate statistical significance
Covariates that were considered but not statistically significant ($P > .10$) in univariate analysis were stress minus resting DBP (ΔDBP), use of calcium channel blockers smoking history, and use of ACE inhibitors
* These values represent overall P values for the parent categorical variables

suggest that diabetic patients have altered sympathetic response to vasodilators, and this can significantly alter these patients' hemodynamic response with regards to heart rate response.[21] Given that nearly one third of the patients in this cohort had a known diagnosis of diabetes, we performed additional sub-analyses comparing diabetic patients to non-diabetic patients using our blood pressure covariates. This sub-analysis did not

reveal any significant differences between the diabetic and non-diabetic subgroups.

Many of the known limitations to the main PET Prognosis Registry have been previously described.[8] Prior studies have demonstrated some differences in observed hemodynamic responses among the different vasodilator agents.[22,23] All patients included in this analysis underwent vasodilator stress, but the specific vasodilator agent used (dipyridamole or adenosine) was not recorded in the registry. Given this limitation, it was not possible to control for the specific vasodilator agent administered, or describe any differences among agents that might exist when determining the relationship between BP response and mortality. Furthermore, we cannot comment on whether our findings would apply to patients undergoing regadenoson stress, as patients in the PET Prognosis Registry did not undergo regadenoson stress. Regadenoson has a similar expected effect on hemodynamics (increase in heart rate and drop in blood pressure) compared with dipyridamole and adenosine, and therefore we might speculate that our findings would likely not change if patients in this study also underwent regadenoson stress. However, future studies are required to address this issue conclusively.

The registry collected data on BP-lowering medications. However, we did not collect data on medication dosing, or whether patients held certain medications (e.g., beta blockers, nitrates, centrally acting calcium channel blockers, etc.) within 24-48 hours of their PET MPI study, as recommended by the American Society of Nuclear Cardiology guidelines. A concern common to all prospective cohort studies is selection bias; however, this bias was reduced by the consecutive enrollment of patients undergoing vasodilator PET MPI at participating centers. Finally, this is an observational study that can only suggest associations, and causal inferences cannot be drawn between any variables in the model and the outcome of mortality.

Finally, it is worth noting that while the results of this analysis indicate that BP response during vasodilator stress imaging does not provide added prognostic value at the population level, this does not mean that monitoring and recording BP changes during the course of the exam should not be performed. Indeed, in individual patients, measuring BP response following vasodilator stress is essential to ensure patient safety and to provide context for clinical interpretation of PET studies.

In summary, our study shows that lower resting systolic and diastolic BP but not BP response conferred independent prognostic value for mortality in patients undergoing vasodilator PET MPI, when considered in addition to resting BP and other clinical, hemodynamic stress, and MPI variables. Our findings differ from studies of exercise SPECT MPI in which BP response has been shown to be prognostic. Additional studies are needed to determine whether the prognostic value of BP response varies according to which vasodilator stress agent is used, and based on the profile of BP-lowering medications (dose, and timing of last dose in relation to the actual stress MPI study).

NEW KNOWLEDGE GAINED

Vasodilator stress MPI is increasingly used as a method for evaluating cardiovascular risk. Blood pressure response is a known independent predictor of mortality in exercise MPI studies and is routinely reported in a similar manner for patients undergoing vasodilator MPI stress as well. However, our analysis using the PET Multicenter Registry indicates that lower resting BP but not BP response had independent prognostic value beyond resting BP in this patient population undergoing vasodilator stress MPI.

Disclosures

This study was supported in part by an unrestricted grant from Astellas Pharma Global Development, Bracco Diagnostics, Inc., National Heart, Lung, and Blood Institute grant (K23HL092299) and by a program grant from the Heart and Stroke Foundation of Ontario (#PRG6242). The NIH Ruth L. Kirschstein National Research Service Awards training grant (5T32HL007745) supported Dr Witbrodt. Dr Goyal is supported by the Robert W. Woodruff Foundation. Dr Beanlands is a Career Investigator supported by the Heart and Stroke Foundation of Canada.

References

1. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: A scientific statement from the American Heart Association. Circulation 2013;128:873–934.
2. Le VV, Mitiku T, Sungar G, Myers J, Froelicher V. The blood pressure response to dynamic exercise testing: A systematic review. Prog Cardiovasc Dis 2008;51:135–60.
3. Bourque JM, Beller GA. Stress myocardial perfusion imaging for assessing prognosis: an update. JACC Cardiovasc Imaging 2011;4:1305–19.
4. Bax JJ, Delgado V. The importance of heart rate response during myocardial perfusion imaging. J Nucl Cardiol 2014;21:245–7.
5. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996;93:1520–6.
6. Miller TD. Exercise treadmill test: Estimating cardiovascular prognosis. Cleve Clin J Med 2008;75:424–30.
7. Bellam N, Veledar E, Dorbala S, Di Carli MF, Shah S, Eapen D, et al. Prognostic significance of impaired chronotropic response to pharmacologic stress Rb-82 PET. J Nucl Cardiol 2014;21:233–44.

8. Dorbala S, Di Carli MF, Beanlands RS, Merhige ME, Williams BA, Veledar E, et al. Prognostic value of stress myocardial perfusion positron emission tomography: Results from a multicenter observational registry. J Am Coll Cardiol 2013;61:176–84.
9. Dorbala S, Hachamovitch R, Curillova Z, Thomas D, Vangala D, Kwong RY, et al. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. JACC Cardiovasc Imaging 2009;2:846–54.
10. Kay J, Dorbala S, Goyal A, Fazel R, Di Carli MF, Einstein AJ, et al. Influence of sex on risk stratification with stress myocardial perfusion Rb-82 positron emission tomography: Results from the PET (Positron Emission Tomography) Prognosis Multicenter Registry. J Am Coll Cardiol 2013;62:1866–76.
11. Merhige ME, Breen WJ, Shelton V, Houston T, D'Arcy BJ, Perna AF. Impact of myocardial perfusion imaging with PET and (82)Rb on downstream invasive procedure utilization, costs, and outcomes in coronary disease management. J Nucl Med 2007;48:1069–76.
12. Dilsizian V, Bacharach SL, Beanlands RS, Bergmann SR, Delbeke D, Gropler RJ, et al. PET myocardial perfusion and metabolism clinical imaging. J Nucl Cardiol 2009;16:651.
13. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, et al. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. Eur Heart J 2011;32:1012–24.
14. Lozano R, Murray CJL, Lopez AD, Satoh T, Policy WHOG-PoEfH. Miscoding and misclassification of ischaemic heart disease mortality 2001.
15. D'Amico M, Agozzino E, Biagino A, Simonetti A, Marinelli P. Ill-defined and multiple causes on death certificates: A study of misclassification in mortality statistics. Eur J Epidemiol 1999;15:141–8.
16. DeHenauw S, de Smet P, Aelvoet W, Kornitzer M, DeBacker G. Misclassification of coronary heart disease in mortality statistics. Evidence from the WHO-MONICA Ghent-Charleroi Study in Belgium. J Epidemiolo Community Health 1998;52:513–9.
17. Rhoades DA. Racial misclassification and disparities in cardiovascular disease among American Indians and Alaska Natives. Circulation 2005;111:1250–6.
18. Hage FG, Heo J, Franks B, Belardinelli L, Blackburn B, Wang W, et al. Differences in heart rate response to adenosine and regadenoson in patients with and without diabetes mellitus. Am Heart J 2009;157:771–6.
19. Hage FG, Dean P, Iqbal F, Heo J, Iskandrian AE. A blunted heart rate response to regadenoson is an independent prognostic indicator in patients undergoing myocardial perfusion imaging. J Nucl Cardiology 2011;18:1086–94.
20. Hage FG, Iskandrian AE. Cardiac autonomic denervation in diabetes mellitus. Circulation 2011;4:79–81.
21. Bockus LB, Humphries KM. cAMP-dependent protein kinase (PKA) signaling is impaired in the diabetic heart. J Biol Chem 2015;290:29250–8.
22. Johnston DL, Daley JR, Hodge DO, Hopfenspirger MR, Gibbons RJ. Hemodynamic responses and adverse effects associated with adenosine and dipyridamole pharmacologic stress testing: A comparison in 2,000 patients. Mayo Clin Proc 1995;70:331–6.
23. Vasu S, Bandettini WP, Hsu L-Y, Kellman P, Leung S, Mancini C, et al. Regadenoson and adenosine are equivalent vasodilators and are superior than dipyridamole: A study of first pass quantitative perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2013;15:85.