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ORIGINAL ARTICLE

Heart rate reserve is a long-term risk predictor in women undergoing myocardial perfusion imaging

Caroline E. Gebhard[1,2] · Monika Marędziak[1,3] · Angela Portmann[1,3] · Susan Bengs[1,3] · Ahmed Haider[1,3] · Michael Fiechter[1,3] · Bernhard A. Herzog[1] · Michael Messerli[1] · Valerie Treyer[1] · Ken Kudura[1] · Elia von Felten[1] · Dominik C. Benz[1] · Tobias A. Fuchs[1] · Christoph Gräni[1] · Aju P. Pazhenkottil[1] · Ronny R. Buechel[1] · Philipp A. Kaufmann[1] · Catherine Gebhard[1,3]

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Abstract

Background Although women with cardiovascular disease experience relatively worse outcomes as compared to men, substantial knowledge gaps remain regarding the unique female determinants of cardiovascular risk. Heart rate (HR) responses to vasodilator stress mirror autonomic activity and may carry important long-term prognostic information in women.

Methods and results Hemodynamic changes during adenosine stress were recorded in a total of 508 consecutive patients (104 women) undergoing clinically indicated ^{13}N-ammonia Positron-Emission-Tomography (PET) at our institution. Following propensity matching, 202 patients (101 women, mean age 61.3 ± 12.6 years) were analyzed. During a median follow-up of 5.6 years, 97 patients had at least one cardiac event, including 17 cardiac deaths. Heart rate reserve (% HRR) during adenosine infusion was significantly higher in women as compared to men (23.8 ± 19.5 vs 17.3 ± 15.3, $p = 0.009$). A strong association between 10-year cardiovascular endpoints and a blunted HRR was observed in women, while this association was less pronounced in men. Accordingly, in women, but not in men, reduced HRR was selected as a strong predictor for adverse cardiovascular events in a Cox regression model fully adjusted for imaging findings and traditional risk factors (HR 2.41, 95% CI 1.23–4.75, $p = 0.011$). Receiver operating characteristics (ROC) curves revealed that a blunted HRR <21% was a powerful predictor for MACE in women with a sensitivity of 77% and a specificity of 68%.

Conclusion Blunted HRR to adenosine stress adds incremental prognostic value for long-term cardiovascular outcomes in women beyond that provided by traditional risk factors and imaging findings.

Keywords ^{13}N-ammonia PET · Adenosine · Heart rate response · Coronary artery disease · Women

Abbreviations

BMI	Body mass index
CAD	Coronary artery disease
CFR	Coronary flow reserve
CT	Computed tomography
HRR	Heart rate reserve
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
CMVD	coronary microvascular dysfunction

Caroline E. Gebhard and Monika Marędziak contributed equally to this work.

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✉ Catherine Gebhard
Catherine.gebhard@usz.ch

[1] Department of Nuclear Medicine, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland

[2] Department of Anesthesiology, University Hospital Basel, Basel, Switzerland

[3] Center for Molecular Cardiology, University of Zurich, Zurich, Switzerland

Introduction

Cardiovascular disease (CVD) continues to be the most frequent cause of death in Europe [1]. Over the past five decades, the incidence of CVD has continuously declined in men, but less so in women, with an CVD incidence of 5.3 million being currently reported in the female population across 47 European Society of Cardiology member countries [1, 2].

Despite a growing awareness of sex-disparities in CVD incidence and outcomes, female-specific determinants of cardiovascular risk are still lacking. Indeed, women are less likely to have obstructive coronary artery disease (CAD) than men with similar symptoms, and tend to suffer more often from coronary microvascular dysfunction (CMVD), a condition which is associated with severe symptoms and an increased risk of adverse cardiovascular events [3–5]. Diagnosis of CMVD is a major challenge and requires a high index of suspicion as it is based on costly and invasive procedures such as documentation of normal epicardial coronaries, absence of spasm of epicardial coronaries, and reduced coronary flow reserve (CFR) [6]. The latter, however, has recently been shown to provide only limited long-term prognostic value in women [7]. Similarly, contemporary imaging modalities for the diagnosis of CAD all have substantial limitations in women resulting in diagnostic and, thus, therapeutic uncertainty hampering the delivery of guideline-based care to the female population [8, 9].

Sex differences in the autonomous nervous control of the cardiovascular system have recently been described in the context of Takotsubo syndrome and normal aging, with a higher sympathetic activity being observed in women [10, 11]. As the latter has been associated with a higher mortality in patients with CAD, this sexual dimorphism in cardiac autonomic physiology might be of prognostic relevance [12]. However, quantification of cardiac sympathetic activity usually requires costly and sophisticated technologies such as ^{123}I meta-iodobenzylguanidine (MIBG) Single Photon Emission Tomography (SPECT) or ^{11}C-*meta*-Hydroxyephedrine (^{11}C mHED) Positron-Emission-Tomography (PET). Heart rate (HR) responses to adenosine have been shown to depend on baseline sympathetic activity and might therefore be used as a simple and inexpensive surrogate parameter of sympathetic tone in clinical routine [13, 14]. As women frequently undergo pharmacological stress testing with adenosine due to their often reduced exercise capacity and given the scarcity of long-term unique female determinants of cardiovascular risk, we sought to assess the prognostic value of HR responses to adenosine in patients with known or suspected CAD.

Methods

Study population

Five hundred eight consecutive patients who underwent a pharmacological stress/rest myocardial perfusion imaging (MPI) ^{13}N-ammonia PET protocol with adenosine between August 1995 and October 2006 at our institution were included in this study. Hemodynamic responses to adenosine infusion were recorded in all patients. Patients were stratified by sex, and propensity-matched models were applied to adjust for baseline differences between women and men. Following propensity matching, 202 patients (101 women) remained in the final analysis. The patient's history including risk factors, medication use, and key symptoms including chest pain and shortness of breath were recorded at the time of the imaging study by patient interview as well as by review of medical records. The study conforms to the principles outlined in the Declaration of Helsinki and was evaluated and approved by the local ethics committee (BASEC No. 2017–01112). The need for informed written consent was waived. The study population was partly shared with the PET imaging registry reported elsewhere [7, 15, 16].

Adenosine stress protocol and PET imaging protocol

All patients underwent ^{13}N-ammonia myocardial perfusion PET in a 1-day protocol at rest and during adenosine stress at a standard rate (0.14 mg/min/kg) over 6 min, as previously reported [15, 16]. Patients were advised to refrain from theophylline or caffeine containing beverages for at least 12 h before the study. Medications (including beta-blockers) were withheld for 24 h prior to MPI-PET. PET was performed either on a GE Advance PET scanner ($n = 104$ [51.5%], matched cohort) or on a discovery (LS/RX) PET/computed tomography (CT) scanner ($n = 98$ [48.5%] matched cohort), both from GE Healthcare, Milwaukee, Wisconsin. Each patient received a CT transmission scan for photon attenuation correction. ^{13}N-ammonia was intravenously injected (700–900 MBq), and standardized rest and pharmacological stress imaging protocols were performed. HR and blood pressure (BP) were measured at baseline and every minute throughout adenosine infusion and recovery time in all patients. Peak effect HR and BP were defined as HR and BP achieved 3 min after the start of adenosine infusion. HR response to adenosine was defined as % heart rate reserve (HRR, [(peak effect HR minus baseline HR)/baseline HR]*100) in order to account for baseline differences.

Data reconstruction and image analysis

Filtered back projection was used for image reconstruction. For evaluation, images were resliced in vertical, horizontal long-axis, and short-axis orientation. The 17-segment scoring system was used to visually score rest and stress images. The percentage of abnormal myocardium at stress was determined from the summed stress score, with a summed stress score (SSS) <4 being considered abnormal [16]. Diverging interpretations were classified by consensus. Myocardial and blood pool time-activity curves corrected for radioisotope decay from the dynamic frames were determined to quantify myocardial blood flow (MBF) by using the PMOD software package (version 2.1 to 2.8, PMOD Technologies Ltd., Zurich, Switzerland). MBF was estimated by model fitting of the

blood pool and myocardial time-activity curves correcting for partial volume and spillover, as previously described [16]. Per-patient global CFR was calculated as the ratio of stress to rest absolute MBF for the whole left ventricle, and CFR >2.0 was considered normal [17].

Assessment of outcomes

Information on follow-up was obtained by telephone interview, from medical records, and from the referring physician. Primary study endpoint was the occurrence of major adverse cardiac events (MACE) including cardiac death, non-fatal myocardial infarction (MI), hospitalization for any cardiac reason, and late revascularization. Secondary study endpoints were all-cause mortality and cardiac death. Cardiac death was defined as fatal MI, sudden cardiac death or death due to heart failure. All other deaths were categorized as all-cause deaths. Patients undergoing revascularization within 60 days after ^{13}N-ammonia PET were not included in our study cohort as these revascularizations might be triggered by MPI findings rather than reflecting disease progress. All patients were followed for a median of 5.6 years (interquartile range 4.1–7.1 years). The date of the last examination or consultation was used to determine follow-up.

Statistical analysis

The study population was stratified by sex, and propensity score matching was used to balance men and women for baseline differences (age, body mass index [BMI], diabetes, smoking, hypertension, dyslipidaemia, family history of CAD, prior MI, and prior revascularization). The propensity score was then used to match women and men with similar estimated propensity to two decimal places. Data are presented as mean ± standard deviation (SD) for continuous variables and frequency, and percentage for categorical variables. Prior to analyses, basic assumptions were checked. Student's t test, Mann-Whitney test, analysis of variance (ANOVA) or Kruskal-Wallis test were used for group comparisons of continuous variables. For clinical convenience, CFR was displayed as a dichotomous variable using ≤2 as a cut point for an impaired ratio. The time to cardiac events was estimated using a Cox proportional hazards survival model. The effect size of HHR on cardiac mortality was evaluated by constructing Cox proportional hazard models containing HHR as dichotomic predictor variable. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Cumulative event-free survival curves for the primary MACE end point of cardiovascular death, non-fatal MI, late revascularization, and hospitalization for cardiac reasons were compared across dichotomous categories of HRR by use of the Kaplan-Meier methodology and log-rank test. A two-tailed *P* value of 0.05 was considered statistically significant. SPSS version 24.0 (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses.

Results

Patient characteristics

Following propensity score matching, a total of 202 subjects (101 [50.0%] women, mean age 61.3 ± 12.6) were analyzed. Before matching, men had a higher BMI (27.3 ± 4.3 vs 25.6 ± 4.6, $p = 0.001$, Table 1), were more often smokers (69.3% vs 42.3%, $p < 0.001$, Table 1), and had more often dyslipidemia (75.2% vs 55.8%, $p < 0.001$, Table 1) or diabetes (28.5% vs 16.3%, $p = 0.01$, Table 1) than women. More men than women had previously undergone revascularization (57.9% vs 36.5%, $p < 0.001$, Table 1) or had previously experienced a myocardial infarction (MI) (56.9% vs 32.7% in women, $p < 0.001$, Table 1). Accordingly, the average Framingham risk in our study population was 17.0% (9.7% in women and 18.7% in men, $p < 0.001$). Patient's characteristics of both, unmatched and matched cohorts, stratified by sex are depicted in Table 1.

Myocardial perfusion findings and hemodynamic changes during adenosine stress

In the matched cohort, reversible perfusion defects were found in 15.8% of patients, while 27.7% of patients showed an irreversible perfusion defect (Table 2). Men had a higher prevalence of fixed perfusion defects than women (37.6% vs 17.8%, $p = 0.002$, Table 2), while a slightly higher prevalence of reversible perfusion defects was seen in women as compared to men (18.8% vs 12.9%, $p = 0.25$, Table 2). Abnormal CFR ≤2.0 was detected in 40.6% of women and 55.4 of men ($p = 0.035$, Table 2). No significant sex differences were found for baseline (1.1 ± 0.4 mL/min/g in women vs 0.9 ± 0.3 mL/min/g in men, $p = 0.10$) and stress MBF (2.2 ± 0.9 mL/min/g in women vs 1.9 ± 1.1 mL/min/g in men, $p = 0.36$, Table 2) as well as for CFR (2.4 ± 0.7 in women vs 2.0 ± 0.9 in men, $p = 0.09$, Table 2). Baseline left ventricular ejection fraction (LVEF) and baseline HR were significantly higher in women as compared to men ($p < 0.05$, Table 2), while diastolic blood pressure (DBP) during pharmacological stress was higher in men ($p = 0.04$ vs women, Table 2). Peak HR during pharmacological stress with adenosine was significantly higher in women as compared to men (88.8 ± 15.4 bpm vs 77.6 ± 14.0 bpm, $p < 0.001$, Table 2). Accordingly, HRR was significantly higher in women as compared to men (23.8 ± 19.5 vs 17.3 ± 15.3, $p = 0.009$, Table 2). A significant and positive correlation was seen between HRR and CFR in women (Pearson r = 0.16, p = 0.04), but not in men (Pearson r = 0.01, $p = 0.89$). All

Table 1 Characteristics of the study population by sex

Baseline characteristics	Unmatched cohort				PS Matched cohort			
	Total N = 508	Women N = 104	Men N = 404	p value	Total N = 202	Women N = 101	Men N = 101	p value
Age (years), mean ± SD	60.9 ± 11.9	60.8 ± 12.7	61.0 ± 11.5	0.8	61.3 ± 12.6	61.6 ± 12.0	61.0 ± 13.2	0.73
BMI, mean ± SD	26.9 ± 4.4	25.6 ± 4.6	27.3 ± 4.3	0.001	25.9 ± 4.0	25.7 ± 4.6	25.9 ± 3.1	0.62
Hypertension, *n*(%)	322(63.3)	63(60.6)	259(64.1)	0.4	130(64.4)	63(62.4)	67(66.3)	0.56
Smoking, *n*(%)	324(63.8)	44(42.3)	280(69.3)	<0.001	84(41.6)	44(43.6)	40(39.6)	0.57
Diabetes, *n*(%)	132(25.9)	17(16.3)	115(28.5)	0.01	35(17.3)	17(16.8)	18(17.8)	0.85
Dyslipidemia, *n*(%)	362(71.3)	58(55.8)	304(75.2)	<0.001	175(86.6)	58(57.5)	117(57.9)	0.89
Family history of CAD, *n*(%)	248(48.8)	55(52.9)	193(47.8)	0.3	108(54.0)	55(54.5)	53(52.5)	0.67
Previous MI, *n*(%)	264(52.0)	34(32.7)	230(56.9)	<0.001	76(37.6)	34(33.7)	42(41.6)	0.25
Previous PCI/CABG, *n*(%)	283(55.7)	38(36.5)	234(57.9)	<0.001	78(38.6)	38(37.6)	40(39.6)	0.77
Angina symptoms (CCS class ≥2), *n*(%)	41(8.1)	11(10.6)	30(7.4)	0.29	22(10.9)	11(10.9)	11(10.9)	1.0
Dyspnea (NYHA functional class ≥2), *n*(%)	16(3.1)	4(3.8)	12(3.0)	0.65	9(4.5)	4(3.9)	5(4.9)	0.73
Medication								
Platelet inhibitor	32(6.3)	8(7.7)	24(5.9)	0.51	19(9.4)	8(7.9)	11(10.9)	0.47
Anti-ischemic agents	24(4.7)	5(4.8)	19(4.7)	0.96	11(5.4)	5(5.0)	6(5.9)	0.76
Lipid lowering agents	146(28.7)	28(26.9)	118(29.2)	0.65	63(31.2)	28(27.7)	35(34.7)	0.29
Framingham risk (%, mean ± SD)	17.0 ± 11.6	9.7 ± 5.7	18.7 ± 12.0	<0.001	13.9 ± 10.2	9.9 ± 5.6	17.8 ± 12.1	<0.001
MACE, *n*(%)	272(53.5)	43(41.3)	229(56.7)	0.005	97(48.0)	42(41.6)	55(54.5)	0.07
Cardiac death, *n*(%)	51(10.1)	7(6.8)	44(10.9)	0.21	17(8.4)	7(6.9)	10(9.9)	0.45
Death (any cause), *n*(%)	85(16.7)	11(10.6)	74(18.3)	0.06	28(13.9)	11(10.9)	17(16.8)	0.22

Unmatched (*left*) and matched (*right*) cohort following propensity score (PS) matching. Data are presented as mean ± SD or % of patients, *BMI* body mass index, *CAD* coronary artery disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *MACE* major adverse cardiovascular events

imaging findings and hemodynamic variables of both, unmatched and matched cohorts, stratified by sex are shown in Table 2.

Adenosine-induced hemodynamic changes and their association with clinical endpoints

In the overall study population, the cumulative 10-year event rate was 48.0% for MACE (=cardiac death, non-fatal MI, hospitalization for any cardiac reason, and late revascularization), 8.4% for cardiac death, and 13.9% for all-cause mortality (Table 1). In women who experienced a MACE, HRR was significantly lower as compared to women who remained free of MACE during follow-up (17.8 ± 18.3 vs 28.0 ± 19.3, p = 0.003, Fig. 1a) while no such difference was observed in men (16.2 ± 14.5 vs 19.5 ± 15.2, p = 0.22, Fig. 1a). Similarly, a substantial reduction in HRR was observed in women who died due to cardiovascular cause (4.0 ± 8.4 vs 25.3 ± 19.3, p < 0.001) or due to any cause (6.4 ± 8.7 vs 25.9 ± 19.4, p < 0.001, Fig. 1c). A reduction in HRR was also seen in men who died from cardiovascular or any cause; however, differences were less pronounced than in women (Fig. 1b and c). No association with adverse cardiovascular events were found for baseline HR and stress systolic blood pressure (SBP) (Fig. 1d and f), while blunted stress DBP was associated with MACE in women (p = 0.048, Fig. 1e), but not in men (p = 0.38, Fig. 1e). When HRR was dichotomized by splitting the sample at the median, Kaplan-Meier survival curves showed that an HRR above median value was associated with event-free survival in women (log rank p < 0.001, Fig. 2a), but not in men (log rank p = 0.861, Fig. 2b). Importantly, no fatal events (cardiac death and death of any cause) occurred in women with an HRR above median value (log rank p = 0.002 for cardiac death and log rank p < 0.001 for all-cause mortality, Fig. 2c and e). No differences in all-cause mortality were observed in men with an HRR above median value (log rank p = 0.123 vs men with reduced HRR, Fig. 2d), while men with a higher HRR died less often from cardiovascular cause than men with a reduced HRR (log rank p = 0.047, Fig. 2f). However, differences were less striking in men than in women.

Prognostic value of heart rate reserve in women and men

Univariate Cox regression analysis identified reduced HRR (HR 2.75, 95%CI 1.42–5.35, p = 0.003), age (HR 1.04,

Table 2 Patient hemodynamic and ^{13}N-ammonia PET parameters

^{13}N-Ammonia PET and hemodynamic variables	Unmatched cohort				PS Matched cohort			
	Total N = 508	Women N = 104	Men N = 404	p value	Total N = 202	Women N = 101	Men N = 101	p value
Perfusion defect								
Fixed, *n*(%)	170(33.5)	18(17.3)	152(37.6)	<0.001	56(27.7)	18(17.8)	38(37.6)	0.002
Reversible, *n*(%)	60(11.8)	20(19.2)	40(9.9)	0.009	32(15.8)	19(18.8)	13(12.9)	0.25
Baseline MBF (mL/min/g), mean ± SD	0.9 ± 0.3	1.1 ± 0.4	0.8 ± 0.3	0.002	1.0 ± 0.4	1.1 ± 0.4	0.9 ± 0.3	0.10
Stress MBF (mL/min/g), mean ± SD	1.9 ± 0.9	2.2 ± 0.9	1.7 ± 0.8	0.047	2.0 ± 1.0	2.2 ± 0.9	1.9 ± 1.1	0.36
CFR, mean ± SD	2.1 ± 0.8	2.4 ± 0.7	2.1 ± 0.8	0.05	2.2 ± 0.8	2.4 ± 0.7	2.0 ± 0.9	0.09
Abnormal CFR (≤2), *n*(%)	236(46.5)	41(39.4)	195(48.3)	0.11	97(48.0)	41(40.6)	56(55.4)	0.035
LVEF	51.8 ± 17.3	58.3 ± 15.5	50.1 ± 17.4	<0.001	55.0 ± 16.9	58.3 ± 15.7	51.9 ± 17.6	0.014
Diastolic blood pressure (DBP)								
Baseline (mmHg), mean ± SD	75.8 ± 10.9	72.9 ± 11.5	76.6 ± 10.6	0.002	74.8 ± 11.5	73.4 ± 11.2	76.3 ± 11.7	0.08
Peak effect (mmHg), mean ± SD	73.1 ± 11.5	70.3 ± 12.4	73.9 ± 11.2	0.006	72.5 ± 12.2	70.7 ± 12.4	74.3 ± 11.9	0.04
Systolic blood pressure (SBP)								
Baseline (mmHg), mean ± SD	129.4 ± 20.5	134.5 ± 22.7	128.1 ± 19.7	0.005	132.8 ± 21.6	135.2 ± 22.6	130.4 ± 20.4	0.12
Peak effect (mmHg), mean ± SD	126.0 ± 19.7	128.4 ± 20.2	125.4 ± 19.5	0.17	128.0 ± 20.8	128.7 ± 20.4	127.3 ± 21.3	0.69
Mean arterial pressure (MAP)								
Baseline (mmHg), mean ± SD	93.6 ± 12.5	93.5 ± 13.4	93.6 ± 12.3	0.90	94.1 ± 13.2	94.1 ± 13.2	94.2 ± 13.3	0.96
Peak effect (mmHg), mean ± SD	90.6 ± 13.0	89.4 ± 14.1	90.9 ± 12.7	0.30	90.8 ± 14.1	89.7 ± 14.2	92.0 ± 14.0	0.23
Heart rate								
Baseline (bpm), mean ± SD	68.9 ± 13.2	71.7 ± 12.8	68.2 ± 13.1	0.015	69.1 ± 12.6	71.7 ± 12.8	66.5 ± 12.0	0.004
Peak effect (bpm), mean ± SD	80.3 ± 15.8	88.3 ± 16.2	78.3 ± 15.1	<0.001	82.7 ± 15.5	88.8 ± 15.4	77.6 ± 14.0	<0.001
% HRR, mean ± SD	17.5 ± 17.8	24.2 ± 19.7	15.7 ± 16.8	<0.001	20.5 ± 17.8	23.8 ± 19.5	17.3 ± 15.3	0.009
Baseline heart rate * SBP product (RPP), mean ± SD	8905 ± 2206	9685 ± 2438	8704 ± 2099	<0.001	9196 ± 2427	9727 ± 2445	8655 ± 2297	0.002
Peak heart rate * SBP product (RPP), mean ± SD	10,123 ± 2639	11,305 ± 2679	9811 ± 2542	<0.001	10,602 ± 2845	11,268 ± 2633	9923 ± 2905	0.001

Unmatched (*left*) and matched (*right*) cohort following propensity score (PS) matching. Data are stratified by sex

MBF myocardial blood flow, *CFR* coronary flow reserve, *LVEF* left ventricular ejection fraction, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *MAP* mean arterial pressure, *bpm* beats per minute, *HRR* heart rate reserve, *RPP* rate pressure product

95%CI 1.00–1.07, $p = 0.01$), abnormal MPI (HR 4.12, 95%CI 1.83–3.50, $p = 0.001$), LVEF (HR 0.97, 95%CI 0.95–0.99, $p = 0.003$), and diabetes (HR 2.35, 95%CI 1.17–4.71, $p = 0.016$) as significant predictors of MACE in women, while abnormal MPI (HR 3.47, 95%CI 1.56–7.69, $p = 0.002$), LVEF (HR 0.98, 95%CI 0.97–1.00, $p = 0.047$), and smoking (HR 1.96, 95%CI 1.1–3.33, $p = 0.013$) were associated with future clinical events in men (Table 3). In addition, a stepwise Cox regression model adjusted for age, BMI, LVEF, cardiovascular risk factors, and abnormal perfusion selected a blunted HRR as a significant predictor of 10-year MACE in women, thereby outperforming traditional risk factors and MPI findings (final model: HR 2.41, 95%CI 1.23–4.75, $p = 0.011$, Table 4). Conversely, in men, amongst all variables, only abnormal MPI findings was selected as a significant predictor of 10-year MACE (HR 4.55, 95%CI 1.92–10.80, $p = 0.001$, Table 4). When a subgroup analysis in patients without reversible or fixed perfusion defect on PET-MPI was performed, the multivariate Cox regression model—adjusted for cardiovascular risk factors and LVEF—selected a blunted HRR as a significant predictor of future MACE in women (women: HR 4.2, 95% CI 1.99–8.87, $p < 0.001$), but not in men (significant predictors in men: age [HR 1.05, 95%CI 1.00–1.09, $p = 0.02$] and smoking [HR 3.2, 95%CI 1.47–6.93, $p = 0.003$]). Accordingly, receiver operating characteristics (ROC) curves revealed that an HRR <21% was a powerful predictor for MACE in women (area under the curve, AUC 0.79, $p < 0.001$, Fig. 3a), but not in men (AUC 0.48, $p = 0.8$, Fig. 3b), with a sensitivity of 77% and a specificity of 68% (Fig. 3a).

Discussion

Our study is the first demonstrating a long-term prognostic value of hemodynamic responses to vasodilator stress test in

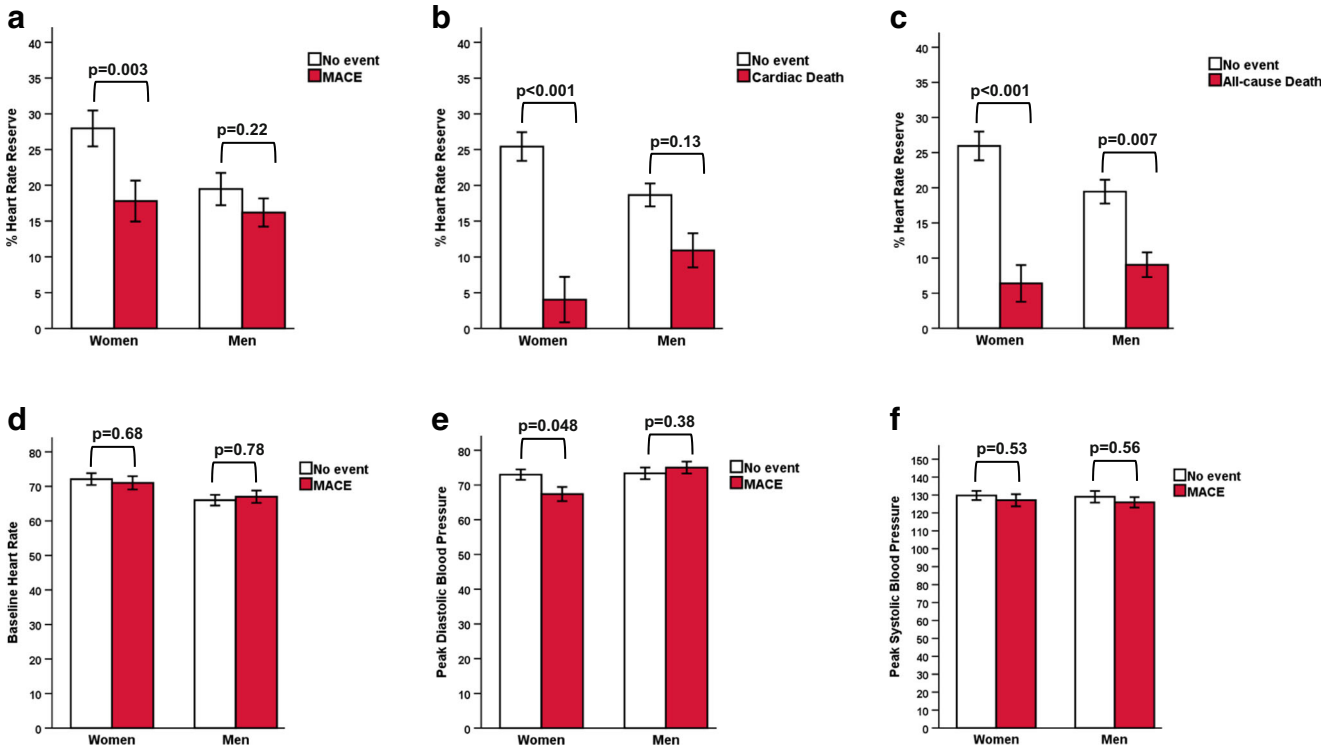

Fig. 1 Association between hemodynamic changes during adenosine vasodilator stress and clinical endpoints by sex. **a** % Heart rate reserve in women and men with and without major adverse cardiovascular events (MACE) during follow-up. Values are reported as percent [(peak HR minus baseline HR)/baseline HR]*100). **b** % Heart rate reserve in women and men who died due to cardiovascular cause during follow-up. **c** % Heart rate reserve in women and men who died (any cause) during follow-up. **d** Baseline heart rate in women and men with and without MACE during follow-up. Values are reported in beats per minute (bpm). **e** Peak diastolic blood pressure during adenosine infusion in women and men with and without MACE during follow-up. Values are reported in mmHg. **f** Peak systolic blood pressure during adenosine infusion in women and men with and without MACE during follow-up. Values are reported in mmHg and as mean ± SEM

women undergoing ^{13}N-ammonia PET MPI for evaluation of CAD. In our sex-stratified analysis, a blunted HRR was selected as a significant predictor of 10-year MACE in women, but not in men, thereby outperforming traditional risk factors and imaging findings. Given the relatively worse outcomes of women with CAD, taking into account hemodynamic variables routinely obtained during adenosine stress testing may help to identify female patients at increased risk that should undergo further testing.

The prognostic importance of hemodynamic responses to coronary vasodilator stress has previously been demonstrated in sex aggregated populations. Consistent with our observation, Hage et al. found that HRR to regadenoson in the lowest quartile independently predicted mortality after 22 months of follow-up in patients undergoing SPECT-MPI [18]. Similarly, Abidov et al. reported an increased risk of cardiac death in patients >55 years with a low peak/rest HR ratio during adenosine infusion, while Batheja et al. observed higher rates of death in patients with normal SPECT-MPI scan and a low peak/rest HR ratio during dipyridamole stress [19, 20]. To date, only one study has reported data derived from a female-only population. These authors, however, did not detect any association between chronotropic responses to adenosine and cardiovascular outcomes during 2 years of follow-up in women undergoing SPECT-MPI [21]. As HR responses to vasodilator stress have been shown to be influenced by timing of HR recording, age, and comorbidities, different study populations and inclusion criteria might have accounted for the conflicting findings between this previous report and our study. Indeed, as we have recently shown that young women with myocardial ischemia show a stronger HR increase during adenosine infusion as compared to other demographic groups, age of the study cohort might be an important confounding factor which has to be considered when interpreting these data [22]. Finally, consensus is currently lacking regarding the time point of HR recording during adenosine infusion which is mirrored by a wide variety of reported HRR values [18, 20, 23–25]. Indeed, while most studies do not provide methodological information regarding baseline and peak HR measurements, some studies calculated HRR from the maximum HR observed during vasodilator infusion [18, 25] or after completion of adenosine infusion [20]. In contrast, in the present study, peak HR was recorded 3 min after the start of adenosine infusion. This choice was made because a fixed time point does not neutralize time-dependent phenomena such as later or earlier peaking of HR

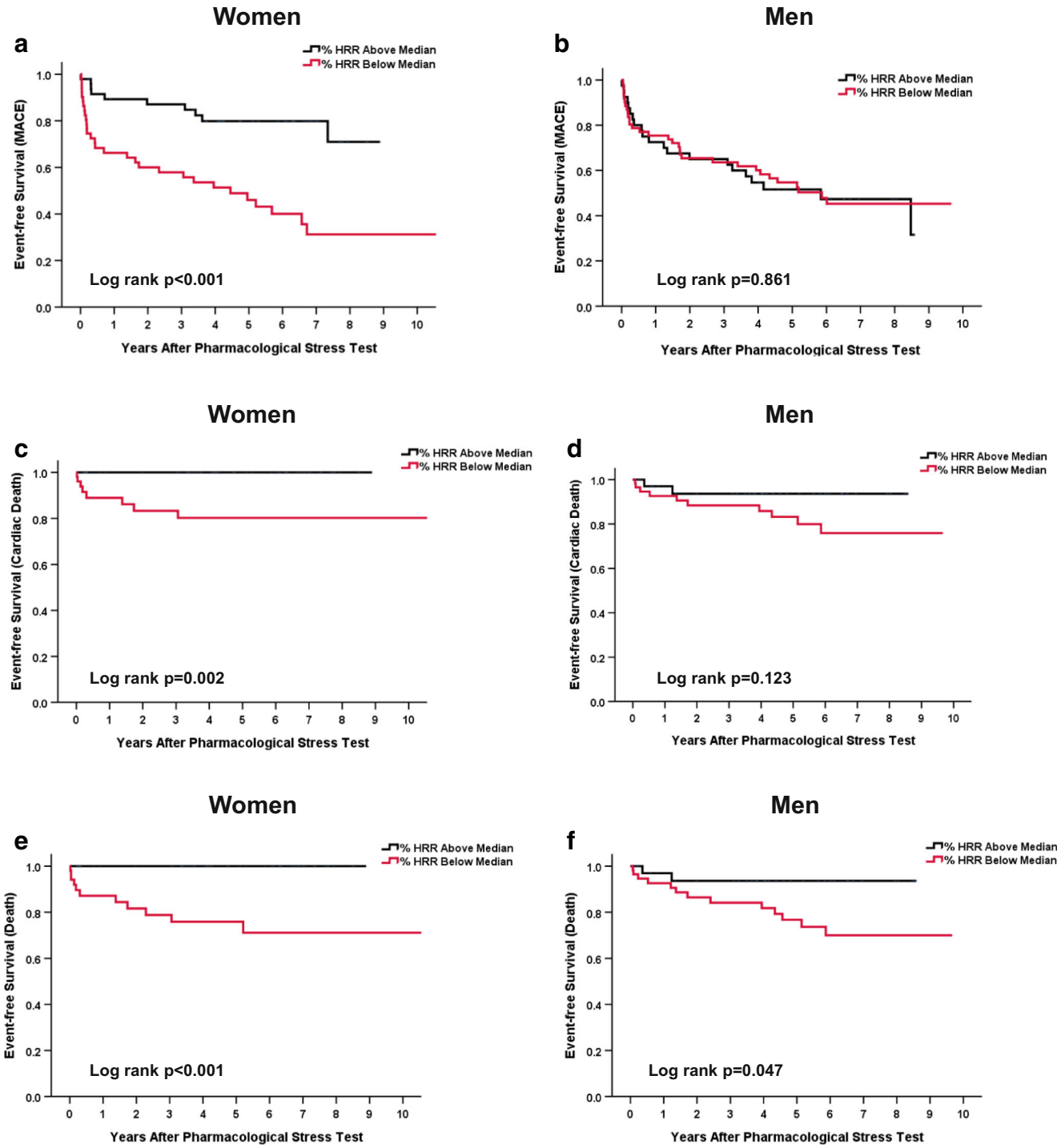

Fig. 2 Kaplan-Meier survival curves (unadjusted) in women (*left*) and men (*right*) for the occurrence of major adverse cardiac events (MACE) (**a, b**), cardiac death (**c, d**), and all-cause mortality (**e, f**) in patients with reduced (below median) versus higher (above median) heart rate reserve (HRR). Log rank *p* values are reported

depending on baseline sympathetic tone and allows for standardization of measurements in clinical routine.

The differential results in women and men in our study add to our knowledge of a sexual dimorphism in cardiac sympathetic control. Indeed, in line with previous reports, we observed a higher baseline HR and HRR to adenosine in women as compared to men [18, 20, 23, 26]. Previous work suggests that hemodynamic responses to adenosine depend on baseline autonomic tone; thus, a blunted HRR to vasodilator stress might be indicative of autonomic dysregulation [18, 20, 27]. A potential key role of the sympathetic nervous system in determining outcomes in

Table 3 Predictors of major adverse cardiovascular events (MACE) at univariate Cox regression analysis in women and men

Univariate analysis	Women (N = 101)			Men (N = 101)		
Independent variables	HR	95% CI	p value	HR	95% CI	p value
Age	1.04	1.00–1.07	0.01	1.02	0.99–1.04	0.16
BMI	1.03	0.97–1.10	0.33	1.07	0.99–1.16	0.074
Abnormal MPI	4.12	1.83–3.50	0.001	3.47	1.56–7.69	0.002
LVEF	0.97	0.95–0.99	0.003	0.98	0.97–1.00	0.047
Reduced HRR	2.75	1.42–5.35	0.003	1.59	0.93–2.70	0.13
Hypertension	1.62	0.83–1.67	0.16	1.06	0.6–1.87	0.84
Diabetes	2.35	1.17–4.71	0.016	1.02	0.52–2.03	0.95
Dyslipidemia	1.11	0.59–2.08	0.75	1.48	0.85–2.58	0.17
Smoking	1.62	0.88–2.99	0.12	1.96	1.1–3.33	0.013

BMI body mass index, *MPI* myocardial perfusion imaging, *LVEF* left ventricular ejection fraction, *HRR* heart rate reserve, *HR* hazard ratio, *CI* confidence interval

patients with CAD is further supported by an earlier report demonstrating an increased mortality in individuals with high sympathetic activity following a myocardial infarction [12]. Along this line of reasoning, the strong predictive value of HRR for MACE and mortality in our female study population agrees with the concept that women are disproportionally vulnerable to the adverse effect of a high sympathetic outflow. Indeed, estrogen has been attributed an important role in modulating autonomous nervous system activity [28–30], and pathologies associated with increased sympathetic activity such as stress-induced cardiomyopathy (Takotsubo syndrome) or CMVD are highly prevalent in women [11, 31]. The latter is not a benign condition, as women with CMVD encounter a three times higher risk of adverse cardiovascular events than men [3, 32]. Notably, consistent with earlier reports [33, 34], we observed in our study a significant and positive correlation between HRR and CFR. This correlation was present in women but not in men, suggesting that taking into account HR responses during stress test may not only help to identify women with an increased risk for MACE, but might also risk stratify the heterogeneous population of patients with non-obstructive CAD. Finally, although our study cohort comprised mainly postmenopausal women thereby limiting its generalizability to younger cohorts, a recent study suggests that high sympathetic outflow might be a powerful risk marker in young women [35]. These authors reported a reduced HR variability (HRV) in sedentary young women (mean age 23 years) which, in turn, adversely impacted their quality of life. While these data reinforce the potential role of variables reflecting autonomous activity as early marker of cardiovascular risk, larger-scale investigations across different age- and risk-groups will have to delineate the prognostic significance and underlying mechanisms of these findings.

As with any study, certain design limitations are inherent. First, this study is a single-center retrospective analysis conducted in a cohort of aged individuals with high prevalence of CAD, which limits its generalizability. Also, it is known that patients who undergo pharmacological stress testing are older and have more comorbidities and perfusion defects than patients undergoing exercise stress testing [36]. Thus, our results may not be applicable

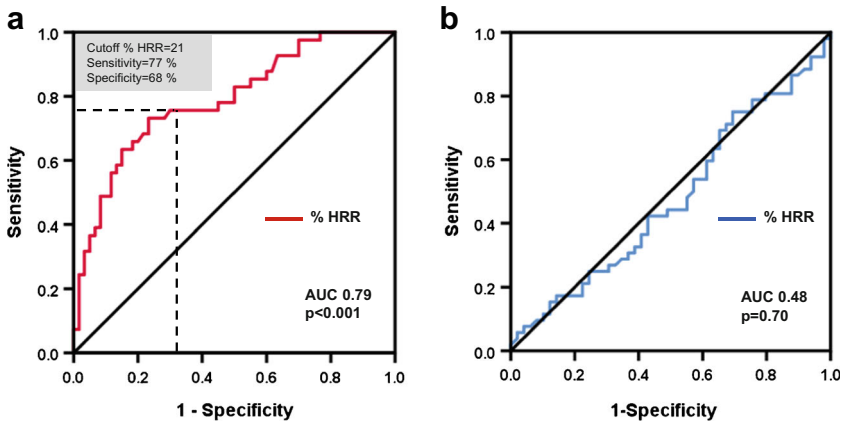

Fig. 3 Receiver operating characteristics (ROC) curves for the occurrence of major adverse cardiovascular events (MACE) in women (**a**) and men (**b**). Area under the ROC curve (AUC) and *p* value for heart rate reserve (HRR) following pharmacological stress with adenosine are reported

Table 4 Predictors of major adverse cardiovascular events (MACE) at multivariate logistic regression analysis in women (A) and men (B)

Independent variables	HR	95% CI	*p* value
Women: Stepwise Cox regression model for 10-year MACE (N = 101)			
Model 1:			
Reduced HRR	3.07	1.57–6.02	0.001
Model 2:			
Reduced HRR	2.59	1.32–5.11	0.006
Abnormal MPI	3.18	1.39–7.28	0.006
Model 3:			
Reduced HRR	2.41	1.23–4.75	0.011
Abnormal MPI	2.87	1.25–6.6	0.013
Age	1.04	1.00–1.07	0.037
Men: Stepwise Cox regression model for 10-year MACE (N = 101)			
Model 1:			
Abnormal MPI	4.55	1.92–10.80	0.001

Stepwise method was performed among heart rate reserve (HRR, dichotomous variable), age, body mass index (BMI), abnormal myocardial perfusion scan, and cardiovascular risk factors including smoking status, hypertension, diabetes, and dyslipidemia

Only variables staying in the model are presented

MPI myocardial perfusion imaging, *HR* hazard ratio, *CI* confidence interval

to a broader population. Second, although a comprehensive group of adjustment variables was employed, unmeasured factors such as sex hormone levels, hormone use, menopausal status or socio-economic factors may have affected the results. Also, unmeasured variables not incorporated into the propensity-matched models may have affected the results. Third, although patients were asked to omit their regular medication, in particular β-blockers, 24 h prior to ^{13}N-ammonia PET, we cannot completely rule out an effect of individual treatment regimens on our study endpoints. Nevertheless, previous studies have demonstrated that β-blocker treatment does not interfere with the expected HR increment during adenosine infusion [22, 27]. Finally, we did not normalize rest MBF to rate pressure product (RPP), a measure that may reduce variability within and between individuals [17]. However, previous work has demonstrated that sex differences in baseline MBF persisted after correction for RPP indicating that other variables account for the higher baseline MBF observed in women [37].

In summary, our study demonstrates that HR responses to vasodilator stress carry important long-term prognostic information in women and highlights the importance of cardiac autonomic modulation as a marker of cardiovascular risk. Recording and taking into account HRR in clinical routine may help to improve diagnostic uncertainty in the female population by identifying patients at increased risk that should undergo further testing. Further research in larger cohorts is warranted to assess whether our findings are replicable across different imaging modalities and younger age groups with low prevalence of CAD.

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Compliance with ethical standards

Conflict of interest All authors have the following to disclose: The University Hospital of Zurich holds a research contract with GE Healthcare. CG has received research grants from the Novartis Foundation, Switzerland.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The study was approved by the local ethics committee (BASEC No. 2017–01112). The need for informed written consent was waived by the ethics committee.

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