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Coronary artery microvascular dysfunction: Role of sex and arterial load☆·☆☆

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ABSTRACT

Background: The prognosis of cardiovascular disease is worse in women than men, and coronary microvascular dysfunction explains the excess cardiovascular risk in women. In addition, age-related increases in pulsatile arterial load are greater in women than men; and lower arterial compliance has been shown to independently predict cardiovascular events. However, whether arterial load differentially affects the coronary microvasculature in men and women remains unknown. We hypothesized that lower arterial compliance would be associated with coronary artery microvascular dysfunction in women.
Methods and results: 285 subjects (60% women, age: 61.2 ± 11.0 yrs) undergoing cardiac ^{82}Rb positron-emission tomography between 2010 and 2013, with ejection fraction ≥50%, no heart failure, dyspnea, coronary artery disease or regional perfusion defects were included. Left ventricular microvascular function was assessed by myocardial flow reserve (MFR). Pulsatile arterial load was estimated by indexed arterial compliance [ACi: (stroke volume/pulse pressure)/BSA]. Multivariable linear regression evaluated associations of arterial compliance with myocardial flow reserve after adjustment for confounders. ACi was lower in women than men [0.39 ± 0.15 *vs.* 0.52 ± 0.28 (mL/mm Hg)/m^2, $P < 0.0001$]. We found that the effect of ACi on MFR differs by sex: lower ACi was associated with lower MFR in women (β ± SE: 0.20 ± 0.07, $P = 0.004$) but not in men (0.03 ± 0.11, $P = 0.75$).
Conclusions: Lower ACi was associated with altered coronary microvascular function in women, but not in men. Our findings highlight low arterial compliance as a potential link between hypertension, coronary microvascular dysfunction and adverse cardiovascular events in women.

1. Introduction

Coronary microvascular dysfunction is a robust predictor of adverse cardiovascular events, [1–4] and is more prevalent in women than men [5]. One of the proposed mechanisms for this sex difference is the fact that women have smaller coronary arteries [6] with higher blood flow than men. This leads to greater endothelial shear stress, which has detrimental effects on coronary anatomy and function [8]. Another important determinant of microvascular dysfunction in women is hypertension, [9] leading to vascular remodeling of intramural arterioles and interstitial fibrosis, which in turn causes a decrease in microvascular density [10].

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One of the proposed mechanisms linking hypertension to microvascular disease is mediated by decreased arterial compliance: lower arterial compliance leads to higher pulsatile arterial load, which increases pulse pressure [11] and contributes to isolated systolic hypertension [12]. Isolated systolic hypertension, in turn, has a more profound contribution to impairment of coronary microvascular function than combined systolic/diastolic hypertension [13]. This mechanism is particularly relevant in women, since age-related increases in pulsatile arterial load are greater in women than men, [14] explaining the higher prevalence of isolated systolic hypertension in elderly women [15]. As a result, it is possible that lower arterial compliance and greater pulsatile arterial load in older women may help explain sex differences in coronary microvascular dysfunction and cardiovascular outcomes. Thus, we hypothesized that lower arterial compliance would be independently associated with worse coronary microvascular function in women but not in men. To this end, we sought to evaluate potential sex differences in associations of arterial load with coronary microvascular dysfunction in a sample consisting of middle-age to elderly adults with high prevalence of hypertension.

2. Methods

The study was approved by the University of Ottawa Heart Institute's Research Ethics Board and conducted according to Institutional guidelines. Participants gave informed consent. This was a retrospective analysis using ^{82}Rb positron emission tomography (PET) imaging data from the University of Ottawa Heart Institute. Our goal was to evaluate subjects without heart failure, epicardial coronary artery disease or dyspnea (as a potential sign of heart failure) in order to identify early alterations in coronary microvascular function. Thus, we considered individuals referred for cardiac ^{82}Rb PET myocardial perfusion imaging at the University of Ottawa Heart Institute between 2010 and 2013 who had a summed stress score < 4 (suggesting low likelihood of obstructive epicardial coronary artery disease) and left ventricular ejection fraction ≥50% (n = 1319). We then excluded 900 who had a history of dyspnea, 92 with heart transplant, 21 with known coronary artery disease (CAD), 21 with heart failure, leaving 285 participant for analyses. Complete data were available for all participants.

2.1. Vital signs, anthropometric measures and comorbidities

Weight (in kg) was measured on the day of the imaging study by an electronic scale, height (in meters) by a stadiometer, and body mass index was calculated in units of kg/m^2. Body surface area (BSA) was calculated using the Gehan method [16]. Resting blood pressure and heart rate were measured while participants were lying quietly on the exam table, before the imaging test commenced. Mean arterial pressure (MAP) was calculated as 2/3 of diastolic blood pressure + 1/3 of systolic blood pressure. Pulse pressure (PP) was calculated as systolic – diastolic blood pressure. Hypertension was defined as a previous diagnosis of hypertension and/or current treatment with medications for hypertension. Diabetes was defined as a diagnosis of diabetes mellitus and/or treatment with insulin or oral hypoglycemic agents. Dyslipidemia was defined as a previous diagnosis of dyslipidemia made by a health care provider. Smoking was defined as previous or current history of tobacco use.

2.2. Assessment of coronary artery microvascular function

Coronary artery microvascular function was assessed by ^{82}Rb PET using a 3-dimensional PET system (Discovery Rx/VCT, GE Healthcare, Milwaukee, WI), which was used to quantify myocardial flow reserve (MFR) as described. [17] MFR is a validated measure predictive of cardiovascular events [4], representing the relative vasodilatory reserve of the coronary circulation and expressed as the ratio of myocardial blood flow (MBF) during maximal coronary vasodilation to resting MBF. In the absence of obstructive epicardial CAD, varying MFR represents changes in coronary microvascular function.

Subjects refrained from caffeine and anti-anginal medications before the study. A low-dose computed tomography scan was acquired for attenuation correction, followed by a 10 MBq/kg intravenous injection of ^{82}Rb using a custom elution system. This was followed by an 8-minute PET scan with a parallel list-mode acquisition. After the rest study, dypiridamole was injected at 0.14 mg/kg/min for 5 min to induce vasodilator stress. ^{82}Rb was again administered 3 min after completion of dypiridamole infusion, and stress PET images were acquired. Review of the PET image alignment for attenuation correction was performed manually for each study using the vendor ACQC Software. Dynamic (9 × 10 s, 3 × 30 s, 1 × 60 s, 2 × 120 s), static (2–8 min), and gated (1.5–8 min) images were reconstructed using the vendor ordered subset expectation maximization (OSEM) iterative reconstruction software (VuePoint HD) with 8, 12, and 16-mm Hann 3D post-filtering, respectively.

Expert readers performed semi-quantitative perfusion analysis using a 17-segment (5 point) model and the SSS and summed rest score were calculated. Gated images using Corridor 4DM-PET software (INVIA, Ann Arbor, MI) were used to estimate left ventricular end-diastolic and end-systolic volumes, and stroke volume was calculated as their difference. For absolute quantification of MBF, automated software (FlowQuant, Ottawa, ON) was used to reorient images, extract mean myocardial and left ventricular (LV) cavity time–activity curves and to calculate absolute MBF at rest and peak stress. MFR was then calculated as the ratio of the stress to rest MBF.

2.3. Assessment of arterial load

Blood pressure was measured on the day of the PET study, after withholding anti-anginal drugs and before vasodilator administration. Arterial load is separated into steady (systemic vascular resistance) and pulsatile (arterial compliance) components. Systemic vascular resistance was estimated as (MAP * 80) / cardiac output. The stroke volume/PP ratio correlates well with invasively measured arterial compliance ($r = 0.98$, $P < 0.0001$) [18] and is independently associated with CV events and mortality [19]; thus it was used as a measure of arterial compliance. Given peripheral PP amplification, we estimated central PP as: central PP = brachial PP * 0.49 + age * 0.30 + 7.11, [20] and re-calculated arterial compliance using central rather than brachial PP for comparative purposes. We indexed arterial load to body surface area (BSA) by dividing arterial compliance by BSA (ACi) and multiplying systemic vascular resistance by BSA (SVRi). This linear indexation is justified because these measures have been shown to have approximately linear relationships to BSA [21].

2.4. Assessment of left ventricular structure and diastolic function

A transthoracic echocardiogram was available within 6 months of the PET study in 74 participants. This was used to quantify left ventricular mass, left atrial volume (area-length method) and diastolic function parameters (mitral inflow E/A ratio, myocardial annular velocities and E/e′ ratio as an estimate of filling pressures) as per guidelines [22].

2.5. Statistical analyses

Continuous variables were reported as mean ± standard deviation (SD). Differences between sexes were compared with a *t*-test. Categorical variables were reported as number and percentage, and differences between sexes were assessed with chi-square test.

To determine associations of SVRi and ACi with MFR, we performed multivariable linear regression including: age, sex, heart rate, MAP, serum creatinine, history of hypertension, diabetes, dyslipidemia and smoking, and use of aspirin, statins and anti-hypertensives. "*Low MFR*" was defined as MFR ≤ 2.0, [2] Using "*Low MFR*" as the dependent variable, we performed multivariable logistic regression analyses using the above covariates. In all multivariable analyses, covariates univariately associated with the dependent variable at $P \leq 0.20$ were included in the final models. Further, to ensure that logistic regression models were not overfitted (due to the small number of people with *Low MFR*), we also performed multivariable logistic regression models using a stepwise approach with backward elimination, using criteria of $P < 0.25$ to enter, and $P < 0.10$ to stay in the model.

In addition, to determine whether sex modified the associations of ACi and SVRi with MFR, we tested interaction terms sex*ACi and sex*SVRi in the prediction of MFR. If significant, we repeated regression models while stratifying by sex. All analyses were performed using JMP *vs.* 11.2. (SAS Institute Inc., Cary, NC). A 2-tailed *P*-value ≤ 0.05 was considered statistically significant.

3. Results

A summary of participant characteristics is presented in Table 1. SVRi was higher and ACi was lower in women than men, confirming greater steady and pulsatile arterial load in women. There was no difference between ACi calculated using brachial (0.44 ± 0.22 mL/mm Hg) or central (0.44 ± 0.19 mL/mm Hg) PP, thus the former was used in all analyses. Participant characteristics based on sex and hypertension status, and based on indication for PET are shown in Supplementary Tables S1 and S2, respectively.

In the whole group, univariate predictors of lower MFR and "*Low MFR*" at $P \leq 0.20$ are depicted in Table 2 and Supplementary Table S3, respectively. In multivariable models adjusted for these covariates, lower ACi and SVRi remained independently associated with lower MFR (Table 3) and "*Low MFR*" (Supplementary Table S4).

Interaction term sex*ACi was significant ($P = 0.05$) in the prediction of MFR, but sex*SVRi was not ($P = 0.54$). Thus, we repeated ACi models after stratifying by sex. Supplementary Fig. S1 depicts associations of tertiles of ACi with MFR in men and women. In unadjusted linear regression, lower ACi was associated with lower MFR in women but not in men (Fig. 1), which persisted after multivariable adjustment (β ± SE for 1SD increase in ACi: 0.20 ± 0.07, $P = 0.004$ in women;

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