Gender-Specific Differences in Myocardial Deformation and Aortic Stiffness at Rest and Dobutamine Stress

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Abstract—Elderly women have increased aortic and ventricular stiffness but preserved global systolic function. Possible gender differences in ventricular deformation attributed to increased aortic stiffness at rest or with positive inotropic stress remain unknown. Eighty-four subjects (mean age: 63±8 years) were assessed for aortic stiffness by pulse wave velocity and ventricular deformation at rest and during dobutamine stress using magnetic resonance. At rest, women (n=40) had greater aortic stiffness and ventricular deformation than men (P<0.05). In men, dobutamine increased longitudinal (mean±SD: 3.3±4.1%; P<0.01) and circumferential deformation (2.9±5.1%; P=0.007), whereas women showed an increase in circumferential deformation only (4.8±6.3%; P<0.01). In men there was an inverse association between longitudinal deformation and pulse wave velocity at rest (r=-0.51; P=0.002) and linear at stress (r=0.52; P=0.001). In women there were no significant relations at rest, whereas at stress longitudinal deformation was inversely associated with pulse wave velocity (r=-0.43; P=0.02). We demonstrate gender-specific differences in the relationship between aortic stiffness and ventricular deformation at rest and during dobutamine stress. Although at rest longitudinal deformation is inversely related to aortic stiffness in men, there is no such relationship in women. At stress, men improve longitudinal function, whereas in women such response is limited. (Hypertension. 2012;59:712-718.) ● Online Data Supplement

Key Words: aortic stiffness • pulse wave velocity • myocardial deformation • gender differences • dobutamine stress • cardiac imaging • cardiac physiology and function

Aging influences the structural and functional properties of the arterial and ventricular system: the central arteries dilate, and their walls become thicker and stiffer, adding onto the cardiac workload. Elderly women appear to be particularly affected when compared with their male counterparts, even in the absence of cardiovascular (CV) disease and despite commonly preserved markers of global systolic function.

Aortic stiffness, assessed by the pulse wave velocity (PWV), is a marker of the pulsatile component of arterial afterload. Increased aortic stiffness contributes to increased left ventricular (LV) stiffness, dysfunction, and remodeling. Experimental and clinical models suggest that longitudinal myocardial deformation is impaired early because of increased afterload, even when the global systolic function remains unaffected. To date, no study examined how increased aortic stiffness relates to longitudinal myocardial systolic function or whether there are gender differences in myocardial deformation because of increased aortic stiffness. It is unclear how aortic stiffness and myocardial deformation react to acute alteration of systolic performance, such as with positive inotropic stress, and whether these reactions are gender specific. We investigated gender-related differences of LV deformation and aortic stiffness at rest and dobutamine stress.

Methods

Eighty-four subjects who presented consecutively through a clinical referral for a high-dose dobutamine stress magnetic resonance (DSMR) study were included. Usual contraindications to DSMR (noncompatible metallic implants or claustrophobia, acute coronary syndrome, severe hypertension, significant aortic stenosis, inflammatory heart disease, and pregnancy), or the presence of arrhythmia precluding accurate scanner triggering, were the criteria of exclusion. In addition, significant coronary artery disease was excluded by virtue of the following: (1) negative history of previous coronary events; (2) a negative high-dose DSMR study; (3) absence of myocardial late gadolinium enhancement; and (4) New York Heart Association class ≤II to III. Patients were instructed to refrain from β-blockers or nitrates for 24 hours before the study. Patient

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characteristics were recorded for all of the subjects, including age, gender, body mass index, and history of hypertension, smoking, diabetes mellitus, dyslipidemia, and cardiac medication. Procedures were carried out in accordance with the Declaration of Helsinki (2000). The study was reviewed and approved by the institution’s ethics committee (Charité University, School of Medicine, Berlin). All of the participants provided written informed consent. All of the procedures followed were in accordance with institutional and national guidelines of practice.

Dobutamine Stress MRI
The high-dose DSMR protocol (plus atropine ≤2 mg if needed to reach the target heart rate [HR], defined as the age-predicted submaximal HR [(220–age)*0.85]) was described previously in detail. In brief, imaging studies were performed with the patient supine using a 1.5-T scanner (Philips Achieva, Best, the Netherlands), and a 5-element cardiac synergy coil was used for signal reception, with continuous monitoring of blood pressure (BP), cardiac rhythm, and symptoms. After patient-specific planning, volumetric cavity assessment was obtained by whole-heart coverage of gapless short-axis (SA) sections. Thereafter, cine-images of 3 SA views and 3 long-axis views (4-chamber, 2-chamber, and 3-chamber views) were acquired at every stage of the DSMR study. The 3 SA cine views were distributed to cover the heart at the basal, equatorial, and apical positions by adjusting the gap between the sections (25%, 50%, and 75% of the end-systolic longitudinal axis length of the LV). Velocity encoded images were performed for flow measurements through the midascending and middescending aortas at the level of the pulmonary artery bifurcation (Figure 1). For calculation of the path traveled by the pulse wave, 3 overlapping parallel black-blood images, meticulously planned to cover the aortic arch, were acquired before the start of dobutamine infusion. For cine-images at rest and stress, a balanced steady-state free precession sequence in combination with parallel imaging (sensitivity encoding, factor 2) and retrospective gating was used during an end-expiratory breath hold (repetition time/echo time/flip angle: 3.4 ms/1.7 ms/60°; spatial resolution: 1.8 mm×1.8 mm×8.0 mm; number of reconstructed phases: 50 to 60 per cardiac cycle). The velocity-encoded image flow measurements were acquired during shallow free breathing, using a retrospectively gated gradient echo pulse sequence (repetition time/echo time/flip angle: 3.7 ms/2.2 ms/15°; spatial resolution: 1.6 mm×1.4 mm×10.0 mm; velocity encoding: 200 cm/s at rest and 400 cm/s at peak stress). Sagittal oblique views of the aortic arch were acquired using a black-blood proton density turbo-spin echo sequence (repetition time/echo time: 2–3 heart beats/27 ms; spatial resolution: 1.2 mm×1.4 mm×6.0 mm).

Data Analysis
Analysis of LV function was performed using commercially available software (ViewForum, version 5.1, Philips Healthcare). Endocardial LV borders were manually traced at end diastole and end systole. The papillary muscles were included as part of the LV cavity volume. LV end-diastolic (EDV) and end-systolic (ESV) volumes...
were determined using the Simpson rule. Ejection fraction (EF) was computed as follows: EDV−ESV/EDV. Indices were normalized to body surface area (BSA=\text{[weight (in kilograms) \times 0.425\times\text{height (in meters) \times 0.725}]}) or body surface area (BSA=\text{[weight (in kilograms) \times 0.425\times\text{height (in meters) \times 0.725}]}) as appropriate. HR pressure product (HR\times BP) was computed as the HR\times systolic BP. Mean arterial pressure (MAP) was calculated as sum of diastolic BP and 0.4\times pulse pressure (PP), where PP is a difference between systolic and diastolic BPs. We examined the differential changes in systemic vascular resistance between genders as MAP/cardiac output, assuming a nominal right atrial pressure in this population. Analysis of myocardial deformation, a direct quantitative assessment of cardiac performance by measurement of myocardial thickening and shortening, was performed by tracing the contours within the myocardium in the cine images, using feature-tracking prototype software (TomTec GmbH, Munich, Germany), as described previously and validated (Figure 2). 

Radial and circumferential myocardial deformation was obtained in 3 SA sections for 16 standard segments. Longitudinal deformation was obtained in 3 long-axis views. Deformation is expressed as the average total peak-systolic strain per measured direction. The vascular contours were automatically traced for all phases of the cardiac cycle on both the modulus images of the phase contrast acquisition for flow analysis and on the cine images for aortic diameter/area analysis. PWV was calculated by dividing the length of the aorta between the locations used for ascending and descending aortic flow measurements with the time difference between the arrival of the pulse wave at these locations at rest and stress. Transit time was defined as the temporal shift of the wave “foot” and required the location of both the local velocity minima at end diastole and the highest blood acceleration during the systolic “upslope.” The “feet” were realized at the intersections of constant velocity projections from the local minima and tangential projections from the highest blood accelerations. The velocity signal processing was made using an in-house MATLAB-based program. Total arterial compliance (TAC) was calculated as a ratio between the stroke volume and PP, total arterial elastance as the ratio between (end-)systolic BP and stroke volume, and aortic distensibility (AD) as a relative change in vessel area between systole and diastole divided by PP.

**Statistical Analysis**
For power calculations, we estimated that a sample size of 31 was needed to achieve >90% power to detect continuous associations with a coefficient of determination \( R^2 \geq 0.20 \), using a 2-sided hypothesis test with a significance level of 0.05. Statistical comparisons were performed using paired (within-group) or unpaired (between-group) Student t tests or \( \chi^2 \) tests, as appropriate. Associations between vascular and ventricular measures were explored using single and multivariate linear regressions with stepwise selection of predictive variables (age, HR, BP, deformation, stroke volume, and cardiac output). Univariate ANOVA was used to control for traditional CV risk profile (age, hypertension, diabetes mellitus, dyslipidemia, smoking, family history, and LV mass index) and cardiac medication. All of the tests were 2 tailed, and a \( P \) value of <0.05 was considered significant.

**Results**

**Patient Characteristics**
Men and women were similar for body mass index, age, traditional CV risk factors, and cardiac medication (Table 1). As expected, BSA was significantly greater in men (\( P<0.001 \)). Only 13% of women reported previous hormone replacement therapy. In both groups, cavity volumes and global systolic function were within normal range and similar when corrected for BSA.

**Hemodynamic Variables at Rest and Stress**
Both genders had similar HR-BP products at rest and stress (Table 2). Women had greater resting HR than men (men versus
women: 69±12 versus 75±12 bpm; P=0.002), whereas at stress there was no gender difference (142±8 versus 139±10 bpm; P=0.11). Men had greater resting diastolic BP than women (78.6±18.0 versus 69.3±12.1 mm Hg; P=0.008) and a significant rise in diastolic BP with stress (mean difference±SD: men: 7.8±19.0 mm Hg; P=0.02; women: 3.0±14.1 mm Hg, P=0.21). Cardiac index was higher in women at rest (P=0.004) and stress (P=0.08).

Vascular Measures at Rest and Stress
Resting PWV was greater in women (P=0.05; Table 2). PWV rose significantly in men with stress (P=0.02). In women, PWV at stress was not statistically different from baseline (P=0.21). Ascending AD was similar at rest and stress for both genders, whereas descending AD was greater in men (P=0.01). In men, descending AD decreased with stress (P=0.11). In women, resting PP is higher than in men (P=0.003), whereas there was no gender difference in MAP (P=0.87). Conversely, at stress MAP was significantly greater in women than men (MAP: P=0.05). Changes in systemic vascular resistance, TAC, and total arterial elastance are reported in Table 2.

LV Deformation at Rest and Stress
At rest, women had greater longitudinal, radial, and circumferential deformation than men (P<0.05). In men, dobutamine increased longitudinal and circumferential deformation (longitudinal: 3.3±4.1%, P<0.001; circumferential: 2.9±5.1%, P=0.007), whereas women showed an increase in circumferential deformation only (4.8±6.3%; P<0.001).

Analysis of Relationships
In a nongender-specific analysis, PWV showed significant associations with vascular measures at rest (ascending AD: r=0.39, P=0.02; total arterial elastance: r=0.51, P=0.02; TAC, r=−0.31, P=0.05) and stress (TAC: r=−0.37, P=0.04; total arterial elastance: r=0.47, P=0.03). Results of gender-specific analysis between vascular and ventricular variables are presented in Figure 3 and Table S1 in the online-only Data Supplement. At rest, men showed a negative relationship between PWV and longitudinal deformation (r=−0.5; P=0.002). Women revealed no such associations at rest. At stress, PWV in men correlated linearly with longitudinal function (r=0.52; P=0.001), whereas, in women, longitudinal and circumferential deformations were inversely associated with PWV (longitudinal: r=−0.43; circumferential: r=−0.38; P<0.05 for both).

Multivariate linear regression analysis identified longitudinal deformation as the independent predictive variable of PWV at rest (R²=0.31; F=11; B=−0.42; P=0.001), whereas in women no variable was predictive of resting PWV. At maximal stress, longitudinal function was predictive for both genders in opposing directions, positive for men (R²=0.35; F=17.1; B=0.59; P<0.01) and negative for women (R²=0.29; F=10; B=−0.45; P=0.006). These associations between vascular and ventricular measures of defor-
mation were maintained even when accounted for age, CV risk profile, or hemodynamic parameters, including stroke volume, cardiac index, MAP, and PP.

**Discussion**

By examining vascular and ventricular deformation under resting conditions and during dobutamine stress, our findings characterize for the first time that interdependence of longitudinal myocardial function and vascular stiffness differs by gender. Whereas in men resting longitudinal deformation is directly related to aortic stiffness, there is no such relationship in women. At stress, men improve longitudinal function independent of aortic stiffness, whereas in women such response is limited.

The proximal arterial circulation acts as a central elastic reservoir, which deforms to receive the ejected stroke volume during systole and promotes onward movement to peripheries by diastolic recoil. A ventricle coupled to a stiffer vascular system deals with increased afterload, resulting in higher systolic ventricular wall stress and prolongation of systolic ejection, which, in turn, delays the onset and reduces the speed of diastolic relaxation. Previous studies on gender differences speculated on these associations primarily via increased ventricular thickness and stiffness in women. However, systematic studies on systolic ventricular mechanisms to offset an increased afterload are missing. By testing contractile responses at stress with positive inotropic stimulation, our data suggest that men have the ability to differentially load the aortic reservoir by significant increase in longitudinal (and circumferential) contraction, independent of aortic stiffness, whereas in women such response is limited. Although the observed responses may be associated with gender differences in vascular properties, they may also relate to the different ability of men and women to recruit longitudinal contraction at stress. The capacity of the aortic wall to stretch and accommodate the ejected stroke volume is primarily defined by its elastic properties. A previous study suggested that, in young subjects, PWV is, at least in part, also determined by ventricular systolic performance. The cause of gender-related differences in myocardial responses is unclear and, since only evident later in life, unlikely fully accounted for by the differences in body size or vascular

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**Figure 3.** A linear regression plot shows a differential relationship between pulse wave velocity (PWV) and longitudinal deformation in men and women at rest (A) and positive inotropic stress (B).
length.\textsuperscript{3,24,25} Potentially, these observations may be also explained by a reduced pharmacological response to dobutamine in women. Commonly observed attenuation of adrenergic responses in women is attributed to the differences in distribution and coupling of adrenergic receptors, sensitivity to gender hormones, and changes with aging.\textsuperscript{26} Together with apparent structural predisposition to increased vascular stiffening, women appear subjected to a greater cumulative load and accelerated structural myocardial remodeling, which distinctively harms longitudinal performance.\textsuperscript{10,13} Our cohort of elderly subjects with normal global cardiac function shows relatively lower values in resting longitudinal deformation for both genders, potentially reflecting a long-standing accommodation to higher afterload.\textsuperscript{10–13} Compared with longitudinal function, women also show high resting values of radial and circumferential strains, which may account for previous observations that, in women, global systolic function is often preserved or fractional shortening even increased.\textsuperscript{2,3}

Aging acts as an important determinant of arterial remodeling, leading to a higher stiffness of the large arteries in women, even in the absence of vascular disease or risk factors.\textsuperscript{3,18,25} A substantial body of literature relates to the pursuit of measures that reliably detect alterations of vascular function over lifetime.\textsuperscript{27} In subjects >50 years of age, Redheuil et al\textsuperscript{18} distinguished the MRI-derived aortic arch PWV as the most sensitive measure of vascular aging, whereas in younger populations central AD is the most sensitive parameter of arterial remodeling. Vascular measures in the present study cohort agree well with previously reported values in corresponding age groups.\textsuperscript{18,27,28} We further demonstrate that resting descending AD and TAC are distinctively lower in women and reveal much less change with stress. Our findings thus relate to a highly relevant population, where dynamic changes in vascular measures with inotropic stress have the ability to inform on the deformational capacity of the aortic reservoir.\textsuperscript{1,27,28}

Limitations
Our major limitation is the inability to measure central BP in the MRI environment and reliance on peripheral PP and thus, we potentially report overestimated PP values.\textsuperscript{19} Because we performed automated brachial BP measurement in real time during all stages of dobutamine stress, we were able to reliably register dynamic changes. Furthermore, although this is the first data set providing gender-specific insights into vascular and ventricular function at rest and positive inotropic stress, our observations are based on a relatively small sample of otherwise well-matched subjects. At this stage we are not able to discriminate between cause and effect or to provide more sophisticated data, such as augmentation index or parameters of diastolic function, because these are difficult to extract with current methodology. Lastly, although assessment of myocardial deformation in cine images improves temporal resolution, the clinical applicability of the feature-tracking postprocessing tool remains limited by its low reproducibility (please see the online-only Data Supplement).

Perspectives
We found that the relation between ventricular contraction and aortic stiffness at rest and during dobutamine stress differs by gender. Our study confirms that greater vascular afterload in women is not only associated with previously observed greater diastolic stiffness\textsuperscript{7,8} but also with impaired longitudinal systolic responses at rest and stress. Previous study revealed that such responses might differ by age\textsuperscript{11}; further gender-focused studies in different age groups are needed to characterize the observed interdependence of vascular stiffness and systolic function. Such cross-sectional phenotypic readouts may also improve understanding of the phenotypes that lead to heart failure with preserved systolic function and provide clues to timing of intervention to relent the CV aging.

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Disclosures
None.

References


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Gender Specific Differences in Myocardial Deformation and Aortic Stiffness at Rest and Dobutamine-stress

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Results
Reproducibility of post-processing tools at rest and stress
The interstudy agreement (resting studies) for deformational measures with feature tracking was $r=0.68$, $p=0.02$, and for time delay by PWV velocity tool $r=0.91$, $p=0.01$. Feature tracking in cine images at rest and stress revealed acceptable results for intra-/interobserver repeated measurements (rest: $r\sim0.61-0.72$, $r<0.01$, stress $r\sim0.59-0.68$, $p<0.05$), whereas PWV analysis tool provided reasonable agreements (rest $r=0.89-0.92$, $p<0.01$, stress $r=0.7-0.82$, $p<0.02$).
**Table S1.** Associations between vascular and ventricular measures at rest and positive inotropic stress, PWV – pulse wave velocity, AD – aortic distensibility (*p<0.05, †p<0.01).  

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