Arterial Stiffness and Wave Reflection
Sex Differences and Relationship With Left Ventricular Diastolic Function

Cesare Russo, Zhezhen Jin, Vittorio Palmieri, Shunichi Homma, Tatjana Rundek, Mitchell S.V. Elkind, Ralph L. Sacco, Marco R. Di Tullio

See Editorial Commentary, pp XX–XX

Abstract—Increased arterial stiffness and wave reflection have been reported in heart failure with normal ejection fraction (HFNEF) and in asymptomatic left ventricular (LV) diastolic dysfunction, a precursor of HFNEF. It is unclear whether women, who have higher frequency of HFNEF, are more vulnerable than men to the deleterious effects of arterial stiffness on LV diastolic function. We investigated, in a large community-based cohort, whether sex differences exist in the relationship among arterial stiffness, wave reflection, and LV diastolic function. Arterial stiffness and wave reflection were assessed in 983 participants from the Cardiovascular Abnormalities and Brain Lesions study using applanation tonometry. The central pulse pressure/stroke volume index, total arterial compliance, pulse pressure amplification, and augmentation index were used as parameters of arterial stiffness and wave reflection. LV diastolic function was evaluated by 2-dimensional echocardiography and tissue-Doppler imaging. Arterial stiffness and wave reflection were greater in women compared with men, independent of body size and heart rate (all P<0.01), and showed inverse relationships with parameters of diastolic function in both sexes. Further adjustment for cardiovascular risk factors attenuated these relationships; however, a higher central pulse pressure/stroke volume index predicted LV diastolic dysfunction in women (odds ratio, 1.54; 95% confidence intervals, 1.03 to 2.30) and men (odds ratio, 2.09; 95% confidence interval, 1.30 to 3.39), independent of other risk factors. In conclusion, in our community-based cohort study, higher arterial stiffness was associated with worse LV diastolic function in men and women. Women’s higher arterial stiffness, independent of body size, may contribute to their greater susceptibility to develop HFNEF. (Hypertension. 2012;60:00-00.) ● Online Data Supplement

Key Words: arterial stiffness ■ wave reflection ■ diastole ■ sex ■ echocardiography

Left ventricular (LV) diastolic dysfunction is an asymptomatic abnormality of the filling phase of the cardiac cycle, characterized by an impairment of myocardial relaxation and reduced compliance of the LV, which, in advanced stages, can cause an upward shift of the LV end-diastolic pressure-volume curve, resulting in increased LV filling pressures.1 LV diastolic dysfunction is associated with unfavorable outcome2,3 and is considered to be the main determinant of heart failure with normal ejection fraction (HFNEF), a clinical entity that may affect up to 50% of patients with heart failure.4,5 Several reports showed that, both in patients with isolated diastolic dysfunction and in those with HFNEF, an increase in arterial stiffness is present that is independent of age and other cardiovascular risk factors, suggesting a potential role of increased arterial stiffness in the pathophysiology of HFNEF.6–8

It is known that substantial differences in arterial stiffness exist between men and women, with greater arterial stiffness described in the women compared with age-matched men.9 Since increased arterial stiffness and wave reflection are independent predictors of cardiovascular events, including incident heart failure,10–12 and since patients with HFNEF are more frequently older women with hypertension,13–16 the relationship between arterial stiffness and LV diastolic dysfunction might be a factor in the known predisposition of women toward developing HFNEF17,18; however, whether sex differences exist in the relationship of arterial stiffness with diastolic dysfunction is debated, and the studies pub-
lished so far have shown conflicting results.\textsuperscript{19,21–23} Accordingly, the aims of the present study are: (1) to evaluate differences in arterial stiffness and wave reflection in men and women derived from a large community-based cohort; (2) to test for sex differences in the relationships of arterial stiffness and wave reflection with LV diastolic function; and (3) to evaluate the impact of LV structure and cardiovascular risk factors on these relationships.

Methods

Study Population
The Cardiovascular Abnormalities and Brain Lesions study is a community-based epidemiological study designed to investigate the cardiovascular predictors of subclinical cerebrovascular disease in the community. The study cohort was derived from the Northern Manhattan Study, a population-based prospective study evaluating the incidence, risk factors, and clinical outcome of stroke in the population of northern Manhattan. Study design and methodological details have been described previously.\textsuperscript{21} Briefly, the Northern Manhattan Study cohort consists of 3298 participants, identified through random-digit dialing and enrolled between 1993 and 2001. Subjects were eligible if they had never been diagnosed with a stroke, were \textgtr 40 years of age, and had been residents of northern Manhattan for at least 3 months in a household with a telephone. The overall response rate to the initial call was 68%.

From September 2005, Northern Manhattan Study subjects over age 50 who volunteered to undergo a brain magnetic resonance imaging study and a more extensive cardiovascular assessment were included in the Cardiovascular Abnormalities and Brain Lesions study. Of the 1004 participants enrolled in the Cardiovascular Abnormalities and Brain Lesions study, pulse wave analysis was available in 905, and evaluation of diastolic function was available in 991; 983 had both assessments available and constitute the study population of the present report. The study complies with the Declaration of Helsinki. Informed consent was obtained from all study participants. The study was approved by the Institutional Review Board of Columbia University Medical Center.

Risk Factors Assessment
Hypertension was defined as systolic blood pressure (SBP) \textgtr 140 mm Hg or diastolic blood pressure \textgtr 90 mm Hg at the time of the visit (mean of 2 readings) or patient's self-reported history of hypertension or antihypertensive treatment. Diabetes mellitus was defined as fasting blood glucose \textgtr 240 mg/dL or patient's self-reported history of diabetes or of diabetes medications. Hypercholesterolemia was defined as total serum cholesterol \textgtr 240 mg/dL or patient's self-report of hypercholesterolemia or of use of lipid-lowering treatment. Coronary artery disease was defined as a history of myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, typical angina, or use of anti-ischemic medications. Body mass index (BMI) was calculated as: weight (kilograms)/height\(^2\) (meters\(^2\)). Obesity was defined as BMI \textgtr 30 kg/m\(^2\). Estimated glomerular filtration rate was calculated using the 4-variable Modification of Diet in Renal Disease equation.\textsuperscript{25} Atrial fibrillation was defined from ECG at the time of echocardiography or from self-reported history. Race-ethnicity was based on self-identification modeled after the US census.

Central Hemodynamics, Arterial Stiffness, and Wave Reflection Assessment
Pulse wave analysis of the radial artery by application tonometry was performed using a commercially available device (SphygmoCor, Pulse Wave Analysis System, AtCor Medical). A detailed description of the technique and reproducibility data have been previously published\textsuperscript{26} and technical aspects described in the online-only Data Supplement. (For expanded methods and online-only Data Supplement Figure S1, please see http://hyper.ahajournals.org.) Briefly, central systolic, diastolic, and pulse pressure (cPP) were calculated from the radial pulse wave by a validated generalized transfer function.\textsuperscript{27,28} The ratio of cPP over LV stroke volume index (cPP/SV\textsubscript{I}) was used as an indicator of arterial stiffness.\textsuperscript{29} Total arterial compliance (TAC) was calculated using the area method illustrated by Liu et al.\textsuperscript{30} Pulse pressure amplification (PPA), a prognostically validated indicator of central to periphery pressure augmentation,\textsuperscript{23} was calculated as the ratio of peripheral PP over cPP. The aortic augmented pressure from the reflected wave was measured as the difference between central SBP and the pressure at the onset of the reflected wave from the lower body. The aortic augmentation index (AI\textsubscript{x}), an index of wave reflection, was calculated as the ratio between the augmented pressure and cPP expressed as percent.

Echocardiographic Assessment
Transthoracic echocardiography was performed using a commercially available system (iE 33, Philips) by trained registered sonographers, following a standardized protocol. LV dimensions, wall thickness and left atrial diameter were measured according to the recommendations of the American Society of Echocardiography.\textsuperscript{32} LV mass was calculated using a validated formula\textsuperscript{33} and indexed to the body surface area. LV relative wall thickness was calculated using a standard formula.\textsuperscript{34} LV ejection fraction was calculated by biplane-modified Simpson’s rule, replaced by semiquantitative method or visual estimation in case of technically suboptimal images.

LV diastolic function was assessed as previously published\textsuperscript{35,36} and described in the online-only Data Supplement (see http://hyper.ahajournals.org). Briefly, peak velocities of the early (E) and late (A) phases of the mitral inflow were sampled by pulsed-wave Doppler at the mitral valve leaflet tips from an apical 4-chamber view, and the E/A ratio was calculated. LV myocardial velocities by tissue-Doppler imaging were evaluated at the lateral and septal mitral valve annulus. The peak early diastolic (e\textsuperscript{-}) velocity was measured and the E/e\textsuperscript{-} ratio was calculated as an index of LV filling pressures.\textsuperscript{37}

Statistical Analysis
Data are presented as mean \pm standard deviation for continuous variables and as proportions for categorical variables. Differences between groups were assessed by Student \(t\) test for continuous variables and by 2-sided Fisher exact test for proportions. Simple correlations were assessed by Pearson product correlation coefficients (\(r\)). Analysis of covariance was conducted to assess differences in arterial parameters between men and women after adjusting for covariates. Logistic regression analyses were performed to predict the risk of diastolic dysfunction associated with arterial stiffness and wave reflection, and odds ratios (OR) and 95% confidence intervals (CI) were calculated. Regressions were confirmed by logarithmic transformation of variables when normality assumptions were not met. Covariates (age, height, BMI, heart rate, LV mass index, hypertension, mean arterial pressure, antihypertensive treatment, cigarette smoking, race-ethnicity, and estimated glomerular filtration rate) were entered in the models in a stepwise fashion, with entry and removal criteria set at \(P=0.10\) and \(P=0.20\), respectively. For all statistical analyses, a 2-tailed \(P<0.05\) was considered significant. Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc.).

Results

Characteristics of the Study Population
The demographic and clinical characteristics of the 983 study participants, divided by sex, are reported in Table 1. Mean age was not significantly different between men and women. Women had significantly higher BMI, lower body surface area, shorter height (all \(P<0.01\)), and higher prevalence of hypertension (\(P<0.05\)) and obesity (\(P<0.01\)). Men were more frequently smokers (\(P<0.01\)). Brachial SBP and central SBP were both significantly higher in women than in men, as
was heart rate (all \( P<0.01 \)). Prevalence of subjects taking antihypertensive medications was higher in women than in men. Of those taking antihypertensive medications, 28.2% were taking diuretics; 32.1%, \( \beta \)-blockers; 39.1%, calcium channel-blockers; 41.7%, angiotensin-converting enzyme inhibitors; and 36.5% were taking other vasodilators. Four hundred and twenty-three (59.1%) were taking 2 or more drugs; 82.7% of the treated participants had started treatment during the 12 months before study enrollment, and 17.5% had started during the 12 months before study enrollment.

Table 2 shows the echocardiographic characteristics of the study participants in the 2 sexes. Women had significantly lower LV mass (\( P<0.01 \)), higher relative wall thickness (\( P<0.05 \)), higher LV ejection fraction, and larger left atrial diameter (both \( P<0.01 \)) than men. LV diastolic function analysis showed a lower E/A (\( P<0.05 \)) and a higher E/e’ (\( P<0.01 \)) in women compared with men. Overall prevalence of diastolic dysfunction was slightly higher in women than in men, but the difference was not statistically significant (55.9% versus 51.1%; \( P=0.16 \)).

### Sex Differences in Central Hemodynamics, Arterial Stiffness, and Wave Reflection

Table 3 reports the central hemodynamics and the variables of arterial stiffness and wave reflection in the 2 sexes. Central SBP and PP, global arterial stiffness (cPP/SVi), augmented pressure, and AIx were all significantly higher in women than in men (all \( P<0.01 \)), whereas TAC and PPA were significantly lower in women (all \( P<0.01 \)). After adjusting for age, BMI, mean arterial pressure, and heart rate, arterial stiffness and wave reflection remained significantly higher in women than in men.

### Relationship of Arterial Stiffness and Wave Reflection With LV Mass and Geometry

LV mass showed a weak but significant negative association with cPP/SVi in women (\( r=-0.11; \ P<0.01 \)) but not in men (\( r=-0.04; \ P=NS \)). Relative wall thickness showed correlations with parameters of arterial stiffness in women (\( r=0.37 \) for cPP/SVi, \( r=-0.35 \) for TAC and \( r=0.14 \) for PPA, all \( P<0.01 \)) and men (\( r=0.33 \) for cPP/SVi and \( r=-0.33 \) for TAC, all \( P<0.01 \)).

### LV Diastolic Function and Arterial Stiffness and Wave Reflection

Correlations between arterial stiffness, wave reflection, and diastolic function parameters are shown in Table 4. Higher cPP/SVi and lower TAC were significantly associated with worse LV diastolic function in women and men (all \( P<0.05 \)). In women, PPA and AIx were correlated with E/A (all \( P<0.01 \)), whereas in men, they showed significant correlations with e’ and E/e’ (all \( P<0.01 \)). Antihypertensive treatment had no influence on the correlations between diastolic function parameters and arterial stiffness/wave reflection (Table S1; see http://hyper.ahajournals.org). In logistic models, cPP/SVi and TAC were significantly associated with LV diastolic dysfunction in women and men, whereas PPA and AIx were not.
AIx were not (Table 5). In multivariate analyses, cPP/SVi remained significantly associated with the presence of diastolic dysfunction in both women (adjusted OR, 1.54; 95% CI, 1.03 to 2.30; P < 0.05) and men (adjusted OR, 2.09; 95% CI, 1.30 to 3.39; P < 0.01), independent of potential confounders (Table 5). These results remained unchanged when blood pressure control was added as a covariate (data not shown).

**Discussion**

In this study, we investigated sex differences in the relationship of arterial stiffness and wave reflection with LV diastolic function in a large unselected community-based cohort and found that (1) significant differences in arterial properties are present between men and women, with women showing significantly greater arterial stiffness and wave reflection; and (2) arterial stiffness is associated with worse LV diastolic function in both men and women.

Differences between men and women in central hemodynamics and arterial stiffness have been described in previous studies and have been partially ascribed to differences in hormonal factors, endothelial function, height, aortic wall thickness) in women might have also played a role in this regard. Since arterial stiffness and diastolic dysfunction have been both advocated as possible factors involved in the pathogenesis of HFNEF, the greater arterial stiffness and more impaired LV diastolic function that we observed in women may be a preclinical finding in the pathway to HFNEF.

The relationship between arterial stiffness and diastolic dysfunction was attenuated after controlling for age and cardiovascular risk factors, such as LV mass, geometry, and hypertension. At least part of the association between arterial stiffness and diastolic function may, therefore, be mediated by the shared association with cardiovascular risk factors and, ultimately, be expression of subclinical atherosclerotic burden. Increased vascular stiffness might also have a more direct role on LV diastolic function. In the presence of normal arterial compliance, the systolic-diastolic, ventricular-vascular coupling reduces LV afterload by storing potential energy in systole and transforming the pulsatile cardiac ejection into a mostly continuous aortic flow, thus maintaining diastolic aortic pressure and improving coronary blood flow. With progressive stiffening of the elastic arteries, cardiac afterload increases because of the accelerated return from periphery of the arterial wave reflection during systole, which augments the SBP and poses extra stress on the LV.

On the other side, arterial stiffness is associated with lower diastolic blood pressure and reduced coronary perfusion.

The result is higher systolic work and a mismatch in the myocardial supply/demand oxygen ratio, which can affect dimensions, and heart rate. Consistent with other studies, we found that differences in height and heart rate do not fully explain the observed differences in vascular stiffness between sexes. Whether the impact of arterial stiffness on diastolic function is different in men and women is debated. In our study, arterial stiffness and wave reflection were significantly associated with indexes of LV diastolic function, and the strength of these associations was similar in men and women; however, it is conceivable that the higher arterial stiffness and the higher prevalence of hypertension and obesity in women may at least be, in part, responsible for the lower LV relaxation and higher LV diastolic stiffness observed in this group. The more concentric LV geometry (ie, increased relative wall thickness) in women might have also played a role in this regard. Since arterial stiffness and diastolic dysfunction have been both advocated as possible factors involved in the pathogenesis of HFNEF, the greater arterial stiffness and more impaired LV diastolic function that we observed in women may be a preclinical finding in the pathway to HFNEF.

### Table 3. Central Blood Pressure, Arterial Stiffness, and Wave Reflection Parameters in Men and Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women</th>
<th>Men</th>
<th>P Value</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>cSBP, mm Hg</td>
<td>122.3±19.7</td>
<td>116.9±17.3</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>cDBP, mm Hg</td>
<td>71.7±10.4</td>
<td>72.0±10.1</td>
<td>0.64</td>
<td>0.11</td>
</tr>
<tr>
<td>cPP, mm Hg</td>
<td>50.7±15.7</td>
<td>45.0±15.2</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>cPP/SVi, mm Hg-m²/ml</td>
<td>1.56±0.61</td>
<td>1.38±0.58</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TAC, ml/mm Hg</td>
<td>1.00±0.43</td>
<td>1.37±0.62</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PPA</td>
<td>1.24±0.12</td>
<td>1.31±0.15</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Augmented pressure, mm Hg</td>
<td>16.5±7.7</td>
<td>12.0±7.7</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AIx, %</td>
<td>31.7±8.4</td>
<td>24.6±9.9</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Adjusted for age, body mass index, mean arterial pressure, and heart rate.

The data indicate that AIx were not different between men and women (Table 5). In multivariate analyses, cPP/SVi remained significantly associated with the presence of diastolic dysfunction in both women (adjusted OR, 1.54; 95% CI, 1.03 to 2.30; P < 0.05) and men (adjusted OR, 2.09; 95% CI, 1.30 to 3.39; P < 0.01), independent of potential confounders (Table 5). These results remained unchanged when blood pressure control was added as a covariate (data not shown).

**Discussion**

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Differences between men and women in central hemodynamics and arterial stiffness have been described in previous studies and have been partially ascribed to differences in hormonal factors, endothelial function, height, aortic wall thickness) in women might have also played a role in this regard. Since arterial stiffness and diastolic dysfunction have been both advocated as possible factors involved in the pathogenesis of HFNEF, the greater arterial stiffness and more impaired LV diastolic function that we observed in women may be a preclinical finding in the pathway to HFNEF.

The relationship between arterial stiffness and diastolic dysfunction was attenuated after controlling for age and cardiovascular risk factors, such as LV mass, geometry, and hypertension. At least part of the association between arterial stiffness and diastolic function may, therefore, be mediated by the shared association with cardiovascular risk factors and, ultimately, be expression of subclinical atherosclerotic burden. Increased vascular stiffness might also have a more direct role on LV diastolic function. In the presence of normal arterial compliance, the systolic-diastolic, ventricular-vascular coupling reduces LV afterload by storing potential energy in systole and transforming the pulsatile cardiac ejection into a mostly continuous aortic flow, thus maintaining diastolic aortic pressure and improving coronary blood flow. With progressive stiffening of the elastic arteries, cardiac afterload increases because of the accelerated return from periphery of the arterial wave reflection during systole, which augments the SBP and poses extra stress on the LV.

On the other side, arterial stiffness is associated with lower diastolic blood pressure and reduced coronary perfusion. The result is higher systolic work and a mismatch in the myocardial supply/demand oxygen ratio, which can affect
both cardiac systolic and diastolic performances. In our study, parameters of global arterial stiffness were significant predictors of LV diastolic dysfunction, and cPP/SVi remained significantly associated with diastolic dysfunction after accounting for age and cardiovascular risk factors, supporting the hypothesis of a direct effect of increased stiffness on LV relaxation. Our findings of a stronger association of indexes of global stiffness (rather than wave reflection) with LV diastolic function confirm those from a study by Weber et al, in which the strength of the association between pulse wave velocity, a more direct index of arterial stiffness, and diastolic function was substantially greater than that for Aix.21 Wave reflection and global stiffness parameters express, therefore, different aspects of arterial properties. In line with this hypothesis is the observation that, in a group without cardiovascular risk factors, wave reflection parameters were less affected than indexes of global arterial stiffness by the physiological aging process.22

The association between arterial stiffness and LV diastolic function has been investigated in past studies. In patients undergoing coronary angiography, Weber et al found that E/e’ and LV end-diastolic pressure correlated with Aix and pulse wave velocity in both sexes.21 In another study, Borlaug et al found that indexes of LV relaxation were significantly associated with PP, Aix, and total arterial compliance,47 and these relationships were present in both men and women.22 In another study, in elderly subjects with normal LVEF, Abhayaratna et al found that aortic stiffness was associated with diastolic dysfunction independent of sex.20 We also confirm the findings of the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study, in which a relationship between PP/SVi and diastolic function was found to be independent of possible confounders.20 Of note, the effect of sex in that analysis was too weak to be included in the statistical model. A relation between arterial stiffness and diastolic dysfunction has also been described in patients with hypertension with suspected HFNEF, independent of sex.23 Regional diastolic dysfunction, evaluated by magnetic resonance imaging, was found associated with carotid stiffness, after adjusting for sex and other risk factors.48 Partially different results, however, emerged from a recent study, in which, after adjusting for covariates, PPA was significantly associated with e’ in women but not in men.19 In that study, other parameters of arterial stiffness and wave reflection (such as pulse wave velocity, Aix, and cPP) were not associated with diastolic function in either men or women, even in univariate analyses. The younger age of the study sample and the specific population studied (subjects referred for diastolic stress echocardiography) might, in part, be responsible for the different findings between that study and the present one.

Our study has limitations. The cross-sectional design does not allow the detection of a cause-effect relationship but only of associations between the studied variables. A causal link between arterial stiffness and LV diastolic function can be hypothesized, but longitudinal studies are needed to confirm this hypothesis, as it cannot be excluded that the interrelationship of both factors with age and cardiovascular risk factors might partially explain our findings. The parameters derived from arterial waveform analysis provide information about wave reflection and are only indirect indices of arterial stiffness. The measurement of pulse wave velocity, an important method for assessing arterial stiffness, was not available in our study. Given the observational design of the study, participants were not asked to stop antihypertensive treatment on the day of cardiac and arterial stiffness evaluations; therefore, an effect of medications on the physiological aging process cannot be excluded.

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### Table 5. Risk of Diastolic Dysfunction Associated With Arterial Stiffness and Wave Reflection Stratified by Sex

<table>
<thead>
<tr>
<th>Arterial Variable</th>
<th>Women OR (95% CI)</th>
<th>P Value</th>
<th>Men OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cPP/SVi</td>
<td>2.30 (1.69–3.14)</td>
<td>&lt;0.01</td>
<td>2.65 (1.73–4.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TAC</td>
<td>0.36 (0.24–0.55)</td>
<td>&lt;0.01</td>
<td>0.45 (0.30–0.65)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PPA</td>
<td>2.84 (0.73–11.1)</td>
<td>0.13</td>
<td>0.49 (0.13–1.84)</td>
<td>0.29</td>
</tr>
<tr>
<td>Aix</td>
<td>0.99 (0.97–1.01)</td>
<td>0.26</td>
<td>1.01 (0.99–1.04)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence intervals; cPP, central pulse pressure; SVi, stroke volume index; TAC, total arterial compliance; PPA, pulse pressure amplification; Aix, augmentation index.

*Adjusted for age, height, body mass index, heart rate, LV mass index, hypertension, mean arterial pressure, anti-hypertensive treatment, cigarette smoking, race-ethnicity, and eGFR.
Conclusions
In our cross-sectional, community-based cohort study, increased arterial stiffness was associated with reduced LV diastolic function in both men and women. The greater arterial stiffness observed in women might account (at least, in part) for the observed higher incidence of HFNEF known to exist in women. Further investigations are needed to assess the risk of future heart failure associated with increased arterial stiffness and the possible impact of therapeutic strategies aimed at improving arterial elasticity on the risk of subsequent heart failure.

Perspectives
Up to 50% of patients with heart failure have normal or quasinormal LV ejection fraction (HFNEF). This clinical entity is characterized by an impairment of LV diastolic function, eventually leading to an increase in LV filling pressure and heart failure symptoms. Women are more likely than men to develop HFNEF. It is also known that arterial stiffness is substantially higher in women than in age-matched men, a difference that results in a higher LV afterload. In addition, observations from past studies suggest that women tend to adapt to the chronic pressure overload from arterial hypertension by developing more concentric LV hypertrophy compared with men. These differences may lead to a more impaired LV diastolic function in women and explain (at least, in part) the increased risk of HFNEF observed in women; however, it is not clear whether women are also more vulnerable than men to the deleterious effects of arterial stiffening on LV diastolic function. In our study, in a large community-based cohort, we found that arterial stiffness was inversely associated with diastolic function in both sexes; however, the higher arterial stiffness observed in women may account for a more impaired LV diastolic function and possibly contribute to the future development of HFNEF.

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Disclosures
None.

References
22. Bollang BA. Sex, load, and relaxation are women more susceptible to load-dependent diastolic dysfunction? J Am Coll Cardiol. 2011;57: 1234–1236.
Women are more prone than men to develop HFNEF. The mechanisms of this difference need to be elucidated.

Although the relationship between arterial stiffness and diastolic function was found in men and women, the higher arterial stiffness observed in women represents a possible target for specific interventions to prevent the development of clinical LV dysfunction.

Increased arterial stiffness is associated with LV diastolic dysfunction in both men and women, independent of associated cardiovascular risk factors. The higher arterial stiffness observed in women might play a role in the higher incidence of HFNEF in women.
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Arterial Stiffness and Wave Reflection: Sex Differences and Relationship with Left Ventricular Diastolic Function

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EXPANDED METHODS

Echocardiographic Assessment
Transthoracic echocardiography evaluation was performed using a commercially available system (iE 33, Philips, Andover, MA) by a trained registered sonographer according to a standardized protocol. Left ventricular (LV) end-diastolic diameter (LVEDD), septal thickness, and posterior wall thickness (PWT) were measured at end-diastole from a parasternal long-axis view according to the recommendations of the American Society of Echocardiography (ASE). LV mass, calculated with the Devereux formula, and left atrial antero-posterior diameter were indexed by body surface area to account for the effect of body size. Left ventricular relative wall thickness, an index of LV geometry, was calculated with the formula: \((2 \times \text{PWT})/\text{LVEDD}\). LV ejection fraction was calculated by biplane modified Simpson’s rule as recommended by the ASE, replaced by semi-quantitative method or visual estimation in case of technically suboptimal images.

Diastolic function assessment.
Trans-mitral diastolic flow was measured by pulsed-wave Doppler from an apical 4-chamber view. Color Doppler was used to visualize the trans-mitral flow; the pulsed Doppler sample volume was placed at the level of mitral valve leaflet tips, with the ultrasonic beam perpendicular to the inflow jet. Doppler baseline and velocity scale were adjusted to obtain optimal visualization of the inflow spectrum. At least four cardiac cycles were recorded during patient apnea and the images were stored in digital format for off-line analysis. Peak velocities of the early (E wave) and late (A wave) phases of the mitral inflow pattern from Doppler recordings were measured and their ratio (E/A) was calculated. LV myocardial velocities were evaluated by pulsed tissue-Doppler imaging (TDI). Two-dimensionally guided pulsed TDI sample volume was placed at the level of the lateral and of the septal mitral valve annulus, Doppler gain and wall filter were adjusted to reduce artifacts, and velocity scale was set to ±20 cm/s. Four consecutive beats were recorded at a sweep rate of 100 mm/s during patient apnea and stored in digital format for off-line analysis. The peak early diastolic (e’) velocity of the lateral and septal mitral annulus by pulsed-TDI were measured and the average value was calculated and used in all subsequent analyses. The ratio between the E and the e’ wave (E/e’) was calculated as a pre-load independent index of LV filling pressures. Diastolic dysfunction was defined, according to ASE guidelines and taking into consideration the mean age of our population, as: E/A ratio ≤ 0.7, or E/A ratio > 0.7 and ≤ 1.5 and e’ velocity < 7 cm/s, or E/A ratio > 1.5 and e’ velocity < 7 cm/s. In case of presence of atrial fibrillation, diastolic dysfunction was defined as e’ velocity < 7 cm/s averaged over at least 10 cardiac cycles.

Arterial stiffness and wave reflection assessment
Pulse wave analysis of the radial artery by applanation tonometry at the wrist was performed using a commercially available device (SphygmoCor, Pulse Wave Analysis System, AtCor Medical). After the acquisition of 20 to 30 reproducible sequential waveforms, the radial pulse wave was generated, and the corresponding central aortic
pressure waveform was derived by a validated generalized transfer function.\textsuperscript{5,6} Aortic augmented pressure from the reflected wave was measured as the difference between the peak systolic central pressure and the pressure at the onset of the reflected wave from the lower body (time to reflection, Tr) (Figure S1). Central systolic (cSBP), diastolic (cDBP), and pulse pressures (cPP) were calculated from the radial pulse wave by a validated generalized transfer function.\textsuperscript{5,6} The ratio of cPP over LV stroke volume index (cPP/SVi) was used as an indicator of arterial stiffness.\textsuperscript{7} Total arterial compliance (TAC) was calculated using the area method illustrated by Liu et al.:\textsuperscript{8} 

\[
\text{TAC (ml/mmHg)} = \frac{(d\text{PTI}) (SV)}{(s\text{PTI} + d\text{PTI})(P_s - P_d)},
\]

where dPTI and sPTI are the diastolic and systolic pressure-time integrals calculated from the central pulse waveform, SV is the LV stroke volume, Ps and Pd are the end-systolic and end-diastolic pressures estimated from the pulse waveform. Pulse pressure amplification (PPA), a prognostically validated indicator of central to periphery pressure augmentation,\textsuperscript{9} was calculated as the ratio of peripheral over central pulse pressure. The aortic augmented pressure from the reflected wave was measured as the difference between the peak cSBP and the pressure at the onset of the reflected wave from the lower body. The aortic augmentation index (AIx), an index of wave reflection, was calculated as the ratio between the augmented pressure and cPP expressed as percent.
References

1. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440-1463.


**S1 – Supplemental table.** Correlation between diastolic function parameters and arterial stiffness/wave reflection stratified in participants treated or not treated with anti-hypertensive medications.

<table>
<thead>
<tr>
<th>Diastolic function parameters</th>
<th>PP/SVi</th>
<th>TAC</th>
<th>PPA</th>
<th>AIx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not treated (n=267)</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>e’</td>
<td>-0.15*</td>
<td>0.20**</td>
<td>0.11</td>
<td>-0.11</td>
</tr>
<tr>
<td>E/e’</td>
<td>0.16**</td>
<td>-0.21**</td>
<td>-0.21**</td>
<td>0.19**</td>
</tr>
<tr>
<td><strong>Treated (n=716)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e’</td>
<td>-0.18**</td>
<td>0.19**</td>
<td>0.11**</td>
<td>-0.13**</td>
</tr>
<tr>
<td>E/e’</td>
<td>0.22**</td>
<td>-0.22**</td>
<td>-0.15**</td>
<td>0.17**</td>
</tr>
</tbody>
</table>

PP/SVi: central pulse pressure/stroke volume index, TAC: total arterial compliance, PPA: pulse pressure amplification, AIx: augmentation index.
S1 – Supplemental figure: Arterial pulse waveform analysis by applanation tonometry

Legend: Radial (left) and central (right) waveforms. Central waveform is generated with a transfer function from the radial artery waveform. pSBP: peripheral systolic blood pressure. pDBP: peripheral diastolic blood pressure. pPP: peripheral pulse pressure. cSBP: central systolic blood pressure. cDBP: central diastolic blood pressure. cPP: central pulse pressure. AP: augmented pressure. Tr: time to the beginning of the reflected wave. The aortic augmentation index (AIx) is calculated as 100 x AP/cPP.