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Noninvasive Assessment of Sex Differences in Arterial Load in Healthy Adults

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Abstract

Background: Women have higher risk of heart failure than their male counterparts. Although the mechanical inefficiency of myocardium against an excessive afterload is an important reason of heart failure, little attention has been paid to the sex differences in arterial load and its clinical relevance.

Results: The effective arterial elastance index (Eal), total arterial compliance index (TACI), and systemic vascular resistance index (SVRI) were determined using transthoracic echocardiography combined with cuff-measured brachial blood pressure in 460 healthy adults (230 men). The sex differences in these arterial load indexes were analyzed. No statistical difference was found in the age, heart rate, and stroke volume index (all $P < 0.05$). After adjustment for the cuff-measured blood pressure; the estimated marginal means (95% CIs) of the Eal was higher in women than in men [0.972 (0.952–0.991) vs 0.743 (0.724–0.763) mmHg m^2/mL, $P < 0.001$], the TACI was lower in women than in men [0.924 (0.905–0.944) vs 1.055 (1.036–1.075) mL/mm Hg m^2, $P < 0.001$], and no statistical difference was found in the SVRI between sexes ($P > 0.05$).

Conclusions: For any given cuff-measured blood pressure, greater integrated and pulsatile arterial load are imposed on left ventricle in women than in men, which is a piece of evidence that women have higher risk of heart failure than their counterparts.

Keywords: Heart failure, Afterload, Blood pressure, Echocardiography

1 Background

Sex plays an essential role in modulating cardiovascular function, as well as symptoms and disease presentation [1]. Sex differences widely exist in pathophysiology of heart failure [2–4]. It has been confirmed that women have higher risk of heart failure than their counterparts [2–4], for example: 1) despite similar prevalence of hypertension in both sexes, the risk of heart failure is greater in hypertensive women than their male counterparts; 2) the prevalence of heart failure with preserved ejection fraction is higher in women than in men; 3) women are at higher risk of developing de novo heart failure after myocardial infarction than men.

Consideration of sex differences in research studies would make important impact on the development and testing of preventive and therapeutic interventions [5]. Arterial load is an essential part of left ventricular (LV) afterload [6]. Although the mechanical inefficiency of myocardium against an excessive afterload is an important reason of heart failure [7], little attention has been paid to the sex differences in arterial load and its clinical relevance. Therefore, the aims of this study were to investigate the sex differences in arterial load in healthy adults and to appraise its clinical relevance.

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2 Results

2.1 Baseline Characteristics of the Study Population

A total of 460 healthy Chinese adults (230men) were included, the age ranged from 23 to 64 years old. No statistical difference was found in the age and heart rate (HR) between sexes (all $P > 0.05$) (Table 1). The body surface area (BSA) and body mass index (BMI) were larger in men than in women (all $P < 0.001$) (Table 1).

2.2 Blood Pressure

Although a non-sex-specific definition of normal blood pressure was used as one of the inclusion criteria for both sexes, the cuff-measured systolic blood pressure (SBP) and cuff-measured diastolic blood pressure (DBP) were still slightly higher in men than in women (all $P < 0.05$) (Table 1). The calculated aortic SBP and pulse pressure (PP) were lower in men than in women ($P < 0.001$), and the calculated aortic DBP was slightly higher in men than in women (all $P < 0.05$), and no statistical significance was found in the mean aortic blood pressure (MAP) between sexes ($P > 0.05$) (Table 1).

Table 1 Sex differences in basic characteristics, left ventricular (LV) volume and function, blood pressure, and arterial load in 460 healthy adults

	Men ($n = 230$)	Women ($n = 230$)	*Z* or *t*	*P* value
Basic characteristics				
Age, yrs	43.0 (36.0–49.0)	45.0 (38.0–49.0)	0.723	0.470
Height, cm	169.0 (165.0–173.0)	158.0 (155.0–162.0)	15.747	< 0.001
Weight, kg	63.0 (59.0–68.3)	53.0 (50.0–56.0)	16.627	< 0.001
Body surface area, m^2	1.81 (1.73–1.89)	1.61 (1.57–1.67)	15.791	< 0.001
Body mass index, kg/m^2	22.23 (20.94–23.57)	21.10 (20.08–22.48)	5.622	< 0.001
Heart rate, bpm	72.0 (67.8–75.0)	72.0 (68.0–75.0)	0.469	0.693
Lv volume and function				
LV end-diastolic volume, mL	100.6 ± 14.9	89.3 ± 13.6	8.459*	< 0.001
LV end-systolic volume, mL	32.1 (27.8–36.4)	28.1 (24.7–32.2)	6.807	< 0.001
LV ejection fraction, %	68.2 (66.1–69.6)	68.0 (66.6–70.2)	1.059	0.289
Stroke volume, mL	67.9 (60.4–75.8)	60.3 (54.8–66.8)	7.596	< 0.001
Stroke volume index, mL/m^2	37.7 ± 5.0	37.6 ± 56.0	0.118*	0.906
Cardiac output, L/min	4.90 ± 0.79	4.37 ± 0.73	7.383*	< 0.001
Cardiac index, $L/min{\cdot}m^2$	2.66 (2.40–2.99)	2.64 (2.38–3.00)	0.203	0.389
Blood pressure				
Cuff SBP, mm Hg	108.0 (103.0–113.0)	106.0 (100.0–112.0)	2.236	0.025
Cuff DBP, mm Hg	68.0 (64.0–72.0)	66.0 (62.0–70.0)	2.952	0.003
Aortic SBP, mm Hg	100.7 (95.7–105.7)	103.7 (97.7–109.7)	4.622	< 0.001
Aortic DBP, mm Hg	63.5 (59.5–67.5)	61.5 (57.5–65.5)	2.952	0.003
Aortic PP, mm Hg	36.2 (33.2–41.2)	42.2 (36.2–46.2)	7.501	< 0.001
MAP, mm Hg	75.9 (71.6–79.6)	75.6 (71.6–79.0)	0.162	0.871
Arterial load				
Ea, mmHg/mL	1.35 ± 0.21	1.56 ± 0.25	10.078*	< 0.001
EaI, $mmHg{\cdot}m^2/mL$	0.75 ± 0.14	0.97 ± 0.17	15.262*	< 0.001
TAC, mL/mmHg	1.85 (1.61–2.14)	1.45 (1.26–1.68)	10.489	< 0.001
TACI, $mL/mm\ Hg{\cdot}m^2$	1.02 (0.87–1.18)	0.89 (0.77–1.05)	6.035	< 0.001
SVR, $kdynes{\cdot}s/cm^{-5}$	1.19 (1.06–1.36)	1.34 (1.20–1.52)	6.917	< 0.001
SVRI, $kdynes{\cdot}s{\cdot}m^2/cm^{-5}$	2.14 (1.93–2.41)	2.17 (1.91–2.47)	0.462	0.644
Pulsatile load (aortic PP/MAP)	0.49 ± 0.08	0.55 ± 0.09	8.004*	< 0.001
Tau-W, s	1.67 (1.44–1.88)	1.46 (1.31–1.66)	6.969	< 0.001

Data with normal distribution are expressed as mean ± standard deviation, and those without as median (interquartile range). Independent-sample *t* tests are used to compare the mean of two independent samples with normal distribution, and a *t* value is presented. Nonparametric tests for two independent samples are used to compare the mean of non-normally distributed data, and a *Z* value is presented. In the "*Z* or *t*" column, * indicate *t* value, and others are *Z* value. *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *PP* pulse pressure; *MAP* mean aortic blood pressure; *Ea* effective arterial elastance; *EaI* Ea index; *TAC* total arterial compliance; *TACI* TAC index; *SVR* systemic vascular resistance; *SVRI* SVR index; Tau-W time constant of the Windkessel

2.3 Sex Differences in LV Volumes and Function in Healthy Adults

The LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), stroke volume (SV), and cardiac output (CO) were larger in men than in women (all $P<0.001$); but no statistical difference was found in the SV index (SVI), cardiac index (CI), and LV ejection fraction (LVEF) between sexes (all $P>0.05$) (Table 1).

2.4 Sex Differences in Arterial Load Indexes in Healthy Adults

The sex differences in the arterial load without adjustment for covariates are presented in Table 1. After adjustment for the cuff-measured blood pressure, the sex differences in the estimated marginal means (95% CIs) of arterial load indexes are presented in Table 2. The sex differences in the arterial load indexes without adjustment for covariates were similar to these after adjustment for the cuff-measured blood pressure. The (effective arterial elastance) Ea, Ea index (EaI), systemic vascular resistance (SVR), and pulsatile load were higher in women than in men; the total arterial compliance (TAC) and TAC index (TACI) were lower in women than in men; and the time constant of the Windkessel (Tau-W) was shorter in women than in men (all $P<0.001$). No statistical difference was found in the SVR index (SVRI) between sexes ($P > 0.05$).

3 Discussion

The most comprehensive and precise definition of the arterial load is the time-resolved aortic input impedance measurements, which describes the relationship between pulsatile pressure and flow in the frequency domain, and has dimensions of amplitude and phase [8]. However, the complex nature and interpretation of time-varying aortic input impedance make it unfeasible for daily clinical practice and usual hemodynamic monitoring [8]. Fortunately, noninvasive assessment of arterial load can provide important physiological and prognostic information [9].

3.1 Sex Differences in Arterial Load

The sex differences in arterial load are noninvasively investigated in 460 healthy adults, and the primary finding is that with or without adjustment for the cuff-measured blood pressure; women have higher EaI and pulsatile load, and lower TACI, and shorter Tau-W than men. The arterial load describes all the extracardiac factors opposing ventricular ejection [8]. The SVR, which is mostly dependent on the distal resistive arterioles, modulates the steady component of arterial load [10]. The TAC, which is mostly dependent on the proximal elastic large arteries, modulates the pulsatile component of arterial load [10]. A lower TAC indicates a higher arterial stiffness, which leads to a higher pulsatile load [11]. The Ea is a measure of the net arterial load imposed on the left ventricle that integrates the effects of the SVR, TAC, aortic characteristic impedance, heart rate, and systolic and diastolic time intervals [12, 13]. The allometrically scaled EaI, SVRI and TACI are used for comparative purposes because arterial load is heavily dependent on body size [9]. According to the widely used Windkessel model, the Tau-W represents the time constant of the exponential decay of diastolic aortic pressure [10]. A shorter Tau-W indicates a stiffer aortic wall. In summary, our results demonstrate that healthy women have higher integrated and pulsatile arterial load than their male counterparts for any given cuff-measured blood pressure.

By integrating arterial tonometry with echocardiography, Coutinho et al. found that in 461 participants (189 men and 272 women) without heart failure, women had higher aortic characteristic impedance and lower TAC than men, and the SVRI was similar between sexes [14]. In another paper, Coutinho et al. reported that in 600 non-Hispanic whites belonging to hypertensive sibships (249 men and 351 women), women had higher aortic characteristic impedance and SVR than men, and

Table 2 Sex differences in arterial load in 460 healthy adults after adjustment for cuff-measured blood pressure

	Men ($n=230$)	Women ($n=230$)	*P* value
Ea, mmHg/mL	1.337 (1.309–1.366)	1.571 (1.542–1.599)	< 0.001
EaI, mmHg·m^2/mL	0.743 (0.724–0.763)	0.972 (0.952–0.991)	< 0.001
TAC, mL/mmHg	1.910 (1.874–1.946)	1.499 (1.463–1.535)	< 0.001
TACI, mL/mm Hg·m^2	1.055 (1.036–1.075)	0.924 (0.905–0.944)	< 0.001
SVR, kdynes·s/cm^{-5}	1.204 (1.177–1.232)	1.375 (1.347–1.402)	< 0.001
SVRI, kdynes·s/cm^{-5}·m^2	2.176 (2.129–2.223)	2.229 (2.182–2.276)	0.123
Pulsatile load (aortic PP/MAP)	0.493 (0.492–0.494)	0.548 (0.547–0.548)	< 0.001
Tau-W, s	1.691 (1.671–1.710)	1.512 (1.492–1.531)	< 0.001

Data are estimated marginal means (95% CIs) without adjustment and after the adjustment. Nonstandard abbreviations and acronyms as in Table 1

the SVRI was similar between sexes [15]. Using invasive hemodynamic parameters and direct Fick cardiac output, Lau et al. found that in 190 adults (83 men and 107 women) with heart failure with preserved ejection fraction, the arterial stiffness in women was greater than in men [16]. The evidence from these studies [14–16] also indicate that women have a higher arterial load than their male counterparts.

A higher resting EaI increases the myocardial energetic costs for a given SVI [12]. We find that the SV is larger in men than in women, but the SVI is similar between sexes; which is entirely consistent with the strong heart study [17]. Moreover, we find that women have a higher EaI than men. Haider et al. find that both baseline and hyperaemic myocardial blood flow are typically higher in women as compared to men [18], which implies that women have higher myocardial energy consumption than their male counterparts. The evidence indicates that the myocardial energetic costs are higher in women than in men, and which is closely associated with the relatively higher arterial load in women.

3.2 Clinical Relevance

The arterial load is a key determinant of LV systolic and diastolic function [7, 9]. For example, arterial stiffness, a major contributor to pulsatile load, is the result of a complex interplay of endothelial and smooth muscle cell function, extracellular matrix composition, genetics, hemodynamic factors, and vasoactive properties [11]. A lower arterial compliance indicates a higher arterial stiffness or a greater pulsatile load, which has been shown to be central to the pathogenesis of heart failure with preserved ejection fraction, impairing ventricular-arterial coupling, LV diastolic and sub-clinical systolic dysfunction [19]. In the presence of a normal aortic valve, LV afterload corresponds to the mechanical load imposed by the systemic arterial tree (arterial load). The arterial load is the external opposition that must be overcome by the left ventricle during ejection, which gathers all extracardiac factors opposing the movement of blood out of the heart into the aorta, compromising different arterial properties, blood viscosity, and the effects of arterial wave reflections [20]. In a large-sample investigation; where 27 542 participants (54% women) without baseline cardiovascular disease are followed over 28 ± 12 years, and 4081 subjects develop heart failure [21]. Then the researchers divide the blood pressure into eight categories, and find that the risk of heart failure is higher in women than in men for any level of blood pressure [21]. It has been confirmed that the underlying reasons for heart failure may not always be a primary cardiac pathology but a mechanical inefficiency of myocardium against an excessive afterload [6]. We find that for any given blood pressure, the integrated and pulsatile arterial load are higher in women than in men. Thus, our results lay the mechanical groundwork for the explanation of why the risk of heart failure is higher in women than in men for the same level of blood pressure.

3.3 Limitations and Perspectives

The arterial load compromises not only mechanical properties of the arterial system, such as compliance or arterial resistance, but also the effects of arterial wave reflections [20]. The arterial wave reflections could not be determined here because we used brachial artery blood pressure to calculate aortic pressure instead of quantifying central hemodynamics with arterial tonometry. Thus, although it does not affect our results, the arterial load indexes investigated in this study can only partially represent the comprehensive definition of arterial load. Moreover, notwithstanding the accuracy of the calculated aortic blood pressure is validated with invasive intra-arterial measurements in large groups of adult population [22, 23], the calculated aortic pressure might still slightly differ from the true values due to the individual differences.

Through adequate calibration of aortic and brachial distension waveforms with arterial tonometry or meticulous ultrasonography, the aortic pressure can be noninvasively quantified using cuff-measured brachial blood pressure combined with the form factor calibration [24, 25]. However, our study was limited by the original design, and the arterial distension waveforms were not acquired. Thus, we could not validate the consistency in aortic pressure measurement between the method proposed by Van Bortel et al. [24, 25] and that used in our study. Further studies focusing on this topic have potentially important clinical relevance, and which are clearly warranted.

4 Conclusions

For any given cuff-measured blood pressure, greater integrated and pulsatile arterial load are imposed on left ventricle in women than in men, which is a piece of evidence that women have relatively higher risk of heart failure than their counterparts. Reducing sex differences in arterial load might be a new treatment target to decrease the relatively higher risk of heart failure in women.

5 Methods

5.1 Study Population

From October 2017 to September 2020, a total of 460 healthy Chinese adults (230 men) were prospectively recruited and enrolled in this study. This study included the healthy adults who fulfilled following criteria: 1) $\geq$ 18 years of age; 2) with normal BMI (18.5–24.9 kg/

m^2); 3) with normal transthoracic echocardiography (TTE) results; 4) with normal ECG results, which were examined just before or after the TTE; 5) with normal cuff-measured brachial artery SBP (90–120 mm Hg) and diastolic blood pressure DBP (60–80 mm Hg), which were measured with HBP-1300 oscillometric devices (Omron, Kyoto, Japan) just before the TTE; 6) with normal blood tests results in red blood cell, hemoglobin, triglyceride, serum total cholesterol, high-density lipoprotein, low-density lipoprotein, fasting blood glucose, total protein, albumin, globulin, sodium, potassium, blood urea nitrogen, and creatinine (the blood samples of each subject were taken and analyzed on the same day that the TTE was performed). We excluded subjects who were professional athletes or pregnant women, or were on any medication. Subjects with any kind of known disease, or with any kind of known physical or mental disorders, or with alcohol or drug addiction were also excluded.

5.2 Echocardiography and Calculations

Comprehensive two-dimensional TTE were performed with a Philips iU22, iE33 or EPIQ ultrasound systems (Philips Medical Systems, Bothell, WA, USA); and the images were analyzed, measured, and interpreted according to the recommendations [26, 27]. The two-dimensional TTE was used in this study because we considered that: 1) Two-dimensional TTE is a generally accepted and the most wildly used technique in clinical practice, which has been recommended as a reliable technique in assessment of cardiac structure and function [26, 27]. 2) Although three-dimensional TTE is free of geometric assumptions, the reliability of the measurement in some subjects are inevitably inadequate due to susceptibility to the signal dropout and low frame rates [28]. 3) The bias of the two-dimensional TTE measurements is similar for both sexes, thus the influence on this study is negligible.

The BSA is calculated using the Mosteller formula. The BMI is calculated as the weight in kilograms divided by the square of height in meters squared. The LVEDV, LVESV, and LVEF are derived from the biplane Simpson method. The SV is calculated as LVESV subtracted from LVEDV; and the SVI is calculated as SV divided by BSA. The CO is calculated as SV multiplied by HR; and CI is calculated as SVI multiplied by HR.

The aortic pressure is calculated based on the mean differences between the cuff-measured brachial blood pressure, intra-arterial brachial blood pressure, and intra-arterial aortic blood pressure [22]. According to the comprehensive meta-analyses [22]: 1) The cuff-measured brachial SBP is about 5.7 mm Hg lower than intra-arterial brachial SBP, and the cuff-measured brachial DBP is about 5.5 mm Hg higher than the intra-arterial brachial DBP. 2) The intra-arterial brachial SBP is about 8.0 mm Hg higher than the intra-arterial aortic SBP, and the intra-arterial DBP is about 1.0 mm Hg lower than the intra-arterial aortic DBP. Thus the aortic SBP can be calculated as the cuff-measured brachial SBP + 5.7–8.0 mm Hg, and aortic DBP can be calculated as the cuff-measured brachial DBP–5.5 mm Hg + 1 mm Hg.

The pulse pressure gradual increases as it travels distally from aorta to brachial artery, and the pulse pressure amplification is typically 5 mm Hg higher in healthy men than their female counterparts [23]. To minimize the potential effects of sex difference in pulse pressure amplification on the results, we deducted 5 mm Hg from the aortic SBP in men because the pulse pressure amplification from aortic artery to brachial artery almost exclusively results from the increase in SBP [23]. Thus the aortic SBP in men is calculated as the cuff-measured brachial SBP + 5.7–8.0 mm Hg −5 mmHg, and the aortic SBP in women is calculated as the cuff-measured brachial SBP + 5.7–8.0 mm Hg, and the aortic DBP in both sexes is calculated as the cuff-measured brachial DBP–5.5 mm Hg + 1 mm Hg.

The aortic PP is calculated as aortic SBP minus aortic DBP; the MAP is calculated as double aortic DBP plus aortic SBP, then divided by 3; the pulsatile load is defined as the ratio of aortic PP/MAP [29]. The Ea is commonly approximated by the steady-state LVESP-to-SV ratio, where LVESP is the LV end-systolic pressure; and the LVESP almost equals to 0.9 × aortic SBP [30]. Thus, the Ea is calculated as the ratio of (0.9 × aortic SBP)/SV [30]. The TAC is calculated as the ratio of SV/aortic PP [30]. The SVR is calculated according to following equation [31]:

$$SVR = 79.993432 \times \frac{MAP - CVP}{CO},$$

where CVP is central venous pressure, which equals right atrial pressure and can be substituted with 3 mm Hg for a normal adult [26]. For comparative purposes (biological scaling), the Ea, TAC, and SVR was normalized with the BSA to calculate the EaI, TACI, and SVRI [30, 32]. The EaI is calculated as (0.9 × aortic SBP)/SVI ratio [30]. The TACI is calculated as the ratio of SVI/PP [30]. The SVRI is calculated as the product of SVR and BSA [32]. The Tau-W is calculated as the product of SVR and TAC [10].

5.3 Statistical Analysis

Analyses were performed using SPSS 16.0 (SPSS, Chicago, IL). Continuous variables with normal distribution are summarized as mean ± standard deviation, and those without normal distribution are summarized as median (interquartile range). Testing for normality is

performed with Kolmogorov–Smirnov test. Independent-sample *t* tests are used to compare the mean of two independent samples with normal distribution, and nonparametric tests for two independent samples are used to compare the mean of non-normally distributed data. The univariate procedure of general linear model is used to assess the sex differences in arterial load after adjustment for the cuff-measured brachial blood pressure, and the estimated marginal means (95% CIs) are computed and presented. A P value of < 0.05 is considered statistically significant.

Abbreviations
LV: Left ventricular; BSA: Body surface area; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic pressure; PP: Pulse pressure; MAP: Mean aortic blood pressure; LVEDV: LV end-diastole volume; LVESV: LV end-systole volume; SV: Stroke volume; CO: Cardiac output; SVI: Stroke volume index; CI: Cardiac index; LVEF: LV ejection fraction; Ea: Effective arterial elastance; EaI: Ea index; SVR: Systemic vascular resistance; SVRI: SVR index; TAC: Total arterial compliance; TACI: TAC index; Tau-W: The time constant of the Windkessel.

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Author Contributions
JL acquisition of data; analysis and interpretation of data; drafting of the manuscript; guarantor of integrity of the entire study. LY critical revision of the manuscript; statistical analysis; interpretation of data; critical revision of the manuscript; conception and design; guarantor of integrity of the entire study. All authors read and approved the final manuscript.

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Availability of Data and Materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest
The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate
This study is conducted according to the World Medical Association Declaration of Helsinki, and is granted approval by the Institutional Research Committee of both Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital and School of Medicine, University of Electronic Science and Technology of China.

Consent for Publication
All subjects authorized access of their medical records for research and consent for the publication.

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