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ORIGINAL ARTICLE

Differences in arterial stiffness at rest and after acute exercise between young men and women

Robert J Doonan, Andrew Mutter, Giordano Egiziano, Yessica-Haydee Gomez and Stella S Daskalopoulou

There is controversy as to whether there are sex differences in arterial stiffness. Acute physical stress can elicit vascular abnormalities not present at rest. Our objective was to assess sex differences in arterial stiffness at rest and in response to acute physical stress. Healthy young men ($n=67$) and women ($n=55$) underwent pulse wave analysis and carotid-femoral pulse wave velocity measurements at rest and 2, 5, 10 and 15 min following an exercise test to exhaustion. At rest, aortic systolic, diastolic, pulse and mean pressures were all significantly higher in men as was aortic pulse pressure at 10 and 15 min post exercise and aortic systolic pressure at 15 min. Carotid-femoral pulse wave velocity was significantly higher in men ($6.0\pm0.7\,m\,s^{-1}$ *vs.* $5.6\pm0.6\,m\,s^{-1}$, $P=0.03$) at rest and at all time points post exercise. Heart rate-adjusted augmentation index was significantly lower ($-10.7\pm10.2\%$ *vs.* -4.0 ± 10.9, $P<0.0001$) and subendocardial viability ratio was significantly higher ($176.2\pm43.8\%$ *vs.* 163.4 ± 40.9, $P=0.04$) in men at rest. To our knowledge, this is the first study to assess sex differences in the arterial stiffness response to acute physical stress in young men and women. Although we were not able to elicit differences in vascular function after adjustment, which were not present at rest, we found that young men and women exhibit differences in arterial stiffness at rest and after acute physical stress.
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Keywords: augmentation index; exercise testing; pulse wave velocity; sex differences; subendocardial viability ratio

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality worldwide.[1] It has been extensively demonstrated that CVD affect men and women differently. According to the American Heart Association, the prevalence of CVD is 15.9% in young men, and 7.8% in young women aged 20–39 years, 37.9% and 38.5% for ages 40–59 years, respectively, and up to 79.3% and 85.9% for men and women over age 80 years, respectively.[2] These data indicate a higher prevalence for CVD in men below the age of 40, with advancing age leading to a gradual attenuation and reversal in this trend.

It is clear that there are inherent sex differences related to CVD at all age levels, but the underlying mechanisms that explain these differences remain unclear. It is well documented that arterial stiffness increases with age in both men and women.[3–6] Whereas several studies have reported similar changes in arterial stiffness for both sexes with advancing age,[7] others have demonstrated sex-related differences in arterial stiffness.[3,4,8] Most of these previous studies have been carried out on older age groups or wide age ranges, and have assessed arterial stiffness only at rest. We have previously shown that it is possible to unmask vascular abnormalities that were not present at rest using acute physical stress with a protocol we have termed, 'the arterial stress test'.[9] Therefore, the objective of the current study was to investigate differences in arterial stiffness and hemodynamic parameters in young healthy men and women at rest and after acute physical stress. We hypothesized that there are differences in arterial stiffness and hemodynamics between young men and women at rest and post exercise.

METHODS

Participants

We recruited consecutive healthy men and women via local advertisements and within the McGill University Health Centre Community. Exclusion criteria were previously diagnosed CVD, including congenital heart diseases, traditional cardiovascular risk factors (including diabetes mellitus, hypertension, dyslipidemia and the metabolic syndrome), renal disease, respiratory diseases, inflammatory diseases (that is, rheumatoid arthritis, systemic vasculitis, systemic lupus erythematosus), obesity (body mass index, BMI $\geqslant 30\,kg\,m^{-2}$), pregnancy and history of smoking. Furthermore, participants who were acutely ill (that is febrile), on cardioprotective medications or women on oral contraceptives were not eligible to participate in this study. As there is conflicting evidence that different phases of the menstrual cycle can affect arterial stiffness,[10–12] women were examined during the early follicular phase of the menstrual cycle to minimize this possibility. The phase was ascertained by directly querying the cycle length and date of the start of the last menses. This study was approved by the ethics and scientific review boards of the McGill University Health Centre. Written informed consent was obtained for all participants.

Department of Medicine, Faculty of Medicine, McGill University, Montreal, Quebec, Canada
Correspondence: Dr SS Daskalopoulou, Department of Medicine, Division of Internal Medicine, McGill University, McGill University Health Centre, Montreal General Hospital, 1650 Cedar Avenue, B2.236, Montreal, Quebec, Canada H3G 1A4.
E-mail: stella.daskalopoulou@mcgill.ca
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Information about past medical history, current medication use, smoking history (ever smokers were excluded) and physical activity levels were directly queried. Participants were grouped into low, medium and high activity levels according to the International Physical Activity Questionnaire guidelines.[13]

Height and weight were measured and BMI ($kg\,m^{-2}$) was calculated. Before undergoing the arterial stress test, participants were asked to abstain from all caffeine-containing beverages and ethanol intake for at least 12 h, and from strenuous exercise for 24 h before the assessment. All assessments were performed at the same time of the day throughout the study to reduce circadian variations.[14]

Arterial stiffness measurements

Pulse wave analysis (PWA) and carotid-femoral pulse wave velocity (cfPWV) measurements were performed using applanation tonometry (SphygmoCor, AtCor Medical, Sydney, NSW, Australia). PWA was used to determine the augmentation index (AIx), subendocardial viability ratio (SEVR) and aortic blood pressures (BPs). SEVR is calculated as area under the curve (AUC) during diastole/AUC during systole. An average radial pressure waveform was generated from 10 s of sequential radial pressure waveforms. Using a previously validated generalized transfer function, the SphygmoCor system software calculated an averaged radial artery waveform (calibrated with peripheral systolic and diastolic BPs) and derived a corresponding aortic pressure waveform (as well as the aortic pressure and the AIx75, a heart rate (HR)-adjusted AIx and SEVR).[15,16] The cfPWV was measured using applanation tonometry in combination with a three-lead electrocardiography. CfPWV is automatically calculated from measurements of the pulse transit time and the distance between the two recording sites, carotid and femoral (PWV = distance (m)/transit time (s)).[17]

Arterial stress test protocol

After 10 min of rest in a supine position in a temperature- ($22 \pm 1\,^{\circ}C$) and humidity- ($60 \pm 5\%$) controlled environment, brachial BP, PWA and cfPWV measurements were performed.[9] Brachial BP was measured according to the Canadian Hypertension Education Program guidelines[18,19] in triplicate using cuff sphygmomanometry (HEM-705CP, Omron Corp., Kyoto, Japan). The average of the last two measurements was used. PWA and cfPWV measurements were performed in duplicate and values were averaged for analysis. The points of measurements were marked to ensure that measurements were performed on the same pulse points post exercise. To induce physical stress, participants subsequently completed a supervised incremental treadmill exercise protocol to volitional exhaustion (Bruce protocol[20]), which has been validated in young healthy individuals;[20] throughout the test, HR was monitored. Participants were deemed to reach maximal exercise capacity when all three of the following criteria were met: (i) the participant could no longer continue the exercise protocol, (ii) a minimum of 19 was reached on the Borg scale, which is a subjective parameter for exercise intensity[20] and (iii) the participant reached at least 90% of their age-predicted maximum HR (objective parameter for exercise intensity). Time to exercise completion was recorded.

Immediately post exercise, participants rested in a supine position. At 2 min post exercise, cfPWV was assessed once and at 5, 10 and 15 min post-exercise cfPWV and PWA measurements were each performed once, in that order. Brachial BP was measured at the same time points as arterial stiffness measurements in the contralateral arm, after confirmation of absence of difference in BP between the two arms at rest (<5/3 mm Hg for systolic and diastolic BP).[21] All measurements were in accordance with the Sphygmocor internal quality control system to accomplish a quality index >85%.[22,23] The above-mentioned protocol constitutes the 'arterial stress test'.[9]

Determination of peak metabolic equivalents (METs)

Peak VO_2 was calculated as: VO_2 peak = 0.2 (speed) + 0.9 (speed × grade of treadmill), where speed is in $m\,min^{-1}$.[24] Peak METs was then calculated by dividing the calculated VO_2 peak by the resting metabolic rate (1 MET) of each individual participant calculated by the Harris–Benedict equation:[25] male = 66.4730 + 5.0033 (height, cm) + 13.7516 (weight, kg) −6.7550 (age, years); female = 655.0955 + 1.8496 (height, cm) + 9.5634 (weight, kg)—4.6756 (age, years).

Statistical analysis

SAS version 9.2 software (SAS Institute, Cary, NC, USA) was used for all statistical analyses. Demographic and baseline characteristics of men and women were compared using chi-squared test and independent *t*-tests for categorical and continuous variables, respectively, after assessing the distribution of continuous variables using normal probability plots. Comparisons between men and women of resting parameters were performed using general linear models without and with adjustment. Resting mean arterial pressure (MAP), aortic systolic BP (SBP), aortic diastolic BP (DBP) and aortic pulse pressure (PP) were adjusted for age and BMI, whereas all the other parameters were adjusted for age, BMI and resting MAP using analysis of covariance (ANCOVA). Post-exercise and post-pre exercise changes (= greatest post-exercise value − resting value) between-group comparisons for BPs were performed in a similar manner but with and without adjustment for age, BMI, peak METs and the corresponding resting BP parameter. All other parameters were adjusted for age, BMI, resting MAP, peak METs and the resting value of the parameter of interest.

RESULTS

Participant characteristics

We recruited 122 subjects; 67 men and 55 women. Participant characteristics, resting peripheral BPs and exercise parameters are available in Table 1. Figures 1a–d and 2a–d and Supplementary Table 1 contain resting and post-exercise arterial hemodynamic parameters. Table 2 contains post-pre exercise changes. All subjects reached maximal exercise capacity according to the pre-specified criteria mentioned above.

Arterial stiffness and hemodynamic parameters

HR was not significantly different between groups at rest and 2 min post exercise (Table 1 and Supplementary Table 1). However, at 5, 10 and 15 min after exercise, HR was significantly higher in men. Maximum HR post exercise was 193.5 beats per min in men and 186.2 in women, which corresponds to 98.9% and 94.9% of the estimated maximum HR for men and women, respectively. Aortic SBP, DBP and PP, as well as MAP were all significantly higher in men at rest after adjustment for age and BMI. Post-exercise aortic SBP was significantly higher in men at each time point. However, this lost significance after adjustment at 5 and 10 min. Aortic PP was also significantly higher in men at 5, 10 and 15 min post exercise before adjustment, and at 10 and 15 min after adjustment.

Table 1 Baseline participant characteristics and exercise parameters

	Men (n = *67*)	*Women* (n = *55*)	P-*value*
Age (years)	24.4 ± 6.2	23.7 ± 4.8	n.s.
Height (cm)	176.8 ± 6.3	163.6 ± 8.2	<0.0001
Weight (kg)	71.5 ± 9.4	58.1 ± 7.9	<0.0001
BMI ($kg\,m^{-2}$)	22.8 ± 2.7	21.7 ± 2.1	0.009
Resting peripheral SBP (mm Hg)	114.2 ± 9.8	103.1 ± 6.7	<0.0001
Resting peripheral DBP (mm Hg)	69.7 ± 8.2	65.3 ± 5.6	0.001
Resting peripheral PP (mm Hg)	44.4 ± 8.3	37.8 ± 6.2	<0.0001
Resting HR (beats per min)	62.4 ± 9.5	63.4 ± 9.4	n.s.
Max exercise time (min)	16.2 ± 1.8	14.2 ± 1.2	<0.0001
Max METs	14.8 ± 1.6	13.6 ± 1.6	<0.0001
Max HR (beats per min)	193.5 ± 9.7	186.2 ± 10.1	0.0002
Physical activity—low, *n* (%)	12 (17.9)	13 (23.6)	n.s.
Physical activity—moderate, *n* (%)	33 (49.3)	26 (47.3)	n.s.
Physical activity—high, *n* (%)	22 (32.8)	16 (29.1)	n.s.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; max, maximum; MET, metabolic equivalent; n.s., not significant; PP, pulse pressure; SBP, systolic blood pressure.
All values are mean ± s.d.

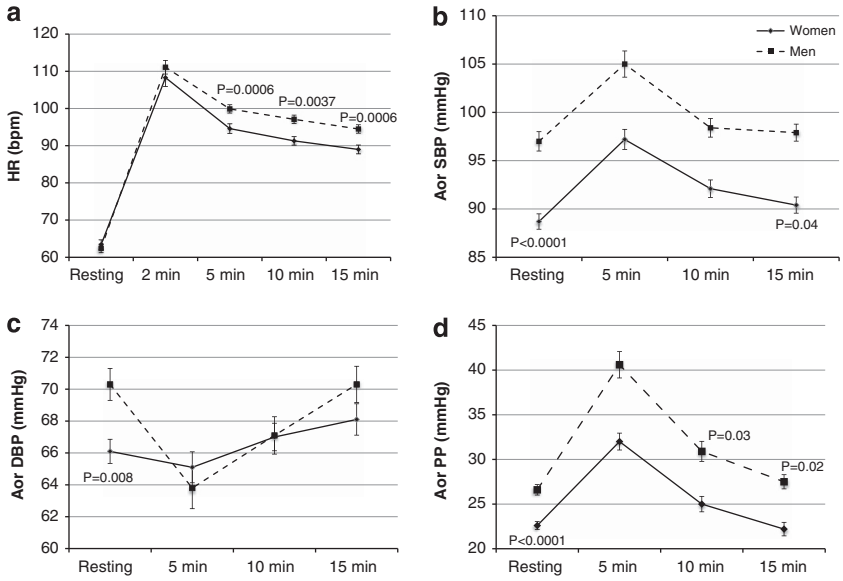

Figure 1 Vessel hemodynamic parameters in men and women at rest and post-exercise. (**a**) heart rate (HR), (**b**) aortic systolic pressure (Aor SBP), (**c**) aortic diastolic pressure (Aor DBP) and (**d**) aortic pulse pressure (Aor PP) are presented. Presented as mean ± s.e. *P*-values are adjusted.

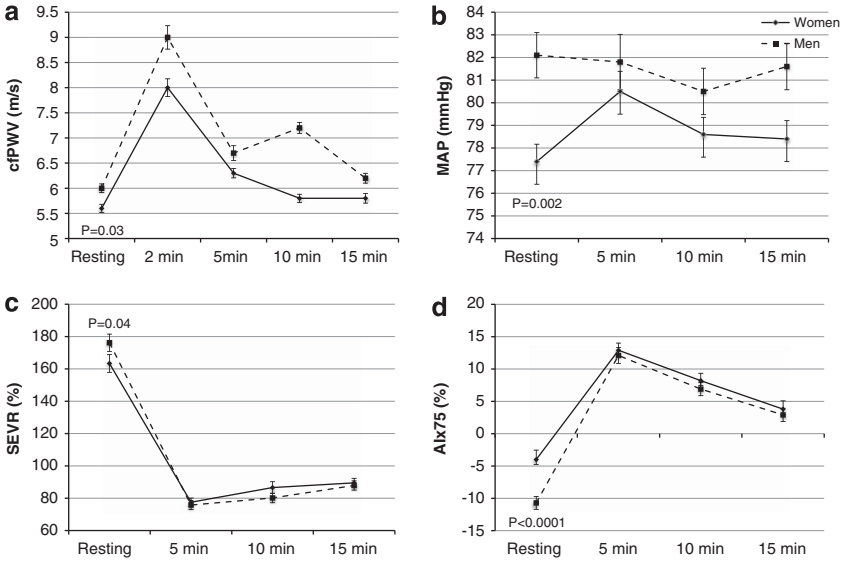

Figure 2 Arterial stiffness and vessel hemodynamic parameters in men and women at rest and post exercise. (**a**) Carotid-femoral pulse wave velocity (cfPWV), (**b**) mean arterial pressure (MAP), (**c**) subendocardial viability ratio (SEVR) and (**d**) heart rate-adjusted augmentation index (AIx75) are presented. Presented as mean ± s.e. *P*-values are adjusted.

Differences between men and women with respect to aortic DBP were non-significant post exercise, and MAP was only significantly higher in men at 15 min without adjustment.

cfPWV was significantly higher in men at rest after adjustment (Figure 2a and Supplementary Table 1). Post-exercise cfPWV was also higher in men at all time points but this lost significance after adjustment for age, BMI, peak METs, resting MAP and resting cfPWV. AIx75 was significantly lower and SEVR was significantly higher in men at rest after adjustment. When height was added to the adjusted AIx75 model, significance was lost. No significant differences were found post exercise for AIx75 or SEVR.

Post-pre exercise changes were calculated (Table 2). We found that men had a greater decrease in aortic DBP, MAP and SEVR and a greater increase in aortic PP, cfPWV and AIx75. However, significance was lost after adjustment for all these parameters, except for aortic DBP.

DISCUSSION

To our knowledge, this is the first study to assess sex differences in the arterial stiffness and arterial hemodynamics at rest and in response to acute physical stress in young men and women. Using 'the arterial stress test', we found that men and women exhibit not only differences in arterial stiffness at rest but also after acute physical stress.

cfPWV is considered to be the 'gold standard' in the assessment of arterial stiffness, as it represents the stiffness of the aorta.[26,27] Therefore, an important finding is that young men have increased

Table 2 Post-pre exercise changes

	Post-pre exercise change	*Adjusted P-value*	*Unadjusted P-value*
HR (beats per min)			
Women	44.7 ± 16.6	n.s.	n.s.
Men	48.7 ± 15.6		
Aor SBP (mm Hg)			
Women	8.4 ± 7.0	n.s.	n.s.
Men	7.7 ± 8.5		
Aor DBP (mm Hg)			
Women	−1.1 ± 8.2	0.02	0.0006
Men	−6.7 ± 8.9		
Aortic PP (mm Hg)			
Women	9.5 ± 6.5	n.s.	0.01
Men	13.9 ± 10.6		
MAP (mm Hg)			
Women	3.0 ± 6.8	n.s.	0.01
Men	−0.54 ± 8.1		
cfPWV ($m\,s^{-1}$)			
Women	2.4 ± 1.1	n.s.	0.03
Men	3.0 ± 1.7		
AIx75 (%)			
Women	17.2 ± 10.1	n.s.[a]	0.007
Men	22.9 ± 11.4		
SEVR (%)			
Women	−85.9 ± 32.6	n.s.	0.05
Men	−100.7 ± 47.8		

Abbreviations: AIx75, augmentation index adjusted to heart rate of 75 beats per minute; Aor, aortic; cfPWV, carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; n.s., not significant; PP, pulse pressure; SBP, systolic blood pressure; SEVR, subendocardial viability ratio.
cfPWV and HR post-pre exercise changes were calculated as the difference between the parameter at 2 min post exercise and at rest. All other parameters were calculated as the difference between the paramater at 5 min post exercise and at rest.
All values are mean ± s.d.
[a]*P* = n.s. after adjustment for height.

cfPWV at rest and after acute physical stress compared with women (Figure 2a and Supplementary Table 1). The pathophysiological explanation for this is unclear. However, differences in hormone and endothelin-1 (ET-1) production between men and women could contribute to the increased cfPWV seen in men. Estrogens decrease vascular resistance, improve endothelial dysfunction and decrease BP.[28] Indeed, it has been previously shown that the increased estrogen concentrations found in women is associated with reduced aortic stiffness.[29] Pearson *et al.*[30] found that testosterone induces upregulation of endothelin-1 mRNA in human aortic endothelial cells and an increase in the number of ET-1-secreting cells, whereas Stauffer *et al.* found than men are under greater ET-1 receptor tone than age-matched women.[31] Furthermore, ET-1 has been shown to be associated with arterial stiffness.[32,33] Although we did not measure sex hormones or ET-1 in this study, it is possible that differences in estrogen, testosterone and/or ET-1 between men and women contributed to the increased cfPWV seen in men.

The previous literature is not clear with respect to sex differences in cfPWV. The Anglo-Cardiff Collaborative Trial has demonstrated that there was no significant difference in cfPWV at rest between healthy men and women.[34] Other previous studies found similar results.[7,35,36] While the Reference Values for Arterial Stiffness' Collaboration recently demonstrated that there were sex differences in cfPWV, men had only 0.1 $m\,s^{-1}$ greater cfPWV than women after adjustment for traditional cardiovascular risk factors.[37] However, many studies also have found sex differences in aortic stiffness.[8,28,38,39] Aortic distensibility index and aortic impedence were higher in young men compared with women, but the reverse was true in an older population.[8] Furthermore, the age-related increase in cfPWV was also greater in women than in men.[38] It was noted that cfPWV is higher in middle-aged men.[39] Moreover, another study measuring brachial-ankle PWV (baPWV) found that men had higher baPWV until age 60, whereas it was similar between sexes after age 60.[4] It is clear that the heterogeneity of previous results was due, at least partly, to the different techniques used and age ranges of participants in these studies.

In the Framingham Heart Study, a one s.d. increment in arterial stiffness, as measured by cfPWV, was associated with a 48% increase in arterial disease risk, independently of individual vascular risk factors.[40] Furthermore, a meta-analysis found that an increase in cfPWV by 1 $m\,s^{-1}$ corresponded to an age-, sex- and risk factor-adjusted risk increase of 14%, 15% and 15% in total CV events, CV mortality and all-cause mortality, respectively.[41] An increase in cfPWV by 1 s.d. was associated with respective increases of 47%, 47% and 42%.[41] These studies did not assess sex differences and they were performed in much older populations compared with this study. Therefore, we cannot be sure of the applicability, especially considering 1 s.d. in cfPWV in our population represents ~0.7 $m\,s^{-1}$, which is less than the 1 $m\,s^{-1}$ and 1 s.d. used in these studies. Longitudinal studies in younger populations are needed to determine if cfPWV can be used as a marker for premature cardiovascular risk. Moreover, it is possible that using the arterial stress test may be useful to unmask further differences in vascular function. Longitudinal studies are needed to establish if this difference in response to acute physical stress is associated with the greater premature CVD seen in men.

It is also interesting that men showed an increased cfPWV after exercise despite a concomitant decrease in MAP (Figure 2a, Table 2 and Supplementary Table 1) even though it is well established that cfPWV and MAP are positively correlated.[42] It has been shown that nitric oxide (NO) synthase activity correlates to exercise capacity[43] and that decreased NO synthesis is associated with increased arterial stiffness.[44] Therefore, as men achieved higher workloads (greater exercise time, maximum HR and maximum METs), it is possible that an increase in NO synthesis was responsible for the decrease in MAP, which may underestimate the differences in cfPWV between groups.

We also found that at rest, women have higher AIx75. These findings agree with previous studies.[35,45,46] A significantly higher AIx, which represents systemic wave reflection, was noted in women above the age of 30 compared with age-matched men, with a similar trend between the ages of 10 and 29 years.[45] Furthermore, significantly higher AIx in women than men was previously found, even after adjustment for age, HR and MAP.[35,46] However, women have smaller body height at all ages, and this was shown to also be true in our study population ($P<0.0001$). This has been hypothesized to cause earlier wave reflection resulting in an increased AIx. Indeed, in our population, when height was added to the adjusted model, significance was lost. Others have also found that after adjusting for height, sex differences in AIx are lost.[35,46] However, in a group of elderly hypertensive men and women, a significantly elevated AIx was noted in women ($P<0.001$) even though the groups were matched for height.[47] It was also found that prepubescent women had a significantly greater AIx than men of similar age and height.[48] Therefore, it appears that although some sex differences in AIx can

be attributed to differences in height, it may not be the only contributor. Along those lines, it has also been shown that part of the increased AIx in women may be due to increased tapering of arterial diameter from the aorta to the periphery, which increases wave reflections.[49]

We found that men have higher aortic PP both pre- and post-exercise and that their post-pre exercise change of SEVR was significantly lower (greater decrease) than women before adjustment. The difference in aortic PP is expected and is in line with the fact that men have higher stroke volumes and body sizes.[50,51] As men achieved higher workloads (greater exercise time, maximum HR and maximum METs), they also likely achieved higher cardiac outputs and stroke volumes post exercise, which may explain the increased aortic PP in men post exercise. As the lowest SEVR achieved at 5 min post exercise was relatively similar in men and women (men, 75.8 ± 22.8; women, 77.5 ± 19.5, $P =$ n.s.), the difference in post-pre exercise change was due to the resting differences (men, 176.2 ± 43.8; women, 163.4 ± 40.9, $P = 0.04$). As SEVR represents cardiac O_2 supply/demand ratio,[52,53] our results suggest that young healthy men have a greater reserve, which may explain in part the fact that men were able to achieve higher workloads. Though we cannot be certain if men achieved greater workloads because they have a greater reserve or if men appear to have a greater reserve because they achieved higher workloads. In line with these results, others noted that men have higher SEVR at all ages from the first to the seventh decade.[45] Another study found that men have higher SEVR in a group with mean age in their 40s.[54]

Using the arterial stress test, we were not able to elicit differences between men and women in arterial stiffness that were not already present at rest. We have previously shown that in very light smokers who are otherwise healthy, acute physical stress can elicit vascular abnormalities that were not present at rest.[9] However, here we noted that differences in cfPWV, aortic BPs, AIx and SEVR between men and women existed already at rest.

There are limitations to this study. As we recruited consecutive participants who responded to our advertisements, we were not able to match for age and height. However, we did adjust for these covariates as well as others. In fact, to take a conservative approach, we adjusted more extensively than many other studies are able to, as we have a relatively large sample size. Because of the technical limitations of applanation tonometry, we were not able to measure arterial stiffness throughout exercise, only immediately post exercise. However, this is the most important information, as we needed to measure the ability of the vascular system to respond to maximal physical stress in men and women. Furthermore, as the time limitations for measurements post exercise were strict, we did not perform the PWA analysis at 2 min. We also did not measure VO_{2max} to confirm that the subjects reached their maximal exercise capacity. However, VO_2 peak was calculated using a validated formula from the American College of Sports Medicine (ACSM)[24] and we used three well-established criteria to ensure our subjects reached maximal exercise capacity, as mentioned in the Methods section.[20] Moreover, men reached a greater workload (greater exercise time, maximum HR and maximum METs) than women making direct comparisons for some arterial stiffness parameters difficult to interpret.

CONCLUSION

We have shown for the first time using 'the arterial stress test' that young men and women exhibit differences not only in arterial stiffness at rest but also after acute physical stress. Using the arterial stress test, we confirmed differences in vascular function that were present at rest but did not elicit further differences. This is likely because sex differences at rest were already present in cfPWV, aortic BPs, AIx and SEVR. Further longitudinal studies need to determine whether these sex differences seen in young populations are associated with cardiovascular risk differences seen later in life between men and women.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)