CALL FOR PAPERS | Sex and Gender Differences in Cardiovascular Physiology - Back to the Basics

Hemodynamic and arterial stiffness differences between African-Americans and Caucasians after maximal exercise

Huimin Yan,1 Sushant M. Ranadive,1 Kevin S. Heffernan,2 Abbi D. Lane,1,3 Rebecca M. Kappus,1,3 Marc D. Cook,1 Pei-Tzu Wu,1 Peng Sun,1 Idaethia S. Harvey,4 Jeffrey A. Woods,1 Kenneth R. Wilund,1 and Bo Fernhall1,3

1Department of Kinesiology and Community Health, University of Illinois, Urbana, Illinois; 2Department of Exercise Science, Syracuse University Syracuse, New York; 3Department of Kinesiology and Nutrition, University of Illinois, Chicago, Illinois; and 4Department of Human Development and Family Studies, University of Connecticut, Storrs, Connecticut

Submitted 16 September 2013; accepted in final form 27 October 2013

AfRican-AMericanS (AA) have a much higher prevalence of hypertension, cardiovascular disease (CVD), and renal disease compared with their Caucasian-American (CA) counterparts (55). Hypertension in AA subjects is characterized by higher incidence, earlier onset, longer duration, higher prevalence, and higher rates of hypertension-related mortality and morbidity (15).

Reduced arterial compliance is associated with hypertension and coronary artery disease. Carotid to femoral pulse wave velocity (PWV) has been regarded as the gold standard method (36) because of its accessibility and reliability (16). It is associated with incident CVD, independently of traditional risk factors in various populations (35). Even in young individuals, arterial compliance is a predictor of CVD events (61), and it is associated with functional and structural characteristics of the vasculature (13).

AA men have higher resting aortic blood pressure (BP) and aortic stiffness compared with age- and fitness-matched CA men (20, 21). An acute bout of maximal aerobic exercise also elicits a differential response in peripheral arterial stiffness in AA men compared with CA men (20). However, these studies used relatively small subject numbers and included only men. The differences in arterial stiffness may be attributed to a heightened BP response in AA subjects during exercise (47, 57) and the absence of postexercise hypotension after exercise in AA subjects but not in CA subjects (41). AA subjects also have elevated central BP despite comparable brachial BP compared with CA subjects (21). However, we are not aware of any study examining central BP after exercise in AA subjects. Furthermore, postexercise BP may have important diagnostic and prognostic implications (22). Postexercise hypotension is also associated long-term adaptations in BP with exercise training (19, 30); thus, the BP response to acute exercise can provide important clinical and physiological information.

Although young women have lower CVD mortality than men, women have higher resting levels of aortic wave reflection compared with men (10, 29) despite having lower pulse pressure and similar or lower arterial stiffness (2). This has been speculated to be due to the shorter stature in women, creating earlier reflection points and thus increasing wave reflection (49). However, the higher aortic wave reflection in women has been shown to be independent of height (4); thus, factors other than shorter stature likely contribute as well. Limited research has shown that the sex difference in aortic wave reflection may be maintained after an acute bout of exercise (3). Interestingly, sympathetic nerve activity affects aortic wave reflection differentially in men and women (10), as
HEMODYNAMIC CHANGES AFTER EXERCISE

Methods

Participants. This study was approved by the Institutional Review Board of the University of Illinois. One hundred young (age range: 18–37 yr), healthy individuals (28 AA men, 24 AA women, 25 CA men, and 23 CA women) volunteered for this study and provided signed informed consent.

All subjects were free of CVD, metabolic, renal, or respiratory disease and were nonsmokers. Subjects did not take any medications, including over-the-counter pain/anti-inflammatory medication. All subjects were in normal sinus rhythm and had no history arrhythmias. Subjects were self-defined as AA or CA if they reported that both parents were of African descent or both parents were of Caucasian descent. All subjects were recruited from the local community or university population.

Study design. All subjects reported to the laboratory for 2 days of testing (i.e., fasting blood draws on day 1 and vascular assessment on day 2). For vascular measures on day 2, all subjects were at least 3 h postprandial and did not exercise or consume caffeine or alcohol for 24 h before being tested. Female subjects were tested for vascular assessment during the early follicular phase of their menstrual cycle.

On day 2, subjects rested in the supine position for a period of 10 min in a temperature-controlled room before being tested. The sequence of measures was as follows: brachial artery oscillometry, arterial tonometry, peak O2 uptake (V̇O2peak) exercise testing, and recovery cardiovascular measurements at 15 and 30 min after exercise. These measurement periods were based on prior research showing racial differences in peripheral arterial stiffness after maximal exercise in men (20).

Antropometrics. Height and weight were recorded as previously described (21).

Brachial artery BP assessment. After 5 min of quiet supine rest in a dimly lit room, resting systolic BP (SBP) and diastolic BP (DBP) were measured with an automated oscillometric cuff following established guidelines (31). All BP measurements were repeated, and the average of the two values was recorded and used for analysis. If values differed by ≥5 mmHg, a third measurement was obtained, and the two closest values were averaged.

Wave reflection and aortic BP. Applanation tonometry was performed using a high-fidelity strain-gauge transducer (SphygmoCor, AtCor Medical, Sydney, NSW, Australia) on the radial artery to obtain pressure waveforms. Aortic SBP, aortic DBP, aortic mean arterial pressure (MAP), augmented pressure, augmentation index (AIx), and normalized AIx at a HR of 75 beats/min were derived from radial pressure waveforms as previously described (20).

Using a generalized validated transfer function (40), a central aortic pressure waveform was reconstructed from the radial artery pressure waveform to obtain aortic SBP and aortic DBP. This transfer function has been validated at rest and during exercise through invasive methods (48). Aortic MAP was derived from integrating the area under the central BP waveform. The reflected wave pressure amplitude (augmented pressure) was defined as the difference between peak SBP and pressure at the inflection point of the aortic waveform. AIx was calculated as the ratio of the amplitude of the pressure wave above its systolic shoulder (i.e., the difference between the early and late systolic peaks of the arterial waveform) to the total pulse pressure (pulse pressure = SBP – DBP). The result was expressed as a percentage and was used as an index of aortic pressure wave-reflection reflection. Because AIx is influenced by HR, AIx values were also normalized to a HR of 75 beats/min as previously described (20).

PWV. PWV was measured following current guidelines (54). Values from the carotid artery to the femoral artery (cPWV) and from the femoral artery to the superior dorsalis pedis artery (fPWV) were obtained as previously described (SphygmoCor, AtCor Medical) (20). A single high-fidelity strain-gauge transducer (Millar Instruments, Houston, TX) was used to sequentially obtain pressure waveforms between 1) the right common carotid artery and right femoral artery and 2) the right femoral artery and ipsilateral superior dorsalis pedis artery. Consecutive waveforms were captured for a 10-s epoch. Simultaneous ECG gating, as a timing marker, was assessed via a three-lead CM5 configuration and further used to obtain HR. The foot of the pressure wave was identified automatically, removing potential observer bias, using an algorithm that detects the initial upstroke via a line tangent to the initial systolic upstroke point of the pressure tracing and an intersecting horizontal line through the minimum point (12). This algorithm has been shown to be highly reproducible (12). Distances from the suprasternal notch to the femoral artery, carotid artery, and femoral artery sampling site to the superior dorsalis pedis artery were measured as straight lines with a tape measure. The distance from the carotid artery to the sternal notch was then subtracted from the sternal-femoral segment to correct for differences in propagation direction along the arterial path length and taken as a measure of central arterial stiffness. fPWV values were taken as indexes of peripheral arterial stiffness. cPWV values were taken as a measure of central/aortic stiffness. Integral software assessed the pulse wave quality (strength of the pulse wave signal, pulse height variation, pulse length variation, and baseline variation) and SD of mean time differences (SphygmoCor, AtCor Medical). This technique has been shown to be highly reproducible (60).

Department of Family Medicine, Case Western Reserve University, Cleveland, Ohio.

Supported by National Institutes of Health Grant HL-88086.
V̇O\textsubscript{peak} tests. V̇O\textsubscript{peak} was determined using an incremental graded cycling exercise test to exhaustion. V̇O\textsubscript{peak} was measured during all tests using a breath-by-breath metabolic system (Quark h2, Cosmed, Rome, Italy). Subjects completed a brief warmup consisting of cycling against no resistance for 1 min. The first workload was set at 50 W. Workload was increased by 30 W every 2 min until test termination. Subjects were asked to maintain a preferential cadence of 60–100 rpm. HR was measured using a HR monitor (Polar Electro, Woodbury, NY). Ratings of perceived exertion were also assessed once per stage. After termination of the test, the recovery protocol for leg ergometry consisted of 2 min of light cycling (50 rpm and 0 W) followed by 1 min of quiet sitting on the ergometer. Subjects were then immediately transferred to a table and assumed a supine position for the arterial measurements at 15 and 30 min postexercise.

Fasting blood chemistries. All blood draws were carried out in the morning with subjects in a fasted state for at least 12 h. Fasting glucose was assessed via an oxygen rate method using a Beckman Coulter oxygen electrode (Beckman Coulter, Villepinte, France). Total cholesterol, HDL-cholesterol, and triglycerides were measured using enzymatic techniques. LDL-cholesterol was calculated using the Friedewald formula. VLDL-cholesterol was calculated by dividing triglycerides by 5. White blood cell counts were measured using a quantitative automated hematology analyzer (Sysmex XE-2100, Sysmex, Kobe, Japan).

Renal function assessment. Given known racial differences in renal function, the estimated glomerular filtration rate (eGFR) was estimated from serum creatinine in accordance with recommendations from the Laboratory Working Group of the National Kidney Disease Education Program (34). eGFR was estimated from the Modification of Diet in Renal Disease Study formula (34).

Statistical analysis. All data are presented as means ± SE. Descriptive variables and baseline hemodynamic variables preexercise were analyzed with multivariate ANOVA to test for possible sex, race, and their interaction effects.

To evaluate the effect of maximal exercise in arterial and hemodynamic variables, absolute change values were calculated by subtracting postexercise from preexercise values. Three-way repeated-measures ANOVA was used to test for possible sex, race, time, and their interaction effects. Three-way repeated-measures analysis of covariance (ANCOVA) was used to test for possible sex, race, time, and their interaction effects after controlling for body mass index (BMI) or V̇O\textsubscript{peak}. Significant three-way interactions were probed by two-way ANOVAs with repeated measures (race by time, sex by time, and race by sex). We also conducted these probes using ANCOVAs controlling for V̇O\textsubscript{peak} and BMI. Bivariate correlations between changes in arterial stiffness measurements and changes in BP were assessed using Pearson’s correlation coefficients, respectively. Statistical significance was set at P < 0.05. SPSS 17.0 (SPSS, Chicago, IL) was used for all analyses.

RESULTS

Subject characteristics and hemodynamic variables are shown in Tables 1 and 2. There were significant interactions between race and sex in eGFR, HR, and BMI at rest (P < 0.05). AA subjects had significantly lower height, lower V̇O\textsubscript{peak}, higher weight, and greater BMI and eGFR compared with CA subjects (P < 0.05). Women had lower height, weight, V̇O\textsubscript{peak}, brachial SBP, AIx, normalized AIx at a HR of 75 beats/min, HR, augmented pressure, cPWV, VLDL-cholesterol, and triglycerides than men (P < 0.05). Women also had significantly higher HDL-cholesterol than men (P < 0.05; Table 1). No racial difference or sex by race interaction were found in any blood lipid levels.

Postexercise hemodynamics. Hemodynamic changes at 15 and 30 min after exercise are shown in Figs. 1–4. The change in brachial SBP was greater at 30 min postexercise than at 15 min.
Hemodynamic Changes After Exercise

There were no significant race effects or interactions. The sex effect was still significant after normalization for HR ($P < 0.05$). There were no significant race effects or interactions for normalized AIx at a HR of 75 beats/min. A significant time by sex effect and main effect of time, race, and sex were

![Graph](http://ajpheart.physiology.org/)

Fig. 1. A: change from rest to 15 min (P15) and 30 min (P30) after exercise for brachial systolic blood pressure (bSBP). §The change in bSBP was greater at 30 min compared with 15 min after exercise ($P < 0.05$). There were no significant race, sex, or interaction effects. B: change from rest to 15 and 30 min after exercise for brachial diastolic blood pressure (bDBP). There was a significant three-way interaction. *Caucasian-American (CA) men exhibited a different change from African-American (AA) men ($P < 0.05$). §The change in bDBP was different at 30 min compared with 15 min after exercise ($P < 0.05$) for both AA and CA men. There were no significant differences between AA and CA women and no significant differences between 15 and 30 min after exercise for either AA or CA women. Values are means ± SE.

![Graph](http://ajpheart.physiology.org/)

Fig. 2. A: change from rest to 15 and 30 min after exercise for aortic systolic blood pressure (aoSBP). †There was a significant race difference ($P < 0.05$). The change in aoSBP was greater in CA subjects compared with AA subjects. There were no significant time, sex, or interaction effects. B: change from rest to 15 and 30 min after exercise for aortic diastolic blood pressure (aoDBP). *CA men exhibited a different change from AA men ($P < 0.05$). §The change in bDBP was different at 30 min compared with 15 min after exercise ($P < 0.05$) for both AA and CA men. There were no significant differences between AA and CA women and no significant differences between 15 and 30 min after exercise for either AA or CA women. C: change from rest to 15 and 30 min after exercise for aortic mean arterial pressure (aoMAP). §There was a significant time by race interaction for men, showing that the change in aoMAP from 15 to 30 min after exercise was greater in CA men compared with AA men. †There was an overall race effect ($P < 0.05$) showing a greater change in aoMAP in CA subjects compared with AA subjects. Values are means ± SE.
The change in HR in AA men was greater at 15 and 30 min after exercise than AA women (men: 25 ± 2 to 15 ± 2 beats/min; women: 14 ± 2 to 10 ± 2 beats/min). The change in HR was similar in CA men and CA women (men: 26 ± 2 to 18 ± 2 beats/min; women: 23 ± 2 to 16 ± 2 beats/min). CA women also exhibited a greater change in HR compared with AA women (P < 0.05). The change in HR was also greater at 15 min compared with 30 min after exercise in all groups (P < 0.05). There were no statistically significant effects for the change in cPWV or fPWV. Covariance for VO₂peak did not alter any of these findings. However, after adjustment for BMI, a significant time by race interaction was found for the change cPWV (P < 0.05). The change in cPWV was significantly different in CA subjects compared with AA subjects at the 30-min time point after exercise (Fig. 4), with cPWV being below baseline in CA subjects and above baseline in AA subjects, making the difference between the change in cPWV between AA and CA subjects (men and women combined) significant.

The change value of Alx from rest to 15 min after exercise was negatively correlated with the change value of HR (r =
0.249, $P < 0.05$) and positively correlated with aortic SBP ($r = 0.266, P < 0.05$). No correlation was found between the change in AIx and arterial stiffness (cPWV and fPWV) and the change in any of the BP measurements.

**DISCUSSION**

The main finding of the study was that acute maximal exercise induced differential central arterial stiffness and BP responses during exercise recovery in AA and CA subjects. An acute bout of maximal cycling exercise elicited a small increase in central stiffness in AA subjects but a small decrease in central stiffness in CA subjects, making the change in central stiffness significantly different between AA and CA subjects. Another novel finding was that the change in central BP after maximal exercise was reduced in AA subjects compared with CA subjects but that the change in central stiffness was not associated with the change in central BP. These differences cannot be attributed to resting differences in cardiovascular risk factors, as kidney function was normal, resting BP and blood lipids did not differ between CA and AA subjects, and we statistically controlled for differences in BMI. In addition, women exhibited higher aortic wave reflection and a greater change in AIx after maximal aerobic exercise compared with men.

**Racial comparisons.** AA subjects have been shown to exhibit cardiovascular hyperreactivity to stress with an exaggerated BP response to behavioral and physiological (7) sympathoexcitation, which is in accordance with the present study. AA subjects have also been shown to have higher SBP and DBP during submaximal dynamic exercise compared with CA subjects (57). The BP response to exercise is clinically significant since a higher exercise BP response is related to higher CVD risk (52). The exaggerated cardiovascular hyperreactivity may be a result of reduced $\beta$-adrenergic sensitivity and augmented $\alpha_1$-adrenergic receptor sensitivity (27), resulting in higher vascular resistance (6). An altered response to sympathetic stimuli might be implicated in the stiffening of large arteries and thus contribute to the development and progression of hypertension and its complications.

Earlier work from our laboratory (21) has shown that resting central BP is elevated in AA subjects despite comparable brachial BP at rest. Here, we extend our previous work by showing that central SBP after exercise changed differently in AA and CA subjects despite comparable changes in brachial BP. However, we did not note increased central arterial stiffness in AA participants compared with their CA counterparts at rest, nor did we see differential responses of leg peripheral arterial stiffness after exercise. It should be noted the studies revealing structural differences between AA and CA groups were population-based studies with a wide age range from teenagers to older individuals. The fact that we did not observe differences in central stiffness between AA and CA subjects at rest confirmed the use of acute exercise as physiological perturbation to evoke racial difference in elastic properties in the central arteries in young individuals free of overt CVD.

**Sex comparisons.** In agreement with previous studies (10, 29), women demonstrated higher baseline levels of aortic wave reflection compared with men. When normalized for HR, AIx remained higher in women. Augmented pressure was also increased in women. The majority of wave reflection as seen by the heart is attributable to the branching of the aorta at the celiac trunk and renal arteries and its terminal tapering (33). These sex differences have been attributed to women with shorter body height and an associated shorter aorta, which, in turn, results in earlier wave reflections (49). Even in height-matched elderly hypertensive subjects, women had earlier
arterial wave reflection, although of similar magnitude, compared with men, possibly explained by a reduced aortic arterial diameter of ~5% and increased aortic stiffness (17). Both factors are likely to lead to an increased cPWV; however, in our study as well as another study in young healthy individuals (43), cPWV was higher in men at rest, suggesting there may be other factors modulating central arterial stiffness. It should also be noted that the traditional way of interpreting wave reflection was based on the assumption that the central arterial was a uniform tube with single reflection site and that forward and backward waves maintain their shape while traveling to the end of the tube and back (50, 51). The disassociation between resting cPWV and AIx in men and women in our study may be explained by recent evidence suggesting the traditional model may be oversimplified and that backward waves are likely compound waves consisting of echo from many reflection sites (58, 59). In an elastic aorta, AIx is more likely to be related to the intensity of the reflected wave rather than to its velocity. Also, in healthy men, vasoactive drugs can change aortic AIx independently from changes in cPWV, suggesting that AIx and cPWV are not necessarily associated (23).

To our knowledge, the present study is the first study examining sex differences in arterial wave reflection after an acute bout of maximal aerobic exercise. The change in wave reflection after maximal exercise was greater in women than in men. Submaximal exercise at a HR of 100 beats/min has been shown to decrease AIx in young men and women similarly during exercise (3). Sex differences during recovery from high-intensity exercise may be due to differential levels of catecholamines, as higher levels of catechamaines in men result in increased AIx and greater HR during recovery (8). Thus, the difference in AIx could be a function of differences in HR, as higher HR is independently associated with a reduction in aortic AIx during β-adrenergic stimulation (26). However, the difference in HR between men and women is unlikely to explain the sex difference in AIx, since there was still a sex difference in the change in wave reflection when we controlled for HR (normalized AIx at a HR of 75 beats/min).

Muscle sympathetic nerve activity may play an important role in modulating aortic waveforms in men and women, as positive correlations have been found between sympathetic activity and wave reflection in men but a negative association was found in women (10). Considering the large increase in sympathetic nerve activity with exercise, it may not be surprising to find differential changes in aortic wave reflection during recovery. However, the mechanism underlying the inverse relationship remains unknown; therefore, we can only speculate the potential mechanisms. An increased sensitivity to β-adrenergic receptor stimulation in women may be partly responsible for the observed differential responses (24). Greater β-adrenoceptor-mediated vasodilatation in resistance arteries in women during recovery from exercise may contribute to differences in central wave patterns compared with men.

Female sex hormones may also be responsible for this differential response in women. Follicle-stimulating hormone (FSH) is highly correlated with arterial mechanical properties and may be the most sensitive marker of declining arterial function with aging (56). Our female subjects were all tested during the early follicular phase of the menstrual cycle, which is characterized by a rise in FSH during the first days of the cycle. It is possible that the differences between men and women were increased due to FSH. Finally, estrogen has direct vasodilatation effects by stimulating endothelial nitric oxide synthase activity via activation of estrogen receptor-α (11, 18) and potentially decreases wave reflection. However, the contribution of estrogen is probably limited because the surge of estrogen and the associated decline in AIx occurs only during late follicular phase of the menstruation cycle (1). Future research is warranted to examine the hormone levels and other potential mechanisms responsible for the observed differential responses in men and women.

Strength and limitations. The strength of the present study is a relatively large sample size. In addition, women were tested during the early follicular phase of their menstrual cycle to minimize the effect of female hormones. The design of the study also allowed us to examine baseline differences in our four groups as well as cardiovascular responses after an acute bout of exercise. Standard maximal aerobic exercise was used as a stressor to elicit cardiovascular responses that may not be evident at rest.

We did not control for socioeconomic status; however, we recruited most of our subjects from university students, and, therefore, they had a similar level of education. Furthermore, this is a cross-sectional study, and cause-effect cannot be inferred.

We did not directly measure aortic stiffness or central wave reflection but used noninvasive validated and well-accepted techniques. cPWV is an accepted standard measure of arterial stiffness and has been used in most large-scale studies. Also, central wave reflection, although derived from a transfer function, is valid both at rest and after exercise, as shown by validation compared with invasive techniques (48). Furthermore, although we screened subjects based on health history, we do not know if any of the subjects had latent coronary artery disease, diastolic dysfunction, or left ventricular hypertrophy, which might have affected our results. However, given the young age and general health status of our subject population, it is unlikely that these factors exhibited a significant influence on our results. Also, none of the subjects experienced any signs or symptoms of coronary artery disease during the maximal exercise test.

Conclusions. Young AA and CA subjects exhibited differential responses in central stiffness and central BP after acute maximal exercise. Premenopausal women had greater AIx and augmented pressure at rest and exhibited greater reduction in aortic wave reflection after maximal aerobic exercise.

GRANTS
This work was supported by National Heart, Lung, and Blood Institute Grant 1-R01-HL-093294-01A1 (to B. Fernhall) and a grant from the American Heart Association (to K. S. Heffelman).

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
REFERENCES


