Comparison of abdominal aortic hemodynamics between men and women at rest and during lower limb exercise

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Introduction: **Biologic variations between men and women have been hypothesized to contribute to the differences in atherosclerosis epidemiology of the two genders. Hemodynamics are also hypothesized to play an important role in the localization of atherosclerosis in the abdominal aorta. However, the hemodynamics of men and women have not been compared at this location at rest or during lower limb exercise conditions.**

Methods: **A magnetic resonance–compatible exercise bicycle, magnetic resonance imaging techniques, and custom data processing software were used to quantify blood flow rate, wall shear stress, and oscillations in flow and wall shear stress at the supraceliac and infrarenal levels of the abdominal aorta of young healthy men and women at rest and during lower limb exercise.**

Results: **Heart rate increased from 73 ± 6.2 bpm at rest to 110 ± 8.8 bpm during exercise ($P < .0001$). No statistical differences were found at the infrarenal level for mean blood flow rate (men, 0.9 ± 0.4 L/min; women, 0.8 ± 0.4 L/min) or mean wall shear stress (men, 1.2 ± 0.5 dynes/cm^2; women, 1.4 ± 0.7 dynes/cm^2) at rest or mean blood flow rate (men, 5.9 ± 1.3 L/min; women, 5.2 ± 0.8 L/min) or mean wall shear stress (men, 5.1 ± 0.8 dynes/cm^2; women, 5.4 ± 2.1 dynes/cm^2) during exercise. Also, no differences were seen in temporal flow and wall shear stress oscillations between men and women at rest or during exercise. Similarly, no significant hemodynamic differences were found between the genders at the supraceliac level.**

Conclusion: **These similarities suggest that hemodynamics may not play a significant role in abdominal aortic disease differentiation between the genders and that biologic factors may be more important. (J Vasc Surg 2003;37:118-23.)**

Cardiovascular diseases are the greatest cause of mortality in the United States, with three quarters of these cases attributed to atherosclerosis.[1] Although approximately the same percentage of women die of atherosclerosis as men,[1] specific disease statistics are different between the genders. For instance, epidemiologic evidence has shown that the onset of coronary artery disease, the greatest contributor to atherosclerosis-related mortality, occurs about 10 years later in life in women as compared with men.[1] Also, large-vessel peripheral artery disease is 50% more prevalent in men as compared with women before the age of 75 years, and abdominal aortic aneurysms occur in six times as many men as women for all ages.[2]

Observational and experimental evidence shows that the development of atherosclerosis in the human abdominal aorta proceeds more slowly in women as compared with men. On inspection of the aortas of accident victims between the ages of 9 and 30 years, most preatherosclerotic lesions were found to be present by the age of 15 years and no statistical difference was seen in scope and severity in the preatherosclerotic lesions between the genders.[3] Because of the greater extent of aortic disease in age-matched men as compared with women in the later years of life, it follows that the progression of disease is faster in men.[3]

Hemodynamics play an important role in the development of atherosclerosis. Low flow, flow recirculation, low mean wall shear stress, and oscillations in shear stress are hypothesized to play a role in the localization of atherosclerotic lesions in the carotid bifurcation, coronary arteries, and abdominal aorta.[4-7] These low shear stress areas are hypothesized to be more susceptible to cholesterol accumulation because of low local diffusional efflux from the arterial wall to the flowing blood and enhanced monocyte adhesion.[4,8] In contrast to the effects of low shear stress, increases in blood flow have been shown to stimulate the expression of nitric oxide synthase and superoxide dismutase, resulting in the reduction of cellular superoxide anion concentration and expression of monocyte chemotactic protein–1 and vascular cell adhesion molecule–1.[8,9] These effects reduce the adhesiveness of monocytes on the endothelium and are hypothesized to protect arteries from atherosclerotic plaques. Furthermore, elevated mean wall shear stress stimulates cellular structural changes, including cell elongation in the direction of maximum stress, inhibiting cholesterol accumulation from less permeable endothelial cell junctions.[10]

Although biologic factors have been examined to elucidate mechanisms by which atherosclerosis develops more slowly in females, and in some cases less often than in males, hemodynamic differences between men and women have

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not been well documented. Lev et al[11] compared left ventricular function of postmenopausal women and middle-aged men with Doppler ultrasound scan, although only at rest. Gender differences in abdominal aortic flow and wall shear stress have not been previously reported at all. We have used a custom magnetic resonance (MR)–compatible bicycle in open-magnet and cine phase contrast MR imaging (MRI) techniques[12] to measure blood flow velocities in the abdominal aortas of young healthy men and women during upright rest and light lower limb exercise conditions. We quantified blood flow rate and wall shear stress conditions at the supraceliac and infrarenal levels of the aorta and compared the hemodynamics of men and women.

MATERIALS AND METHODS

Six healthy nonsmoking male subjects (mean age, 22.3 years; range, 20 to 24 years) and five healthy nonsmoking female subjects (mean age, 25.2 years; range, 23 to 28 years) underwent imaging at rest and during lower limb exercise with a 0.5-T open magnet (GE Signa SP, GE Medical Systems, Milwaukee, Wis). The subjects were securely strapped to an upright seat in the open magnet to permit full range of leg motion with positioning of the abdomen in the center of the magnet for optimal imaging (Fig 1). The MR-compatible bicycle then was adjusted to promote comfortable pedaling and minimize abdomen movement.

Fig 1. Subject pedaling MR-compatible bicycle in 0.5-T open magnet.

MRI studies were performed at rest and during steady-state exercise conditions (150% of resting heart rate). Subjects monitored their own heart rate (displayed in real time on a monitor) and adjusted pedaling speed as necessary to maintain a constant exercise heart rate. Cine phase contrast MRI techniques were used to measure spatial maps of through-plane blood flow velocity at the supraceliac and infrarenal levels at rest and during exercise.[13] Image acquisitions were gated to the cardiac cycle with a plethysmograph placed on the right index finger, and the image data were reconstructed to 16 evenly spaced time points within the cardiac cycle. The subjects breathed normally during the acquisitions, and respiratory compensation algorithms were used.[14] Scan parameters included: time of repetition, 25 ms; time of echo, 9 ms; flip angle, 30 degrees; slice thickness, 5 or 10 mm (to maximize signal depending on the anatomy of the subject); square field of view, 28 cm $\times$ 28 cm; matrix dimensions, 256 $\times$ 128 pixels; and through-plane velocity encoding gradient, 150 cm/s. This imaging protocol was approved by the Stanford University Panel on Human Subjects in Medical Research.

We quantified volume flow rate and wall shear stress at the supraceliac and infrarenal levels of the aorta with the spatial maps of anatomy and blood flow velocity. With the cross section of the aorta isolated with threshold segmentation of the anatomic data and the blood flow velocity values associated with each pixel within that cross section, pixels volume flow rates were summed to calculate total volume flow rate.[12] For the wall shear stress computation, we used a level set method to segment the lumen[15,16] and represented the velocity profile of the blood flow near the vessel wall with third order Lagrangian interpolation functions.[17] Next, we computed the gradient of the through-plane velocities along the curve of the lumen by differentiating these functions and evaluated the wall shear stress by multiplying the gradient by the viscosity of blood, taken as a constant 4 cP.[17]

The flow data are presented as temporally averaged over the cardiac cycle, and the wall shear stress data are presented as circumferentially averaged along the lumen curve and temporally averaged over the cardiac cycle. To quantify temporal oscillations in blood flow and shear stress, we defined the oscillatory flow index (OFI)[18] and oscillatory shear index (OSI)[19] as follows:

Table I. Gender averages for hemodynamic quantities

	Men (n = 6)	*Women (n = 5)*	*Statistical difference*
Age (y)	22.3 ± 1.4	25.2 ± 2.2	–
Height (m)	1.74 ± 0.08	1.73 ± 0.05	–
Weight (kg)	71.1 ± 9.3	60.4 ± 9.0	$P < .05$
BMI (kg/m^2)	23.6 ± 2.3	20.2 ± 2.1	$P < .05$
Heart rate (bpm)			
Rest	71 ± 6	75 ± 6	–
Exercise	107 ± 9	111 ± 9	–
Flow rate (L/min)			
Rest-SC	3.0 ± 0.6	2.8 ± 0.7	–
Exercise-SC	7.6 ± 1.4	6.7 ± 1.3	–
Rest-IR	0.9 ± 0.4	0.8 ± 0.4	–
Exercise-IR	5.9 ± 1.3	5.2 ± 0.8	–
Wall shear stress (dynes/cm^2)			
Rest-SC	3.6 ± 0.9	3.4 ± 0.7	–
Exercise-SC	7.2 ± 0.5	6.1 ± 0.4	–
Rest-IR	1.2 ± 0.5	1.4 ± 0.7	–
Exercise-IR	5.1 ± 0.8	5.4 ± 2.1	–
OFI			
Rest-SC	0.01 (0.00-0.06)	0.00 (all 0.00)	–
Exercise-SC	0.00 (all 0.00)	0.00 (all 0.00)	–
Rest-IR	0.12 (0.06-0.27)	0.10 (0.00-0.22)	–
Exercise-IR	0.00 (all 0.00)	0.00 (all 0.00)	–
OSI			
Rest-SC	0.01 (0.00-0.03)	0.01 (0.00-0.03)	–
Exercise-SC	0.00 (all 0.00)	0.03 (0.00-0.09)	–
Rest-IR	0.14 (0.06-0.25)	0.12 (0.00-0.26)	–
Exercise-IR	0.01 (0.00-0.02)	0.00 (all 0.00)	–

Gender averages of age, height, weight, BMI, rest and exercise heart rates, and rest and exercise blood flow rate, wall shear stress, OFI, and OSI at supraceliac and infrarenal levels of abdominal aorta. Data are presented as average ± standard deviation except for OFI and OSI, which are presented as average (range). Men had significantly higher weights and BMIs as compared with women. No statistical differences were seen in any of hemodynamic quantities between men and women. P value < .05 indicates statistically significant difference between male and female sample groups.
SC, Supraceliac; *IR*, infrarenal.

$$(1) \quad \mathrm{OFI} = \frac{1}{2}\left(1 - \frac{\left|\int_0^T Q\,dt\right|}{\int_0^T |Q|\,dt}\right) \qquad \mathrm{OSI} = \frac{1}{2}\left(1 - \frac{\left|\int_0^T \tau\,dt\right|}{\int_0^T |\tau|\,dt}\right)$$

where Q is blood flow rate, τ is wall shear stress, and T is the period of the cardiac cycle.

The mean hemodynamic quantities of the male and female subjects were compared with standard *t* tests to identify statistical significance. Correlations with height, weight, and body mass index (BMI) were also explored with linear regression analysis.

$$(2) \quad \mathrm{BMI} = \frac{\mathrm{BodyWeight}}{\mathrm{Height}^2}\frac{\mathrm{kg}}{\mathrm{m}^2}$$

RESULTS

Table I shows the average data for men and women for age, height, weight, BMI, and rest and exercise heart rates. Also included are the average hemodynamic quantities of blood flow rate, wall shear stress, OFI, and OSI at rest and during lower limb exercise conditions. Age and height were not statistically different between men and women; however, the men had a statistically higher weight ($P < .05$) and BMI ($P < .05$). None of the hemodynamic conditions were statistically different between men and women either at rest or during exercise.

Temporally resolved plots (for a cardiac cycle) of blood flow rate and wall shear stress at the supraceliac and infrarenal levels for men and women are shown in Fig 2. Blood flow rate increased for all time points from rest (Fig 2, *A*) to exercise (Fig 2, *B*) for both anatomic locations, with a larger increase at the infrarenal level. The difference between the supraceliac and infrarenal flows represents the flow to the digestive and renal circulations. Wall shear stress also increased from rest (Fig 2, *C*) to exercise (Fig 2, *D*), with a larger increase at the infrarenal level. Note that the negative values of flow rate (Fig 2, *A*) and wall shear stress (Fig 2, *C*) during diastole at rest at the infrarenal level were eliminated during exercise.

Total abdominal aortic flow increased 2.4-fold for men and 2.6-fold for women, and infrarenal flow increased 8.0-fold for men and 7.4-fold for women from rest to exercise (Fig 3, *A*). Less than 30% of the total abdominal aorta blood flow persisted into the infrarenal aorta at rest for both men and women; during exercise, this proportion increased to nearly 80%. Blood flow to the celiac, superior mesenteric, and renal arteries (as calculated by subtracting infrarenal flow from supraceliac flow) decreased signifi-

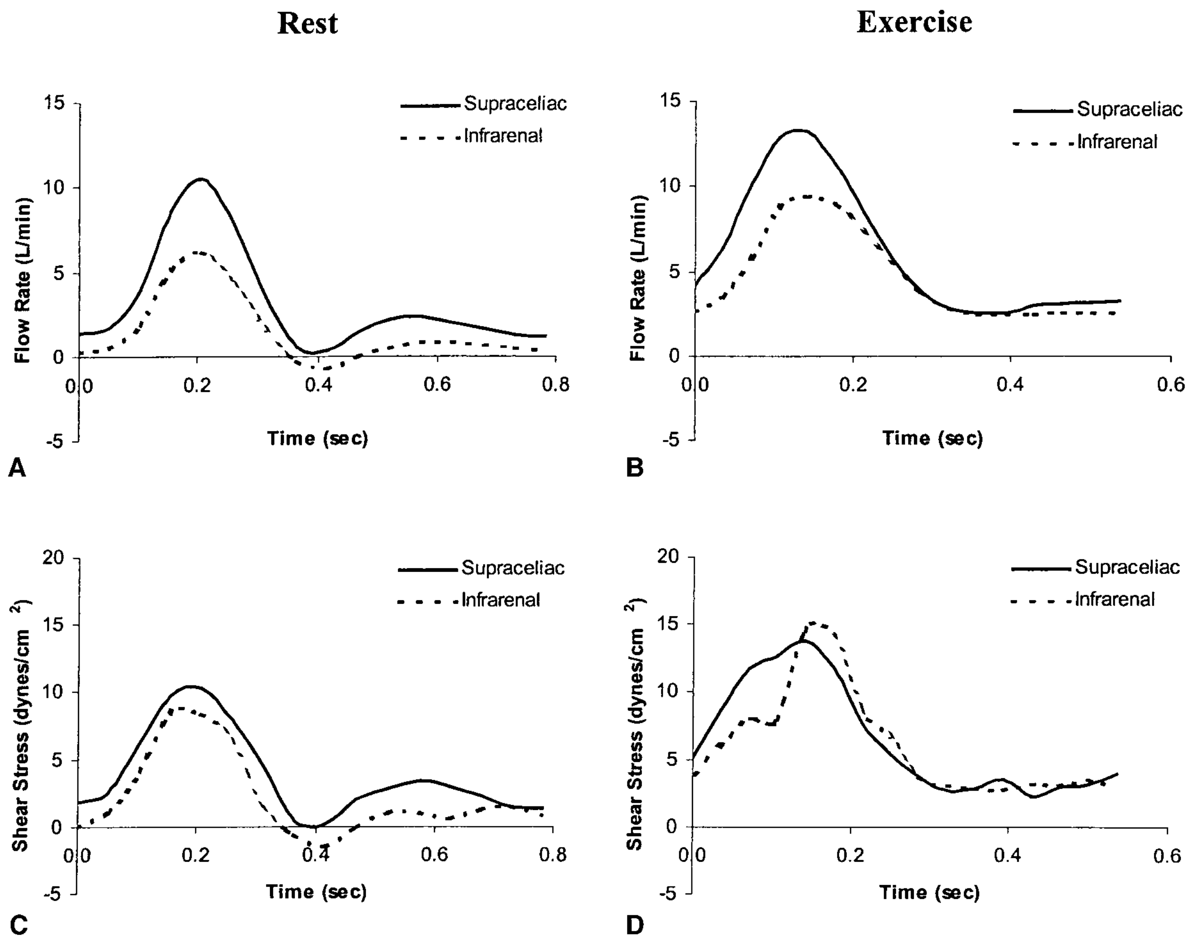

Fig 2. Time-resolved blood flow rate (**A** and **B**; *top*) and wall shear stress (**C** and **D**; *bottom*) curves for supraceliac and infrarenal levels of abdominal aorta of representative male subject at rest (**A** and **C**; *left*) and during lower limb exercise (**B** and **D**; *right*). Note that at rest infrarenal region experiences reverse flow and wall shear stress at end systole, whereas supraceliac region does not. Also note that flow rate and wall shear stress increase for entire cardiac cycle for both supraceliac and infrarenal regions during exercise, with complete elimination of reverse flow and wall shear stress.

cantly from rest (2.2 ± 0.4 L/min) to exercise (1.7 ± 0.4 L/min) in men ($P < .05$) and nonsignificantly from rest (2.0 ± 0.5 L/min) to exercise (1.4 ± 1.1 L/min) in women ($P < .1$). Mean wall shear stress approximately doubled (2.0 for men; 1.8 for women) in the supraceliac aorta and approximately quadrupled (4.4 for men; 3.8 for women) in the infrarenal aorta from rest to exercise (Fig 3, *B*). Flow and wall shear stress reversal, as measured with the OFI and OSI, observed in the infrarenal aorta at rest were significantly decreased with exercise for both genders.

Table II shows the results from the linear regression analysis, performed to find the strength of correlation of flow rate and wall shear stress to height, weight, and BMI. Moderate to strong correlations were found between blood flow at the supraceliac and infrarenal levels with height, weight, and BMI during exercise conditions. No other correlations were significant.

DISCUSSION

No statistically significant differences were found, at rest or during lower limb exercise, for flow rate, wall shear stress, OFI, or OSI at either the supraceliac or infrarenal levels of the abdominal aorta between the men and women of this study. In addition, lower flow rate, lower wall shear stress, and greater oscillations in flow and shear stress were observed at the infrarenal as compared with the supraceliac aorta at rest, for both men and women. This was consistent with the observation that atherosclerotic disease is found more prevalently at the infrarenal level as compared with the supraceliac level.[4,6,20] Moreover, the increases in blood flow rate and wall shear stress were not statistically different between men and women from rest to exercise, and oscillations in flow and wall shear stress present at rest in the infrarenal aorta were essentially eliminated during exercise. Also of interest was that blood flow to the digestive and

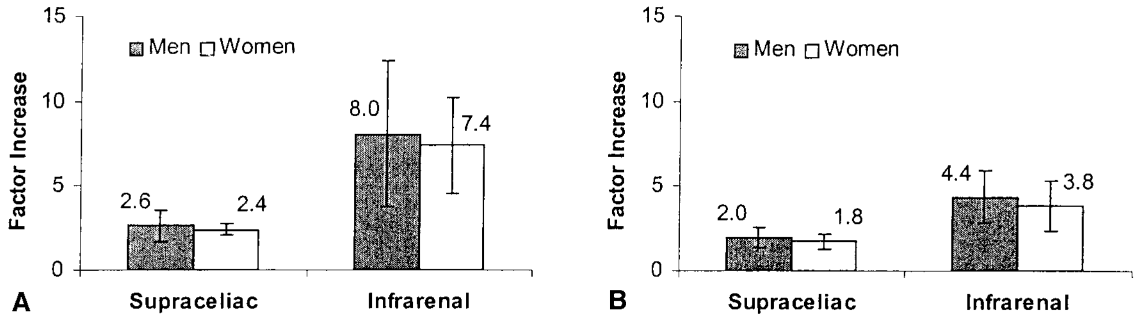

Fig 3. Average ± standard deviation of factor increase in blood flow rate **(A)** and wall shear stress **(B)** at supraceliac and infrarenal levels of abdominal aorta from rest to exercise for men and women. For both genders, increases in blood flow rate and wall shear stress from rest to exercise were greater at infrarenal level as compared with supraceliac level.

Table II. Strength of correlation of flow rate and wall shear stress to anthropometric data

	Rest-SC	*Rest-IR*	*Exercise-SC*	*Exercise-IR*
Flow versus				
Height	0.402	0.274	0.555	0.501
Weight	0.318	0.000	0.896	0.717
BMI	0.145	0.145	0.756	0.561
WSS versus				
Height	–0.207	0.044	–0.157	–0.026
Weight	–0.289	–0.280	0.204	0.201
BMI	–0.222	–0.320	0.329	0.228

Strength of correlation of flow rate and wall shear stress at supraceliac and infrarenal levels of aorta at rest and during exercise as compared with height, weight, and BMI. Moderate to strong correlations were found for flow rate during exercise for both supraceliac and infrarenal levels for height, weight, and BMI. All other correlations were weak.
With r as coefficient of correlation, $r < 0.5$, weak correlation; $0.5 < r < 0.8$, moderate correlation; and $r > 0.8$, strong correlation.
WSS, Wall shear stress; *SC*, supraceliac; *IR*, infrarenal.

renal circulations decreased in men and women from rest to exercise. The decrease was statistically significant for men ($P < .05$) but not significant (but nearly) for women ($P < .1$).

These alterations in hemodynamics from rest to exercise may be important mechanisms by which exercise protects large arteries from atherogenesis and disease progression. Even though the direct hemodynamic benefits of exercise may only last for short periods of time, the biologic changes triggered by the fluid mechanical forces may have extended effects. Wang, Wolin, and Hintze[21] found that bouts of exercise enhanced the production of nitric oxide in the large coronary artery of dogs, which persisted after the cessation of activity. These hemodynamic and biologic effects, in addition to the systemic benefits achieved with exercise (eg, enhanced cholesterol metabolism and lower blood pressure) may contribute to the correlation of physical activity and reduced incidence of atherosclerosis.

The approximately 8-fold increase of infrarenal blood flow observed in this study (for both genders), as a result of lower limb exercise, is greater than those values previously published. For instance, Pedersen et al[22] reported a flow rate increase of 4.6-fold in the infrarenal aorta immediately after supine lower limb exercise (80% increase in resting heart rate). Note that our measurements were performed during exercise and the lower limb exercise was upright. Other flow measurements in humans during exercise were either supine at lower exercise intensities[23] or not conducted in the abdominal aorta.[24,25] Furthermore, our quantification of in vivo wall shear stress during exercise can be used to study the effects of physiologic arterial wall shear stress during exercise via endothelial cell culture experiments.

Our results also showed some correlation of hemodynamics with our subject anthropometric data. Significant correlations were found between flow rate during exercise and height, weight, and BMI. This is consistent with the fact that the quantity of oxygenated blood flow is closely related to the exercise intensity and the amount of metabolically active muscle. The weak correlation of wall shear stress with body size is consistent with the theory that wall shear stress is constant in similar vessels across populations.[26,27] In comparison of our men and women subject groups, men were found to have statistically higher body weight and BMI. Considering the statistically similar blood flow rates between men and women, this may seem to conflict with the correlation of blood flow with body size. However, anthropometric data show that women have proportionally higher lower limb mass than men (when compared with total body mass),[28] which could explain the relatively higher lower limb blood flow.

On the basis of animal studies, the disparity in atherosclerosis development between the genders has been hypothesized to be accounted for by biologic differences between males and females at the molecular level. Nathan et al[29] investigated the effects of estradiol, the most potent human estrogen, on atherogenic processes in hypercholesterolemic rabbits. Not only did they find that male rabbits had more monocyte adhesion and subendothelial migration in the aorta as compared with females, they also showed that the administration of physiologic levels of estradiol in oophorectomized rabbits reduced the protein expression of vascular cell adhesion molecule–1 and monocyte adhesion.[29] Hayashi et al[30] also found that after 10-week and 15-week periods of a cholesterol-enhanced diet female rabbits had significantly higher levels of endothelium-derived relaxation factor/nitric oxide release in their aortic tissue as compared with males.

The similarity in hemodynamic conditions that we find in the abdominal aorta of men and women has significant implications. First, this investigation suggests that hemodynamic studies in the human abdominal aorta may not need to be gender specific, at least for young healthy subjects. Also, it suggests that abdominal aortic atherosclerosis development differences may be mainly the result of biologic variations between men and women, rather than hemodynamic factors. A limitation to this research is that we only performed measurements in the abdominal aortas of young healthy subjects for a specific type and intensity of exercise. Further research is needed to elucidate gender dependence of hemodynamics in locations other than the abdominal aorta and for different age populations, higher exercise intensities, and other forms of exercise.

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