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# Sex Differences and Arterial Stiffness

## Die Methode ist Alles

We are concerned about methods used by our esteemed colleagues, Coutinho et al. (1), and question their conclusion, based on higher characteristic impedance ($Z_c$) and lower total arterial compliance (TAC), that the aorta and large elastic arteries of women are stiffer than those of men. Both calculated $Z_c$ and TAC relate volume to pressure without scaling. The aorta of a child is small. With growth, $Z_c$ decreases and TAC increases, but this cannot be interpreted as lower stiffness because arteries become more, not less, stiff with age (2). Likewise, small animals have higher $Z_c$ and lower TAC than larger animals. Because there are systematic differences in weight and height between male and female adult cohorts (2), the (smaller) females will appear to have stiffer arteries (i.e., higher $Z_c$ and lower TAC) than men if not appropriately scaled for body size. When appropriately scaled to aortic cross-sectional area in Table 1 of Coutinho et al. (1), $Z_c$ in males ($172 \times 10\ cm^2 = 1{,}720$ dynes $\cdot$ s $\cdot$ $cm^{-3}$) and in females ($211 \times 8.3 = 1{,}751$ dynes $\cdot$ s $\cdot$ $cm^{-3}$) are virtually identical. With the same scaling, TAC also appears identical.

Scaling is used elsewhere in the authors' data analysis, but not consistently. Smaller echo dimensions in females are consistent with smaller body size (Table 1 [1]). Height and weight are not provided in the table, text, or online appendix.

The authors' Table 1 (1) contains many anomalies that ought be considered and explained. Amplification of the pressure wave between the central and peripheral sites is 3%, not 5%, in males, and −3%, not zero, in females. Both values are much lower than measured invasively (2). Mean pressure, calculated as (brachial diastolic blood pressure × 2 + systolic blood pressure) ÷ 3 (data supplement [1]), is 93, not 97, mm Hg for males and 92, not 98, mm Hg for females. Values for left ventricular (LV) outflow tract diameter must be centimeters, not millimeters (i.e., 2.3 cm male, 2.0 cm female). Taper in diameter of 55% in males (35.6/23.0) and 63% for females (32.6/20.0) over a length of <5 cm between the LV outflow tract and site of aortic diameter measurement (which we do not challenge) must create secondary flow and turbulence in the aorta (2). There is concern also on the low value of pressure amplification compared with those in the authors' reference 9 (1) and in the paper by Safar et al. (3) in the same issue of the *Journal*.

The authors are highly respected clinical investigators and colleagues, and may not be aware of the aforementioned anomalies, if their data were analyzed in an outside center without adequate technical scrutiny. We have not been able to trace the source of the quoted "NIHem" on the Internet. We need stress in papers such as this, Carl Ludwig's dictum: "Die Methode ist Alles" (2).

Differences in arterial hemodynamics between adult males and females do exist, but can be attributed to shorter body length with earlier return of wave reflection, and hence, greater aortic pressure augmentation in females (the authors' Table 1). Such greater pressure augmentation accounts for impaired LV relaxation and the higher prevalence of diastolic heart failure in females (2). In this, we certainly agree.

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Please note: Prof. O'Rourke is the Founding Director of AtCor Medical and significant shareholder.

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## Reply

We thank Drs. O'Rourke and Safar, on behalf of all the authors, for their interest in our paper (1). They highlight the importance of "scaling" for aortic size, given the known inverse relationship between aortic diameter and characteristic impedance ($Z_c$) (2). The multivariable models presented in our study (1) adjusted for aortic diameter as a measure of body size and demonstrated that women had higher $Z_c$ even after adjusting for aortic size. The augmentation index (AIx) was indeed higher in women than men in our study, but was not associated with left ventricular diastolic function or ventricular–arterial coupling. In our cohort of older, predominantly hypertensive participants, increased proximal aortic

stiffness and early systolic load ($Z_c$), rather than peripheral wave reflection and late systolic load (AIx), were associated with altered diastolic function and ventricular–arterial coupling in women. In addition, the lower pressure amplification in our study compared to the study by Safar et al. (3) is possibly due to the use in their study of the transfer function, which may overestimate aortic–brachial amplification, particularly in women (4).

We reported mean body mass index (BMI) in Table 1 (and not height and weight), and included this in the multivariable regression analyses. When we included height or body surface area instead of BMI in the multivariable models, our inferences did not change. The mean LV outflow tract and aortic diameters in men and women were within the normal range. The Non-Invasive Hemodynamics (NIHem) system (Cardiovascular Engineering, Norwood, Massachusetts) has been validated and used in previous studies (5,6). All analyses were performed onsite by the study authors.

We have submitted an erratum to correct the minor typographical errors in Table 1. Mean brachial pulse pressure (PP) in women is 69 mm Hg instead of 70 mm Hg; and mean PP amplification in women is 0.99 instead of 1.00. Mean PP amplification in men is 1.03 instead of 1.05. Mean ±SD arterial pressure was 93 ± 10 mm Hg and 92 ± 10 mm Hg in men and women, respectively. The LV outflow tract is indeed reported in centimeters, and not in millimeters.

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