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The Role of Body Size on Cardiovascular Function: Can We See the Meat Through the Fat?

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Physiological comparisons of cardiovascular (CV) structure/function among individuals or groups of individuals are often difficult, due to differences in body dimensions. In order to have meaningful clinical and scientific comparisons, differences in body size must be accounted for. Although there is a plethora of data demonstrating that body size is an important determinant of CV structure/function, and although most researchers recognize the need to adjust CV parameters for differences in body size, there remains considerable confusion as to the most appropriate method to account for these differences. Chirinos et al in this issue of the *Journal*¹, highlight two important issues facing CV research: which body dimension descriptor, height, weight, body mass index (BMI), or body surface area (BSA) is optimal for scaling various CV measures; and which mathematical scaling method should be used?

Chirinos et al¹ examined the relationship between measures of resting CV parameters, with height, body weight, and BSA and concluded, as have numerous previous studies, that BSA was the most appropriate descriptor, because it incorporates changes in both height and weight, which were evident between their lean vs. obese groups. It is important that the selection of the body size descriptor be based both on the accuracy of its measurement, and its physiological relevance to the CV parameter. In most circumstances BSA is not measured, but rather is estimated through formulae. BSA incorporates both low (adipose tissue) and high (skeletal and cardiac muscle) metabolically active tissues. A greater muscle mass necessitates a larger energetic requirement, and thus theoretically, the scaling of CV parameters to fat free mass (FFM) may be the most appropriate body size descriptor.

But what role does adipose tissue (AT) have on the changes in CV function, and should this be included when scaling these data? During exercise the extra weight from AT places extra burden on the CV system to respond to exercise, and blood flow to the AT increases to facilitate fatty acid metabolism. O'Connor et al.,² have previously shown that the reserve capacity during exercise of CV parameters varied significantly with the percentage of body fat. Thus in this setting would body weight, BSA or fat mass be a more appropriate body dimension descriptor than FFM?

Perhaps more important than selecting the body dimension descriptor is the scaling technique used to adjust for differences in body size? There is a misconception that simply dividing the CV parameter to a measure of body size (i.e., ratiometric scaling) removes the effects of body size on the CV parameter. Instead, a preferred approach might be the allometric scaling method, whereby the CV function is divided by the variable of interest raised to a scalar exponent, which is derived from an equation that linearly relates the two³. The allometric method accounts

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for the non-linearity of the relationship between a CV parameter and body size providing a dimensionless variable. Indeed Chirinos et al¹ reported that when the arterial variables were scaled allometrically to height, weight or BSA, the effects of body size on CV parameters were completely removed. However, they also reported that many of the CV parameters could be scaled ratiometrically to BSA¹, producing dimensionless variables, an approach that would be more suitable for clinical research.

The work of Chirinos et al¹ illustrates the importance of scaling for body size in order to separate the normal physiological relationship between body size and CV function from the pathologic effects of excess AT on CV function. Of note, in Chirinos et al¹, with the exception of characteristic impedance (Z_c), the differences in arterial function between individuals without and with abdominal obesity are evident when normalized to BSA irrespective of the scaling approach used. For example, individuals with abdominal obesity had a higher arterial elastance, resistance, augmentation index and a lower compliance compared to lean individuals when scaled ratiometrically or allometrically to BSA (Figure 1). Thus despite the allometric modeling process being theoretically and statistically superior to the ratiometric method, both methods had similar findings. Z_c , however, did not differ when scaled allometrically to BSA, but was higher when scaled ratiometrically to BSA in individuals with abdominal obesity vs. no abdominal obesity (Figure 1). Could this lack of difference in Z_c with ratiometric vs. allometric scaling to define the effect of obesity be attributed to the transfer of the power function exponent, which was derived from a subset of their lean cohort to the entire population? The relationship between the body descriptor and CV parameter is likely to differ in the lean vs. obese individuals, therefore, is it correct to extrapolate the b-exponent calculated from the lean to the mixed individuals? This is the conundrum that perplexes this field.

But can we see the meat through the fat? While once thought of as an inert tissue, AT is now considered a complex endocrine organ that releases a variety of factors that regulate energy metabolism, cardiovascular function, reproductive status, and immune function⁴. Abnormal production or regulation of adipokines occurs in obese individuals and is implicated in the development of a variety of associated co-morbidities including metabolic syndrome, type 2-diabetes, atherosclerosis, and heart disease. AT expression of TNF- α and IL-6 interferes with insulin signaling⁵ and glucose production⁶. Interestingly IL-6 and TNF- α were significantly correlated with BMI, however, IL-6 levels were mostly associated with visceral adiposity, and TNF- α levels appeared to be more related to subcutaneous fat⁷; therefore perhaps visceral adiposity, rather than BMI, would be a better measure of obesity.

In addition, perivascular and pericardial AT have also been implicated in CV dysfunction. The secretion of adiponectin (an anti-inflammatory adipokine that modulates local vascular tone) from perivascular AT is lost with obesity leading to hypoxia, inflammation, and oxidative stress damaging the endothelial function of small-arteries⁸. Pericardial AT is associated with coronary artery calcification and left ventricular remodeling⁹. An increase in triglyceride content within the heart, which is evident in both obese and diabetic individuals¹⁰, has also been associated with ventricular diastolic dysfunction¹¹. These data highlight the important of examining region specific effects of AT on CV structure/function and these associations are likely to go beyond this issue of appropriate scaling. Thus, future research must go beyond examining the role of total adiposity and examine the regional location of AT on CV structure/function.

In summary, Chirinos et al¹ raise an important issue regarding the effects of body size on arterial function and other CV parameters, and have observed that obese individuals had a stiffer arterial system compared to lean individuals after adjusting for differences in BSA. The effects of obesity on arterial function were evident, however, with the exception of Z_c , when scaled either ratiometrically or allometrically to BSA. Future research needs to move beyond

examining the effects of whole (or central) adiposity and examine the regional specific effects of adipose tissue, and its interactions with the inflammatory and cytokine processes on CV structure/function.

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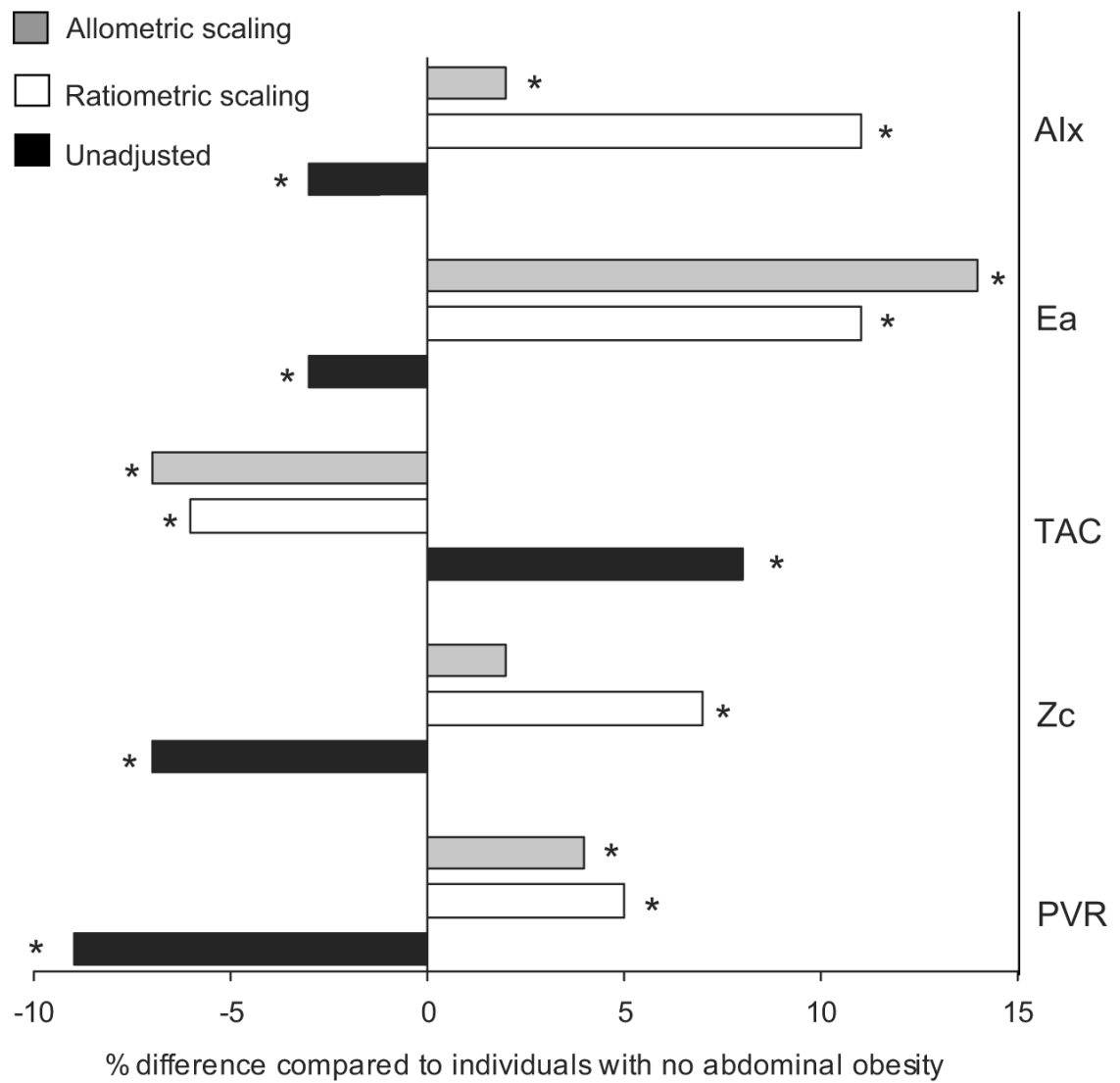


Figure 1.

The percentage difference in peripheral vascular resistance (PVR), characteristic impedance (Zc), total arterial compliance (TAC), arterial elastance (Ea) and augmentation index (AIx) in individuals with abdominal obesity compared to those without. Data obtained from Table 6 in Chirinos et al¹. *P<0.05 compared to individuals without abdominal obesity. It is noticeable that the differences in arterial parameters between abdominal vs. no abdominal obesity are in the opposite direction when unadjusted vs. when scaled. Furthermore, apart from Zc, both ratiometric and allometric scaling successfully discriminated between lean and obese individuals.