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EDITORIAL COMMENT

Sex-Specific Evaluation of Arterial Stiffness and Left Ventricular Remodeling

Can We Rely on Dimensionless Ratios?*

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Investigations regarding various aspects of the interaction between vascular properties and ventricular pump performance intensified over the past decades.[1] Arterial stiffness increases with certain types of disease but also with aging in the absence of disease. Higher arterial stiffness may have consequences for left ventricular (LV) size, LV mass, and geometry, often leading to adverse remodeling.[2] Approaches for proper quantification of arterial stiffness and optimal evaluation of ventricular remodeling are still under debate. A common route to estimate arterial stiffness refers to pulse wave velocity (PWV). A newer candidate concerns the cardio-ankle vascular index (CAVI) which looks more sophisticated by also including pulse pressure (PP) and the ratio of systolic and diastolic arterial blood pressure (SBP and DBP, respectively), resulting in:

$$\mathrm{CAVI} = a\left[\ln\left(\frac{\mathrm{SBP}}{\mathrm{DBP}}\right) \times \frac{\mathrm{PWV}^2}{\mathrm{PP}} \times 2\rho\right] + b$$

where a, b, and ρ are constants, while "ln" refers to the natural logarithm.[3]

The evaluation of LV function based on the traditional metric of ejection fraction (EF) has recently been revisited in connection with the ventricular-arterial coupling concept.[1] Alternatives for EF have been proposed and include global longitudinal strain (GLS) and other strain components. Also, the ratio of early mitral inflow (E) and late (A) peak velocity has been advanced. The ratios EF, E/A, and GLS are bare numbers, having no physical dimension. The same shortcoming partly applies to CAVI (see the SBP/DBP term), in contrast to PWV which is expressed as cm/s.[4]

In this issue of *JACC: Advances*, Yoshida et al[5] report on the sex-specific connection between arterial stiffness and LV remodeling within the landscape characterized by CAVI and GLS. Their study includes 317 participants (median age 63 years, and 42% women) recruited from individuals who underwent repeated cardiovascular health check-up. After a median follow-up of 26.8 months, the CAVI increased ($P < 0.001$) and was found to be associated with GLS deterioration ($P = 0.006$), but only in women. Interestingly, the change in CAVI was associated with a lower E/A ratio, but only in men ($P = 0.01$). These sex-specific findings are remarkable.

Efforts to interpret these results require a detailed analysis of the nature regarding the mathematical definitions referring to the various metrics used. The CAVI consists of PP, SBP/DBP, and PWV, besides blood density (ρ) and 2 other constants. However, the PP and SBP/DBP components are not independent, but inversely correlated, in 1 study yielding $R = -0.92$ for 420 healthy individuals (age 20-80 years).[4] Also, the pressure-related term was shown to depend on age, and to differ for men and women, especially at younger ages.[3] Additionally, GLS depends not only on EF but also on circumferential strain[6] and on end-diastolic volume (EDV),[7] meaning that this metric

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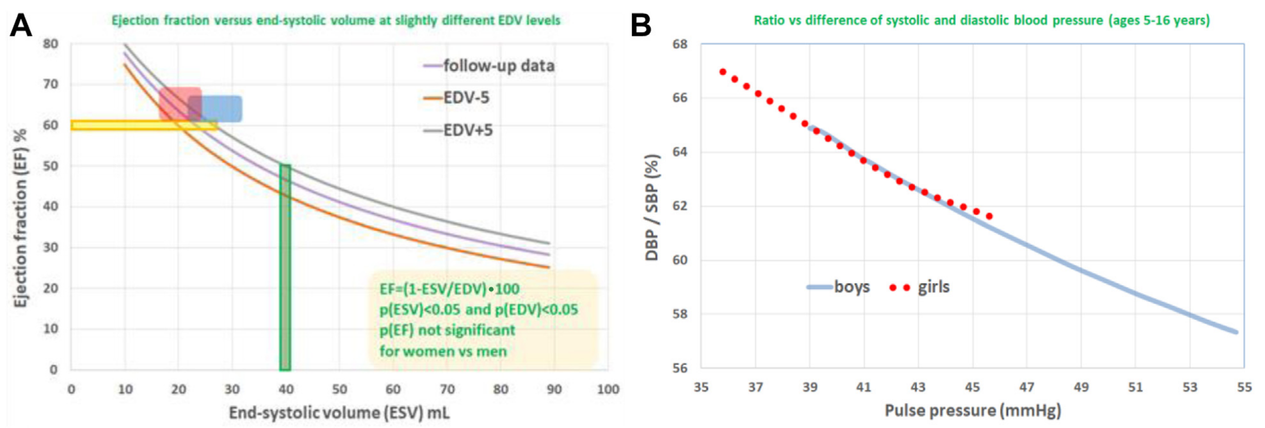
FIGURE 1 Dimensionless Ratio-Based Metrics as Used in Cardiovascular Studies May Have a Linear or Nonlinear Association With Primary Variable(s)



(A) Ejection fraction vs end-systolic volume shows a nonlinear inverse relationship that to a minor degree depends on end-diastolic volume (EDV) variation, see curves referring to EDV at a suggested level ±5 mL. This variation means that at any fixed ESV value (green bar) the EF may assume slightly different values. Also, identical values for EF (yellow bar) may result from various suitable combinations of ESV and EDV. The red and blue areas refer to the follow-up data (25th-75th percentile) for women and men, respectively.[5] **(B)** A simple inverse relationship is found for the ratio vs the difference of systolic blood pressure (SBP) and diastolic blood pressure (DBP). Note the partly overlap for data obtained from boys and girls. Both the ratio and PP are incorporated in the formula for CAVI. Graph based on Wühl et al.[10]
CAVI = cardio-ankle vascular index; EF = ejection fraction; ESV = end-systolic volume; PP = pulse pressure.

(when used in isolation) provides incomplete information.

Appreciating the inherent limitations of dimensionless metrics such as EF, GLS, and E/A, the fundamental question now arises: can we still derive conclusions from data sets that are incomplete? Perhaps. The crucial step to make is to acknowledge the existence of companion metrics and understand that these complementary metrics often can be replaced by accepted surrogate measures.[8] For example, the EF companion can be replaced by EDV.[6]

One of the strengths of the paper under discussion concerns the fact that the authors also list primarily variables, permitting better insight into underlying mechanisms. For example, both end-systolic volume (ESV) and EDV differ ($P < 0.05$) for follow-up data when men and women are compared, but the significance is not reflected by EF (Figure 1A). This is an important observation, as EF is often relied on for phenotyping and decision-making. Similarly, judging from their Table 2, the significant difference found for E/A primarily follows from the difference of A in women.

The CAVI, ESV, EDV, SBP, and DBP are known to be sex-specific and to depend on age, making a comparison between male and female participants in this study somewhat troublesome as the women were ($P < 0.001$) older (65 vs 59 years at baseline). The typically smaller ESV in women implies a higher EF, purely on mathematical grounds, as EF can be expressed as an exclusive function of ESV, schematically documented in Figure 1A with relevant ranges for male and female participants marked.[9]

Figure 1B illustrates the sex-specific range for the ratio SBP/DBP and for PP in children during daytime as a function of age (5-16 years).[10] Similar patterns have been documented for adults, thus affecting the CAVI score which is significantly higher ($P < 0.005$) for men and was found to increase from 6.5 to 8.5 for ages from 30 to 70 years in a large healthy Japanese population,[11] but for unknown reasons not found in the present study.

The authors considered GLS rather than EF to evaluate LV function. Note that, although significant, the difference for GLS in men amounts to 0.4% only. The connection between EF and GLS is complex,[12] and it has been shown that EDV should also be considered in addition to EF and GLS.[7,8] Rather than focusing on yet another ratio (such as GLS), it would be important to focus on ESV, as its value was shown to predict heart failure.[13] Additionally, ESV is the major determinant of ventriculo-arterial coupling, as defined by the ratio of LV elastance and effective arterial elastance.[1] Also, ESV is an important element for predicting (super-)response to resynchronization therapy, especially in women.[14]

It can be concluded that the interpretation of dimensionless ratios such as EF, GLS, DBP/SBP, CAVI, E/A, and E/e' is challenging. An attractive alternative route is to consider the primary measurements such as the (ESV, EDV) and (DBP, SBP) pairs, or other metrics that carry a physical dimension, for example, LV mass, PWV, A, and E. Sex-specific analysis is mandatory, but not every difference detected for composite mathematical expressions may refer to (patho)physiology, especially when dimensionless ratios are involved.

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