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Letter to the Editor: Presence of a high-flow-mediated constriction phenomenon prior to flow-mediated dilation in normal weight, overweight, and obese children and adolescents

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Letter to the Editor: Presence of a high-flow-mediated constriction phenomenon prior to flow-mediated dilation in normal weight, overweight, and obese children and adolescents

Dear Editor,

There are now many indices of vascular function that are based on imaging techniques to quantify the difference in arterial diameter between a resting baseline (D_{base}) and after a certain blood flow intervention. For example, researchers have reported one or more of the following indices; flow-mediated dilation (FMD%), nitroglycerin-mediated dilation (NMD%), low-flow-mediated constriction (L-FMC%), high-flow-mediated constriction (H-FMC%) and even a “composite” constriction and dilation index, e.g., L-FMC% + FMD%.[1] Some researchers have also suggested dividing some of these indices by each other, e.g. FMD% / FMC%.[2]

Importantly, all these proposed indices of vascular function are expressed in ratio terms as the percentage change from D_{base}. This percentage-based approach was adopted in an attempt to normalise consistently for artery size and, therefore, compare the indices between certain populations or conditions. Nevertheless, it is now well-documented that the first-proposed index, FMD%, does not serve this size-scaling role sufficiently well, leading to biased estimates of mean differences in vascular function and the emergence of spurious correlations.[3]

Because L-FMC% and H-FMC% are also ratio indices, it is likely that they suffer from the same size-scaling drawbacks as FMD%. Crucially, the D_{base} that is the denominator in the calculation of FMD% (equation 1) is also the denominator in the

FMC% calculation (equation 2). This essentially paves the way for spurious (non-biological) correlations between the indices, and potentially other variables of interest, because they are already mathematically coupled by their common denominator of D_{base}. This confounding would also be present in a composite index. These issues could be relevant to the data reported by Ostrem *et al.*[1], as well as any other study in which FMD% and FMC% are examined together.

$$FMD\% = \frac{100(Dpeak - Dbase)}{Dbase} \quad [1]$$

$$L - FMC\% = \frac{100(Dmin - Dbase)}{Dbase} \quad [2]$$

First, it was reported by Ostrem et al.[1] that FMD% was 5.4% and 8.1% in two samples of children formed on the basis of H-FMC% being present or absent, respectively. Mean peak diameter differed between these samples by only 0.01 mm, but mean D_{base} (the only other term in the FMD% calculation) differed by almost 0.1 mm. Therefore, it appears to be the latter difference in resting arterial structure that best explained the sample differences in the purported functional index of FMD%. This observation is surprisingly common, and calls into question the notion that differences in endothelial function *per se*, rather than general arterial structural modelling, are being quantified by the FMD% index.[3]

Second, because there is a common denominator of D_{base} in both FMD% and FMC%, one would expect a spurious correlation between these two indices to exist due, at least in part, to mathematical coupling. Spurious correlations have a mathematical rather than a physiological underpinning and can, therefore, be very misleading in research. Such a correlation between FMD% and L-FMC% was reported by Ostrem et al.[1], i.e., the children who evidenced the greatest low-flow-mediated constriction also recorded the lowest FMD%. This correlation would be expected even with randomly-generated data because D_{base} is the common denominator for both FMD% and L-FMC%.

Ratio indices and percentage changes are endemic in biology even though biologists have presented persuasive arguments for them to be replaced by allometric approaches[4]. Investigations into vascular function, including some of the most highly cited studies in the field, have already been compromised by the indiscriminate use of a ratio size-scaling index; FMD%.[3] Before yet more ratio indices like H-FMC%, L-FMC% and FMC%+FMD% become routinely-reported, appropriate allometric approaches to size-scaling the arterial diameter change should be considered. It is important that all measures for indicating flow-mediated constriction and dilation are independent of D_{base}, otherwise there is a danger that vascular function and vascular structure (or any other variable correlated with structure) are obfuscated.

References

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mediated dilation index. *Curr Hypertens Rep* 2015;17: 1-9.

4. Packard GC, Boardman TJ. The use of percentages and size-specific indices to normalize physiological data for variation in body size: wasted time, wasted effort? Comp Biochem Physiol Part A 1999;122:37.

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References

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