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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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 ($D_{\text{base}}$) 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%. Some researchers have also suggested dividing some of these indices by each other, e.g. FMD% / FMC%.

Importantly, all these proposed indices of vascular function are expressed in ratio terms as the percentage change from $D_{\text{base}}$. 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.

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 $D_{\text{base}}$ 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 $D_{\text{base}}$. This confounding would also be present in a composite index. These issues could be relevant to the data reported by Ostrem et al., as well as any other study in which FMD% and FMC% are examined together.

\begin{equation}
FMD\% = \frac{100(D_{\text{peak}} - D_{\text{base}})}{D_{\text{base}}} \quad [1]
\end{equation}

\begin{equation}
L - FMC\% = \frac{100(D_{\text{min}} - D_{\text{base}})}{D_{\text{base}}} \quad [2]
\end{equation}

First, it was reported by Ostrem et al. 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 $D_{\text{base}}$ (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 \textit{per se}, rather than general arterial structural modelling, are being quantified by the FMD% index. \textsuperscript{3}

Second, because there is a common denominator of $D_{\text{base}}$ 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 \(D_{\text{base}}\) 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 \(D_{\text{base}}\), otherwise there is a danger that vascular function and vascular structure (or any other variable correlated with structure) are obfuscated.

References


3. Atkinson G, Batterham AM. The clinical relevance of the percentage flow-

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