



**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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Manuscripts

Review

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

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16 There are now many indices of vascular function that are based on imaging  
17 techniques to quantify the difference in arterial diameter between a resting baseline  
18 ( $D_{\text{base}}$ ) and after a certain blood flow intervention. For example, researchers have  
19 reported one or more of the following indices; flow-mediated dilation (FMD%),  
20 nitroglycerin-mediated dilation (NMD%), low-flow-mediated constriction (L-FMC%),  
21 high-flow-mediated constriction (H-FMC%) and even a “composite” constriction and  
22 dilation index, e.g., L-FMC% + FMD%.<sup>1</sup> Some researchers have also suggested  
23 dividing some of these indices by each other, e.g. FMD% / FMC%.<sup>2</sup>  
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35 Importantly, all these proposed indices of vascular function are expressed in ratio  
36 terms as the percentage change from  $D_{\text{base}}$ . This percentage-based approach was  
37 adopted in an attempt to normalise consistently for artery size and, therefore,  
38 compare the indices between certain populations or conditions. Nevertheless, it is  
39 now well-documented that the first-proposed index, FMD%, does not serve this size-  
40 scaling role sufficiently well, leading to biased estimates of mean differences in  
41 vascular function and the emergence of spurious correlations.<sup>3</sup>  
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51 Because L-FMC% and H-FMC% are also ratio indices, it is likely that they suffer  
52 from the same size-scaling drawbacks as FMD%. Crucially, the  $D_{\text{base}}$  that is the  
53 denominator in the calculation of FMD% (equation 1) is also the denominator in the  
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3 FMC% calculation (equation 2). This essentially paves the way for spurious (non-  
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5 biological) correlations between the indices, and potentially other variables of  
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7 interest, because they are already mathematically coupled by their common  
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9 denominator of  $D_{base}$ . This confounding would also be present in a composite index.  
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11 These issues could be relevant to the data reported by Ostrem *et al.*<sup>1</sup>, as well as any  
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13 other study in which FMD% and FMC% are examined together.  
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$$16 \quad FMD\% = \frac{100(D_{peak} - D_{base})}{D_{base}} \quad [1]$$

$$17 \quad L - FMC\% = \frac{100(D_{min} - D_{base})}{D_{base}} \quad [2]$$

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25 First, it was reported by Ostrem *et al.*<sup>1</sup> that FMD% was 5.4% and 8.1% in two  
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27 samples of children formed on the basis of H-FMC% being present or absent,  
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29 respectively. Mean peak diameter differed between these samples by only 0.01 mm,  
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32 but mean  $D_{base}$  (the only other term in the FMD% calculation) differed by almost 0.1  
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34 mm. Therefore, it appears to be the latter difference in resting arterial structure that  
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36 best explained the sample differences in the purported functional index of FMD%.  
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38 This observation is surprisingly common, and calls into question the notion that  
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40 differences in endothelial function *per se*, rather than general arterial structural  
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42 modelling, are being quantified by the FMD% index.<sup>3</sup>  
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54 due, at least in part, to mathematical coupling. Spurious correlations have a  
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14 Ratio indices and percentage changes are endemic in biology even though biologists  
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## 41 References

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7 normalize physiological data for variation in body size: wasted time, wasted effort?  
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12 Greg Atkinson, Lorenzo Lolli and Alan M Batterham

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21 Running title: *Scaling and FMC*  
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25 *There was no financial support for any author of this study and no relationships with industry*  
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29 Total number of words: 604 (not including references)  
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