The dependence of FMD% on baseline diameter: a problem solved by allometric scaling – no problem in this case

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We recently published an original research article in Clinical Science reporting that the age-associated impairment in brachial artery FMD (flow-mediated dilation), a non-invasive measure of conduit artery endothelial function, was exacerbated in MA/O (middle-aged and older) adults with IFG (impaired fasting plasma glucose) concentrations, but this was not observed in MA/O adults with IFG who perform regular aerobic exercise [1]. This paper was the latest report in an extensive series of studies performed by our laboratory over the last decade investigating the effects of aging on vascular endothelial function in humans, the modulatory influences involved and the underlying mechanisms [2]. Several of the articles in this series have reported results on brachial artery FMD among different groups of young and MA/O healthy adults, as was the case in the present study [1].

After the publication of our paper [1], Professor Atkinson in his Correspondence to the Journal has suggested that a statistical issue related to scaling the FMD values may have confounded the interpretation of our results. This suggestion was apparently based on the findings of two articles that are just now being published in final form [3,4], i.e. several months after the online publication of our article. Using only the group means reported in our paper [1], Professor Atkinson found a strong correlation between %ΔFMD [calculated as [(peak – baseline diameter)/baseline diameter×100]] and baseline diameter (r = −0.74), which he suggested may have led to an underestimation of %ΔFMD in some groups, especially those with higher baseline diameters. He stated further that our analysis of covariance was not the correct approach for accounting for differences in baseline diameter. Rather, the correct approach would have been to use allometric scaling.

We wish to reply to the comments of Professor Atkinson. To be able to accurately discern a possible confounding effect of baseline diameter on our results, individual subject data, not mean group values, should be used. When the individual data from our study are plotted, the relationship between %ΔFMD and baseline diameter is weaker (r = −0.43) than calculated by Professor Atkinson, with the latter explaining only 19% of variation in %ΔFMD (R² = 0.188). Moreover, the group with the largest baseline diameter, i.e. the non-exercising MA/O adults with IFG, do not meet the criteria for allometric scaling [common slope of logarithmically transformed baseline and peak diameter = 0.998 (95% confidence interval, 0.95–1.04)]. As a result, allometric scaling of FMD does not alter our primary findings and conclusions (Table 1), which remain that the age-related impairment in FMD is exacerbated in MA/O adults with IFG and that MA/O adults who exercise regularly, including those with IFG, have significantly higher FMD than their age-matched non-exercising peers with IFG.

Readers should be aware that, since the technique of brachial artery FMD was first introduced two decades ago, more than 2000 articles have been published using the conventional presentation of FMD as %Δ and/or mmΔ. During this period, several normalization and scaling adjustments have been suggested to improve the accuracy, sensitivity and potential physiological/clinical significance of the data. Certainly, the standard expressions of FMD as %Δ and mmΔ have their limitations, at least in theory. At this time, however, the only values of brachial artery FMD shown to be predictive of future cardiovascular events are these conventional expressions [2,5]. Presently there is no evidence that any normalization of the values is predictive of incident events or disease, although such evidence may emerge as more data using these procedures are acquired. Moreover, group differences in %Δ and mmΔ FMD associated with age, exercise status, the presence of major risk factors and other influences reported by our laboratory and others have been consistent over time and multiple investigations [2]. These group differences in FMD generally have been supported by independent, indeed, ‘gold standard’ assessments of vascular endothelial function using forearm blood flow responses to intra-brachial artery infusion of endothelium-dependent dilators such as acetylcholine [2].

In the future, allometric scaling or other normalization approaches for expressing FMD may prove superior to the conventional approaches of %Δ and mmΔFMD used since the inception of the technique. Such procedures may be particularly effective when large differences in baseline diameter, shear or other factors exist between groups. However, caution should be exercised before these proposed scaling/normalizing techniques are adopted until they are properly validated in large data sets from

Abbreviations: FMD, flow-mediated dilation; IFG, impaired fasting plasma glucose; MA/O, middle-aged and older

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multiple laboratories. In the specific case of our paper [1], however, allometric scaling does not change the primary conclusions of our study.

REFERENCES


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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-exercising young NFG</th>
<th>Non-exercising MA/O NFG</th>
<th>Non-exercising MA/O IFG</th>
<th>Trained MA/O NFG</th>
<th>Trained MA/O IFG</th>
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<tbody>
<tr>
<td>FMD (% Δ)</td>
<td>7.93 ± 0.33</td>
<td>5.27 ± 0.37†§</td>
<td>3.39 ± 0.35∗†‡</td>
<td>6.38 ± 0.35∗</td>
<td>6.99 ± 0.69</td>
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<tr>
<td>Allometrically scaled FMD (equivalent % Δ)</td>
<td>7.90 ± 0.30</td>
<td>5.23 ± 0.30∗§</td>
<td>3.77 ± 0.30∗†‡</td>
<td>6.08 ± 0.40∗</td>
<td>6.82 ± 0.40∗</td>
</tr>
<tr>
<td>FMD change in diameter (mm)</td>
<td>0.32 ± 0.01</td>
<td>0.21 ± 0.01∗§</td>
<td>0.15 ± 0.02∗†‡</td>
<td>0.24 ± 0.01∗</td>
<td>0.27 ± 0.02∗</td>
</tr>
<tr>
<td>FMD baseline diameter (mm)</td>
<td>4.00 ± 0.09</td>
<td>3.98 ± 0.09</td>
<td>4.40 ± 0.13∗†‡</td>
<td>3.79 ± 0.09</td>
<td>3.94 ± 0.15</td>
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