The dependence of FMD% on baseline diameter: a problem solved by allometric scaling

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DeVan et al. [1] undertook a comprehensive cross-sectional study involving the independent variables of IFG (impaired fasting glucose) and exercise training status. In keeping with the effects of many other independent variables, including age [2,3], exercise [4], red wine [5] and cardiovascular disease [6], both FMD% [percentage FMD (flow-mediated dilation)] and Dbase (baseline artery diameter) were found to be different between the study samples. For example, Dbase was 0.46 mm larger in non-exercising older adults with IFG than the trained older adults with IFG, whereas FMD% was 3.6% higher in the latter sample.

Brachial FMD% is mathematically equivalent to the ratio of Dpeak (peak diameter) divided by Dbase, i.e. Dpeak/Dbase1, where ‘1’ is the power exponent assumed ubiquitously whenever FMD% is selected as a study outcome. Given that Dbase is the denominator in the FMD% ratio statistic, it can be questioned to what extent the sample differences in Dbase are explaining the sample differences in FMD% [2,3]. This statistical issue may confound the findings of the otherwise completely sound study rationale and design in [1].

Figure 1 presents the relationship (r = −0.74) between the sample mean values of FMD% and Dbase reported in [1]. One of the most consistent findings in FMD% research is this moderate-to-strong negative correlation between Dbase and FMD%, and this is not surprising given that Dbase is inherent in the FMD% calculation. However, it is only recently that this correlation has been recognized as a fundamental scaling problem with the FMD% ratio statistic [2,3].

DeVan et al. [1] reported that FMD%, the study outcome, was covariate-adjusted for Dbase in their statistical analyses. However, this is not the correct approach to ensure that the change in artery diameter is independent from variability in Dbase [2,3]. With this approach, one is attempting to statistically adjust the ratio of Dpeak/Dbase by Dbase yet again. This approach might make the distributional properties of the FMD% ratio even less Gaussian thereby influencing population estimates of FMD [3]. The FMD% ratio is clearly an unsuccessful attempt to adjust the change in diameter for variability in Dbase in a consistent manner. The correct approach for quantifying a change in artery diameter that is truly independent from initial diameter is via allometric scaling.

This approach does not involve a ratio statistic like FMD%, and all its pitfalls, at all.

As detailed in [2] and [3], the allometric approach to quantifying FMD involves logarithmically transforming the Dpeak and Dbase data. The individual participant differences between the resulting datasets can then be calculated. These data, on a log scale, are then treated as the outcome in a general linear model, in which logarithmically transformed Dbase is entered as a covariate (among other covariates if desired). The model should also include the fixed factor of ‘group’ (five levels) in the case of [1]. The resulting Dbase-adjusted mean changes in diameter can then be back-transformed to be interpreted as percentages if desired.

Commonly, the magnitudes of the sample differences in Dbase-adjusted FMD are smaller than those described by FMD%, which are biased by the Dbase-FMD% correlation [2,3]. Such findings are important, since the clinical significance of differences in properly scaled diameter change (indicating endothelial function) should be judged properly against the clinical significance of differences in Dbase, which is easier to measure and is more reproducible than FMD%.

Abbreviations: Dbase, baseline artery diameter; Dpeak, peak diameter; FMD, flow-mediated dilation; IFG, impaired fasting glucose.

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