Dynamic Interaction Between Micro- and Macro-Circulation: A Concept With Feet of Clay

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To the Editor: We read with interest the article “Association between retinal vessel caliber and arterial stiffness in a population comprised of normotensive to early-stage hypertensive individuals” by Triantafyllou et al.,¹ published in the December 2014 issue of the Journal. In 137 hypertensive patients and 86 normotensive controls, these authors measured central retinal arterial equivalent (CRAE) and carotid-femoral pulse wave velocity (PWV) and systolic augmentation index (Alx). In line with numerous earlier publications, Triantafyllou reported that compared with normotensive controls, hypertensive patients had significantly increased PWV (8.1 vs. 7.1 m/sec; P < 0.0001) and Alx (23.9% vs. 18.8%; P = 0.01), but decreased CRAE (86.47 vs. 91.44 μm; P = 0.001). However, Triantafyllou et al. left several issues unaddressed.¹ First, in all participants combined, there was a significant inverse association between CRAE and PWV (r = −0.205; P = 0.002). Before pooling all participants, the authors should have tested that the regression lines in hypertensive patients and normotensive people were coincident, using analysis of covariance according to the model: CRAE = β₁ PWV + β₂ (group) + β₃ interaction (PWV × group).² Significance of β₂ and β₃ indicate between-group differences in intercept and regression slope, respectively. To illustrate this issue, we analyzed 200 hypertensive patients and 306 normotensive controls recruited in the framework of the Flemish Study on Environment, Genes and Health Outcomes (Figure 1).³ In our analysis, the P-values of β₂ and β₃ were 0.0005 and 0.015, respectively. The correlation in all 506 participants combined was therefore spurious, resulting from pooling two groups. Second, common knowledge dictates that women compared with men have a higher Alx, but lower PWV.³ In Triantafyllou’s article, there was no sex difference in PWV (data not shown), but women had a higher Alx than men had (32% vs. 19%; P < 0.001). We believe that this reflects high selection bias, which limits the generalizability of Triantafyllou’s findings. Third, to ensure recruitment of patients with recent onset hypertension, Triantafyllou and coworkers recruited patients with reported normal office and/or home blood pressure. Reported blood pressure, compared with measured levels, represents soft data. The authors did not engage in out-of-the-office blood pressure measurement once their participants were enrolled in the study and can therefore not exclude white-coat hypertension in patients and masked hypertension in the normotensive controls. In the Discussion, the authors refer to the accumulating evidence that retinal narrowing precedes the development of hypertension. However, all studies included the referenced subject-level meta-analysis⁴ applied a single or only two office measurements to define hypertension. Given that in the general population, white-coat and masked hypertension have a prevalence of 11% and 15%,⁵ respectively. In our view, the evidence that retinal narrowing precedes hypertension is weak at best. Indeed, masked hypertension is a condition that easily progresses to sustained hypertension and might explain why retinal narrowing is already present when office blood pressure is still normal. Finally, Alx is an indirect measure of arterial stiffness that is under the influence of heart rate, body height, left ventricular ejection time, and cardiac output and provides information on the timing of the forward and reflected waves rather than on arterial stiffness.

Triantafyllou et al. suggested that their study for the first time to show association between quantitatively assessed retinal abnormalities and increased arterial stiffness, suggesting that micro- and macro-circulatory impairment in hypertension is a dynamic, mutual, interdependent process present from its very early stage. Taking into account the cross-sectional nature of their study and the above concerns, this conclusion is not substantiated by the data presented and remains a concept with clay feet.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

2. Kleinbaum DG, Kupper LL, Nizam A, Muller KE. Applied Regression Analysis and


Figure 1 Correlations of central retinal arteriolar equivalent (CRAE) with pulse wave velocity (PWV) in 306 normotensive (A), 200 hypertensive (B) and all 506 (C) participants. The solid lines were regression lines. *R* indicates correlation coefficient. *P*-values denote the significance of the associations.