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COMMENTARY

Relationships between blood pressure variability and indices of large artery stiffness: does the microvasculature play a role?

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The main aim of the study by Omboni *et al.*,[1] published in the current issue of *Hypertension Research*, was to evaluate possible relationships between different indices of 24-h blood pressure variability and indices of arterial stiffness and wave reflection. The authors demonstrated that, in hypertensive patients, 24-h systolic blood pressure variability is moderately and independently associated with 24-h central blood pressure, pulse wave velocity (PWV) and the augmentation index. The study was non-randomized, cross-sectional and retrospective, and was performed in a relatively large number of hypertensive patients ($n=661$). The study limitations are properly recognized by the authors; among them should be mentioned that the estimation of central blood pressure, augmentation index and PWV was performed with an electronic, oscillometric automated device (BPLab, Hessen, Germany) that has not been extensively used in clinical studies to date; although the algorithm for the calculation of the investigated parameters was previously validated, more experience with this approach is probably necessary.

Although the cross-sectional nature of the study does not allow for a proper evaluation of the causal relationships between the investigated variables, it is interesting to postulate a possible role of microvascular alterations in explaining such relationships between blood pressure variability and indices of large artery stiffness/wave reflection.

Many decades ago, Bjorn Folkow hypothesized that alterations in the microvessels might have a relevant effect in terms of resistance to flow and thus in the determination of blood pressure values. In fact, he postulated that for the same amount of shortening of vascular smooth muscle cells, in hypertension, owing to the presence of an increased media to lumen ratio of the vessels, the increase in vascular resistance is far more evident than it is in normotensive controls.[2] This postulate has provided the basis for the hypothesis of the 'vascular amplifier':[3] an increase in the media to lumen ratio of small-resistance arteries may increase the effect of any hypertensive stimulus.[2,3]

The effects of some vasoconstrictor agents appear to be more pronounced in the presence of an increased media to lumen ratio in both animal models of hypertension[4] and humans.[5]

Although the 'amplifier hypothesis' is not unanimously accepted,[6] it is conceivable that an amplification of the effects of any hypertensive stimulus (e.g., activation of the renin-angiotensin-aldosterone system, adrenergic system, other circulating factors) might increase peripheral blood pressure variability. It has also been suggested that alterations in the microcirculation may be involved in the abrupt rise in blood pressure during the early morning hours, which is in turn associated with an increased incidence of cardiovascular events;[7] in addition, systolic blood pressure after 6 min of exercise[8] and 24-h blood pressure variability (calculated as unweighted standard deviation)[9] have been demonstrated to be correlated with minimal forearm vascular resistance, an indirect index of structural alteration in the forearm microcirculation.

It is well accepted that hypertension and aging are associated with an increased stiffness of the large arteries and that high blood pressure values accelerate the effects of physiological aging.[10,11] In healthy young subjects, a forward pressure wave is generated by left ventricular systolic contraction travelling through the elastic arterial system. From reflection sites located distally in the vascular tree and probably close to the microcirculation, a reflected wave is generated that travels backward toward the ventricle. Because the vascular tree is elastic, PWV is low, and the reflected wave merges with the forward wave in diastole; therefore, there is no increase in central systolic or pulse pressure. However, in elderly or in hypertensive patients, PWV is increased by the increased stiffness of the proximal vessels, and therefore the reflected wave travels faster, arriving during the mid-systole and thus increasing the central systolic and pulse pressure.[12]

This phenomenon may have a relevant effect on left ventricular diastolic function in terms of arterial-ventricular coupling and loading sequence. In fact, Chirinos *et al.*,[13] performing a waveform analysis, have demonstrated that, whereas the characteristic impedance of the proximal aorta is a determinant of peak myocardial stress, the reflection magnitude (an index of the contribution of reflected waves to the waveform) is a major determinant of end-systolic myocardial stress. Late systolic load is negatively associated with diastolic relaxation, whereas early systolic load is associated with a faster relaxation.[13] This association may have significant clinical

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relevance, because an early return of waves reflected from the periphery may increase late myocardial wall stress, impair diastolic relaxation and trigger the onset of clinical symptoms. The calculation of the augmentation index provides a only partial estimate of the contribution of reflected waves to peripheral or central systolic pressure, because a proper estimation of pulse wave reflection, with separate calculation of the forward and backward waves, requires complex waveform (and wave separation) analysis, an evaluation that was not performed in the study by Omboni *et al.*[1]

This point is crucial, because microvascular alterations may have influenced the pulse wave reflection and, therefore, the central blood pressure. In fact, as mentioned, microvascular structure is not only the site of vascular resistance but also, probably, the origin of most of the wave reflections generating increased central systolic blood pressure in the elderly,[11] although the proper location of a reflection site may be elusive. However, increased pulsatility of the conduit arteries is transmitted to the small arteries and may contribute to vascular injury in the resistance vasculature.[11]

Possible relationships between indices of large artery stiffness and the media to lumen ratio of subcutaneous small-resistance arteries (an accurate index of microvascular structural alterations) have been investigated.[14] The media to lumen ratio is significantly related to the brachial systolic blood pressure and pulse pressure and to the central systolic and pulse pressure.[14] A positive correlation has been observed between the media to lumen ratio and the carotid-femoral pulse wave velocity; this correlation remains statistically significant after adjustment for age and mean blood pressure. The media to lumen ratio is also associated with the aortic augmentation index, and these correlations remain statistically significant after adjustment for potential confounders.[14]

Using a non-invasive, innovative approach, Ott *et al.*[15] have recently demonstrated that central pulse pressure is correlated with the wall to lumen ratio, and the central augmentation index normalized to a heart rate of 75 beats per minute is correlated with the wall to lumen ratio of the retinal arterioles. Multiple regression analysis has revealed an independent relationship between the wall to lumen ratio and the central pulse pressure, but not with other classical cardiovascular risk factors.[15] Through the same technique, it has been demonstrated that the wall to lumen ratio of the retinal arterioles is significantly related to the clinical systolic and pulse pressure, to the 24-h systolic and pulse pressure, and to the central systolic and pulse pressure.[16] Thus, the central pulse pressure, indicative of changes in the large conduit arteries, is an independent determinant of vascular remodeling in small retinal arterioles.

Such a relationship indicates coupling and crosstalk between the microvascular and macrovascular changes attributable to hypertension.[11,17] In fact, an increased wall-to-lumen ratio and rarefaction of the small arteries are major factors contributing to an increase in mean blood pressure; the higher mean blood pressure, in turn, may increase the large-artery stiffness through the loading of stiff components of the arterial wall at high blood pressure levels; finally, the increased large-artery stiffness may be a major determinant of the increased pulse pressure, which, in turn, damages small arteries in different organs (heart, brain, retina, kidney) and in general favors the development of target organ damage.[11,17] Thus, the cross-talk between the small and large artery exacerbates arterial damage, following a vicious circle (Figure 1).[11,17]

Finally, an association between peripheral blood pressure variability and a directly investigated index of microvascular structure (retinal arteriolar diameter) has been observed in a population of diabetic patients,[18] thus supporting the hypothesis that alterations in the microvasculature might represent a possible link between peripheral blood pressure variability and indices of large artery distensibility and stiffness, including the pulse wave velocity, augmentation index and central blood pressure observed in this study.[1]

In conclusion, interrelationships between alterations in the macro and microcirculation and the mechanisms that might be involved, including blood pressure variability, represent an extremely interesting topic of clinical

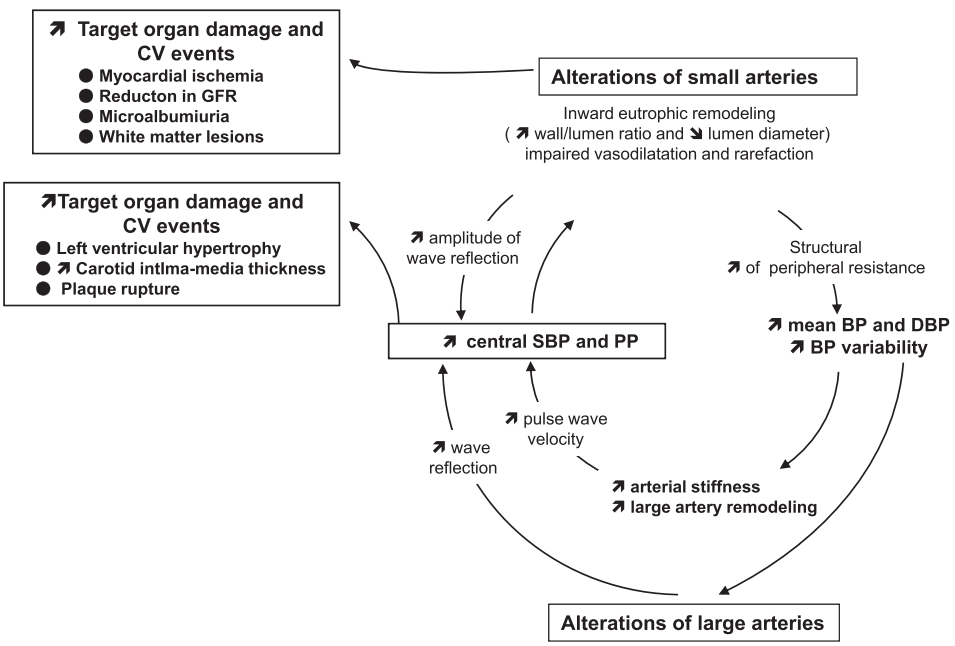

Figure 1 Cross-talk between the microcirculation and macrocirculation and the possible effects of blood pressure variability in patients with hypertension/accelerated aging (redrawn from references 11 and 17). ↑: increase or increased, ↓ decrease or decreased. BP, blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; PP, pulse pressure; SBP, systolic blood pressure.

research and deserve further and thorough investigation, particularly considering their relevant clinical impact, especially in terms of therapeutic targets and the possible prevention or regression of these alterations.[19,20]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Omboni S, Posokhov IN, Rogoza AN. Relationships between 24-h blood pressure variability and 24-h central arterial pressure, pulse wave velocity and augmentation index in hypertensive patients. *Hypertens Res* 2017; **40**: 385–391.
2 Folkow B. Physiological aspects of primary hypertension. *Physiol Rev* 1982; **62**: 347–504.
3 Lever AF. Slow pressor mechanisms in hypertension: a role for hypertrophy of resistance vessels? *J Hypertens* 1986; **4**: 515–524.
4 Mulvany MJ, Halpern W. Contractile properties of small resistance vessels in spontaneously hypertensive and normotensive rats. *Circ Res* 1977; **41**: 19–26.
5 Aalkjaer C, Heagerty AM, Bailey I, Mulvany MJ, Swales JD. Studies of isolated resistance vessels from offspring of essential hypertensive patients. *Hypertension* 1987; **9**(6 Part 2): III155–III158.
6 Izzard AS, Heagerty AM, Leenen FH. The amplifier hypothesis: permission to dissent? *J Hypertens* 1999; **17**(12 Part 1): 1667–1669.
7 Rizzoni D, Porteri E, Platto C, Rizzardi N, De Ciuceis C, Boari GEM, Muiesan ML, Salvetti M, Zani F, Miclini M, Paiardi S, Castellano M, Agabiti Rosei E. Morning rise of blood pressure and subcutaneous small resistance artery structure. *J Hypertens* 2007; **25**: 1698–1703.
8 Fossum E, Høieggen A, Moan A, Rostrup M, Kjeldsen SE. Insulin sensitivity is related to physical fitness and exercise blood pressure to structural vascular properties in young men. *Hypertension* 1999; **33**: 781–786.
9 Rizzoni D, Muiesan ML, Montani G, Zulli R, Calebich S, Agabiti-Rosei E. Relationship between initial cardiovascular structural changes and daytime and nighttime blood pressure monitoring. *Am J Hypertens* 1992; **5**: 180–186.
10 Boutouyrie P. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: establishing normal and reference values. *Eur Heart J* 2010; **31**: 2338–2350.
11 Laurent S, Agabiti-Rosei E. The cross-talk between the macro- and the microcirculation. In: Nilsson P, Olsen MH, Laurent S (eds). *Early Vascular Aging (EVA): New Directions in Cardiovascular Protection*. 1st edn. Academic Press: Cambridge, MA, USA, 2015, pp 105-118.
12 Weber T, Segers P. Changes in central hemodynamics, wave reflection, and heart-vessel coupling with normal and accelerated aging. In: Nilsson P, Olsen MH, Laurent S (eds). *Early Vascular Aging (EVA): New Directions in Cardiovascular Protection*. 1st edn. Academic Press: Cambridge, MA, USA, 2015, pp 83-95.
13 Chirinos JA, Segers P, Rietzschel ER, De Buyzere ML, Raja MW, Claessens T, De Bacquer D, St John Sutton M, Gillebert TC. Asklepios Investigators. Early and late systolic wall stress differentially relate to myocardial contraction and relaxation in middle-aged adults: the Asklepios study. *Hypertension* 2013; **61**: 296–303.
14 Muiesan ML, Salvetti M, Rizzoni D, Paini A, Agabiti-Rosei C, Aggiusti C, Bertacchini F, Stassaldi D, Gavazzi A, Porteri E, De Ciuceis C, Agabiti-Rosei E. Pulsatile hemodynamics and microcirculation: evidence for a close relationship in hypertensive patients. *Hypertension* 2013; **61**: 130–136.
15 Ott C, Raff U, Harazny JM, Michelson G, Schmieder RE. Central pulse pressure is an independent determinant of vascular remodeling in the retinal circulation. *Hypertension* 2013; **61**: 1340–1345.
16 Salvetti M, Agabiti Rosei C, Paini A, Aggiusti C, Cancarini A, Duse S, Semeraro F, Rizzoni D, Agabiti Rosei E, Muiesan ML. Relationship of wall-to-lumen ratio of retinal arterioles with clinic and 24-hour blood pressure. *Hypertension* 2014; **63**: 1110–1115.
17 Laurent S, Briet M, Boutouyrie P. Large and small artery cross-talk and recent morbidity-mortality trials in hypertension. *Hypertension* 2009; **54**: 388–392.
18 Veloudi P, Blizzard L, Srikanth VK, McCartney P, Lukoshkova EV, Hughes AD, Head GA, Sharman JE. Associations of blood pressure variability and retinal arteriolar diameter in participants with type 2 diabetes. *Diab Vasc Dis Res* 2016; **13**: 299–302.
19 Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HAJ. Microcirculation in hypertension. A new target for treatment? *Circulation* 2001; **104**: 735–740.
20 Safar ME, Rizzoni D, Blacher J, Muiesan ML, Agabiti-Rosei E. Macro and microvasculature in hypertension: therapeutic aspects. *J Hum Hypertens* 2008; **22**: 590–595.