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The main strength of the article by Zachariah et al¹ was that it investigated the association of several hemodynamic factors and multiple growth factors in a large population of well-explored subjects. Its major finding is the emergence of insulin-like growth factor (IGF) 1 and vascular endothelial growth factor (VEGF) as the 2 growth factors that were significantly related to several measures of vascular function. Specifically, the authors observed a pattern of negative correlations between circulating IGF-1 and both carotid-femoral pulse wave velocity (PWV; CF-PWV) and reflection coefficient but a positive association between VEGF concentration and CF-PWV. This latter relationship disappeared, however, after adjustment for mean arterial pressure, thus providing valuable information on the possible implication of growth factors on the steady component of arterial hemodynamics (continuous load) and on microcirculation status. Although similar results regarding the relationship between growth factors and arterial stiffness have already been reported in previous studies, the originality of the present analysis is 3-fold: (1) the simultaneous analysis of several growth factors and their receptors; (2) the measurement of several arterial parameters providing complementary information on both microcirculation and macrocirculation; and (3) achieving all of these analyses in a large, well-explored population.

Multiple Approaches for Central Hemodynamic Assessment

Recent development and validation of various software for applanation tonometry have enabled the analysis of pulse waves in several arterial segments with high accuracy. Among these, CF-PWV has been shown to be a more powerful cardiovascular risk factor than mean arterial pressure, systolic blood pressure, or pulse pressure.² This relationship has been demonstrated in the general population, as well as in several subgroups of patients. CF-PWV is also considered as a marker of early atherosclerosis. All of the above data have led to the recognition of CF-PWV as an

independent factor of cardiovascular risk,³ and reference values have been proposed recently.⁴ In addition, complementary approaches have been developed in the last few years, allowing the analysis of arterial pulse waveform and providing key information regarding the amplitude and timing of forward and backward arterial waves.⁵

Recent studies indicate the interest in combining measurements of both propagation velocity of the pressure waves (ie, PWV) and pressure contour analyses (ie, forward and backward waves, augmentation index, pulse pressure amplification, global reflection coefficient, etc). It has been shown that these 2 approaches provide complementary data on arterial health from both a microcirculation and macrocirculation perspectives.^{5,6} Hence, measuring all of these arterial parameters is certainly an important element in the value of the study of Zachariah et al.¹

To date, these arterial parameters have been extensively studied in relation to genetic determinants (mainly of the renin-angiotensin-aldosterone system), cardiovascular metabolic risk factors, and outcomes, such as morbidity and mortality. The innovative aspect of the present article is the assessment of the impact of growth factors on various parameters of arterial hemodynamics.

Focus on Growth Factors and Arterial Stiffness

Several elements of the growth hormone/IGF axis (IGF receptor, IGF binding protein 1, IGF binding protein 3, and growth hormone receptor) are potential candidate genes in regions of suggestive linkage for PWV and pulse pressure,^{7,8} although polymorphism studies and genome-wide association studies have failed to identify any significant associations between these factors and arterial stiffness. Few studies have shown a positive relationship between IGF-1 levels and arterial stiffness.^{9,10} Thus, very high levels of serum IGF-1 in the presence of acromegaly have been associated with increased ambulatory arterial stiffness.⁹ However, the majority of the studies have reported a negative correlation between the growth hormone/IGF axis and arterial stiffness assessed by PWV,¹¹ which is in agreement with the present findings of Zachariah et al.¹

The relations among arterial stiffness, endothelial dysfunction, and markers of inflammation have been explored recently. It has been demonstrated in pulmonary microvascular endothelial cells that increased flow pulsatility, a parameter reflecting increased arterial stiffness in vivo, upregulates expression of intercellular adhesion molecule 1, E-selectin, monocyte chemoattractant protein 1, VEGF, and its receptor Flt-1.¹² This result indicates that increased arterial stiffness via expression of growth factors may result in cellular inflammation and proliferation in microcirculation. In the presence of chronic NO synthase inhibition in rats, increased

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arterial pressure and arteriolar wall stiffness is not associated with changes in plasma VEGF levels.¹³ In hypertensive patients, arterial stiffness is observed to be weakly associated with serum human growth factor levels after adjustment for age and blood pressure.

Angiopoietins are proangiogenic growth factors that specifically activate endothelial cells. In both chronic kidney disease and hypertension, increased plasma angiopoietin 2 is correlated with target organ damage and cardiovascular outcome. However, in chronic kidney disease, angiopoietin 2 is not associated with the degree of calcification and arterial stiffness.¹⁴ In contrast, in hypertensive patients, angiopoietin 2 expression in peripheral blood monocytes is significantly correlated with PWV, suggesting a link between angiopoietins, angiogenic mechanisms, inflammation, and arteriosclerosis.¹⁵

These data raise a certain number of hypothetical mechanisms through which growth factors could influence arterial stiffness. It can, thus, be suggested that the effects of growth factors at the level of smooth muscle cell phenotype modulation and matrix remodeling can accelerate arterial stiffness. Taken together, these results indicate a dual relationship between growth factors and arterial stiffening, the latter being either the cause or the result of the activity of several growth factors. This complexity may explain some contradictory results also reported in the present study.

Perspectives and Conclusions

Over the past few years, major progress has been observed in the evaluation of arterial structure and function; hence, direct arterial measurements, including analysis of central and peripheral arterial waveforms and assessment of PWV, can be reliable and easily performed. Attempts in associating these measurements with new biomarkers of arterial ageing, such as senescence markers, cellular activation, endothelial dysfunction, vessel wall inflammation, and fibrosis, as well as new molecular imaging techniques, could also greatly contribute to the overall understanding of the underlying mechanisms governing these processes. In this respect, plasma growth factor levels constitute a key measurement in the comprehension of the relationship between vascular biology and arterial stiffness. The results obtained in the present study with respect to IGF are certainly more consistent, suggesting that this factor is involved in arterial stiffness. However, investigating these questions in clinical observational studies presents several limitations because of difficulties in assessing underlying mechanisms, especially given the following: (1) the chicken and egg conundrum between alteration of the vascular wall and modulation of growth factors; (2) adaptive and causal mechanisms may modify growth factor levels (this may be particularly relevant for increased levels of VEGF in the presence of high stiffness and ischemia; and (3) the role of growth factors may not be similar according to the disease environment.

In this context, *in vitro* and *in vivo* experimental studies should not only assess the effects of modulation of the activity of growth factors on arterial parameters but also the influence of arterial stiffness on synthesis and release of these molecules. Longitudinal and interventional clinical studies could also be of major interest to clarify the main actions of growth factors on chronic age-related modifications of the

arterial wall, as well as interactions with the main determinants of arterial stiffness. In the longer term, comprehension of the role of growth factors on the pace of arterial stiffening and central hemodynamics may contribute to the identification of new biomarkers of cardiovascular risk and in the development of arterial destiffening strategies.

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