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COMMENTARY

Arterial stiffness and carotid intima–media thickness: together they stand

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Noninvasive arterial testing, when used for the purpose of cardiovascular risk assessment, is performed with the understanding that functional and early structural changes in arteries are precursors to the clinical manifestations of atherosclerotic disease and that these changes characterize the entire arterial tree and are not confined to a single arterial bed. Novel arterial biomarkers must assess the risk over and beyond traditional risk factors, a task that is not so easily accomplished. On the other hand, arterial biomarkers have the theoretical advantage that they can integrate the cumulative effect of a traditional risk factor on the arterial wall over a long period of time, as well as any synergistic effects from risk factor combinations. Furthermore, arterial testing is very appealing because it is noninvasive, easy, reproducible and relatively inexpensive. Improvement of risk prediction is particularly important in patients at low or intermediate risk, such as hypertensive patients. Thus, the European Society of Hypertension and the European Society of Cardiology have rightfully included carotid-femoral pulse wave velocity and carotid intima–media thickness (IMT) as indices of subclinical organ damage in their latest recommendations.[1]

Although assessing the risk of hard end points, such as mortality and coronary events, is the ultimate verification of a biomarker's predictive ability, assessing the intermediate end points is also a valid step. The more pathophysiogically relevant the intermediate end point, the more the chances that the biomarker will predict the hard end points. During the progression of arterial hypertension, changes in coronary microcirculation ensue even in the absence of epicardial coronary stenosis. These modifications result predominantly from structural changes in the intramyocardial arteries, such as the accumulation of fibrillar collagen, increased coronary arteriolar tone, endothelial dysfunction, and/or extravascular compression.[2] The state of coronary microcirculation may be studied noninvasively by assessing the coronary flow reserve (CFR). Impaired CFR has been associated with left ventricular concentric remodeling and hypertrophy, and, importantly, with a poor prognosis for hypertensive patients, especially those with left ventricular hypertrophy. However, the measurement of CFR requires specific equipment and training in addition to a well-organized echocardiography department.

The study by Tzortzis *et al.*[3] demonstrates that increased carotid IMT and arterial stiffness are independent and complementary determinants of impaired CFR in never-treated patients with essential hypertension. These results reinforce the pathophysiological association of pulse wave velocity and IMT with cardiovascular events in several populations, such as hypertensive individuals, patients with coronary artery disease and apparently healthy individuals.[4–6]

Interestingly, aortic stiffness has an independent predictive role not only for all-cause mortality but also for coronary events.[4–6] Causal relationships explaining this role do exist, and the findings of Tzortzis *et al.*[3] provide a link. Increased arterial stiffness increases the velocity of the incident and reflected pulse waves, which in turn shifts the pressure wave reflections from diastole to systole. This increases the left ventricular afterload, while also reducing the aortic pressure during diastole, which leads to a decrease in myocardial perfusion. Thus, arterial stiffness causes a mismatch between myocardial oxygen demands and myocardial perfusion

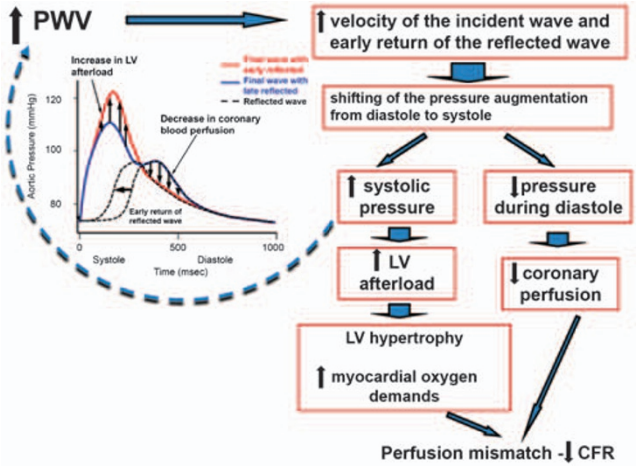

Figure 1 Pathophysiological links between increased arterial stiffness and impaired coronary perfusion. Abbreviations: CFR, coronary flow reserve; LV, left ventricle; PWV, pulse wave velocity.

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that results in subendocardial ischemia, left ventricular diastolic dysfunction and an elevation of diastolic filling pressure, which further hinders myocardial perfusion (Figure 1).[7] On the other hand, the causal background underlying the link between increased carotid IMT and impairment of CFR is not readily apparent, and only indirect associations can be inferred at this time. As the authors point out, a logical association involves endothelial dysfunction.

It would be worthwhile for future studies to incorporate two additional measures of arterial function, namely pulse wave analysis for the estimation of central blood pressures and indices of wave reflections,[8] and brachial flow-mediated dilatation to evaluate endothelial function.[6] This global approach to arterial function,[9] in addition to potentially solidifying the concepts elaborated in the study by Tzortis *et al.*,[3] could further improve risk stratification for impaired CFR. Furthermore, it is interesting to consider that certain types of antihypertensive drugs improve CFR beyond what would be expected solely on the basis of a reduction in blood pressure.[10] Accordingly, further analysis of arterial function will provide a better understanding of the underlying mechanisms, as well as a means of estimating the additional effects of antihypertensive treatment in both micro- and macrocirculation.

A holistic approach to evaluating arterial function and the early structural changes has the potential to increase our ability to predict the risk of future cardiovascular events. When divided, arterial stiffness and IMT do not fall; however, they probably stand better together.

1 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Kjeldsen SE, Erdine S, Narkiewicz K, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Cifkova R, Dominiczak A, Fagard R, Heagerty AM, Laurent S, Lindholm LH, Mancia G, Manolis A, Nilsson PM, Redon J, Schmieder RE, Struijker-Boudier HA, Viigimaa M, Filippatos G, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Kiowski W, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Viigimaa M, Waeber B, Williams B, Zamorano JL, The task force for the management of arterial hypertension of the European Society of Hypertension, The task force for the management of arterial hypertension of the European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007; **28**: 1462–1536.

2 Galderisi M, de Simone G, D'Errico A, Sidiropulos M, Viceconti R, Chinali M, Mondillo S, de Divitiis O. Independent association of coronary flow reserve with left ventricular relaxation and filling pressure in arterial hypertension. *Am J Hypertens* 2008; **21**: 1040–1046.

3 Tzortzis S, Ikonomidis I, Lekakis J, Papadopoulos C, Triantafyllidi H, Parissis J, Trivilou P, Paraskevaidis I, Anastasiou-Nana M, Kremastinos DT. Incremental predictive value of carotid intima-media thickness to arterial stiffness for impaired coronary flow reserve in untreated hypertensives. *Hypertens Res* 2010; **33**: 367–373.

4 Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. European network for non-invasive investigation of large arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; **27**: 2588–2605.

5 Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010 (in press).

6 Kullo IJ, Malik AR. Arterial ultrasonography and tonometry as adjuncts to cardiovascular risk stratification. *J Am Coll Cardiol* 2007; **49**: 1413–1426.

7 Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*, 5th edn. Hodder Arnold Publishing: London, 2005.

8 Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, Wang JG, Wilkinson IB, Williams B, Vlachopoulos C. Central blood pressure measurements and antihypertensive therapy: a consensus document. *Hypertension* 2007; **50**: 154–160.

9 Vlachopoulos C, Ioakeimidis N, Aznaouridis K, Bratsas A, Baou K, Xaplanteris P, Lazaros G, Stefanadis C. Association of interleukin-18 levels with global arterial function and early structural changes in men without cardiovascular disease. *Am J Hypertens* 2010 (in press).

10 Barrios V, Escobar C, Echarri R. Coronary flow reserve: a new target for treating hypertension. *Hypertens Res* 2009; **32**: 316.