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CORRESPONDENCE

Response to Aboyans, *et al.*: Estimation of pulse wave velocity in patients with peripheral artery disease: a word of caution

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We would like to thank Aboyans *et al.*[1] for their interest and useful comments regarding our work.[2] Aboyans *et al.*[1] examined 76 patients with peripheral artery disease (PAD) who did not have a previous clinical history of coronary artery disease (CAD). The PAD patients were compared with 86 patients who were hospitalized for severe CAD requiring coronary bypass grafting. Their work demonstrated that carotid–femoral pulse wave velocity (cfPWV) was significantly lower in PAD patients with aorto-iliac disease than in PAD patients without aorto-iliac segment involvement (9.5 ± 2.5 *vs.* 11.8 ± 3.9 m s^{-1}, $P = 0.03$). Furthermore, in PAD patients, cfPWV did not predict cardiovascular outcomes, which were defined as mortality, cardiovascular events and limb amputation. In contrast, cfPWV was predictive of the outcomes in CAD patients.[1] This discrepancy in the results was explained by the presence of stenotic lesions and arterial remodeling in the aorto-iliac segment, as well as the reinjection of the collateral circulation downstream of the stenotic lesion.[1] Both human studies[3] and animal experiments[4] have demonstrated that aortic diameter is a major determinant of aortic stiffness. In a recent study, Brand *et al.*[5] showed that patients with critical limb ischemia have reduced cfPWV compared with age- and gender-matched controls. A delay in the propagation of pulse waves[6] and a decrease in the amplitude of the pressure waveform[7] in the leg arteries has been demonstrated in patients with PAD. Similarly, we recently demonstrated in 117 patients with symptomatic PAD during a follow-up of 4.1 ± 2.2 years that cfPWV was not predictive of mortality.[8] In contrast, small-artery elasticity that was derived from diastolic pulse contour analysis was independently associated with all-cause and cardiovascular mortality. Stiffening of the small arteries may increase pulse reflection, promote earlier arrival of the reflected waves and elevate central pulse pressure, which is an important determinant of outcome[9] and is related to critical limb ischemia in patients with PAD.[5]

We agree that advanced atherosclerotic lesions in the aorto-iliac segment may affect the measurement of cfPWV. In our study, there were 18 patients with hemodynamically significant stenosis or occlusion of the aorto-iliac segment and 24 patients without aorto-iliac disease. We did not find a statistically significant difference between the patients with proximal and distal atherosclerotic disease (9.7 ± 1.5 *vs.* 10.2 ± 1.7 m s^{-1}, $P = 0.35$). Moreover, we recently recruited 49 patients with symptomatic PAD, 49 patients with symptomatic CAD and 41 age- and gender-matched healthy controls (unpublished data). cfPWV was measured by SphygmoCor (AtCor Medical, Sydney, NSW, Australia). The location and severity of atherosclerotic lesions in the PAD patients were determined by digital subtraction angiography. The cfPWV values in the PAD patients, CAD patients and control subjects were 10.4 ± 2.5, 9.7 ± 2.6 and 8.2 ± 1.7 m s^{-1}, respectively ($P < 0.001$). Among the PAD patients, 26 subjects had aorto-iliac disease, 19 subjects did not have significant aorto-iliac segment involvement, and the angiographic score was not measured in four patients for technical reasons. There was no significant difference in cfPWV between PAD patients with involvement of the aorto-iliac segment and PAD patients without evidence of aorto-iliac disease (10.4 ± 2.4 *vs.* 10.9 ± 2.5 m s^{-1}, $P = 0.47$). In the present study, aortic stiffness was higher in patients with lower-extremity atherosclerosis than in CAD patients. PAD is a manifestation of systemic atherosclerosis and is associated with an increased risk of myocardial infarction and stroke.[10] It was recently shown that both patients with incident PAD and PAD patients with a history of myocardial infarction had higher long-term mortality than patients with myocardial infarction alone.[11] The discrepancy in the results of our studies and the data reported by Aboyans *et al.*[1] may be due to differences in the severity of PAD. In our cohorts, most of the patients presented with intermittent claudication, whereas the presence of critical limb ischemia was observed in only 26% and 33% (unpublished data) of patients. We agree with Aboyans *et al.* that cfPWV should be used with caution in PAD patients with aorto-iliac disease. However, we do not support the suggestion that tonometric methods should be completely avoided in patients with lower-extremity atherosclerosis. If the femoral pulse can be palpated and no severe stenoses or occlusions have been identified by previous imaging studies, cfPWV may still be useful in patients with PAD. In cases of unilateral aorto-iliac involvement, femoral tonometry may be performed on the contralateral side. However, if clinical history, as well as clinical and radiologic examinations, suggests the presence of bilateral aorto-iliac disease, the measurement of cfPWV should be abandoned.

Functional profiling of vascular injury via assessment of arterial stiffness is a well-established determinant of cardiovascular outcome.[11] Similarly, structural evaluation and quantification of atherosclerosis by ultrasound, computed tomography, magnetic resonance imaging and digital subtraction angiography are widely used in clinical

practice. In recent years, metabolomics has emerged as a promising area for the assessment of atherosclerosis.[12] In our previous study, we showed that tyrosine and oxidized low-density lipoprotein (oxLDL) are independently associated with aortic stiffness in patients with lower-extremity atherosclerosis.[1] In addition, oxLDL adds predictive power for determining the survival of patients with PAD.[8] An interesting histopathologic study has recently shown that vascular lesions in PAD are characterized by a high prevalence of medial calcification and intimal thickening without lipid accumulation.[13] The abundance of nonatheromatous lesions suggests that the pathogenesis of PAD has some distinctive features compared with other forms of atherosclerosis. Wider application of genomics, transcriptomics and metabolomics may help to elucidate the complex mechanisms involved in the development of PAD, which may assist in the identification of novel biomarkers of PAD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Maksim Zagura[1,2,3], Jaak Kals[1,2,4], Kaido Paapstel[1,2,3], Martin Serg[2,3], Priit Kampus[2,3], Jaan Eha[2,3] and Mihkel Zilmer[1,2]

[1]Department of Biochemistry, Institute of Biomedicine and Translational Medicine, Centre of Excellence for Genomics and Translational Medicine (Nos. IUT20-42; GMVBS1169P), University of Tartu, Tartu, Estonia; [2]Endothelial Centre, University of Tartu, Tartu, Estonia; [3]Department of Cardiology (No. IUT2-7), University of Tartu, Tartu, Estonia and [4]Department of Surgery, University of Tartu, Tartu, Estonia
E-mail: Maksim.Zagura@kliinikum.ee

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