Endothelial dysfunction and peripheral arterial disease

We read with interest the study of Loffredo et al. investigating the association of oxidative stress and endothelial function in patients with peripheral arterial disease (PAD). The authors demonstrated that flow-mediated vasodilatation (FMD) of the brachial artery was significantly lower in patients with PAD compared with controls, whereas 8-hydroxy-2-deoxy-2-deoxyguanosine (a marker of oxidative stress) was higher in PAD patients. In addition, infusion of propionyl-L-carnitine increased FMD in PAD patients. Despite a thorough study design, in our opinion, some important issues have not been addressed by the authors.

In the Framingham cohort (one of the largest population ever investigated using FMD), Benjamin et al. have reported a mean FMD value of 3.3 ± 3.0 and 2.4 ± 2.4% in women and men, respectively. In the present study, FMD was 6.7 ± 3.0% in PAD patients and even 10.3 ± 2.1% in controls. How do the authors explain these differences between FMD values? In our opinion, the present data support the variability in FMD values and the great overlap between groups.

According to Table 1, arterial hypertension, diabetes mellitus, and the percentage of ex-smokers were higher in PAD patients. These risk factors have an important influence on FMD results. Therefore, on the basis of the present data and univariate statistical analyses, one cannot conclude that endothelial function is significantly reduced in PAD.

Additionally, not all studies have demonstrated a positive correlation between FMD and cardiovascular events. In fact, two studies with the greatest number of patients were not able to show a significant relation between peripheral endothelial function and cardiovascular events. Consequently, one could argue that an improvement in FMD using propionyl-L-carnitine has limited relevance.

The authors report that they have assessed intima-media thickness of the carotid artery. However, no results of these measurements are provided. It would be interesting to see whether intima-media thickness was different between controls and patients with PAD. If yes, it would further support the theory that FMD more closely reflects risk factor burden, whereas intima-media thickness is associated with prevalent atherosclerotic disease.

We would like to thank Frick et al. for the comments related to our recent paper on endothelial dysfunction in patients with peripheral arterial disease (PAD). We found that PAD patients have a reduced flow-mediated dilatation (FMD) with an inverse correlation between FMD and oxidative stress. Short-term treatment with an antioxidant reduced oxidative stress and increased nitric oxide (NO) generation simultaneously with FMD restoration, so suggesting that oxidative stress may be implicated in arterial dysfunction via interference with NO biosynthesis/degradation. The values of FMD observed in our study were in the same order of magnitude of other studies performed in this clinical setting. Thus, in a previous study performed in 88 PAD patients, Brevetti et al. found a median value of 7.3% (inter-quartile range 5.1–9.5) and 11.4% (9.3–12.9) in PAD and control group, respectively. Furthermore, in other clinical settings such as coronary artery disease (CAD), FMD values did not seem much different compared with those observed in our study. For instance, in a population without CAD, Frick et al. showed values close to 8%, which are much higher than those found in the Framingham cohort. The surprisingly very low values of FMD observed in the Framingham study are not easy to explain, but we cannot exclude that some differences in the methodology may account for it. For instance, in the Framingham study, more than 50% of patients performed a 6-minute walking test before the brachial artery study.

As outlined in our paper, patients with PAD have several risk factors, such as hypertension, dyslipidaemia, diabetes, and smoking habit, that could contribute to lower FMD independently from PAD, but the sample size did not permit to solve this issue. Larger sample size is, therefore, necessary to explore if these risk factors, alone or in combination, are determinant of low FMD or if PAD per se is independently associated with reduced arterial dysfunction.

The aim of our study was not to investigate the clinical relevance of arterial dysfunction in PAD population; therefore, the FMD restoration after antioxidant treatment should be regarded as an element in favour of the key role played by oxidative stress in reducing arterial dilation. It is of note, however, that in PAD patients arterial dysfunction seems to be associated with adverse cardiovascular complications, but we believe that further studies are necessary to validate these data. We agree with Frick et al. that the intima-media thickness (IMT) may be another important information to stratify the atherosclerotic risk in the PAD population. In our study, when compared with controls, patients with PAD had a significant higher carotid IMT (0.61 ± 0.10 vs. 0.86 ± 0.18 mm;