We thank Dr Yavuzer Koza for his interest and important comments on our recent paper entitled “High leukocyte count is associated with peripheral vascular dysfunction in individuals with low cardiovascular risk”, published in the Circulation Journal. In that paper we concluded that a relatively high leukocyte count is independently associated with vascular dysfunction in persons at low cardiovascular risk.

Dr Koza noted that the measurement of endothelial function may be altered by some factors; and also questioned the cut-off point ≤1.67. We strongly agree with Dr Koza that there are factors, such as change in room temperature, mental stress, medication, timing of information gathering and menstrual cycle for women, which may have an influence on blood flow in the finger, or on index calculation. In our study, all tests were performed in a room with consistent temperature (21–24°C) and a stress-free environment. All patients were required to discontinue vasodilators at least 24 h before tests. Endothelial function was measured by assessing reactive hyperemia-induced vasodilation (peripheral arterial tonometry, PAT) in a finger of 1 arm, adjusted for the changes in a finger on the contralateral arm (reactive hyperemia index: RHI). Mean PAT amplitude was measured between 90 s and 150 s after occlusion. By measuring both arms, EndoPAT automatically corrects for any systemic changes that may occur during the course of the test and calculates a final EndoScore based on information gathered from both finger monitors. We believe all these methods may reduce the impact of confounding factors on the accuracy of the endothelial function test. Furthermore we included this point in the limitation section of the paper.

The cut-off point of EndoPAT was based on our studies. In a prior paper, we defined a cut-off value of 1.35 as best predicting coronary endothelial dysfunction. It was calculated using an older version of the analysis. The value of 1.67 was derived from clinical data submitted (later) to the FDA using a further developed analysis, and was validated by our group. The analysis was done on the same study cohort that we had used in our paper; the FDA endorsed this as the RHI cut-off point and this was consequently reflected in the manual of the EndoPAT device.

Higher leukocyte level may generate secretion of inflammatory cytokines and cytotoxic products affecting endothelial cells, similar to what occurs in other chronic inflammatory diseases (eg, rheumatoid arthritis and psoriasis). Adhesion molecules on leukocytes are upregulated in atherosclerosis and increase chemotaxis of monocytes beneath the endothelium in early stages of atherosclerosis. Neutrophils can influence the inflammatory response through direct cell–cell interactions with endothelial cells. Polymorphonuclear neutrophil-derived pro-oxidative enzymes may catalyze reactions that consume vascular nitric oxide, resulting in impaired endothelial function. Thus, leukocytes and leukocyte subtypes are not only inflammatory markers, but also play important roles in inflammation by virtue of their ability to produce a series of effects or functions that collectively represent a major mechanism of innate immunity. Besides patients with low cardiovascular risk, we have recently shown that higher leukocyte count is associated with endothelial dysfunction in patients with high cardiovascular risk. Therefore, we are also looking forward to future studies on the effect of anti-inflammatory treatment and reduction in leukocyte count on primary prevention.

The suggestion by Dr Koza that neutrophil/lymphocyte ratio is another useful indicator of endothelial dysfunction, is a good idea and may strengthen our conclusion.

Finally, we would like to thank Dr Yavuzer Koza again for pointing out a typographical error in Table 1. The number of menopausal women should have been 33. We are sincerely sorry for this negligence.

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