As a conclusion, at least the 3 previously suggested "nondownstream" factors should probably be discussed as major causes of the relative absence of relation between the degree of hemodynamic impairment and functional limitation. Integrative (proximal and distal) vascular investigations, as well as estimation of blood oxygen transport capacity and content during exercise, are likely required when one analyzes the relationship between the severity of perfusion impairment in PAD and functional limitation.

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## Reply

We thank Dr. Abraham and colleagues for their interest in our paper (1). They suggest that proximal claudication may be in part responsible for functional limitation in patients with peripheral artery disease. We most certainly agree and have shown data to that effect in our paper (1). The measure of the runoff index from the magnetic resonance angiogram performed in each patient was an assessment of extent of peripheral atherosclerosis, corrected for the proximal nature of the disease (2). The more proximal the atherosclerosis, the worse was the score on the runoff index. The runoff index correlated with all of the outcome measures performed, including treadmill time, time to claudication, 6-min walk, and oxygen consumption (see Table 3 in Anderson et al. [1]). The perfusion measures made using magnetic resonance imaging in our study (1) were made at the calf muscle level and are thus certainly dependent on upstream macrovascular disease as well as local microvascular disease.

Abraham et al. also suggest that anemia could play a role in the functional capacity in peripheral artery disease patients, an excellent point. Unfortunately, we did not measure complete blood counts at the time of the imaging studies and thus do not have data to answer this particular question. They also assert that exercise-induced hypoxemia may contribute to exercise intolerance in peripheral artery disease patients. Although we agree with this in theory, with the low-to-moderate level of exercise performed by the patients in this particular study, they were generally limited far more by claudication than by cardiopulmonary symptoms. In summary, we would submit that our study did present data that integrated both "proximal and distal" assessment of the extent of atherosclerosis and its consequences using a comprehensive magnetic resonance imaging approach.

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## Reply

In their response to the paper by Anderson et al. (1) and my editorial comment (2), Dr. Abraham and colleagues make an important point in highlighting the importance of "nondownstream" factors in peripheral artery disease. The fact that cellular metabolism was the parameter that correlated best with the clinically most relevant treadmill exercise results in the study by Anderson et al. (1) supports the potential influence of other factors such as proximal claudication, anemia, and hypoxemia. The common features in the etiology of atherosclerosis and pulmonary disease may be a key factor here; for instance, peripheral artery disease and coronary artery disease are more common in moderate and heavy cigarette smokers than in never smokers (3). Further analyses of, for example, anemia (by measurements of hemoglobin) may have shed more light (4) on the pathophysiological interactions and correlation with magnetic resonance imaging parameters in the study by Anderson et al. (1). Nevertheless, their study is a great step forward on the path of developing a clinically meaningful use of imaging (5). Finally, I would like to remind everybody that it is impossible to achieve all that is possible in a single clinical study.