standing of left ventricular (LV) outflow gradients in hypertrophic cardiomyopathy (HCM) (1). Dr. Murgo has had an important role in this conversation, which has spanned virtually the last 5 decades (2), for this heterogeneous disease with complex ejection dynamics (1,3).

However, on the issue of whether obstruction represents true mechanical impedance we must depart sharply from ideas resolutely held by Dr. Michael Criley in the 1960s, which we believe have plagued the contemporary understanding of HCM and its management, that is, that somehow LV outflow gradients are incidental to this disease and are not responsible for heart failure symptoms that disable many patients.

We would like to take this opportunity fortuitously afforded by Dr. Murgo's letter to once again underscore a crucial principle in HCM, that is, subaortic gradients due to mitral valve systolic anterior motion represent true mechanical obstruction to LV outflow and are responsible for high intraventricular pressures and increased wall stress, which (in association with mitral regurgitation) lead to exertional dyspnea and physical limitation compromising quality of life.

Fifty years after the initial description of HCM (1), evidence for the clinical significance of true obstruction to outflow in HCM is overwhelming, having recently been demonstrated in large cohorts followed up for long periods of time (1,4,5). Relief of LV outflow obstruction by surgical septal myectomy (or selectively by alcohol ablation) has been shown repeatedly to relieve heart failure symptoms, and in the case of myectomy, to enhance long-term survival (5). Indeed, this is not unlike the clinical experience with obstruction due to aortic valve stenosis, albeit with different ejection dynamics.

The present discussion is reminiscent of the "second HCM obstruction debate" 25 years ago at the American College of Cardiology meeting (1) when Dr. Murgo lectured passionately about the nuances of LV ejection dynamics and nomenclature, but in the process may not have addressed the essential clinical message, that is, that outflow gradients (and secondary mitral regurgitation) are associated with substantially elevated LV systolic (and diastolic) pressures, which can cause disabling symptoms but are mechanically reversible by septal reduction intervention and with resultant restoration of quality of life and longevity.

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Determinants of Functional Capacity in Peripheral Arterial Disease

In their excellent paper, Anderson et al. (1) showed that cellular metabolism correlated better with treadmill exercise results than estimation of muscle perfusion in patients with peripheral artery disease (PAD). Anderson et al. (1) suggested that factors independent of blood flow and located downstream from the obstruction are believed to play an important role in the relative absence of relation of the degree of hemodynamic impairment to functional limitation. Why should only downstream vascular parameters be factors to play a role in this result?

First, in the accompanying editorial, Dewey (2) briefly recalls that PAD may affect various arterial territories (among which the pelvic circulation) further limiting their clinical prognosis. In perspective with the high prevalence (22%) of patients with prior revascularization among the 85 studied patients, it is likely that functional limitation from proximal claudication may have interfered with the expected relationship between calf perfusion and exercise capacity. Indeed, proximal claudication may persist in approximately one-third of PAD patients early after aortobifemoral bypass surgery (3) or be present in a comparable proportion in those who have a patent aortobifemoral bypass with a median delay of 2 years from surgery (4). In these patients as well as those with isolated occlusion of the internal iliac artery, PAD may result in severe functional impairment whereas distal (calf) perfusion is not impaired.

Second, many studies have underlined that the impairment of aerobic and anaerobic capacity is significantly correlated with the severity of anemia. Although blood samples were available in the study of Anderson et al. (1) for cholesterol estimation and inflammatory markers, the evaluation of hemoglobin content is not reported. Anemia is a common comorbid condition in elderly patients. Of 732 consecutive patients admitted to an acute geriatric ward, 24% were found to be anemic (5). The proportion of anemic patients may even be higher in patients with advanced PAD (6).

Lastly, limb pain while walking may be the sole reported symptom of exercise-induced hypoxemia (7). Respiratory parameters at rest may remain in normal limits despite the presence of exercise-induced hypoxemia. Pulmonary disease and vascular disease share a number of common risk factors (age, overweight, tobacco). Not all patients with pulmonary disease have hypoxemia, but 15% of patients with PAD (8,9) have pulmonary disease. Therefore, exercise-induced hypoxemia may be a frequent aggravating cause of exercise intolerance in PAD patients.
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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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.