Journal of the American College of Cardiology Vol. 55, No. 6, 2010

ISSN 0735-1097/10/$36.00

CORRESPONDENCE

## Letters to the Editor

# Have We Really Come to Understand the Relationship Between the Left Ventricular Outflow Tract Gradient and Left Ventricular Emptying in Hypertrophic Cardiomyopathy?

In the recent review of hypertrophic cardiomyopathy (HCM) by Maron et al. (1), historical controversies relating to the relationship between left ventricular outflow tract (LVOT) pressure gradients and left ventricular (LV) ejection dynamics are revisited. The crux of these controversies is an assumption that the very presence of such gradients negatively impacts LV emptying (outflow) in obstructive HCM.

Maron et al. (1) point to earlier studies in which LV emptying and aortic volumetric flow were shown to be rapid and fairly complete by midsystole, whether a gradient was present or not (2–5). Furthermore, even in the same patient, LV emptying was shown to be faster in cardiac cycles in which gradients were present compared with those in which they were absent (3,6). The investigators of those studies concluded that an LVOT gradient was not associated with an impediment to LV emptying. Maron et al. (1) state that these conclusions were subsequently proven to be invalid, but cite a study that never investigated LV emptying or aortic flow in volumetric terms (7).

Unfortunately, much of this lack of agreement derives from the fact that we often use, in discussing hemodynamics, colloquial terms that have no rigorous mathematical or physical definitions in the field of physics or its subdiscipline of fluid dynamics. For example, the terms obstruct or impede are not found in the physical sciences. Surely, one can find them defined in dictionaries: "to block or fill (a passage) with obstacles . . ." or "to impede, retard, or interfere with; hinder (sic) progress. . . ." (8). However, such terms are subjective and are not defined by quantitative physical measurements.

Another major problem in these debates has been the difficulty that most clinical cardiologists have in understanding the physical relationships between pressure gradients and flow. We were all trained in the resistance concept of Poiseuille's law, in which forward flow is always associated with a positive pressure gradient. However, this concept is only a small part of the physics of pressure and flow, in which the additional impact of inertial and convective acceleration components plays a major role and the significance of pressure gradients is more completely understood (9).

So, what does the term outflow obstruction mean? Where has it ever been actually defined so that all participants in these debates are operating from the same platform? Unfortunately, no rigorous definition exists. This has resulted in confusion, semantic differences, and much misunderstanding.

If one examines the issue of obstruction from a muscle mechanics viewpoint, the presence of marked LVOT gradients must result in inappropriate endocardial wall stress, which can lead to exacerbation of the diastolic abnormalities that underlie many of the congestive symptoms in HCM. However, from a pump function standpoint, where LV volume or aortic volumetric flow is actually measured as a function of time through systole, there is no evidence that outflow is compromised as a result of an LVOT gradient.

Such an understanding does not imply that elimination of LVOT gradients is not potentially beneficial. Rather, one hopes that when one does recommend an intervention to eliminate such gradients, one understands that that intervention is not designed to improve ejection itself.

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doi:10.1016/j.jacc.2009.08.071

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## Reply

We appreciate the correspondence from Dr. Murgo, stimulated by our recent historical review focused on the evolving under-

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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doi:10.1016/j.jacc.2009.10.030

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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.