replicate in a population of patients fulfilling the criteria used in their study. We recently evaluated 4,004 patients with interpretable electrocardiograms undergoing treadmill exercise echocardiography in whom chest pain or ischemic electrocardiographic changes during exercise did not develop (3). Applying the criteria used in the study by Bourque et al. (1) to this population would yield 2,005 patients who achieved both ≥10 METs and >85% of MAPHR. Of them, new or worsening wall motion abnormalities developed in 301 (15%) patients, 187 (9.3%) patients had ischemia involving at least 3 myocardial segments, and 138 (6.9%) patients underwent coronary revascularization. Thus, these results do not suggest that a high exercise workload may confidently rule out myocardial ischemia or significant coronary artery disease in our patients. It is important to point out that images were acquired at peak exercise, which enhanced the sensitivity of the tests (4).

Although patients achieving a high exercise workload undoubtedly have a better prognosis, a correct diagnosis is still desirable, even when coronary revascularization is not deemed necessary. It would be interesting to validate the results obtained by Bourque et al. (1) at other institutions, with different noninvasive imaging modalities, and using cardiac events or coronary angiography results as end points.

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Reply

We thank Dr. Bouzas-Mosquera and colleagues for their comments regarding our paper (1). They report the prevalence of ischemic wall-motion abnormalities by stress echocardiography in 2 studies that seem to have fundamental differences compared with ours (2,3). One important distinction is the variation in study cohort clinical characteristics. They analyzed 1 group of 1,433 patients with high exercise capacity and a 30% rate of stress-induced wall-motion abnormalities (3). Compared with our population, this cohort had a higher prevalence of previous myocardial infarction (29.0% vs. 11.8%) and included individuals with exercise ST-segment depression (14%) and achievement of <85% of their maximum age-predicted heart rate (19%). We excluded these types of patients from our low-risk cohort (1). Their inclusion in the analysis by Bouzas-Mosquera and colleagues likely contributed to the increased ischemia observed in their cohort. Moreover, they included women who reached only 8 metabolic equivalents (METs) of exercise workload compared with our cutoff of ≥10 METs for both men and women. This is an important difference because those patients in our study who achieved 7 to 9 METs of workload had a 10-fold increase in the prevalence of ≥10% left ventricular ischemia (4.3% vs. 0.4%).

The analysis of ischemia in our study was quantitative in nature. The qualitative (i.e., visual) approach used by Bouzas-Mosquera et al. (2) is associated with a higher rate of false positives for ischemia, especially in the setting of resting dysfunction, as seen in previous myocardial infarction.

To match our population more closely, Bouzas-Mosquera et al. (2) examined a second population reaching ≥10 METs and ≥85% of maximum age-predicted heart rate that expectedly had a lower prevalence of stress wall-motion abnormalities (15%) than in their other cohort (30%). It is unclear how many of these positive echocardiographic studies represent true ischemia versus false positivity because the echocardiographic results were not correlated with coronary angiography and no cardiac outcomes were provided. Thus, the 15% ischemia prevalence in this population was not validated against a gold standard and seems high for patients achieving a high workload. In our study, the rate of any ischemia in such patients was 4.0%, which is more in line with what is expected in individuals reaching high exercise workloads and target heart rate and with what has been described in previous reports. This suggests that a significant proportion of the stress wall-motion abnormalities in the study of Bouzas-Mosquera et al. (2) may have been falsely positive for ischemia. If there were in fact such a high rate of ischemia in their ≥10 METs cohort (15%), an increased event rate could be expected. Unfortunately, the survival data for this subgroup were not provided. Previous prognostic studies show low mortality rates in patients with high exercise capacity.

We agree with Dr. Bouzas-Mosquera and colleagues that additional research is necessary to confirm that the very low risk of significant ischemia in our population is associated with a comparably low rate of cardiac events. In fact, we performed a preliminary outcomes analysis of our cohort that showed no cardiac deaths over 1 year for subjects achieving ≥10 METs and ≥85% maximum age-predicted heart rate during exercise stress myocardial perfusion testing (4).

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Clinical Classification of Pulmonary Hypertension

I read with interest the recently published Dana Point clinical classification of pulmonary arterial hypertension (PAH) in the *Journal* supplement (1). Any globally relevant scheme of clinical classification cannot and should not lose sight of the prevalence of the disease state worldwide. Although the classification is not based on prevalence, and causes such as left ventricular systolic and diastolic dysfunction, in which PAH is not of primary importance, are kept in group 2 only, downgrading PAH associated with congenital heart disease (CHD) in their classification scheme to 1.4.4 seems unjustified. Although precise epidemiological data are not available for most causes of PAH, it is easy to understand the importance of PAH due to CHD on a global scale. In 2009, nearly 80% of the world's population lives in the less and least developed regions of the world. These regions also have a younger population profile, higher growth rates despite high infant mortality, and poor facilities for the management of CHD. Because the incidence of CHD is more or less uniform at 6 to 8 per 1,000 live births, these data easily would translate into a very high burden of PAH associated with CHD in the world, more than any cause listed in group 1.4. Most patients with CHD in the Western world undergo surgery early in life, and therefore this facet of CHD is less and less evident there, but the various aspects of the pathogenesis of PAH associated with CHD are also far from resolved. In view of the continued epidemiological, scientific, and pedagogical importance, PAH associated with CHD should be classified as 1.4.1 or even higher.

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Reply

The relevance of congenital heart disease (CHD) in the setting of pulmonary arterial hypertension (PAH) is unquestionable, as stated in the letter by Dr. Kothari. However, it is important to emphasize that the core structure of the updated clinical classification of pulmonary hypertension (1) is not based on the relevance of the topic or on the prevalence of the disease; thus, there is no hierarchical level within each one of the groups. The fact that schistosomiasis-associated PAH is classified as item 1.4.5 does not make it more or less important than human immunodeficiency virus infection–associated PAH, classified as item 1.4.2. The same can be directly extrapolated to the other 4 groups. Consequently, one could not consider that CHD-associated PAH has been downgraded from the previous classification. This classification has even strengthened the role of CHD by describing not only the anatomic-pathophysiologic classification of congenital systemic-to-pulmonary shunts associated with PAH (see Table 4 in the classification [1]) but also the clinical classification of congenital systemic-to-pulmonary shunts associated with PAH (see Table 5 in the classification [1]) to disseminate the current knowledge on the management of such relevant conditions.

The prevalence of the different forms of pulmonary hypertension is extremely important for the appropriate understanding of the whole pulmonary hypertension scenario, mainly considering that regional characteristics, such as local altitude, sanitary conditions, and health care infrastructure and organization, may play a significant role (2). Even considering that this is not related to the order in the updated classification, the commentary from Dr. Kothari should be considered as a reinforcement of the need for robust registries of the different forms of pulmonary hypertension (3) to serve as a basis for international collaborative efforts in the pulmonary hypertension field.

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