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## Reply

We would like to thank Drs. MacFadyen and Chuen for their interest in our study (1). They seem to conclude that our population-based report advocates screening for all persons with dyspnea. Unfortunately, the majority of the issues they raise are based on this false assumption. We believe that it is necessary to await the results from studies evaluating the cost-effectiveness before introducing pro-B-type natriuretic peptide (proBNP) as a screening tool of all breathless persons in the community. We agree that if one sought to examine the cost-effectiveness of the natriuretic peptides in primary care, they should include the additional information that is obtainable for the general practitioner.

The aim of our study was to examine whether or not plasma proBNP could be used in discriminating between cardiac and pulmonary dysfunction in the general population with dyspnea. Our findings that plasma proBNP is increased in left ventricular dilation, hypertrophy, systolic and diastolic dysfunction, but unaffected by pulmonary dysfunction, should be viewed in this perspective. Drs. MacFadyen and Chuen also point out that 48% of the population in our study reported dyspnea without having an abnormal conventional echocardiogram or pulmonary function test. It is important to emphasize that a normal conventional echocardiogram does not rule out cardiac dysfunction. Most of these people (83%) were only complaining of mild dyspnea. Compared with their nondyspneic counterparts, they had a higher frequency of ischemic heart disease and risk factors for ischemic heart disease. Conventional echocardiography does not provide much information about longitudinal myocardial contractility, which is impaired initially in ischemic heart disease. In fact, we suspect that breathless persons with a high level of plasma proBNP have a high risk of cardiac dysfunction, although they might have normal conventional echocardiograms. Further research with more

advanced modalities (e.g., tissue Doppler imaging) within such groups is needed.

Intraindividual and interindividual variability of plasma proBNP should not be extrapolated from studies of BNP or N-terminal proBNP. The interindividual variability is one of the major reasons for the assay's gray zone reported in our study, whereas the intraindividual variability of the assay is small (2). Regarding the ability to rule out parenchymal lung disease by spirometry, pulse oxymetry, and clinical history, we agree that additional information from computed tomography scans and lung biopsy would have been interesting but obviously not possible in this population study. Concerning the last issue of pulmonary hypertension in parenchymal lung disease, we have previously shown that plasma proBNP only increases at elevated mean pulmonary artery pressures >50 mm Hg in patients with terminal parenchymal lung disease (3).

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doi:10.1016/j.jacc.2007.12.023

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## Plaque Burden, Intravascular Ultrasound, and Distal Embolization Phenomenon

Although embolization of atherothrombotic material during stent deployment is probably ubiquitous, its causes and consequences remain poorly characterized. In a recent issue of the *Journal*, both Kawaguchi et al. (1) and Kawamoto et al. (2) suggested that vessels most likely to sustain distal embolization could be identified using virtual histology (VH) intravascular ultrasound (IVUS) to quantify

the necrotic core. It was suggested that patients with plaques exhibiting these characteristics might benefit from selective use of distal protection devices. Neither study suggested that a relationship exists between original plaque volume and the occurrence of embolization.

In our opinion, these studies have a number of limitations. Kawaguchi et al. (1) chose ST-segment re-elevation immediately after stent implantation as a proxy for embolization. This parameter has not previously been linked to the more recognized end points of myocardial blush grade or 90-min ST-segment resolution (3). Additionally, the limited ability of the 20-MHz Eagle Eye IVUS catheter (Volcano Therapeutics, San Diego, California) to identify luminal thrombus may be particularly relevant in their patients who received only aspirin as a procedural antiplatelet therapy. Moreover, the possibility of side branch occlusion during stent deployment as a cause of myocardial necrosis does not appear to have been considered. In patients with stable angina, Kawamoto et al. (2) suggested that plaques with larger necrotic cores were more likely to exhibit high-intensity transient signals detected by a Doppler guidewire. Histopathological correlates between VH-IVUS and pathology are questionable, and neither study uses post-procedure IVUS imaging of residual plaque. Using 40-MHz IVUS imaging, a direct relationship has been demonstrated between the change in plaque volume and evidence of new myocardial necrosis (4). Thus, although it is perhaps intuitive that friable plaque elements are more likely to be liberated than are more readily compressed fibrotic components, further investigation is required.

In the accompanying editorial, Shah (5) questions whether no reflow is merely a marker of myocardial injury or whether it is the cause of further myocardial damage. There is currently no data to support the notion that, in established no reflow, administration of any pharmacologic agent has any impact on subsequent prognosis, and perfusion in areas of new myocardial necrosis remains impaired for at least 24 h despite normal perfusion in viable areas of myocardium subtended by the same vessel (6). These data suggest that no reflow is predominantly a marker of downstream myocardial necrosis. As more diffuse and challenging diseases are being tackled by percutaneous coronary intervention (PCI), further research into the prevention of plaque embolization is essential to allow further improvement in PCI outcomes.

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doi:10.1016/j.jacc.2007.11.066

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## Reply

We appreciate the interest in our recent study (1) by Dr. Porto and colleagues. Myocardial blush grade (MBG) and early ST-segment resolution are well-known parameters used for describing the effectiveness of myocardial reperfusion, which is an independent predictor of long-term mortality (2). However, the aim of our study was to investigate distal embolization that occurs immediately after stent implantation: in other words, distal embolization induced by stent implantation. Although stent-induced distal embolization is one of the causes of low blush grade or early ST-segment resolution, it is not the only cause—several factors such as vasoconstriction, additional pharmacologic therapy, and time interval after stent implantation may also affect the outcome of these parameters. Because we were not investigating final coronary flow and prognosis, we believed that we did not need to consider the relationship between ST-segment re-elevation (STR) and MBG or early ST-segment resolution. Thus far, we have not come across parameters specific to estimating the extent of stent-induced distal embolization, and certainly, as we mentioned in the limitations section, we need to validate our measurements in a different cohort to see how the predictive algorithm correlates with STR. However, STR during percutaneous coronary intervention is recognized as a predictor of the no-reflow phenomenon (3,4). In the no-reflow cases, distal embolization of the plaque or thrombus from the lesion site is a likely mechanism (5,6). Therefore, distal embolization of the plaque or thrombus from the lesion site induced by stent deployment is the probable cause of STR. Based on these data, we believe that STR occurring immediately after stent implantation reflects distal embolization induced by stent implantation.

We had mentioned in the limitations section about the presence of residual luminal thrombus and the ability of the 20-MHz intravascular ultrasound catheter to assess the plaque component. Moreover, we did not have any cases with side branch occlusion in the 11 STR cases, and it should have been included in the exclusion criteria of our study.

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doi:10.1016/j.jacc.2007.12.026