that these commonly used anesthetics increase risk in hemodynamically stable patients, their use is recommended.

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Biomarker Sensitivity and Specificity Require Pre-Test Probability of Disease Diagnosis to Be Collated

Additional Points on the Interpretation of Pro–B-Type Natriuretic Peptide Triage of Dyspnea in the Copenhagen Heart Study

The Copenhagen City Heart study (1) provides important insight into community assessment of breathlessness. The report could be taken to support pro–B-type natriuretic peptide (proBNP) triage of all breathless patients in this setting. We feel this is a simplistic analysis of the potential contribution of biomarker technology and that a number of additional points should be considered.

The relationship of BNP measures to cardiac impairment has been confirmed, and their utility tested in a variety of settings (1,2). However, the sampling frame of most surveys (2,3) is of little relevance to the general practitioner. Importantly in the Copenhagen study, 48% of their breathless patients had *neither* cardiac nor pulmonary abnormality. In fact, the major causes of dyspnea in a population-based study were obesity, depression, and older age (4). Thus, even before addressing the performance of proBNP analysis, the authors must surely also address the relative diagnostic void that is presented for almost half of the patients in their study.

Secondly, the incremental value of proBNP testing is not clearly put in the context of clinical history; physical examination and simple bedside tests such as a 12-lead electrocardiogram and a chest roentgenogram. Although these may individually have low sensitivity and specificity and are operator specific (5,6), they contribute to pre-test diagnostic probability, which, in turn, affects the performance of any biomarker and the post-test probability of the presence of cardiac dysfunction (7). By excluding the contribution of the physician, the ability of the test to function cost-effectively could alternatively be compromised or enhanced. Thus, a dyspneic patient with a high proBNP level could undergo echocardiography, even in the absence of abnormalities on examination and bedside investigations. Surely in such patients resources would be better employed establishing a noncardiac cause for dyspnea.

Thirdly, although the authors accounted for age and gender, they need to interpret point measurement of proBNP levels with great care due to their large intraindividual and interindividual variability (33.3% and 36.5%, respectively, in normal individuals [8]). Both symptomatic and asymptomatic patients with stable systolic heart failure present with wide ranges of plasma BNP, with up to 21% of symptomatic patients having BNP levels below what would be considered "diagnostic"(9).

Finally, the concept that pulmonary disease can be defined by spirometry alone is not acceptable. This limited technique does not rule out the presence of significant parenchymal lung disease. Moreover, proBNP levels can be elevated in lung conditions resulting in right heart strain and pulmonary hypertension (10,11).

The authors are to be congratulated on their effort in challenging the use of biomarker technology for the community assessment of breathlessness. However, its commercial exploitation needs to be based on its cost-effectiveness and applicability to realistic clinical practice. It needs to be interpolated in the light of clinical assessment, particularly given the large percentage of true negative results for either cardiac or pulmonary abnormalities.

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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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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