same clinical entity, cardiogenic shock, and succumb to the so-called downward spiral after all. Any thought to the contrary would be real “hubris” indeed.

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To the Editor:

We thank Dr. Joffe for his comments on our article. Although interesting, the concept of single-beat analysis should be regarded with caution. We strongly disagree with Dr. Joffe’s hypothesis suggesting that most of the differences can be explained by differences in heart rate. Indeed, this would imply that stroke volume was lower or equal, but surely not higher, in the high cardiac index group. However, we observed just the reverse: stroke index decreased over time by 9% in the low cardiac index group, while it increased by 38% in the normalized cardiac index group. In addition, heart rate decreased over time in the normalized cardiac index group, while it increased by 38% in the low cardiac index group. Finally, the stroke systemic vascular resistance index, a parameter of doubtful value, proposed by Dr. Joffe (Table 1 of his letter) was stable in the low cardiac index group. In addition, heart rate decreased over time in the normalized cardiac index group, while it was stable in the low cardiac index group. Finally, the stroke systemic vascular resistance index, a parameter of doubtful value, proposed by Dr. Joffe (Table 1 of his letter) was stable in the low cardiac index group but decreased by 33% in the normalized cardiac index group. Altogether, these data are in accordance with the observation that 9 of the 23 nonsurvivors acquired hyperdynamic shock, excluding pump failure as the primary cause of death. Other mechanisms, including endotoxin and cytokine release, and excessive nitric oxide release leading to peroxinitrile formation may also explain why these patients present pronounced microcirculatory alterations,1,2 which are more severe in nonsurviving than in surviving patients,2 and are remarkably similar to those observed in patients with septic shock.1,2

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Differeniating Asthma and COPD Patients

To the Editor:

I read with interest the article by Hanania et al1 in September 2003, where the combination of fluticasone propionate (250 µg)/salmeterol (50 µg bid) was found to improve FEV1 better than salmeterol in COPD. Moreover, fluticasone alone improved FEV1. I am concerned that the article has inadvertently allowed the inclusion of asthmatic patients who were mislabeled as “COPD.”

1. Patients’ ages were ≥ 40 years. Moderate-to-severe COPD is rare below the age of 50 years.2
2. The exclusion criteria removed patients with “current diagnosis of asthma”. This implies that patients who had asthma in the past were recruited. And who decided they were no more asthmatic? Over a hundred doctors at 76 investigative sites across the United States, where the standards of clinical judgment vary.
3. The patients recruited where classified as “reversible” and “nonreversible.” The mean percentage increase of FEV1 in the reversible group—after administering 400 µg of albuterol—was 30% (range not given). As the inclusion criteria included patients with baseline FEV1 < 65%, it is very likely that many patients in the reversible group had achieved an FEV1 of > 80% after albuterol, which takes them out of the definition of COPD.3
4. The patients’ response to medications is typical of asthma in that fluticasone was effective at a small dose. Several previous studies on COPD have failed to demonstrate such effect even though larger doses of inhaled corticosteroids were used.4 In addition, the response to fluticasone was manifest 24 h only after the initiation of treatment. This is too quick a response for patients with COPD outside acute exacerbation.

My concern is highlighted by the fact that differentiation between asthma and COPD can sometimes be difficult.5 Also, a metaanalysis6 of eight articles showed that inhaled corticosteroids had improved FEV1 in patients with COPD.6 The same analysis—after excluding the articles that included patients with asthma/COPD—showed no such effect. The inclusion of a few asthmatic cases can tip the balance towards response.

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Chest 2004; 126 (2) 653
only 53 patients (7%) were the disease. In fact, only three patients in the study reversed to often misdiagnosed during the early stages of COPD and we did a previous diagnosis of asthma. Importantly, many patients are reversed in chronic obstructive pulmonary disease: a metaanalysis. Ann Intern Med 2003; 138:969–973

To the Editor:

We sincerely appreciate Dr. El-Kassimi's interest in our article.1 While the inclusion criteria for our study may appear to be broad, they were designed to select patients with COPD as defined by both the American Thoracic Society (ATS)2 and Global Initiative for Chronic Obstructive Lung Disease (GOLD)3 guidelines. We agree with Dr. El-Kassimi that COPD is rare in patients 40 to 50 years old; however, it does exist.4 In this study, only 53 patients (7%) were <50 years of age.

It is true that patients included in our study may have received a previous diagnosis of asthma. Importantly, many patients are often misdiagnosed during the early stages of COPD and we did not want to exclude patients who had clear clinical evidence of the disease. In fact, only three patients in the study reversed to albuterol to >80% predicted FEV1, thus supporting that this was a COPD population. Similar inclusion criteria have been used in many other large COPD studies. In fact, the mean percentage of reversible patients in this study (35 to 56%) was comparable to that seen in clinical trials with salmeterol in COPD (57 to 65%),5,6 and it was lower than that seen in clinical trials of ipratropium/albuterol in COPD (68 to 73%).7

In Table 3 of our article, lung function response is reported by reversibility. Surprisingly, the difference in predose FEV1 between fluticasone propionate/salmeterol combination (FSC) therapy and salmeterol was highest among the nonreversible subgroup. Within the nonreversible subgroup, the change from baseline for FSC was approximately 100 mL greater than that for salmeterol. By comparison, the effect of the combination was higher in the reversible subgroup (325 mL vs 221 mL), but the difference between FSC and salmeterol in this subgroup was smaller (approximately 60 mL). This is counterintuitive to those that expect an inhaled corticosteroid (ICS) to make a greater contribution among reversible patients. For many years, patients with COPD were defined by having irreversible airflow obstruction and therefore would derive little benefit from treatment with an ICS. This assumption has now been shown to be incorrect. While most studies8–10 have failed to demonstrate a reduction in the rate of lung function decline with the use of high dose of ICS, several studies11–13 have demonstrated that ICS therapy improves lung function, reduces the rate of exacerbations, and improves quality of life in patients with COPD.8–10 In addition, there is now compelling evidence demonstrating the benefits of ICS/long-acting β-agonist (LABA) in combination in COPD with respect to improving lung function and reducing exacerbations.11–14 In a retrospective study,15 this combination therapy has also been shown to reduce morbidity and mortality in such patients, although prospective studies are needed to confirm this finding.

There is no evidence of a dose response to ICS in patients with COPD, and therefore there is nothing to support that the response to the medium-dose fluticasone propionate observed in our study was atypical. In fact, in a similarly designed study with a higher dose of fluticasone propionate, the magnitude of response in lung function was comparable to that seen in our study.11

The concerns raised by Dr. El-Kassimi underscore an important point: the differential diagnosis between asthma and COPD can sometimes be very difficult. Both diseases involve inflammation and bronchoconstriction and result in airflow obstruction that can lead to similar symptoms of dyspnea, cough, and wheezing. Our results show that similar to asthma, the combination of a long-acting bronchodilator and an antiinflammatory results in a significant improvement in lung function compared with either agent alone, even in a disease which has been historically defined as “irreversible.” We believe that reversibility to albuterol should not be a criterion for the diagnosis of COPD, nor should it dictate therapy. This opinion is supported by both GOLD and ATS, and this study demonstrates that ICS/LABA together in the treatment of COPD play a beneficial role and should not be reserved for patients with COPD with an “asthmatic response.”

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