First, there are few studies about the VEGF levels in tuberculous pleural effusions, as Dr. Kiropoulos mentioned. Momi et al\(^2\) and Hamed et al\(^3\) measured VEGF levels both in the serum and pleural fluid of tuberculous pleurisy patients. They found elevated VEGF levels both in the serum and pleural fluid of tuberculous pleurisy patients compared with congestive heart failure patients. In congestive heart failure patients, both of the studies reported higher VEGF levels in serum than in pleural fluid, as expected.

Second, pleural fluid VEGF levels in tuberculous pleurisy patients were lower than the respective serum levels found in the study by Kiropoulos. However, in the studies by Momi et al\(^2\) and Hamed et al\(^3\), VEGF levels in pleural fluid were higher than those in the serum of tuberculous pleurisy patients. This is an important discrepancy since the proposed mechanism for the increase in VEGF levels in the pleural fluid may be strictly different. The proposed mechanisms for the increase of VEGF in pleural fluid are increased vascular permeability, and local production by mesothelial cells and/or pleural macrophages. Another important issue is the standardization of tuberculous patients. A tuberculous pleurisy patient may also have a tuberculous lesion in the lung parenchyma. In this situation, VEGF may be secreted from active tuberculosis lesions beside those in the pleura.

In conclusion, while we agree with Dr. Kiropoulos on the importance of VEGF as a mediator of pleural fluid formation, we think that well-standardized studies with more tuberculous patients are needed in order to clarify the underlying mechanisms. We appreciate the contributions by Dr. Kiropoulos.

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At Least Three FEV\(_1\) Blows Are Required at Each Time Point During the Assessment of Bronchial Hyperresponsiveness

To the Editor:

Bronchoprovocation tests are used routinely in clinical practice and research to detect and quantify the presence of bronchial hyperresponsiveness. Histamine, methacholine, and 5′-adenosine monophosphate (AMP) are some of the bronchoprovocative agents used to test bronchial hyperresponsiveness. After obtaining the baseline FEV\(_1\) value, subjects are asked to inhale increasing concentrations of bronchoprovocative agents with a dosimeter, until the postchallenge FEV\(_1\) drops by 20% from the baseline value (measured as provocative dose causing a 20% fall in FEV\(_1\) [PD\(_{20}\)], or provocative concentration causing a 20% fall in FEV\(_1\)). According to American Thoracic Society guidelines,\(^1\) subjects are asked to perform at least three FEV\(_1\) maneuvers at each time point after administering the bronchoprovocative dose. This may mean performing up to 75 forced expiratory maneuvers over a period of 1 h, which can be very tiring to many patients undergoing this test.

Cockcroft and colleagues\(^2,3\) have described test-shortening procedures for bronchial challenge, in which they have recommended a single forced expiratory maneuver at each time point following administration of the bronchoprovocative substance. However, because of wide variability between FEV\(_1\) values in the same subject when performed at the same time, using only one forced expiratory maneuver may not be reliable to obtain the highest FEV\(_1\) value.

We aimed to study whether three forced expiratory blows are really necessary at each time point following the bronchoprovocative challenge and whether the first or second forced expiratory maneuver gives the highest FEV\(_1\) value > 90% of the time. We conducted a study in 12 subjects who underwent two bronchoprovocation tests on separate days at least a week apart with AMP and determined how frequently the best FEV\(_1\) value was obtained during the first, second, and third forced expiratory maneuvers after sufficient motivation to give their best effort at each of the three blows. These were recorded as best, second best, and third best (highest to lowest FEV\(_1\) values), and their corresponding blow numbers were recorded (first blow, second blow, and third blow). The first blow produced the best FEV\(_1\) in 43.49% of the times, while the second and third blows produced the best FEV\(_1\) values 24.59% and 31.92% of the times, respectively. Using only one blow (as suggested by Cockcroft and colleagues) would have missed the best FEV\(_1\) value 56.51% of the times, while using two FEV\(_1\) blows would have missed the best FEV\(_1\) value 31.92% of the times. We therefore conclude that in order to obtain reliable FEV\(_1\) values during bronchoprovocation testing, at least three forced expiratory blows are required at each time point.

Asking the subject to perform only one forced expiratory blow would give unreliable FEV\(_1\) values, which would likely give false PD\(_{20}\) values.

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To The Editor:

We thank Jantikar et al for their interest in our publications. They raise some valid points regarding patient fatigue during methacholine challenge and the reproducibility of FEV₁ maneuvers. Their points regarding the best FEV₁ occurring on the first, second, or third attempt are valid. However, we cannot agree with their conclusions.

The use of a single technically acceptable spirogram at each time point (ie, 30 and 90 s following inhalation) was not introduced in the two publications outlined by these authors.1,2 It dates back to the original description of the method in 1977.2 For the majority of this almost 30-year period, we have further reduced patient fatigue by performing truncated spirograms to capture only the FEV₁. This procedure requires an astute and well-trained technician or research assistant who can properly train the subjects prior to starting inhalations, and who can promptly identify unacceptable maneuvers, be it due to poor effort, coughing, or other conditions, and discard them. In such instances, which occur relatively infrequently, a repeat spirogram is performed within 20% of highest post-challenge FEV₁, at each time point, as outlined by these authors, we have historically used the lowest FEV₁ for two reasons. First we are looking for the maximum effect of the bronchoconstricting agent and second, the time course of the response is relatively brief. A comparison of highest and lowest spirograms has revealed no significant difference.

While it is true that the best FEV₁ may well occur on the second, third, or even later attempt, this issue per se is probably not relevant to the number of spirograms performed during bronchoprovocation. The more important issue is the magnitude of the difference between FEV₁ attempts (ie, the repeatability of the FEV₁). If the three determinations of FEV₁ are, as we suspect, within ±5%, then we would suggest that the additional time and effort required to obtain three maneuvers vs two maneuvers is of little advantage. Additional factors other than the number of FEV₁ maneuvers and subject fatigue must be considered. It is important to maintain a consistent dosing interval to assure that any cumulative effect is constant. We1–3 and the American Thoracic Society5 have recommended a 5-min interval between the start of one concentration and the start of the next concentration. One is therefore obtaining spirograms within about a 2-min window between 30 s after the completion of one inhalation and 30 s before the commencement of the next. It would be difficult to obtain six acceptable spirograms in a 2-min window. Additionally, consideration must be given to the potential effect of the maneuver on the measurement of the response. Total lung capacity inhalations may bronchodilate or bronchoconstrict, thus inhibiting the response and potentially leading to the unnecessary administration of higher concentrations of bronchoconstricting stimuli. This situation is evident particularly in mildly responsive individuals,6 and represents the range that is most often seen in a diagnostic laboratory and could result in false-negative results or an underestimation of airway responsiveness. By contrast, repeated forced expiratory maneuvers may enhance bronchoconstriction, a feature that would be limited to subjects with more marked airway hyperresponsiveness.

In summary, we believe that, with meticulous attention to subject training and with the immediate recognition and disposal of technically unacceptable spirograms, single FEV₁ measurements from a truncated spirogram at the two time points are adequate and preferable to the alternatives expressed here.

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Transfusion-Related Acute Lung Injury, Acute Lung Injury, and ARDS

Close Relatives

To the Editor:

The article by Looney et al (July 2004)2 argues strongly for a separate and distinct entity for the ARDS-like reaction occurring with the transfusion of blood and blood products (curiously, human serum albumin is not mentioned).1 Although Barnard3 as early as 1951 described four cases, presumably of divers sensitivity reactions to transfusion; only one case had pulmonary edema. The pulmonary edema component did not enter the literature seriously until well after the description of ARDS, when the great majority of blood transfusions consisted of packed RBCs and generally large amounts of crystalloid fluid. The authors acknowledge that because of the frequency of the latter association, transfusion-related acute lung injury (TRALI) cannot be diagnosed without a fairly rigorous exclusion of "volume overload." It is clear also from the text the authors are satisfied that volume overload can be excluded by ruling out an elevation of pulmonary artery pressure (PAP) or central venous pressure (CVP). This is not possible with these central pressures, and it is likely therefore that TRALI is overreported, rather than underreported as suggested.

TRALI is a noncardiogenic pulmonary edema, as is ARDS. This, of course, presents the profession with the conundrum alluded to above: volume overload in the form of pulmonary edema is present before either the CVP or PAP rise to abnormal levels. This is possible because the microvascular membrane of the lung and elsewhere is completely and rapidly permeable to infused isotonic fluid.

Imprecise language is a problem here. In clinical use, overload refers to an active (iatrogenic) intervention, and volume refers to the amount of fluid infused. This becomes essentially fluid overload. Fluid overload is an excessive expansion or transfusion of the extracellular fluid space with crystalloid, high in salt.

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