
To the Editor:
Peno-Green et al.1 reported an individual with rheumatoid arthritis who acquired worsening lung infiltrates while receiving infliximab therapy. Transbronchoscopic lung biopsy demonstrated granulomas, and subsequent cultures on the BAL fluid grew Mycobacterium avium-intracellulare complex (MAC). Withdrawal of infliximab therapy together with the addition of prednisone resulted in rapid clinical improvement. The case reported by Peno-Green et al. emphasizes the possibility that certain infectious organisms (such as MAC) that are usually kept in control by the normal immune system, may flourish when tumor necrosis factor (TNF)-α is neutralized. Thus, rather than contradicting our report of potential benefit associated with TNF-α inhibition in the course of lung fibrosis associated with rheumatoid arthritis, the report by Peno-Green et al. emphasizes the need for clinicians to be aware of the increased predisposition of infliximab-treated individuals to mycobacterial (and fungal) infection. Numerous reports have cited the potential for reactivation of mycobacterial and fungal infection in patients receiving infliximab, mandating appropriate tuberculosis screening prior to drug initiation. The US Food and Drug Administration has received a total of 117 cases of infliximab-associated tuberculosis through November 30, 2001. This concern has resulted in the package insert of the product including a warning about the risk of tuberculosis and the need to screen patients for tuberculosis before treatment with infliximab is initiated. The specific role of TNF-α in the pathogenesis of rheumatoid arthritis associated lung fibrosis is yet to be determined. In addition to the study by Gossel et al.8 there are numerous animal studies implicating TNF-α as an important factor in the pathogenesis of lung fibrosis. TNF-α receptor knockout mice are resistant to the development of lung fibrosis induced by inhaled asbestos, silica, and bleomycin, supporting the concept that signaling through TNF-α receptors is fundamental to the development of lung injury and fibrosis in these animal models.9,10 Furthermore, treatment of mice with antagonistic TNF-α antibodies or a human recombinant soluble TNF-α receptor (TNF antagonist)11 reduced fibrosis induced by bleomycin in mice.

Lung fibrosis is a devastating clinical problem with limited treatment options. Considering the substantial data supporting a role for TNF-α in mediating lung injury and fibrosis in animal models, we believe that infliximab and other inhibitors of TNF-α signaling merit consideration for the management of lung fibrosis associated with rheumatoid arthritis. However, clinicians must be vigilant about associated risks of infection and appropriate measures undertaken to minimize this risk. Finally, although it is possible that more case reports may provide some additional insight, the contribution of TNF-α inhibition in the course of lung fibrosis associated with rheumatoid arthritis can only be firmly established by prospective randomized trials. In view of the lack of proven therapies for lung fibrosis, the demonstrated efficacy of TNF-α inhibitors for the joint manifestations of rheumatoid arthritis, and the data from animal studies, we believe that a prospective clinical trial with the primary aim of establishing the effect of TNF-α inhibition on the course of lung fibrosis in rheumatoid arthritis is reasonable.

R. Vassallo, MD
Eric L. Matteson, MD
Charles F. Thomas, Jr., MD, FCCP
Mayo Clinic
Rochester, MN

References
12 Piguet PF, Vesin C. Treatment by human recombinant soluble TNF receptor of pulmonary fibrosis induced by bleomycin or silica in mice. Eur Respir J 1994; 5:515–518

Underutilized Tools for the Assessment of Intravascular Volume Status

To the Editor:

I read with interest the study by Martin et al.1 (December 2002) describing correlations between the findings of portable chest radiographs and fluid balance in critically ill patients. In the study, the authors suggested that the vascular pedicle width (VPW) is an underutilized tool for the assessment of intravascular volume status. However, although the relationships reported in the study are statistically significant, those between the VPW and the wedge pressure or the fluid balance are weak (r2 range, 0.25 to 0.3), such that a given VPW value cannot be recommended to

Correspondence to: Charles F. Thomas, Jr., MD, FCCP, Mayo Clinic, 200 First St SW, Rochester, MN 55905

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).
accurately predict intravascular volume status. Moreover, from a methodologic point of view, demonstrating that a parameter is sensitive to changes in volume status does not allow one to conclude that this parameter is useful in assessing intravascular volume. For example, central venous pressure goes up during fluid loading, goes down during fluid depletion, but cannot be used to assess intravascular blood volume, simply because intravascular volume is not the only determinant of central venous pressure. It must also be pointed out that chest radiographs were interpreted by one experienced thoracic radiologist, which is usually not the case in real life.

The respiratory changes in arterial pressure were recognized as a clinical sign of hypovolemia > 35 years ago and have been shown to be correlated very closely with intravascular volume. In contrast to chest radiograph interpretation, the quantification of arterial pressure variation is not operator dependent and even now is automatically calculated by commercially available devices. Since most patients with acute lung injury/ARDS are sedated (at least transiently for the correct measurement of plateau inspiratory pressure and total positive end-expiratory pressure) and instrumented with an arterial line, there is no doubt that the arterial pressure variation is also an underutilized tool for assessing intravascular volume status. Finally, since the echocardiographic study of respiratory changes in aortic blood flow provides information that is similar to that from arterial pressure waveform analysis, I am afraid that the VPW cannot be considered as the “most sensitive noninvasive indicator of intravascular volume.”

Frederic Michard, MD, PhD
Bicetre Hospital
Le Kremlin Bicetre, France

REFERENCES
4 Perel A, Fitz B, Cotef S. Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. Anesthesiology 1987; 67:498–502

To the Editor:

We appreciate Dr. Michard highlighting the importance of monitoring intravascular volume in critically ill patients. Variations in arterial pressure are a useful and valid tool in estimating intravascular volume, particularly as it relates to cardiovascular responsiveness to fluid loading. Fluid responsiveness may be predicted based on variations in systolic pressure alone or, more accurately, on variations in pulse pressure. Variations in aortic blood velocity may provide even more information, but require transesophageal echocardiography, and may reflect changes in airway pressure and intrathoracic pressure more than changes in cardiovascular hemodynamics. As with variations in arterial pressure related to intrathoracic pressure and cardiac preload, variations in pulse oximetry tracings correlate with intrathoracic pressure changes in patients with acute exacerbations of obstructive airway disease. As Dr. Michard points out, new methods for quantifying systolic pressure variations in critically ill patients are available at selected institutions. The utility and accuracy of repeated measures over time for predicting changes in intravascular volume remains uncertain.

Despite the moderate correlation between radiographic vascular pedicle width (VPW) and fluid balance or hydrostatic pressure, practicing physicians use less reliable information on a daily basis. In the absence of invasive monitoring in the ICUs, we often base our estimates of intravascular volume on notoriously unreliable findings from the physical examination and vital signs. Even worse, we currently integrate findings from the readily available chest radiograph (such as the character of infiltrates, peribronchial cuffing, or effusions) in our daily patient evaluation without recognizing the superior nature of VPW in predicting volume status compared to classical roentgenographic findings. The consistent relationship between VPW and blood volume has been shown previously, making VPW in the context of this study the most sensitive radiographic indicator of intravascular volume. Furthermore, > 500 independent evaluations of VPW by multiple radiologists show interreader and interreader reproducibility correlation to be excellent (r = 0.94 to 0.96).

In assessing intravascular volume or fluid responsiveness, true volumetric measures are better than pressure measures traditionally available from pulmonary artery catheterization. Despite growing availability and acceptance, these measurements are invasive. As with our data, VPW historically has been shown to correlate better with blood volume than with hydrostatic pressure, making the chest radiograph an essential tool for monitoring intravascular volume in critically ill patients. We as clinicians must integrate the emerging literature regarding noninvasive assessment of intravascular volume into our practice. Given the ready availability and familiarity of chest radiographs, the information available from this medium should be optimized and incorporated into a diagnostic algorithm for patient care.

Greg S. Martin, MD, FCCP
Emory University
Atlanta, GA
E. Wesley Ely, MD, MPH, FCCP
Vanderbilt University
Nashville, TN

REFERENCES
3 Denault AY, Gasior T, Goresan J, et al. Determinants of aortic pressure variation during positive-pressure ventilation in
Talc for Pleurodesis

Hero or Villain?

To the Editor:

We read with interest the article by Fraticelli et al1 and its editorial2 (December 2002). Talc has been considered the most effective agent to induce pleurodesis; however, reports of respiratory failure after the intrapleural use raises concerns about its safety.3 The experimental study of Fraticelli et al1 using calibrated talc (95% of particles > 5 μm) and observing that the migration of talc, if it occurs, it is not significant, represents an important contribution to the understanding of the physiopathology of ARDS.

In our previous study4 with talc (85% of particles > 10 μm), we observed presence of talc in several organs. These findings suggest that the size of the particles should be decisive to the dissemination of talc. The controversy exists. Could the talc introduced into the pleural cavity migrate through the circulation with risk of respiratory failure? Would the size of the particles be decisive for the migration?

Several points should be considered: (1) the pulmonary re-expansion after drainage of large amount of fluid or after thoracoscopy modifies the permeability of the pulmonary vasculature producing accumulation of fluid; (2) the talc introduced into the pleural space releases inflammatory mediators inducing capillary vasodilatation, cellular migration, and stimulus of the extra cellular matrix; (3) the absorption of pleural fluid and particles from the pleural space occurs through the stomas described on the parietal pleura of animals (in rats, the medium area of the stomas is 12.9 ± 10.5 μm2 [mean ± SD], suggesting that particles of talc could migrate through lymphatics in a normal pleura6); and (4) not only the size of the particles should be considered, the shape is very important; we can hypothetically accept that thin particles measuring approximately 20 μm2 could migrate through lymphatics.

The irregular form of the particles and the probable changes in the mobility of the lymphatic produced by the pleural inflammation could modify the physiology of the pleural cavity. We believe that in the presence of pleural inflammation, the increment of the permeability could facilitate the migration of talc.

Sanchez et al7 (Fanadero’s group), studying the characteristics of 13 samples of talc used in Brazil (n = 9) and in Spain (n = 4) demonstrated that the samples containing the highest percentage of small particles (< 5 μm) were associated with higher morbidity. In agreement with this author, not only the size, but also the shape of the particle seems to be a decisive factor in the absorption of the talc by the lymphatics. In this way, particles with axis < 5 μm are present in 21% of the Brazilian samples and in only 3% of the French talc. Consequently, to obtain a more accurate interpretation of the results, in future studies the physical and chemical characteristics of the talc should be specified.

Exaldo Marchi, MD, FCCP
Lisete R. Teixeira, MD
Francisco Vargas, MD
University of São Paulo, Medical School
São Paulo, Brazil

REFERENCES

To the Editor:

We thank our colleagues from Brazil for their interest in reading our article devoted to the distribution of calibrated talc after intrapleural administration. This study was carried out after the publication by this team of experimental results showing talc particles in every organ of rats killed 24 h and 48 h after the talc was administrated intrapleurally, which was very far from our clinical experience. The data we obtained using the same experimental design are not similar, clearly suggesting a difference between the two talc preparations. It is common sense, and we agree with Marchi and colleagues in assuming that the size and/or the shape of talc particles are the key factors for particle...