electrolytes), together with a marker of volume responsiveness. We believe that dynamic parameters such as stroke volume variation are currently the best markers of volume responsiveness. While the models of Guyton and Starling are magnificent in their simplicity, therapeutic interventions based on these principles may lead to therapeutic errors in complex critically ill patients. This is demonstrated by the fact that no clinical study (of which we are aware) has shown central venous pressure to be a reliable tool in the fluid management of critically ill or injured patients. Indeed, the data suggest that the reliability of central venous pressure for predicting fluid responsiveness is no better than flipping a coin. While the study by Rivers et al\(^2\) (and the Surviving Sepsis Campaign\(^3\)) are often quoted to support the use of central venous pressure as the preferred goal for fluid resuscitation (at least in patients with sepsis), it should be pointed out that the same central venous pressure goals were utilized in both the intervention and control groups.\(^2\) Should the data by Rivers et al\(^2\) be valid, it should be noted that the control group has the highest reported mortality of any sepsis study.\(^4,5\) Based on the current data, we believe that guiding therapy based on central venous pressure is misguided, will lead to serious errors and should be abandoned (at least until supporting data are published).

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The authors have no conflicts of interest to disclose.

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DOI: 10.1378/chest.08-2172

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Yellow Nail Syndrome Chyloous Pleural Effusions

Defective Lymph Valves Involved?

To the Editor:

We read with great interest the article by Maldonado and coworkers (August 2008),\(^1\) and we would like to comment on the rather frequent occurrence (nearly 32\%) of chyloous pleural effusions secondary to yellow nail syndrome (YNS) reported by the authors. It is widely accepted that YNS results from abnormal (anatomically or functionally) lymphatic network. Indeed, in a patient with typical YNS (yellow nails, lymphedema, chronic pleural effusions) in our hospital, jejunal biopsy results revealed intestinal lymphangiectasis that further confirm the systemic lymphatic network abnormality encountered in these patients.\(^2\)

Contrary to physiologic conditions in which pleural fluid is absorbed mainly through solute-coupled liquid absorption by the mesothelium, in pleural effusions the main mechanism is lymphatic drainage through parietal pleura stomata.\(^3\) However, the partial occurrence of chyloous effusions leads us to the hypothesis that in those patients there may be a defect in the intrinsic lymphatic mechanism (lymphatic smooth-muscle cells and valves) involving impaired lymph valves that permit lymph reflux in the pleural cavity in cases of chyloous effusions.

Forkhead transcription factor (FOXC2) is normally expressed in lymphatic endothelium and is essential for the morphogenesis of lymphatic valves and the establishment of a pericyte-free lymphatic capillary network.\(^4\) An abnormally large proportion of skin lymphatic vessels was covered with smooth-muscle cells in individuals with lymphedema distichiasis and in mice heterozygous for FOXC2.\(^5\) Moreover, heterozygous mutations in FOXC2 in humans cause lymphedema distichiasis syndrome, although there are mutation carriers that do not suffer from lymphedema despite lymph reflux being present.\(^6\) Based on the above, we suggest that patients with YNS presenting chylothorax might have abnormalities in the intrinsic lymphatic mechanism, and mutations in FOXC2 gene could be a possible explanation.

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DOI: 10.1378/chest.08-2021

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Response

To the Editor:

Zarogiannis and colleagues raise several important issues. As they correctly point out, a defect in lymphatic function, either acquired or hereditary in nature, seems the most likely culprit in explaining the diverse manifestations of yellow nail syndrome (YNS). Indeed, the first description of YNS included lymphangiectasia...