Pulmonary Alveolar Proteinosis
Specific or Nonspecific Response?

Twenty-four years ago, Rosen et al. described the entity they called "pulmonary alveolar proteinosis" (PAP). The characteristics of this lung disease were that alveoli were filled with granular proteinaceous material which was periodic acid Schiff-positive and that the alveolar septae were relatively normal except for increased numbers of cuboidal "septal cells" (type 2 pneumocytes) in the alveolar lining. They noted very little inflammatory response to this process in the lung and few macrophages in the alveoli. The pathologic description was remarkably accurate and complete, and except for ultrastructural descriptions, little new information has been added.

Rosen and colleagues believed that most of the intra-alveolar granular material was derived from the proliferating septal cells that sloughed into the alveolar spaces and underwent degeneration. These investigators were aware of the significant lipid content of the intra-alveolar material. They thought this was either a new disease or a very rare lung disorder that was increasing in incidence. However, relatively few cases have materialized, and PAP remains uncommon. In fact, many people believe PAP is becoming even more uncommon, although there are no epidemiologic data to support such a view. This perception may be only an aberration created by changes in referral patterns as a result of the ever-increasing number of well-trained pulmonologists in the private sector of medicine. However, information regarding the incidence and distribution of cases of PAP could be useful in investigating the etiology of this disease. Correlating peaks of incidence with clusters of cases of PAP, along with various environmental conditions and infectious epidemics, might give important clues regarding the cause, which is the greatest gap in our knowledge of PAP at this time. Understanding more about the cause of PAP could also further our understanding of the lungs' response to injury and the kinetics of various types of lung cells.

The specificity of the PAP response has been questioned because of similar pathologic findings in experimental animals and in humans exposed to silica dust, in immunosuppressed patients with hematologic disorders, and in rats fed iprindole, and because hyperplasia of type 2 alveolar epithelial cells occurs as an element of the reparative process of the lung after various types of injury.

However, these findings may not be a good argument for the nonspecificity of the PAP reaction in the lung, as shown by the report of Singh et al. With the use of specific immunologic staining of surfactant apoprotein, these authors demonstrate that histologic appearance and periodic acid-Schiff staining of intra-alveolar granular material are not sufficient to establish the diagnosis of PAP. The intra-alveolar proteinaceous material from patients with PAP and no other associated disease stained densely and uniformly for surfactant apoprotein, whereas the intra-alveolar material of patients with PAP-like histologic appearance of the lung who also had leukemia or lymphoma did not. The lung sections from patients with Pneumocystis carinii pneumonia also show focal rather than uniform staining for surfactant apoprotein. This study not only suggests that PAP may be more specific than has generally been thought, but also raises questions regarding the true incidence of PAP for many of the reported cases have been associated with illnesses. With this type of diagnostic aid, more meaningful epidemiologic studies could be performed with the hope of producing information about the etiology of PAP.

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References
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On the Analysis of Left Ventricular Volume from Gated Radionuclide Ventriculograms

Radionuclide blood pool imaging has been used to estimate intravascular fluid volumes of the left side of the heart, 14 lung, 19 and peripheral vessels. 10,11 Most of these approaches actually assess relative volumes, and either examine sequential changes in volume during interventions or use linear regression equations between radionuclide and traditional "gold standard" estimates of volume (area length or indicator-dilution) to extrapolate absolute volumes from relative volumes.

To a large extent, these studies are based on the premise that the intravascular volume of a region-of-interest applied to an equilibrium radionuclide image (such as the left ventricle) is proportional to the emitted activity of the region-of-interest and inversely proportional to the radioactivity of a reference blood sample. The key word here is proportional, rather than equal, as a variety of factors may vary this relationship, and include the attenuation effects of the system (due to the radiopharmaceutical and the patient), the constancy of the blood pool label, and the counting characteristics of the imaging system, among many others. Photon attenuation and scatter which occur in the myocardium, pleural cavity, and chest wall (intercostal muscles, cartilage and bone), all reduce the transmitted photon flux and the resulting projected count values. That these parameters change throughout the cardiac and respiratory cycles would be expected to contribute to the variability of the measurements. Simplifying assumptions may be made with regard to the nonvariance of some of these parameters; however, they all ultimately influence the measurement and calculation of chamber volume.

Both Links et al 4 and Thomsen and co-workers in this issue of Chest (see page 6) have attempted to remedy the interpatient vagaries of variable attenuation of left ventricular count rates by the following: (1) devising a method for estimating the depth of the ventricle from the camera; and (2) assuming the tissue attenuation to be well represented by water attenuation (ie, correction factor for depth attenuation = e^(-u.d) where u = attenuation coefficient for water and d = distance to the left ventricle). Both of these assumptions are somewhat arbitrary (substantial left ventricular contraction disturbances such as an apical aneurysm might be expected to invalidate the approach proposed by Thomsen and co-workers, and water attenuation is only a rough approximate of the attenuation produced by a multiplicity of structures between the cardiac blood pool and the camera). Thomsen and co-workers use the distance from the chest wall to the left ventricle in the parasternal two-dimensional echocardiographic view to determine the "distance of attenuation," though the actual "average" attenuation distance may only be a fair approximate of the attenuation of the entire heart. Nonetheless, these assumptions appear workable, although we have noticed that variations in patient positioning alone can alter volume results 14 and variability in volume estimates may average 10 percent to 15 percent in asymptomatic male subjects with normal chest configurations. 13 Recent investigators have also used esophageal emissions as a simple approach for in vivo attenuation correction. 14

During exercise, venous activity may change unrelated to the quality of the blood pool label (Massie B and Kronenberg M, personal communications). As time transpires, venous activity will decline as a function of any number of factors and thus, multiple samples need to be obtained during interventions. Finally, it is to a large extent fortuitous that Thomsen and coworkers did not require a regression equation to relate absolute and relative volumes (there is even a regression equation to relate single plane and biplane contrast angiograms). In laboratories using different region-of-interest and background assignments, results would be expected to differ. 15 Each radionuclide laboratory will need to establish its own in-house accuracy and reproducibility.

To a large extent, it has been my feeling that this approach for measuring left ventricular volume is best applied to individual subjects during interventions (using the individual as his/her own control) or when comparing groups of patient populations, rather than when assessing an individual subject at rest (and comparing that subject to others). The methodologic improvements proposed by Thomsen and colleagues provide a simple approach for possibly circumventing some of the difficulties inherent in the equilibrium radionuclide technique. Whether this refinement will make the technique more useful in an individual