ARDS

Lessons Learned From the Heart

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A syndrome encompasses a number of nosologic entities that do not necessarily share the same cause, pathogenesis, structural abnormalities, and treatment. The identification of a syndrome has different diagnostic and therapeutic implications because it prompts further testing to achieve the diagnosis of a specific disease. For instance, the diagnosis of acute coronary syndrome in a patient presenting with chest pain requires a more-specific diagnosis (ie, acute myocardial infarction) to direct therapy. The discovery of biomarkers has been a key advance to define one of the underlying causative entities (eg, acute myocardial infarction) and, therefore, allows appropriate identification of patients with a specific condition and treatment.

What Is Meant by ARDS?

ARDS was described in 1967 in a series of 12 patients who presented with dyspnea, hypoxemia refractory to oxygen therapy, decreased lung compliance, and diffuse alveolar infiltrates evident on chest radiograph.[1] Histologic findings at autopsy included hyperemia, alveolar atelectasis, interstitial and intraalveolar hemorrhage and edema, numerous alveolar macrophages, the presence of hyaline membranes (in six of seven patients), and diffuse interstitial fibrosis without notable hyperemia in two patients who died after a protracted course (both had hyaline membranes).

Since the description of the syndrome, ARDS is generally considered in clinical practice and research as a condition defining a homogeneous population of patients. However, when ARDS is diagnosed clinically, diffuse alveolar damage (DAD) is present on histologic examination in only 40% to 60% of cases.[2-5] Pathologic manifestations that can be found in patients with clinically diagnosed ARDS include heterogeneous conditions, such as pneumonia, diffuse alveolar hemorrhage, cardiogenic pulmonary edema, pulmonary embolism, metastatic malignancies, pulmonary lymphoma, eosinophilic pneumonia, fibrosis, bronchiolitis obliterans organizing pneumonia, and drug reactions.[3,5] These conditions differ in their pathogenesis, treatment, and prognosis.

It is, therefore, not surprising that research on biomarkers of ARDS, genetic risk factors, or new therapies has yielded disappointing results because roughly one-half of the patients under study have, in fact, a nosologic entity (eg, DAD).[1,3,5] Indeed, only a specific condition characterized by clinical diagnostic criteria as well as by defined structural abnormalities is expected to benefit from treatment specifically targeting the biologic mechanisms leading to the defined structural abnormalities.[6-8]

What Does the Presence of DAD Mean?

The presence of DAD in histologic examination is not specific for ARDS. DAD indicates injury to the lung epithelium, such as that caused by drug toxicity (eg, by chemotherapeutic agents such as bleomycin and busulfan, amiodarone, or nitrofurantoin), connective tissue disease, complications of lung transplantation, oxygen toxicity, and aspiration. These cases do not necessarily have to meet the clinical criteria for the diagnosis of ARDS and often do not largely because the clinical presentation may be subacute (>7 days) and may not require mechanical ventilation. These conditions, therefore, are not usually classified as ARDS. In addition, DAD can be found in patients who present with the clinical characteristics of ARDS but without an identifiable risk factor, a condition termed "acute interstitial pneumonia".[9,10] Thus, DAD by itself cannot define the clinical syndrome of ARDS, nor can the clinical syndrome reliably identify the presence of DAD.

Does DAD Matter?

It can be argued that the presence of DAD on histologic examination is not required for the diagnosis of ARDS.

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Indeed, not all experts agree that DAD is the sole manifestation of ARDS.[11] For instance, bilateral pneumonia could be part of ARDS as a syndrome. Pneumonia is one of the most common risk factors for ARDS and is associated with lung inflammation and hyperpermeability pulmonary edema. If pneumonia is bilateral and severe, the clinical and radiographic criteria for ARDS would be met. In fact, whereas the Berlin Definition only modestly predicts the presence of DAD in patients with clinically diagnosed ARDS (only 45% of cases having DAD at autopsy),[5] it is more specific to detect patients with either diffuse pneumonia or DAD (72% of patients meeting the Berlin Definition criteria have either DAD or pneumonia at autopsy), making it a good definition of inflammatory lung injury.[5,12] On the other hand, experts agree that DAD is the pathologic hallmark of ARDS.[11,13,14]

Is ARDS a Distinct Clinical Entity?

Is ARDS a designation for a number of heterogeneous conditions with differing pathogenesis, histologic manifestations, and treatments, or, rather, is it a separate clinical entity characterized by distinctive clinical and histologic manifestations? If DAD and the acute pathophysiologic processes causing it are amenable to targeted therapies, then enriching the population of patients with ARDS who actually have DAD will be crucial for identifying and testing such therapies. This will almost certainly require the identification of a biomarker specific for DAD.

One approach to determining the potential importance of DAD is to see whether a specific endophenotype of patients with ARDS is associated with DAD and whether this endophenotype differs from that of patients with ARDS without DAD. The difficulty in attempting to define different endophenotypes within ARDS lies on the requirement of lung specimens from a large number of patients, and such a study has yet to be conducted.

In conclusion, the disappointing or conflicting results of previous research on biomarkers and specific pharmacologic treatments for ARDS may be explained by the fact that several nosologic entities are subsumed under the clinical diagnosis of ARDS. Other reasons worth mentioning for why biomarker research has been disappointing are that investigators may not have searched for the adequate biomarker or there simply is no relevant biomarker.

Among patients with ARDS, whether those with DAD are clinically different from those with other histologic findings (mainly pneumonia) remains to be proven. This characterization is of paramount importance for the conceptual framework of the syndrome and to test the assumption that DAD is an essential element in the definition of ARDS.

The discovery of a biomarker of myocardial cell injury has completely changed the way acute myocardial infarction is diagnosed, treated, and prognosticated. In alignment with these advances, the search for specific biomarkers of DAD (and not for ARDS as clinically identified) should be encouraged. If we can define the subgroup of patients under the diagnostic umbrella of ARDS who actually have DAD, then we can focus biomarker discovery and targeted therapies on this subgroup that may or may not be the responsive one of interest.

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