Cells in Crisis
Cellular Bioenergetics and Inadequate Oxygenation in the Intensive Care Unit

Most bodily oxygen consumption is devoted to the generation of cellular energy in the form of adenosine triphosphate (ATP). When energy requirements exceed the ability of the cell to synthesize ATP, net ATP degradation occurs. Degradation of ATP leads to the release of purine metabolic intermediates (i.e., adenosine, inosine, hypoxanthine, and xanthine) and the purine catabolic end product, uric acid. The presence of elevated hypoxanthine, xanthine, or uric acid levels in bodily fluids has been interpreted to reflect net ATP degradation in clinical conditions in which inadequate cellular oxygenation is likely to occur. Increased levels of ATP degradation products have been demonstrated in subjects who exercise above the anaerobic threshold and in patients with sleep apnea, hypotension, critical illness (i.e., intensive care unit [ICU] patients), and ARDS. In this issue of Chest (see page 556), Christensen et al extend this observation to adult patients with acute respiratory failure requiring mechanical ventilation, who are clearly at high risk for inadequate cellular oxygenation. These patients had a pronounced excretion of uric acid, the magnitude of which was related to the severity of the respiratory failure. This study therefore suggests that net ATP catabolism is occurring at the cellular level, in response to the hypoxia of respiratory failure.

Increased ATP degradation has ominous clinical implications in the ICU setting. Principally, it indicates a cellular bioenergetic crisis with depletion of oxygen and high-energy stores. Net ATP hydrolysis and the accompanying cellular shift to anaerobic metabolism cause a release of hydrogen ions and a fall in cellular pH. Cellular acidosis is a critical step in the deterioration of cellular integrity because it leads to changes in the structure and function of regulatory proteins and ultimately the lysis of organelle and cellular membranes. The production of uric acid indicates an irretrievable loss of energy potential, as this compound cannot be reutilized in the ATP biosynthetic pathway.

Degradation of ATP may also activate secondary processes that directly augment cellular injury, apart from its effect on bioenergetics. In some tissues, ischemia converts xanthine dehydrogenase to xanthine oxidase. Xanthine oxidase uses the accumulating ATP degradation intermediates (hypoxanthine and xanthine) as substrates, and molecular oxygen as its electron acceptor, to form superoxide anion, hydrogen peroxide, and other toxic oxygen metabolites. In humans, xanthine oxidase is most abundant in endothelial cells in the liver and small intestine. However, the demonstration of circulating levels of xanthine oxidase in patients with ARDS raises the possibility that local activation and release of xanthine oxidase may cause damage at distal sites.

Attention must also be focused on the contributions of ATP degradation products as modulators of ischemia and inflammation. Adenosine has a myriad of biologic functions, including being a regulator of vascular and bronchial tone and a regulatory cofactor for numerous enzymes. It also imparts regulatory signals to the interior of the cell by binding to specific receptors on the plasma membrane. Adenosine receptors with both stimulatory and inhibitory effects have been described in leukocytes and other cells, indicating that adenosine can have a major impact on cell function in most organ systems.

Early detection of cellular energy crisis is critical if therapeutic interventions are to be effective in limiting ATP degradation and its attendant consequences. Analysis of adequate oxygenation has been, in large part, focused on the whole-body and tissue levels. The emphasis has been on oxygen delivery and oxygen uptake analysis, which indirectly measures events occurring within tissue beds. Four approaches show promise in directly monitoring events at the cellular level to assess the adequacy of oxygenation. Two of these, magnetic resonance imaging and positron emission tomography, are excellent research tools. However, these techniques are not suitable to application at the bedside, especially in ICUs. In critically ill patients, tonometric assessment of intestinal intramural pH has been shown to accurately reflect tissue oxygenation and to predict patient outcome in early studies. The current study by Christensen et al provides further evidence that monitoring ATP degradation products offers another strategy for recognizing cellular energy crisis.

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Minimally Invasive Thoracic Surgery, Video-assisted Thoracic Surgery and Thoracoscopy

Over the last several years, general thoracic surgeons have been developing a minimally invasive approach to the chest. Thoracotomies now are accomplished through smaller and less disfiguring incisions which spare the major muscles of the chest. Small axillary thoracotomies, muscle-sparing lateral thoracotomies, and CT-directed minithoracotomies all have improved the postoperative management and decreased postoperative complications for many patients.1,2,3

Although thoracoscopy has been available for many years, it has been limited in its usefulness because of the poorly designed associated technology and instrumentation. Now, with the rapid explosion of technology, including video coupling to thoracoscopes, thoracoscopy provides visualization in areas not seen well before through a standard thoracotomy incision. This makes it a powerful tool for thoracic procedures. As surgeons have become more facile with this technique, the associated incisions have become smaller still, resulting in nearly incisionless thoracic surgery. An example of this evolution was reported by Lewis and colleagues demonstrating the versatility of the technology.4 These techniques are far more complex than the simple thoracoscopic procedures of the past, such as evaluation of the pleura and small forceps biopsies of the lung alluded to by Mathur and Martin.5 Under the controlled conditions of general anesthesia, procedures such as large lung biopsies, pleural stripping and resection of peripheral nodules can be performed easily. In addition, a host of other procedures are potentially aided by this approach.

As surgeons have expanded the scope and complexity of procedures done in this manner, the potential for complications rises. The uncontrolled spread of laparoscopy has already led to poor regulation and serious complications among the less experienced.6 Recognizing the importance of continued quality improvement both in patient care and patient safety, the Society of Thoracic Surgeons and the American Association for Thoracic Surgery formed a joint committee to specifically address video-assisted thoracic procedures. In order to prevent potential complications from this new technology, the committee established training courses to develop a basic competence among thoracic surgeons. The committee has also addressed the issue of guidelines for credentialing with this new technology to assist hospitals in assuring that quality of care continues to improve.

Physicians and surgeons must be mindful that claims of superiority of this technology over traditional methods are premature. Unscientific preliminary reports presented in the news media and the lay press only heighten patient expectations and place undo pressure on the medical community to engage in an unproven but potentially very expensive and underdeveloped new technology. Careful, thoughtful comparative studies are necessary and exposure to the peer-review process of scientific meetings and journals is important in establishing the crediblity of this new technology.

Toward this end, the Video-assisted Thoracic Surgery Study Group was formed. This group encompasses thoracic surgeons at over 40 centers throughout North America. This group will perform studies which compare video-assisted technology to established conventional therapy for such conditions as malignant pleural effusion, recurrent pneumothorax, and the evaluation of trauma. It will measure such important variables as hospital cost, patient days away from work, pain management, patient outcome, etc. The group has also established a registry of cases which will help to define the scope of this technique and enumerate the potential complications.

There is no doubt that video-assisted thoracic surgery will become an important tool in the management

References:

330

Editorials