determining lung volumes, but a fat distribution index may be. An effect of aging may result because age is significantly related to BMI and has a small effect on abdominal girth-hip breadth ratio.

But is the effect of upper body fat distribution on lung function simply a mechanical one? Obesity is an independent risk factor for cardiovascular disease, but obese nonsmoking women with the highest waist-to-hip ratio (upper body fat distribution) have a ninefold increase in relative risk for coronary death; this association is stronger than the effect of BMI alone. Glucose intolerance, hyperinsulinemia, and hypertriglyceridemia, important potential links to hypertension and cardiovascular complications, are more marked in women with increased upper body fat distribution. While a mechanism connecting cardiovascular and metabolic risks of upper body fat distribution to pulmonary function would be difficult to envision, distribution of fat to the upper body does seem to be a more specific marker of the health hazards of obesity than overweight alone. A potentially adverse effect on pulmonary function may be one more consequence of upper body fat distribution.

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Rescue Therapy for the Acute Respiratory Distress Syndrome (ARDS)

In this issue of CHEST (see page 1000), Payen and coworkers describe their experience using a therapeutic optimization strategy in patients with severe ARDS. This strategy employed a stepwise escalation of therapies which included: (1) diuresis to reduce extravascular lung water; (2) ventilator settings to optimize oxygenation while keeping peak airway pressures below 35 cm H2O (ie, permissive hypercapnia); (3) patient repositioning; (4) inhaled nitric oxide; (5) intravenous almitrine bisemyslate; and (6) drainage of pleural or peritoneal effusions. Among their 36 study patients, 19 (53%) responded to these medical interventions with improvements in oxygenation, while 17 (47%) did not respond. The mortality rate of the responders was significantly less than the mortality rate of the nonresponders (21% vs 88%; p<0.001). Two of the responders deteriorated and, along with eight of the nonresponders, received extracorporeal carbon dioxide removal with low-frequency positive pressure ventilation (ECCO2R-LFPPV). ECCO2R-LFPPV represented the final mode of rescue therapy offered to patients in this optimization strategy. The nonresponders (n=9) with contraindications to the use of ECCO2R-LFPPV all died. However, four (40%) of the patients receiving ECCO2R-LFPPV survived.

At first glance these results can be interpreted simply as another, albeit complex, method for the classification of ARDS based on patient responses to the described optimization regimen.1,2 However, a potentially more important question is raised by this study. Did the survivors, particularly the four patients receiving ECCO2R-LFPPV, survive directly as a result of the therapy they received or in spite of it? There is no way of knowing the exact answer to this question based on the study design employed by Payen et al. A randomized controlled trial (RCT), with the control group receiving standard medical therapy alone and the intervention groups receiving various combinations of rescue therapy, would be the best method for obtaining an objective answer to this question. However, performing such a study would be difficult due, in large part, to the multiple treatments administered in the intervention groups. Such a study would require enrollment of large numbers of patients and a comprehensive decision-making algorithm to define and guide standard patient management. Similar algorithms or protocols that have been employed in other recent studies of ARDS.3

Another difficulty in performing RCTs of rescue

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therapies for ARDS is deciding what exactly constitutes “standard” medical management. Recent analyses have found that the survival rate of patients with ARDS has improved in the last 15 years. One can only assume that this is due to advances in our supportive care of these patients, because no proven therapies for ARDS currently exist. Potential changes in supportive care which may explain the observed survival improvement include: (1) ventilation at lower lung volumes to reduce volutrauma; (2) diuresis/fluid restriction to reduce lung water; (3) improved ability to diagnose pulmonary and nonpulmonary infections; and (4) enhanced support of nonpulmonary organ function. Several of the interventions employed in the study of Payen et al have already been subjected to RCTs and have been shown to improve specific patient parameters and outcomes (eg, lung compliance, oxygenation, duration of mechanical ventilation). However, no proposed treatment for ARDS subjected to large or multiple RCTs (exogenous surfactant, extracorporeal membrane oxygenation, extracorporeal carbon dioxide removal, prophylactic positive end-expiratory pressure [PEEP], diuresis, early corticosteroids, high-frequency ventilation, prostaglandin-E2) has been shown to significantly improve patient survival. This has made it problematic to develop definitive recommendations regarding the pharmacologic and nonpharmacologic treatment of patients with this syndrome.

Despite the negative results of past trials, other therapies are currently undergoing investigation for survival benefit in patients with ARDS including: inhaled nitric oxide, partial liquid ventilation, corticosteroids for the fibroproliferative phase of ARDS, antioxidant therapy, ketoconazole, and permissive hypercapnia. It seems unlikely that any one of these interventions will demonstrate a significant survival benefit compared to “optimal” supportive care of the patient with ARDS. However, it is possible that each of these therapies could allow individual patients to survive who otherwise would have succumbed to ARDS. The magnitude of such an effect would not be detected in a conventional RCT of any single intervention. This raises the question of whether a study employing multiple interventions, compared to “optimal” supportive care, would produce a detectable improvement in patient survival.

The first RCT aimed at evaluating the incremental benefit of combination rescue therapy for ARDS is currently underway by the ARDS Clinical Trial Treatment Group, which is sponsored by the Lung Division of the National Heart, Lung and Blood Institute (NHLBI). The application of permissive hypercapnia with low tidal volumes (ie, lung-protective ventilatory strategy) is being studied along with ketoconazole, an antifungal drug with anti-inflammatory properties. This study is designed so that an additive effect between these two therapies resulting in a survival benefit can be detected. Combination drug therapy and multimodality therapy have already been successfully developed for certain infectious disorders and cancers. It is possible that a therapeutic strategy employing a combination of new treatments may also be more successful than any single treatment for patients with ARDS. The NHLBI-sponsored study should serve as a template for future RCTs evaluating the effects of combination therapy in ARDS. Because these studies are expensive and difficult to perform, the challenge to investigators will be to decide which of the emerging rescue therapies warrants inclusion in future studies.

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