Malnutrition and the Respiratory System

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Malnutrition is a relatively common problem in critically ill patients who are being ventilated mechanically. Moreover, approximately 40 percent of the patients with chronic obstructive pulmonary disease (COPD) have lost 10 percent or more of their ideal body weight, with associated abnormalities of anthropometric, biochemical, and immunologic indices of impaired nutritional status. Mortality in critically ill patients is highly correlated with a variety of somatic and visceral expressions of protein-calorie malnutrition, including anergy, reductions in total lymphocyte count and muscle cell mass, and low serum levels of albumin, transferrin, and iron. Sepsis, pneumonia, and respiratory failure are among the major causes of death in malnourished critically ill patients. In COPD, malnutrition predisposes to respiratory failure and death. Thus, it is appropriate to consider how malnutrition affects the respiratory system and what impact nutritional repletion has on correcting deficits resulting from inanition.

When protein and caloric intake are restricted for one to several weeks, abnormalities develop in pulmonary defense mechanisms, pulmonary structure and function, control of breathing, and respiratory muscular contractility. Since many of these have been reviewed elsewhere, we will review selected recent reports concerning pulmonary defense mechanisms, structure, and function; however, our primary focus will be on how malnutrition reduces the capacity to sustain adequate levels of ventilation and their correction by hyperalimentation.

Pulmonary Defense Mechanisms

Pulmonary defense mechanisms depend on the integrity of respiratory epithelium and the immune system. It is said that malnutrition interferes with regeneration of respiratory epithelium, but we have seen no report concerning alterations in respiratory epithelial permeability or ciliary function. Four weeks of protein-calorie malnutrition in infant rats caused the thymus to atrophy and reduced the T-lymphocyte transformation response to phytohemagglutinin. The in vitro pulmonary defense mechanisms of these animals were assessed by measuring the rate of clearance of organisms aerosolized into the lung. Clearance of Staphylococcus aureus depends on alveolar macrophages, clearance of Pseudomonas aeruginosa depends on alveolar macrophages and polymorphonuclear leukocytes, and clearance of Listeria monocytogenes requires that T-lymphocytes in the lung activate alveolar macrophages. In the malnourished infant rats, pulmonary clearance of L monocytogenes was markedly impaired, but clearance of the other two species of organisms was normal, as were vitro alveolar macrophage chemotaxis and microbicidal activity. In adult rats subjected to three weeks of protein restriction, there were 40 percent fewer alveolar macrophages, but alveolar macrophage phagocytic capacity was normal despite structural changes at the cellular surface. Malnourished children were found to have marked reductions of secretory IgA in respiratory fluids, as well as low serum levels of immunoglobulin complement. Presumably, these abnormalities of the immune system contribute to the incidence and severity of pulmonary infections in malnourished critically ill patients, but other factors such as impaired respiratory epithelial function and atelectasis may be of equal importance.

Pulmonary structure and function are also adversely affected by chronic malnutrition. Lungs of rats starved to lose 40 percent of total body weight in about three weeks showed emphysema-like changes with remodeling of elastic fibers, increase in the size of airspaces, and reduction in alveolar wall surface. These morphometric abnormalities were accompanied in the pulmonary tissue by reduction in desaturated lecithin (phosphatidylcholine), a major component of surfactant, and reductions in levels of protein and RNA and in the RNA/DNA ratio in the pulmonary tissue. The biochemical abnormalities were fully correctible with refeeding, but the morphologic damage was not completely repaired.

Ventilatory Drive and Respiratory Muscles

One of the most striking effects of malnutrition on the respiratory system is to reduce the capacity of patients to sustain adequate levels of ventilation. This
results from the effects of nutritional depletion on both the central nervous control system and the respiratory muscles which comprise the air pump. Healthy human volunteers restricted to a daily oral intake of 550 kcal from glucose for ten days had a 20 percent reduction in basal oxygen consumption and a 58 percent reduction in their ventilatory response to hypoxia. Another group of normal volunteers given 440 kcal of glucose intravenously per day for a week had 12 percent to 15 percent reduction in oxygen consumption and carbon dioxide production, coupled with 26 percent reduction in minute ventilation and mean inspiratory flow rate, which is an index of neural ventilatory drive. After only four hours of intravenous infusion of amino acids on the eighth day, metabolic rate, minute ventilation, and ventilatory drive had recovered by 50 percent or more, with complete recovery after 24 hours of infusion of amino acids.

The effects of weight loss on diaphragmatic muscular dimensions was assessed at necropsy in previously normal subjects who died suddenly and unexpectedly, as well as in patients without chronic pulmonary disease who died after illnesses of weeks to months' duration. Diaphragmatic muscular mass, area, and thickness were within normal limits in patients whose body weight was normal at the time of death. By way of contrast, in patients whose body weight averaged 71 percent of normal at the time of death, diaphragmatic muscular mass was reduced by 43 percent, about half of the deficit resulting from thinning of the diaphragmatic muscle and the remainder resulting from reduction in diaphragmatic muscular length. In these patients, heart weight, hematocrit, and serum level of albumin were 14 percent, 30 percent, and 31 percent below normal, respectively. In an equally underweight group of living patients, who were also free of chronic pulmonary disease, respiratory muscular strength, judged from maximum inspiratory and expiratory mouth pressures, was reduced by 63 percent as compared to controls matched for age and sex. The respiratory muscular weakness was accompanied by a 37 percent reduction in vital capacity and a 59 percent reduction in maximum voluntary ventilation, which is an index of ventilatory endurance. The results of these two studies, coupled with a geometric analysis of the forces exerted by the diaphragm, suggest to us that malnutrition weakens the diaphragm in two ways: it not only reduces muscular mass, but also markedly reduces the contractile strength of the remaining muscle fibers.

Inspiratory muscular weakness per se causes hypercapnic respiratory failure when inspiratory muscular strength is less than 30 percent of normal. Severe malnutrition in critically ill surgical patients produces a comparable degree of inspiratory muscular weakness, and there is a good correlation between maximum inspiratory mouth pressure and body cell mass, as estimated from total exchangeable potassium (S. M. Kelly and P. T. Macklem; written communication, August, 1983). In COPD, inspiratory muscular strength is reduced in proportion to the mechanical disadvantage imposed on the diaphragm and other inspiratory muscles by hyperinflation of the lung. Poorly nourished patients with COPD have an even greater degree of respiratory muscle weakness, which often approaches the critical level. Nutritionally depleted patients with COPD also have greater limitation of expiratory air flow, lower diffusing capacities and more emphysema, as judged from morphometric evidence. Both diaphragmatic muscle weight and sternocleidomastoid muscle thickness are reduced in underweight as compared to normal-weight patients with COPD. Thus, it is not surprising that nutritionally compromised patients with COPD are prone to develop acute hypercapnic respiratory failure.

**Effects of Nutritional Repletion**

Several studies suggest that enteral or parenteral hyperalimentation can improve ventilatory function. In a retrospective analysis, 14 malnourished patients who were dependent on mechanical ventilators were grouped according to their ultimate success or failure at weaning from mechanical ventilation. Both groups received comparable levels of nutritional support for equivalent periods, but the group which could be weaned responded with increases in serum levels of albumin and transferrin, whereas the failures did not. Two other studies addressed the issue of adequate supplemental nutritional support vs inadequate caloric intake on the ability of patients to wean from mechanical ventilation. Combining their results, 22 of 25 patients who received nutritional support, but only ten of 31 patients who did not, were able to discontinue mechanical ventilation ($p<0.001$). By way of contrast, parenteral nutritional support immediately following open-heart surgery in patients who had previously developed cardiac cachexia was without apparent benefit. The treated group required more time on ventilators and had longer costlier hospitalizations; however, failure to respond to nutritional support in the five days following major surgery could have been the result of metabolic disturbances which can only be overcome by giving sufficiently large quantities of amino acid nitrogen.

The metabolic consequences of nutritional repletion are increases in oxygen consumption, carbon dioxide production, and respiratory quotient. When ambulatory patients with stable COPD were fed a single oral dose of 920 kcal carbohydrate, oxygen consumption and carbon dioxide production increased about 10 percent and 20 percent, respectively, in less than one hour. Minute ventilation increased about 25 percent.
in eucapnic patients and about 14 percent in hypercapnic patients, but no patient developed symptoms or further elevation of arterial carbon dioxide pressure (PaCO₂). The chronically hypercapnic patients had an increase in arterial oxygen pressure and ventilatory response to inhaled carbon dioxide after the carbohydrate meal. These results suggest that gas exchange becomes more efficient after carbohydrate loading and indicates that patients with stable COPD tolerate carbohydrate loads quite well. By way of contrast, one critically ill malnourished patient developed dyspnea, and five other critically ill patients on mechanical ventilators increased their PaCO₂ up to 90 mm Hg when given 2,000 to 5,000 kcal of carbohydrate per day. Three of the patients on ventilators had previously undergone major surgery, and all were being ventilated because they had become hypercapnic. Three patients had normal values of PaCO₂ during mechanical ventilation but documented increases in carbon dioxide production and PaCO₂ with hyperalimentation, despite continued mechanical ventilation.

There are several possible explanations for dyspnea and carbon dioxide retention after carbohydrate loading. Patients who are nutritionally depleted but not exposed to the stress of severe injury or sepsis have about a 25 percent reduction in resting energy expenditure but exhibit a normal metabolic response to carbohydrate administration; however, the presence of respiratory muscle weakness and reduced ventilatory drive would hinder their ability to increase minute ventilation sufficiently to compensate for the increased carbon dioxide production. Coexistent pulmonary disease which reduces the efficiency of ventilatory gas exchange would aggravate the problem. Patients already on ventilators may not be able to increase their ventilation beyond the level fixed by the ventilator. When minute ventilation is fixed, an increase in carbon dioxide production necessarily elevates PaCO₂. The stress of major surgery, trauma, burns, and sepsis adds to the problem by creating a hypermetabolic state and altering metabolic responses to nutritional repletion. The resting energy expenditure of such patients was about 25 percent higher than that of patients suffering from nutritional depletion alone. When challenged with carbohydrate hyperalimentation, the hypermetabolic patients increased their oxygen consumption and carbon dioxide production by about 35 percent and 60 percent, respectively. This is twice the magnitude of the carbon dioxide production response in patients who are malnourished but not otherwise stressed. When 40 percent of the caloric intake of hyperalimentation was provided as fat emulsion, carbon dioxide production increased by only 10 percent in depleted patients and by 30 percent in stressed hypermetabolic patients, about half the increase that occurred when an equivalent caloric intake without fat was given.

Physicians responsible for the management of critically ill nutritionally depleted patients need to be aware of what constitutes adequate replacement therapy and how long it takes for patients to respond to hyperalimentation. The normal resting energy expenditure is about 25 kcal/kg of body weight per day. To obtain positive nitrogen balance, it is necessary to administer about 1.5 times the resting energy expenditure and about 200 to 240 mg of amino acid nitrogen per day, depending on the extent to which the patient is hypermetabolic. The recommended ratio of calories to nitrogen is 180:1.

A study of elderly patients nutritionally depleted from a variety of causes provides insight into the rate at which indices of nutritional status return to normal. With three weeks of enteral hyperalimentation via Dobhoff tube, there were significant increases in body weight, appetite, mental status, and mobility.

The serum level of albumin, total iron-binding capacity, and number of committed granulocyte/macrophage progenitor cells also approached normal levels in three weeks, but the level of hemoglobin did not become normal until six weeks of therapy. A recent prospective study at McGill University has assessed the impact of total parenteral nutrition with glucose, fat emulsion, and amino acids on body cell mass and inspiratory muscular strength (S. M. Kelly and P. T. Macklem; personal communication). Inspiratory muscle strength was significantly lower in patients whose body cell mass was severely reduced. In a subset of 29 patients studied before and after two weeks of parenteral alimentation, body cell mass increased in 18 and decreased in 11, and changes in inspiratory muscle strength were highly correlated with the change in body cell mass over the two-week period of treatment. From this and another study, it can be seen that appropriate hyperalimentation for several weeks improves both nutritional status and ventilatory capacity in approximately 60 percent of critically ill medical and surgical patients.

There are a number of unanswered questions regarding the efficacy of hyperalimentation for the critically ill. It has been suggested that improving the nutritional status of critically ill nutritionally depleted patients does not improve the prognosis for recovery, because the more nutritionally compromised patients are likely to have more serious underlying diseases. This must be true in many cases, as suggested by the observations that nutritional and ventilatory function improved in only 60 percent of critically ill medical and surgical patients. Uncontrolled infections, including pneumonias, are indicators of extremely poor prognosis for recovery from cardiopulmonary resuscitation and the adult respiratory distress syndrome. Short-term survival from acute respiratory failure is 70 per-
cent to 100 percent in COPD, drug overdose, crushed chest, neuromuscular disease, and postoperative respiratory failure but is only 25 percent to 50 percent in the adult respiratory distress syndrome, heart disease, after cardiopulmonary arrest, neurologic emergencies, and cancer.41 Even in the patients with cancer, one can identify pulmonary and infectious complications which worsen the prognosis for discontinuing mechanical ventilation. We believe that prospective randomized clinical trials of nutritional supportive therapy are indeed indicated to test the long-term benefits to patients with acute and chronic respiratory failure. We recommend that patients in such studies be classified carefully so that benefits to patients who can respond will not be masked by the failures in patients whose underlying diseases and complications cannot be controlled. We believe that the experience to date is more positive than negative, and we think that appropriately designed studies will confirm the hypotheses that therapy with nutritional repletion is of short-term and long-term benefit for patients with respiratory failure.

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