Depressed Central Respiratory Drive Causing Weaning Failure*
Its Reversal with Doxapram

Ronald E. Haake, D.O.; Leslie A. Saxon, M.D.; Steven J. Bander, M.D.; and Robert J. Haake, D.O.

A patient failed to wean from mechanical ventilation. Her problem was unique in that she had a depressed central drive to breathe manifested by hypopnea when removed from the ventilator. After excluding the known problems that impair successful weaning, we empirically administered three separate infusions of doxapram, a respiratory stimulant. These infusions produced a dramatic improvement in spontaneous ventilation and led to successful weaning and hospital discharge. (Chest 1989; 95:895-97)

A patient had a particular problem uncommonly found on the list of reversible causes of failure to wean. Her problem was unique in that she had a reduced central drive to breathe manifested by hypopnea and hypercapnia when removed from the ventilator during weaning trials.

Tobin et al. have recently examined the development of hypercapnia in unsuccessful weaning trials. In this study, the respiratory rate was increased and the tidal volume was decreased in the group that failed relative to the group that was successfully weaned. They concluded that hypercapnia seen in failed weaning attempts was secondary to shallow breathing and inefficient gas exchange. They observed that reduced central respiratory drive was infrequently causal in failed weaning attempts. No large trial, however, has specifically examined the frequency with which failed weaning attempts were secondary to a reduced central drive to breathe. We present such a case and a therapeutic intervention which allowed successful weaning.

CASE REPORT

A 61-year-old obese woman was admitted to the hospital with a three-day history of severe dyspnea. The patient suffered from severe chronic obstructive pulmonary disease in the setting of long-standing tobacco abuse. Her medical record showed a baseline room air arterial blood gas value pH of 7.38, PaO₂, 50 mm Hg, and PaCO₂, 56 mm Hg. Pulmonary function studies performed one year prior to admission revealed a forced expiratory volume in one second (FEV₁) of 45 percent of predicted.

On admission, the respiratory rate was 30 breaths per minute with a palpable blood pressure of 90 mm Hg and no audible paradox. The pulse rate was regular at 130 beats per minute. The oral temperature was 38.8°C. Perioral and acral cyanosis were present. Lung examination showed poor air movement, diffuse wheezing, and ronchi. The cardiac impulse was shifted rightward. There was no jugular venous distention. Distal pulses were strong. Abdominal, rectal, and neurologic examination results were normal.

The admission room air arterial blood had a pH of 7.21; PaO₂, 40 mm Hg; and PaCO₂, 75 mm Hg. The hemoglobin level was 16 g/100 ml, hematocrit value was 52 percent, and the white blood cell count was 19,500/μm with a normal differential. Abnormal blood chemistry values included an albumin of 2.9 g/dL (3.5 to 5.0); phosphorus, 0.2 mg/dL (2.6 to 4.9); and a magnesium of 1.4 mg/dL (1.8 to 2.4). The serum theophylline level was 11 μg/ml. The thyroxine level was 6.5 μg/dL (5.2 to 11.4). A chest roentgenogram showed new bilateral infiltrates. A postintubation radionuclide lung scan showed no perfusion defects. The sputum Gram stain showed numerous leukocytes and a packed field of heterogeneous Gram-negative rods.

The patient was intubated and mechanically ventilated. Empiric broad spectrum antibiotic coverage was instituted together with intravenous methylprednisolone, aminophylline, and nebulized bronchodilator therapy. Enteral tube-feedings were begun providing 1,600 calories per day. Over the next several weeks, persistent pulmonary infiltrates were treated with multiple courses of antibiotics adjusted to cover organisms cultured from the sputum including beta-lactamase negative Hemophilus sp and mezlocillin resistant Pseudomonas aeruginosa, ultimately followed by clearing of the chest x-ray film and normalization of the peripheral leukocytosis. Tracheostomy was performed on hospital day 26.

On hospital day 30, the unassisted tidal volume was 430 ml, respiratory rate was 19 breaths per minute, vital capacity was 850 ml, maximum negative inspiratory negative force was 40 mm H₂O, and the minute ventilation was 8.25 L/min. Repeated T-tube weaning trials were attempted but were unsuccessful, however, because of the rapid development of hypopnea, hypercapnia, and obtundation. Intracranial mass lesion and CNS infection were excluded by CAT scan and lumbar puncture. The only potential respiratory depressant the patient had received was low dose Navane, an antipsychotic, and this had been discontinued. The serum phosphorous value had been corrected shortly after admission. Normal hemodynamic function was demonstrated on day 23 by Swan-Ganz catheter measurements.

On hospital day 71 after 42 days of unsuccessful weaning attempts, an intravenous infusion of doxapram hydrochloride was initiated at a rate of 2 mg/min while the patient was receiving 40 percent oxygen by T-tube. The preinfusion arterial blood had a pH of 7.27, PaO₂ of 51 mm Hg, and a PaCO₂ of 82 mm Hg. The respiratory rate was six breaths per minute, and the patient was lethargic but arousable. After five minutes of continuous doxapram infusion, the respiratory rate increased to 16 breaths per minute, and the arterial blood gas determinations revealed pH, 7.31; PaO₂, 81 mm Hg; and PaCO₂, 49 mm Hg. The patient became alert. At that time, both she and her family refused further mechanical ventilatory support. An attempt to exchange the tracheostomy tube for a tracheostomy button was unsuccessful. Doxapram was therefore continued over the next day with preservation of the increased respiratory rate and alert mental status. No signs of respiratory muscle fatigue were observed. Daily efforts to stop the doxapram infusion resulted in the return of hypopnea and hypercapnia. The patient received three separate prolongations (18 to 24 hours) infusions of doxapram. After the third infusion, the patient's baseline respiratory rate was sufficient to provide adequate ventilation and ultimately successful weaning (Fig 1).

DISCUSSION

We were careful to eliminate reversible causes for failure to wean. We noted, however, an atypically slow respiratory rate when removed from the ventilator and placed on the Briggs for T-tube weaning. Typically, a reduced spontaneous tidal volume on the Briggs T-tube upon removal from the ventilator obligates the patient to increase the respiratory rate to maintain an adequate minute volume and PaCO₂. Our patient's respiratory rate decreased when removed from the ventilator despite an increase in the PaCO₂ and drop in the pH. The patient apparently had a depressed central chemical and/or neurogenic ventilatory drive. The manage-
Depressed Central Respiratory Drive (Haake et al)

Department questions at this time were twofold: (1) Was there an identifiable and reversible factor responsible for the observed hypoventilatory response? (2) What can be done to facilitate weaning in this patient?

Much has been written on weaning from mechanical ventilation. Successful weaning demands systematic exclusion of identified impairments to the weaning process. One of the most common causes of failure to wean in respiratory muscle fatigue. Fatigue is usually manifested sequentially by an increase in respiratory rate, respiratory alternans, and/or paradoxical abdominal respirations, and ultimately a rise in PaCO2. Our patient manifested no evidence of respiratory muscle fatigue. As evident in Figure 1, the patient had an inappropriately depressed respiratory response when removed from the ventilator. If this response had been a manifestation of terminal fatigue, then further stimulation of the respiratory muscles with doxapram would have inevitably made the fatigue worse. Without a period of rest, the patient would have succumbed or required reintubation.

Other causative factors for an ineffective ventilatory response include hypoventilation and metabolic alkalosis. Hypothyroidism and myxedema depress both the hypoxic and hypercapnic ventilatory drive. However, in our patient, thyroid function was within normal limits. Compensatory hypoventilation observed in metabolic alkalosis occurs by the same mechanism that causes the hyperventilatory response seen in metabolic acidosis. This appears to be a straightforward CSF hydrogen ion concentration dependent process. Fabey et al demonstrated the rather common occurrence of a “won’t breathe phenomenon” in COPD patients who were CO2 retainers. He found that nine of 12 of these patients had a depressed central neurogenic or chemical drive to breathe. This was found to be secondary to bicarbonate retention and reduced CSF hydrogen ion concentration. Our patient was a baseline CO2 retainer and likely had a chronically diminished respiratory drive. Mechanical ventilatory minute volume was titrated to maintain the patient’s own baseline PaCO2 and bicarbonate concentration to attenuate the acute respiratory acidosis that predictably occurs when patients are abruptly removed from the ventilator during T-piece weaning. We were careful to maintain the pH at less than 7.4 during the time of active weaning. The patient had no evidence of primary metabolic alkalosis from volume depletion, diuretics or steroids.

We were scrupulous to correct and maintain normal serum phosphorous levels in our patient as hypophosphatemia has been shown to impair both the contractile properties of the diaphragm in patients with acute respiratory failure. Metabolic attention was also paid to the patient’s nutritional support, and a normalized albumin testifies to its success.

A high dead space to tidal volume ratio (VdVT) as a source of hypercapnia was effectively ruled out by a normalized PaCO2 during controlled ventilation and a documented minute volume of 8 L noted prior to weaning efforts.

The etiology of the hypopneic response in our patient upon removal from the ventilator was not readily apparent. We could find no reversible cause to this detrimental respiratory response nor could we cite a contraindication for the use of doxapram.

Doxapram has been available since 1962. It has been shown to work on both peripheral and central respiratory receptors. Ventilation is increased in conscious healthy individuals receiving this drug through an increase in both the respiratory frequency and the tidal volume. Since its release, doxapram has been used in acute management of COPD exacerbations, obesity-hyperventilation syndrome, primary alveolar hypoventilation syndrome, and to reverse ventilator dependence in brain-damaged patients. It has also been used extensively in stuporous postanesthetic patients. The manufacturer currently recommends that the infusion of doxapram be limited to two hours. However, in a double-blind placebo controlled study of 78 patients where doxapram was used in a two-hour study period for acute exacerbation of COPD, there were very few serious side effects observed. Diaphoresis was observed in ten of 40 (25 percent), agitation and restlessness was found in five of 40 (12.5 percent). Two patients who were hypertensive prior to infusion developed worsening hypertension. There were no arrhythmias associated with doxapram infusion. In addition,
in 17 of 40 (42 percent) who received doxapram infusions for greater than six hours, no tachyphylaxis developed between six and 48 hours.

As our patient had no apparent reversible cause for her repeated failures to wean, and since the patient's symptoms very closely paralleled those seen in primary alveolar hypoventilation, we empirically used doxapram. As evident from Figure 1, the change was dramatic, and the use of doxapram obviated the need to reintubate the patient. Moreover, a "recruitment" phenomenon was observed wherein each successive use of doxapram resulted in a sustained increase in respiratory rate which persisted after discontinuance of the drug. This same phenomenon has been observed when doxapram was used to facilitate weaning in brain-damaged patients.13 We could find no previous reports where doxapram had been used to assist weaning from mechanical ventilation in adults. Nor has newly developed central hypoventilation been identified as an impediment to weaning in the literature to date.

Fahey and Hyde's study identified a subgroup of COPD patients who were "won't breathers" and CO₂ retainerers and who, in addition, had a depressed ventilatory drive relative to nonretainers ("pink puffers"). Our patient had an amplification of this depressed ventilatory drive for reasons which remain unclear. We suspect that this condition exists in other patients requiring prolonged mechanical ventilation and may contribute to their failure to wean. It may remain unrecognized when masked by the other factors which impair weaning outlined above.

Further investigations are needed to support the existence and frequency of this problem and the potential benefits of treatment with doxapram.

ACKNOWLEDGMENT The authors gratefully acknowledge the assistance of Mrs. Martha Rhodes and Shirley Haake in the preparation of this manuscript.

REFERENCES


3 Hughes RL, Davison R. Limitations of exercise reconditioning in COPD. Chest 1983; 83:241-49


11 Houser WC, Sluchterm PD. Prolonged doxapram infusion in obesity-hypoventilation syndrome. JAMA 1978; 239:340-41


14 Freeman J. The effectiveness of doxapram administration in hastening arousal following general anesthesia in outpatients. AANA-J 1986; 54:16-20


Endurance Exercise in the Presence of Heart Disease

Ramela S. Douglas, M.D.,* Alison Sigler, M.D.,* Mary L. O'Toole, Ph.D.;† and W. Douglas B. Miller, M.D.†

Although patients with heart disease have successfully completed marathon runs, the immediate cardiac effects of similar and greater distance endurance exercise competition are unknown. Two such cases are presented, demonstrating that vigorous exercise and extreme levels of fitness are not precluded in the cardiac patient.

(Chest 1989; 95:697-99)

If a cardiac patient chooses to exercise at all, the activity is usually moderate in intensity and duration, and noncompetitive. However, patients who have undergone coronary bypass grafting or myocardial infarction or who have hypertrophic cardiomyopathy have successfully completed endurance racing events such as marathons.4,5 While such exercise is pursued by a select few, the physician has limited scientific knowledge to draw upon in advising the increasingly common, aspiring cardiac patient-athlete.

Accordingly, we studied the immediate cardiac effects of endurance exercise competition in two patients with different forms of heart disease, one following myocardial infarction and bypass grafting, and one following receipt of a cardiac transplant.

CASE REPORTS

CASE 1

At age 48, this previously healthy white man began experiencing progressive, exertional angina, culminating in an anterior myocardial infarction. Treadmill exercise stress test was positive and cardiac catheterization showed a 100 percent obstruction in the proximal left anterior descending coronary artery, with collateral flow provided by the right coronary artery. There were 50 percent lesions in both the first diagonal and the first circumflex marginal arteries. The right coronary artery was small but had a mid-90 percent

*From the Cardiovascular Section, Hospital of the University of Pennsylvania, Philadelphia, and the Baptist Memorial Hospital, Campbell Clinic, University of Tennessee, Memphis.

Reprint requests: Dr. Douglas, Hospital, University of Pennsylvania, 3400 Spruce Street, Philadelphia 19104

CHEST / 95 / 3 / MARCH, 1989 697