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J. Maher
F. Rutledge
H. Remtulla
A. Parkes
L. Bernardi
C.F. Bolton

Neuromuscular disorders associated with failure to wean from the ventilator

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J. Maher · H. Remtulla · A. Parkes
L. Bernardi · C.F. Bolton (✉)
Department of Clinical Neurological Sciences,
The University of Western Ontario,
Victoria Hospital, 375 South Street,
London, Ontario, Canada N6A 4G5

F. Rutledge
The Richard Ivey Critical Care/Trauma Centre,
The University of Western Ontario,
Victoria Hospital, 375 South Street,
London, Ontario, Canada N6A 4G5

Abstract *Objective:* To determine, by retrospective chart analysis, the frequency, type and significance of neuromuscular disorders in patients whose clinical features suggested a neuromuscular cause of failure to wean.
Background: Failure to wean is a common and difficult problem in critical care units. While a neuromuscular cause may be suspected in some patients, the frequency and type has not been determined utilizing comprehensive electrophysiological studies of limbs and the respiratory system. Such knowledge may aid in patient management and prognosis.
Methods: The clinical setting was a critical care/trauma centre that admits 1500 patients per year, approximately 500 being on ventilators for longer than five days. We analyzed the hospital charts of 40 patients admitted to the unit during three years, whose respiratory assessment suggested a neuromuscular cause for failure to wean from the ventilator. To investigate this possibility, we performed electrophysiological studies of the limbs and also of the respiratory system by phrenic nerve conduction and needle electromyography of the chest wall and diaphragm. The results were compared to 25 healthy controls.
Results: 38 of 40 patients (95%) had a neuromuscular disorder: 25 – critical illness polyneuropathy, 2 – Guillain-Barré syndrome, 4 – diabetic and critical illness polyneuropathy, 2 – uremic and critical illness polyneuropathy, 10 – an abnormality of central drive, 5 – unilateral phrenic nerve palsy, 3 – a neuromuscular transmission defect, and 5 – a primary myopathy. Fifteen (38%) had a combination of disorders. Patients with more severe polyneuropathy took longer to wean, a mean of 136 versus 52 days ($p = 0.007$).
The severity of the polyneuropathy had no effect on mortality.
Conclusions: Electrophysiological studies of limbs and the respiratory system are together valuable in confirming the presence, and identifying the specific type of neuromuscular cause for difficulty in weaning from the ventilator. This information is important in patient management and prognosis.

Key words Electrophysiology · Respiration · Ventilatory failure · Neuromuscular disorders

Introduction

Failure to wean from a ventilator increases long term complications, disability, and the cost of medical care. The precise definition of failure to wean is still debated, but we [1] recognize it when, on discontinuation of ventilatory support, the respiratory rate becomes unacceptably high (>35/min), the tidal volumes unacceptably low (≤5 ml/kg) and respiratory acidosis develops. At this stage, the underlying disease has been successfully treated and the clinical status is otherwise good [1]. The majority of critical care unit patients may wean from mechanical ventilation without difficulty, although the reported incidence of failed weaning vaires from 6–75%, depending on the types of patient in each unit [2]. Common underlying causes of failure to wean include lung or cardiac disease, increased airway resistance, fever, electrolyte and pH disturbances, ongoing sepsis, malnutrition, impaired respiratory drive, or neuromuscular disease [2, 3].

In the study by Lemaire and colleagues [2], the incidence of neuromuscular disease was 17% among 500 patients who took longer than two days to wean. There are difficulties in assessing the neuromuscular system in the critical care unit by history and physical examination, and electrophysiological studies have proven valuable [4]. Such methods, at times supplemented by nerve and muscle biopsy, have shown critical illness polyneuropathy [5–7] or myopathy [8] (frequent complications of sepsis and multiple organ failure), Guillain-Barré syndrom [9], diaphragmatic paralysis [10], myasthenia gravis [10] and possibly toxicity of neuromuscular blocking agents and steroids [11], are all potential causes of failure to wean. Utilizing electrophysiological studies of limbs and incorporating computer analysis of motor unit potentials, Spitzer et al. [12] studied 21 patients with prolonged ventilatory dependence of more than seven days. Of these 62% had a neuromuscular cause, usually a critical illness neuropathy or myopathy.

In the last ten years, we have further perfected and applied the techniques of phrenic nerve conduction and needle electromyography of the diaphragm. They have been useful in establishing the precise cause of neuromuscular respiratory insufficiency, particularly in the critical care unit [10, 13]. Thus, the presence of impaired central drive, axonal or demyelinating neuropathies of the phrenic nerve and primary myopathies of the diaphragm can be discerned. Consequently, we utilized these techniques, in addition to neurophysiological studies of the limbs, in 40 patients whose respiratory status suggested an underlying neuromuscular disorder as a cause of difficulty in weaning from the ventilator.

Materials and methods

The clinical setting

The Critical Care/Trauma Centre (CCTC), Victoria Hospital, London, Ontario, admits 1500 patients per year with major medical and surgical illnesses. One-third require mechanical ventilation for longer than five days. Patients had a neurophysiological assessment if they failed to wean even though they were: i) capable of spontaneous breathing; ii) the underlying disease process responsible for their acute respiratory failure was felt to be reversed or controlled; iii) their clinical status was good, including a normal level of consciousness; iv) there was no or minimal evidence of cardiac failure, high airway resistance, electrolyte of pH disturbance, ongoing sepsis, or malnutrition (all received appropriate total parenteral nutrition or nasogastric feeds, as determined by a dietary team); and v) they were haemodynamically stable and not on inotropic, vasopressor or sedative drugs at the time of attempted weaning from ventilation or at the time of neurophysiological assessment.

Methods of weaning

Prior to weaning, patients had respiratory rates (RR) <35/min, tidal volumes >5 ml/kg, adequate oxygenation, as defined by a PaO_2 >60 mmHg, on an FIO_2 of <0.5, on minimally assisted ventilation. The determination of failure to wean was made by experienced physicians who regularly cared for patients on mechanical ventilation. A patient was deemed as having failed to wean when, on discontinuation of ventilatory support, the RR became unacceptably high (RR>35/min), tidal volumes became unacceptably low (≤5 ml/kg) and respiratory acidosis developed. Weaning was considered successful if breathing was spontaneous, without mechanical ventilatory support after two days. Measurements that may have been more descriptive, such as vital capacity (Vc), RR/Vc, peak negative inspiratory pressure, maximum voluntary ventilation, or occlusion pressure, were not routinely recorded.

Neurophysiological studies

These were performed in the Critical Care/Trauma Centre with an Advantage EMG System (Clark-Davis Medical Systems, London, Ontario, Canada). Distal limb temperatures were normal or mildly elevated: correction factors for temperature for electrophysiological measurements were not applied since they are not significant in this patient population [14]. All patients had conventional motor and sensory nerve conduction studies (NCS), F wave determinations, repetitive nerve stimulation at 3 and 20 Hz, and monopolar needle electromyography of limb and chest wall muscles and diaphragm (EMG) [15]. Abnormal spontaneous activity, as demonstrated by the presence of fibrillation potentials and positive sharp waves, was graded on a scale of 0–4, 0 being normal, 1–2 being mild/moderate, and 3–4 being severe [15]. Phrenic NCS were performed with surface electrodes for both stimulation and recording [16, 17]. EMG of the respiratory muscles was performed according to the technique described by Bolton et al. [18] and Koepke [19]. Critical illness polyneuropathy was differentiated from Guillain-Barré syndrome based on previously described criteria [14].

In the present study, central respiratory drive refers to the various supersegmental neural influences on the phrenic nerve motor neurons, whether they be behavioral or metabolic. In the critical care unit, central respiratory drive was assessed by temporarily decreasing ventilatory support to 5–8 cmH_2O of pressure support or continuous positive airway pressure (to overcome airway/ventilator

resistance), for a maximum of 15 min. Mechanical ventilation was restored if there was evidence of respiratory distress, arterial oxygen saturation <90% (based on a pulse oximeter reading), or a significant rise in heart rate or blood pressure. Prior to neurophysiological assessment, the P_aCO_2 or pH were not monitored during the assessment of respiratory drive. In order to assess central drive, the inspiratory bursts recorded by needle EMG of the diaphragm were compared by visual inspection to 25 healthy control subjects of similar ages and sex (unpublished data from our Electrophysiology Laboratory). Disorders of pattern, such as Cheyne-Stokes respirations, or decrease in amplitude and duration of the inspiratory bursts in the presence of normal phrenic nerve conduction studies and otherwise normal needle EMG of the diaphragm were considered abnormal [10].

Methods of chart analysis

We reviewed, according to a detailed protocol, all medical records of patients who were referred for neurophysiological assessment for failure to wean, from August 1989 to June 1992. We excluded patients with neuromuscular disorders that had been diagnosed before admission to the CCTC, or those who required a tracheostomy tube for airway protection despite good ventilatory capacity.

Since neurologic clinical signs are often unreliable in patients in the critical care unit, we relied on electrophysiological measurements to determine the type and severity of the neuromuscular disorders. It was decided to identify and grade the polyneuropathy, the commonest disorder. Since all polyneuropathies were of the axonal type, including those with Guillain-Barré syndrome, only the amplitudes of compound muscle and sensory nerve action potentials were considered. These were judged abnormal if they were outside 95% confidence limits, greather then 2 SD from mean control values (established in our laboratory for limb studies [5], and for phrenic nerve conduction and needle EMG of the chest wall and diaphragm (25 control subjects, unpublished data).

The polyneuropathy was graded as: i) severe – markedly diminished or absent compound muscle and sensory nerve action potentials, and grade 3–4 spontaneous activity on EMG of muscle, in the limbs; ii) mild/moderate – all lesser grades of polyneuropathy.

Respiratory studies were graded as: i) severe – markedly reduced or absent compound diaphragm muscle action potential amplitude, and grade 3–4 spontaneous activity on EMG of respiratory muscles; ii) mild/moderate – all lesser grades of abnormality of the respiratory system.

Statistical analysis

Data for control subjects were calculated as mean ± standard deviations. An association between the presence of a polyneuropathy in the limbs and neurophysiologically determined respiratory impairment was estimated by Craemer's V statistic. We used a Kaplan-Meier curve to compare the time to wean from ventilation among survivors. Differences between groups were determined using a log-rank test. p values < 0.05 were considered statistically significant.

Results

Forty patients (21 men and 19 women) were studied. The mean (range) age was 66 (18–84) years. They were ventilated in total for 38 (11–251) days, and for 14 (1–108) days prior to neurophysiological assessment. They had a variety of primary and secondary illnesses (Table 1). A chest X-ray was normal in all patients, except for mild pulmonary edema in four patients.

The incidence and type of neuromuscular disorder

Of the 40 patients 38 (95%) had a neuromuscular disorder at the time of neurophysiological testing; 15 (38%) had a combination of neuromuscular disorders, 12 having two, and three having three, combinations (Fig. 1).

There were 33 patients (83%) with a polyneuropathy: 25 critical illness polyneuropathy (CIP), 2 Guillain-Barré syndrome (GBS), 4 a combination of diabetic and critical illness polyneuropathy, and 2 a combination of uremic and critical illness polyneuropathy. (The GBS patients were previously undiagnosed and had axonal degeneration secondary to primary demyelination. One presented to the critical care unit as a post-operative failure to wean, the second presented prior to admission to the critical care unit as a subacute onset respiratory failure which was disproportionately severe compared to the limb weakness). Ten patients (25%) had electromyographically confirmed abnormal central respiratory drive, which had not been noted clinically. Five patients had a unilateral phrenic nerve palsy: 1 due to thoracic surgery and 4 of unknown etiology. Five patients with electromyographic evidence of a myopathy all had normal creatinine phosphokinase (CPK) levels. Thus, these 5 patients may not have had a myopathy, since CPK values tend to be normal in neuropathy, and it may be difficult to distinguish electrophysiologically between a myopathy and a neuropathy [20]. Moreover, one of these 5 patients had a muscle biopsy which showed only mild denervation atrophy. Three patients had a defect in neuromuscular transmission. In the first, this was due to previously undiagnosed myasthenia gravis presenting as isolated respiratory failure, which had caused isolated denervation of the respira-

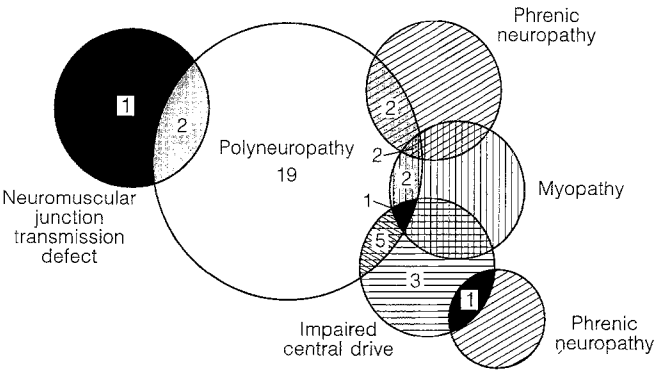

Fig. 1 The types of neuromuscular disorders among 40 patients who failed to wean from ventilation. There were 38 (95%) with a neuromuscular disorder and 15 (38%) with a combination of disorders

Table 1 Primary condition which precipitated mechanical ventilation and neuromuscular disorders subsequent associated with difficulty weaning from ventilation. (*NCS* Nerve conduction studies, *EMG* electromyography, *CIP* critical illness polyneuropathy, *NMJ* neuromuscular junction, *MODS* multiple organ dysfunction syndrome, *DM* diabetes mellitus, *COPD* chronic obstructive pulmonary disease, *IHD* ischemic heart disease)

N	Primary conditions	Secondary conditions	Limbs NCS/EMG	Phrenic NCS + diaphragm EMG
1	Lung cancer surgery	COPD; sepsis	Mild CIP; myopathy	Abnormal central respiratory drive
2	Bowel obstruction surgery	MODS; parkinsonism	Moderate CIP	Abnormal central respiratory drive; bilateral phrenic neuropathy
3	Abdominal aorta surgery	MODS	Normal	Abnormal central respiratory drive
4	Carcinoid with metastases	Pneumonia	Mild CP	Abnormal central respiratory drive; bilateral phrenic neuropathy
5	Pneumonia	Chiari 1 malformation	Normal	Abnormal central respiratory drive
6	IHD surgery	Aortic dissection	Moderate CIP	Abnormal central respiratory drive; bilateral phrenic neuropathy
7	Closed head injury	MODS; pneumonia	Mild CIP	Abnormal central respiratory drive
8	Colon cancer surgery	MODS; COPD	Normal	Abnormal central respiratory drive
9	Bowel obstruction surgery	MODS; COPD subdiaphragmatic abscess (left)	Normal	Abnormal central respiratory drive; left phrenic neuropathy
10	Cardiac surgery	MODS; pneumonia	Mild CIP	Abnormal central respiratory drive; bilateral phrenic neuropathy
11	Diabetic ketoacidosis	MODS; pneumonia	Severe polyneuropathy	Bilateral phrenic neuropathy
12	COPD	MODS; cardiac failure; septic encephalopathy	Severe CIP	Normal phrenic nerves; denervated chest wall muscles
13	COPD	Cholecystitis; MODS	Mild CIP	Right phrenic neuropathy
14	Cardiac failure	IHD; MODS; DM	Severe polyneuropathy	Bilateral phrenic neuropathy
15	Cardiac surgery	Post-operative Guillain-Barré syndrome (GBS)	Severe GBS	Bilateral phrenic neuropathy
16	Cardiac surgery	Pneumonia; DM	Mild polyneuropathy	Normal
17	Acute pancreatitis; sepsis	Pneumonia	Mild CIP	Normal
18	Cardiac failure	IHD; MODS; COPD	Severe CIP	Bilateral phrenic neuropathy
19	Cardiac surgery	Septic encephalopathy	Severe CIP	Normal
20	Pneumonia	DM	Mild polyneuropathy	Bilateral phrenic neuropathy
21	Lung cancer surgery	Sepsis	Mild CIP; myopathy	Right phrenic neuropathy
22	Pneumonia	COPD; sepsis	Severe CIP	Bilateral phrenic neuropathy
23	Asthma; pneumonia	Gastric bleed	Mild CIP; myopathy	Normal
24	Cancer oesophagus surgery	MODS; septic encephalopathy	Mild CIP	Normal
25	Abdominal aorta surgery	ARDS	Mild CIP	Left phrenic neuropathy
26	Asthma; pneumonia	IHD	Mild CIP	Normal
27	ARDS	Cardiac failure	Mild CIP	Normal
28	Pneumonia	Parkinsonism	Mild CIP; myopathy	Right phrenic neuropathy
29	Guillain-Barré syndrome (GBS)	Sepsis; renal failure	Severe GBS	Bilateral phrenic neuropathy
30	Oophorectomy for cancer	Septic encephalopathy; pulmonary embolus	Severe CIP	Bilateral phrenic neuropathy
31	Renal failure	Pneumonia	Severe polyneuropathy	Bilateral phrenic neuropathy
32	Cervical cord infarct	Sepsis	Mild CIP	Normal
33	Cardiac failure	IHD; toxic encephalopathy	Mild CIP	Normal
34	ARDS	MODS; renal failure; sepsis	Severe polyneuropathy; NMJ transmission defect	Bilateral phrenic neuropathy
35	Flail chest; closed head injury	Sepsis	Mild CIP	Bilateral phrenic neuropathy
36	Asthma; pneumonia	Septic encephalopathy	Mild CIP; NMJ transmission defect	Normal
37	Cardiac surgery	Metabolic encephalopathy	Normal	Normal
38	Wallenberg syndrome	Cardiac pacing	Normal	Normal
39	Abdominal aorta surgery	Septic encephalopathy; MODS	Severe CIP	Bilateral phrenic neuropathy
40	Myasthenia gravis	Pneumonia	NMJ transmission defect	Isolated diaphragmatic denervation; normal phrenic nerves

tory muscles, a unique finding [21]. In the second, it was due to the neuromuscular blocking agent, vecuronium bromide, in the presence of advanced renal failure. In the third, it was presumed due to aminoglycoside antibodies.

Neuromuscular blocking agents and steroids

There were 33 patients who received competitive neuromuscular blocking agents, vecuronium bromide, pancuronium bromide or atracurium besylate. The dosages used were small, usually single injections for investigative or neurosurgical procedures, and never for longer than 48 h. Sixteen received steroids, again in small dosages for short periods. Statistical analysis showed no correlation between the use of drugs and a polyneuropathy or myopathy. As noted above, one patient had a prolonged neuromuscular transmission defect due to vecuronium bromide in the presence of renal failure.

Mortality

A total of 25 patients survived and weaned from mechanical ventilation. Of 33 with polyneuropathy, 18 survived as did 6 of 10 with impaired central respiratory drive. Although all patients who died had a polyneuropathy, it is likely that polyneuropathy had little effect on mortality, as mortality was independent of its severity. Thus, 9 of 21 (43%) with mild/moderate polyneuropathy died versus six of 12 (50%) with severe polyneuropathy ($p > 0.05$). Similarly, the risk of death at 30 days was 19% in those with a mild to moderate polyneuropathy and 16% for those with a severe polyneuropathy ($p > 0.05$). Death occurred in 39% of those with critical illness polyneuropathy, which is similar to that reported in a study from our unit [14].

Morbidity

The severity of polyneuropathy affected the length of time on mechanical ventilation. Of 12 survivors 6 (50%) with mild/moderate polyneuropathy weaned within 52 days, whereas 3 of 6 (50%) survivors with severe polyneuropathy weaned within 136 days ($p = 0.007$) (Fig. 2).

Polyneuropathy in the limbs was associated with abnormal phrenic nerve conduction studies and denervation of the diaphragm (Craemer's V = 0.45), although the association was not precise (see Discussion). Thus, 20 of 33 patients with polyneuropathy had neurophysiological evidence of diaphragmatic denervation and phrenic neuropathy, 12 of whom survived and weaned from mechanical ventilation after an average of 56 (16–178) days. In contrast, 13 patients with polyneuropathy had no neurophysiological evidence of diaphragmatic denervation and had normal phrenic nerve conduction studies, six of whom survived and weaned from mechanical ventilation after an average of only 33 (11–78) days. However, the difference was not statistically significant ($p = 0.06$).

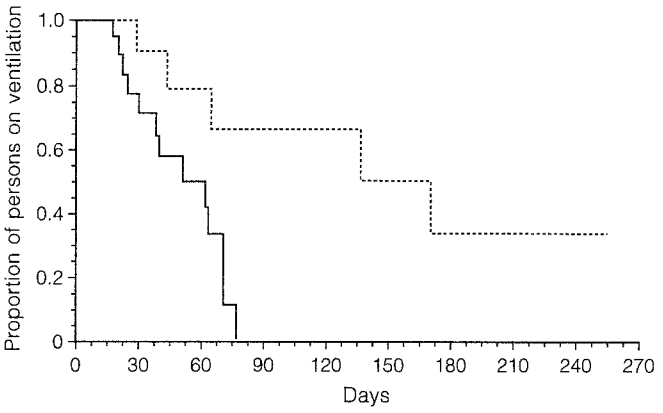

Fig. 2 Kaplan-Meier survival curves showing that those who survived with a mild/moderate polyneuropathy (– – –) weaned from mechanical ventilation earlier than those with a severe polyneuropathy (· · · ·) ($p = 0.007$)

Impaired central respiratory drive did not significantly increase the duration of mechanical ventilation in comparison to the remaining patients without such a disorder. Thus, 3 of 6 (50%) patients with impaired central respiratory drive survived and weaned from mechanical ventilation within 39 days, two of whom had a polyneuropathy and one a unilateral phrenic neuropathy. Of the remaining 19 survivors who had a variety of peripheral nervous system disorders 50% weaned within 64 days ($p > 0.05$).

Discussion

Of 40 patients in our study 38 (95%) had a neuromuscular disorder as a cause of failure to wean from the ventilator. Thus, a neuromuscular cause can be strongly suspected when, on attempted weaning, respirations became excessively rapid (>35/min) and shallow (≤5 ml/kg) in a patient whose underlying disease process responsible for acute respiratory failure has resolved and whose clinical status is good. By performing neurophysiological assessment of both the limb and the respiratory system, it is possible to identify these disorders. This may explain why the incidence of neuromuscular disorders was higher in our study than in the study of Spitzer et al. [12], who studied essentially the limbs, not the respiratory system, and found 62% of their patients with protracted difficulty in weaning had a neuromuscular disorder.

Polyneuropathy, mainly critical illness polyneuropathy, less often combined diabetic and critical illness polyneuropathy, uremic and critical illness polyneuropathy, or Guillain-Barré syndrome, was the most common

neuromuscular disorder in our study, being present in 33 (83%). Identification of critical illness polyneuropathy is important, since it means that respiratory training may not be beneficial and spontaneous recovery in weeks or months, depending on severity, will eventually occur. Similarly, Guillain-Barré syndrome and myasthenia gravis can be treated with plasmapheresis or hyperimmune globulin [9]. Less commonly identified disorders were impaired central respiratory drive, unilateral phrenic nerve palsies, myopathy, and primary and secondary neuromuscular junction transmission defects. Notably, a combination of these occurred in 38%. Our study failed to implicate competitive neuromuscular blocking agents or steroids as a cause of polyneuropathy or myopathy. However, administration of these drugs, either singly or in combination, in higher dosages and for more prolonged periods of time, may be toxic, as suggested in recent reports [11, 22, 23].

Neurophysiological study of the respiratory system aids diagnosis and management in the critical care unit. Phrenic neuropathy, unilateral or bilateral, diaphragmatic denervation and impaired central respiratory drive, would not have been detected by neurophysiological studies of the limbs alone. Demonstration of a neuropathy of one or both phrenic nerves indicates that the patient should be nursed in the upright position, if possible. Also, if the phrenic nerve injury is only partial, as is usually seen in open heart surgery due to exposure of the phrenic nerve to ice/slush topical hypothemia, it can be predicted that regeneration of the phrenic nerves will occur over a number of months [24]. Impaired central drive was present in 25% of our patients, which contrasts with other reports where it was considered uncommon [25]. Its identification aids management by drawing attention to the brain as a cause of the respiratory difficulty.

Neurophysiological studies aid in prognostication, which is of particular value considering the high cost of care in the critical care unit. Thus, the mean period of weaning among 12 survivors with mild to moderate polyneuropathy was 52 days, whereas it was 136 days in the 6 survivors with severe polyneuropathy ($p = 0.007$). In those with impaired central respiratory drive, it was only 39 days. Our study also showed that patients with polyneuropathy associated with diaphragmatic denervation and phrenic neuropathy required, on average, 23 days longer on mechanical ventilation than those with polyneuropathy but no diaphragmatic denervation and normal phrenic nerve conduction studies, although this difference was not statistically significant.

Patients who fail to wean may have a disuse atrophy [27, 28] or fatigue [29–31] of the diaphragm, both of which would not have been detected by our methods. Their detection is of some import, as judicious use of respiratory muscle training may be beneficial. Sophisticated imaging studies may help to detect atrophy of the diaphragm. Also, computer analysis of needle EMG signals may detect diaphragm fatigue in which there is a demonstrated shift from high to low frequencies [30, 31]. Prospective studies may help to answer these and other questions not answered by this retrospective study.

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