Electrophysiological Respiratory Studies in the Critical Care Unit

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ABSTRACT: Respiratory electrophysiological studies are useful in the investigation and monitoring of respiratory failure. Phrenic nerve conduction studies and needle electromyography of the diaphragm are invaluable in establishing the diagnosis, determining the severity, and following the progression of peripheral respiratory muscle dysfunction. In addition to these established methods, repetitive phrenic nerve stimulation is of diagnostic value in patients with neuromuscular transmission defects and dyspnea. The diagnosis of impaired central respiratory drive can often be accomplished by the newly-developed techniques of transcortical magnetic stimulation of the motor cortex with recording of the diaphragm and phrenic nerve somatosensory evoked potentials. These studies are of particular value in critically ill patients where both the central and peripheral lesions may impair respiration.

RÉSUMÉ: Études respiratoires électrophysiologiques à l'unité de soins intensifs. Les études électrophysiologiques de la respiration sont utiles pour l'investigation et la surveillance de l'insuffisance respiratoire. Les études de conduction du nerf phrénique et l'électromyographie (EMG) du diaphragme sont précieuses pour établir le diagnostic, déterminer la sévérité et suivre la progression de la dysfonction périphérique des muscles respiratoires. En plus de ces méthodes d'investigation bien établies, la stimulation répétitive du nerf phrénique a une valeur diagnostique chez les patients qui ont un défaut de la transmission neuromusculaire et de la dyspnée. Le diagnostic d'un déficit respiratoire d'origine central peut souvent être posé au moyen de techniques nouvelles de stimulation magnétique transcorticale du cortex moteur avec enregistrement des potentiels évoqués somesthésiques au niveau du diaphragme et du nerf phrénique (PES). Ces études sont particulièrement utiles chez les patients dont l'état est critique parce que des lésions centrales et périphériques peuvent perturber la respiration.

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Disorders of the central and peripheral nervous system frequently contribute to the need for assisted ventilation in critically ill patients.[1] They either can be the primary reason for the initiation of mechanical ventilation, or may develop as complication in the critical care unit. In many instances, it is clinically difficult to differentiate the lack of central drive from respiratory muscle weakness. In such patients electrophysiological studies are useful in the diagnosis and management.[2]

Central nervous system disorders often lead to disturbance of the respiratory drive. Clinical observation of some breathing patterns, such as Cheyne-Stokes, apneustic, or ataxic breathing is of localizing value.[3] However, in many patients these specific breathing patterns may be absent and they cannot be observed in ventilated patients.

Respiratory failure from neuromuscular diseases may present clinically with rapid respiratory rate and shallow breathing. However, this is variable and some patients present in ventilatory failure with a normal or reduced respiratory rate. Paradoxical abdominal movement with inspiration is a sign of diaphragmatic weakness, wheras intercostal and abdominal muscle weakness is characterized by paradoxical movement with inspiration.[4]

This paper describes recent developments in the electrophysiological diagnosis of neurological disorders affecting the respiratory system.

Electrophysiology of Peripheral Respiratory Pathway

Phrenic nerve conduction

The technique was originally described by Newsom-Davis[5] and modified by Bolton and his collaborators.[6,7] The phrenic nerve is stimulated percutaneously in the supraclavicular fossa with single electrical stimuli, to obtain a pure phrenic nerve response seen as a characteristic waveform. Inadvertent stimulation of the brachial plexus is seen as arm movement and as a diaphragmatic compound muscle action potential (CMAP) with an initially positive deflection. Surface recording electrodes are applied 5 cm superior to the tip of the xiphoid process (G1) and to the costal margin 16 cm from the G1 electrode as the G2 electrode ipsilaterally. The ground electrode is positioned on the ipsilateral upper arm. Normal mean values for the latency to the onset of the negative peak, the diaphragmatic CMAP amplitude from the baseline to the negative peak, the negative peak area, and duration from the negative peak onset to return to baseline are established.[7] The latency of the phrenic nerve CMAP increases with age.[7] The diaphragmatic CMAP amplitude increases with

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chest circumference and correlates with smoking history, being higher in ex-smokers than non-smokers.[7] Using this technique routinely in both ambulatory care and critical care unit settings, we found it useful in the diagnosis and management of both axonal and demyelinating neuropathies.[8,9] The phrenic nerve may also be stimulated with cervical magnetic stimulations and with magnetic stimulations above the suprasternal fossa.[10]

Intercostal and thoracic nerve conduction

In patients with suspected neuromuscular cause of dyspnea and normal phrenic nerve conduction intercostal and thoracic nerve conduction studies may be of some help. However, these techniques are time consuming and the CMAPs are variable.[11]

Repetitive phrenic nerve stimulation

Repetitive phrenic nerve stimulation at 3 Hz with recording from the diaphragm is useful in the assessment of the phrenic nerve-diaphragm neuromuscular junction.[12] Because of the influence of different lung volumes on the size and shape of diaphragm CMAPs, all trains of stimuli are given at the end of quiet expiration, and the subjects are instructed to hold their breath during the stimuli. Due to pseudofacilitation of the diaphragmatic CMAP observed in healthy subjects[13] the negative peak area is used for analysis of repetitive phrenic nerve stimulations. The value of the first diaphragmatic CMAP is compared with that of either the fifth or sixth, and the percent increment or decrement is calculated. The recording has to be rejected if electrocardiogram artifacts, seen as prolonged and abnormally high amplitude deflections, are encountered at the first or during both the fifth and sixth diaphragmatic CMAP. If electrocardiogram artifacts occur either between the second and fifth or only during the sixth diaphragmatic CMAP, the analysis of the decrement is not impaired. Each train consists of six stimuli at a rate of 3 Hz (stimuli/second). This method causes little discomfort, is highly reproducible and technically easy.

Diaphragmatic needle electromyography

Needle electromyography (EMG) from the diaphragm is safe, causes little discomfort, and provides excellent recording of diaphragmatic activity.[14] Examinations are performed with a needle electrode inserted between the anterior axillary line and the medial clavicular lines, just above the costal margin.[14] The spontaneous breathing pattern, the presence of spontaneous activity, and the appearance and firing pattern of motor unit potentials are analyzed. In ventilated patients diaphragmatic needle EMG studies are done during temporarily discontinued ventilation. The detection of abnormal motor units is sometimes difficult because normal diaphragmatic motor units are of short duration and small amplitude. Automated interference pattern analysis[15] and power spectral analysis of diaphragmatic EMG[16] are promising new ways to detect abnormalities, especially myopathic changes. As the EMG needle passes through the external oblique or rectus abdominus muscle, then the external and intercostal muscles can also be studied. Involvement of these muscles also contributes to respiratory failure.

Clinical implications of peripheral respiratory electrophysiology

Guillain-Barre' syndrome (GBS) developing before admission and critical illness neuropathy (CIP) developing after admission to the critical care unit are the most common polyneuropathies in the critical care setting.[5]

Mechanical ventilation is required in 14 - 44% of patients with GBS.[4] Respiratory electrophysiological studies in patients with GBS performed within three days of admission to hospital showed phrenic nerve involvement in 88%.[9] Diaphragmatic needle EMG was complementary to phrenic nerve conduction studies in detecting phrenic nerve abnormalities (Figure 1). Phrenic nerve conduction studies and needle EMG of the diaphragm were also useful in predecting respiratory failure. Diaphragmatic CMAP amplitude and negative peak area, and the finding of abnormal diaphragmatic needle EMG correlated with the need for ventilation. In addition, no patient with initially normal electrophysiological respiratory studies developed respiratory failure. Hence, these studies are useful in detecting respiratory involvement in patients with GBS and in identifying those at risk of respiratory failure.

The systemic inflammatory response syndrome (SIRS)[17] occurs in 20-50% of patients in major medical or surgical critical care units.[18] Prospective studies in our unit indicate that 70%

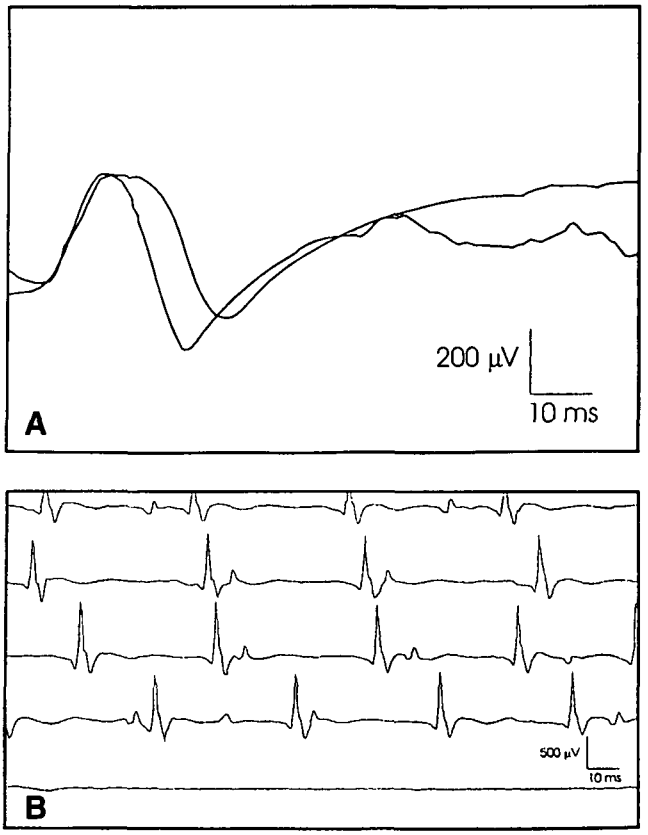

Figure 1: Phrenic nerve conduction study and diaphragmatic needle EMG in a 53-year-old male patient with Guillain-Barre syndrome (day of the disease). (A) The latency (6.8 msec), diaphragmatic CMAP amplitude (340 µV), area 4.2 mVms), and duration (19.9 ms) were all normal. However, the duration fluctuated with each stimulus, suggesting variable excitation thresholds of some axons due to demyelination. (B) Right diaphragmatic needle EMG during quiet breathing. Only a very few motor unit potentials fired during each inspiration (Sweeps 1-4). The fifth sweep was recorded during expiration. Despite near normal phrenic nerve conduction, the needle EMG showed markedly reduced number of motor unit potentials, no fibrillation potentials or positive sharp waves were recorded. This was consistent with severe demyelination proximal to the point of stimulation.

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of such patients will suffer from CIP.[19] CIP causes difficulty in weaning from the ventilator, varying degrees of limb weakness, and has the potential for complete recovery should the patient survive the SIRS. Morphological studies indicate the presence of a primary, axonal, motor and sensory polyneuropathy.[20] CIP is being recognized and reported from an increasing number of centres around the world.[21-26] CIP may show predominant involvement of the limbs or the respiratory system, therefore both areas should be studied electrophysiologically to obtain an overall assessment of the severity and distribution of the neuropathy. Phrenic nerve conduction studies usually show near-normal latencies but reduced CMAP amplitudes, and are helpful in determining the prognosis for weaning from the ventilator.[27] Needle EMG of the diaphragm may show fibrillation potentials and positive sharp waves. Such signs of denervation are associated with a longer period of mechanical ventilation. Reduced number of motor units firing during inspiration may be caused by neuropathy or concomittant septic encephalopathy.

There has been a debate as to the incidence and nature of a myopathy which may occur independently or in association with CIP, and the role that electrophysiological testing and muscle biopsy may play in differentiating neuropathy from myopathy.[28-31] Neuromuscular blocking agents and steroids, which are used commonly in some intensive care units have been implicated in inducing polyneuropathy[32,33] or several types of myopathy.[28-31] This is of practical importance since both drugs are beneficial in certain circumstances. Unpublished observations in our intensive care unit showed in 62 patients with CIP no influence on dosage and duration of those medications on electrophysiological parameters, duration on mechanical ventilation, or duration of stay in the intensive care unit.

Occasionally, diaphragmatic weakness is caused by bilateral traumatic phrenic nerve damage due to birth trauma or operative procedures.[34] These patients have severe ventilatory insufficiency, often requiring artificial ventilation. In the absence of spontaneous recovery, either longterm ventilation or operative procedures, such as autologuous nerve transplantation, are necessary for longterm management.[35]

Dyspnea occurs frequently in patients with MG, either in association with other symptoms or occassionally isolated.[36-40] Respiratory failure in MG may be on the basis of the underlying disease, or a result of cholinergic excess as a consequence of treatment with acetylcholinesterase inhibitors, or even a result of denervation of the diaphragm. Apart from the failure of neuromuscular transmission, patients may also have coexistent cardiac or pulmonary disease which can cause respiratory failure. Thus, in a patient presenting with respiratory difficulties it may be difficult to clinically differentiate between these several potential causes of respiratory failure.[41,42] We studied the clinical value of repetitive electrical stimulation of the phrenic nerve in 25 patients with myasthenia gravis and compared the results to repetitive electrical stimulation of the accessory nerve. Twelve patients (48%) had abnormal decrement of diaphragmatic CMAP. Repetitive stimulation of the accessory nerve with recording of the trapezius CMAP was abnormal in 9 patients (36%). The three patients with abnormal decrement of the diaphragmatic CMAP despite normal trapezius CMAP had symptoms of dyspnea. This information is of particular therapeutic interest in MG patients with concomittent cardiopulmonary disorders and in MG patients with predominantly respiratory muscle involvement. Weakness in the respiratory muscles may also imitate the clinical appearance of MG making the diagnosis occasionally difficult. Those patients are in danger of being admitted to intensive care unit because of unknown respiratory failure. The clinical value of repetitive phrenic nerve stimulation was also demonstrated in the management of patients with Lambert-Eaton myasthenic syndrome.[43] Hence, this technique should be part of electrophysiology in patients with undiagnosed respiratory failure.

Causes of myopathies affecting respiratory muscles are summarized in the Table.

Electrophysiology of the Central Respiratory Pathway

Transcortical magnetic stimulation

Transcortical and cervical magnetic stimulation can assess the central respiratory drive, and is helpful in the assessment of failure to wean, which is often caused by a combination of central and peripheral nervous system disorders.[44] The optimal site for magnetic stimulation depends on the coil being used. With a circular 90 mm coil, the best responses are obtained with the coil over Cz (International 10-20 EEG system). With a 70 mm figure-of eight coil, C3 and C4 are the optimal stimulation sites.[45] Recording electrodes are positioned similiar to phrenic nerve conduction studies (see above). The latency and amplitude of the motor evoked potentials (MEPs) are compared with that obtained by cervical magnetic stimulation and direct phrenic nerve stimulation (Figure 2). The parameters of magnetic stimulation studies that can be analyzed are: diaphragmatic motor threshold (the lowest stimulator output that evoke three or more responses in a six trials), MEP latency and negative peak amplitude, central motor conduction time (cortical latency minus cervical latency), amplitude-ratio (phrenic nerve electrical stimulation versus transcortical and cervical magnetic stimulation). It can also

Table: Myopathies as Causes of Respiratory Failure.

Disease	Diagnostic Studies
Myotonic dystrophy	Electromyography, DNA studies
Muscular dystrophy	Muscle biopsy
Polymyositis, Dermatomyositis	Blood CK, Muscle biopsy
Thick filament myopathy	Blood CK, Muscle biopsy
Glycogen storage diseases:	
Pompe's disease	PAS stain of blood film, muscle biopsy and enzyme assay
McArdle disease	PAS, ischemic exercise test, muscle biopsy and enzyme assay
Tarui's disease	PAS, muscle biopsy and enzyme assay
Acute rhabdomyolysis	Electromyography, blood CK
Hypokalaemia	Blood potassium
Hypophosphataemia	Blood phosphate
Mitochondrial myopathy	Blood and CSF lactate, muscle biopsy, mitochondrial and DNA analysis
Nemaline myopathy	Muscle biopsy

Abbreviations:
CK: Creatinine kinase
PAS: Periodic acid Schiffs stain

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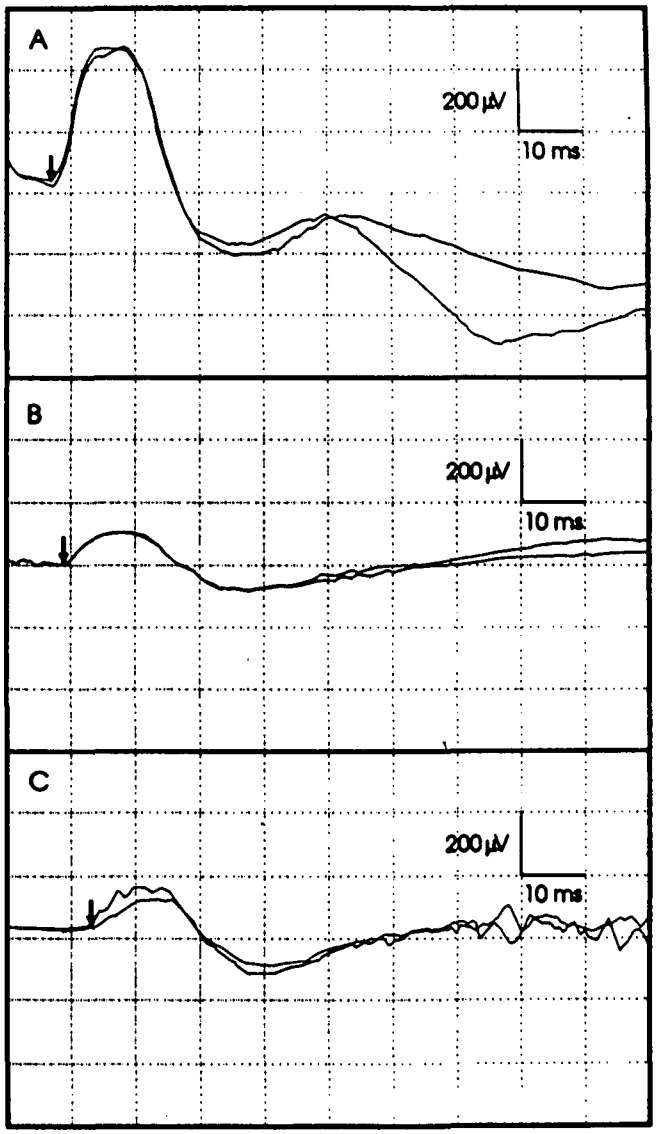

Figure 2: Electrical phrenic nerve (A), cervical magnetic stimulation (B), and transcortical magnetic stimulation in a healthy subject. (With permission, Zifko.[45])

detect unilateral central respiratory dysfunction, and is useful in determining the prognosis of respiratory insufficiency. In patients with central respiratory disorders, transcortical magnetic stimulation studies will likely be abnormal while cervical magnetic stimulation and phrenic nerve conduction studies will be normal.[45]

Phrenic nerve somatosensory evoked potentials

A new technique of recording phrenic nerve SEPs with 2 Hz stimulation of the phrenic nerve at the neck has been developed.[46] The optimal recording site is CP3, determined by the modified 10-20 EEG system, as the active electrode and Fz as the reference electrode (Figure 3). In normal subjects, the first positive wave (P1) occurs at about 12 msec and the first negative wave (N1) occurs at about 17 msec. The peak to peak amplitude ranges from 0.3-0.6 µV. Phrenic nerve SEP provides a new method of assessing the phrenic sensory fibers and its central projections.[47] Its utility in investigation of respiratory failure in the intensive care unit remains to be determined.

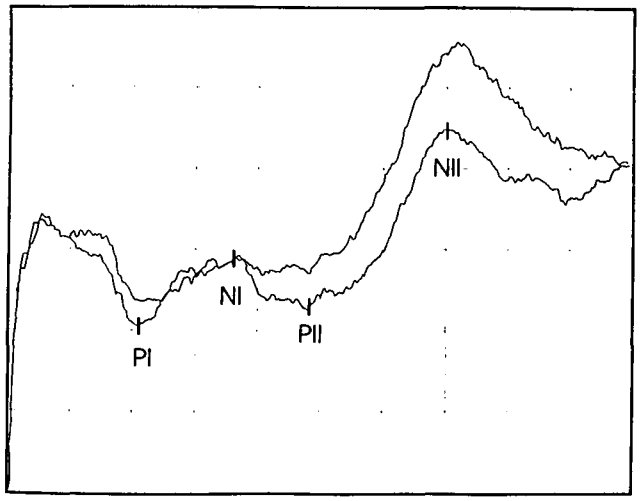

Figure 3: Stimulation of the right phrenic nerve and recording with needle electrodes over CP3 and reference over Fz (5 ms/div and 0.62 µV/div) in a healthy subject. The vertical bars indicate when the main components occurred. (With permission, Zifko.[46])

Clinical implications of central respiratory electrophysiology

Disorders of the central nervous system leading to respiratory failure include metabolic encephalopathies, acute stroke, lesions of the motor cortex and brainstem respiratory centers, and their descending pathways. Metabolic encephalopathies with impaired level of consciousness frequently contribute to prolonged ventilator dependency.[1,48] There may be flaccid quadriparesis and hyporeflexia in the acute stage of encephalopathy, making the differentiation from neuromuscular causes of respiratory failure difficult.

Central and peripheral respiratory electrophysiological studies are also helpful in diagnosing and managing patients with myotonic dystrophy and dyspnea.[49] Transcortical magnetic stimulation with recording of the diaphragm showed abnormalities of the central respiratory drive in 20% of patients with myotonic dystrophy. Patients with abnormal respiratory electrophysiological parameters also had significantly lower functional vital capacity.

Respiratory complications are common in advanced multiple sclerosis and may occur in acute relapses.[50] Respiratory failure may be due to respiratory muscle weakness, bulbar weakness, impaired voluntary control or impaired automatic control.[50,51] Assisted ventilation is often necessary and many patients can be later weaned from the ventilator.[51]

Lesions of the spinal cord may disrupt the descending pathways or the lower motor neuron at the segmental levels. The lesion can usually be localized with clinical examination and neuroimaging findings. Electrophysiological studies are helpful in determining its severity and prognosis. We observed in a patient with high cervical spinal cord infarction an absent diaphragmatic response to transcortical magnetic stimulation at the early stage of the disease. Despite improvement of magnetic stimulation studies the patient could not be weaned from the ventilator. Phrenic nerve and limb nerve conduction studies at that time indicated the development of CIP. This observation

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demonstrates the value of central and peripheral electrophysiological studies in localizing the site of neurological causes of respiratory failure.[52]

Respiratory failure is common in the advanced stages of motor neuron disease and is the major cause of mortality. Early deterioration in respiratory function is usually gradual, with an accelerated decline in the 12-15 months preceding death.[53] Electrophysiological and pathological studies in these patients suggest that ventilatory failure is due to diaphragmatic weakness from degeneration of phrenic motoneurons, with only minimal upper motor neuron involvement.[54]

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References

1. Kelly BJ, Matthay MA. Prevalence and severity of neurologic dysfunction in critically ill patients: influence on need for continued mechanical ventilation. Chest 1993; 104: 1818-1824.
2. Zifko UA, Chen R. The respiratory system. *In*: Bolton CF, Young GB, eds. Bailiere's Clinical Neurology. Bailliere Tindall, 1996; 5: 477-495.
3. Plum F, Posner JB. The Diagnosis of Stupor and Coma. Philadelphia: F.A Davis Company, 1980.
4. Hughes RAC, Bihari D. Acute neuromuscular respiratory paralysis. J Neurol Neurosurg Psychiatry 1993; 56: 334-343.
5. Newsom-Davis J. Phrenic nerve conduction in man. J Neurol Neurosurg Psychiatry 1967; 30: 420-426.
6. Bolton CF. Clinical neurophysiology of the respiratory system. Muscle Nerve 1993; 16: 809–818.
7. Chen R, Collins S, Remtulla H, Parkes A, Bolton CF. Phrenic nerve conduction study in normal subjects. Muscle Nerve 1995; 18: 330-335.
8. Zifko U, Auinger M, Albrecht G, et al. Phrenic neuropathy in chronic renal failure. Thorax 1995; 50: 793-794.
9. Zifko U, Chen R, Remulla H, et al. Respiratory electrophysiologic studies of the diaphragm in Guillain Barre syndrome. J Neurol Neurosurg Psychiatry 1996; 60: 191-194.
10. Similowski T, Mehirir S, Duguet A, et al. Comparision of magnetic and electrical phrenic nerve stimulation in assessment of phrenic nerve conduction time. J Appl Physiol 1997; 82(4): 1190-1199.
11. Chokroverty S, Deutsch A, Chandralekha G, et al. Thoracic spinal nerve and root conduction: a magnetic stimulation study. Muscle Nerve 1995; 18: 987-991.
12. Mier A, Brophy C, Moxham J, Green M. Repetitive stimulations of phrenic nerves in myasthenia gravis. Thorax 1992; 47: 640-644.
13. Zifko UA, Nicholle MW, Remtulla H, Bolton CF. Repetitive phrenic nerve stimulation study in healthy subjects. J Clin Neurophysiol 1997; 14: 235-241.
14. Bolton CF, Grand'Maison F, Parkes A, Shrkum M. Needle electromyography of the diaphragm. Muscle Nerve 1992; 15: 678-681.
15. Collins SJ, Chen R, Remtulla H, Parkes A, Bolton CF. Novel parameters for automated electromyographic interference pattern analysis of the diaphragm: results in normal subjects. Muscle Nerve 1994; 17: 1115-1116.
16. Chen R, Collins SJ, Remtulla H, Power K, Bolton CF. Needle EMG of the human diaphragm: power spectral analysis in normal subjects. Muscle Nerve 1996; 19: 324-330.
17. Bolton CF. Sepsis and the systemic inflammatory response syndrome: neuromuscular manifestations. Crit Care Med 1996; 24: 1408-1416.
18. Tran DD, Groeneveld ABJ, van der Meuien J, et al. Age, chronic disease, sepsis, organ system failure, and mortality in a medical intensive care unit. Crit Care Med 1990; 18: 474-479.
19. Witt NJ, Zochodne DW, Bolton CF, et al. Peripheral nerve function in sepsis and multiple organ failure. Chest 1991; 99: 176-184.
20. Zochodne DW, Bolton CF, Wells G, et al. Critical illness polyneuropathy: a complication of sepsis and multiple organ failure. Brain 1987; 110: 819-842.
21. Leijten FSS, De Weerd AW. Critical illness polyneuropathy: a review of the literature, definition and pathophysiology. Clin Neurol Neurosurg 1994; 96: 10-19.
22. Wijdicks EF, Litchy WJ, Harrison BA, et al. The clinical spectrum of critical illness polyneuropathy. Mayo Clin Proc 1994; 69: 955-959.
23. Gorson KC, Ropper AH. Acute respiratory failure neuropathy: a variant of critical illness polyneuropathy. Crit Care Med 1993; 21: 267-271.
24. Hund EF, Fogel W, Krieger D, et al. Critical illness polyneuropathy: clinical findings and outcomes of a frequent cause of neuromuscular weaning failure. Crit Care Med 1996; 24: 1328-1333.
25. Berek K, Margreiter J, Willeit J, et al. Polyneuropathies in critically ill patients: a prospective evaluation. Intensive Care Med 1996; 22: 849-855.
26. Leijten FAA, De Weerd AW, et al. Critical illness polyneuropathy in multiple organ dysfunction syndrome and weaning from the ventilator. Intensive Care Med 1996; 22: 856-861.
27. Maher J, Rutledge F, Remtulla H, et al. Neuromuscular disorders associated with failure to wean from the ventilator. Intensive Care Med 1995; 21: 737-743.
28. Op de Coul AAW, Verheul GAM, Leyten ACM, et al. Critical illness polyneuromyopathy after artificial respiration. Clin Neurol Neurosurg 1991; 93: 27-33.
29. Hirano M, Ott BR, Raps EC. Acute quadriplegic myopathy: complication of treatment with steroids, nondepolarizing blocking agents, or both. Neurology 1992; 42: 2082-2087.
30. Lacomis D, Giuliani M, Van Cott A, Kramer DJ. Acute myopathy of intensive care: clinical, electromyographic, and pathological aspects. Am Neurol Assoc 1996; 40: 645-654.
31. Latronico N, Flavio F, Daniela R, et al. Critical illness myopathy and neuropathy. Lancet 1996; 347: 1579-1582.
32. Barohn RJ, Jackson CE, Rogers SJ, et al. Prolonged paralysis due to nondepolarizing neuromuscular blocking agents and corticosteroids. Muscle Nerve 1994; 17: 647-654.
33. Giostra E, Magistris Mri, Pizzolato G, et al. Neuromuscular disorders in intensive care unit patients treated with pancuronium bromide. Chest 1994; 106: 210-220.
34. Zifko U, Hartmann M, Girsch W, et al. Diagnostic and therapeutic advances in birth traumatic phrenic nerve injury. Can J Neurol Sci 1995; 22: S23.
35. Zifko U, Hartmann M, Gitsch W, et al. Diaphragmatic paresis in newborns due to phrenic nerve birth injury. Neuropediatrics 1995; 26:281-284.
36. Gracey DR, Southorn PA. Respiratory failure in Lambert Eaton myasthenic syndrome. Chest 1987; 91: 716-718.
37. O'Neill JH, Murry MMF, Newsom Davis J. The Lambert Eaton Myasthenic syndrome. Brain 1988; 111: 577-596.
38. Maher J, Bolton CF, Grand'Maison F, Strong M. Diagnostic difficulties in myasthenia gravis. Can J Neurol Sci 1995; 22: 51.
39. Barr WC, Claussen G, Thomas D, et al. Primary respiratory failure as the presenting symptom in Lambert Eaton myasthenic syndrome. Muscle Nerve 1993; 16: 712-715.
40. Beydoun SR. Delayed diagnosis of Lambert-Eaton myasthenic syndrome in a patient presenting with recurrent refractory respiratory failure. Muscle Nerve 1994; 17: 689- 690.
41. Mier A, Laroche C, Green M. Unsuspected myasthenia gravis presenting as respiratory failure. Thorax 1990; 45: 422-423.
42. Hopkins. *In*: Sanders DB, ed. Myasthenia gravis and myasthenic syndromes. Philadelphia: W.B. Saunders Company, 1994: 243-261.
43. Nicolle MW, Stewart DJ, Remtulla H, Chen R, Bolton CF. Lambert-Eaton myasthenic syndrome presenting with severe respiratory failure. Muscle Nerve 1996; 19: 1328-1333.
44. Zifko UA. Die Elektrophysiologie der Atmung. Nervenarzt 1997; *in press*.

45. Zifko UA, Remtulla H, Power K, Harker L, Bolton CF. Transcortical and cervical magnetic stimulation with recording of the diaphragm. Muscle Nerve 1996; 19: 614-620.
46. Zifko UA, Young GB, Remtulla H, Bolton CF. Somatosensory evoked potentials of the phrenic nerve. Muscle Nerve 1995; 18: 1487-1489.
47. Zifko UA, Slomka PJ, Reid RH, et al. The cortical representation of somatosensory evoked potentials of the phrenic nerve. J Neurol Sci 1996; 139: 197-202.
48. Young GB, Bolton CF, Austin TW, et al. The encephalopathy associated with septic illness. Clin Invest Med 1990; 13: 297-304.
49. Zifko UA, Hahn AF, George CFP, et al. Central and peripheral respiratory electrophysiologic studies in myotonic dystrophy. Brain 1996; 119: 1911-1922.
50. Garland SJ, Lavoie BA, Brown WF. Motor control of the diaphragm in multiple sclerosis. Muscle Nerve 1996; 19: 654-656.
51. Howard RS, Wiles CM, Hirsch NP, et al. Respiratory involvement in multiple sclerosis. Brain 1992; 115: 479-494.
52. Zifko UA, Young GB, Bolton CF. Electrophysiological monitoring in neurological respiratory insufficiency. J Neurol Neurosurg Psychiatry 1997; 61: 329-330.
53. Braun SR. Respiratory system in amyotrophic lateral sclerosis. Neurol Clinics 1987; 5: 9-31.
54. Chen R, Grand'Maison F, Strong MJ, Ramsay DA, Bolton CF. Motor neuron disease presenting as acute respiratory failure: a clinical and pathological study. J Neurol Neurosurg Psychiatry 1996; 60: 445-458.