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Magnetic stimulation for the measurement of respiratory and skeletal muscle function

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Magnetic stimulation for the measurement of respiratory and skeletal muscle function. W.D-C. Man, J. Moxham, M.I. Polkey. ©ERS Journals Ltd 2004.
ABSTRACT: Respiratory and skeletal muscle function is of interest in many areas of pulmonary and critical care medicine. The capacity of the respiratory muscle pump to respond to the load imposed by disease is the basis of an understanding of ventilatory failure. Over the last four decades, considerable progress has been made in quantifying the capacity of the respiratory muscles, in terms of strength, endurance and fatigue. With the development of magnetic stimulation, it has recently become possible to nonvolitionally assess the respiratory muscles in a clinically acceptable way. This is of particular interest in the investigation of patients receiving critical care, those with neuromuscular disease, and in children where volitional efforts are either not possible or likely to be sub-maximal. Furthermore, the adaptation of these techniques to quantify the strength of peripheral muscles, such as the quadriceps, has allowed the effects of muscle training or rehabilitation, uninfluenced by learning effect, to be assessed. This article focuses on the physiological basis of magnetic nerve stimulation, and reviews how the technique has been applied to measure muscle strength and fatigue, with particular emphasis upon the diaphragm. The translation of magnetic stimulation into a clinical tool is described, and how it may be of diagnostic, prognostic and therapeutic value in several areas of pulmonary medicine. In particular, the use of magnetic stimulation in neuromuscular disease, the intensive care setting, chronic obstructive pulmonary disease and paediatrics will be discussed.
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The nonvolitional assessment of skeletal muscles

For routine muscle strength measurements, the force generated from a maximum voluntary contraction (MVC) is often used. However volitional, effort-dependent manoeuvres for measuring strength are not always suitable for patients as the ability to perform a true MVC relies upon subject motivation and cooperation. This is particularly so in patients on intensive care units (ICU), children, patients with cognitive difficulties, and those patients prevented from performing a true MVC by pain (for example, following surgery). However, even in well-motivated subjects, sub-maximal muscle activation is common in routine clinical practice [1]. As volitional manoeuvres are influenced by a learning effect, the value of MVC is also limited in studies of training or rehabilitation. Consequently, there has been a need for nonvolitional methods to assess muscle strength.

Skeletal muscle physiology

Skeletal muscle is controlled by electrical impulses conducted by motor neurones that lead to the release of acetylcholine from the motor end plate, thus depolarising the muscle cell membrane. The force generated by muscle contraction is dependent upon a number of factors, including the number of muscle fibres stimulated, muscle length at the time of stimulation and the frequency of stimulation. The force-frequency curve of a muscle is of particular relevance in the understanding of nonvolitional techniques to assess muscle strength. A single impulse conducted by the nerve will result in a twitch contraction and subsequent relaxation. If further stimuli are conducted before full relaxation occurs, a tension greater than the single twitch is produced [2]. If stimulation frequency is further increased, the maximum tetanic tension is eventually obtained, which is the true strength of the muscle. The graph of tension plotted against stimulation frequency is the force-frequency curve (fig. 1). Construction of the force-frequency curve is neither practical nor tolerable in the clinical arena. Hence, techniques using single supramaximal stimulation of the nerve have been developed. Supramaximality implies that a further increase in stimulus intensity does not result in a further increase in tension. The tension generated then enjoys a constant relationship with maximal tetanic tension. For the human diaphragm, the ratio of the single twitch to MVC is 0.23–0.24 [3, 4]. The implication of the force-length relationship is that muscle fibres produce less force at shorter or longer lengths than the optimum length [5]. This is of clinical relevance, particularly with regards to the diaphragm, as changes in lung

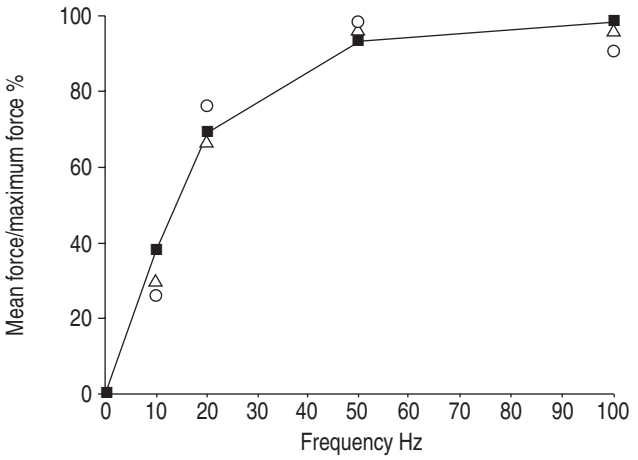

Fig. 1. – Force-frequency curve of the diaphragm (■), quadriceps (○) and adductor pollicis (△) from three healthy subjects repeated three times (J. Moxham, Respiratory Muscle Laboratory, Guy's, King's and St Thomas Hospital, London, UK, personal communication).

volume (specifically, hyperinflation) can reduce diaphragm length and alter diaphragm configuration, with a subsequent loss in diaphragm pressure-generating capacity [6].

Skeletal muscle fatigue

Fatigue of skeletal muscle is defined as the loss of force-generating capacity resulting from activity under load that is reversible by rest [7]. Of particular clinical interest is low frequency fatigue (LFF), which results in loss of force generated in response to low-frequency stimulation (10–20 Hz), the typical motor neurone firing frequencies during human skeletal muscle contractions [8, 9]. LFF results in a right shift of the force-frequency curve. Tetanic stimulation is often impractical and not tolerable to patients. An acceptable alternative is therefore to measure the pressure or tension elicited from a single supramaximal stimulus, since a right shift of the force-frequency curve reflects the reduced single twitch amplitude [10].

Electrical *versus* magnetic stimulation

It has long been known that externally applied electrical currents, through surface, needle, or implanted electrodes, can stimulate nerves. Although electrical stimulation techniques have been described for several muscles, these have not been adopted for routine clinical assessment of muscle strength due to the discomfort, poor reproducibility and difficulty in reliably achieving supramaximality [11–13]. From a patient's perspective the most significant disadvantage is discomfort. Nerve trunk stimulation using surface electrodes requires currents flowing in the skin to be higher than in the vicinity of the nerve. To ensure supramaximality, the electrical stimulus is often large enough to stimulate sensory nerve endings in the skin, thus causing pain. Alternatives to surface electrodes include needle electrodes or implantable electrodes close to the nerve trunk; however, the invasiveness of these techniques (as well as the small risk of trauma, bleeding or infection) preclude widespread clinical use outside the specialist laboratory setting. In contrast, magnetic stimulation can ensure nerve trunk stimulation without inducing high currents in the skin. Furthermore, the wider field of stimulation means that it is technically easier to perform, requiring less trial stimulations to confirm supramaximality, and therefore more suitable for clinical purposes.

Historical perspective of magnetic stimulation

Electromagnetic induction, first described by Faraday in 1831, forms the underlying scientific principle of magnetic stimulation. Faraday wound two coils of wire around an iron ring, and demonstrated that whenever one coil was connected or disconnected from a battery source, an electrical current flowed briefly through the second coil. Although the presence of the iron ring enhanced induction, Faraday found this not to be essential, and later demonstrated electromagnetic induction with two coils closely positioned in air. The ability of magnetic fields to stimulate nervous tissue was first demonstrated in 1896 when D'Arsonval [14] reported flickering lights in the visual fields, probably *via* direct stimulation of the retina, after placing his head between two coils driven by an alternating 110-volt supply at 30 amperes. However, it was not until 1982 that Polson *et al.* [15] produced a magnetic stimulator capable of peripheral nerve stimulation, and not until 1985 that Barker *et al.* [16] first described magnetic stimulation of the human motor cortex. Since then, there has been rapid progress, and transcranial magnetic stimulation is extensively used in clinical neurophysiology in the investigation of the central nervous system. In comparison, despite magnetic stimulation of the phrenic nerves being first described in 1989 [17], the technique remains rarely used in respiratory and critical care medicine outside the research laboratory setting. Over the last decade, increasing data suggests that magnetic stimulation may have clinical value in the measurement and monitoring of respiratory and peripheral muscle function.

Principles of magnetic stimulation

The aim of both electrical and magnetic stimulation is to cause current to flow in nervous tissue, resulting in depolarisation of the nerve cell membrane and the initiation of an action potential. Magnetic stimulation creates intense, rapidly changing magnetic fields that are able to penetrate clothing, soft tissue and bone, to reach deep nervous structures. These magnetic pulses produce electrical fields, and if the induced current is of sufficient amplitude and duration such that depolarisation occurs, neural tissue will be stimulated in a similar manner to conventional electrical stimulation. Thus, the magnetic field is simply the means by which the electrical current is generated, and does not itself directly cause depolarisation of cell membranes. Importantly, the magnetic fields preferentially activate larger fibres, so avoiding the smaller fibres that mediate pain [18].

Equipment

Several magnetic nerve stimulators are commercially available. Figure 2 is a schematic representation of a magnetic stimulator, which typically consists of two important components: a high current pulse generator unit (of which the most important component is the capacitor) and a stimulating coil. The capacitor is charged by a transformer under microprocessor control, with the operator able to adjust the power level. An electronic switch connects the capacitor to the

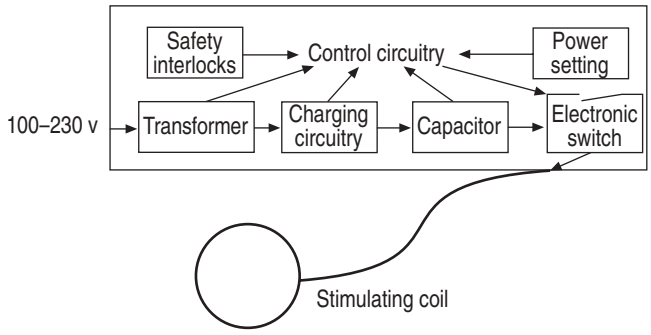

Fig. 2. – Schematic diagram of a magnetic stimulator.

stimulating coil, allowing the operator to apply the stimulus at the required time.

The stimulating coil consists of windings of well-insulated copper wire tightly wound with safety switches and temperature sensors. Although coils may be custom-designed and in a range of shapes and sizes, they are generally circular or double circular, allowing them to be conveniently positioned over many parts of the body. However, the precise site of stimulation is uncertain as the induced tissue lies under the coil windings, rather than the coil centre [18]. Recently, in an attempt to focus the stimulation, figure-of-eight coils (also known as double or butterfly coils) have been developed. These, as the name suggests, consist of two circular coils placed side by side, and connected in such a manner that current from the stimulator in one coil rotates in the opposite direction to the other. With this arrangement, the maximum induced tissue current is directly under the point where the two coils meet, giving a more focused point of stimulation [18]. The biophysics of the induced electrical field and the depth of penetration are dependent on many factors, including the intensity of the applied stimulus, coil design, coil geometry and anatomical features. A comprehensive review of these factors is beyond the scope of this article, but the reader is referred to a recent publication of these matters [18].

Safety aspects

From the start of human work with magnetic stimulation, there have been concerns about potential side-effects. This is particularly relevant for repetitive transcranial magnetic stimulation; very few untoward incidents or side-effects have been reported with single magnetic stimuli [19], although certain precautions should be taken. Researchers have failed to induce cardiac arrhythmias by direct magnetic stimulation over the heart, but the induced currents are easily sufficient to damage cardiac pacemakers [18]. Another contraindication is the presence of metallic objects within the field during the impulse; in particular, the presence of shrapnel, aneurysm clips or cochlear implants must be noted [20]. The authors' practice is to avoid magnetic stimulation during pregnancy, although no evidence exists to justify this view. Another theoretical problem is acoustic damage from the noise generated when the windings move as current is discharged into the coil. Studies in rabbits have shown permanent threshold shifts due to cochlear hair cell damage [21]. However, no evidence of acoustic damage has been found in humans, even in subjects repeatedly exposed to magnetic stimulation for many years [22]. Nevertheless, ear protectors may be prudent in subjects undertaking repeated studies.

Magnetic stimulation and the inspiratory muscles

The diaphragm is the principal muscle of inspiration, accounting for ~70% of minute ventilation in humans [23]. It is the only inspiratory muscle for which specific force output can be quantified (by measuring transdiaphragmatic pressure (Pdi)). Each hemidiaphragm is supplied by a phrenic nerve arising principally from C4, and to a lesser extent C3 and C5. The nerves run down the mediastinum, to the borders of the heart and thence into the diaphragm muscle. The surface stimulation point of the phrenic nerve is generally located just beneath the posterior border of the sternomastoid muscle at the level of the cricoid cartilage.

Electrical stimulation of the phrenic nerve was first described in 1819 [24], but there are several problems with using it for the measurement of diaphragm strength. First, it may not be possible to locate the nerve; secondly, there may be difficulty in being confident of supramaximality of the Pdi response. This is made doubly difficult by requiring maximal symmetrical stimulation of the phrenic nerves to obtain a bilateral Pdi. Thirdly, whilst locating the nerves, repetitive stimulation may be required, which can increase the twitch pressure by the phenomenon of potentiation (see below). Fourthly, in order to achieve optimal contact between the stimulating electrode and the nerve, it may be necessary to apply pressure on the neck, which can be painful for the patient. Furthermore, as mentioned previously, the intensity of the stimulus required to achieve supramaximality may itself activate skin pain fibres. Finally, in the critical care setting, where oedema and in-dwelling neck catheters are often present, it may simply be impossible to position the stimulating electrodes near the phrenic nerves. Although there are several laboratory studies that have measured Pdi during electrical stimulation [12, 25–28], the technique is, in general, not sufficiently accurate for clinical purposes. MIER *et al.* [12] obtained normal values of between 8 and 33 cmH_2O, with significant overlap between control subjects and patients with weakness, and the test discriminated only patients with very severe diaphragm weakness or paralysis.

There are three options available for magnetic phrenic nerve stimulation: cervical magnetic stimulation (CMS), anterior pre-sternal magnetic stimulation (aMS) and unilateral/bilateral anterolateral stimulation (UMS/BAMPS). These techniques are illustrated in figure 3. Before a description of these techniques, a brief discussion of what variables are measured during phrenic nerve stimulation is necessary.

Diaphragm muscle and phrenic nerve function can be assessed either as a pressure or an electromyographic (EMG) response. The function of the diaphragm is to lower intrathoracic pressure, and to raise intra-abdominal pressure. Intrathoracic pressure can be measured from a pressure catheter placed in the mid-lower oesophagus (Poes), whilst intra-abdominal pressure can be assessed from the gastric pressure measured using a catheter placed in the stomach (Pga). Previous studies have confirmed that Poes and Pga are valid measurements by comparing them with directly measured pleural and abdominal pressures [29, 30]. Pdi is the arithmetic difference between Pga and Poes, and has become the "gold standard" for assessing diaphragm contractility. The disadvantage of Pdi is the invasiveness of the technique. This is not a problem in sedated patients, and, in our experience, over 90% of nonsedated outpatients tolerate the pressure catheters well. However, it is clear that whilst advances have been made in phrenic nerve stimulation, the same advances have not been made in measuring diaphragmatic pressure. This is a priority area if magnetic stimulation is to become widely adopted in clinical practice. A noninvasive alternative is the measurement of mouth pressure (Pmo) or endotracheal

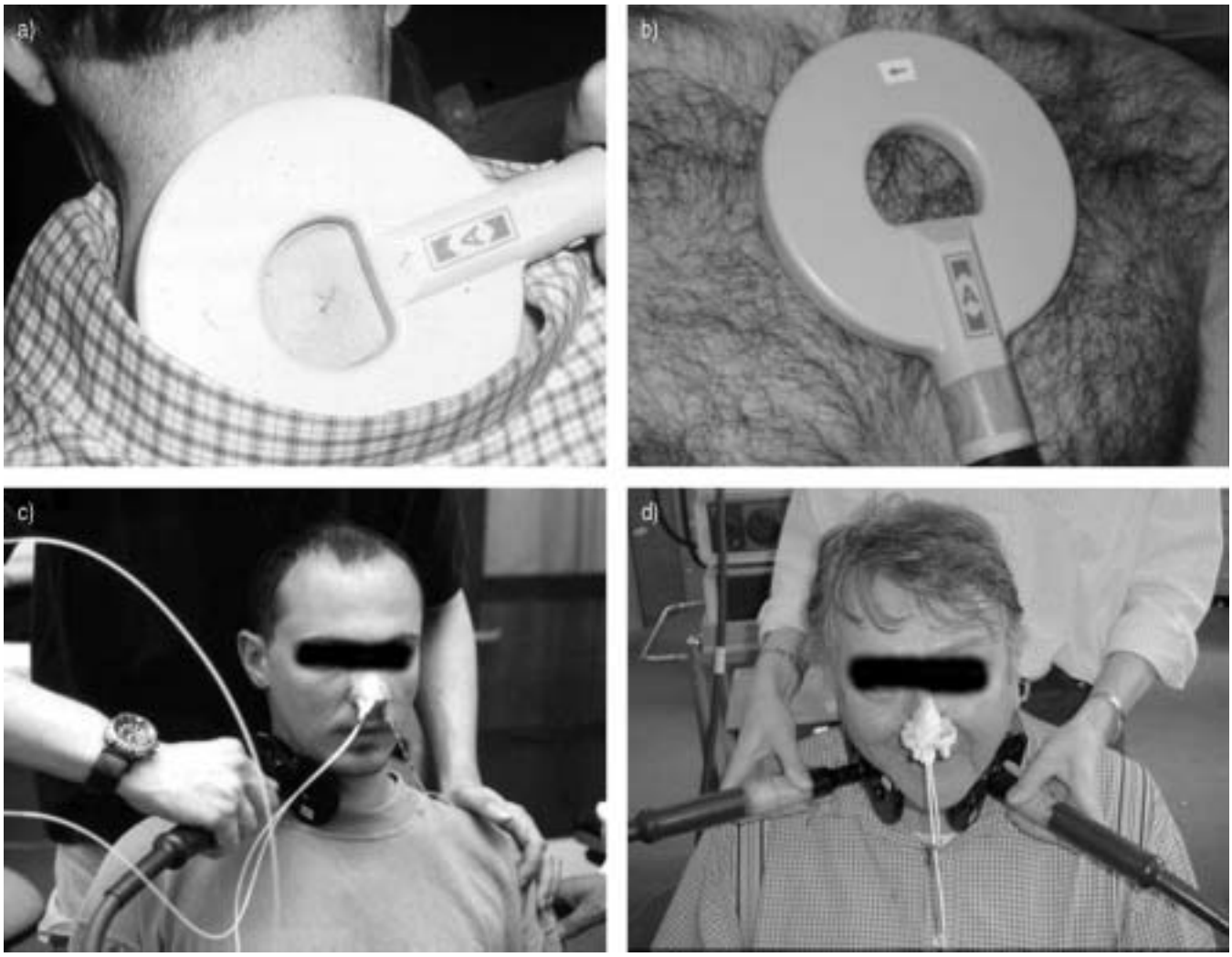

Fig. 3. – Magnetic stimulation techniques to stimulate the phrenic nerves: a) cervical magnetic stimulation, b) anterior magnetic stimulation, c) unilateral phrenic nerve stimulation, and d) bilateral anterolateral magnetic stimulation.

tube pressure (Pett). Theoretically Pmo should accurately reflect Poes following diaphragm contraction, provided there is adequate transmission of alveolar pressure to the airways opening. However, glottic closure is a problem, and controversy remains over how well twitch mouth pressure (Pmo,tw) reflects twitch oesophagus pressure (Poes,tw) or twitch transdiaphragmatic pressure (Pdi,tw), even in healthy subjects [31–33]. Certainly, in patients with chronic obstructive pulmonary disease (COPD), the increased airway time constant leads to a dampened and delayed Pmo,tw compared with Poes,tw [34]. Pmo,tw is harder to measure accurately in patients with reduced Pdi,tw due to the larger noise-to-signal ratio. Nevertheless, a Pmo,tw more negative than -11 cmH_2O can be considered normal [32].

The EMG response to phrenic nerve stimulation is the diaphragm compound muscle action potential (CMAPdi). This represents the summated electrical activity produced by all motor units synchronously activated. Of interest is the amplitude of the CMAPdi, and the latency, a representation of the phrenic nerve conduction time (PNCT). Generally, demyelinating lesions (*e.g.* Guillain Barre syndrome) lead to a prolonged PNCT, whilst axonal and traumatic neuropathies are associated with near normal PNCT but a reduced CMAPdi. The absence of a CMAPdi following phrenic nerve stimulation occurs in diaphragm paralysis [35], but may occur with a normally functioning diaphragm if there are technical recording problems. Presence of a normal CMAPdi with phrenic nerve stimulation in the absence of a CMAPdi following cortical stimulation has been used to identify spinal cord injury patients suitable for phrenic nerve pacing [36]. The CMAPdi amplitude, when taken in conjunction with the Pdi,tw, can also be used to distinguish between peripheral contractile failure (normal CMAPdi amplitude, reduced Pdi,tw) and neural or neuromuscular transmission defects (both CMAPdi and Pdi,tw reduced) [37].

The EMG can be recorded with surface, intramuscular needle or oesophageal electrodes. Most clinical studies have been performed with surface electrodes due to the ease of application and their noninvasive nature. Electrodes are usually applied to the skin over the costal diaphragm in the intercostal spaces level with the xiphisternum between the midline and the midclavicular line [38]. The disadvantage is that surface electrodes may record potentials from extra-diaphragmatic muscles, resulting in signal contamination; this may be a particular problem when there is co-activation of the brachial plexus [39] or when using some magnetic stimulation techniques [40]. Furthermore, variations in body habitus, such as subcutaneous fat or chest wall deformity, can lead to variable attenuation of the signals. Consequently, whilst normal values for PNCT following electrical or magnetic

stimulation are available with surface electrodes and are similar, no such data exist for CMA*P*di amplitude.

Intramuscular needle electrodes avoid the problem of muscle cross-talk and the filtering effects of body habitus. Additionally, apart from recording potentials following nerve stimulation, needle electrodes can be used to examine the spontaneous activity of the diaphragm [41, 42]. The disadvantage is that needle electrodes only sample the portion of the diaphragm into which they are inserted. Widespread clinical application is also unlikely given that it is relatively difficult to place the electrodes, painful for the subject, and there is a small risk of pneumothorax, as well as the usual minor bleeding and bruising associated with tissue penetration.

A compromise solution is to use oesophageal electrodes. These are metal rings mounted on a catheter (fig. 4) that is passed *via* the nose into the lower oesophagus [43]. The crural diaphragm encircles the lower oesophagus; in adults, the electrically active region of the crural diaphragm lies 1–3 cm above the gastro-oesophageal junction [44]. Like needle electrodes, oesophageal electrodes are invasive, but the discomfort of pernasal passage is relatively minor. The signals obtained are relatively free of muscle cross-talk, and are not affected by body habitus.

Whilst theoretically the EMG obtained from the crural diaphragm may not be representative of the muscle as a whole, there is no evidence to suggest that there is any costal-crural dissociation in humans [45]. Normal values for PNCT and CMA*P*di amplitude have been published using oesophageal electrodes and magnetic stimulation [46], albeit in small numbers of young volunteers. Despite the advantages of oesophageal EMG, the technique has been little used in research or clinical practice, principally because a lack of consensus over catheter design and the nonavailability of a commercial device.

Cervical magnetic stimulation

CMS was the first technique described for magnetically stimulating the phrenic nerves in humans [17]. The subject, seated comfortably, flexes the neck slightly, whilst a 90-mm circular coil is applied over the back of the neck, centred approximately over the spinous process of the seventh cervical vertebra (fig. 3a). The optimal coil position may vary depending on anatomical factors, and it is usual to monitor pressures whilst stimulating at slightly higher and lower positions along the midline of the neck. Although it is generally thought that CMS leads to diaphragm contraction *via* stimulation of the cervical phrenic nerve roots, some investigators have argued that the field passes through the neck and stimulates the phrenic nerves anteriorly at a point more distal than electrical stimulation [47].

CMS is not painful, and provides an easy method to stimulate the phrenic nerves bilaterally with only one stimulator. As the best described method, and due to the relative ease of the technique, CMS has been used in the majority of clinical studies, and normal values have been published for both the young and elderly [4, 17, 48–50]. The principal limitation of the technique is that there is co-activation of extra-diaphragmatic muscles innervated by the cervical roots and the brachial plexus. This can influence both *P*di,tw and electromyogram measurements. *P*di,tw elicited by CMS is often greater than bilateral supramaximal transcutaneous electrical stimulation [48, 49, 51], and the PNCT may be erroneously short due to recording potentials from extra-diaphragmatic muscles, especially when using surface electrodes [40]. A further limitation is that the technique is performed with the subject sitting with the neck flexed; this is not possible in patients required to be supine, for example, those in intensive care.

Fig. 4. – A multi-electrode oesophageal catheter designed to record crural diaphragm electromyographic response.

Anterior pre-sternal magnetic stimulation

This technique was designed to elicit bilateral diaphragm contraction in supine patients, particularly those mechanically ventilated [52]. A circular 90-mm stimulating coil is placed anteriorly over the sternum, with the axis of the coil coinciding with the midline (fig. 3b). It is generally positioned with the upper rim of the coil at the level of the sternal notch, but again it is best to monitor pressures whilst stimulating at slightly higher and lower positions along the midline. Like CMS, aMS requires only one stimulator, and is easy to perform. It is also applicable in supine patients when access to the neck is not possible. However, limited data currently exist for normal subjects. POLKEY *et al.* [52] demonstrated that *P*di,tw values obtained with aMS approached those of bilateral supramaximal electrical stimulation, but supramaximality could not be demonstrated. It also probably activates extra-diaphragmatic muscles as small wave activity is commonly observed preceding the main action potential.

Unilateral/bilateral anterolateral magnetic phrenic nerve stimulation

As discussed previously, in an attempt to focus magnetic stimulation, figure-of-eight coils (also known as double or butterfly coils) have been developed. For the phrenic nerves, investigators have positioned 45mm figure-of-eight coils on the anterolateral neck, adjacent to the posterior body of the sternomastoid muscle at the level of the cricoid cartilage (fig. 3c, d).

UMS is the only magnetic technique that allows the assessment of a single hemidiaphragm *P*di,tw response, and has the significant advantage over electrical stimulation of not requiring precise localisation of the nerve. Sometimes a *P*di,tw response is not elicited with electrical stimulation due to localisation problems or the presence of a neck catheter. UMS is a simple technique that can identify unilateral phrenic nerve injury, for example iatrogenic nerve injury following surgery. Although UMS is relatively specific with regards to *P*di,tw measurements, there is a degree of cross-stimulation such that a small EMG signal can be recorded from the contralateral

hemidiaphragm. However, the PNCT recorded with UMS, particularly when using a high stimulating position [53], is close to that of electrical stimulation.

BAMPS consists of simultaneous UMS of the right and left phrenic nerves, and therefore requires two stimulators and two 45-mm figure-of-eight coils. Despite the expense and bulk of the additional equipment, BAMPS has a significant advantage over CMS and aMS in that it reliably produces a supramaximal $P_{di,tw}$ [6, 54, 55] that is closely similar to values obtained with optimal electrical stimulation. This is probably because BAMPS results in less co-activation of extradiaphragmatic muscles, demonstrated by the similar oesophageal and gastric pressure contributions to $P_{di,tw}$ observed with BAMPS and electrical stimulation [54]. Other advantages are that the technique can be applied in the supine subject, and over obstructing objects, such as neck catheters, yet still ensuring a supramaximal response [56]. In the clinical setting, BAMPS is usually the magnetic stimulation technique of choice when studying diaphragm contractility, although normal values have been principally obtained from studies of small numbers of young healthy male individuals [57].

Confounding factors

There are several factors that need to be considered when interpreting $P_{di,tw}$ as an index of diaphragm strength. Supramaximality is crucial. As mentioned previously, an important factor to consider is the effect on diaphragm length and configuration of lung volume, which is commonly altered in disease (*e.g.* COPD) or by the application of positive end-expiratory pressure. At total lung capacity $P_{oes,tw}$ is almost zero [28, 58, 59]. It is often appropriate to add a "correction factor" of 3.5–5.0 cmH_2O for every litre above predicted function residual capacity in chronically hyperinflated patients [58, 60].

For all skeletal muscles, preceding activity leads to a transient increase in twitch amplitude, a phenomenon known as potentiation. $P_{di,tw}$ has been reported to increase by up to 60% of unpotentiated values [50, 61]. This is important when assessing serial changes in $P_{di,tw}$; data suggest that the between-occasion coefficient of variation of $P_{di,tw}$ measured with BAMPS is 11% [57]. In our laboratory, a period of 20 min quiet breathing without sniffing is allowed before recording $P_{di,tw}$, and a period of at least 30 s between individual stimulations.

Most studies of phrenic nerve stimulation have been performed in the seated posture, but the supine posture makes little difference to $P_{di,tw}$ values [62], an important point using the technique in the intensive care setting. However, both abdominal binding and a recent meal increase $P_{di,tw}$ [55, 63], presumably through a change in abdominal compliance. Studies in intensive care are best performed at least 1–2 h after nasogastric feeding has been stopped, whilst in the outpatient setting, subjects should be studied with the abdomen unbound (*e.g.* belts loosened), having fasted for at least 4 h. These precautions may also reduce the theoretical risk of aspiration during the insertion of balloon catheters.

Magnetic stimulation and the expiratory muscles

The expiratory muscles are of considerable clinical importance. Weakness impairs cough, crucial in the protection against chest infection, a serious cause of morbidity and mortality in patients with respiratory and neuromuscular disease. The function of the expiratory muscles can be assessed by maximum voluntary manoeuvres, such as the maximum expiratory mouth pressure ($P_{E,max}$), with the usual limitation of ensuring a truly maximum effort. A recent study of patients referred for suspected respiratory muscle dysfunction demonstrated that >40% of patients with a $P_{E,max}$ below the lower 95% CI of values obtained from healthy volunteers had normal expiratory muscle strength [64]. Hence, a nonvolitional, clinically applicable test of expiratory muscle contractility would be a potentially useful diagnostic tool.

The principal expiratory muscles are those of the abdominal wall, and, therefore, measurement of gastric pressure (as a surrogate for abdominal pressure) during contraction of the abdominal muscles provides a quantitative measure of expiratory muscle strength. Electrical stimulation has been used in humans to stimulate the abdominal muscles [65], but is painful, and it is difficult to activate all the muscle groups at once (and hence achieve supramaximality and reproducibility); hence, the technique is unlikely to be clinically applicable. With magnetic stimulation, the field of stimulation is wider, and much, even if not all, of the abdominal musculature can be stimulated. The current authors have used a 90-mm circular coil, placed over the vertebral column and centred over the midline at approximately the level of the tenth thoracic vertebra [66–69] (fig. 5).

The stimulation is applied at functional residual capacity. Normal values of twitch gastric pressure ($P_{ga,tw}$) are sparse, but the tolerability of the method by patients suggests that it may be a valuable clinical tool in selected cases. The technique has been successfully used to demonstrate abdominal muscle fatigue [66] and weakness in patients with neuromuscular and spinal cord disorders [68, 70]. In amyotrophic lateral sclerosis (ALS), an effective cough is unlikely in patients with a $P_{ga,tw}$ of <7 cmH_2O [68].

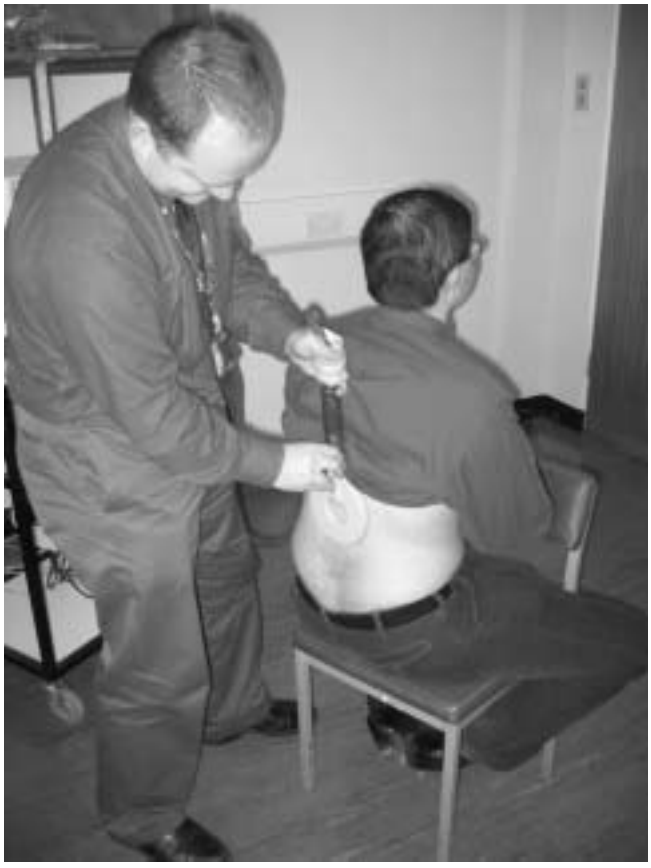

Fig. 5.–Twitch gastric pressure obtained by magnetic stimulation of the thoracic nerve roots.

Magnetic stimulation of the peripheral muscles

Peripheral muscle function is now recognised as being highly relevant in respiratory and critical care medicine. Skeletal muscle dysfunction is common in COPD [71], and contributes to reduced exercise capacity [72] and increased healthcare resource usage [73]. As advances in intensive care medicine and mechanical ventilation have led to improved survival from severe illness, it is increasingly recognised that critical care myoneuropathy is a significant problem in survivors, requiring prolonged rehabilitation. Magnetic stimulation techniques to measure force have been described for the quadriceps and adductor pollicis muscles, and these techniques are proving useful in the investigation of peripheral muscle function.

Quadriceps

The quadriceps is a primary locomotor muscle, and therefore of great functional importance to patients. Although electrical stimulation of the femoral nerve is possible, it is technically difficult, and reproducibility is poor [11]. Peripheral branches of the femoral nerve can be stimulated using flat cutaneous surface electrodes placed over the muscle, but the fraction of the muscle that is activated is variable [11].

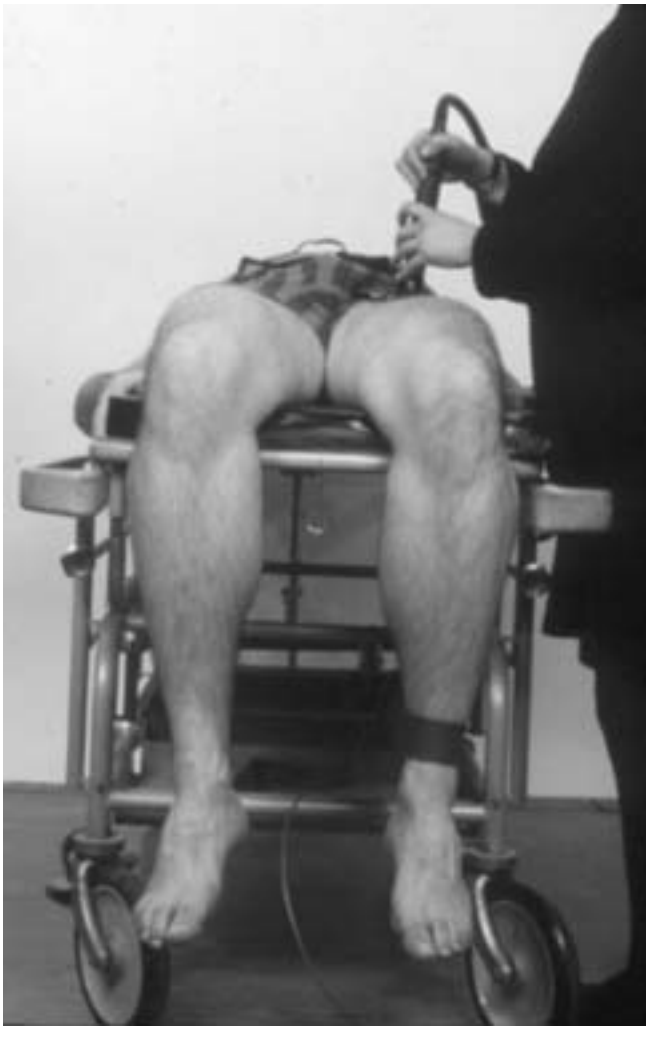

Fig. 6. – Magnetic stimulation of the femoral nerve: the twitch quadriceps technique.

POLKEY *et al.* [74] first described the technique of magnetic stimulation of the femoral nerve in 1996. The coil head is placed high in the femoral triangle, lateral to the femoral artery (fig. 6). Quadriceps force, in terms of the twitch quadriceps tension (Qtw), is measured with the knee flexed *via* an inextensible ankle strap connected to a transducer. Minor positional adjustments are made to the coil whilst simultaneously monitoring quadriceps force during stimulation to determine the optimum position. Preliminary studies with a circular 90-mm coil did not demonstrate a supramaximal response. However, using a 45-mm figure-of-eight coil, POLKEY *et al.* [74] were able to demonstrate supramaximality in 10 healthy subjects and 10 patients with suspected muscle weakness. Furthermore, in seven subjects undergoing a standard fatiguing protocol, Qtw fell to a mean of 55% of baseline values, thus demonstrating the technique could be used to detect low-frequency fatigue of the quadriceps. In obese subjects and those unable to lie completely flat, it is occasionally not possible to achieve supramaximal stimulation with this technique, and the current authors presently use two magnetic stimulator units in tandem to power a 70-mm figure-of-eight coil.

Adductor pollicis

The adductor pollicis is an easily accessible hand muscle, which has sole innervation from the ulnar nerve. The use of electrical stimulation of the ulnar nerve to elicit adductor pollicis contraction is a classic physiological technique, but few data on patients exist. In the critical care setting, the presence of venous or arterial lines, and peripheral oedema may preclude electrical stimulation. Magnetic stimulation of the ulnar nerve can be used to assess twitch adductor pollicis tension (APtw). Using a modified handboard to ensure hand and forearm immobilisation, a 45-mm figure-of-eight coil is applied over the ulnar nerve, with the edge of the coil at approximately the level of the ulnar styloid (fig. 7). HARRIS *et al.* [75] measured APtw in 50 subjects (including 12 patients in the ICU and six patients undergoing elective surgery). Supramaximality, as judged by twitch force, was demonstrated in 48 of the 50 patients, and stimulation was well tolerated. The technique has also been used to measure APtw in patients with COPD and healthy elderly subjects [76].

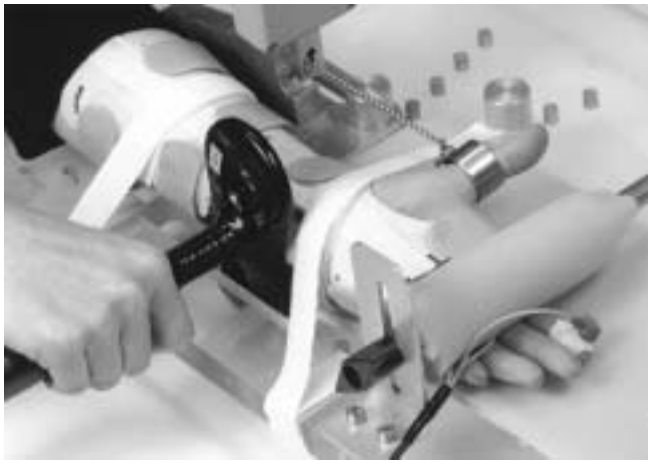

Fig. 7. – Magnetic stimulation of the ulnar nerve: the twitch adductor pollicis technique.

Twitch interpolation

Although this review has placed emphasis upon the nonvolitional assessment of muscle strength, it is important to note that magnetic stimulation can be used to assess the degree of activation of skeletal muscle during voluntary manoeuvres, a technique known as twitch interpolation. A twitch, generated by either electrical or magnetic stimulation, is superimposed upon a voluntary contraction; the amplitude of this superimposed twitch is zero if voluntary activation is maximal, and the amplitude of the twitch increases linearly as the intensity of the voluntary contraction decreases. Detailed description of the technique has been covered previously [77], and will not be discussed here, except to say that the technique is a useful research tool to assess the degree of central activation associated with voluntary manoeuvres [78] and in the discrimination of central and peripheral fatigue [79].

Clinical applications

Neuromuscular disease

Hypercapnic respiratory failure occurs when there is an imbalance between the load placed upon the respiratory muscle pump and its ventilatory capacity. Pulmonary physicians are very familiar with treating disorders of increased load (*e.g.* airways obstruction, fibrosis). The primary abnormality of neuromuscular disorders, however, is the reduced capacity of the respiratory muscle pump (*i.e.* respiratory muscle weakness). As magnetic stimulation techniques to test respiratory muscle function have developed, it is not surprising that the first patients to be assessed were those with neuromuscular disorders, and in particular those with pathology of the phrenic nerves. Pdi,tw elicited by CMS is a sensitive method of detecting patients with bilateral diaphragm paralysis secondary to neuralgic amyotrophy [80], and monitoring their long-term recovery [81]. The technique can also be used to detect iatrogenic phrenic nerve injury, following cardiac surgery [13] or central venous cannulation [82]. HAMNEGARD *et al.* [3] tested the clinical value of CMS by measuring Pdi,tw in 23 normal subjects, and 66 patients referred with suspected respiratory muscle dysfunction (many of whom had final diagnoses of idiopathic phrenic nerve injury, neuralgic amytrophy or ALS). Mean Pdi,tw for the normal subjects and patients were 31 and 19 cmH_2O, respectively. Almost 20% of patients with a low value for volitional sniff transdiaphragmatic pressure had a normal Pdi,tw. The same group also measured Pmo,tw in response to CMS in eight patients with suspected respiratory muscle weakness [32]. The UMS technique has also been used to assess unilateral diaphragm weakness in 54 patients with a variety of conditions associated with diaphragm dysfunction and phrenic nerve injury [13]. Clinical studies have not been confined to measuring muscle strength. LUO and coworkers [35, 46] have used magnetic stimulation, in conjunction with oesophageal EMG, to measure PNCT and CMAPdi amplitude in patients with idiopathic diaphragm paralysis, neuralgic amyotrophy and ALS.

Ventilatory failure, secondary to respiratory muscle weakness, is the commonest cause of death in ALS. Consequently, investigations to evaluate the clinical sequelae of respiratory muscle weakness, as determined by magnetic phrenic nerve stimulation, have focused on this progressive disease. The largest study to date was reported by LYALL *et al.* [83]. This investigation examined the relationship between tests of respiratory muscle strength (including Pdi,tw determined by CMS) with important clinical predictors of survival (namely, hypercapnia and sleep-disordered breathing) in 81 patients with ALS. The mean CMS Pdi,tw was 16 cmH_2O. Cut-off levels for the different tests of respiratory muscle strength in predicting hypercapnia were determined using receiver operating characteristic curves. Using a cut-off of 7 cmH_2O, CMS Pdi,tw had a sensitivity, specificity, positive predictive value and negative predictive value of 78, 89, 63 and 95%, respectively (fig. 8).

The odds of having hypercapnia were 31 times more likely for patients with a CMS Pdi,tw <7cmH_2O. Vital capacity (the traditional measure of respiratory muscle strength in ALS) had good specificity (89%), but had poor sensitivity. The investigators also performed polysomnography in 35 patients, and demonstrated a high incidence of sleep-disordered breathing. Mean apnoea/hypopnoea index (AHI) was $30 \cdot h^{-1}$ (normal $<5 \cdot h^{-1}$). Out of a wide range of tests of respiratory muscle strength, the nonvolitional CMS Pdi,tw had the strongest correlations with indices of sleep-disordered breathing, including significant negative relationships with AHI, hypopnoeas during rapid eye movement (REM) sleep and hypopnoeas during non-REM sleep. ARNULF *et al.* [84] have shown that ALS patients with diaphragmatic dysfunction have reduced time spent in REM sleep, and dramatically shorter median survival times compared with patients without diaphragm dysfunction (217 days *versus* 619 days). The same group also demonstrated that ALS patients with dyspnoea had significantly lower Pmo,tw following phrenic nerve stimulation than those without dyspnoea (3.71 *versus* 7.26 cmH_2O; p=0.001) [85].

It is important to note that in generalised neuromuscular disease, respiratory muscle weakness may be asymptomatic because limb muscle weakness may prevent patients from being active enough to impose a significant load upon the respiratory muscle pump. Similarly, many patients with ALS have sleep-disordered breathing without necessarily having daytime symptoms [84]. The level of respiratory muscle weakness at which sleep-disordered breathing occurs is not clear, nor the optimum time to initiate noninvasive ventilation, an intervention that prolongs survival [86] and improves quality of life [87]. Although full polysomnography may give detailed information about sleep-disordered breathing, it is time consuming and expensive, requires an overnight hospital stay, and is obviously inconvenient for patients who may be severely disabled. Serial polysomnography is clearly not

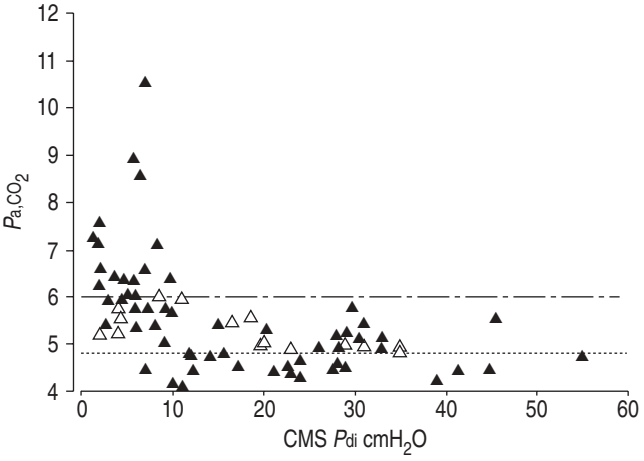

Fig. 8. – The relationship between hypercapnia and twitch transdiaphragmatic pressure elicited by cervical magnetic stimulation (CMS) in amytrophic lateral sclerosis (△: bulbar patients; ▲: nonbulbar patients). P_{a,CO_2}: carbon dioxide arterial tension; P_{di}: transdiaphragmatic pressure. Reproduced with permission from [83].

practical. A combination of respiratory muscle tests, including magnetic stimulation of the phrenic nerves, plus nocturnal oximetry could be used to alert the clinician to patients at risk of ventilatory failure and stimulate discussion of patients' preferences in relation to ventilatory support. Although there are no prospective data of nonvolitional measurements of respiratory muscle strength (and their potential prognostic value), this is currently being examined in our laboratory. Whereas the traditional measure of vital capacity is a prognostic test for survival [88], it has only a weak correlation with respiratory failure and is insensitive to significant change in respiratory muscle function [89]. There is likely to be a role for nonvolitional tests of respiratory muscle strength in clinical trials, to allow better stratification of patients, and as trial end-points, the greater discriminatory power ensuring smaller sample sizes.

Although inspiratory muscle weakness appears to be the primary determinant of both ventilatory failure and respiratory symptoms in neuromuscular disease, the expiratory muscles are also of clinical interest as weakness predisposes to impaired cough and subsequent increased risk of lower respiratory tract infection, a common cause of morbidity and mortality. There is growing evidence that cough augmentation techniques may benefit patients with expiratory muscle weakness [90]. The nonvolitional assessment of expiratory muscles is attractive given that the best established volitional test (PE,max) commonly underestimates strength [64]. The reasons for poor performance are not well understood, but presence of facial muscle weakness and bulbar symptoms are contributory factors. Some patients with pseudobulbar features often have an apraxia of facial movements and cannot blow effectively despite having good abdominal muscle function. Pga,tw, obtained by magnetic stimulation of the lower thoracic nerve roots, has been measured in patients with ALS. POLKEY *et al.* [68] demonstrated that in many patients, Pga,tw values were substantially lower than those observed in normal subjects. Furthermore, Pga,tw values were related to the ability to generate supramaximal cough flows; cough spikes were absent in patients with a Pga,tw <7 cmH_2O [68]. Paired magnetic stimuli, rather than a single twitch, have been used to confirm expiratory muscle weakness in patients with tetraplegia compared with control subjects (29.9 cmH_2O *versus* 76.0 cmH_2O) [70]. In addition, these paired stimuli produced increases in expiratory flow, and there is preliminary evidence that it is possible to use trains of magnetic stimuli applied over the lower thoracic roots, to functionally simulate cough [69].

Critical illness

Acquired neuromuscular abnormalities in the ICU are common [91], and are associated with difficulty in weaning from mechanical ventilation, increased hospital costs and increased mortality [92, 93]. There is also increasing interest in the long-term sequelae of critical illness, particularly as advances in intensive care medicine and mechanical ventilation have led to improved survival. However, the nature of volitional tests mean that objective quantification of muscle strength is not feasible when patients are sedated, and even when awake it is doubtful that critically ill patients are able to achieve maximum voluntary muscle activation. It is therefore not surprising that volitional tests of respiratory muscle strength, such as maximal mouth inspiratory pressure (PI,max), have been useful [94]. Viewed in this light, the ability to nonvolitionally assess muscle strength with magnetic stimulation appears to be particularly valuable on the ICU. Respiratory muscle function and critical illness neuromuscular abnormalities in the ICU have recently been reviewed [95, 96], and the focus of discussion here will be confined to the use (present and potential) of magnetic stimulation.

Respiratory muscle weakness and fatigue may contribute to prolonged weaning, and investigators have used magnetic stimulation to assess diaphragm contractility. WATSON *et al.* [56] described the technique of BAMPS in 41 mechanically ventilated patients (fig. 9), measurements were not available in eight patients due to difficulty with pressure catheter placement or endotracheal tube cuff leak. As well as measuring Pdi,tw and Poes,tw, the authors measured endotracheal tube pressure during phrenic nerve stimulation (twitch

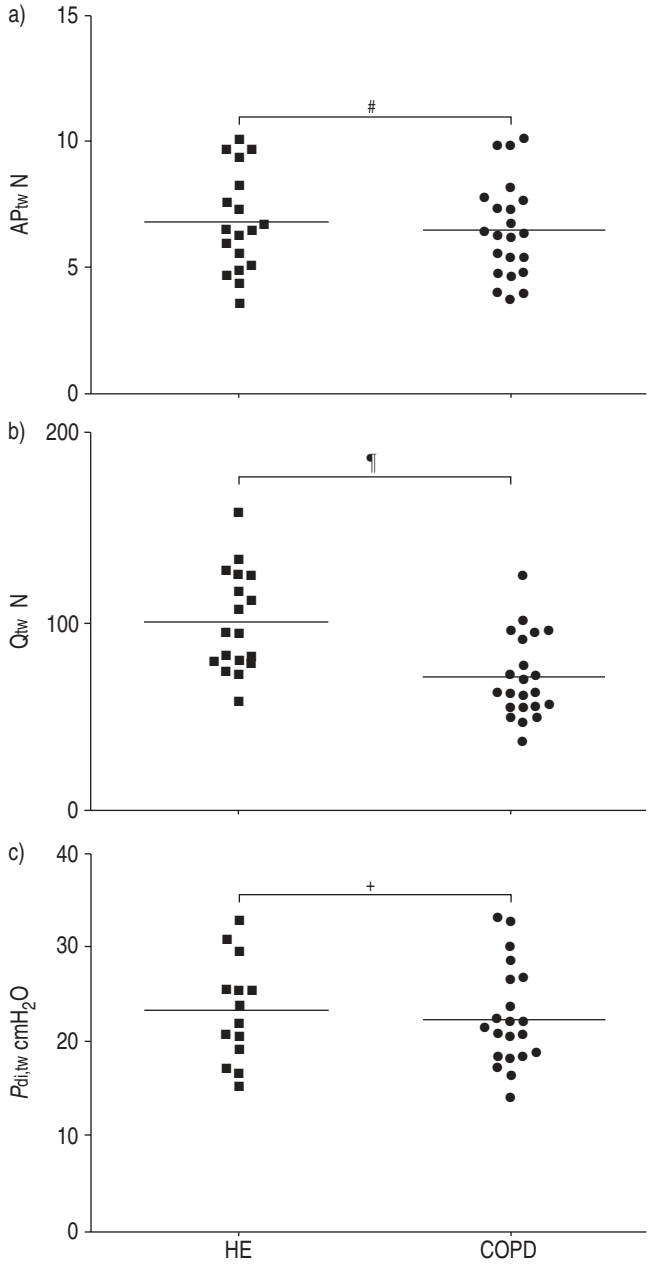

Fig. 9. – Nonvolitional assessment of diaphragm, quadriceps, and adductor pollicis strength in patients with chronic obstructive pulmonary disease (COPD). AP_{tw}: adductor pollicis; Q_{tw}: twitch quadriceps; $P_{di,tw}$: twitch transdiaphragmatic pressure; HE: healthy elderly. #: p=0.65; ¶: p=0.0005; +: p=0.81. Reproduced with permission from [76].

endotracheal tube pressure (Pett,tw)) by using a custom-built occlusion valve linked to the magnetic stimulators. At the time of stimulation, the airway was occluded by the valve, keeping the system isovolumic. Of 27 patients who underwent the full protocol, 25 were shown to be supramaximally stimulated; the mean Pdi,tw and Poes,tw were approximately 11 and 7 cmH_2O, respectively. One of the obvious difficulties of measuring Pdi,tw in ventilated patients is that it may not be possible to pass balloon catheters. Consequently, the relationship between the noninvasive twitch airway pressure (Paw,tw) or Pett,tw with Pdi,tw following magnetic stimulation has generated interest. CATTAPAN *et al.* [97] studied 13 mechanically ventilated patients, and showed a significant correlation between Pdi,tw and Poes,tw with Paw,tw, corroborating the earlier findings of MILLS *et al.* [98], and WATSON *et al.* [56]. However, all three studies showed wide levels of agreement between Paw,tw and the invasive measures of contractility, and Paw,tw was not reliable in predicting either Poes,tw or Pdi,tw. Despite this, Paw,tw has excellent reproducibility, and may be a useful noninvasive and nonvolitional means of monitoring respiratory muscle contractility prospectively in ventilated patients.

Another question of interest is whether weaning failure is caused by contractile fatigue of the diaphragm. LAGHI *et al.* [99] measured Pdi,tw, using the BAMPS technique, before and after spontaneous breathing trials in nine weaning-failure and seven weaning-success patients. Despite the weaning-failure patients experiencing a greater respiratory load and generating increased diaphragmatic effort, Pdi,tw did not decrease following the weaning trials (pre: mean Pdi,tw 8.9 cmH_2O *versus* post: mean Pdi,tw 9.4 cmH_2O). Although fatigue did not appear to be associated with weaning failure, the authors pointed out that clinical signs of distress probably led to the re-institution of mechanical ventilation before the development of overt diaphragm fatigue. It was also noteworthy that Pdi,tw was low in many of the patients, with similar values to WATSON *et al.* [56].

Measurement of the strength of the peripheral muscles is also of interest in the ICU. Early identification of weakness may lead to interventions designed to preserve or restore muscle function, thus reducing the considerable rehabilitation needs of survivors. Recent evidence suggests that in survivors of the acute respiratory distress syndrome, there is reduced exercise capacity and impaired quality of life, principally due to muscle weakness and fatigue, up to 1 yr after hospital discharge [100]. Furthermore, the relationship between peripheral muscle and respiratory muscle function in critically ill patients remains unknown; conceivably, peripheral muscle monitoring may offer an accessible marker of respiratory muscle function. Apart from clinical examination, however, there are few ways of assessing peripheral muscle strength, and until recently, none that are independent of patient effort. As discussed previously, adductor pollicis strength can now be nonvolitionally assessed on the ICU using supramaximal magnetic stimulation of the ulnar nerve [75]. Similarly, Qtw following magnetic stimulation of the femoral nerve [74] is a technique easily adaptable to the intensive care setting [101].

The introduction of these nonvolitional methods to assess skeletal muscle function in the ICU should facilitate large, prospective clinical studies, and may help answer the many questions that remain. The deleterious effects of prolonged mechanical ventilation or sepsis on diaphragm function are well-documented in animals [102, 103], but yet to be confirmed in patients. Prospective measurements of muscle strength, correlated with biochemical, immunological, electrophysiological, histological and clinical data, should elucidate the aetiological basis of critical illness neuromuscular abnormalities. Furthermore, these measures should help identify ventilated patients at risk of long-term rehabilitation requirements, who may benefit from early intervention. Finally, nonvolitional assessment of muscle contractility offers measurable, objective clinical end-points to assess the effects of present and future interventions designed to reduce morbidity both in the ICU and the recovery period.

Chronic obstructive pulmonary disease

COPD is increasingly seen as a systemic disorder [71], and skeletal muscle dysfunction is common, contributing to impaired exercise capacity and quality of life [72]. Magnetic stimulation has made a significant contribution towards the understanding of respiratory and peripheral muscle physiology in COPD. Although unlikely to play a routine role in clinical assessment, the derived measurements from magnetic stimulation of the phrenic or femoral nerve are becoming important clinical end-points in interventional studies, particularly those assessing the effects of training and rehabilitation.

PI,max is commonly reduced in COPD [104]. This has led to the assumption that there are intrinsic problems with the diaphragm muscle itself, inherent weakness or fatiguability that may be amenable to strength or endurance training. However recent studies of magnetic phrenic nerve stimulation suggest that *in vivo* diaphragm contractility is normal in COPD. POLKEY *et al.* [60] measured Pdi,tw in 20 patients with severe COPD using CMS. There was no difference in Pdi,tw between the patients and age-matched normal subjects (25.6 *versus* 25.4 cmH_2O) when lung volume was taken into account. MAN *et al.* [76] corroborated these results using the BAMPS technique, again showing that Pdi,tw when corrected for the increased lung volume in COPD patients, was not reduced compared with elderly healthy subjects (23.0 *versus* 23.5 cmH_2O; p=0.81). These patients were stable and nonweight losing, but Pdi,tw has not been found to be reduced in moderately malnourished COPD patients with low body mass index [105].

The reproducibility of Pdi,tw [57] has allowed diaphragm contractility to be assessed nonvolitionally during interventional studies in patients with COPD. For example, HATIPOGLU *et al.* [106] demonstrated that inhaled albuterol improved potentiated Pdi,tw (induced by the BAMPS technique) from a mean of 21.6 to 25.2 cmH_2O. The improvement in Pdi,tw could be explained by reduction in lung volume, suggesting that clinical doses of β_2-agonists do not improve diaphragm contractility *per se*. Similarly, a 2-week course of oral corticosteroids does not have any detrimental effect on diaphragm strength [107]. One of the proposed benefits of lung volume reduction surgery is the reduction of hyperinflation and subsequent improvement in the force-length relationship of the diaphragm. Interestingly, studies from both surgical and bronchoscopic approaches have shown improvements in Pdi,tw that cannot simply be explained by the effects of volume change [108, 109], suggesting either an intrinsic effect on the muscle, or more likely, a more complex configurational change in the diaphragm.

Given the high loads placed upon the respiratory muscle pump, patients with COPD could perhaps be more susceptible to diaphragm fatigue. Recent studies have measured the pressure or tension elicited from a single supramaximal stimulus since a right shift of the force-frequency curve, reflecting low-frequency fatigue, is a result of a reduction in twitch amplitude. POLKEY and coworkers [110, 111] measured Pdi,tw, using magnetic stimulation, before and after exhaustive treadmill exercise and maximum voluntary ventilation in COPD patients. No fall in Pdi,tw was observed in either study, suggesting that the diaphragm is relatively fatigue resistant in COPD. This is supported by the observation that COPD

patients appear to be better at sustaining maximum voluntary ventilation than normal subjects [111] and, indeed, histologically, the cellular adaptations of the diaphragm in COPD show an increased proportion of type I slow muscle fibres or slow myosin heavy-chain isoforms [112]. With this in mind, it is unsurprising that the effects of inspiratory muscle training in COPD remain controversial. A recent meta-analysis of 15 studies found no benefit in either respiratory muscle strength or exercise capacity, although COPD patients with pre-existing inspiratory muscle weakness seem to improve $P_{I,max}$ [113]. This finding needs to be interpreted with caution, particularly as $P_{I,max}$ has been shown to increase up to 17.5% in COPD patients allocated to control training [114]. A recent study of inspiratory muscle training in normal healthy subjects demonstrated a significant change in $P_{I,max}$ without any change in $P_{di,tw}$ measured by BAMPS [115]. Certainly, when using an outcome measure such as $P_{I,max}$, there is the possibility that the improvement is mere learning effect, and the subjects are simply better at performing the test. The effects of inspiratory training on diaphragm contractility could be simply answered by using nonvolitional $P_{di,tw}$ as an outcome measure. To date, only preliminary data exist [116].

The peripheral muscles of patients with COPD are of considerable interest, because these muscles represent a potential target to improve overall function despite the largely irreversible impairment of the lungs. In particular, attention has focused on the quadriceps, an important locomotor muscle likely to be underused in breathless patients with COPD. Histological, metabolic and biochemical data have been gathered, and recently magnetic stimulation of the femoral nerve has allowed investigation of quadriceps contractility. MAN *et al.* [76], using the nonvolitional Qtw elicited by magnetic stimulation of the femoral nerve, confirmed previous reports (based on the measurement of maximum voluntary contraction force) that the quadriceps is ~30% weaker in COPD than in healthy elderly subjects. In contrast, these investigators demonstrated that the nonvolitional strength of the adductor pollicis muscle of the hand and the diaphragm (as measured by APtw and $P_{di,tw}$ following magnetic stimulation of the ulnar and phrenic nerves, respectively) were normal compared with control subjects (fig. 9). These data suggest that chronic inactivity and subsequent disuse atrophy are necessary factors for the development of skeletal muscle weakness, given that there is the greatest decrease in activity in the primary locomotor muscles in COPD.

The contractile abnormalities of the quadriceps in COPD are not confined to the *in vivo* strength of the muscle. Several studies have demonstrated quadriceps fatigue (defined as a reduction in unpotentiated and potentiated Qtw) following exhaustive cycling exercise [117–119]. MADOR and co-workers [102, 104] have shown that the quadriceps is more fatiguable in COPD patients compared with healthy age-matched controls, following both exercise [118] and maximum voluntary contractions [120]. Some investigators have suggested that contractile leg fatigue may explain why some patients with COPD fail to improve cycling endurance time following a bronchodilator therapy [121]. However, it is important to note that quadriceps fatiguability in COPD is likely to be specific to the type of exercise task employed, and neither quadriceps fatigue nor leg tiredness are common following exhaustive walking [119].

The technique of magnetic stimulation is useful when testing interventions aimed at improving muscle strength and function. One study, in patients with COPD, examined the effects of pulmonary rehabilitation on quadriceps fatiguability (as determined by fall in potentiated Qtw) [122]. Following rehabilitation, MADOR *et al.* [122] demonstrated a significant improvement in Qtw from 6.9–7.6 kg ($p=0.049$), and a decrease in quadriceps fatiguability (pre-rehabilitation 26.1% *versus* post-rehabilitation 15%; $p<0.001$). As magnetic stimulation is nonvolitional, twitch measurements are likely to be valuable in situations when either learning placebo effects might be significant (*e.g.* inspiratory muscle training, pulmonary rehabilitation) or when patients may not be able to perform maximum voluntary contractions. For example, a recent study demonstrated a reduced quadriceps maximum voluntary contraction force in patients with COPD admitted into hospital for an acute exacerbation compared with stable, matched patients [123]. However, the investigators could not exclude the probability that severely ill, breathless patients were not good at achieving maximum voluntary activation.

Children

Although many of the volitional tests used to assess respiratory muscle strength in adults can be performed in children, the limitations of effort dependent manoeuvres are substantial. Tests such as the vital capacity or maximum mouth pressures are unlikely to be well performed in children <6 yrs. Even the sniff, which is a more natural manoeuvre that children find easier to perform, is unreliable <4 yrs [124]. Hence, the ability to assess respiratory muscle strength nonvolitionally is an attractive option.

The majority of magnetic stimulation studies in children have been performed in neonates, in whom impaired diaphragm function can cause respiratory distress. Magnetic stimulation is well tolerated. RAFFERTY *et al.* [125] measured $P_{di,tw}$ using CMS, UMS and BAMPS in 25 sleeping, non-sedated infants, who continued to sleep throughout the study. Unlike CMS, BAMPS and UMS were supramaximal, with a mean bilateral $P_{di,tw}$, right P_{di} and left P_{di} of 8.7, 4.1 and 4.5 cmH_2O, respectively. $P_{di,tw}$ correlated with gestational age at birth and postconceptional age [126]. Using similar techniques, the same group have demonstrated that diaphragm function is impaired in postoperative infants with congenital diaphragmatic hernia and gastroschisis [127], and that $P_{di,tw}$ elicited by UMS is sensitive enough to diagnose neonatal diaphragm paralysis [128]. However, there are no studies that have looked at the relationship between $P_{di,tw}$ or diaphragm fatigue and respiratory distress or weaning outcome.

Data from older children is limited. RAFFERTY *et al.* [129] have demonstrated supramaximal $P_{di,tw}$ responses with UMS and BAMPS in eight ventilated supine and sedated children with a mean age of 7.3 yrs. Although one research group has demonstrated that the measurement of $P_{di,tw}$ with BAMPS is well accepted and tolerated in children and adolescents with cystic fibrosis [130], the invasiveness of balloon pressure catheter placement means that the measurement of $P_{di,tw}$ is unlikely to be practical in older children outside of the paediatric ICU. A focus on noninvasive measures of diaphragm contractility is required if magnetic stimulation is to be more clinically applicable in children.

Summary

This review has described the basic principles of magnetic stimulation, and the nonvolitional measurements available with this technique. Some of the studies that have used these measurements have been described, particularly in relation to patients with neuromuscular disease, the intensive care setting, chronic obstructive pulmonary disease and children. At present, indications for clinical use are the investigation and diagnosis of diaphragm weakness (especially when

volitional tests are inconclusive), the investigation of unexplained dyspnoea, the investigation of unexplained ventilatory or weaning failure, the identification of patients suitable for phrenic nerve pacing, and the investigation of respiratory muscle involvement in neuromuscular disease. In the next decade, the challenge is to translate magnetic stimulation from a useful research tool to one that will provide the clinician with important diagnostic and prognostic clinical information. In particular, the present authors hope to see further evidence of the correlation between prospective measurements of respiratory muscle strength and clinical outcomes in neuromuscular disease patients and those on the intensive care unit. Increasing use of nonvolitional tests of muscle strength in the intensive care unit may help understand the aetiology, detect the presence and monitor the progression of critical illness neuromuscular abnormalities, and provide useful clinical end-points in studies designed to test the effect of interventions on skeletal muscle function.

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