Intensive Care Med (2000) 26: 1065–1075

ORIGINAL

M. I. Polkey
A. Duguet
Y. Luo
P. D. Hughes
N. Hart
C.-H. Hamnegård
M. Green
T. Similowski
J. Moxham

Anterior magnetic phrenic nerve stimulation: laboratory and clinical evaluation

Received: 11 November 1999
Final revision received: 17 April 2000
Accepted: 26 April 2000

M. I. Polkey (✉) · P. D. Hughes · N. Hart · M. Green
Respiratory Muscle Laboratory,
Royal Brompton Hospital, Fulham Rd,
London SW3 6NP, UK
e-mail: m.polkey@rbh.nthames.nhs.uk
Tel. + 44-171-351 8939
Fax: + 44-171-351 8029

A. Duguet · T. Similowski
Laboratoire de Physiopathologie
Respiratoire & Unité de Réanimation,
Service de Pneumologie,
Groupe Hospitalier Pitié-Salpêtrière,
Assistance Publique-Hôpitaux de Paris and
UPRES EA 2379, Université Paris VI,
Paris, France

Y. Luo · J. Moxham
Respiratory Muscle Laboratory,
Kings College Hospital, Bessemer Rd,
London SE5 9PJ, UK

C.-H. Hamnegård
Department of Pulmonary Medicine,
Sahlgrenska University Hospital,
S-413 45 Göteborg, Sweden

Abstract *Objective*: Anterior magnetic stimulation (aMS) of the phrenic nerves is a new method for the assessment of diaphragm contractility that might have particular applications for the clinical assessment of critically ill patients who are commonly supine.
Design: We compared aMS with existing techniques for measurement of diaphragm weakness and fatigue in 10 normal subjects, 27 ambulant patients with suspected diaphragm weakness and 10 critically ill patients.
Setting: Laboratory and intensive care unit of two university hospitals.
Results: Although aMS was not demonstrably supramaximal in normal subjects, the mean value of twitch transdiaphragmatic pressure (Tw Pdi) obtained at 100 % of stimulator output, 23.7 cmH_2O, did not differ significantly from that obtained with bilateral supramaximal electrical stimulation (ES), 24.9 cmH_2O, or bilateral anterior magnetic phrenic nerve stimulation (BAMPS), 27.3 cmH_2O. A fatiguing protocol produced a 20 % fall in aMS-Tw Pdi and a 19 % fall in BAMPS-Tw Pdi; the fall in aMS-Tw Pdi correlated with the fall in BAMPS-Tw Pdi ($r^2 = 0.84$, $p = 0.03$) indicating that aMS can detect diaphragm fatigue. In ambulant patients aMS agreed closely with existing measures of diaphragm strength. The maximal sniff Pdi correlated with both the aMS-Tw Pdi ($r^2 = 0.60$, $p < 0.0001$) and the BAMPS-Tw Pdi ($r^2 = 0.65$, $p < 0.0001$) and the aMS-Tw Pdi was a mean (SD) 2.2 (4.3) cmH_2O less than BAMPS-Tw Pdi. In addition, aMS correctly identified diaphragm dysfunction in patients studied on the ICU.
Conclusions: We conclude that aMS is of clinical value for the investigation of suspected diaphragm weakness.

Key words Magnetic stimulation · Phrenic nerves · Diaphragm · Fatigue

Introduction

The diaphragm is normally the most important inspiratory muscle in man [1]. Diaphragm dysfunction, in the form of weakness [2] or fatigue [3, 4], may lead to ventilator dependence. Indeed in patients whose cardiac and respiratory problems have resolved, acquired abnormalities of neuromuscular function contribute to weaning difficulties in a majority of patients [5]. Critically ill patients are unable to make a maximal voluntary effort and therefore traditional measures of respiratory muscle function, for example the upper airway pressure during a maximal voluntary effort, are not valid measures of respiratory muscle strength in the intensive care unit (ICU) [6].

Techniques to assess diaphragm function in ventilator-dependent patients, who are generally supine, are therefore of clinical interest to physicians caring for the critically ill. Measurement of transdiaphragmatic [7, 8]

or mouth pressure [9, 10] following cervical magnetic stimulation (CMS) of the phrenic nerves is an established technique for the assessment of diaphragm function in ambulant patients. Unfortunately this technique is impractical in the supine patient since it requires the coil to be positioned behind the cervical spines. An alternative approach, bilateral anterior magnetic phrenic nerve stimulation (BAMPS), requires the positioning of two coils (each driven by their own magnet) anteriorly over each phrenic nerve [11]. Although this technique is attractive in many respects, a limitation is the financial disadvantage associated with the need for two magnets (US$ 12,900 in 1998) as well as the practical difficulties if the technique is attempted by a single operator. Magnetic stimulators are increasingly used both in respiratory medicine and also in neurophysiology. Consequently, while many centres might have access to a single stimulator, few currently have the two stimulators and 2 45 mm coils required for BAMPS. As with ambulant patients, the clinician may measure transdiaphragmatic pressure or endotracheal or tracheostomy tube pressure. A brief airway occlusion is required for all twitch measurements and we have recently described a rapidly responsive valve suitable for use in the ICU [12].

Recently Similowski et al. noted that an action potential could be recorded from electrodes placed over the surface markings of the diaphragm if a single circular coil was discharged over the anterior chest wall [13]. This observation was of potential practical importance, for if a supramaximal stimulation of the diaphragm could be obtained in this manner then diaphragm contractility could be assessed in the supine subject with a single stimulator. Moreover, even if a near-maximal response could be obtained, the technique could be clinically useful for the confirmation (or refutation) of the possibility of diaphragm weakness. The aim of the present study, therefore, was an electrophysiological, mechanical and clinical evaluation of the technique of anterior magnetic stimulation (aMS).

Methods

The protocols were approved by our ethics committee and all subjects gave informed consent to participate. The subjects for Study 1 were normal healthy volunteers (eight men and two women) who were free of neurological and respiratory disease. These subjects had a mean age of 35 years, mean height 1.79 m and mean weight 80 kg. In Study 2 we studied 27 patients referred to our laboratories for assessment of diaphragm function and 10 patients in ICU with suspected diaphragm dysfunction.

Measurements

Gastric, oesophageal and transdiaphragmatic pressures

Gastric, oesophageal and transdiaphragmatic pressures (Pga, Poes, Pdi) were obtained using a pair of commercially available latex balloon catheters (PK Morgan, Rainham, Kent, UK) 110 cm in length placed in the stomach and oesophagus in the conventional manner. The catheters were connected to differential pressure transducers (Validyne MP45–1, Validyne, Northridge, Calif., USA), carrier amplifiers (PK Morgan, Rainham, Kent, UK), a 12-bit NB-MIO-16 analogue-digital board (National Instruments, Austin, Tex., USA) and a Macintosh Quadra Centris 650 personal computer (Apple Computer, Cupertino, Calif., USA) running LabView software (National Instruments, Austin, Tex., USA). Transdiaphragmatic pressure (Pdi) was obtained on-line, by subtraction of Poes from Pga. A minimum sampling frequency of 100 Hz was used.

Compound diaphragm action potential

The compound diaphragm action potential was obtained via a custom-built oesophageal electrode [14]. This electrode was passed pernasally and swallowed until the centre was positioned at the electrically active centre of the diaphragm (EARdi) as judged by reversal of the polarity of the signal elicited by bilateral electrical phrenic nerve stimulation. These signals were passed via short leads to a Neurosign 100 amplifier (Magstim, Whitland, Dyfed, Wales) and displayed using LabView software with a recording frequency of 2 kHz or greater. The signals underwent bandpass filtering in the amplifier to exclude signals outside the range 10 Hz and 10 kHz, but were not subsequently altered.

Stimulation techniques

All stimuli were performed with the subject seated at relaxed end-expiration (usually judged by on-line display of Poes) wearing a noseclip. In order to minimise twitch potentiation [15] a 20-min rest period preceded all experimental sessions. Where appropriate, an independent measure of diaphragm strength was obtained by measuring the Pdi during a maximal voluntary sniff [16]. Sniffs were performed from FRC in the seated position; the subjects were helped to maximise their effort by being able to view their effort in real time [17].

Electrical stimulation (ES)

Bilateral and unilateral supramaximal ES of the phrenic nerves was performed using hand-held felt-tipped bipolar electrodes (Medelec, Old Woking, UK) powered by a constant voltage stimulator (Dgitimer 3072, Digitimer, Welwyn Garden City, UK) producing square waves 100 μs in duration. The electrodes were sited at the posterior border of sternomastoid at the level of the cricoid cartilage. In the present study a supramaximal stimulation intensity is defined as one 30 % or 50 V greater than that which produces no further increase in twitch Pdi (Tw Pdi) or action potential (CMAP).

Anterior magnetic stimulation (aMS)

Anterior magnetic stimulation was performed using a 90 mm circular coil (P/N 8443), powered by a Magstim DEM stimulator [18] (Magstim, Whitland, Dyfed, UK), firmly placed centrally over the upper sternum such that the upper border of the coil touched the cricoid cartilage, with the handle vertically downwards. Great care was taken to angle the coil in a way to obtain maximal apposition to the portion of the sternum cranial to the angle of Louis

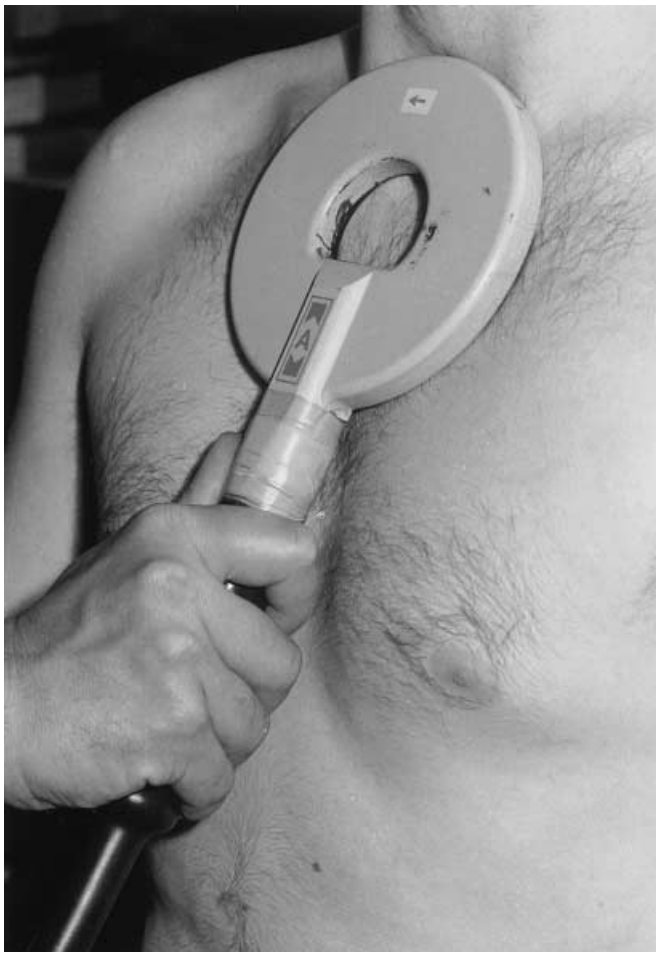


Fig. 1 Normal subject undergoing anterior magnetic stimulation

(Fig. 1). The coil orientation (clockwise or anti-clockwise) generating the biggest Tw Pdi was determined using submaximal stimuli and this combination was used for the remainder of the study session.

Bilateral anterior magnetic phrenic nerve stimulation (BAMPS)

Bilateral anterior magnetic stimulation was performed as previously described [11]. Two 45 mm figure-of-eight coils were employed, each of which was powered by a Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK). Each coil was placed anterolaterally over the course of the phrenic nerve.

Cervical magnetic stimulation (CMS)

Cervical magnetic stimulation was performed with a 90 mm circular coil (P/N 8443), powered by a Magstim DEM stimulator (Magstim, Whitland, Dyfed, UK), placed over the cervical spine with the neck flexed forward. The position and coil orientation generating the biggest Tw Pdi was determined using submaximal stimuli and this combination was used for the remainder of the study session.

Experimental protocols

Normal subjects

Assessment of supramaximality was obtained by the use of pressure and electromyographic recruitment curves in five subjects; pressure and electromyographic data were usually, but not invariably, obtained during the same study session. For this study aMS was given at the following stimulation intensities in random order: 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%. Five stimuli were applied at each intensity and their results averaged. For comparison five stimuli each of supramaximal bilateral ES, BAMPS (at 100% of stimulator output) and CMS (at 100% of stimulator output) were also obtained. In a further five subjects aMS recruitment curves were established for Pdi alone and compared with five stimuli each of BAMPS (at 100% of stimulator output) and CMS (at 100% of stimulator output) and supramaximal bilateral ES (two subjects).

Between-occasion variability was examined by comparing the Tw Pdi obtained with aMS at 100% of stimulator output in four subjects on two to three occasions over a period of 18 months. An independent measure of diaphragm strength was obtained on each occasion by measurement of Pdi during a maximal sniff (Sn Pdi).

In five subjects the ability of aMS to detect diaphragm fatigue was examined by measuring the Tw Pdi elicited by aMS (at 100% of stimulator output) with that obtained by BAMPS (at 100% of stimulator output) before and 20 min after a fatiguing protocol. The fatigue protocol used was 2 min of maximal isocapnic ventilation (MIV). We have previously shown that MIV can induce low frequency diaphragm fatigue in normal subjects [19, 20].

Clinical studies

Laboratory studies. Data were collected in 27 patients referred for assessment of respiratory muscle function. The Tw Pdi values obtained with aMS at 100% of stimulator output were compared with those obtained with BAMPS and CMS (both at 100% of stimulator output) and the Pdi generated during a maximal voluntary sniff [16]. Data are also presented from an additional four naive normal subjects who did not participate in the more detailed studies described above.

Intensive care unit studies. These studies were conducted for various clinical reasons in 10 intubated or tracheostomised patients cared for in the ICU of the Hôpital Pitié-Salpêtrière. Patient data are shown in Table 1. The patients were studied using CMS and aMS using a conventional Magstim 200 stimulator, with measurements of Poes and tracheal pressure (Ptr, at a side port of the endotracheal prostheses) in all cases and of Pdi in three. In eight of ten patients measurement of phrenic nerve conduction time (PNCT) in response to ES was also performed; in two of these patients needle electrodes were used and in the remainder surface electrodes were used.

The patients were studied in a semi-recumbent position at approximately 45°. Abdominal displacements were monitored using a belt-mounted piezoelectric strain gauge placed at the level of the umbilicus, in order to deliver all stimulations at end-expiration, and with a roughly constant abdominal configuration.

Conventions

Action potential was measured peak to peak and phrenic nerve conduction time was measured from stimulus to the point of first

Table 1 Characteristics and results of ten patients studied on intensive care unit (*ES* electrical stimulation, *PNCT* phrenic nerve conduction time, *CMS* cervical magnetic stimulation, *aMS* anterior magnetic stimulation, *Pdi* transdiaphragmatic pressure, *Poes* oesophageal pressure, *Ptr* tracheal pressure)

Patient No.	Sex	Age	Clinical problem	ES	PNCT (ms)	CMS	PNCT (ms)	aMS	PNCT (ms)	CMS	Pressure (cmH_2O)	aMS	Pressure (cmH_2O)	CMS-Pdi	aMS-Pdi
				Right	Left	Right	L eft	Right	Left	Poes	Ptr	Poes	Ptr	(cmH_2O)	(cmH_2O)
1	F	56	C2 tetraplegia ? For phrenic pacing	Failed	Failed	5.6	5.4	5	5.1	1.8	1.9	1.6	2	Not attempted	Not attempted
2	F	16	C2 tetraplegia ? For phrenic pacing	6.4	5.8	Failed	Failed	Failed	Failed	1.6	1.9	1	1.4	Not attempted	Not attempted
3	F	44	Myasthenia gravis Steroid myopathy	7.7	Failed	6.9	5.9	6	5.4	1.5	1.5	1.4	1.6	Not attempted	Not attempted
4	F	82	Cardiac surgery Slow to wean	Failed	7.7	6.0	6.0	Failed	Failed	4.5	5	5	5.5	Not attempted	Not attempted
5	F	51	Abdominal surgery Slow to wean Probable steroid myopathy	Not attempted	Not attempted	6.7	6.7	5.8	6.4	Not attempted	2.8	Not attempted	2.5	Not attempted	Not attempted
6	F	24	Acute respiratory failure Polymyositis	5.8	6 .0	4.9	5.0	4.5	4.8	0.5	Not attempted	0.5	Not attempted	2.5	3.2
7	M	49	Amyotrophic lateral sclerosis Ventilator dependent	8.8	8.7	8.2	8.3	7	7	1.9	2.5	2	3	Not attempted	Not attempted
8	M	29	C2 Tetraplegia ? For phrenic pacing	7.4	7.6	6.9	6.9	5.4	5.6	3.1	2.1	4.5	5.5	7.0	9.0
9	M	25	Acquired hypoventilation (Post encephalitis)	Not attempted	Not attempted	6.1	6.0	Failed	Failed	13	15.5	12	13	29.0	26.0
10	F	26	Acquired hypoventilation (Post neurosurgery)	7.2	7.8	5.9	6.1	5.2	5	15	16.5	12	12	Not attempted	Not attempted

Failed means the measurement was attempted but failed (e. g. inability to find the nerve or artefact)
In patients 8 & 10 PNCT was measured using needle electrodes placed in the diaphragm

deflection from baseline. Action potentials overlying the electrocardiogram were discarded. Pdi, Pga and Poes were measured from baseline to peak. Pressures were only accepted for analysis in the absence of peristaltic waves and if the subject was at relaxed end-expiration, as determined by Poes.

Statistics

Statistics were computed using Statview 4.0 (Abacus Concepts, Berkeley, Calif.) and a level of p less than 0.05 was taken as significant. To assess differences between stimulation techniques we used ANOVA for repeated measures with the Scheffé post-hoc test. Intra-subject variability was assessed using the method of Colton [21].

Results

The technique proved acceptable to both normal subjects and patients. No side effects were noted; in particular no subject complained of palpitations or bradycardia.

The Tw Pdi elicited by the different stimulation techniques are shown in Table 2. There was no statistical difference between aMS and ES or BAMPS, but aMS was significantly different from CMS ($p = 0.02$). The partitioning, as judged by the ratio Tw Poes:Tw Pdi was not, as judged by ANOVA, significantly different between stimulation modalities. In aMS ramp studies the ratio Tw Poes:Tw Pdi was not correlated with stimulation intensity and ANOVA testing showed no significant differences for this ratio at any level of stimulator output.

Table 2 Transdiaphragmatic pressure and partitioning (ratio Tw Poes:Tw Pdi) produced by different stimulation modes in ten normal subjects

Subject	Sex	Anterior magnetic-stimulation		Supramaximal electrical stimulation		Bilateral anterior magnetic stimulation		Cervical magnetic stimulation	
No.	M/F	Tw Pdi (cmH_2O)	Tw Poes: Tw Pdi	Tw Pdi ($cm\ H_2O$)	Tw Poes: Tw Pdi	Tw Pdi ($cm\ H_2O$)	Tw Poes: Tw Pdi	Tw Pdi ($cm\ H_2O$)	Tw Poes: Tw Pdi
1	F	26.0	0.823	23.2	0.578	33.9	0.712	34.7	0.859
2	M	21.2	0.517	29.9	0.487	29.0	0.543	30.2	0.602
3	M	24.8	0.658	22.1	0.661	25.7	0.634	35.4	0.736
4	M	23.6	0.468	27.0	0.377	26.4	0.408	30.1	0.587
5	M	28.2	0.607	31.1	0.579	31.1	0.627	36.4	0.735
6	M	20.2	0.573	20.7	0.476	22.7	0.564	24.5	0.301
7	M	25.5	0.500	20.2	0.604	25.3	0.571	22.5	0.434
8	F	30.5	0.456		Not performed	29.7	0.519	33.2	0.627
9	M	20.2	0.503		Not performed	24.2	0.434	32.8	0.627
10	M	16.4	0.586		Not performed	25.5	0.546	22.1	0.643
Mean		23.7	0.569	24.9	0.538	27.3	0.556	30.2	0.615

N.B. Magnetic stimuli were given at 100% of maximal output

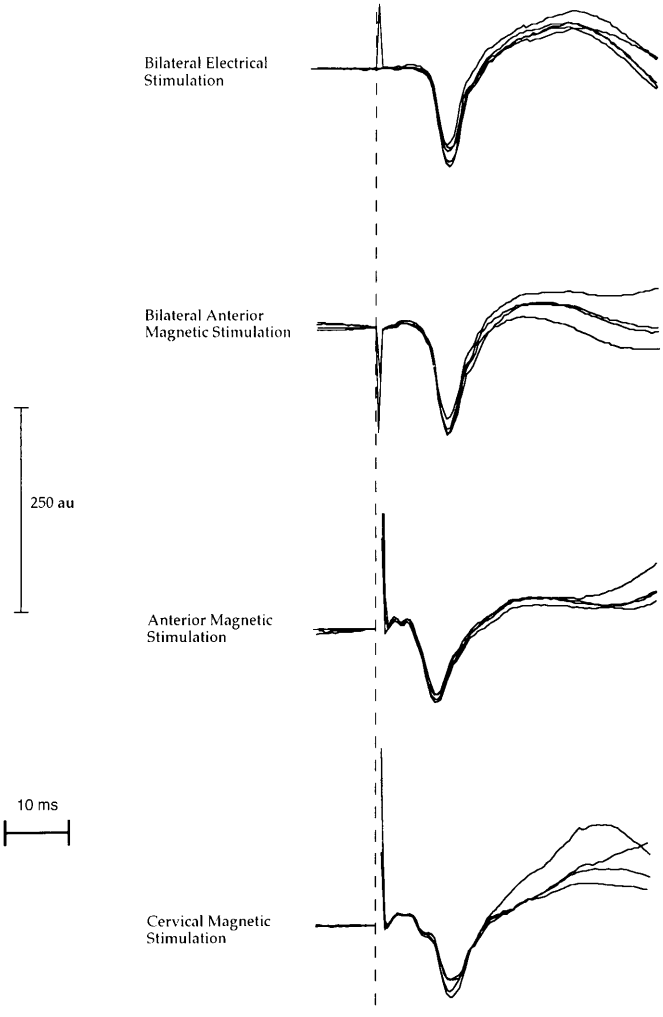


Fig. 2 Examples of action potentials recorded from an oesophageal electrode in one subject

Good quality action potentials were obtained in all subjects (Fig. 2); the mean (SD) phrenic nerve latency was 7.4 (0.5) ms for ES, 7.2 (0.4) ms for BAMPS, 6.9 (0.9) ms for CMS and 6.0 (0.6) ms for aMS at 100% of stimulator output. ANOVA with the Scheffé post-hoc test showed a significant difference between ES and aMS ($p = 0.03$) but not between other stimulation modalities. Small wave activity preceding the main action potential was sometimes observed with aMS and CMS. CMS is well known to activate extradiaphragmatic muscles [22] and, although we did not investigate activation of these muscles with aMS in the present study, there was visible contraction of pectoralis major.

As judged by recruitment curves, no subject fulfilled the criteria for supramaximality; i.e. a plateauing of CMAP. Mean data for Tw Pdi and CMAP are shown in Figs. 3 and 4, respectively.

The between-occasion reproducibility of Sn Pdi, BAMPS Tw Pdi and aMS Tw Pdi was assessed in four subjects; the mean variance for these tests was 28 $(cmH_2O)^2$, 6.2 $(cmH_2O)^2$ and 11.8 $(cmH_2O)^2$, respectively, against mean absolute values of 145 cmH_2O, 27.0 cmH_2O and 25.1 cmH_2O. Using these data we calculated the change in Sn Pdi, BAMPS Tw Pdi and aMS Tw Pdi that would have a more than 95% probability of reflecting genuine change, using SD = $\sqrt{}$(mean variance), to be 7.4 cmH_2O (5.1%), 3.5 cmH_2O (13.0%) and 4.8 cmH_2O (19.2%), respectively. The within-occasion reproducibility of the aMS-Tw Pdi was calculated from data obtained in the ramp studies in ten subjects; the mean variance for these data was 2.7 $(cmH_2O)^2$ against a mean absolute value of 23.7 cmH_2O. The within-occasion change in aMS-Tw Pdi which would have a greater than 95% probability of reflecting genuine change was therefore 2.3 cmH_2O (9.8%). The comparable results for ES ($n = 7$), BAMPS and CMS were

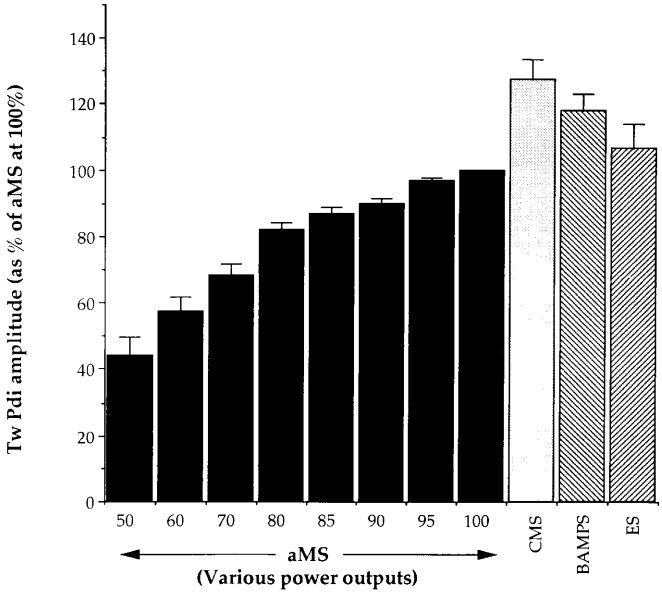


Fig. 3 Relationship between stimulator output used for anterior magnetic stimulation (aMS) and twitch transdiaphragmatic pressure. Data from cervical magnetic stimulation and bilateral anterior magnetic phrenic nerve stimulation (at 100% stimulator output) and supramaximal electrical stimulation are also shown. Values are expressed as a percentage of those obtained using aMS at 100%. *Error bars* are SEM

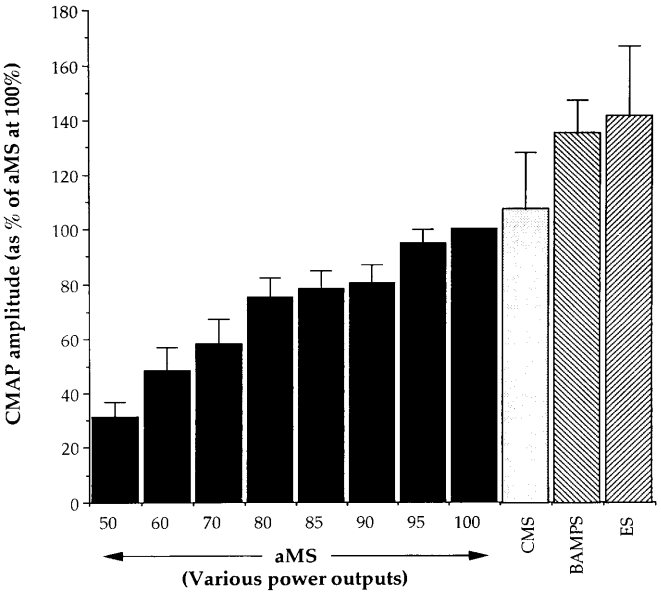


Fig. 4 Relationship between stimulator output used for anterior magnetic stimulation (aMS) and action potential amplitude. Data from cervical magnetic stimulation and bilateral anterior magnetic phrenic nerve stimulation (at 100% stimulator output) and supramaximal electrical stimulation are also shown. Values are expressed as a percentage of those obtained using aMS at 100%. *Error bars* are SEM

3.1 cmH_2O (12.3%), 2.3 cmH_2O (8.4%) and 2.0 cmH_2O (7.5%).

The fall (in percent) in Tw Pdi after a fatiguing protocol was 20% with aMS and 19% with BAMPS; individual data are shown in Table 3. The fall in aMS-Tw Pdi correlated with the fall in BAMPS-Tw Pdi ($r^2 = 0.84$, $p = 0.03$). The change in partitioning, judged by the ratio Tw Poes:Tw Pdi was similar for aMS and BAMPS.

Anterior magnetic stimulation was well tolerated by patients; diagnoses and pressure data are shown in Table 4. Sniff Pdi correlated with the aMS-Tw Pdi ($r^2 = 0.60$, $p < 0.0001$), the BAMPS-Tw Pdi ($r^2 = 0.65$, $p < 0.0001$) and the CMS-Tw Pdi ($r^2 = 0.65$, $p < 0.0001$). A Bland and Altmann plot was used to compare aMS and BAMPS and CMS (Fig. 5). The aMS-Tw Pdi was a mean (SD) 2.2 (4.3) cmH_2O less than BAMPS-Tw Pdi and a mean (SD) 5.4 (5.8) cmH_2O less than the CMS-Tw Pdi. Examination of Fig. 5 shows that the majority of the discrepancies arose from patients with a mean Tw Pdi above 20 cmH_2O, although the differences between aMS and both BAMPS and CMS were not systematically related to diaphragm strength. A subgroup analysis was therefore performed in patients with definite diaphragm weakness. We defined definite dia-

Table 3 Twitch transdiaphragmatic pressure (Tw Pdi) (and % fall) in five subjects during maximal isocapnic ventilation (MIV) as judged by both anterior magnetic stimulation (aMS) and bilateral anterior magnetic phrenic nerve stimulation (BAMPS)

Subject	aMS-Tw Pdi (cmH_2O)			BAMPS-Tw Pdi (cmH_2O)			AMS partitioning (Poes/Pdi)			BAMPS partitioning (Poes/Pdi)		
No.	Before MIV	20 min after MIV	% Fall	Before MIV	20 min after MIV	% Fall	Before MIV	20 min after MIV	% Fall	Before MIV	20 min after MIV	% Fall
2	18.3	15.5	15	22.7	20.3	11	0.37	0.31	16	0.53	0.47	11
3	22.2	17.2	23	24.1	19.4	20	0.68	0.54	21	0.56	0.52	7
4	20.6	15.4	25	27.0	20.5	24	0.57	0.36	37	0.51	0.31	39
5	25.8	23.4	9	31.6	27.4	13	0.59	0.64	–8	0.62	0.51	18
7	24.2	17.3	28	22.6	16.3	28	0.47	0.34	28	0.49	0.37	24
Mean	22.2	17.8	20	25.6	20.8	19	0.54	0.44	19	0.54	0.44	20
SD	3.0	3.3	8	3.8	4.1	7	0.12	0.14	17	0.05	0.09	13

Table 4 Diaphragm strength data in 27 patients and 4 (further) normal subjects (*Sn* sniff, *Pdi* transdiaphragmatic pressure, *aMS* anterior magnetic stimulation, *Tw Pdi* twitch transdiaphragmatic pressure, *BAMPS* bilateral anterior magnetic phrenic nerve stimulation, *CMS* cervical magnetic stimulation)

Patient No.	Age (year)	Sex (Male/female)	Diagnosis	Sn Pdi (cm H_2O)	aMS-Tw Pdi (cmH_2O)	BAMPS-Tw Pdi (cmH_2O)	CMS-Tw Pdi (cmH_2O)
1	48	F	Unexplained dyspnoea	54	16.6	21.6	18.9
2	56	F	Syndrome X	120	19.0	29.8	31.3
3	80	F	Past polio	44	2.5	5.7	6.1
4	41	F	Syndrome X	132	31.0	32.9	35.5
5	52	M	Unexplained dyspnoea	124	21.2	20.4	26.6
6	55	M	Asthma	164	35.6	35.1	37.6
7	54	M	Hemidiaphragm paralysis	47	9.9	10.8	11.3
8	65	M	Une xplained dyspnoea	154	13.2	20.4	19.2
9	67	M	Unexplained dyspnoea	131	24.5	23.1	31.9
10	55	F	Unexplained dyspnoea	95	18.6	27.7	39.4
11	50	F	Limb girdle myopathy	80	7.1	9.8	15.3
12	66	M	Amyotrophic lateral sclerosis	26	2.8	2.4	3.4
13	74	M	Idiopathic diaphragm paralysis	20	4.2	2.9	3.3
14	51	F	Myopathy	69	14.2	12.4	21.0
15	74	F	Myasthenia	58	12.2	19.4	26.7
16	53	F	Past polio	106	27.7	31.5	31.6
17	58	M	Unexplained dyspnoea	99	17.4	20.4	29.1
18	58	M	Amyotropic lateral sclerosis	18	1.9	3.3	3.6
19	74	M	Pleural plaques	112	25.7	22.6	30.6
20	66	F	Dystonia	32.2	3.2	3.5	3.9
21	67	M	Amytrophic lateral sclerosis	27.8	2.5	3.2	3.9
22	33	M	Amyotrophic lateral sclerosis	21	0.6	0.6	0.6
23	36	M	Myopathy	43.5	6.2	9.6	7.9
24	78	M	Amyotrophic lateral sclerosis	40.5	2.7	4.0	2.7
25	57	M	Amyotrophic lateral Sclerosis	4.6	0.1	–0.9	0.1
26	52	F	Amyotrophic lateral sclerosis	13.4	2.1	3.9	4.2
27	36	M	Gulf War syndrome	43	21.9	28	23.4
28	30	F	Normal	128	36.4	37.5	44.8
29	23	M	Normal	113	45.3	47.1	56.1
30	22	M	Normal	86.3	41.1	32.3	43.0
31	30	F	Normal	96.3	17.9	30.9	38.6

phragm weakness as a Tw Pdi of less than 20 cmH_2O for BAMPS (based on results obtained from normal subjects in this study; Table 1) and less than 19 cmH_2O for CMS [8]. Among these patients the aMS-Tw Pdi was a mean (SD) 1.2 (2.2) cmH_2O less than the BAMPS-Tw Pdi and a mean (SD) 1.6 (2.2) cmH_2O less than the CMS-Tw Pdi; this plot is shown in Fig. 6.

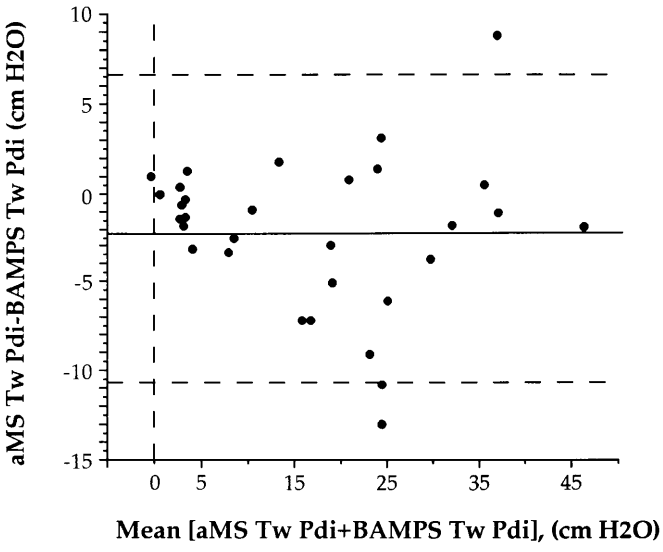
Data from the ten patients studied in the ICU are shown in Table 1. aMS and CMS were always very close to each other in terms of the Poes, Ptr or Pdi produced. In two cases, CMS classified the patients (9 & 10) as free of diaphragm dysfunction on the basis of a Pdi above 19 cmH_2O or of an airway opening pressure above 10 cmH_2O [8, 9]. In the remaining eight cases, the diagnosis of diaphragm dysfunction was retained, extremely severe in most cases. If the same criteria applied for CMS were used for aMS then the same classification would have been obtained in all patients. PNCTs measured with the different techniques were consistent with previously reported data [13].

Discussion

The present data provide an evaluation of a new method of magnetic phrenic nerve stimulation to assess its role in the investigation of phrenic nerve and diaphragm function both in normal subjects and patients with suspected respiratory muscle weakness. We further demonstrate that the technique is practical for use on the ICU and, although aMS has features which undermine its value for physiological studies, the data show that it can be used clinically to confirm or refute the diagnosis of diaphragm weakness. The discussion will address the strengths and weaknesses of aMS in relation to relevant issues in the evaluation of diaphragm function.

Safety

Discharge of a magnetic field in the region of the heart and vagus nerves could be considered potentially hazardous, but we found no evidence of dysrhythmia in



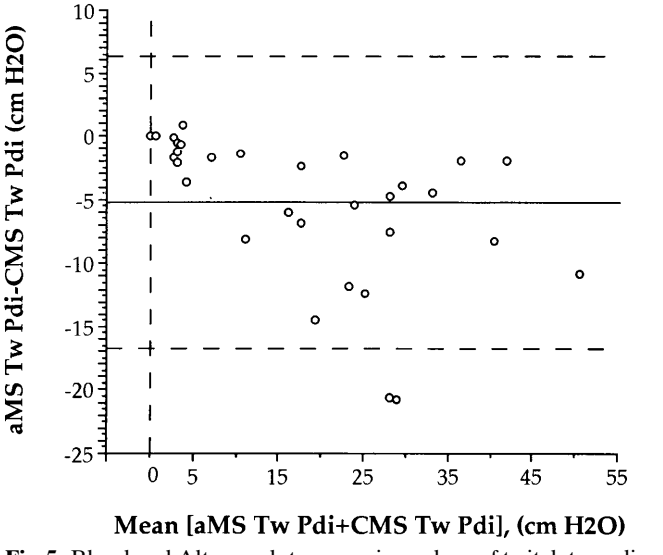
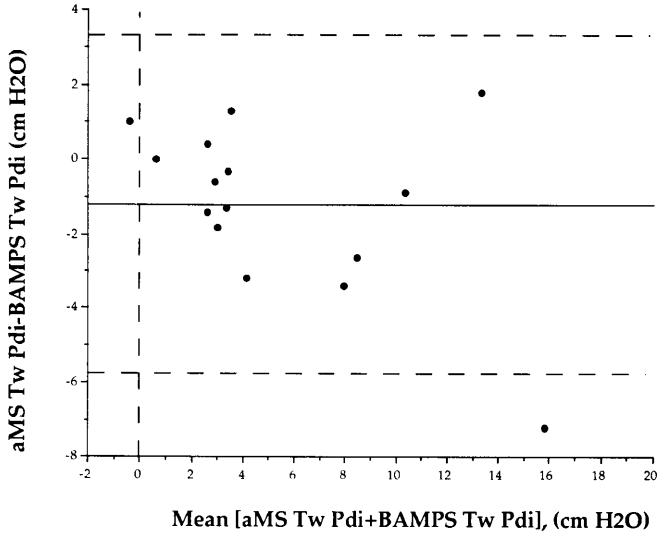


Fig. 5 Bland and Altman plot comparing values of twitch transdiaphragmatic pressure elicited by anterior magnetic stimulation (aMS) with those elicited by bilateral anterior magnetic phrenic nerve stimulation (BAMPS) (*upper panel*; *solid symbols*) and cervical magnetic stimulation (CMS) (*lower panel*; *open symbols*). Data from 27 patients and 4 normal subjects. In this figure the *horizontal continuous line* represents the mean difference [aMS-BAMPS] (*upper panel*) and [aMS-CMS] (*lower panel*). In both panels the *dashed horizontal lines* indicate 2 standard deviations above and below the mean difference



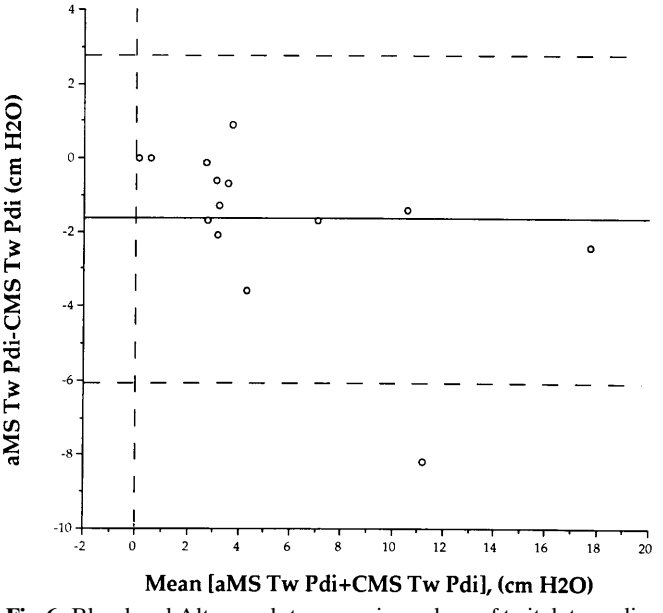


Fig. 6 Bland and Altman plot comparing values of twitch transdiaphragmatic pressure elicited by anterior magnetic stimulation (aMS) with those elicited by bilateral anterior magnetic phrenic nerve stimulation (BAMPS) (*upper panel*; *solid symbols*) and cervical magnetic stimulation (CMS) (*lower panel*; *open symbols*). Data from patients with diaphragm weakness only (for criteria see text). In this figure the *horizontal continuous line* represents the mean difference [aMS-BAMPS] (*upper panel*) and [aMS-CMS] (*lower panel*). In both panels the *dashed horizontal lines* indicate 2 standard deviations above and below the mean difference

studies of either normal subjects or patients. This is expected because cardiac muscle is substantially more difficult to depolarise than skeletal muscle [23]. Thus we find no evidence against aMS on safety grounds. Magnetic stimulation is contraindicated if implanted metallic objects lie within the stimulation field; thus aMS will not be applicable in patients with pacemakers (permanent or temporary) or coronary artery stents. Equally, if sternal deformities prevent close apposition of the coil then suboptimal results may be obtained; in our ex-

perience female gender itself does not prevent good signals being obtained.

Supramaximality; how much of a problem?

In the assessment of skeletal muscle contractility it is desirable to show that the applied stimulus is supramaximal; that is, that increasing stimulus intensity results in no further increase in the electrical (i.e. action potential amplitude) or mechanical (i.e. Tw Pdi) output of the diaphragm. In the present study this could not be demonstrated with aMS in any subject for either parameter.

Although this represents a limitation of the technique, it should be recalled that there are concerns about the supramaximality of CMS, a technique which is currently established for the assessment of diaphragm contractility [8]. For this technique it can also be difficult to show a clear plateau in Tw Pdi (for example [11]) or CMAP (for example [22]). However, in the case of CMS this has not precluded its use in the investigation of clinical aspects of diaphragm function (for example [24]). In particular, in the present study we were able to show good correlation between the aMS-Tw Pdi and the Sn Pdi and a relatively close numerical agreement between aMS-Tw Pdi and the BAMPS-Tw Pdi (Fig. 5). Thus, even though we could not demonstrate supramaximality, our data show that aMS can be used for the clinical assessment of diaphragm function. In particular, for ambulatory patients with diaphragm weakness demonstrated by BAMPS the mean difference between BAMPS and aMS was 1.3 cmH_2O; a magnitude of little clinical importance. Similarly in ICU patients aMS was able to classify correctly all patients as judged by CMS.

Specificity of anterior magnetic stimulation

One feature of CMS, which is considered to be a disadvantage, is that muscles of the brachial plexus and upper thorax are also activated. Our groups have previously shown that, as with ES [25, 26], stimulation of these muscles alone (by the use of CMS in patients with diaphragm paralysis) produces little [27] or no [28] inspiratory pressure. Nevertheless, one currently held view is that activation of these muscles stiffens the rib cage and thereby results in a proportionately greater Tw Poes (and consequently Tw Pdi). This mechanism explains why the CMS-Tw Pdi was greatest in the present study although the CMS-CMAP was the lowest. Furthermore differential fatigue of diaphragm and the extradiaphragmatic muscles can change the partitioning of CMS-Tw Pdi [29], but this concern is not thought to apply to ES-Tw Pdi or BAMPS-Tw Pdi. It is of interest, therefore, to consider how specific for the diaphragm aMS is.

In the present study we did not perform detailed studies of other muscles to delineate accurately the extent of co-activation of the upper thoracic muscles. That some extradiaphragmatic muscles (especially pectoralis major) are activated is evidenced by visual inspection during stimulation. Nevertheless, as shown in Table 2,, the partitioning of the aMS-Tw Pdi was closer to ES and BAMPS than CMS; additionally, as shown in Fig. 3, aMS tended to yield a lower CMAP and Tw Pdi than ES or BAMPS, in contrast to CMS. These data suggest greater specificity for the diaphragm than CMS even though, as noted above, the stimulus was submaximal. In this context it is also of interest that the change in the ratio Tw Poes:Tw Pdi after fatigue was the same for BAMPS and aMS.

Assessment of low frequency diaphragm fatigue

Some investigators currently hypothesise that respiratory muscle fatigue is linked to the need for mechanical ventilation. Since our technique is feasible in supine patients, it is worthwhile considering its ability to detect low frequency diaphragm fatigue.

Examination of the data in Table 3 shows that, in comparison with a method recognised to be supramaximal for the diaphragm, BAMPS, aMS could also detect a fall in Tw Pdi. In particular, the magnitude of the fall detected with aMS correlated well with the magnitude of the fall detected by BAMPS. Thus the current data support the potential use of aMS to investigate diaphragm fatigue.

Reproducibility

For aMS to be useful as a measure of strength it would need to be reproducible over time. Analysis of previous data from our group suggested that, for CMS, the change in Tw Pdi that would have a greater than 95% probability of reflecting genuine strength change between two occasions was approximately 6 cmH_2O [30]. The present data therefore suggest that aMS is comparably reproducible to CMS, but less reproducible than BAMPS and that both are, at least in laboratory staff, less reproducible than the Sn Pdi. This finding is not wholly unexpected since, in previous studies of the quadriceps muscle, we demonstrated that submaximal stimuli are more variable than supramaximal stimuli [31].

Translation of the technique to the intensive care unit

To support our assertion that the technique is practical on the ICU, data are presented from clinical studies in

ten patients; these patients were studied using a conventional Magstim 200 machine. Although these results must be taken with extreme caution and can only be viewed as preliminary, they confirm that aMS is feasible in ICU patients, and suggest that, once fully validated, it could indeed be used to detect and monitor diaphragm function in this setting. We acknowledge that balloon positioning in the ICU is more challenging than in ambulatory patients, but this problem relates to all stimulation modalities including aMS.

In conclusion, aMS using existing stimulator technology produces a substantial, but submaximal, stimulation of the phrenic nerves; it is therefore acknowledged that aMS has limitations for purely physiological studies. However we show that the technique is capable of detecting diaphragm fatigue. Moreover, our data show that, in both normal subjects and patients, the aMS-Tw Pdi has a close relationship with existing measures of diaphragm strength. In particular, aMS agrees closely with BAMPS-Tw Pdi in patients with diaphragm weakness. We suggest that aMS may have potentially wide clinical applications to confirm or refute the presence of diaphragm weakness in supine patients who are unable to make a maximal voluntary effort and in whom CMS is technically or practically difficult. We also believe that the technique could be used to follow diaphragm contractility sequentially in such patients, provided great care is taken to ensure constancy of stimulation.

References

1. Mead J, Loring SH (1982) Analysis of volume displacement and length changes of the diaphragm during breathing. J Appl Physiol 53: 750–755
2. Chen R, Grand'Maison F, Strong MJ, Ramsay DA, Bolton CF (1996) Motor neuron disease presenting as acute respiratory failure: a clinical and pathological study. J Neurol Neurosurg Psych 60: 455–458
3. Brochard L, Harf A, Lorino H, Lemaire F (1989) Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. Am Rev Respir Dis 139: 513–521
4. Goldstone JC, Green M, Moxham J (1994) Maximum relaxation rate of the diaphragm during weaning from mechanical ventilation. Thorax 49: 54–60
5. Spitzer AR, Giancarlo T, Maher L, Awerbuch G (1992) Neuromuscular causes of prolonged ventilator dependency. Muscle Nerve 15: 682–686
6. Multz AS, Aldrich TK, Prezant DJ, Karpel JP, Hendler JM (1990) Maximal inspiratory pressure is not a reliable test of inspiratory muscle strength in mechanically ventilated patients. Am Rev Respir Dis 142: 529–532
7. Similowski T, Fleury B, Launois S, Cathala HP, Bouche P, Derenne JP (1989) Cervical magnetic stimulation: a new painless method for bilateral phrenic nerve stimulation in conscious humans. J Appl Physiol 67: 1311–1318
8. Hamnegård C-H, Wragg SD, Mills GH, Kyroussis D, Polkey MI, Bake B, Moxham J, Green M (1996). Clinical assessment of diaphragm strength by cervical magnetic stimulation of the phrenic nerves. Thorax 51: 1239–1242
9. Hamnegård C-H, Wragg S, Kyroussis D, Mills G, Bake B, Green M, Moxham J (1995) Mouth pressure in response to magnetic stimulation of the phrenic nerves. Thorax 50: 620–624
10. Hughes PD, Polkey MI, Kyroussis D, Hamnegard C-H, Moxham J, Green M (1998) Measurement of sniff nasal and diaphragm twitch mouth pressure in patients. Thorax 53: 96–100
11. Mills GH, Kyroussis D, Hamnegard C-H, Polkey MI, Green M, Moxham J (1996) Bilateral magnetic stimulation of the phrenic nerves from an anterolateral approach. Am J Respir Crit Care Med 154: 1099–1105
12. Spicer M, Hughes P, Green M (1997) A non-invasive system to evaluate diaphragmatic strength in ventilated patients. Physiol Meas 18: 355–361
13. Similowski T, Mehiri S, Duguet A, Attali V, Straus C, Derenne J-P (1997) Comparison of magnetic and electrical phrenic nerve stimulation in assessment of phrenic nerve conduction time. J Appl Physiol 82: 1190–1199
14. Luo YM, Polkey MI, Johnson LC, Lyall RA, Harris ML, Green M, Moxham J (1998) Diaphragm EMG measured by cervical magnetic and electrical phrenic nerve stimulation. J Appl Physiol 85: 2089–2099
15. Wragg SD, Hamnegard C-H, Road J, Kyroussis D, Moran J, Green M, Moxham J (1994) Potentiation of diaphragmatic twitch after voluntary contraction in normal subjects. Thorax 49: 1234–1237
16. Miller JM, Moxham J, Green M (1985) The maximal sniff in the assessment of diaphragm function in man. Clin Sci 69: 91–96
17. Laporta D, Grassino A (1985) Assessment of transdiaphragmatic pressure in humans. J Appl Physiol 58: 1469–1476
18. Polkey MI, Harris ML, Hughes PD, Hamnegard C-H, Lyons D, Green M, Moxham J (1997) The contractile properties of the elderly human diaphragm. Am J Respir Crit Care Med 155: 1560–1564
19. Hamnegård C-H, Wragg SD, Kyroussis D, Mills GH, Polkey MI, Moran J, Road J, Bake B, Green M, Moxham J (1996) Diaphragm fatigue following maximal ventilation in man. Eur Respir J 9: 241–247
20. Polkey MI, Kyroussis D, Hamnegard C-H, Hughes PD, Rafferty GF, Moxham J, Green M (1997) Paired phrenic nerve stimuli for the detection of diaphragm fatigue. Eur Respir J 10: 1859–1864
21. Colton T (1974) Statistics in medicine. Little, Brown & Co, Boston
22. Laghi F, Harrison MJ, Tobin MJ (1996) Comparison of magnetic and electrical phrenic nerve stimulation in assessment of diaphragmatic contractility. J Appl Physiol 80: 1731–1742
23. Bourland JD, Mouchawar GA, Nyenhuis JA, Geddes LA, Foster KS, Jones JT, Graber GP (1990) Transchest magnetic (eddy-current) stimulation of the dog heart. Med Biol Eng Comput 28: 196–198
24. Laghi F, Jubran A, Topeli A, Fahey P, Garrity ER, Arcidi JM, De Pinto DJ, Edwards LC, Tobin MJ (1998) Effect of lung volume reduction surgery on neuromechanical coupling of the diaphragm. Am J Respir Crit Care Med 157: 475–483

25. Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F (1991) Contractile properties of the human diaphragm during chronic hyperinflation. N Engl J Med 325: 917–923
26. Wanke T, Merkle M, Zifko U, Formanek D, Lahrmann H, Grisold W, Zwick H (1994) The effect of aminophylline on the force-length characteristics of the diaphragm. Am J Respir Crit Care Med 149: 1545–1549
27. Attali V, Mehiri S, Straus C, Salachas F, Meininger V, Derenne JP, Similowski T (1997) Influence of neck muscles on mouth pressure response to cervical magnetic stimulation. Am J Respir Crit Care Med 156: 509–514
28. Mills GH, Kyroussis D, Hamnegard C-H, Wragg S, Polkey MI, Moxham J, Green M (1997) Cervical magnetic stimulation of the phrenic nerves in bilateral diaphragm paralysis. Am J Respir Crit Care Med 155: 1565–1569
29. Similowski T, Straus C, Attali V, Duguet A, Derenne J-P (1998) Cervical magnetic stimulation as a method to discriminate between diaphragm and rib cage muscle fatigue. J Appl Physiol 84: 1692–1700
30. Hamnegård C-H, Mills GH, Kyroussis D, Polkey MI, Moxham J, Green M (1996). Variability of the transdiaphragmatic pressure following cervical magnetic stimulation in normal subjects. Am J Respir Crit Care Med 153: A785
31. Polkey MI, Kyroussis D, Hamnegard C-H, Mills GH, Green M, Moxham J (1996). Quadriceps strength and fatigue assessed by magnetic stimulation of the femoral nerve in man. Muscle Nerve 19: 549–555