Assessment of upper airway dynamics by anterior magnetic phrenic stimulation in conscious sleep apnea patients

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Submitted 14 December 2011; accepted in final form 23 January 2012

Magnetic stimulation (MS) is a widely employed and painless technique capable of inducing skeletal motor activation through central or peripheral stimulation of dedicated corticomotor/nerve structures (14). It has been applied in respiratory physiology studies to assess diaphragmatic strength and peripheral fatigue (9), to evaluate the corticomotor responsiveness of respiratory as well as upper airway (UA) dilator muscles (12, 19, 20), and to investigate UA passive mechanical properties (18). Peripheral phrenic nerve stimulation (electric or magnetic) bypasses central respiratory controller commands and thus elicits diaphragm contraction dissociated from activation of the UA dilator muscles. Because of this ability, MS of phrenic nerves is a useful tool for appraising UA mechanical properties during consciousness in a unique situation where twitches can be applied in the presence or absence of phasic activity of the UA dilator muscles. Three techniques are available for such purposes: 1) cervical magnetic stimulation (CMS), in which phrenic nerve roots are stimulated with a circular, nonfocal coil placed behind the 7th cervical vertebra (21); 2) bilateral anterior magnetic phrenic stimulation (BAMPS), which consists of stimulating the phrenic nerves with two focal coils placed over each nerve’s route at the base of the neck (13); and 3) anterior magnetic stimulation (a-MS), which comprises stimulation of the phrenic nerves at their entry in the thorax with a single circular nonfocal coil placed over the sternum (15).

With CMS methodology, optimal placement can be easily ascertained after the location of cervical anatomical landmarks. Furthermore, CMS has proven to be capable of inducing flow-limited twitches in healthy (3) and sleep apnea patients (18). However, coactivation of the neck and upper thoracic muscles (7) is considered a drawback of CMS, because upper thoracic muscle activation may influence UA dynamic properties by changing rib cage mechanics (16, 23). Indeed, CMS does not represent an optimal approach to evaluate UA passive mechanical properties in sleep apnea patients owing to its inability to generate high-twitch peak esophageal pressure in these patients, thus accounting for the low percentage of flow-limited twitches (18).

For these reasons, BAMPS is actually employed most frequently to assess UA passive mechanical properties because of its ability to activate the diaphragm and to generate flow-limited twitches, even in obese subjects (4, 17, 18). Despite these advantages of BAMPS, its applicability may be limited by the time needed to precisely locate the phrenic nerves, by operator efforts to precisely place and maintain coil positioning throughout the stimulation period and by the necessity of having two magnetic stimulators/coils for stimulation with two operators to ensure its efficiency.

Polkey et al. (15) introduced a-MS as a practical and useful approach to appraise the diaphragm strength of healthy subjects and patients with suspected diaphragm weakness (15). We recently investigated the ability of a-MS to assess UA dynamic properties in conscious, healthy subjects and demonstrated that a-MS generated a higher percentage of flow-limited twitches than CMS (3). However, before considering a-MS as a standard in studies of UA mechanical properties during consciousness, there is a need to analyze flow limitation patterns and UA dynamic properties compared with BAMPS in sleep apnea patients. Therefore, the aims of this work were to determine the ability of BAMPS and a-MS to evaluate UA dynamic properties and to assess thoraco-abdominal motion in conscious sleep apnea patients. We considered that if a-MS could induce a similar percentage of flow-limited twitches as...
BAMPS in conscious sleep apnea patients, gauging UA dynamic properties by phrenic nerve MS would be simplified.

MATERIALS AND METHODS

Subjects

Ten male patients with clinical symptoms of obstructive sleep apnea (OSA), confirmed by full night polysomnography, volunteered to participate in this study. None of them had neurologic, cardiac, or chronic respiratory disease, previous UA surgery, or sleep disorders other than OSA. The Ethics Review Board of our institution approved the protocol, and written, informed consent was obtained from all study subjects.

Pressure and Airflow Recordings

To measure nasopharyngeal, velopharyngeal, and oropharyngeal pressures, a pressure-tipped catheter with three sensors (model CT/S X1058, Gaeltec, Hackensack, NJ) was inserted through an anesthetized (xylocaine 2% spray) nostril. The distance between the upper and middle sensors was 4 cm, and the distance between the middle and lower sensors was 3 cm. The catheter was positioned visually so that the upper sensor lay ~2 cm above the soft palate to measure nasopharyngeal pressure. Thus the middle sensor was 2 cm below the soft palate, quantifying velopharyngeal pressure, and the bottom sensor gauged oropharyngeal pressure. To measure esophageal pressure, an esophageal balloon catheter (Cooper Surgical, Trumbull, CT) containing 1.0 ml of air was placed in the mid-esophagus through the other nostril (anesthetized with 2% xylocaine spray) and connected to a transducer (Cooper Surgical, Trumbull, CT). Its air-tightness was assessed by occlusion of its opening during maximal inspiratory effort. A third catheter, connected to a transducer (Validyne Engineering, Northridge, CA). Its correct positioning was ascertained by occlusion testing (2). A plastic nasal stent (Nozovent, WPM International AB, Göteborg, Sweden) was inserted in the anterior nares to prevent nasal collapse, and a tightfitting nasal mask (Respironics, Murrysville, MO) covered the nose. Its air-tightness was assessed by occlusion of its opening during maximal inspiratory effort. A third catheter, connected to a transducer (Validyne Engineering), was passed through a mask hole to measure mask pressure. Instantaneous airflow was quantified by a heated pneumotacograph (model 112647–3850A, Hans-Rudolph, Kansas City, MO) attached to the nasal mask.

Thoraco-Abdominal Motion

Thoraco-abdominal motion was recorded by stethographs (8) placed at the angle of Louis and at the umbilicus. Pressure within the stethographs varied according to compartmental circumference that, in turn, was related to changes in lung volume (1, 8). The stethographs were constructed by attaching latex tubing (length 10 cm, 2 mm ID, 10 mm OD) to a three-way plastic piece connected to nonextensible bands with adjustable length to perfectly fit patient thoracic and abdominal circumferences. Pressure measured within each stethograph was recorded by connecting one port of the three-way plastic piece to a pressure transducer (Validyne Engineering).

Phrenic Nerve MS

BAMPS was applied with two Magstim 200 stimulators (Magstim, Whitland, Dyfed, UK) connected to two figure 8-shaped coils with 90°-handle and 45-mm diameter (13, 18). Each stimulating coil was positioned anterolaterally over phrenic nerve anatomical landmarks in the neck and at the posterior border of the sternomastoid muscle at the level of the cricoid cartilage; the handle of each coil made a 45° axis with both the mid-saggital plane of the body and the horizontal plane. a-MS was applied with one 90-mm diameter, circular, nonfocal coil powered by one Magstim 200 stimulator (Magstim). The coil was placed centrally over the upper sternum so that its upper border was in contact with the cricoid cartilage (3, 15).

Protocol

MS twitches were evoked at end expiration according to real-time computer display of instantaneous flow (17). Five twitches were induced at each stimulation intensity with the two techniques. Stimulation intensities ranged from 50% of the stimulator’s maximal output to maximal tolerated intensity with 10% increments. Stimulation sites and intensities were chosen in random order. At the end of each series of stimulations at a given intensity, the study subjects were asked to quantify their sensation of discomfort on a modified Borg scale.

Data Analysis

UA dynamics. Twitch-induced breaths were classified as non-flow limited or flow limited. For non-flow-limited twitches, twitch-induced flow increased until its maximum value (V˙Inax) and pharyngeal and esophageal pressures decreased simultaneously to peak values (Pph,peak and Peso,peak, respectively). V˙Imax, Pph,peak, and Peso,peak were reached at the same time and were followed by passive expiration (Fig. 1A).

For flow-limited twitches, twitch-induced flow increased until V˙Inax and decreased abruptly to a minimum value (V˙Imin) despite a decline of at least 1 cmH2O in driving pressure. By taking this approach, we could identify the site(s) of pharyngeal obstruction according to the divergence between flow and UA pressure tracings. Oropharyngeal obstruction was identified in the presence of flow plateauing with increasing driving pressure below the velopharyngeal site (Fig. 1B). Velopharyngeal obstruction was depicted when such increases in driving pressure occurred below the nasopharyngeal site (Fig. 1C). Pharyngeal and esophageal pressures at V˙Inax are referred to as Pph,lim and Peso,lim, respectively. Upper airway resistance (UAR) during the linear portion of the pressure-flow loop [linear UAR (10)] was computed at V˙Inax and V = 300 ml/s. The UA dynamic response of flow-limited twitches was modeled by characterizing the pharyngeal pressure vs. airflow relationship (flow range from 0 to V˙Imax) with a second-degree polynomial regression model (V˙Imin = k1Pph + k2Pph^2), as described elsewhere (25). Solving this equation for V provides a theoretical value of the pharyngeal pressure at which the UA would close (Pclose = −k1/k2). Hence, the k1/k2 ratio describes UA stability (the less negative is k1/k2, the higher is UA collapsibility). Custom-made software (Matlab 7.0; The Mathworks, Natick, MA) semi-automatically performed polynomial model fitting and k1 and k2 determination.

Thoraco-abdominal motion. At baseline (prior to phrenic nerve MS), spontaneous breathing was recorded for 5 min to assess tidal thoraco-abdominal motion. Thoraco-abdominal motion induced by phrenic nerve MS was analyzed qualitatively and quantitatively. In addition to characterizing thoraco-abdominal motion as inward or outward, we quantified their amplitude and reported them as a percentages of baseline motion tidal breathing. Furthermore, whenever phrenic nerve MS induced outward followed by inward thoracic motions, we determined the ratio of maximal outward/maximal inward amplitudes to obtain a dimensionless index: the motion index (MI; Fig. 2, A and B).

Data Acquisition

All signals were filtered and amplified (Grass P122 Grass Technologies, West Warwick, RI), recorded digitally at a 2,000-Hz sample rate (Digidata 1320, Axon Instruments, Foster City, CA), and stored in a microcomputer. All data were collected and analyzed by Axoscope software, version 10 (Axon Instruments).

Statistical Analysis

Normal data distribution (Shapiro-Wilk test) and homogeneity of variances (Levene median test) were computed. Paired Student’s t-test compared maximal tolerated intensity, minimal stimulation intensity capable of generating flow-limited twitches, and percentages of flow.
Fig. 1. Examples of nonflow-limited twitch (A), flow-limited twitch with oropharyngeal limitation (B), and flow-limited twitch with velopharyngeal limitation (C). $V_{\text{I}_{\text{max}}}$, maximal inspiratory flow; $V_{\text{I}_{\text{min}}}$, minimal inspiratory flow; $P_{\text{ph}3}$, nasopharyngeal pressure; $P_{\text{ph}2}$, velopharyngeal pressure; $P_{\text{ph}1}$, oropharyngeal pressure; $P_{\text{eso}}$, esophageal pressure; $P_{\text{ph}3,_{\text{lim}}}$, nasopharyngeal pressure at maximal inspiratory flow; $P_{\text{ph}2,_{\text{lim}}}$, velopharyngeal pressure at maximal inspiratory flow; $P_{\text{ph}1,_{\text{lim}}}$, oropharyngeal pressure at maximal inspiratory flow; $P_{\text{eso,lim}}$, esophageal pressure at maximal inspiratory flow; $P_{\text{ph}3,_{\text{peak}}}$, nasopharyngeal peak pressure; $P_{\text{ph}2,_{\text{peak}}}$, velopharyngeal peak pressure; $P_{\text{ph}1,_{\text{peak}}}$, oropharyngeal peak pressure; $P_{\text{eso,peak}}$, esophageal peak pressure.
limited twitches between the two stimulation sites. Sensation of discomfort between BAMPs and a-MS was assessed by the Mann-Whitney-Wilcoxon test. Student’s $t$-test for independent variables compared the UA dynamic properties of BAMPs-induced non-flow-limited and flow-limited twitches according to thoracic displacement patterns. A split-plot design served to separately analyze the effects of stimulation site and stimulation intensity on the measured variables. Stimulation site was assigned to the main plot, and stimulation intensity, to the split-plot. Interaction between stimulation site and stimulation intensity factors was included in the model. All analyses were conducted by SPSS package, version 13.0 (Chicago, IL), and the significance level was set to 5%.

Fig. 2. Representative example of thoraco-abdominal displacement in a study subject with bilateral anterior magnetic phrenic stimulation (BAMPs) at 60% (A) and 100% (B) of stimulator output as well as with anterior magnetic stimulation (a-MS) at 100% of stimulator output (C). Note the outward followed by inward thoracic motion in B and C (shaded areas).
RESULTS

Patients

The anthropometric characteristics of patients were age: 54.9 ± 14.4 yr; body mass index: 30.2 ± 3.7 kg/m²; apnea-hypopnea index (AHI): 38.6 ± 23.2 events/h; neck circumference: 41.5 ± 2.1 cm; Epworth sleepiness scale: 11 ± 4; and oxygen desaturation index: 31.3 ± 34.8 events/h (values are means ± SD).

Characteristics of Phrenic Nerve MS Twitches

There was no difference in maximal tolerated intensity between BAMPS and a-MS (94.4 ± 4 vs. 91 ± 4.6%, respectively; P = 0.2). At maximal stimulator output, the stimulation-related discomfort level was similar between the two stimulation sites [BAMPS: median 7, interquartile range (5–8); a-MS: median 6, interquartile range (5–8); P = 0.7]. The minimum stimulation intensity associated with flow-limited twitches did not differ between the two stimulation sites (BAMPS: 62.2 ± 19.8%; a-MS: 64.4 ± 17.4%; P = 0.8). Overall, BAMPS and a-MS induced similar percentages of flow-limited twitches (56 ± 35 vs. 57 ± 40%, respectively; P = 0.9). Among flow-limited twitches, 33 ± 62% occurred exclusively at the oropharynx and 67 ± 61% at the oropharynx and velopharynx levels. There was no difference in UA collapsing site between the two stimulation procedures (i.e., 18 ± 31 and 27 ± 41% of flow-limited twitches occurred at the oropharynx with BAMPS and a-MS, respectively; P = 0.4).

UA Dynamic Properties

The mean value of P_{eso,peak} of nonflow-limited twitches was more negative with BAMPS than with a-MS (BAMPS: −11.3 ± 0.8 cmH₂O; a-MS: −6.0 ± 0.9 cmH₂O; means ± SE; P < 0.0001). Examining the effects of stimulation site, stimulation intensity, and site*intensity interaction on the characteristics of non-flow-limited twitches, only the first factor accounted for the more negative mean value of P_{eso,peak}. No differences were found in the mean values of any other UA dynamic variables of non-flow-limited twitches induced by BAMPS and a-MS.

Concerning flow-limited twitches, P_{eso,peak} and P_{close} were more negative and linear UAR was higher with BAMPS than with a-MS (Table 1). Only the stimulation site effect accounted for these differences. No difference in V_{max} or peak pharyngeal pressure at which the UA will be closed.

Table 1. Characteristics of flow-limited twitches induced by BAMPS and a-MS

<table>
<thead>
<tr>
<th>Variables</th>
<th>BAMPS</th>
<th>a-MS</th>
<th>P Value for Stimulation Site Effect</th>
<th>P Value for Stimulation Intensity Effect</th>
<th>P Value for Stimulation Site-Intensity Interaction Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>V_{max}, ml/s</td>
<td>694.1 ± 45.4</td>
<td>768.8 ± 52.5</td>
<td>0.28</td>
<td>0.93</td>
<td>0.62</td>
</tr>
<tr>
<td>P_{ph1,peak}, cmH₂O</td>
<td>−9.7 ± 0.9</td>
<td>−7.6 ± 1</td>
<td>0.13</td>
<td>0.33</td>
<td>0.77</td>
</tr>
<tr>
<td>P_{eso,peak}, cmH₂O</td>
<td>−11.5 ± 0.9</td>
<td>−6.5 ± 1.1</td>
<td>0.002</td>
<td>0.71</td>
<td>0.97</td>
</tr>
<tr>
<td>Linear UAR, cmH₂O·1^{-1}·s^{-1}</td>
<td>3.5 ± 0.4</td>
<td>2.2 ± 0.4</td>
<td>0.02</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>P_{close}, cmH₂O</td>
<td>−7.7 ± 0.5</td>
<td>−5.8 ± 0.6</td>
<td>0.02</td>
<td>0.57</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. BAMPS, bilateral anterior magnetic phrenic stimulation; a-MS, anterior magnetic stimulation; V_{max}, maximal inspiratory flow; P_{ph1,peak}, oropharyngeal peak pressure; P_{eso,peak}, esophageal peak pressure; UAR, upper airway resistance; P_{close}, theoretical value of oropharyngeal pressure at which the UA will be closed.

Thoraco-Abdominal Motion

In 1 of 10 subjects, BAMPS caused outward motion of the thoracic region regardless of stimulator output level. In four subjects, BAMPS evoked inward displacement of the thoracic region independently of stimulation intensity (Fig. 2A). In the five other subjects, BAMPS induced a shift of the thoracic motion pattern with increasing stimulator output level. The mean stimulator output level associated with modulation of the thoracic motion pattern in these five patients was 70 ± 11% (SD). BAMPS caused inward displacement of the thoracic region under this threshold and, above it, the thoracic motion pattern changed to outward followed by inward displacement (Fig. 2B). In all 10 study subjects, BAMPS induced outward displacement of the abdominal region regardless of stimulator output level.

In all subjects and regardless of stimulation intensity, a-MS elicited outward followed by inward displacement of the thoracic region and outward motion of the abdominal compartment (Fig. 2C).

The amplitude of outward thoracic displacement was higher with a-MS than with BAMPS and was only determined by the stimulation site effect. The time required to achieve maximal displacement was significantly lower with a-MS (Table 2). The amplitude of outward abdominal displacement did not differ between stimulations sites. Time to maximal displacement was significantly lower with a-MS and was influenced by stimulation site and intensity effects but not by their interaction (Table 2).

For twitches in which the thoracic compartment moved outwardly and then inwardly, the MI tended to be higher with
a-MS than with BAMPS ($P = 0.06$), remaining close to one regardless of stimulator output level (Fig. 3).

Analyzing the effects of the BAMPS-induced thoracic displacement pattern on UA dynamic properties, the linear UAR of flow-limited twitches performed at identical maximal intensity was lower in patients with outward/inward thoracic displacement than in those with exclusive inward thoracic movement. There were no differences in all other variables of non-flow-limited and flow-limited twitches, depending on the thoracic motion pattern (Table 3).

**DISCUSSION**

This study provided data on the utility of a-MS to assess UA dynamic properties in conscious sleep apnea patients. We demonstrated that the percentage of flow-limited twitches was similar between BAMPS and a-MS, even if BAMPS generated higher driving pressure. Furthermore, the a-MS linear UAR of flow-limited twitches was lower and the thoracic displacement pattern was different between the two stimulation techniques.

**a-MS Ability to Generate Driving Pressure and Flow-Limited Twitches**

The ability to create flow-limited twitches by a given phrenic nerve stimulation technique critically depends on its capacity to generate a sufficient level of intra-thoracic negative pressure and on UA collapsibility. The present results show that BAMPS and a-MS created similar percentages of flow-limited twitches (~55%) with the same minimal output stimulator level (~60%). The difference in $P_{eox, peak}$ observed between BAMPS and a-MS could relate to the ability of these stimulation techniques to recruit the diaphragm. Indeed, a-MS can stiffen the upper rib cage by coactivating extra-diaphragmatic inspiratory muscles (discussed below) and thus theoretically allowing for greater twitch esophageal pressure (15). However, with a-MS, stimulator output is delivered by a single coil, which activates both phrenic nerves. In contrast, with BAMPS, each phrenic nerve is stimulated by the entire output of a single stimulator, but the technique is more prone to producing thoracic paradoxes. It must be noted that the percentage of BAMPS-induced flow-limited twitches was lower in the present investigation (56%) than previously reported in our laboratory (77%) (18). Differences in apnea severity (AHI: 38.6 ± 23.2/h and 47.2 ± 11.2/h, respectively), neck tissue loading (neck circumference 41.5 ± 2.1 cm and 46.0 ± 3.8 cm, respectively), and the fact that stimulator output was set at 100% intensity in our earlier study could account for these variations.

**UA Dynamic Properties Assessed by BAMPS and a-MS**

Stimulation site accounted for the dissimilarities in UA dynamic properties assessed by BAMPS and a-MS. Interestingly, UAR induced by a-MS was found to be lower than with BAMPS. Because twitches were applied at the same timing during tidal breathing, we do not believe that differences in lung volume at twitch onset could explain such variations. Upper rib cage stabilization induced by a-MS, and to a lesser extent by BAMPS (discussed below), may have enhanced the inspiratory-related tracheal caudal traction effect and increased airway length (22) and airway wall longitudinal tension (24). We recently compared the ability of a-MS and CMS to evaluate UA dynamic properties in conscious, healthy subjects and demonstrated that, even with similar pharyngeal pressures, inspiratory flow was greater and UA isoflow resistance was lower with a-MS (3). We hypothesized that these differences in UA mechanical properties were influenced by upper rib cage stiffening induced by upper thoracic muscle coactivation, although we did not measure rib cage displacement or the electrical activity of such muscles (3). The present study indicated that with a-MS, early diaphragm depolarization occurred as the thoracic cage was stabilized by the activation of accessory inspiratory muscles because the upper thorax moved outwardly and inwardly systematically in all subjects (MI above or close to 1; Fig. 3). In contrast, BAMPS induced outward/inward thoracic movement in 50% of patients with increasing stimulator output. In these five patients, the linear UAR of flow-limited twitches was lower than that observed in four other subjects in whom BAMPS elicited inward thoracic displacement only (Table 3), expected to be due to the effect of rib cage stabilization exerted on UA patency. This difference in the pattern of upper rib cage displacement induced by the two stimulation techniques may account for the lower UAR values produced by a-MS (Table 1).

Modeling the pharyngeal pressure-airflow relationship by second-degree polynomial regression provides theoretical pressure at which the UA would close and is thus a measure of UA collapsibility (25). $P_{close}$ was more negative with BAMPS than with a-MS (Table 1). In the context of decreased UAR during the non-flow-limited portion of flow-related twitches (reduced upstream and downstream resistance with a-MS), the increased

Table 3. UA dynamic properties of BAMPS-induced flow-limited twitches according to the thoracic displacement pattern obtained at identical maximal intensity

<table>
<thead>
<tr>
<th>Variables</th>
<th>Outward Inward Thoracic Displacement</th>
<th>Inward Thoracic Displacement</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{I, max}$, ml/s</td>
<td>621.3 ± 145.5</td>
<td>678.2 ± 173.6</td>
<td>0.8</td>
</tr>
<tr>
<td>$P_{Ph1,peak}$, cmH2O</td>
<td>$-6.0 ± 2.4$</td>
<td>$-8.3 ± 2.2$</td>
<td>0.06</td>
</tr>
<tr>
<td>$P_{Peso,peak}$, cmH2O</td>
<td>$-6.4 ± 1.8$</td>
<td>$-9.6 ± 2.4$</td>
<td>0.33</td>
</tr>
<tr>
<td>Linear UAR, cmH2O-1·s⁻¹</td>
<td>2 ± 0.05</td>
<td>4.3 ± 1.5</td>
<td>0.03</td>
</tr>
<tr>
<td>$P_{close}$, cmH2O</td>
<td>$-8.6 ± 1$</td>
<td>$-9.1 ± 1$</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Values are means ± SE.
UA stability seen with BAMPS could be attributed to an effect of the MS technique on UA dilating forces. In fact, with BAMPS, magnetic coils are in the immediate environment of anterior neck structures, and even if twitches were not focused on UA motoneurons, MS at this site could potentially interact with UA muscle activity (i.e., genioglossus, geniohyoid), which, in turn, could stabilize UA structures. Different attempts were made in our laboratory to characterize genioglossus activity after BAMPS, but stimulation artifacts systemically interfered with our ability to analyze electromyographic activity. We anticipate that such BAMPS-induced UA muscle activation should not occur with a-MS because of the distance between the sternal coil and UA structures.

**Thoraco-Abdominal Motion**

The thoraco-abdominal motion pattern, the time required to achieve maximal displacement, and thoracic amplitude differed significantly between BAMPS and a-MS (Table 2). These differences were attributed to the stimulation site effect. Paradoxical thoracic movement induced by BAMPS and a-MS results from uncoordinated contraction (or even nonrecruitment) of inspiratory accessory muscles that physiologically move the ribs cranially and stabilize the rib cage (5, 6).

BAMPS generated inward motion of the thoracic compartment in 4 of our 10 patients. It is interesting that in five other patients, BAMPS evoked outward/inward thoracic movement with increasing stimulator output. To precisely locate phrenic nerves in the neck base, the coils were placed in or near the supra-clavicular fossa, leading to potential depolarization of brachial plexus branches and activation of the upper thoracic muscles (11). In these patients, as the MI remained below one throughout stimulation (Fig. 3), recruitment of the upper rib cage-stabilizing muscles was mild and did not last the entire twitch-flow duration.

With a-MS, the upper rib cage moved outward/inwardly in all patients, and the MI was above or close to one (Fig. 3), meaning that outward and inward displacement amplitudes throughout stimulation were similar. With the nonfocal coil placed over the sternum, we expect upper rib cage-stabilizing muscles, such as the pectoralis major, parasternal, and scalenes, to be recruited (5–7), because the thoracic displacement induced by a-MS is greater than that elicited by BAMPS (Table 2). Although largely recruited, the activation of such muscles, as occurring with BAMPS, did not last the entire twitch-flow duration.

**Conclusions**

In summary, we found that the stimulation site effect is the most important factor determining driving pressure, UA dynamic properties, and thoraco-abdominal motion during phrenic nerve MS. Furthermore, as a-MS is as efficient as BAMPS in inducing flow-limited twitches in conscious sleep apnea patients, assessment of UA dynamic properties by phrenic nerve MS could be simplified by using only one stimulator with its output adjusted to a level capable of producing flow-limited twitches. We demonstrate that a-MS is an easy, practical, and well-tolerated approach capable of eliciting pharyngeal flow-limited twitches, as obtained with BAMPS, considered as “gold standard” methodology to reproduce UA closure in apneic patients during wakefulness, one of the most important outcomes in the context of UA dynamics evaluation.

Finally, a-MS could be employed in clinical studies and in fundamental research aimed at evaluating physiological determinants of UA dynamics and the efficiency of treatment modalities aimed at improving UA stability in patients with obstructive sleep-disordered breathing.

**GRANTS**

This work was funded by Canadian Institutes of Health Research (CIHR) Grant 89985. Dr. Borel is a postdoctoral fellow supported by Agiradom (Meylan, France) and Fonds de dotation “Recherche en Santé Respiratoire et de l’ANTADIR”.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

Author contributions: C.A.M.-S., J.-C.B., and S.G. performed experiments; C.A.M.-S. and J.-C.B. analyzed data; C.A.M.-S., S.G., and F.S. interpreted results of experiments; C.A.M.-S. prepared figures; C.A.M.-S. drafted manuscript; J.-C.B., S.G., and F.S. edited and revised manuscript; F.S. conception and design of research; F.S. approved final version of manuscript.

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