

Discriminative power of phrenic twitch-induced dynamic response for diagnosis of sleep apnea during wakefulness

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Verin, Eric, Thomas Similowski, Antonio Teixeira, and Frédéric Sériès. Discriminative power of phrenic twitch-induced dynamic response for diagnosis of sleep apnea during wakefulness. *J Appl Physiol* 94: 31–37, 2003. First published September 6, 2002; 10.1152/jappphysiol.00216.2002.—The diagnosis of the obstructive sleep apnea syndrome relies on polysomnography. Bilateral anterior magnetic phrenic stimulation (BAMPS) mimics the dissociation between upper airway (UA) muscles and diaphragm commands that leads to UA closure during sleep. We evaluated BAMPS as a mean to identify obstructive sleep apnea syndrome patients through the characterization of the UA dynamics in 28 consecutive awake patients (18 apneic and 10 nonapneic). Driving pressure (Pd) and instantaneous flow (\dot{V}) were recorded in response to BAMPS to determine the point of flow limitation (\dot{V}_{max}) and of minimal flow (\dot{V}_{min}) and the flow-pressure relationship [$\dot{V}_I = (k_1 \times \text{Pd}) + (k_2 \times \text{Pd}^2)$]. \dot{V}_{max} , \dot{V}_{min} , UA resistance at \dot{V}_{min} , and the coefficient of the flow-pressure relationship (k_1) were correlated with apnea-hypopnea index (respectively, $R = -0.735$, $P < 0.0001$; $R = -0.584$, $P = 0.001$; $R = 0.474$, $P = 0.01$; and $R = -0.567$, $P < 0.01$). Body mass index was also correlated with apnea-hypopnea index ($R = 0.500$, $P < 0.01$). Apneic patients had a lower \dot{V}_{max} ($\dot{V}_{\text{max}} = 678 \pm 386$ vs. $1,247 \pm 271$ ml/s; $P < 0.001$), a lower \dot{V}_{min} ($\dot{V}_{\text{min}} = 460 \pm 313$ vs. 822 ± 393 ml/s; $P < 0.05$) and a lower k_1 ($k_1 = 162 \pm 67$ vs. 272 ± 112 ml·cmH₂O·s⁻¹; $P < 0.01$) than nonapneic ones. Using a classification and regression tree approach, we found that a \dot{V}_{max} of <803 ml/s ($n = 12$) selected only apneic patients. When \dot{V}_{max} of >803 ml/s ($n = 16$), a k_1 of >266.7 ml·cmH₂O·s⁻¹ identified only nonapneic patients ($n = 5$). In 11 cases, $\dot{V}_{\text{max}} > 803$ ml/s and $k_1 < 266.7$ ml·cmH₂O·s⁻¹. These included five nonapneic and six apneic patients. We conclude that UA dynamic properties studied with BAMPS during wakefulness significantly differ between nonapneic and apneic patients.

sleep apnea syndrome; phrenic nerve; stimulation; magnetic; upper airway

OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS) is highly prevalent in middle-aged overweight adults, affecting

as many as 2% of women and 4% of men (34). Because of its morbid consequences, it is a major social and public health problem.

Upper airway (UA) dynamics abnormalities are pivotal in the pathogenesis of the OSAS (22). From a mechanical point of view, UA instability during sleep results from several phenomena such as an increase in UA resistance, the development of more negative inspiratory pressure swings (1), and/or an impairment of UA muscle contractile properties (4). From a functional point of view, a major determinant of sleep-induced UA closure is the loss of the preactivation of UA dilator muscles that normally precedes the activation of inspiratory muscles (10).

Experimentally, UA collapsibility can be studied through the flow response to the application of changing UA pressure. This can be obtained by decreasing the pressure at the nose (upstream pressure) (8, 21, 23), the UA then tending to narrow and close when the pharyngeal transmural pressure gradient decreases to zero, as a function of intrinsic UA characteristics (namely their shape, dimension, and compliance; Ref. 17). The only force available to maintain the patency of the UA faced with the negative pressure related to inspiratory efforts is provided by the adapted contraction of UA dilator muscles. Conversely, partial UA obstruction can be obtained by applying a negative pressure downstream (i.e., trachea), which has been consistently shown in experiments using a feline UA model (19) and using an Emerton tank respirator (20). This strategy is useful to evaluate the influence of different physiological conditions on the dynamics of UA structure in a quasi-passive state because the driving pressure (Pd) is developed mechanically and independently of the central respiratory control input.

Phrenic nerve stimulation provides a most realistic model to study the inspiratory flow dynamics of the

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passive (or, more precisely, not phasically active) UA (24, 29, 31) in awake individuals. Indeed, it mimics the OSAS typical dissociation between the activation of UA dilators and that of inspiratory muscles, because it provokes a diaphragm contraction and the corresponding negative intrathoracic pressure independently of any coincident phasic control of UA muscles activity and provokes inspiratory flow limitation.

The present work was conducted, in an unselected population of patients referred to a sleep laboratory by their attending physicians, to study the discriminative power of UA mechanical properties determined with phrenic nerve stimulation regarding the results of polysomnography (PSG) taken as the gold standard diagnosis and staging tool. We hypothesized that the degree of flow limitation induced by the phrenic nerve stimulation-induced diaphragm twitch should be correlated to the OSAS severity.

MATERIALS AND METHODS

Patients

Twenty-eight patients referred to the sleep laboratory of the institution where the study took place (Université Laval, Québec) to undergo a diagnostic polysomnography participated in the study, after approval of the corresponding institutional review board and recording of their written consent (Table 1).

Table 1. *Anthropometric and polysomnographic data*

Subject	Classification	AHI	BMI
1	NI	12.7	24.9
2	NI	14.1	29.9
3	NI	15.8	29.2
4	NI	0.8	25.8
5	NI	9.2	24.4
6	NI	0.4	18.5
7	NI	6.4	30.9
8	NI	3.7	19.7
9	NI	12.5	22.2
10	NI	15.4	28.7
Mean ± SD		9.1 ± 5.6	25.4 ± 4.1
11	OSAS	26.5	48.4
12	OSAS	64.9	36.6
13	OSAS	51.1	33.2
14	OSAS	33.9	31.3
15	OSAS	25.0	35.2
16	OSAS	28.9	27.3
17	OSAS	76.1	32.3
18	OSAS	35.6	24.9
19	OSAS	22.2	25.3
20	OSAS	46.7	30.8
21	OSAS	62.3	38.3
22	OSAS	37.4	27.8
23	OSAS	33.5	30.1
24	OSAS	17.6	27.8
25	OSAS	62.8	27.3
26	OSAS	23.0	31.3
27	OSAS	58.6	32.6
28	OSAS	20.9	24.6
Mean ± SD		40.4 ± 17.6	31.4 ± 5.6

NI, normal subjects; OSAS, obstructive sleep apnea patients; AHI, apnea-hypopnea index (n/h of sleep); BMI, body mass index (kg/m²).

Sleep Recordings

PSG consisted of in-lab continuous acquisitions of electroencephalogram (C₄/A₁, C₃/A₂, O₂/A₁ and O₁A₂), electrooculogram, submental electromyogram (EMG), arterial oxyhemoglobin saturation from transcutaneous sensing with an ear oximeter (504 pulse oximeter, Criticare System, Waukesha, WI), naso-oral airflow with thermistors, nasal pressure with nasal prongs connected to a pressure transducer (Validyne MP 45 ± 100 cmH₂O) (27), chest and abdominal movements by inductive plethysmography (Respirace, Ambulatory Monitoring, Ardsley, NY), electrocardiogram, and breathing sounds (to detect snoring) with two microphones placed at the head of the bed (28). All variables were digitally recorded (Sandman Elite system, Mallinckrodt, Kenilworth, NJ). Sleep position was continuously monitored by the attending technician on the monitor of an infrared camera. The apnea-hypopnea index (AHI) and the arousal index were calculated throughout the night and in the different sleep positions.

UA Characteristics During Wakefulness

Pressure and flow measurements. Esophageal pressure (Pes), a reflection of pleural pressure, was obtained from a balloon-catheter system (1.6 mm internal diameter) passed through one nostril after topical anesthesia and positioned according to established technique (2). The pressure at the airway opening was measured in an airtight nasal mask (Profile light nasal mask, Respironics, Pittsburgh, PA). Pes and mask pressure were measured by using differential pressure transducers (Validyne MP 45 ± 100 cmH₂O) and referenced to one another to determine Pd. Flow was obtained from a pneumotachograph (Hans Rudolph, model 112467-3850A, Kansas City, MO) connected to the mask and opened to atmosphere via a nonbreathing valve (Respironics). Pressures and flow were digitally recorded at a 300-Hz sample rate (Digidata 1320, Axon Instrument, Foster City, CA).

Diaphragm EMG. Surface recordings of the right and left costal diaphragmatic EMG activities were obtained by using silver cup electrodes placed on the midclavicular line in the lowest accessible intercostal space (32) and connected to an EMG (Biopac system, Biopac, Santa Barbara, CA).

Phrenic nerve stimulation. Bilateral anterior magnetic phrenic nerve stimulation (BAMPS) was performed with two Magstim 200 stimulators (Magstim, Whitland, Dyfed, UK), connected to two 90° handle 45-mm eight-shaped coils (14), and set at their maximal output.

Protocol. BAMPS studies were performed within the week after the PSG recording. The patients were seated in a comfortable armchair with a 60° inclination. A premolded pillow maintained the head in the neutral position. Special attention was paid to avoid any change in body, neck, or head position throughout the experiment because such changes are known to influence the UA dynamics characteristics as assessed by phrenic stimulation (31). A nasal stent placed in the anterior nostrils (Nozovent; WPM international; Göteborg, Sweden) prevented nasal collapse. BAMPS was performed at the end of a relaxed expiration, according to the monitoring of the Pes and flow traces, with the subjects breathing exclusively by the nose. BAMPS studies took place during room air breathing at the atmospheric pressure. Five stimulations were then delivered at a four- to five-breath interval.

Data Analysis

BAMPS-induced twitches were considered flow limited when flow plateaued or decreased despite an increase in Pd

(24). We term limiting pressure ($P_{d,lim}$) as the P_d value corresponding to the maximal flow value of flow-limited twitches (\dot{V}_{imax}). Beyond \dot{V}_{imax} , flow dropped down to a minimal value (\dot{V}_{imin}) despite the increasing P_d ($P_{d,peak}$). Total respiratory resistances were calculated at \dot{V}_{imax} and \dot{V}_{imin} ($R_{V_{imax}}$ or $R_{V_{imin}}$) as the ratio of the corresponding P_d ($P_{d,lim}$ or $P_{d,peak}$) and \dot{V}_I (\dot{V}_{imax} and \dot{V}_{imin} , respectively). The twitch-flow dynamics were characterized by the P_d -flow relationship obtained for each twitch in each subject from zero flow up to \dot{V}_{imin} . This relationship was most accurately fitted by a polynomial regression model of order 2 ($\dot{V}_I = k_1 P_d + k_2 P_d^2$, k_2 being negative).

Statistical Analysis

The statistical analysis was performed by using the Statview 5.0 software (SAS Institute, Berkeley, CA) running on an Apple Macintosh computer and the S-Plus 2000 statistical package release 2 (Mathsoft, Seattle, WA) running on an emulated IBM-PC-compatible computer. All the results are expressed as means \pm SD. Differences were considered significant when the probability P of a type I error was 0.05 or less.

Pressure-flow fits were obtained by using the least square regression method. Statistical associations between twitch-flow characteristics and the severity of sleep-related respiratory disturbances were studied by using the z -test for correlation.

The phrenic nerve stimulation-derived UA characteristics ($P_{d,lim}$, $P_{d,peak}$, \dot{V}_{imax} , \dot{V}_{imin} , k_1 , k_2) obtained in the 28 patients were used to construct tree-based models according to the nonparametric classification and regression tree (CART) methodology (3, 5). The models are fitted by binary recursive partitioning to successively split a population into increasingly homogeneous subpopulations, each split depending solely on the value of a single variable. Using the PSG-derived diagnosis of OSAS as a dichotomous outcome (normal subject vs. OSAS patients, normal subjects defined by an $AHI \leq 15/h$; Ref. 1a), we reapplied this procedure to study how accurately the subjects could be classified as OSAS patients or normal subjects from the flow-pressure response to phrenic nerve stimulation.

RESULTS

Eighteen patients were stratified as "OSAS" and 10 as "normal" according to the conventional PSG studies. Their anthropometric and polygraphic characteristics are presented in Table 1.

During spontaneous breathing at atmospheric pressure, flow limitation was never detected in either group. Conversely, BAMPS induced a typical flow-limitation pattern in all cases (Fig. 1). The pressure-flow relationship up to \dot{V}_{imin} being adequately fitted by the $\dot{V}_I = k_1 P_d + k_2 P_d^2$ equation (mean $r^2 \pm$ SD = 0.94 ± 0.06 ; range 0.71–0.99). The values used to characterize each subject below represent the average of five responses to BAMPS.

\dot{V}_{imax} , \dot{V}_{imin} , $R_{V_{imin}}$, and k_1 were correlated with the AHI (respectively, $R = -0.73$, $P < 0.0001$; $R = -0.58$, $P = 0.001$; $R = 0.47$, $P = 0.01$; and $R = -0.57$, $P < 0.01$) (Fig. 2). The body mass index (BMI) was also correlated with the AHI ($R = 0.50$, $P < 0.01$).

On average, the 18 OSAS patients had a lower \dot{V}_{imax} than the 10 normal ones ($\dot{V}_{imax} = 678 \pm 386$ ml/s vs. $1,247 \pm 271$ ml/s; $P < 0.001$), a lower \dot{V}_{imin}

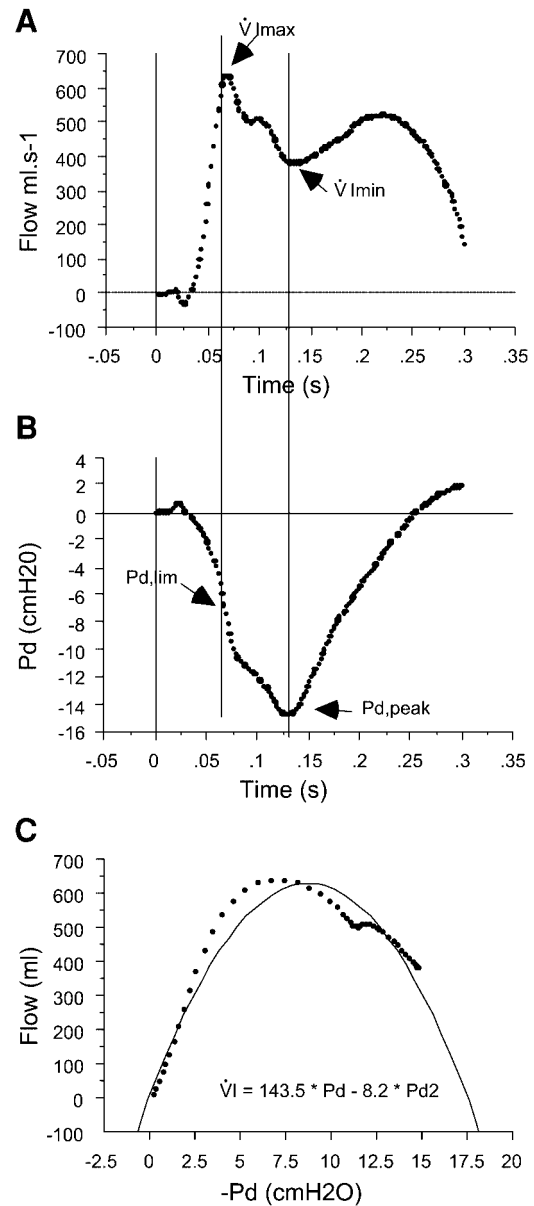


Fig. 1. Example, in 1 subject, of the evolution with time of the twitch-induced flow (A), the twitch-induced driving pressure (P_d) (B), and the corresponding transnasal flow- P_d relationship (C) up to the minimal flow value reached during the twitch (\dot{V}_{imin}). \dot{V}_{imax} , maximal flow value reached during the twitch; $P_{d,lim}$, corresponding pressure; $P_{d,peak}$, P_d corresponding to \dot{V}_{imin} . The pressure-flow fit up to \dot{V}_{imin} is excellent, and it was the case for every twitch for every subject.

($\dot{V}_{imin} = 460 \pm 313$ ml/s vs. 822 ± 393 ml/s; $P < 0.05$), and a lower k_1 ($k_1 = 162 \pm 67$ vs. 272 ± 112 ml·cmH₂O·s⁻¹; $P < 0.01$) (Fig. 3).

The PSG established AHI as being taken as a dichotomous outcome, and the CART approach selected three BAMPS-derived UA dynamics characteristics measured at atmosphere (\dot{V}_{imax} , k_1 , and $P_{d,lim}$) as decision knots. The BMI was not selected as a discriminative parameter. A \dot{V}_{imax} of <803 ml/s ($n = 12$) selected exclusively OSAS patients. When \dot{V}_{imax} was >803 ml/s ($n = 16$), a k_1 value of >266.7 ml·cmH₂O·s⁻¹

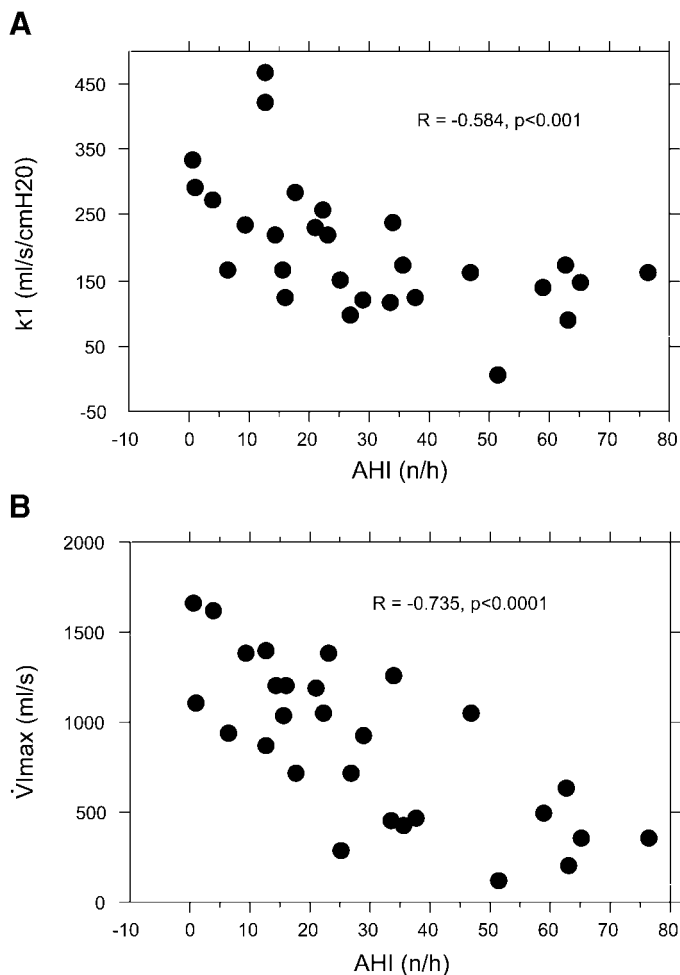


Fig. 2. Correlation between the individual values of the apnea-hypopnea index (AHI) and the corresponding values of maximal flow value reached during the twitch (\dot{V}_{max} ; A) and coefficient of the $\dot{V}_I = k_1P + k_2P^2$ flow-pressure relationship (k_1 ; B), where \dot{V}_I is instantaneous flow and P is the driving pressure.

identified only normal subjects ($n = 5$). In the remaining 11 cases ($\dot{V}_{\text{max}} > 803$ ml/s and $k_1 < 266.7$ ml \cdot cmH₂O \cdot s⁻¹), a $P_{d,\text{lim}}$ of less than -8 cmH₂O selected five patients (1 normal subjects and 4 OSAS patients), and a $P_{d,\text{lim}}$ of less than -8 cmH₂O identified the remaining six patients (2 OSAS patients and 4 normal subjects) (Fig. 4). BAMPS-derived UA indexes thus permitted correct identification of 61% of the 28 patients as apneic or nonapneic.

DISCUSSION

This study suggests that the assessment of UA mechanical properties by use of phrenic nerve stimulation during wakefulness could usefully contribute to the diagnosis of the OSAS and to the evaluation of its severity, by alleviating the need for overnight PSG in a considerable number of patients.

Methodological Considerations

Because we used P_{es} to measure P_d rather than the supralaryngeal pressure, only the total resistance of

the respiratory system was measured, rather than UA resistance. This must be kept in mind when interpreting the results but is probably not a major issue because UA resistance accounts for the most part of the total respiratory resistance during nasal breathing (9, 30). The pharyngeal segment of the UA accounts for most of their resistance to flow during a diaphragm twitch (25). We allocated two patients with an AHI below 15/h to the OSAS group because they fit the definition of the UA resistance syndrome. In line with previous contention (6), their BAMPS-derived UA characteristics were within the ranges observed in the OSAS patients.

Pressure-Flow Relationship

There are dramatic differences in the UA behavior during spontaneous breathing and in response to phrenic nerve stimulation. The UA can be viewed as three segments arranged in series: the nasopharynx, the pharynx, and the hypopharynx. The first and the third of those are relatively stiff. Conversely, the pharyngeal segment, not supported by bony and cartilaginous structures, is collapsible and thus subject to partial or complete occlusion (9) in front of the negative pressure consecutive to inspiratory efforts. The only dilating force available to counteract this process and

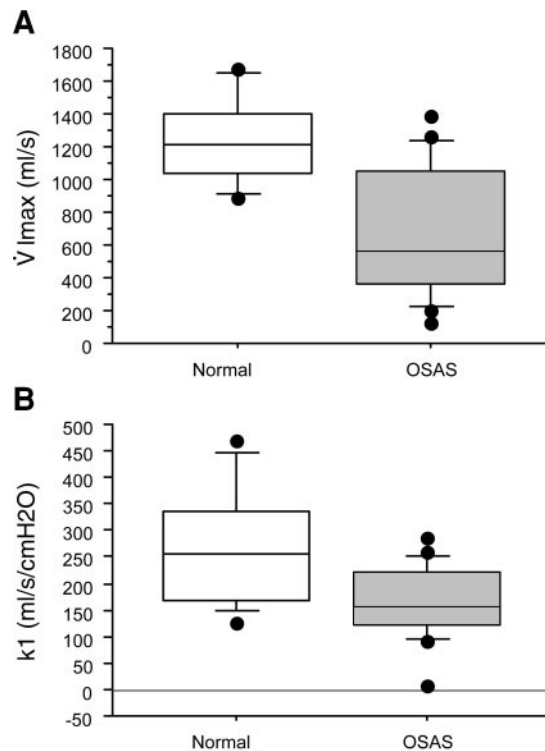


Fig. 3. Values of the twitch-induced flow (\dot{V}_{max} ; A) and the k_1 coefficient of the $\dot{V}_I = k_1P + k_2P^2$ flow-pressure relationship (B) measured in the subjects identified as normal by the polysomnography (white boxes) and those identified as patients with the obstructive sleep apnea syndrome (gray boxes). Boxes depict the 25th to 75th percentile of the data with indication of the median value; horizontal lines outside the boxes depict the 10th and 90th percentile; outliers are shown as closed circles.

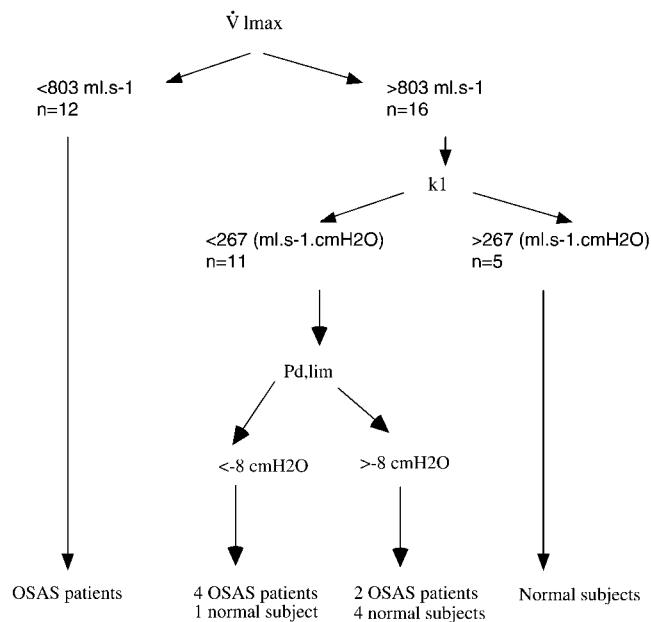


Fig. 4. Schematic representation of the results of the classification and regression tree analysis. See text for details.

maintain UA patency is physiologically provided by the contraction of UA dilator muscles. Therefore, the timing of their phasic inspiratory activation is crucial, because it must precede that of inspiratory muscles (10). If the strength and the timing of UA dilator contractions are adequate, the inspiratory flow through the UA linearly increases with Pd, as is observed during spontaneous breathing in normal subjects. If this is not the case, typically in OSAS patients while asleep, flow first increases with Pd and then reaches a plateau at which it is independent of the intensity of the inspiratory effort. Because of the absence of preinspiratory UA stabilization, phrenic nerve stimulation is a powerful promoter of flow limitation (24). However, the observed flow pattern does not generally include a plateau as in spontaneously breathing OSAS patients, but is typically “M” shaped (Fig. 1). This is consistent with the UA being passive (or only tonically active) when the BAMPS-related inspiration occurs, the late reincrease in flow being probably accounted for by a negative pressure-triggered reflex activation of UA dilators (24). Because the main advantage of phrenic nerve stimulation is to study UA properties free of UA dilators phasic activity, it is justified to limit the analysis of the flow pressure relationship to the segment of this relationship that precedes the activation of the genioglossus. This explains why the best descriptor of the pressure-flow relationship in our study was a polynomial regression of order 2 [$P = k_1\dot{V}_I + k_2\dot{V}_I^2$ (18)] and not a rectangular hyperbolic regression ($\dot{V} = Pd/\alpha + Pd$) that has been shown to adequately characterize the flow-pressure relationship of flow-limited breaths during sleep (11). Of note, because of the constancy of highly significant relationships between Pd and instantaneous flow in response to phrenic stimulation, we feel that the computation of

the k_1 and k_2 coefficients of the above equations should be systematically included in the characterization of the UA dynamics assessed with this technique.

Clinical Management Perspectives

For phrenic nerve stimulation as an “UA tool” to be useful in the management of the OSAS, it must provide information consistent with known pathophysiological findings and be operative for screening purposes. In our study, both these criteria seem to be met.

From the point of view of the pathophysiological findings, we found that OSAS patients had BAMPS-derived UA characteristics significantly different from those observed in normal subjects. This agrees well with well-established data indicating that OSAS patients have a marked decrease in UA cross-sectional area that increases UA resistance (1) and pharyngeal collapsibility (23). Complete UA collapse leading to apnea is common during sleep in OSAS patients, but we did not observe this feature in our awake patients in response to BAMPS. Although BAMPS mimics the dissociation between the action of UA dilator muscles and that of the diaphragm that is typical in the OSAS, the UA so explored are not actually “passive,” but only “nonphasically active.” It can thus be speculated that the absence of BAMPS-induced UA closure during wakefulness is due to a preserved UA muscle tone, of which the decline during sleep is a source of a further impairment of UA stability. In this regard, Sériès and Marc (26) have shown that increasing the tonic activity of the genioglossus improved the stability of the UA, as assessed from phrenic stimulation.

Our OSAS patients had a significantly higher BMI than the non-OSAS patient, and the AHI was correlated with the BMI, which corresponds well to known facts in the OSAS and probably corresponds to the impact of neck tissue volume in the pathophysiology of airway closure. The AHI and BMI being linked, a correlation between BMI and UA descriptors such as \dot{V}_{max} and \dot{V}_{min} is not surprising. It is thus most interesting to note that the BMI was not selected as a decision knot by the CART analysis. This tends to suggest that BAMPS-derived UA descriptors are likely to identify OSAS patients in the absence of obesity, a rather frequent situation [BMI < 30 kg/m² in about 50% of cases in the study by Mortimore et al. (15)].

From the diagnostic point of view, we found, in addition to significant differences in UA dynamic properties between normal and OSAS patients, a significant association between the individual values of some of these flow-pressure characteristics and the corresponding AHI (Fig. 3). This is in accordance with parallel findings already reported in the literature by several research groups studying various functional and/or anatomical features of the UA during wakefulness [UA collapsibility (8), genioglossus activity (13), UA diameter (16), and expiratory flow limitation using negative expiratory pressure (12, 33)]. In these studies, OSAS patients and normal subjects were found to be different on average, but overlaps between the results

obtained in OSAS and non-OSAS subjects were such that it was difficult to foresee the performance of such investigations as practical diagnostic tools. In this regard, using the CART methodology to analyze of our data provides a novel and practical approach in evaluating the usefulness of diagnosis methods such as BAMPS. Indeed, this approach is specifically designed to examine how homogeneous groups of patients can be constituted from continuous or noncontinuous variables. Being nonparametric, it makes no assumption about the distribution of the data (3, 5). In our study population, BAMPS alone would, with the CART approach, have identified about two-thirds of the patients as OSAS or non-OSAS ones. Thus a diagnostic PSG recording would still be needed after the BAMPS procedure in only one-third of the referred patients. Apart from this potential advantage in the diagnosis management of patients with a clinical suspicion of OSAS, it can be anticipated that this method could be also helpful in determining during wakefulness the adequate setting of an effective treatment such as continuous positive airway pressure or anterior mandibular prosthesis.

Our results confirm that the UA flow dynamics measured during wakefulness by using phrenic nerve stimulation differ between normal subjects and OSAS patients and suggest that these differences are such that they open new perspectives for the diagnosis of the disease, with potential major financial impacts. However, these results are exploratory in nature, and it must be kept in mind that the CART approach is dependent on the size of the sample studied. It will be necessary to validate the concept through a large-scale prospective multicenter approach.

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