Detecting upper airway obstruction in patients with tracheal stenosis

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Verbanck S, de Keukeleire T, Schuermans D, Meysman M, Vincken W, Thompson B. Detecting upper airway obstruction in patients with tracheal stenosis. J Appl Physiol 109: 47–52, 2010. First published May 13, 2010; doi:10.1152/japplphysiol.01103.2009.—We propose a forced oscillation test modality for detecting upper airway obstruction (UAO) as an alternative to spirometric UAO indices in patients with tracheal stenosis. From oscillometry performed at different breathing flow rates, airway resistance at 5 Hz was determined at 0.5 l/s (R), and flow dependence of resistance was computed as the regression slope (e-mail: sylvia.verbanck@uzbrussel.be).

In patients with chronic obstructive pulmonary disease (COPD), resistance is expected to be greater than in normal subjects, yet there is no reason for resistance to show any constriction. By contrast, the occurrence of upper airway constriction. The detection of UAO via the dependence of resistance on increased flow rate (whether or not induced by exercise) has been explored before (2, 3, 7, 9), on the basis of fluid dynamics principles relating pressure drop to flow rate in the case of external orifices. Ingelstedt and Tormemalm (13) measured airway resistance on a tracheal stenosis model, showing a marked increase in resistance with flow rate between 0.5 and 4.0 l/s, and more so for smaller stenosis sizes. Fasano et al. (8) measured airway resistance at different breathing frequency rates by body plethysmography (panting at 30–90 bpm), obtaining a similar resistance at 30 and 90 bpm in normal subjects, but significantly greater resistance for 90 bpm than for 30 bpm in patients with laryngeal hemiplegia. Although the breathing flow dependence of resistance can be exploited to propose a UAO test, its success in a clinical setting will partly depend on ease of use for the patient (e.g., that the patient not be required to have to breathe up to 4 l/s).

The airway resistance measurement method of choice that can be easily modified to assess its dependence on breathing flow rate is the forced oscillation technique (18). With this method, respiratory input impedance is obtained by superimposing a small oscillating pressure wave on the respiratory flow generated by the test subject and simultaneously measuring pressure and flow. The resulting respiratory impedance, most commonly measured at 5 Hz, potentially represents airway, tissue, and chest wall mechanics, and the resistive component can be distinguished from the nonresistive one (reactance). The resistance of the lung tissue, on account of its viscoelastic properties, decreases monotonically with increasing oscillation frequency such that it becomes essentially negligible at 5 Hz. This means that resistance at 5 Hz corresponds to a minor contribution from the Newtonian component of the chest wall plus the flow resistance of the bronchial tree, also including resistance of peripheral airways.

In patients with chronic obstructive pulmonary disease (COPD), resistance is expected to be greater than in normal subjects, yet there is no reason for resistance to show any breathing flow dependence in the absence of upper airway constriction. By contrast, the occurrence of upper airway con-
striction is expected to generate increases in flow dependence of resistance, both in normal subjects and in patients with COPD with peripheral airway obstruction. The first aim of this study was to measure the degree of resistance and flow dependence of resistance generated by varying degrees of constriction simulated by external orifices. We then verified whether the behavior of resistance predicted by external orifices is applicable to patients with tracheal stenosis for whom orifice flow is generated internally.

**MATERIALS AND METHODS**

The study protocol was approved by the UZ Brussel ethics committee (#B14320072713), and informed consent was obtained from all participants. To test whether resistance and the flow dependence of resistance could be meaningful parameters for UAO detection, external orifices of various sizes were presented to 10 normal subjects and 10 patients with COPD. Spirometric and forced oscillation measurements were carried out in all 20 subjects, first with the performance of each test without any obstruction, followed by a random order of 6-mm, 8-mm, 10-mm, and 12-mm orifices plugged in between the mouthpiece and the bacterial filter (that the subject could not see the orifice when performing each test); each test sequence was concluded with another unobstructed measurement.

Subsequently, 10 consecutive patients with tracheal stenosis who were specifically referred to our hospital for a therapeutic interventional bronchoscopy were recruited. Spirometric and forced oscillation measurements were performed between 1 day and a few hours before intervention on all patients, including repeat measurements in two patients who were readmitted for restenosis. In most patients (8/10), the same functional measurements could also be obtained 1 day after the intervention, at discharge from the hospital. During intervention, the pneumologist estimated the lumen area of the narrowest passage in the trachea before treatment of the stenosis. The minimal lumen area postintervention was inferred from the stent inner diameter or from visual inspection at intervention when the procedure simply involved coagulation or dilatation. Calibrated olive-shaped Teflon endings attached to a long metal stick or the rigid biopsy forceps were used as in situ measurement aids.

Spirometry (Vmax Encore; Viassys, Bilthoven, the Netherlands) was obtained using standardized procedures (15). From the forced expiratory flow-volume curve, we used peak expiratory flow (PEF), forced expiratory flow after expiration of 50% forced vital capacity (FEF50), forced expiratory volumes in one and in half a second (FEV1, FEV0.5), and forced expiratory flow between 25% and 75% of forced vital capacity (FEF25–75). The forced inspiratory flow-volume curve following forced expiration was analyzed for midinspiratory forced inspiratory flow (FIF50). The spirometric UAO indices FEV1/PEF, FEV1/FEV0.5, and FEF25–75/FIF50 were also computed (2, 19). Impulse inspiratory flow (FIF50). The spirometric UAO indices FEV1/PEF, FEV0.5), and forced expiratory flow between 25% and 75% of forced

For our statistical analysis, the differences in peripheral airway function (spirometry and impulse oscillimetry) between normal patients and patients with COPD was verified with a Mann-Whitney U-test. For the tracheal stenosis patients, a Wilcoxon paired r-test was used to test for significant differences between pre- and postintervention. Pearson product correlations were performed to test for associations between the impulse oscillimetry parameters and stenosis size (lumen area) or between impulse oscillimetry parameters and spirometric indices. During the performance of all of the above tests (Statistica 5.1; StatSoft, Tulsa, OK), the level of significance was set at \( P = 0.05 \), and data are represented as means \( \pm SD \).

**RESULTS**

To verify how the presence of peripheral airway obstruction influences \( R \) and \( \Delta R/\Delta V \), normal subjects and patients with COPD are first compared in the absence of any external orifice. The COPD group was characterized by low FEV1 [64 \pm 19 \% predicted (% pred) (COPD) vs. 106 \pm 10 \% pred (normal); \( P < 0.001 \), and low FEF25–75 [20 \pm 9 \% pred (COPD) vs. 97 \pm 24 \% pred (normal); \( P < 0.001 \), attesting to the presence of peripheral airways obstruction. In the COPD group, \( R \) values were greater (\( R = 0.42 \pm 0.12 \text{ kPa·L}^{-1}\text{s} \)) than in the normal subjects (\( R = 0.29 \pm 0.06 \text{ kPa·L}^{-1}\text{s} \) (\( P = 0.015 \), yet \( \Delta R/\Delta V \) did not differ significantly between normal \( \Delta R/\Delta V = 0.06 \pm 0.7 \text{ kPa·L}^{-2}\text{s}^{-2} \) and COPD \( \Delta R/\Delta V = 0.03 \pm 0.12 \text{ kPa·L}^{-2}\text{s}^{-2} \) groups (\( P > 0.1 \)).

Figure 1, A and B, illustrates, in a representative normal subject and patient with COPD, that resistance is quasi-independent of breathing flow when no external orifice is applied. With an orifice of decreasing diameter, there is a gradual increase in resistance as well as a gradual increase in the flow dependence of resistance. In a stenosis patient (Fig. 1C), there is a flow dependence of resistance before intervention, which almost disappears after intervention. In Fig. 2, average \( R \) and \( \Delta R/\Delta V \) values (\( \pm SD \)) are provided for normal and COPD groups without external obstruction and with the various external orifices applied. The shaded area corresponds to the interval between lower and upper limit of normal on the basis of the average and standard deviation obtained in the normal group.

The stenosis patients (FEV1 = 68 \pm 32 \% pred) had varying indications for intervention and a range in degree of tracheal stenosis (Table 1). Before intervention, the stenosis patients (Fig. 2, ) showed increased \( R \) and \( \Delta R/\Delta V \) values with respect to normal (shaded area), generally consistent with the increases seen in normal subjects when they breathe through corresponding external orifices. Significant decreases in both \( R \) (\( P = 0.028 \)) and \( \Delta R/\Delta V \) (\( P = 0.008 \)) were observed following intervention in the tracheal stenosis patients. For the eight patients who could be assessed postintervention (, Fig. 2A), \( R \) values were lower, yet only one patient showed a postintervention \( R \) value within the limits of normal. By contrast, in 6 out of 8 patients, postintervention \( \Delta R/\Delta V \) values fell within the limits of normal (Fig. 2B). When including all data points obtained on the stenosis patients before and after intervention, both \( R \) (\( r = −0.68; \) \( P = 0.001 \)) and \( \Delta R/\Delta V \) (\( r = −0.65; \) \( P = 0.001 \)) were inversely correlated to minimal tracheal lumen area.

The corresponding spirometric UAO indices (Fig. 3) show marked FEV1/PEF and FEV1/FEV0.5 increases for decreasing orifice size in the normal group. However, in the
COPD group, these same indices hardly emerge from the limits of normal even for the smallest orifice size. In the stenosis patients, FEV1/PEF and FEV1/FEV0.5 are more variable, including increased and normal values both pre- and postintervention. The UAO index FEF50/FIF50 has an even greater intrinsic variability (as evidenced by the data in normal subjects without obstruction) and falls within the normal range for almost all stenosis patients under study. Using data points before and after intervention (closed and open symbols in Fig. 3), the correlation coefficients of FEV1/PEF, FEV1/FEV0.5, and FEF50/FIF50 with minimal tracheal lumen area were \( r = -0.45 \) (\( P = 0.042 \)), \( r = -0.58 \) (\( P = 0.006 \)), and \( r = 0.18 \) (\( P > 0.1 \)). Canceling out actual lumen size by directly correlating spirometric UAO indices with resistance-derived ones, correlation coefficients were +0.66 (\( P = 0.001 \)) between \( R \) and FEV1/FEV0.5 and +0.67 (\( P = 0.001 \)) between \( \Delta R/\Delta V \) and FEV1/FEV0.5; all correlations with the other two spirometric UAO indices were inferior to the above two.

**Fig. 1.** Respiratory resistance (\( R \)) as a function of breathing flow in a normal subject (A) and in a patient with chronic obstructive pulmonary disease (COPD) (B), in the case of external orifices with diameters ranging 6–12 mm, and in the absence of an external orifice (no obstr). In the stenosis patient (C), corresponding data were obtained before and after intervention (● and ○, respectively).

**Fig. 2.** Respiratory resistance at 0.5 l/s (\( R \)) (A) and its dependence on breathing flow (\( \Delta R/\Delta V \)) (B) as a function of lumen area. In the case of stenosis patients, lumen area refers to the minimal tracheal passage (● and ○ are pre- and postintervention, respectively). In the case of normal subjects (■, means ± SD) or patients with COPD (▲; means ± SD), lumen area refers to the size of external orifices placed in front of the test subjects’ mouths. Shaded areas delimit lower and upper limit of normal, determined on basis of the average and SD obtained from the normal subjects without obstruction (detached ■ on the right).
DISCUSSION

On the basis of the fluid dynamics of tracheal stenosis (6), we have proposed a simple diagnostic tool derived from an existing lung function test, the forced oscillation technique, and tested its validity for UAO detection in patients for whom the degree of tracheal stenosis could be quantified. Aware of the potentially complex models used to interpret the forced oscillation test (4), we took a pragmatic approach and verified whether one of its simplest parameters, namely resistance obtained at an oscillation frequency of 5 Hz \( (R) \) and its dependence on breathing flow rate \( (\Delta R/\Delta V) \), could be used to detect UAO. In particular, we verified the prediction that airway resistance determined in this way increases with flow rate and more so with decreasing stenotic area (shape and length of the stenosis having a negligible effect) (6). Although forced oscillation resistance at 4 or 5 Hz has been previously reported to increase in patients with tracheostenosis (12) or laryngeal obstruction (11), its lack of specificity for UAO detection has also been recognized (11). The present study shows a more specific finding, namely flow dependence of resistance (a hallmark of orifice flow), which, in addition to \( R \), provides an attractive diagnostic tool for UAO detection.

One key feature specific to fluid dynamics in the trachea is that the upper airway resistance generated by an excessive narrowing in the trachea should increase with breathing flow (6). Grossly abnormal \( \Delta R/\Delta V \) values are particularly apparent in our tracheal stenosis patients before intervention (Fig. 2B). It is shown that the degree of tracheal stenosis that is usually considered for intervention is situated on the steep part of the predicted \( \Delta R/\Delta V \) increases with decreasing stenosis size. In addition to the observed \( \Delta R/\Delta V \) increases, the \( R \) values obtained in the stenosis patients before intervention appear to be considerably greater than normal reference values (16), or even than \( R \) values reported in the literature for patients with COPD (rarely exceeding 0.5–0.6 kPa·L\(^{-1}\)·s\(^{-1}\)) (21, 22). In this respect, one could argue that, in cases of severe tracheal stenosis, \( R \) at one breathing flow would suffice to diagnose UAO, even in the presence of concomitant peripheral obstruction. However, the flow dependence of \( R \) \( (\Delta R/\Delta V) \), which is more specific of UAO, should also be considered when examining patients with a milder degree of tracheal stenosis and/or for whom \( R \) is expected to be increased owing to peripheral airway obstruction. In the case of stenosis patients with a smoking history, it is otherwise unclear which part of \( R \) is attributable to tracheal obstruction and which part arises from more peripheral obstruction.

The value of considering both \( R \) and \( \Delta R/\Delta V \) to diagnose UAO and assess the benefit of a tracheal dilation procedure can also be appreciated from Fig. 2 (C). Although both \( R \) and \( \Delta R/\Delta V \) show consistent decreases with increases in estimated lumen area, \( \Delta R/\Delta V \) falls in the normal range after intervention, whereas \( R \) does not. This indicates that, when the appearance of a tracheal stenosis reaches a critical level, orifice flow supervenes and can be detected by flow dependence of resistance (nonzero \( \Delta R/\Delta V \)) and that a tracheal dilation procedure brings the stenosis below the critical level (with \( \Delta R/\Delta V \) falling to zero). It is possible that, after an intervention, some residual obstruction persists or some mucosal swelling appears owing to the procedure itself (e.g., granulation tissue, sputum impaction), impairing a complete resolving of \( R \) to normal values. In fact, possible swelling postintervention implies that lumen area at the time of postintervention functional testing could have been slightly smaller than that estimated in situ at intervention. If it had been possible to obtain the actual lumen size at the time of \( R \) measurement, this would have implied a slight horizontal shift to the left of the open circles in Fig. 2A, bringing them even closer to the values predicted by the external orifices. It is also important to consider that, after a proper tracheal dilation procedure, the narrowest passage in the upper airway including the trachea is in fact the glottis with a typical lumen area of 100 mm\(^2\) during normal breathing (5). This explains why, in the case of lumen area exceeding 100 mm\(^2\) (whether induced externally or internally), \( \Delta R/\Delta V \) values generally fall within the limits of normal (Fig. 2B), i.e., not generating a critical orifice flow.

Finally, the direct correlation of resistance measurements pre- and postintervention to the corresponding spirometric indices of UAO, regardless of respective area lumen size, confirms that both \( R \) and \( \Delta R/\Delta V \) bear a distinct relationship to obstruction in the upper airway. Studies that have previously

### Table 1. Indication for tracheal dilatation intervention

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Smoking History, py</th>
<th>Indication for Intervention</th>
<th>Lumen Area, mm(^2)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1 (F)</td>
<td>26</td>
<td>0</td>
<td>Postintubation tracheal stenosis</td>
<td>20</td>
</tr>
<tr>
<td>Patient 2 (F)</td>
<td>71</td>
<td>0</td>
<td>Idiopathic subglottis stenosis/ stent migration/ pseudomembranous</td>
<td>24/20/55</td>
</tr>
<tr>
<td>Patient 3 (F)</td>
<td>20</td>
<td>0</td>
<td>Posttracheostomy tracheal stenosis</td>
<td>28</td>
</tr>
<tr>
<td>Patient 4 (M)</td>
<td>65</td>
<td>55</td>
<td>Nonsmall cell carcinoma - endotracheal metastasis</td>
<td>113</td>
</tr>
<tr>
<td>Patient 5 (F)</td>
<td>80</td>
<td>0</td>
<td>Posttracheostomy tracheal stenosis - granulation tissue due to stent</td>
<td>38</td>
</tr>
<tr>
<td>Patient 6 (M)</td>
<td>45</td>
<td>15</td>
<td>Postsurgery tracheal stenosis - granulation tissue due to stent</td>
<td>41</td>
</tr>
<tr>
<td>Patient 7 (F)</td>
<td>65</td>
<td>0</td>
<td>Thyroidcarcinoma</td>
<td>26</td>
</tr>
<tr>
<td>Patient 8 (M)</td>
<td>31</td>
<td>0</td>
<td>Tracheal stenosis postintubation of chemicals/ stent migration</td>
<td>57/79</td>
</tr>
<tr>
<td>Patient 9 (M)</td>
<td>65</td>
<td>56</td>
<td>Posttracheostomy tracheal stenosis - granulation tissue due to stent</td>
<td>38</td>
</tr>
<tr>
<td>Patient 10 (M)</td>
<td>87</td>
<td>30</td>
<td>Postintubation tracheal stenosis - stent occlusion</td>
<td>13</td>
</tr>
</tbody>
</table>

Lumen area = the area of the minimal passage in the trachea at time of intervention. py, pack yr.
employed spirometric UAO indices in an attempt to relate the severity of UAO to breathing symptoms (10) or a radiological UAO assessment (14) could benefit from the use of $R$ and $\Delta R/\Delta V$ instead. Alternatively, follow-up protocols in patients at risk for tracheal stenosis or recidivism can help determine clinically relevant threshold values for $R$ and $\Delta R/\Delta V$. Various parameters derived from the forced oscillation technique have been previously proposed to detect UAO as an alternative to spirometric measurements in patients who are unable to adequately perform spirometry (11, 12). For instance, Horan et al. (12) found an inverse correlation between the so-called resonant frequency (18) and stenosis diameter (ranging 2–13 mm) when assessing patients with neurological injury before and after dilation of tracheostenosis. Van Noord et al. (24) used the forced oscillation technique with associated model simulations to observe that the resistance vs. frequency curve (between 4 and 25 Hz) is affected to a lesser extent by supporting the cheeks in patients with UAO than in patients with COPD, making it a discriminating feature to distinguish upper from lower airway obstruction. However, the above two studies require that impedance measurements be made at various oscillation frequencies. Considering only resistance at low frequency (4–5 Hz), both Horan et al. (12) and Hoijer et al. (11) indicated that resistance was responsive to stenotic narrowing in patients without lower respiratory disease, consistent with our finding of increased $R$ in the stenosis patients.

The use of $R$ and $\Delta R/\Delta V$ shown here in the case of patients with fixed UAO potentially extends to patients with variable tracheal obstruction, for instance, because of goiter (17) or in patients with vocal chord dysfunction, as has recently been shown to be the case in a significant proportion of patients diagnosed with difficult-to-control asthma (25). Variable extrathoracic or intrathoracic UAO, where upper airway resistance may be increased preferentially during inspiratory and expiratory phases, respectively, may warrant the separation between resistances measured during the inspiratory or expiratory breathing phases. Wassermann et al. (26) measured in situ tracheal pressure drops in patients with a range of extrathoracic obstructions and found that inspiratory resistance across the stenosis was almost double the expiratory resistance (except for one patient with a fixed stenosis). Wassermann et al. (26) also proposed that such in situ measurement of resistance could be used to select patients eligible for surgical intervention. An alternative noninvasive technique that can diagnose UAO early and reliably could benefit the outcome of bronchoscopic procedures in these patients (1). Finally, in some disorders of the upper airway such as a goiter, UAO may be more pronounced in the recumbent body posture, and the minor adjustments of the forced oscillation technique for being performed in the recumbent posture presents another advantage.

In summary, we adopted the forced oscillation technique for its ease of use with patients suffering a potential UAO for whom spirometry may be uncomfortable and for its capability to determine resistance breath by breath at various breathing flow rates. This enabled us to test the potential of the flow rate dependence of resistance in patients with a relatively fixed degree of upper airway narrowing. We showed that, in addition to resistance itself, which did increase with increasing tracheal stenosis, the degree of breathing flow dependence of $R$ was sensitive to obstruction in the upper airway and was not affected by concomitant peripheral airway dysfunction. Finally, the proposed forced oscillation indices perform at least as well as common spirometric UAO indices in the case of tracheal stenosis.
ACKNOWLEDGMENTS

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GRANTS

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DISCLOSURES

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

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8. Essa AM,牵头的项目。