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Delamanid shows low minimal inhibitory concentrations *in vitro* against *M. avium-intracellulare* strains http://ow.ly/xDiM304ul7O

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Specific airway resistance in preschool children: why not panting after all?

To the Editor:

Specific airway resistance (sR_{aw}) is measured with minimal cooperation in the preschool child during tidal breathing [1]. Methodological difficulties have been encountered in modern plethysmographs when the warming and humidification of the inspired gas [2] are replaced by numerical algorithms to eliminate the thermo hygrometric artefact [1, 3, 4]. Measuring sR_{aw} during panting [5] had been dismissed in preschool children based on the assumption that the ventilatory manoeuvre would be difficult to perform and

standardise. The feasibility of such an assumption, however, has not been verified. Therefore, the aim of this study was to assess the feasibility of measuring sR_{aw} during panting in preschool children with asthma and compare the outcome with the tidal breathing method.

Preschool children with a doctor diagnosis of asthma were recruited from the paediatric pulmonology clinics (Hôpital d'enfants, Vandoeuvre-lès-Nancy, France). Written informed consent was obtained from the children and their parents. The protocol was approved by the ethics committee (Comité de Protection des Personnes EST III, CHU de Nancy, Nancy, France). The plethysmography equipment, which has been described elsewhere [6], is operated by software that includes an algorithm which should eliminate the thermo hygrometric artefact from the plethysmographic volume signal (ΔV_{pleth}), which may be activated during tidal breathing and disabled during panting. Acquisition consisted of a series of four breaths selected automatically by the software and displayed on the computer screen. Three acquisitions were collected for each condition. Measurements were selected to retain those showing no artefact and where breathing frequency was lower than 50 breaths·min^{-1} during tidal breathing or higher than 60 breaths per·min^{-1} during panting. sR_{aw} was computed between points of maximum ΔV_{pleth} (sR_{tot}) and in the flow range±0.5 L·s^{-1} (s$R_{aw_{0.5}}$). The overall flow interval within a given acquisition was measured graphically. Data were analysed with Pearson's Chi-squared test or analysis of variance as appropriate, and are expressed as mean±SD.

A total of 127 preschool children (73 boys) aged 3.5–6.5 years took part in the protocol. Measurements were achieved during tidal breathing in 83 children (34±7 breaths·min^{-1}; flow amplitude 1.3±0.3 L·s^{-1}) and during panting in 90 children (130±36 breaths·min^{-1}; flow amplitude 2.0±0.6 L·s^{-1}; p<0.0001 for both breathing frequency and flow amplitude). Feasibility of measurement during tidal breathing and panting was not significantly different overall (65 and 71% respectively; p=0.35), nor within age categories (figure 1a; p>0.05). There was no difference between boys and girls during tidal breathing (64 *versus* 67%; p=0.9) or panting (71 *versus* 70%; p=0.9). In those with successful measurements, the average number of validated breaths was 8.9±2.8 during tidal breathing and 9.6±2.4 during panting (p=0.089). The percentage of valid breaths obtained did not differ between either breathing regimens (figure 1b) or sexes.

s$R_{aw_{0.5}}$ and sR_{tot} were significantly smaller during panting (0.71±0.2 kPa·s·L^{-1} and 0.96±0.3 kPa·s·L^{-1}) than the respective value during tidal breathing (1.14±0.2 kPa·s·L^{-1} and 1.33±0.2 kPa·s·L^{-1}; p<0.0001 for both s$R_{aw_{0.5}}$ and sR_{tot}). sR_{tot} was also significantly larger than s$R_{aw_{0.5}}$ for both protocols (p<0.0001). The intra-subject coefficient of variation was significantly larger during panting than during tidal breathing for both s$R_{aw_{0.5}}$ (13±7% *versus* 8.5±6%; p<0.0001) and sR_{tot} (15±9% *versus* 10±7%; p=0.0001) and significantly larger for sR_{tot} than s$R_{aw_{0.5}}$ during panting (p=0.02).

The potential of sR_{aw} in paediatric lung function testing was formerly demonstrated in studies where the thermal component in ΔV_{pleth} was properly eliminated by warming and humidifying the respired gas [2]. Recent studies eventually showed important equipment-dependent variability [1, 3] when numerical algorithms were used to correct for the thermo hygrometric artefact. The lack of agreement on sR_{aw} standardisation in lung function centres across the world was recently highlighted [7]. The finding that panting achieves a similar rate of successful measurements as tidal breathing suggests the interesting possibility of avoiding the methodological difficulties encountered with automated software that corrects for the thermo hygrometric component using algorithms only known to the manufacturers. With smaller tidal volumes and higher breathing frequencies, the thermo hygrometric component in ΔV_{pleth} is minimised [8] and the ΔV_{pleth}–flow relationship is studied within a time domain mostly unaffected by the dynamics of airways – gas thermo hygrometric exchanges [9].

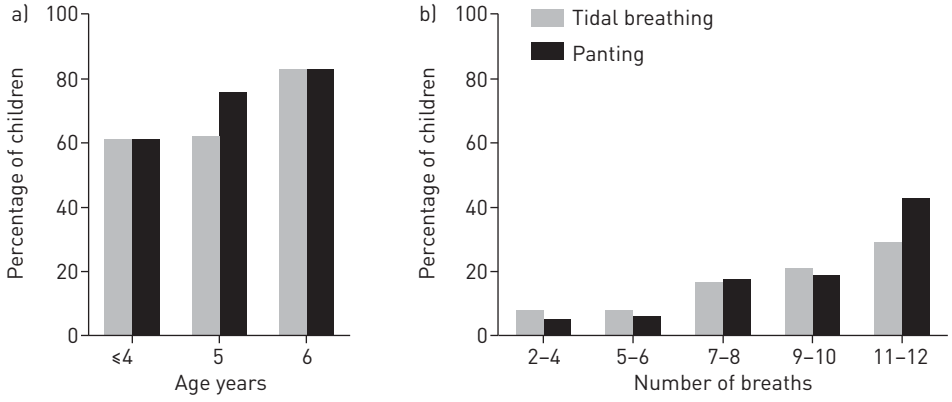

FIGURE 1 a) The success rate of specific airway resistance among age groups and b) the percentage of children achieving a given number of valid breaths are similar during tidal breathing and panting.

The current results raise the question of which estimate of sRaw would be optimal as a routine paediatric lung function end-point. Panting opens the glottis [10], but turbulent airstream has the opposite influence on the measurement outcome. When sRaw$_{0.5}$ is examined, however, the second mechanism is minimised, and the glottic opening should be more fully expressed to decrease sRaw. In fact, similar to a previous report in older children [6], in the current study sRaw was consistently lower during panting than during tidal breathing, and the highly significant difference was observed with both sRtot and sRaw$_{0.5}$. During tidal breathing, sRaw was also reported to be smaller in preschool children when the respired gas was conditioned to body temperature, ambient pressure, saturated with water vapour (BTPS) than when it was numerically corrected for the thermo hygrometric effect [11]. Taken together, these observations in preschool children indicate that either BTPS conditioning or panting, by adequately correcting for the thermo hygrometric artefact, lead to an estimate of sRaw being smaller than that achieved through software corrections applied during tidal breathing. However, the intra-subject variability in the current study was larger during panting than during tidal breathing, and whatever the mechanism, this might impede the ability of sRaw to detect airway obstruction and reversibility. The fact that sRtot was significantly larger than the corresponding sRaw$_{0.5}$ was expected because of the enhanced contribution of nonlinearities and increased slope of airway pressure–flow relationship. Since flow is turbulent mostly in proximal airways, the diagnostic value of sRtot may be lower than for sRaw$_{0.5}$. Furthermore, the larger variability observed with sRtot compared with sRaw$_{0.5}$ was also expected, especially during panting, as the ventilatory effort is likely to vary from one breath to another, resulting in variable flow amplitude and contribution of nonlinearities throughout the acquisition. Hence, computation over a limited flow interval as reported in adults should be recommended [12], with the recent indication of better separation of children with asthma from controls based on sRaw$_{0.5}$ [13]. However, it should be kept in mind that, in preschool children where ΔV_{pleth} and flow signals are small, computation of sRaw within a limited flow range may compromise the signal-to-noise ratio. The fixed flow interval $\pm 0.5\ L \cdot s^{-1}$ is also likely to provide age-dependent estimates of sRaw with more significant nonlinearities in shorter than taller children. An important step towards standardisation would be to define the optimal flow range to estimate sRaw and the optimal breathing frequency interval for measuring with minimal variability.

In summary, valid measurements of sRaw may be obtained during panting in preschool children. Since ΔV_{pleth} requires no correction, the test should be more readily applicable to any equipment, which is particularly helpful in the context of international collaborative studies. Compared with tidal breathing, however, the technique achieves lower sRaw and larger intra-subject variability. Further case–control studies, including other lung function outcomes such as spirometry, are required to establish normative data and assess which estimate of sRaw is the most useful for routine paediatric lung function studies.

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Specific airway resistance may be measured in preschool children during routine lung function
http://ow.ly/pvxr3034Bo8

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Dichotomy in pulmonary graft-*versus*-host disease evident among allogeneic stem-cell transplant recipients undergoing lung transplantation

To the Editor:

Allogeneic haematopoietic stem-cell transplantation (HSCT) has become a life-saving treatment option for numerous benign and malignant diseases, with more than 14 500 procedures being performed annually in Europe alone [1]. Late-onset noninfectious pulmonary complications (NIPCs) have emerged as the main hurdle to long-term survival, affecting up to 26% of HSCT recipients and conferring 2- and 5-year survival rates of 44% and 13%, respectively [2, 3].

Current diagnostic criteria remain based on those proposed by the National Institutes of Health (NIH) in 2005 for pulmonary graft-*versus*-host disease (GvHD), which considered bronchiolitis obliterans exclusively accountable [4, 5]. Whilst histological confirmation was encouraged, invasive diagnostics have remained contentious due to reported complication rates from open lung biopsies and limited interpretability of trans-bronchial biopsies [6, 7].

Inevitably, surrogate parameters such as new-onset airway obstruction on spirometry and "air-trapping" on computed tomography (CT) have gained precedence in establishing a diagnosis. NIH guidance for monitoring pulmonary GvHD currently incorporates the lung function score that assesses symptoms, forced expiratory volume in 1 s (FEV_1) and diffusing capacity of the lung for carbon monoxide. Currently, diagnosis of pulmonary GvHD requires [4]: 1) FEV_1/forced vital capacity (FVC) <0.7, FEV_1 <75% predicted or residual volume >120% predicted; 2) high-resolution CT demonstrating air trapping, small airway thickening or bronchiectasis; 3) exclusion of infection; and 4) chronic GvHD in at least one extrapulmonary site.

Recently, evidence has emerged suggesting the presence of an additional restrictive form, due to interstitial disease rather than skin GvHD of the chest wall, as has been previously suggested [8, 9]. Through novel assessment of explanted native lungs from patients undergoing lung transplantation (LTx) for end-stage lung disease following allogeneic stem cell transplantation, we compared clinical, radiographic and histological data in this sub-group in an attempt to improve understanding of the pathological processes involved.

Patients who underwent cadaveric LTx between May 1, 2003 and May 1, 2014 at 12 European centres were included. Clinical, imaging and pathological data were collected using standardised reporting forms to facilitate central retrospective analysis. Spirometry was performed in accordance with American Thoracic