Title: Airway Sizes and Proportions in Children Quantified by a Video-Bronchoscopic Technique

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Author's response to reviews:

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Response to Reviewers
We thank the editors for reviewing and considering our paper for publication and we thank the reviewers for their constructive and fair comments. We have outlined our detailed responses to their questions and comments below. We hope the changes made are acceptable to the Editorial group and the reviewers.

B Masters

Reviewer : Raanan Arens

Major Comments:
1. The authors’ assessment of upper airway size was based on cross sectional area measurements at specific locations. However upper airway size during development should also include its length for assessment of linear growth and estimated volume of the large airways. Such a study would be more comprehensive and lead to more definite conclusions.

Response to reviewer: We agree that it would be interesting to assess linear growth and make volumetric measurements during development but we are not certain that it would necessarily lead to more definite conclusions at this point in time. Our reasons are:
1a. Current technological limitations. There is currently no validated technique that would allow us to accurately measure length and airway volume. We believe that making assessments of volume based on linear measurements between sites of measurement and the apparent taper between these measurements is likely to be erroneous given the curvilinear appearances that are mainly present in the LMS and to some degree in the trachea and the uncertainty over tapering or a step change in the first place. Considerable precision of measurement is required for these volumetric assessments however the bronchoscope-based technologies are not sufficiently developed at this point in time to achieve this, even though this is precisely what we were alluding to in the discussion where we mentioned the use of optic flow techniques: "The use of repeated and sequential assessments while approaching and withdrawing the bronchoscope from the object of interest and the application of optic flow techniques [27] and its recent advances [28, 29] that could be applied to bronchoscopic assessments might overcome these issues and measurement failures and offer an even more detailed assessment of airway anatomy."

Indeed with further developments of these techniques we believe it will not only be possible to make linear measurements but to make volumetric measurement and have precise 3D reconstructions. We have adjusted the discussion to incorporate these issues (see below highlighted).

"Another potential limitation relates to the methodology of measurement, in particular our using a 10 mm viewing distance to measure angulated sites such as the RML and RUL. Indeed we excluded these sites from our measurements because using even shorter viewing distances to overcome angulation difficulties results in even greater magnification, thus rendering the image outside the limits of measurement. The use automated distortion correction along with repeated and sequential assessments while approaching and withdrawing the bronchoscope from the object of interest using the applications of optic flow techniques [27] and its recent advances [28, 29] that could be applied to bronchoscopic assessments, might overcome these issues and measurement failures and offer an even more detailed assessment of airway anatomy. This would potentially include a three-dimensional (3-D) reconstruction image of the accessible airways.
Despite these current limitations, the advantages of this technique exceed those of reconstruction CT and or CT “virtual bronchoscopy” where their capacity to localize specific sites such as the distal end of the cricoid and the origins of lobar bronchi are limited. In addition when used in this context, the radiation doses for extensive, localised and particularly for repeated assessments remain a considerable safety concern to both clinical and research work in children[30, 31]."

Because of the taper in the shape of the larynx and that of the trachea and large airways estimates of volume through length measurements applied to a proximal fixed point cross sectional area will not add much to the subject, indeed it would only enhance error estimates.

lb. The second point is that while the cricoid does have a volumetric measurement, which possibly changes over childhood (conical to cylindrical) in its longitudinal plane, the outlet, which is what we have measured, is constant in its circular shape at its distal margin. Indeed one of the points of the study was to suggest that a reference point system is necessary for the bronchoscopist to make comparisons and to assess sizes of different airways and airway lesions. Importantly not all lesions such as stenoses and very small airways can be penetrated thus volumetric measurements could not be done.

lc. Using a validated technique, we measured and reported the relative proportions of mainstem and lobar bronchi to the cricoid as the comparator/denominator and as shown in the Table 1 these proportions remain constant across childhood thus it is very unlikely that there would be disproportionate changes in length between these points of measurement.

Given the above reasons, we do not believe that measurement of length for assessment of linear growth and estimated volume of the large airways at this stage would be helpful. We have however added this point to the discussion in the revised manuscript (page 9 paragraph 1).

2. The authors finding of no gender differences in airway size based on cross sectional area measurements alone. However as mentioned above since linear measurements were not performed it is possible that such a difference does actually exist. In the Discussion, the authors explain the differences in lung function noted between genders by other authors may be related to small airway differences. This explanation is possible. However based on the limitations of the present study I think we cannot rule out changes in the large airway size at this time based on the data presented.

Response to reviewer: We agree with these statements and comments and have made some adjustment to the abstract and discussion. The following paragraphs show the changes that have been made in the Abstract Conclusions and the Discussion (see below).

Abstract Conclusions: The large airways progressively increase in cross sectional area size, maintain constant proportional relationships to the cricoid and are gender independent across childhood. Anthropometric factors (body length and weight) are significantly related to but only have weakly predictive influences on major airway size. The cricoid is the most suitable comparator for other airway site measurements. These data provide for quantitative comparisons of airway lesions.

Discussion
This is the first study reporting detailed in-vivo airway cross-sectional area measurements from cricoid to lobar bronchial divisions and area based airway proportion measurements from children using a validated bronchoscopic methodology. We found that body length and weight but not gender influenced the size of major airways measured. In addition we found that there were no gender differences in large airway sizes as assessed by cross sectional area measurements and the cricoid to be most suitable for comparative measurements as ETT derived areas underestimated comparative assessments.

Airway proportion measurements from cadaver studies suggest that the airways progressively and proportionately reduce size from the central to peripheral airways in both children and adults[8-10, 25]. However the numbers in these studies were small. Our study with far greater numbers of subjects confirms these findings and indeed shows the large airway proportions remain constant across the whole infancy and childhood periods. Combining these factors with the lack of gender differences in size of the large airways and therefore proportions, lends support to the small airways being the likely sites of gender related differences in lung function in children [13-17]. This raises the possibly of gender differences in factors governing growth of the small airways. However these interpretations require some caution, as even though we accounted for the dynamic respiratory cycle changes by measuring the cross sectional area at end expiration and the proportions remained constant across age groups, we did not control for lung volume, and we did not make independent confirmatory assessments of growth of the large airways using
volumetric and length measurements. In addition to this new information, these data provide the clinician and researcher with both absolute values and greater perspective of the range of changes that could be expected during transitions from the trachea to mainstem and to lobar bronchi respectively.

Minor Comments
1. Anthropometric data on both genders presented as Z scores would be helpful. Did both genders have similar height, weight and BMI?
Response: We accept that Z scores could have been used but feel they would not necessarily have been particularly helpful. As shown/mentioned in the paper the regression based predictive values of age, height and weight were all poor and even worse for BMI. But in addition and most importantly we did show that the proportions remained constant across the age groups; therefore, it is unlikely that Z scores would have allowed a clearer explanation of the scatter of measurements for any particular age or anthropometric parameter. This factor points to our data being real and not simply some function of size eg. a heavy young child with a small airway being grouped with a thin older child with a small airway and so on.
In addition there were no significant differences in height, weight or BMI between genders. The p values for these respective comparisons between males and females were 0.247,0.187 and 0.563.

Furthermore, clinicians arguably usually find it easier to conceptualise weight in mass measurements rather than Z weight scores.

Reviewer: C Witt
There are two minor comments:
- The precise distance between the bronchoscope and the "target area" is one of the key problems. Withdrawing the bronchoscope fro precisely 10 mm from a carina is already difficult but doing the same for a target area somewhere in the main bronchi is even more difficult sine all structures are mobile. The fact that certain areas (eg, left upper lobe) image acquisition and or measurement was possible in only 71% (89/125) reduces the clinical value of the technique.
- Using CHMT measurements must somehow be influenced by the angle in which the bronchoscope is with respect to the target lumen. The authors should comment on this.
Response to point 1: The two comments above are indeed limitations of our CHMT technique which has been pointed in our papers outlining the technique (Ref #4 and #5), as well as in our original manuscript (page 11, para 2). The issue about mobility was also commented in our original manuscript whereby we overcame this by doing the measurement in end expiration by advancing the digitalised image by one frame a time on a 25frame/sec capture rate. To clarify this further we have further elaborated this in the revised manuscript (para just before conclusion, as shown below). Again these issues could be overcome by automated measurements of distance, which at this stage are potentially gained through optic flow techniques and its modifications as mentioned in the discussion of the original manuscript.
We have now commented on these issues in the discussion in the paragraph as shown below with the changes highlighted.

"Another potential limitation relates to the methodology of measurement, in particular our using a 10 mm viewing distance to measure angulated sites such as the RML and RUL, and our ability to precisely define this10mm distance." These issues were discussed in our previous paper [4,5] Also, we excluded these sites from our measurements because using even shorter viewing distances to overcome angulation difficulties results in even greater magnification, thus rendering the image outside the limits of measurement. The use automated distortion correction along with repeated and sequential assessments while approaching and withdrawing the bronchoscope from the object of interest using the applications of optic flow techniques [27] and its recent advances [28, 29] that could be applied to bronchoscopic assessments, might overcome the various limitations of our current technique which includes measurement failures and offer an even more detailed assessment of airway anatomy. Despite these current limitations, the advantages of this technique exceed those of reconstruction CT and or CT "virtual bronchoscopy" where their capacity to localize specific sites such as the distal end of the cricoid and the origins of lobar bronchi are limited. In addition when used in this context, the radiation doses for extensive, localised and particularly for repeated assessments remain a considerable safety concern to both clinical and research work in children[30, 31]."