# Positive Airway Pressure to Enhance Computed Tomography Imaging for Airway Segmentation for Virtual Bronchoscopic Navigation

**Authors**: [1]Marta Diez-Ferrer[#] and [2,3]Debora Gil[#], [4]Cristian Tebe, [2]Carles Sanchez, [1]Noelia Cubero, [1]Rosa Lopez-Lisbona, [1]Jordi Dorca and [1]Antoni Rosell on behalf of the PAP-enhanced CT study group*

[#] Both authors contributed equally to this work.

**Affiliations**:

1. Department of Respiratory Medicine, Hospital Universitari de Bellvitge – Bellvitge Biomedical Research Institute (IDIBELL). Universitat de Barcelona. Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES). Feixa Llarga s/n, 08907, L'Hospitalet de Llobregat, Barcelona, Spain.
2. Computer Vision Center (CVC) – Universitat Autònoma de Barcelona. Edificio O. 08193 Bellaterra, Barcelona, Spain.
3. Serra Hunter Fellow
4. Department of Statistics, Bellvitge Biomedical Research Institute (IDIBELL). Feixa Llarga s/n, 08907, L'Hospitalet de Llobregat, Barcelona, Spain.

**Corresponding author**: Antoni Rosell. Department of Respiratory Medicine. Hospital Universitari de Bellvitge. Feixa Llarga s/n, 08907, L'Hospitalet de Llobregat, Barcelona, Spain. arosell@bellvitgehospital.cat.

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**Keywords:** bronchoscopy; continuous positive airway pressure; multidetector computed tomography; image enhancement; virtual bronchoscopic navigation.

## ABBREVIATIONS LIST

BMI: body mass index

CT: computed tomography

Exp-PAP: expiration with PAP

$FEV_1$: forced expiratory volume during first second

FVC: forced vital capacity

Ins: inspiration

Ins-PAP: inspiration with PAP

$MMEF_{25\%–75\%}$: maximum mid-expiratory flow between 25% and 75% of forced vital capacity

mSv: millisievert per milligram

PAP: positive airway pressure

$PAP10_F$: PAP at 10 cmH2O from the flow device, acquisitions soon after placement

$PAP10_T$: PAP at 10 cmH2O from the turbine device, acquisitions soon after placement

$PAP10_{T15}$: PAP at 10 cmH2O, acquisitions after 15 min on PAP

$PAP14_{T15}$: PAP at 14 cmH2O, acquisitions after 15 min on PAP

PPL: peripheral pulmonary lesion

VBN: virtual bronchoscopic navigation

## ABSTRACT

**Rationale:** Virtual bronchoscopic navigation guidance to peripheral pulmonary lesions is often limited by insufficient segmentation of the peripheral airways.

**Objectives**: To test the effect of applying positive airway pressure during computed tomography acquisition to improve segmentation, particularly at end-expiration.

**Methods:** Computed tomography acquisitions in inspiration and expiration with four positive airway pressure protocols were recorded prospectively and compared to baseline inspiratory acquisitions in 20 patients. The four protocols explored differences between devices (flow vs. turbine), exposures (within seconds vs. 15-min) and pressure levels (10 vs. 14 $cmH_2O$). Segmentation quality was evaluated with the number of airways and number of endpoints reached. A generalized mixed-effects model explored the estimated effect of each protocol.

**Measurements and Main Results:** Patient characteristics and lung function did not significantly differ between protocols. Compared to baseline inspiratory acquisitions, expiratory acquisitions after 15 min of 14 $cmH_2O$ positive airway pressure segmented 1.63-fold more airways (95% CI 1.07–2.48; $P$=0.018) and reached 1.34-fold more endpoints (95% CI 1.08–1.66; $P$=0.004). Inspiratory acquisitions performed immediately under 10 $cmH_2O$ positive airway pressure reached 1.20-fold (95% CI 1.09–1.33; $P$<0.001) more endpoints; after 15 min the increase was 1.14-fold (95% CI 1.05–1.24; $P$<0.001).

**Conclusions:** Computed tomography acquisitions with positive airway pressure segment more airways and reach more endpoints than baseline inspiratory acquisitions. The improvement is particularly evident at end-expiration after 15 min of 14 $cmH_2O$ positive airway pressure. Further studies must confirm that the improvement increases diagnostic yield when using virtual bronchoscopic navigation to evaluate peripheral pulmonary lesions.


**Abstract word count:** 248

## Introduction

Bronchoscopy, a safe technique for diagnosing peripheral pulmonary lesions (PPLs), has a complication rate of 0% to 4% for pneumothorax [1] that is considerably lower than the 18.8% to 25.3% pooled rates for percutaneous approaches [2]. Moreover, bronchoscopy is superior to the percutaneous approach because it provides a full examination of the airways — including visualization of the mucosa, evaluation of dynamic movements of the trachea and bronchial wall — and because both diagnostic and therapeutic procedures can be done during the same procedure. While conventional bronchoscopy has an overall sensitivity ranging from 13% to 78% for the diagnosis of PPLs — a highly variable range related to nodule size and location [3] — recently introduced guidance technologies and instruments have achieved a pooled diagnostic yield of 70% [4]. At the center of these technologies is the combination of computed tomography (CT) and endoscopic imaging in the form of virtual bronchoscopic navigation (VBN). VBN systems reconstruct CT data into three-dimensional representations of the tracheobronchial tree, a process referred to as segmentation. Segmentation is used as a bronchial map that helps identify the afferent bronchus to the PPL. VBN systems are particularly useful for guiding ultrathin bronchoscopes and other devices through bronchial bifurcations to the lung periphery [5]. However, segmentations often fall short of PPLs [6]. In cases where insufficient CT data has been extracted for the most peripheral airways, the diagnostic rate of VBN-guided techniques is comparable to that of diagnosis without VBN assistance [3, 7] and the potential usefulness of VBN is debatable [8].

Segmentation is based on computations applied to predetermined information, such as density and shape, extracted from the total volume of CT data. The best possible segmentation comes from the highest possible CT resolution at full inspiration when the lumen is widest. However, we hypothesized that visualization and segmentation of the most distal bronchi could be improved by applying positive airway pressure (PAP) during CT

acquisition to further increase the airway lumen. The effect of PAP could be particularly relevant at end-expiration because the pressure prevents airway collapse, thus increasing CT contrast between the air inside and outside the airways.

We aimed to compare the quality of airway segmentations with baseline inspiration without PAP, to segmentations based on CT acquisitions performed with PAP at end-inspiration and end-expiration. We explored differences between two machines, two exposure durations, and two pressure levels to gain insight into which CT acquisition protocol would be most likely to yield better segmentations than the standard full inspiration acquisition.

## Materials and Methods

### Patients and Study Design

Twenty consecutive outpatients referred by the respiratory medicine department to undergo evaluation of pulmonary lesions and who had not yet undergone CT imaging were enrolled prospectively between July 2015 and August 2016. Spirometry (BodyBox, Medisoft, Sorinnes, Belgium) and chest CT (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) data were available for all patients. Baseline CT acquisitions were performed at end-inspiration as usual. They were followed by end-inspiration and end-expiration acquisitions with four different PAP protocols. We performed all three acquisitions in each patient so that intra-individual comparison could be analyzed.

The study was approved by the local review board (Clinical Research Ethics Committee of Bellvitge University Hospital - Act 08/13) and written informed consent was obtained from all participants.

## Procedures

Once in the CT room, all participants were trained by a pulmonologist participating in the study to hold their breath at maximal end-inspiration following standard instructions [9] for CT acquisitions. Afterwards all patients were retrained to perform end-inspiratory and end-expiratory maneuvers with breath holding under PAP. After training, they were consecutively assigned in four blocks of five participants each for CT acquisitions at end-inspiration and end-expiration under one of the four PAP protocols, which were designed to explore two devices, two exposure times and two pressure levels as follows.

The first five patients were assigned to a flow PAP device and oronasal mask providing air flow set to reach a pressure of 10 $cmH_2O$ (EzPAP system and mask with a paraPAC plus ventilator, Smiths Medical, Ashford, UK). The second set of five were assigned to a turbine device (REMstar, Philips Respironics, Andover, MA, USA) also set for a pressure of 10 $cmH_2O$; an oronasal mask (Mirage Quattro, ResMed, CA, USA) was used. Because a slight superiority of segmentations was observed with the turbine machine on preliminary analysis,[7] the turbine machine was used by the third and fourth groups. The third group rested for 15 min while breathing under 10 $cmH_2O$ PAP before the CT acquisitions. After preliminary comparison [10] between the second and third groups, we chose to use the 15-min exposure again in the fourth group but increase PAP to 14 $cmH_2O$ before CT acquisitions. A flow chart for the study protocol is shown in Fig. 1.

The CT scans (320-detector row, 0.5 mm slice thickness, at intervals of 0.4 mm) were performed with a 80 × 0.5 mm collimator, tube voltage of 100 kVp, and tube current adapted for sex and body mass index. We limited the number of patients in this feasibility study and explained the risk of two additional acquisitions carefully to participants.

## Image Analysis

Two outcome variables were used to evaluate segmentation quality. The first was the number of segmented airways automatically counted by the VBN system (LungPoint, Broncus Medical Inc, San Jose, CA, USA). We chose to also try a second outcome, number of endpoints, to quantify the branches that reach the outmost periphery of the lung. For that purpose, the lung volumes were divided into concentric layers bounded by isosurfaces of the distance map to the pleura. Thus, the number of endpoints of the segmentation centerline lying within the region were counted. The distance map to the pleura took the value 0 at the pleura and maximum values were at the geometric center of the lung. Isosurfaces were sampled every 5% in the range of 5% to 40% (0% corresponding to the pleura and 100% to the geometric center. This range covers the peripheral region of the lung, which is where segmentations often fall short. The number of endpoints was calculated using an image processing library in MATLAB software (MathWorks, Natick, MA, USA). Fig. 2 is an example of a view of segmented airways and their endpoints approaching the pleura. Lung air volume was also automatically calculated in square millimeters based on an assumed attenuation value between –450 and –1024 HU in order to include the whole lung parenchyma at both end-inspiratory and end-expiratory acquisitions. The percentage of voxels with an attenuation value less than –950 HU in the inspiratory acquisitions was also recorded. For these calculations we used commercially available semiautomatic add-on software (Vitrea Advanced v. 6.6, Vital Images, Minnetonka, MN, USA). Both outcome variables — the number airways and the number of endpoints — were recorded for the conventional baseline inspiratory acquisitions and the two PAP acquisitions (inspiration and expiration with all four PAP protocols).

**Statistical Analysis**

Data was managed and analyzed with the software R, version 3.2.5 [11]. Baseline clinical characteristics of patients recruited were described with means (SDs) or counts and

179 percentages. We used Kruskall-Wallis tests to assess similarity between individuals in the
180 cohort with respect to forced expiratory volume during the first second as a percentage of
181 the predicted value (%$FEV_1$), the ratio between $FEV_1$ and forced vital capacity ($FEV_1$/FVC),
182 and the percentage of CT density less than –950 HU.

183 A different generalized mixed linear model of the effect of each PAP protocol on each
184 of the study outcomes (number of airways and number of endpoints) was constructed. Lung
185 volumes were included in both models in order to correct for individual variations in the
186 inspiration and expiration maneuvers with PAP. The relative distance to each patient's
187 pleura was calculated from a percent distance to the pleura and the total distance to the
188 center of the lung and included in the models of number of endpoints reached as adjusting
189 factor. The adjusted models calculated the effect of PAP on each outcome expressed as a
190 rate ratio (on-PAP airway acquisitions with each protocol to baseline acquisitions). A rate
191 ratio of 1 indicates an expectation that the outcome will not change with PAP. A rate ratio
192 greater than 1 indicates an expected improvement (a positive effect of PAP on the outcome
193 relative to baseline inspiratory acquisitions). A rate ratio less than 1 indicates an expected
194 negative effect of PAP on the outcome. We calculated the 95% confidence intervals (CI) of
195 all rate ratios and *P* values. A *P* value <0.05 was considered statistically significant.

196

197 **Results**

198 We included 20 patients. Tolerance to PAP was good in all patients and there were no
199 delays or other technical events related to setting up the device in the CT room. The
200 distributions of clinical, demographic, and lung function data of patients in each PAP protocol
201 are shown in Table 1. Values for %$FEV_1$, $FEV_1$/FVC, and %CT density less than –950 HU
202 were similar between PAP protocols (*P* = 0.300, *P* = 0.08 and *P* = 0.532, respectively). The
203 mean radiation dose for the sum of the three acquisitions was 13.2±2.2. These doses were
204 slightly higher than standard CTs (7-10 mSv).

Rate ratios, their 95% CIs and *P* values for every comparison between a PAP protocol and baseline inspiratory acquisitions for each outcome are shown in Table 2. Line graphs in Figs. 3 and 4 illustrate the comparisons. Expiratory acquisitions after 15 min of PAP at 14 $cmH_2O$ significantly increased both the number of airways (1.63-fold) and the number of endpoints (1.34-fold) over the numbers at baseline. Inspiratory acquisitions with PAP performed both immediately and after 15 min of PAP at 10 $cmH_2O$ also increased the number of endpoints (1.20-fold and 1.14-fold, respectively) compared to baseline inspiratory acquisitions.

## Discussion

Our results show that PAP-enhanced CT acquisitions hold promise for significantly improving segmentation quality over the quality usually achieved with standard inspiratory acquisitions. In particular, expiratory acquisitions after 15 min with PAP set at 14 $cmH_2O$ yield segmentations with the greatest number of airways and endpoints. We found that inspiratory acquisitions also improved under PAP set at 10 $cmH_2O$, although not as greatly. To our knowledge, this is the first study to suggest that distal airway segmentation can be improved with PAP-enhanced CT acquisitions. Although the small number of patients included is a limitation of this study to explore feasibility, our observations not only confirm that PAP-enhanced CT can potentially improve clinical segmentation in inspiration and expiration but also suggest that the enhancement is greater in expiration and with the highest tested level of PAP. This improvement in segmentation, providing the bronchoscopist with a more accurate preview of the bronchial anatomy before starting the procedure, could prove useful for identifying the afferent bronchus in cases were segmentation falls short of a PPL. We hypothesize that better planning can improve patient selection and therefore increase the diagnostic yield of VBN-guided bronchoscopy.

Previous studies have demonstrated that PAP application during CT acquisition has an effect on CT densitometry. For example, one study in healthy volunteers demonstrated different the density thresholds of normally aerated and overdistended lung after application of 30 $cmH_2O$ PAP,[12] and a study in patients with COPD demonstrated lung deflation with 5 $cmH_2O$ PAP and an increment in emphysematous areas with 10 and 15 $cmH_2O$ PAP [13]. Several other studies conducted in patients with acute lung injury syndrome evaluated the density changes produced by different levels of PAP [14-21]. Instead of density changes, we used segmentation data to assess the effect of PAP because we were interested in finding a simple clinical strategy (PAP application during CT acquisition) to enhance segmentation and evaluate the impact.

One previous study assessed segmentation quality by quantifying the number and volume of airways [22], but we doubted that these outcomes could reflect the improvement that PAP might offer in the peripheral airways. The number of airways segmented is related to the bronchial generations reached. Assuming that at each generation the next level has 2 branches, then a rate ratio approaching 2 in the number of branches implies the segmentation is nearing one more generation “out” into the periphery of the lung. Although the number of airways is a reliable, reproducible and robust automatic measure provided by the software, it rather quantifies the increase in the number of airways at any point of the branching airway. We therefore chose an additional outcome — number of endpoints reached — because it could accurately and automatically describe the distal growth of the segmented bronchi, that is, the assessed periphery based on distance maps [23] of the lung.

Our observation of more segmentations with a greater number of endpoints when we used the turbine device could be explained by the flow machine’s delivery of a lower positive end-expiratory pressure, leading to less lung distention [24, 25]. We did not demonstrate a decrease in end-expiratory pressure in this study, but we nonetheless chose to complete the

exploration of protocols with the turbine device because the apparently better results it provided seemed promising.

Tests of PAP increments in patients with acute respiratory distress syndrome have shown that different respiratory variables reach a balanced effect after different adjustment times [26]. Based on the assumption that the effects of PAP on segmentation might be delayed, we explored PAP's immediate effect, within seconds of starting, and after a 15-min exposure time at 10 $cmH_2O$. Although we did not observe significantly different segmentations between the two exposure times, we did find that segmentation with CT acquisitions in expiration after 15 min of PAP were nonsignificantly better and we therefore we chose to test the 15-min exposure protocol with a pressure of 14 $cmH_2O$.

The greatest gain in PAP-enhanced segmentations was observed in expiratory acquisitions after 15 min of 14 $cmH_2O$ PAP. These results are consistent with previously published data where further increments in lung aeration were seen in expiratory CTs as PAP increased [13]. However, in contrast with our observation of improved segmentation with 10 $cmH_2O$ in inspiration, we did not find that the higher pressure improved results in inspiration. Higher PAP levels have been shown to lead to hyperinflation in a study in patients with severe COPD, although the highest level tested in that study was 10 $cmH_2O$ [27]. As De Troyer and Wilson [28] have noted, a healthy diaphragm stops generating inspiratory pressure after acute lung inflation reaches total lung capacity, possibly explaining why the greatest effect in inspiration was seen with 10 $cmH_2O$ instead of 14 $cmH_2O$ PAP in our study.

A strength of this study is that we avoided potential biases on segmentation quality, such as CT resolution, bronchial wall thickness, emphysematous destruction or anatomic size of the lungs [29], since all 3 acquisitions were performed in the same patients and at the same CT resolution and potential density changes derived from individual variations in respiratory maneuvers were corrected for by adjusting for lung volume in all the models for

both outcomes [30]. Finally, we think that the newly developed, automatically analyzed outcome of number of endpoints reached could prove useful for comparing segmentation quality in future studies since it better describes the achieved lung periphery [31].

Since patient radiation exposure was slightly higher than usual in this study, we enrolled few patients. Our conclusions are therefore limited to feasibility and the study is underpowered for formal hypothesis testing. Under these methodological constraints, even large effects may fail to be detected as statistically significant [32] and consequently the absence of significant differences between groups should be interpreted with caution. However, the differences detected for some of the PAP protocols demonstrate that PAP-enhanced CT is a feasible technique to improve the performance of computerized support systems for diagnosis of pulmonary diseases, in particular VBN-guided bronchoscopy, and we suggest further testing of PAP enhancement with more patients and only two acquisitions.

In summary, this study indicates that CT acquisitions with PAP in inspiration and expiration improve segmentation compared to baseline inspiratory acquisitions without PAP. In particular, expiratory acquisitions after 15 min with a PAP of 14 $cmH_2O$ show the greatest effect. Results of this study can be considered as a step toward addressing a major clinical concern about the usefulness of VBN systems when segmentations do not reach PPLs. However, further studies are needed to confirm that the improved peripheral airway segmentation we observed with PAP also leads to higher diagnostic yield when PPLs are evaluated using VBN guidance.

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*__Writing Committee Members for the PAP-enhanced CT study group__: Pablo Naval (Department of Radiology, Hospital Universitari de Bellvitge, Barcelona, Spain), Elena Carreño ( Department of Radiology, Hospital Universitari de Bellvitge, Barcelona, Spain), Agnés Borràs (Computer Vision Center, Autonomous University of Barcelona, Spain), Susana Padrones (Department of Respiratory Medicine, Hospital Universitari de Bellvitge, Barcelona, Spain), Samantha Aso (Department of Respiratory Medicine, Hospital Universitari de Bellvitge, Barcelona, Spain), Vanesa Vicens (Department of Respiratory Medicine, Hospital Universitari de Bellvitge, Barcelona, Spain).

**Author contributions:** A.R. generated the hypothesis; M.D., D.G. and A.R designed the study; M.D., C.S., N.C., R.L., J.D., P.N., E.C., A.B., S.P., S.A. and V.V. contributed to data acquisition. D.G and C.T performed the statistical analysis, and M.D. wrote the manuscript. All Members of the PAP-enhanced CT study group critically revised the submitted article for important intellectual content, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work and ensure that any questions related to the accuracy or integrity of any part of the work can be appropriately investigated and resolved.

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449 **TABLES**

450 **Table 1.** Clinical, Demographic and Lung Function Data of Patients in Each PAP Protocol

| | **$PAP10_F$ (n=5)** | **$PAP10_T$ (n=5)** | **$PAP10_{T15}$ (n=5)** | **$PAP14_{T15}$ (n=5)** |
|---|---|---|---|---|
| Sex, male:female | 4:1 | 4:1 | 3:2 | 5:0 |
| Age, y mean (SD) | 71 (12) | 70 (9) | 76 (5) | 72 (4) |
| BMI, $kg/m^2$ mean (SD) | 24 (3) | 28 (3) | 23 (3) | 27 (2) |
| Smoking never:former:current | 1:4:0 | 1:4:0 | 1:4:0 | 0:4:1 |
| $FEV_1$, L mean (SD) | 1.8 (.8) | 2.4 (.7) | 2.3 (.9) | 2.4 (.4) |
| $FEV_1$, % mean (SD) | 68 (28) | 97 (20) | 98 (21) | 104 (18) |
| $FEV_1$/FVC mean (SD) | 55 (17) | 77 (5) | 73 (3) | 73 (6) |
| MMEF25-75, L/s mean (SD) | 1.1 (.8) | 2.5 (.6) | 2.2 (.9) | 2.3 (.6) |
| MMEF25-75, % mean (SD) | 45 (34) | 91 (22) | 87 (38) | 83 (18) |
| %CT density < –950HU mean (SD) | 33 (3) | 27 (10) | 32 (10) | 35 (8) |

451

452 BMI = body mass index; CT = computed tomography; $FEV_1$ = forced expiratory volume
453 during first second; FVC = forced vital capacity; $MMEF_{25\%-75\%}$ = maximum mid-expiratory
454 flow; $PAP10_F$ = positive airway pressure at 10 $cmH_2O$ from the flow device, acquisitions
455 soon after placement; $PAP10_T$ = PAP at 10 $cmH_2O$ from the turbine device, acquisitions
456 soon after placement; $PAP10_{T15}$ and $PAP14_{T15}$ = PAP at 10 or 14 $cmH_2O$, respectively,
457 acquisitions after 15 min on PAP.

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**Table 2:** Rate Ratios Showing the Effect of Each PAP Protocol Versus Baseline Acquisitions on Each Outcome.

| CT acquisition | Protocol | Rate Ratio | CI95% | *P* value | Rate Ratio | CI95% | *P* value |
|---|---|---|---|---|---|---|---|
| | | Number of airways | | | Number of endpoints | | |
| Inspiration with PAP | $PAP10_F$ | 1.07 | 0.97—1.18 | 0.243 | 1.05 | 0.96—1.15 | 0.4281 |
| | $PAP10_T$ | 0.97 | 0.89—1.06 | 0.645 | **1.2** | **1.09—1.33** | **<0.001** |
| | $PAP10_{T15}$ | 1.08 | 0.99—1.17 | 0.093 | **1.14** | **1.05—1.24** | **<0.001** |
| | $PAP14_{T15}$ | 0.89 | 0.8—0.99 | 0.021 | 1 | 0.91—1.11 | 0.993 |
| Expiration with PAP | $PAP10_F$ | 0.81 | 0.65—1.00 | 0.052 | 0.6 | 0.51—0.71 | <0.001 |
| | $PAP10_T$ | 0.38 | 0.29—0.49 | <0.001 | 0.54 | 0.42—0.68 | <0.001 |
| | $PAP10_{T15}$ | 0.81 | 0.66—1.01 | 0.058 | 0.51 | 0.42—0.62 | <0.001 |
| | $PAP14_{T15}$ | **1.63** | **1.07—2.48** | **0.018** | **1.34** | **1.08—1.66** | **0.004** |

Significant effects are shown in bold face. The rate ratio was obtained from a generalized linear mixed model adjusted for lung volume and (in models of number of points reached) by distance to pleura.

$PAP10_F$ = positive airway pressure at 10 $cmH_2O$ from the flow device, acquisitions soon after placement; $PAP10_T$ = PAP at 10 $cmH_2O$ from the turbine device, acquisitions soon after placement; $PAP10_{T15}$ and $PAP14_{T15}$ = PAP at 10 or 14 $cmH_2O$, respectively, acquisitions after 15 min on PAP.

## FIGURE LEGENDS

**Figure 1.** Study flow chart. *CT = computed tomography; PAP = positive airway pressure; $PAP10_F$ = PAP at 10 $cmH_2O$ from the flow device, acquisitions soon after placement; $PAP10_T$ = PAP at 10 $cmH_2O$ from the turbine device, acquisitions soon after placement; $PAP10_{T15}$ and $PAP14_{T15}$ = PAP at 10 or 14 $cmH_2O$, respectively, acquisitions after 15 min on PAP.*

**Figure 2.** Distance maps. A: Schematic representation of the distance map with 5% and 15% layers in green and maroon, respectively. B and C: Examples of two different layers in the right lung of a patient: layer 5% (B) and layer 15% (C). Arrows point to the surface of the pleura. Asterisks point to layers. The airway endpoints that fall within the layer, and which were counted, are marked with red circles.

**Figure 3.** Line graphs showing estimated number of airways segmented with each acquisition protocol. The estimated number of airways increases as the volume of air in the lung rises. The $PAP14_{T15}$ protocol had a significant effect on the number of airways segmented in expiration. *Exp-PAP = expiration with PAP; Ins = inspiration; Ins-PAP = inspiration with PAP; $PAP10_F$ = positive airway pressure at 10 $mmH_2O$ from the flow device, acquisitions soon after placement; $PAP10_T$ = PAP at 10 $mmH_2O$ from the turbine device, acquisitions soon after placement; $PAP10_{T15}$ and $PAP14_{T15}$ = PAP at 10 or 14 $mmH_2O$, respectively, acquisitions after 15 min on PAP.*

**Figure 4.** Line graphs showing estimated number of endpoints segmented with each acquisition protocol. The estimated number of endpoints increases with the distance from the pleura. The $PAP10_T$ and $PAP10_{T5}$ protocols had a significant effect on the number of endpoints segmented in inspiration. The $PAP14_{T15}$ protocol had a significant effect on the number of endpoints segmented in expiration. *Exp-PAP = expiration with PAP; Ins = inspiration; Ins-PAP = inspiration with PAP; $PAP10_F$ = positive airway pressure at 10*

*$mmH_2O$ from the flow device, acquisitions soon after placement; $PAP10_T$ = PAP at 10 $mmH_2O$ from the turbine device, acquisitions soon after placement; $PAP10_{T15}$ and $PAP14_{T15}$ = PAP at 10 or 14 $mmH_2O$, respectively, acquisitions after 15 min on PAP.*