Simulations

RATIONALE

As described in the manuscript, it should be possible to estimate the reduction rate of the inner cross-sectional area (iCSA) using D of iCSA by $2^{-1/D}$. To confirm this notion, we performed simulations with different scenarios.

METHODS

Sets of iCSAs of virtual airway trees were created starting from a tracheal iCSA of 100 mm^2, which was followed by iterative calculations of iCSA of child branches using a predefined reduction ratio until the terminal branches became less than 1 mm^2. For the first condition, which involved a symmetrical tree with a fixed reduction ratio, the reduction ratio was set at 0.7, and a random error taken from a normal distribution with coefficient of variation (C.V.) = 5% was added to the reduction ratio of each child branch independently of the others. For the second condition of an asymmetrical tree with two fixed reduction ratios, reduction ratios were set to be 0.7 and 0.2, and a random error was added to the reduction ratio in the same way as in the first condition. For the third condition involving an asymmetrical tree with two varying reduction ratios with a fixed average, one reduction ratio was taken randomly from a uniform distribution between 0.2 to 0.8, and the second reduction ratio was calculated to bring the average to 0.5. For the fourth condition, the reduction ratio was chosen from a uniform random distribution between 0.2 to 0.8 completely independent of others, including sibling branches. For the fifth condition, the range from which reduction ratios were randomly picked up was changed from 0.8 to 0.4 (expectation was 0.6) in the proximal part with iCSA above 10 mm^2 to 0.6 to 0.2 (expectation was 0.4) in the distal part. The reduction ratios in these conditions were chosen arbitrarily for the purpose of the simulation and did not represent actual COPD or normal human airways.

D of iCSA was calculated as described in the manuscript as an absolute value of the slope of a linear model applied to iCSA and its descending rank on a log-log plot. Estimation of the reduction ratio from D of iCSA was performed using $2^{-1/D}$. The process of calculation of D and estimation of the reduction ratio was repeated one thousand times, and the estimated reduction ratios were compared to the predefined reduction ratio.

Simulation, analysis, and plotting were performed using R, RStudio, and the tidyverse package.

RESULTS AND DISCUSSION

Condition 1, a symmetrical tree with a fixed reduction ratio of 0.7

A plot from a representative virtual tree is shown in Figure S6a. The points of observations showed a linear trend. D of iCSA ranged from 1.943 to 1.960 with a median value of 1.952. The histogram of the estimated reduction ratios revealed a very slight shift of the median value to the right above 0.7 (median, 0.701 [minimum 0.700 – maximum 0.702], Figure S6b) The right shift may be because of the error of the approximation $\Sigma\ 2^i = 2^n - 1 \approx 2^n$, where n was not big enough. In fact, we could see some discrepancies between the points of ranks 1-4 and the fitted linear line (Figure S6a). Nevertheless, the estimated reduction ratios matched well with the real reduction ratio of 0.7 used to create virtual bronchial trees.

Condition 2, an asymmetrical tree with two fixed reduction ratios of 0.7 and 0.2

The points of observations were located more sparsely than in condition 1, but they were aligned to a line (Figure S7a for a representative data). D of iCSA ranged from 0.848 to 0.880 with a median value of 0.864, and the estimated reduction ratios (median, 0.448 [0.442 – 0.455], Figure S7b) were well matched with the expected reduction ratio of 0.45, which showed an average value of 0.7 and 0.2.

Condition 3, an asymmetrical tree with two varying reduction ratios with a fixed average of 0.5

Since the mathematical implication suggested that the reduction ratios can be varied as far as their estimation is fixed, we varied two reduction ratios at each bifurcation while fixing the average reduction ratio of these two ratios to be 0.5. Similar to condition 2, the points were aligned to a linear line on the log-log plot (Figure S8a). Distribution of the estimated reduction ratios shifted slightly to the right above 0.50 (median 0.506 [0.494 – 0.516], Figure S8b).

Condition 4, a bronchial tree of branches with completely random reduction ratios ranging between 0.2 and 0.8

Furthering the concept of reduction ratios that can be random as far as their expectation is fixed, we took all reduction ratios randomly with their expectation to be 0.6. As in the previous conditions, the points were aligned to a linear line even though reduction ratios were picked up randomly and independently of sibling branches (Figure S9a for a representative plot). The distribution of estimated reduction ratios also showed a slight shift toward the right and was wider than the previous conditions (median 0.505 [0.426 – 0.559], Figure S9b). This wider distribution probably stemmed on complete randomness.

Condition 5, transition of reduction ratios from 0.6 in the proximal part to 0.4 in the distal part

So far, we fixed the expectation of the reduction ratio, and showed that the observed points were aligned on a linear line. To determine the effect of changing expectations of reduction ratios, we ran simulation 5. A representative plot showed points were aligned to a line segment at the range of iCSA $\geq$ 9, and then they were aligned another line segment at the range of iCSA < 9 (Figure S10a). When the segmental Ds of iCSA were calculated as absolute values of slopes of these two line segments, these segmental Ds of iCSA could be used to estimate the segmental reduction ratios at the range of iCSA above and below 9 (Figure S10b), although the segmental D of iCSA above 9 showed a slight shift to the right above 0.6.

Summary of the results

As shown in conditions 1-4, if the expectation of reduction ratios was fixed, the points of observations lined up on a log-log plot. Notably, this was true in a situation where reduction ratios were picked up in a completely random fashion as in the condition 4. In these conditions, D of iCSA, which is an absolute value of the slope of the line, could be used to estimate reduction ratios accurately.

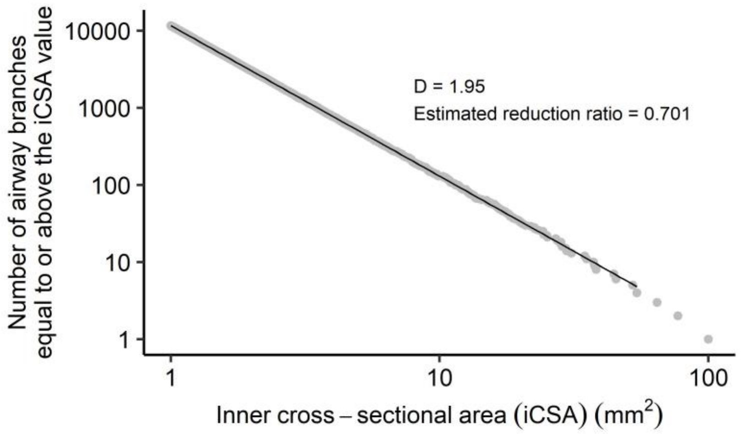
In the situation where reduction ratios were transitioning, points of observations showed multiple line segments. Even in this situation, segmental Ds of iCSA could estimate reduction ratios at each iCSA range.

CONCLUSION

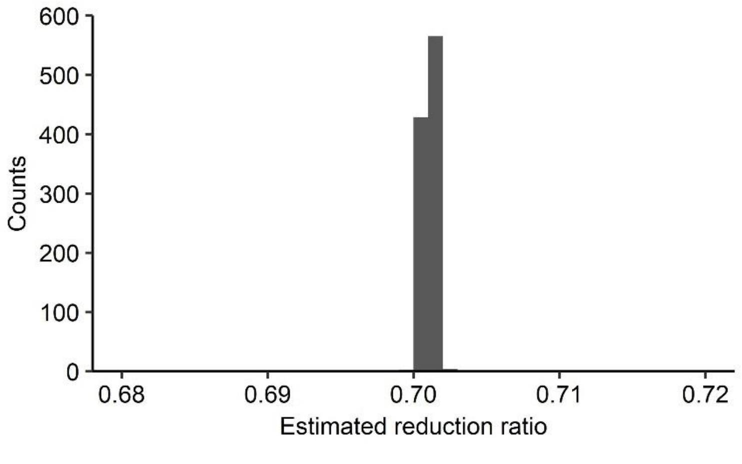
D of iCSA can be used to estimate average reduction ratios of iCSA.

Figure S6. Simulation using virtual symmetrical bronchial trees with a fixed reduction ratio of 0.7

A



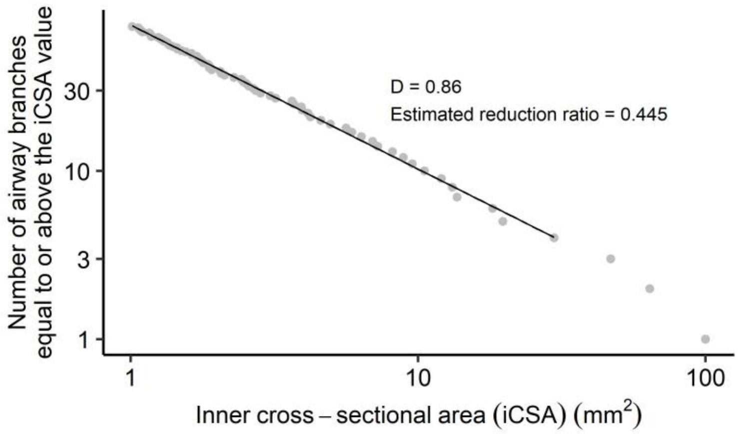
B



A) A representative plot of inner cross-sectional area (iCSA) and cumulative counts above or equal to the iCSA value on the log-log scale. D is the absolute value of the slope of the fitted linear line. The reduction ratio was estimated by $2^{-1/D}$. B) Distribution of reduction ratios estimated from D of iCSA (n = 1,000).

Figure S7. Simulation using virtual asymmetrical bronchial trees with two fixed reduction ratios of 0.7 and 0.2 at each bifurcation

A



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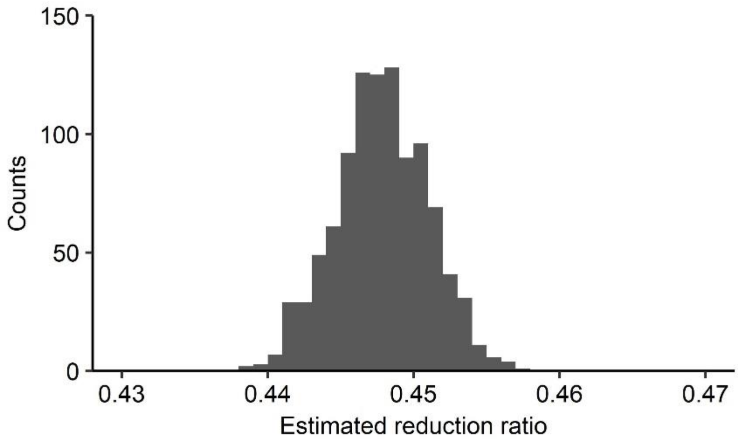
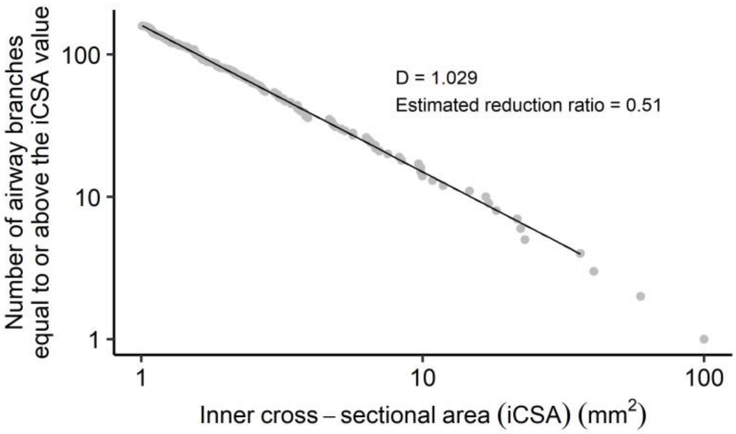


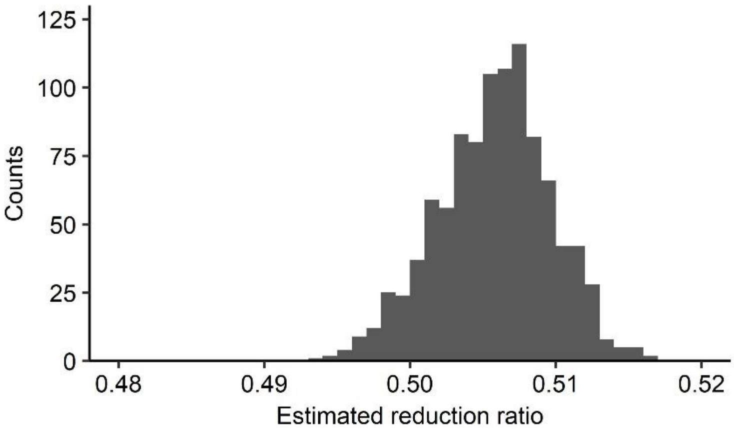
A) A representative plot of inner cross-sectional area (iCSA) and cumulative counts above or equal to the iCSA value on the log-log scale. D is an absolute value of the slope of the fitted linear line. The reduction ratio was estimated by $2^{-1/D}$. B) Distribution of reduction ratios estimated from D of iCSA (n = 1,000).

Figure S8. Simulation using virtual asymmetrical bronchial trees with two random reduction ratios with a fixed average of 0.5 at each bifurcation

A



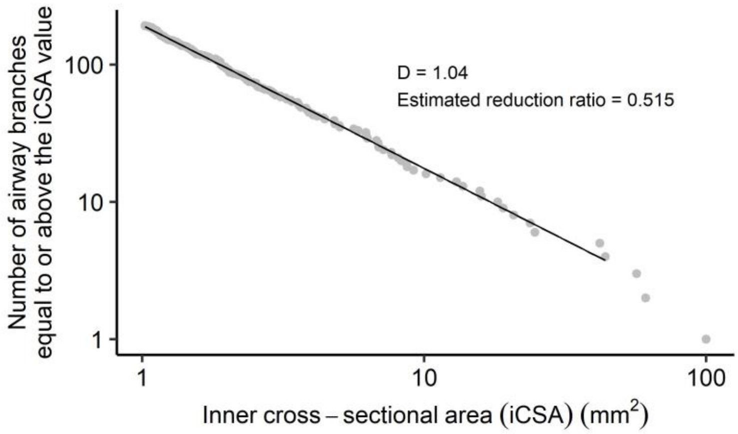
B



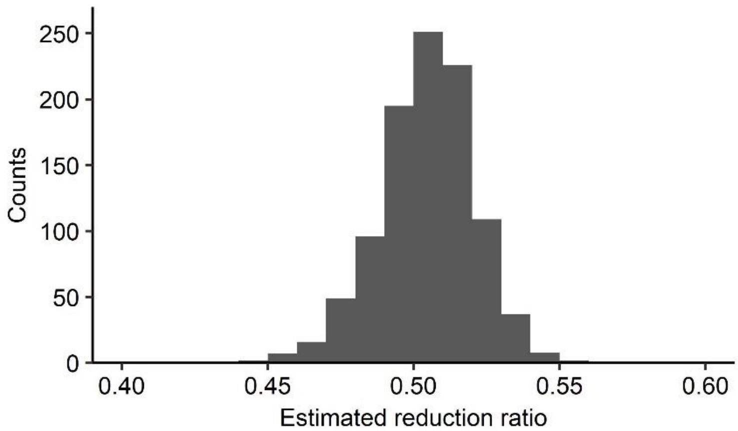
A) A representative plot of inner cross-sectional area (iCSA) and cumulative counts above or equal to the iCSA value on log-log scale. D is the absolute value of a slope of the fitted linear line. The reduction ratio was estimated by $2^{-1/D}$. B) Distribution of reduction ratios estimated from D of iCSA (n = 1,000).

Figure S9. Simulation using virtual bronchial trees with completely random reduction ratios with an expected value of 0.5.

A



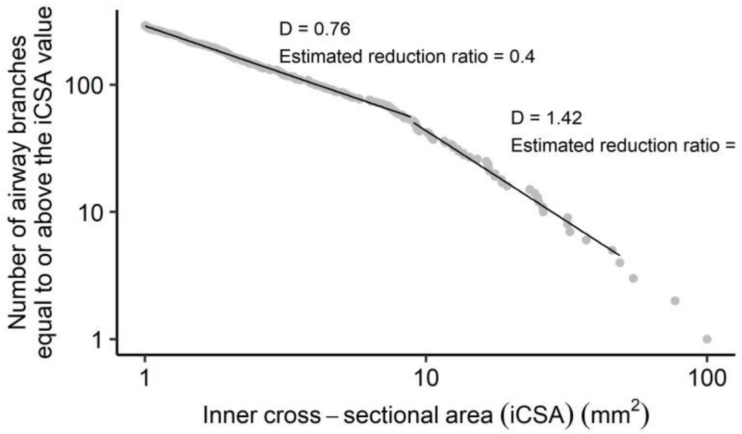
B



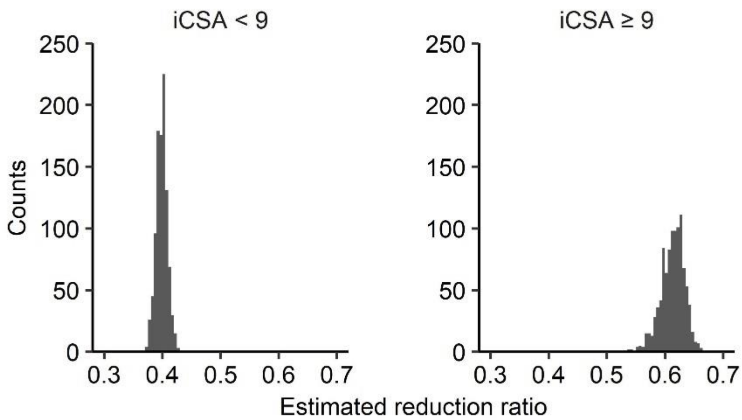
A) A representative plot of the inner cross-sectional area (iCSA) and cumulative counts above or equal to the iCSA value on the log-log scale. D is the absolute value of the slope of the fitted linear line. The reduction ratio was estimated by $2^{-1/D}$. B) Distribution of reduction ratios estimated from D of iCSA (n = 1,000).

Figure S10. Simulation using virtual asymmetrical bronchial trees with changing reduction ratios of 0.6 in the proximal part and of 0.4 in the distal part

A



B



A) A representative plot of inner cross-sectional area (iCSA) and cumulative counts above or equal to the iCSA value on the log-log scale. Segmental Ds are absolute values of slopes of the fitted linear line segments. The reduction ratio was estimated by $2^{-1/D}$. B) Distributions of reduction ratios estimated from D of iCSA at an iCSA range above and below 9 mm^2 ($n = 1{,}000$).