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Appendix from Rahaghi et al., "Pulmonary vascular morphology as an imaging biomarker in chronic thromboembolic pulmonary hypertension" (Pulm. Circ., vol. 6, no. 1, p. 70)

Supplementary Materials

Methods

Vessel detection

The method relies on obtaining volumetric data, meaning that each slice of the CT image must be directly adjacent to or overlapping the neighboring slices, with no gaps between. In the case of the pulmonary embolus protocol at our institution, all clinical scans are obtained in a volumetric manner with 1-mm spacing, with pixel resolutions in each slice being approximately 0.5–0.7 mm. The diameter of a vessel generally has to be >1 voxel before it can be detected, limiting both the detection and the accuracy of scale at high resolution, leading to a significant drop-off in the scale-versus-detection plots, such as that shown in Figure 2, in the vicinity of 3 mm^2.

After the detection of the lung field mask, the image is resampled in all 3 dimensions at a set interval of 0.625 mm. Using the strain energy method[21] and histogram equalization, initialization points are then identified. The core of the method relies on the concept of scale-space particles. Conceptually, these points settle in the location where the Hessian, or second derivative, with respect to each direction is most consistent with the geometry of the vasculature at the scale specific to that particle. Particles are moved in order to minimize an energy term, and points are added and deleted according to a population control scheme that seeks to reduce the total energy. The end result is a collection of particles, with a defined scale (radius), that rest in voxels where the local geometry matches that of a vessel (i.e., where there is a symmetric drop-off of intensity in 2 dimensions without appreciable drop-off in the third). These particles are essentially representative of a small-vessel segment of a set radius defined by the scale of the particle most fitting for that location.

Minimum spanning tree

The topology of the vascular network was derived from connections between neighboring particles based on Kruskal's minimum-spanning-tree algorithm.[22] The algorithm identified a graph of possible connections between vessel particles, taking distance, orientation, and scale into account. Given this graph, the algorithm then identified the tree subgraph consisting of edges between the most similar neighboring particles. An angle tolerance of 20°, a maximum distance of 5 mm, and a scale difference of 1.0 were used for the purposes of separating vessel segments.

AV segmentation

The minimum spanning tree was used to separate each vessel segment from the vascular tree. Very small subsegments (≤ 4 particles) were discarded from this analysis. Central arteries and veins were labeled by tracing their origin to the pulmonary arteries and veins with a 3D rendering of the vasculature superimposed on the initial CT scan, which allowed scrolling in all 3 planes to ensure proper identification. Subsequently, more-distal vessels were labeled by their connection to the central vessels; the same tool was used to verify that connections were accurate. All labeling was performed by a single operator, a pulmonologist, who was not blinded. While artifacts were rare, they were also removed in this process by hand. Quality measure was based on visual inspection of the entire lobe, examining each region to make sure that there was both an arterial and a venous supply, with particular attention to the pleural surface, where an interdigitating arterial and venous supply was expected. Once the tree was appropriately labeled, quantities such as BV5/TBV and ρBV5 were computed as described in the main text.

Tortuosity

Tortuosity is a common observation in vascular disease and has been observed in many different vascular beds. It is believed that tortuosity may be an adaptation to higher pressures in vascular beds.[19] While tortuosity has been observed by researchers, an optimal theoretical description and method of measurement remain an area of active research.

The most common definition of tortuosity involves measuring the total path length of the vessel segment and dividing this by the distance between the two vessel endpoints.[16] This index has a lower bound of 1.0 and becomes higher as the vessel becomes tortuous. To compute this, we used the minimum spanning tree, as described above, to separate the vascular tree into vessel segments. The center point of each vessel particle was used to create a skeletal model of each segment. The endpoints of the segment were identified by finding the two points in the vessel segment farthest from each other. Segments, determined endpoints, and point ordering were visually inspected for quality. The path length was computed by adding the distance between sequential points and dividing it by the distance between the endpoints. We expressed this as a percentage by subtracting 1.0 and multiplying by 100. The distribution of these segmental tortuosity values is bounded by a lower value of 0% and forms a nonnormal distribution. Thus, we used the median tortuosity percentage as a more robust statistical metric for each subject.

Supplementary tables

Table S1. Lobar measures of distal and proximal vessel volume distribution

	CTEPH	Control	*P* value[a]
Small-vessel volume fraction, BV5/TBV			
Right lung, upper lobe	0.52 (0.41–0.56)	0.63 (0.56–0.66)	0.0009
Right lung, middle lobe	0.49 (0.42–0.54)	0.62 (0.45–0.65)	0.002
Right lung, lower lobe	0.42 (0.29–0.53)	0.55 (0.46–0.61)	0.009
Left lung, upper lobe	0.45 (0.31–0.50)	0.58 (0.49–0.65)	0.0003
Left lung, lower lobe	0.34 (0.27–0.43)	0.54 (0.39–0.58)	0.003
Large-vessel volume fraction, BV>10/TBV			
Right lung, upper lobe	0.31 (0.26–0.37)	0.22 (0.21–0.26)	<0.0001
Right lung, middle lobe	0.32 (0.29–0.37)	0.23 (0.21–0.29)	0.01
Right lung, lower lobe	0.37 (0.32–0.47)	0.30 (0.27–0.35)	0.01
Left lung, upper lobe	0.31 (0.29–0.39)	0.24 (0.21–0.29)	<0.0001
Left lung, lower lobe	0.40 (0.35–0.48)	0.31 (0.27–0.38)	0.01
Small-vessel density ρBV5, mL vessel/dL lung			
Right lung, upper lobe	3.1 (2.5–3.4)	3.3 (3.0–4.0)	0.07
Right lung, middle lobe	2.7 (2.4–3.1)	3.3 (2.8–3.7)	0.015
Right lung, lower lobe	2.8 (2.2–3.5)	3.4 (2.9–4.1)	0.06
Left lung, upper lobe	2.4 (1.8–2.9)	3.1 (2.8–3.4)	0.0003
Left lung, lower lobe	2.5 (1.8–2.9)	3.3 (2.5–3.8)	0.02
Large-vessel density ρBV>10, mL vessel/dL lung			
Right lung, upper lobe	1.9 (1.4–2.5)	1.1 (0.9–1.6)	0.002
Right lung, middle lobe	2.0 (1.3–2.2)	1.3 (1.1–1.7)	0.06
Right lung, lower lobe	2.6 (1.8–3.6)	1.8 (1.4–2.6)	0.04
Left lung, upper lobe	1.9 (1.6–2.2)	1.4 (1.1–1.6)	0.003
Left lung, lower lobe	3.0 (2.2–3.3)	2.0 (1.8–3.0)	0.04

Note: Data are reported as median (interquartile range). BV5: blood vessel volume for vessels with a cross-sectional area ≤ 5 mm^2; BV>10: blood vessel volume for vessels with a cross-sectional area > 10 mm^2; TBV: total blood vessel volume; ρBV5: BV5/lung volume; ρBV>10: BV>10/total lung volume.

[a] *P* value based on a Wilcoxon exact test with a 2-sided *P* value.

Table S2. Lobar measures of arterial and venous vessel volume distribution

	CTEPH	Control	*P* value[a]
Arterial fractions			
Small vessels, $BV5_{ART}/TBV_{ART}$			
Right lung, upper lobe	0.51 (0.44–0.55)	0.66 (0.59–0.74)	0.0005
Right lung, middle lobe	0.54 (0.47–0.59)	0.66 (0.62–0.72)	0.002
Right lung, lower lobe	0.45 (0.27–0.53)	0.59 (0.46–0.66)	0.016
Left lung, upper lobe	0.43 (0.35–0.48)	0.58 (0.51–0.72)	0.0003
Left lung, lower lobe	0.36 (0.30–0.44)	0.56 (0.44–0.61)	0.0009
Large vessels, $BV>10_{ART}/TBV_{ART}$			
Right lung, upper lobe	0.31 (0.26–0.37)	0.19 (0.14–0.23)	<0.0001
Right lung, middle lobe	0.28 (0.21–0.35)	0.18 (0.14–0.23)	0.005
Right lung, lower lobe	0.33 (0.30–0.47)	0.26 (0.21–0.33)	0.04
Left lung, upper lobe	0.34 (0.29–0.39)	0.22 (0.16–0.28)	0.0002
Left lung, lower lobe	0.37 (0.33–0.46)	0.27 (0.23–0.35)	0.005
Venous fractions			
Small vessels, $BV5_{VEIN}/TBV_{VEIN}$			
Right lung, upper lobe	0.53 (0.46–0.59)	0.56 (0.54–0.60)	0.15
Right lung, middle lobe	0.51 (0.43–0.53)	0.57 (0.52–0.61)	0.02
Right lung, lower lobe	0.44 (0.35–0.52)	0.51 (0.43–0.59)	0.13
Left lung, upper lobe	0.47 (0.36–0.52)	0.54 (0.49–0.57)	0.02
Left lung, lower lobe	0.39 (0.31–0.46)	0.49 (0.38–0.56)	0.03
Large vessels, $BV>10_{VEIN}/TBV_{VEIN}$			
Right lung, upper lobe	0.25 (0.23–0.29)	0.24 (0.23–0.28)	0.56
Right lung, middle lobe	0.27 (0.22–0.29)	0.23 (0.18–0.30)	0.71
Right lung, lower lobe	0.31 (0.26–0.37)	0.32 (0.28–0.35)	0.58
Left lung, upper lobe	0.25 (0.21–0.30)	0.27 (0.25–0.29)	0.82
Left lung, lower lobe	0.31 (0.29–0.35)	0.33 (0.25–0.37)	0.82
Arterial/venous ratios			
Small vessels, $BV5_{ART}/BV5_{VEIN}$			
Right lung, upper lobe	1.24 (0.96–1.39)	1.15 (1.1–1.36)	0.96
Right lung, middle lobe	1.41 (0.92–1.88)	1.39 (1.18–1.62)	1.0
Right lung, lower lobe	1.20 (0.96–1.46)	1.21 (1.03–1.37)	0.87
Left lung, upper lobe	1.30 (1.14–1.51)	1.27 (1.12–1.36)	0.38
Left lung, lower lobe	1.28 (1.03–1.43)	1.20 (1.05–1.29)	0.20
Large vessels, $BV>10_{ART}/BV>10_{VEIN}$			
Right lung, upper lobe	1.59 (1.25–2.09)	0.79 (0.58–1.15)	<0.0001
Right lung, middle lobe	1.5 (0.8–2.40)	0.88 (0.58–1.49)	0.12
Right lung, lower lobe	1.41 (1.02–2.3)	0.88 (0.77–1.2)	0.01
Left lung, upper lobe	1.8 (1.49–2.88)	1.0 (0.68–1.33)	<0.0001
Left lung, lower lobe	1.87 (1.28–2.42)	0.97 (0.8–1.42)	0.0005

Table S2 (*Continued*)

	CTEPH	Control	*P* value[a]
Overall, TBV_{ART}/TBV_{VEIN}			
Right lung, upper lobe	1.26 (1.1–1.53)	1.05 (0.96–1.19)	.02
Right lung, middle lobe	1.53 (0.96–1.66)	1.16 (1.01–1.34)	0.32
Right lung, lower lobe	1.30 (0.96–1.84)	1.10 (0.98–1.19)	0.19
Left lung, upper lobe	1.43 (1.26–1.68)	1.12 (0.99–1.24)	0.002
Left lung, lower lobe	1.47 (1.24–1.78)	1.08 (0.93–1.17)	0.001

Note: Data are reported as median (interquartile range). ART: arterial; BV5: blood vessel volume for vessels with a cross-sectional area ≤ 5 mm^2; BV>10: blood vessel volume for vessels with a cross-sectional area > 10 mm^2; TBV: total blood vessel volume; VEIN: venous.

[a] *P* value based on a Wilcoxon exact test with a 2-sided *P* value.

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