Preoperative Pulmonary Vascular Morphology and Its Relationship to Postpneumonectomy Hemodynamics

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Rationale and Objectives: Pulmonary edema and pulmonary hypertension are postsurgical complications of pneumonectomy that may represent the remaining pulmonary vasculature's inability to accommodate the entirety of the cardiac output. Quantification of the aggregate pulmonary vascular cross-sectional area (CSA) has been used to study the development of pulmonary vascular disease in smokers. In this study, we applied this technique to demonstrate the potential utility of pulmonary vascular quantification in surgical risk assessment. Our hypothesis was that those subjects with the lowest aggregate vascular CSA in the nonoperative lung would be most likely to have elevated pulmonary vascular pressures in the postoperative period.

Materials and Methods: A total of 61 subjects with postoperative hemodynamics and adequate imaging were identified from 159 patients undergoing pneumonectomies for mesothelioma. The total CSA of blood vessels perpendicular to the plane of computed tomographic (CT) scan slices was computed for blood vessels <5 mm^2 (CSA 5 mm). This measurement expressed as a percentage of lung parenchyma area (CSA 5%) was compared to postoperative hemodynamic measurements obtained by right heart catheterization.

Results: In patients where a contrasted CT scan was used (n = 26), CSA 5% was correlated with postoperative day 0 minimum cardiac index (R = 0.37, P = .03) but not with the maximum pulmonary arterial pressures. In patients with noncontrast CT scans (n = 35), CSA 5% was inversely correlated with postoperative day 0 maximum pulmonary arterial pressures (R = 0.43, P = .03) but not with the minimum cardiac index. The preoperative perfusion fraction of the nonsurgical lung did not correlate with postoperative hemodynamics.

Conclusions: CSA of pulmonary vasculature with an area ≤5 mm^2 has potential in estimating the ability of pulmonary vascular bed to accommodate postsurgical changes in pneumonectomy.

Key Words: Pneumonectomy; hemodynamics; CSA; vasculature.

A detailed preprocedure assessment of patients undergoing lung resection has become a key component for the estimation of perioperative risk (1–3). In the case of patients undergoing pneumonectomy, the goals of this evaluation is to predict postoperative lung function, the potential for ventilatory compromise, pulmonary edema, and Acute Respiratory Distress Syndrome (ARDS) (4–6). Such patients are also at an increased risk for the development of both transient elevations of pulmonary arterial pressures (PAPs) and sustained postoperative pulmonary hypertension (7–9). Previous studies suggest that preoperative pulmonary vascular resistance and intraoperative PAPs are predictive of postoperative respiratory failure and mortality (10,11). In another example, the risk of developing postoperative pulmonary edema and ARDS was related to the preoperative distribution of lung perfusion (6,12). In aggregate, the risk for developing postpneumonectomy complications appears to be related to the ability of the nonoperative lung to accommodate an increase in blood flow to the full cardiac output. Noninvasive identification of compromised pulmonary vasculature in the nonoperative lung may reduce morbidity and mortality associated with this procedure.

Our group has previously described a semiautomated quantification method to calculate the total cross-sectional area (CSA) of the pulmonary vasculature on computed tomographic (CT) scans of the chest. The objective of these

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efforts is to develop and refine techniques to characterize vascular architecture from imaging. Using these tools, we hypothesized that those subjects with the smallest vascular CSA in the nonoperative lung as assessed by preoperative CT scans would be at greatest risk for hemodynamic compromise in the immediate postoperative period. To investigate this hypothesis, we performed a secondary analysis of clinically acquired CT scans and hemodynamic data on subjects undergoing extrapleural pneumonectomy at our institution.

METHODS

We evaluated a sequential cohort of patients who underwent extrapleural pneumonectomy (13) for mesothelioma between January 2008 and March 2013 at our center. Demographic and hemodynamic parameters were retrieved from both electronic- and paper-based medical records. All available CT scans of the chest performed no more than 6 months before surgery were reviewed for quantitative vascular analysis. Only those CT studies with 1 mm or thinner slices were used. A detailed description of the parameters used for image acquisition and reconstruction is available in the Appendix 1. The methods of image analysis used to calculate the vascular CSA have been previously described (14,15). Vascular analysis was performed in three anatomic locations in the lung, which would be spared from the pneumonectomy: 1 cm above the aortic arch, 1 cm below the carina, and 1 cm below the entrance of the right inferior pulmonary vein. These locations were chosen and validated to ensure reproducibility. Measures of the aggregate vascular CSA of structures <5 mm^2 were collected and normalized by the total CSA of the lung in that same slice. The final CSA 5% was calculated by using a weighted average of the three slices (average weighted by the parenchymal area of each slice). The same method was also used to compute the CSA of structures <10 mm^2 to yield the CSA 10%. All image analysis was performed using ImageJ version 1.46r (National Institutes of Health, Bethesda, MD) (16). An example and representation of the process is shown in Figure 1. Please see Appendix 1 for a more detailed description of the image analysis process.

Our STAR (Surgical Intensive Care Unit Translational Research) Center, in collaboration with the Division of Thoracic Surgery, maintains a database of all patients who underwent pneumonectomy since 2008. Institutional Review Board approval was obtained for this analysis. All subjects had a right heart catheterization in the operating room and arrived to the intensive care unit with a pulmonary arterial catheter in place for hemodynamic monitoring. The maximum PAP and the minimum cardiac index (CI) for postoperative day 0 (POD 0) were obtained from archived intensive care unit flow sheets. Only data from POD 0 were used as PA catheters were often removed on subsequent days. Perfusion scans within 1 year of surgery were also evaluated. The fraction of the total perfusion attributable to the nonoperative lung was calculated. Data are presented as means and standard deviations or medians and interquartile ranges where appropriate. Pearson correlation coefficients and their respective statistical significance were evaluated using SAS 9.3 (SAS Institute Inc, Cary, NC). For the comparison of the characteristics of the two groups, the Wilcoxon rank sum test using two-sided *P* values was used for continuous measurements. For the purpose of comparing categorical values a Fisher exact test was used. In all statistical comparisons, *P* values of <0.05 were considered statistically significant.

RESULTS

A total of 159 sequential patients who underwent pneumonectomy between January 2008 and March 2013 were identified in the database. Figure 2 provides a schematic of the review and inclusion of a subset of these subjects. Patients were excluded for inadequate preoperative imaging (n = 83) or lack of hemodynamic data (n = 13) on POD 0 leaving 61 subjects to be included in our analysis. Inadequate imaging was caused predominately by scans without adequately thin sections, usually from outside institutions. Of these 61 subjects, 26 had preoperative CT scans with intravenous contrast (I+), whereas 35 had CT scans without contrast (I−). To our knowledge, there was no specific clinical reason for why certain patients had one type of scan. The subsequent analysis was divided into two groups: patients with (I+) or without (I−) intravenous contrast enhanced CT scans.

The demographics of the cohorts, divided into the two subgroups with or without intravenous contrast enhancement, are shown in Table 1. Between the two subgroups, there was a trend toward left-sided pneumonectomies in patients with I+ CT scans, which did not reach statistical significance.

A summary of CSA calculations for both CSA 5% and CSA 10% is given in Table 4 in Appendix 1. There was a statistically significant difference in CSA 5% between the two groups (P = .001). In the subset of subjects who underwent I− CT scanning there was an inverse relationship between the CSA 5% and peak PAP on POD 0. There was no association between the CSA 5% and CI. In the I+ cohort, there was no association between the CSA 5% and the PAP but the CSA 5% was directly related to CI. These findings are illustrated in Figure 3. Similar findings were noted when using vessel CSAs of 10 mm^2 (CSA 10%), which are summarized in Table 2.

Thirty-four of the 35 patients with I− CT scans and 24 of the 26 patients with I+ CT scans had a perfusion scan available before surgery. We computed the perfusion fraction in the remaining lung as has been suggested by previous studies examining its relation to postoperative respiratory failure (6,12). This was obtained by dividing the perfusion of the unresected lung by total perfusion of both lungs. The perfusion fraction to the nonoperative lung tended to be directly related to the CSA 5% in that same lung. These trends, however, did not reach statistical significance as shown in Table 2. Similar findings were noted for CSA 10% where the correlation in the case of I− scans did reach statistical significance. The perfusion fraction

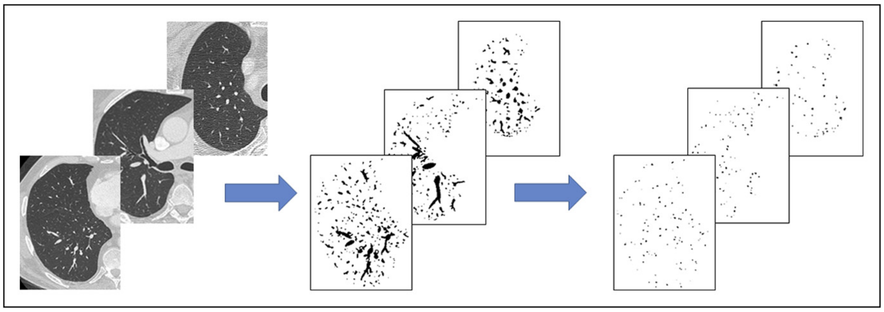

Figure 1. Three slices selected from the computed tomographic scan of a patient before pneumonectomy. The region of interest is selected and thresholding is used to generate the binary images in the middle panels. In this case, circular objects with cross-sectional area (CSA) <5 mm^2 are selected and the overall CSA is counted and normalized by the area of the slice to obtain the CSA 5%.

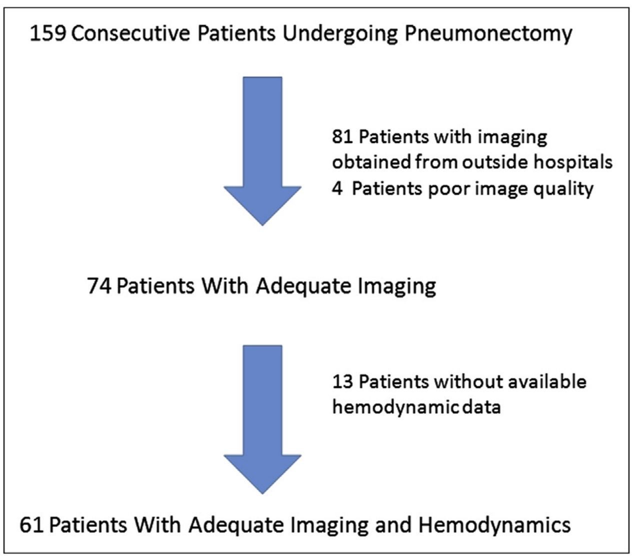

Figure 2. Sixty-one patients were selected from the 164 consecutive patients receiving a pneumonectomy for mesothelioma. Patients were excluded for not having imaging in the 6-month period before surgery at our institution, poor computed tomographic scan quality, and lack of hemodynamic data.

in the spared lung did not correlate with either of the hemodynamic measurements being assessed. These results are summarized in Table 2.

Our vascular CSA method used data from three distinct anatomic sites and presented a weighted average of these measures. We therefore sought to determine if there were differences in the regional CSA measures of postoperative hemodynamics. To do this, we examined the hemodynamic associations of CSA 5% using individual CT slices from each of the three sites. The correlations between vascular morphology and the hemodynamic measurements that had shown statistical significance would retain their individual significance only when the caudal slice CSA 5% was used for analysis. This was true for both the subset of patients with I− and I+ CT scans (Table 3).

DISCUSSION

Pneumonectomy creates a unique physiological state in which the pulmonary vasculature in the nonoperative lung attempts to acutely accommodate the entirety of the cardiac output. Postoperative complications include pulmonary edema, ARDS, and cardiovascular collapse. These and the long-term sequelae, such as pulmonary hypertension, may represent the inability of the vasculature to accommodate this flow. The pulmonary vascular reserve represents the ability of the pulmonary vasculature to accommodate increasing cardiac output without increasing pressures and involves processes such as vasodilation and vessel recruitment (17–19). Previous studies have shown that there are architectural and geometric changes that occur to the parenchymal pulmonary vasculature in disease states that may be visible on CT scans (14,15,20). Previous experience with pneumonectomies also suggests that the relative perfusion of the unresected lung is important in determining surgical outcomes. In this study, we used a method of quantifying pulmonary vascular morphology based on the CSA of blood vessels with an area ≤5 mm^2. Using this method, we found an association between this vascular morphometric measure and postoperative pulmonary hemodynamics after a pneumonectomy.

Our cohort consisted of two groups, one with I+ and other with I− CT scans. We found that the I+ based CSA 5% measures were associated with CI but not with maximum PAPs, whereas in the I− cohort the opposite was true: the CSA 5% was associated with maximum PAPs but not with the CI. A possible explanation for this may be that I+ CT scans highlight different anatomic features, such as perfused blood vessels, providing a functional assessment that correlates with blood flow. Contrast may also enhance the detection of vessels by software algorithms by changing the signal-to-noise ratio of the vessels with respect to the surrounding parenchyma. Supporting this possibility is the observation that in the I+ CT scans, a higher CSA 5% and CSA 10% was detected. Changes in the detection profile of vessels may favor some types of vessels over others leading to observations that correlate with different physiological measurements. Although it did not reach statistical significance, there was also a tendency for those who underwent I+ scanning to have more left-sided pneumonectomies. It is not clear why this would lead to differences in the physiological correlates of CSA 5%, but the removal of the lung from different sides of the chest may have different hemodynamic consequences. Finally, it may be that the underlying clinical conditions, which led to different scanning methods, although

TABLE 1. Demographic Data for 61 Subjects Undergoing Extrapleural Pneumonectomy

Demographics and Characteristics	Without Contrast (I−) *n* = 35	With Contrast (I+) *n* = 26	*P* Value
Right pneumonectomy	21 (60%)	9 (35%)	
Left pneumonectomy	14 (40%)	17 (65%)	.07
Age (years)	62.6	59.7	.51
Female	7 (20%)	7 (27%)	.55
Positive smoking history	18 (51%)	9 (34%)	.30
PY smoking history	11.5	9.8	.51
Maximum systolic PAPs POD 0 (SD)	41 mm Hg (7.5)	39 mm Hg (7.0)	.12
Maximum systolic PAPs POD 1 (SD)	44 mm Hg (9.0)	44 mm Hg (8.0)	.86
Minimum CI POD 0 (SD)	2.9 (0.9)	2.7 (0.8)	.49
Minimum CI POD 1 (SD)	2.6 (0.7)	2.4 (0.4)	.29
Median ICU stay (days)	6	7	.29
Median hospital stay (days)	13	14	.91

CI, cardiac index; ICU, intensive care unit; PAP, pulmonary arterial pressure; POD, postoperative day; SD, standard deviation; PY, pack years.

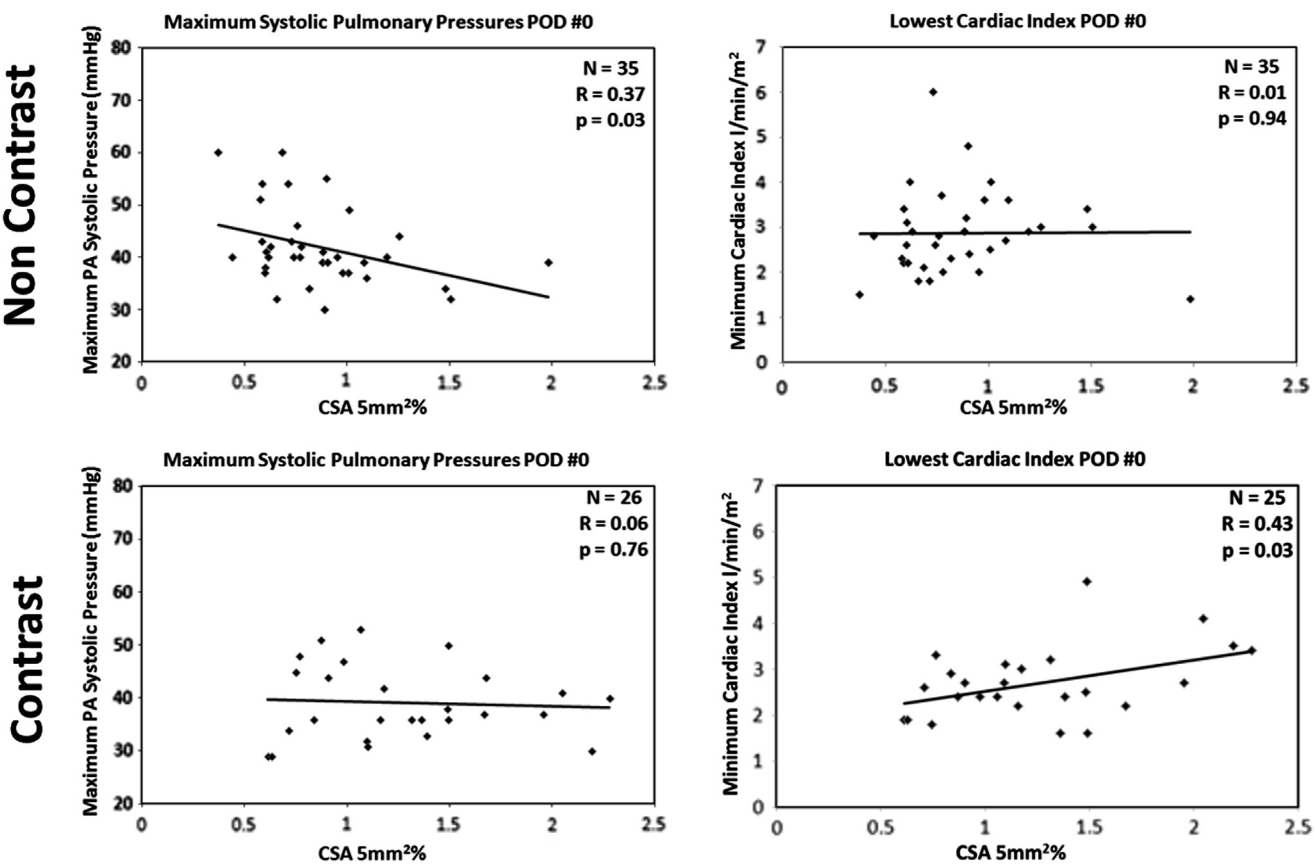

Figure 3. Correlations between cross-sectional area (CSA) of vessels <5 mm^2 expressed as a percentage total lung CSA (CSA 5 mm^2 %) and postoperative hemodynamic parameters for patients receiving noncontrast (*top* two figures) and contrast (*bottom* two figures) preoperative computed tomographic scans.

unknown to us, may have led to different physiological or anatomic differences between the two groups. Contrast specific approaches to morphologic quantification may in the future take advantage of these distinctions.

Previous studies have suggested using the fraction of perfusion attributed to the nonoperative lung as a way to predict potential surgical outcomes related to the overload of pulmonary vasculature. We attempted to apply this marker and compare its utility to the CSA measurements. We did not find a statistically significant correlation between the relative perfusion of the nonoperative lung fraction and the hemodynamic variables analyzed. Furthermore, there was no statistically significant association between lung perfusion and CSA 5%, whereas a correlation was noted between lung perfusion and CSA 10% only in the case of noncontrast CT scans. This suggests that the vascular morphology on CT

TABLE 2. Comparison of the Percentage of Perfusion in the Nonoperative Lung as Assessed by a Nuclear Perfusion Scan and Hemodynamic Parameters, Compared to the Correlation with CSA 5% and CSA 10%

	Without Contrast			With Contrast		
Measurement	Correlation with Nonoperative Perfusion Fraction	Correlation with CSA 5%	Correlation with CSA 10%	Correlation with Nonoperative Perfusion Fraction	Correlation with CSA 5%	Correlation with CSA 10%
Maximum PAP POD 0	$R = 0.06$, $P > .5$	$R = 0.37$, $P = .03$	$R = 0.37$, $P = .03$	$R = 0.07$, $P > .5$	$R = 0.06$, $P > .5$	$R = 0.13$, $P > .5$
Minimum Cardiac Index POD 0	$R = 0.05$, $P > .5$	$R = 0.01$, $P > .5$	$R = 0.12$, $P = .94$	$R = 0.09$, $P > .5$	$R = 0.43$, $P = .03$	$R = 0.45$, $P = .03$
Nonoperative Perfusion Fraction		$R = 0.27$, $P = .11$	$R = 0.34$, $P = .04$		$R = 0.33$, $P = .12$	$R = 0.32$, $P = .12$

CSA, cross-sectional area; POD, postoperative day; PAP, Pulmonary Arterial Pressure.

TABLE 3. Correlation Between Regional Measures of CSA 5% and Postoperative Hemodynamics

Correlation Measured	Apical Slice	Carina Slice	Caudal Slice
Without contrast ($n = 35$)			
POD 0 max PAP versus CSA 5%	$R = 0.30$, $P = .08$	$R = 0.34$, $P = .05$	$R = 0.38$, $P = .03$
With contrast ($n = 26$)			
POD 0 min CI versus CSA 5%	$R = 0.40$, $P = .05$	$R = 0.31$, $P = .13$	$R = 0.46$, $P = .02$

CI, cardiac index; CSA, cross-sectional area; PAP, pulmonary arterial pressure; POD, postoperative day.

scan provides information that is complementary to what is obtained from the perfusion scan. With further development of these techniques, perfusion scan information may be integrated with anatomic information to provide a better composite estimate of the vascular reserve available to accommodate flow.

Our CT scan analysis technique averaged vascular data from three axial slices to provide a more global assessment of vessel morphology. This approach, however, does not explore regional differences in blood flow. In evaluating the relative contribution of information from each image, the correlation only reached statistical significance in the caudal images at the level of the right inferior pulmonary vein. This finding may be related to the relative perfusion in this lung region or may be in part because of the vascular orientation at this site and the accuracy of our measures.

In addition to having statistically significant correlation, the direction of the correlation between CSA 5% and hemodynamics supports the hypothesis that decreased vascular density as measured by CT scans leads to increased postoperative PAPs and decreased cardiac output. This observation further supports the hypothesis that lung parenchymal vascular density obtained from CT scans may be useful in assessing potential pulmonary reserve before lung removal surgery.

This study is limited by being retrospective. The patients receiving CT scans at our institution may not have been representative of all subjects in this population. We used only CT scans from our institution. However, even within the subgroup of contrasted versus noncontrasted CT scans, there may have been significant variability in filtering and image acquisition modalities. The influence of such variability in our imaging data cannot be measured in this cohort. A prospective study with standardized image acquisition and reconstruction is necessary to further substantiate our findings. Without a set protocol for recording hemodynamic data, the degree of the uniformity of data collection cannot be assessed. Finally, the lack of prospective data collection and treatment protocols limits clear assessment of the other clinically relevant surrogates, which cannot be easily reconstructed by chart review. Extrapleural pneumonectomies involve the resection of the diaphragm and pericardium, which may influence pressure gradients, and thus may differ from pleura sparing pneumonectomies in their physiological impact.

CONCLUSIONS

The CSA percentage (CSA %) is a simple threshold-based technique previously used in characterization of pulmonary hypertension in emphysema patients. It is able to use CT scan slices to estimate the vascular density using publicly available software and without significant training and expertise required on the part of the software operator. On the basis of this technique, there exists a correlation between the CT scan–based estimated vascular CSA in the spared lung and postpneumonectomy pulmonary hemodynamics. The observed relationship supports the hypothesis that elevated postoperative pulmonary pressures and decreased cardiac output are related to decreased vascular capacity of the contralateral lung. This association further suggests that the measurement of intraparenchymal vessel morphology may be useful as an imaging-based biomarker in assessing the potential response of the pulmonary vasculature to perturbations. These methods, which could take advantage of already existing imaging techniques, can serve as a way to help assess surgical risk without exposing the patient to additional testing or costs. As has been demonstrated in previous publications, these methods may also find utility in a diverse set of disease processes, both in diagnosis and monitoring of progression and disease response.

The differences between the imaging techniques (I+ vs. I−) and slice location used highlight the potential for refinement of the CSA technique. Our group has developed a method of extraction of a full three-dimensional model of the vasculature from volumetric CT scans (20). We could not perform this analysis retrospectively as volumetric data are needed for this technique, and we hope to collect this in subsequent studies. With uniform imaging techniques, prospective data collection, and optimization of the image processing techniques, quantitative assessment of pulmonary vascular morphology may serve as a biomarker for the prediction of complications related to the pulmonary vasculature in lung surgery.

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APPENDIX 1. METHOD OF COMPUTING CSA 5%

Methods for calculating the CSA have been described in previous publications (14,15). Candidate CT scans must have slices, which are thin enough to minimize the blurring of the small vessels traversing through those slices. For the purpose of this analysis, 1-mm slices were selected, which were obtained at 1-cm intervals. They were selected at three general anatomic locations: 1 cm above the aortic arch, 1 cm below the carina, and 1 cm below the entrance of the right inferior pulmonary vein. These locations were selected to improve the reproducibility of the method between scans and minimize slice selection bias. These slices were then individually analyzed as follows: using a free, publicly available image processing tool developed by the National Institutes of Health (NIH), ImageJ (16). We had chosen this publicly available tool, to develop this algorithm, in part to encourage the use of this method without having to have specialized software. All subsequent analysis took place on the lung, that would remain after the pneumonectomy. Each of the chosen slices first undergoes gaussian blurring with a pixel radius of 0.8 to reduce image noise. The image then undergoes thresholding with a window level of −720 and window width of 1, subsequently converted to an 8-bit binary image. The wand tool is used to select the lung parenchyma region in the lung segment of interest. This is the lung parenchyma, which is then used as the total area of lung in that slice. In this area, objects with circularity of 0.9 and total area of 0–5 mm^2 are analyzed using the “Analyze Particles” function in ImageJ. For CSA 10 mm^2 objects with an area of 0–10 mm^2 would be obtained. The total area of these circular objects is recorded as the CSA 5 mm^2. The area of the parenchyma on the side being analyzed is then calculated by taking the blurred image from the prior steps and applying a thresholding window between −500 and −1024. This is then selected using the region selection wand tool and the area for it is calculated using the analyze command. The CSA 5 mm^2 is divided by the parenchymal area and multiplied by 100 to yield the percentage of the area of the parenchyma accounted for by circular objects <5 mm^2, the CSA 5%. Similar calculations can be made for CSA 10 mm^2 to obtain the CSA 10%. A summary of CSA calculations for both CSA 5% and CSA 10% is given in Table 4.

TABLE 4. Cross-sectional Area (CSA) of Circular Objects Representing Vasculature Running Perpendicular to the Plane of the Computed Tomographic Slices with Area of 5 mm^2 Divided by Area of Lung in the Slice (CSA 5%). CSA 10% Represents Detected Vessels with Area <10 mm^2. Overall There is a Statistically Significant Difference in CSA 5% Between the Subjects with Contrast and Those without (P = .001)

Measurement	CSA 5%	CSA 10%
Without contrast (n = 35)	0.87 ± 0.33	1.22 ± 0.37
Right lung removed (n = 21)	0.76 ± 0.19	1.1 ± 0.23
Left lung removed (n = 14)	1.03 ± 0.41	1.39 ± 0.47
Top slice (n = 35)	1.04 ± 0.33	1.68 ± 0.40
Carina slice (n = 35)	0.84 ± 0.37	1.12 ± 0.43
Caudal slice (n = 35)	0.79 ± 0.34	1.05 ± 0.42
With contrast (n = 26)	1.27 ± 0.48	1.68 ± 0.57
Right lung removed (n = 9)	1.22 ± 0.50	1.61 ± 0.56
Left lung removed (n = 17)	1.30 ± 0.48	1.72 ± 0.59
Top slice (n = 26)	1.35 ± 0.48	1.96 ± 0.64
Carina slice (n = 26)	1.39 ± 0.49	1.69 ± 0.59
Caudal slice (n = 26)	1.20 ± 0.58	1.54 ± 0.70