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Pre-operative Pulmonary Vascular Morphology and its Relationship to Post-Pneumonectomy Hemodynamics

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Introduction

A detailed pre-procedure assessment of patients undergoing lung resection has become a key component for the estimation of peri-operative risk [1–3]. In the case of patients undergoing pneumonectomy, the goals of this evaluation are to predict post operative lung function, the potential for ventilatory compromise, pulmonary edema, and ARDS [4–6]. Such patients are also at increased risk for the development of both transient elevations of pulmonary artery pressures and sustained postoperative pulmonary hypertension [7–9]. Previous studies suggest that preoperative pulmonary vascular resistance and intraoperative pulmonary arterial pressures are predictive of post-operative respiratory failure and mortality [10, 11]. In another example, the risk of developing post operative pulmonary edema and ARDS was related to the preoperative distribution of lung perfusion. [6, 12]. In aggregate, the risk for developing post-pneumonectomy complications appear to be related to the ability of the non-operative lung to accommodate an increase in blood flow to the full cardiac output. Non-invasive identification of compromised pulmonary vasculature in the non-operative lung may reduce morbidity and mortality associated with this procedure.

Our group has previously described a semi-automated quantification method to calculate the total cross sectional area of the pulmonary vasculature on computed tomographic (CT) scans of the chest. The objective of these 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 cross sectional area (CSA) in the non-operative lung as assessed by pre-operative CT scans would be at greatest risk for hemodynamic compromise in the immediate post-operative period. To investigate this hypothesis we performed a secondary analysis of clinically acquired CT and hemodynamic data on subjects undergoing extrapleural pneumonectomy at our institution.

Methods

We evaluated a sequential cohort of patients who underwent extra-pleural pneumonectomy [13] for mesothelioma between January 2008 and March 2013 at our center. Demographics 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 month prior to surgery were reviewed for quantitative vascular analysis. Only those CT studies with 1mm or thinner slices were utilized. A detailed description of the parameters used for image acquisition and reconstruction are available in the online appendix. The methods of image analysis used to calculate the vascular CSA have been described previously [14, 15]. Vascular analysis was performed in three anatomic locations in the lung which would be spared from the pneumonectomy: 1cm above the aortic arch, 1cm below the carina and 1 cm below the entrance of the right inferior pulmonary vein. These locations were chosen and validated in order to ensure reproducibility. Measures of the aggregate vascular cross sectional area of structures less than 5mm² were collected and normalized by the total cross sectional area of the lung in that same slice. The final CSA 5% was calculated by using a weighted average of the three slices (weighted by the axial cross sectional area of the lung in that image). The same method was also used to compute the cross sectional area of structures less than 10mm² to yield the CSA 10%. All image analysis was performed using

ImageJ version 1.46r [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 Research Center in collaboration with the Division of Thoracic Surgery maintains a database of all patients who undergo pneumonectomy since 2008. IRB 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 PA pressure and the minimum cardiac index (CI) for post-operative day zero was obtained from archived ICU flowsheets. Only data from post-operative day zero was 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 non-operative lung was calculated. Data is presented as means and standard deviations (SD) or medians and inter-quartile ranges (IQR) where appropriate. Pearson Correlations coefficients and their respective statistical significance was evaluated using SAS 9.3 (Cary, NC). For the comparison characteristics of the two groups, Wilcoxon Rank Sum test using two sided p-values was used for continuous measurements. For the purpose of comparing categorical values a Fisher's exact test was used. In all statistical comparisons, p values of less than 0.05 were considered statistically significant.

Results

159 sequential patients undergoing pneumonectomy between 1/2008 and 3/2013 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 pre-operative imaging (n=83) or lack of hemodynamic data (n=13) on post-operative day zero (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+) while 35 were 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 shown in Table 1. Between the two subgroups, there was a trend towards 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% shown in table 4 listed in the appendix. There was a statistically significant difference in CSA 5% between the two groups ($p = 0.001$). In the subset of subjects who underwent I- CT scanning there was an inverse relationship between the CSA 5% and peak PAP on post operative day 0. There was no association between the CSA 5% and cardiac index. 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 cross-sectional areas of 10mm² (CSA 10%) which are summarized in Table 2.

34 out of the 35 patients with I- CTs and 24 out of the 26 patients with I+ CTs had a perfusion scan available prior to surgery. We computed the perfusion fraction in the remaining lung as has been suggested by prior studies examining its relation to post-operative respiratory failure [6, 12]. This was obtained by dividing the perfusion of the non-resected lung by total perfusion of both lungs. The perfusion fraction to the non-operative 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 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 post-operative 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.

Discussion

Pneumonectomy creates a unique physiologic state in which the pulmonary vasculature in the non-operative lung attempts to acutely accommodate the entirety of the cardiac output. Post-operative 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]. Prior experience with pneumonectomies also suggests that the relative perfusion of the un-resected lung is important in determining surgical outcomes. In this study we used a method of quantifying pulmonary vascular morphology based upon the cross-sectional area of blood vessels with area of 5mm² or less. Using this method we found an association between this vascular morphometric measure and post-operative pulmonary hemodynamics after a pneumonectomy.

Our cohort consisted of 2 groups, one with I+ and with one with I- CT scans. We found that the I+ based CSA 5% measures were associated with cardiac index but not with maximum PA pressures, while in the I- cohort the opposite was true: the CSA 5% was associated with max PA pressures, but not the cardiac index. 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 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 measurements which correlate with different physiologic measurements. While 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 physiologic 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, though unknown to us, may have led to different physiologic or anatomic differences between the two groups. Contrast specific approaches to morphological quantification may in the future take advantage of these distinctions.

Previous studies have suggested using the fraction of perfusion attributed to the non-operative 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 non-operative lung fraction and the hemodynamic variables analyzed. Furthermore, there was no statistically significant association between lung perfusion and CSA 5%, while a correlation was noted between lung perfusion and CSA 10% only in the case of non-contrast CTs. This suggests that the vascular morphology on CT scan provide 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 anatomical information to provide a better composite estimate of the vascular reserve available to accommodate flow.

Our CT analysis technique averaged vascular data from 3 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 due in part to 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 post-operative PA pressures 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 prior to 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 non-contrasted 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 in from pleura sparing pneumonectomies in their physiologic impact.

Conclusions

The Cross sectional area 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. Based on this technique, there exists a correlation between the CT based estimated vascular cross-sectional area in the spared lung and post-pneumonectomy pulmonary hemodynamics. The observed relationship supports the hypothesis that elevated post-op pulmonary pressures and decreased cardiac output are related to decreased vascular capacity of the contralateral lung. This association further suggests that measurement of intra-parenchymal 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 technique (I+ versus I-) as well as slice location used highlight the potential for refinement of the CSA technique. Our group has developed a method of extraction of a full 3D model of the vasculature from volumetric CT scans [20]. We could not perform this analysis retrospectively as volumetric data is 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 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 prior 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, 1mm slices were selected which were obtained at 1cm intervals. They were selected at three general anatomic locations: 1cm above the aortic arch, 1cm below the carina, and 1cm below the exit of the right inferior pulmonary vein. These locations were selected to improve 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 NIH, ImageJ [16]. We had chosen this tool which is publicly available 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 which 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 $0-5 \text{ mm}^2$ are analyzed using the “Analyze Particles” function in Image J. For CSA 10mm^2 objects with area of $0-10\text{mm}^2$ would be obtained. The total area of these circular objects is recorded as the CSA 5mm^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 5mm^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 less than 5mm^2 , the CSA 5%. Similar calculations can be made for CSA 10mm^2 to obtain the CSA 10%

Figure 1.

Three slices selected from the CT scan of a patient prior to 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 of less than 5mm^2 are selected and the overall cross sectional area is counted and normalized by the area of the slice to obtain the CSA 5%.

Figure 2.

61 patients were selected from the 164 consecutive patients receiving a pneumonectomy for mesothelioma. Patients were excluded for not having imaging in the six month period prior to surgery at our institution, as well as for poor CT scan quality, and lack of hemodynamic data.

Figure 3. Correlations between cross-sectional area of vessels less than 5mm² expressed as a percentage total lung cross sectional area (CSA 5mm² %) and post operative hemodynamic parameters for patients receiving non contrast (top two figures) and contrast (bottom two figures) pre-operative CT scans.

Table 1

Demographic Data for 61 Subjects Undergoing Extrapleural Pneumonectomy

	<u>Non Contrast (I-)</u> <u>N = 35</u>	<u>With Contrast (I+)</u> <u>N = 26</u>	<u>P value</u>
<u>Right Pneumonectomy</u>	21 (60%)	9 (35%)	
<u>Left Pneumonectomy</u>	14 (40%)	17(65%)	p = 0.07
<u>Age (years)</u>	62.6	59.7	p = 0.51
<u>Female</u>	7 (20%)	7 (27%)	p = 0.55
<u>Positive Smoking History</u>	18 (51%)	9 (34%)	p = 0.30
<u>PY Smoking History</u>	11.5	9.8	p = 0.51
<u>Maximum Systolic PA pressures POD #0 (std)</u>	41 mmHg (7.5)	39 mmHg (7.0)	p = 0.12
<u>Maximum Systolic PA pressures POD #1 (std)</u>	44 mmHg (9.0)	44 mmHg (8.0)	p = 0.86
<u>Minimum Cardiac Index POD #0 (std)</u>	2.9 (0.9)	2.7 (0.8)	p = 0.49
<u>Minimum Cardiac Index POD #1 (std)</u>	2.6 (0.7)	2.4 (0.4)	p = 0.29
<u>Median ICU Stay (Days)</u>	6	7	p = 0.29
<u>Median Hospital Stay (Days)</u>	13	14	p = 0.91

Table 2

Comparison of the % of perfusion in the non-operative lung as assessed by a nuclear perfusion scan and hemodynamic parameters, compared to the correlation with CSA 5%.

	<u>Without Contrast</u>			<u>With Contrast</u>		
	Correlation With Non-operative Perfusion Fraction	Correlation with CSA 5%	Correlation with CSA 10%	Correlation With Non-Operative Perfusion Fraction	Correlation with CSA 5%	Correlation with CSA 10%
Maximum PA Pressure POD #0	R = 0.06 p > 0.5	R = 0.37 p = 0.03	R = 0.37 p = 0.03	R = 0.07 p > 0.5	R = 0.06 p > 0.5	R = 0.13 p > 0.5
Minimum Cardiac Index POD #0	R = 0.05 p > 0.5	R = 0.01 p > 0.5	R = 0.12 p = 0.94	R = 0.09 p > 0.5	R = 0.43 p = 0.03	R = 0.45 p = 0.03
Non-operative Perfusion Fraction		R = 0.27 p = 0.11	R = 0.34 p = 0.04		R = 0.33 p = 0.12	R = 0.32 p = 0.12

Table 3

Correlation between regional measures of CSA 5% and post operative hemodynamics.

	<u>Apical Slice</u>	<u>Carina Slice</u>	<u>Caudal Slice</u>
<u>Without Contrast (n = 35)</u>			
POD #0 Max PAP versus CSA 5%	R = 0.30, p = 0.08	R = 0.34, p = 0.05	R = 0.38, p = 0.03
<u>With Contrast (n = 28)</u>			
POD #0 Min CI Versus CSA 5%	R = 0.40, p = 0.05	R = 0.31, p = 0.13	R = 0.46, p = 0.02

Table 4

Cross sectional area of circular objects representing vasculature in running perpendicular to the plane of the CT slices with area of 5mm^2 divided by area of lung in the slice (CSA 5%). CSA 10% represents detected vessels with area less than 10mm^2 . Overall there is a statistically significant difference between CSA 5% between the subjects with contrast and those without ($p = 0.001$).

	<u>CSA 5 %</u>	<u>CSA 10 %</u>
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