NON-INVASIVE INDICATORS OF PULMONARY HYPERTENSION FROM PULMONARY VEINS QUANTIFICATION IN SICKLE CELL DISEASE

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ABSTRACT

Pulmonary hypertension is a common cause of death among patients with sickle cell disease. This retrospective study investigates the use of pulmonary vein quantification to diagnose pulmonary hypertension non-invasively with CT-Angiography images. Ten images from patients with pulmonary hypertension were matched with controls. An adaptive fast marching approach is applied in order to segment the left atrium and pulmonary veins, followed by a geodesic active contour to isolate the atrium. The ostia of the pulmonary veins are determined by computing the skeleton and finding the intersections with the contour of the atrium. 96.3% of the ostia are identified correctly by the technique. The diameters of the veins are then measured and their sum is computed at fixed distances from the ostium. These quantitative indicators are significantly larger in patients as compared to controls (p-values < 0.01). Furthermore, the non-invasive estimations of the method present a high and significant correlation with the clinical hemodynamics measurements obtained from right heart catheterization.

Index Terms—Pulmonary hypertension, pulmonary veins, segmentation, quantification, sickle cell disease.

1. INTRODUCTION

Pulmonary hypertension (PH) is one of the strongest predictors of death among adults with sickle cell disease (SCD) [1]. Using right heart catheterization, an invasive procedure employed clinically to measure the cardiac and pulmonary hemodynamics, it is clear that both arterial and venous PH are common in patients with SCD associated PH. While it has been noted that the pulmonary artery tends to be enlarged in patients with PH [2], there has been limited study of the pulmonary veins (PV) of these patients. Moreover, measurements of PV are affected by the large variability in vessel geometry. This study aims to develop systematic and reproducible measures of the pulmonary vein to predict pulmonary hemodynamics and classify PH non-invasively with 3D CT-Angiography (CTA) images.

The computer-assisted characterization of PV from CTA presents three main challenges. Firstly, it is not known a priori the number of PV for a given patient as there is a high variation in pulmonary venous anatomy and patients may present one of many different patterns of pulmonary venous drainage [3] [4]. Secondly, PV branch quickly when taking into account positions in the PV further away from the ostia [3], and therefore, the characterization of PV needs to be robust to the different number of branches of each vein. Thirdly, the contrast material bolus image is dissipated upon reaching the veins, due to the CTA acquisition protocol, making the edges of these vessels poorly defined in the images.

Most recent work toward the computer-based prediction of PH focused on the analysis and quantization of the pulmonary artery from CTA ( [2] and references within). A semi-automated method using active shape models was developed in [5], where the shape model is learnt with user interaction and is strongly dependent on its initialization [6]. Another semi-automated method was presented in [7], based on a watershed segmentation technique where the user needs to select six marker positions. Most other methods used MRI data.

This study explores the potential of CT with image processing to provide non-invasive markers of pulmonary hemodynamics and assist in the diagnosis of PH. We propose a semi-automated method to quantify the size of the pulmonary veins. The method based on fast marching methods, active contours and skeletonization segments and analyzes the left heart atrium and PV using minimal user interaction. The technique is particularly designed to address the highly variable number of PV and their irregular geometry between patients by using adaptive parameters. The imaging biomarkers estimated from the cumulative size of PV at different depths from the ostia are shown to be significantly larger in sickle-cell patients with PH as compared to controls and correlate significantly with invasive indicators of hemodynamics obtained clinically from right heart catheterization.

2. METHOD

2.1. Data and Materials

Twenty pulmonary CTA studies were analyzed: ten from patients with sickle cell anemia and related PH ranging from mild to severe (documented and quantified by invasive right heart catheterization); and ten from randomly-selected patients without SCD or PH as negative controls. All the scans had some level of...
enhancement of the veins and no large imaging artifacts. Controls were matched to cases on the basis of age and gender. All pulmonary CTA data were collected using GE Lightspeed Ultra (GE Healthcare) and Philips Mx8000 IDT 16 (Philips Medical Systems) scanners. Image resolution ranged from 0.66 to 0.70 mm in the axial projection and slice thickness was between 1.00 and 1.25 mm. Image size ranged from 512 x 512 x 119 to 512 x 512 x 310.

CT data were smoothed using anisotropic diffusion to enhance the homogeneity of blood vessels and ensure boundary preservation. The classic Perona-Malik non-linear model was employed [8].

2.2 Segmentation of the Left Heart Atrium and Pulmonary Veins

The segmentation of the left heart atrium and PV is performed by a fast marching method [9]. The technique takes two user-defined seeds in the left heart atrium, one close to the left ostia and one close to the right ostia, and, given a speed function \( F \), tracks the resulting surface when the speed \( F \) is applied, starting from the seed points. In our application, this specific type of level set method assumes that the surface can only expand starting from the seed points. The speed of expansion is constant and along the surface normal. Let \( T \) be the arrival time of the front, the marching method solves the Eikonal equation

\[
F(x)[\nabla T(x)] = 1,
\]

with \( T = 0 \) in the seed points.

The speed function is determined as follows. In order to correctly segment, the front needs to move slowly near edges and is allowed to move fast in homogeneous regions. Therefore, the sigmoid of the magnitude of the gradient of the image \( |\nabla I| \) is a good candidate to be used as a speed function, that is,

\[
I_a = \frac{1}{1 + e^{-(\frac{L}{\alpha - \beta})}}
\]

where \( \alpha \) is related to the input intensity range and \( \beta \) the intensity around which the range is centered. These parameters can be found adaptively to the image as follows. It is known that a heuristic can be used to compute the parameters [10] by finding the minimum value along the contour of the anatomical structure to be segmented (\( K_1 \)) and the average value of the gradient magnitude in the middle of the structure (\( K_2 \)). Thus, we set the parameters as

\[
\alpha = \frac{K_2 - K_1}{6}, \quad \beta = \frac{K_1 + K_2}{2}
\]

In our case, the values of \( K_1 \) and \( K_2 \) are not known a priori and are approximated as follows. Firstly, in order to find the value of \( K_2 \), noticing that the left heart atrium is a convex object, the line (\( L \)) of points in-between the seed points belong to the left atrium. Then, we approximate \( K_2 \) by computing the average value of all the points in \( L \) in the magnitude of the gradient image. Secondly, to approximate \( K_1 \), the minimum value on the contour is needed. From each point in \( L \), we move in six directions and assume that the contour occurs when a high value of the magnitude of the gradient is observed. We keep the smallest of these contour values and assign it to \( K_1 \).

As the speed image is not perfect (there are artifacts from the heart motion and inconsistent contrast enhancement), the method needs to adaptively determine when to stop the evolution of the fast marching front. In order to do this, the method takes full advantage of the two seeds placed by the user. It first tracks the evolution of the two fronts, each starting from a different seed point, and measures the time \( \tau \) it takes for the two fronts to meet and merge in a unique front. The time \( \tau \) is proportional to the size of the atrium taking into account the contrast of the image. The method then lets the resulting front to evolve for an additional time \( \tau /2 \).

Artifacts and noise lead to holes in the segmentation. Therefore, we use the morphological closing operation [11] to remove holes. The closing operation consists of the application of a dilation operation followed by an erosion.

2.3 Isolation of the Left Heart Atrium and Skeletonization

A level set based on geodesic active contours [9] [12] is used to isolate the left heart atrium from the output of the fast marching segmentation. It can be shown that the fast marching method itself can be written as a level set method by embedding the front as the zero level set of a higher dimension function \( \phi \). Then, the fast marching method is equivalent to solving

\[
\phi_t + F|\nabla \phi| = 0.
\]

By allowing the front to contract aside from expanding, and adding to the driving expansion term a surface tension force term and an attraction to boundaries, the result is a general level set method, that is

\[
\phi_t + F(\omega_1 s - \kappa)|\nabla \phi| + \omega_2 R(\nabla \phi) = 0,
\]

where the weights \( \omega_1 \) and \( \omega_2 \) control, respectively, the speed \( s \) and attraction to edges and \( \kappa \) represents the curvature. In particular, given the segmentation of the left heart atrium and PV, the left atrium can be isolated by applying a level set method penalizing curvature heavily.

In order to find the skeleton of the left heart atrium and PV, thinning was used. The thinning process consists of eroding the object’s surface iteratively until only the skeleton remains. This is done in a symmetric order so that the skeleton consists of the medial position [13] [14].

2.4 Pulmonary Veins Quantification and Analysis

The PV ostia are determined by the intersections of the skeleton and the surface of the left atrium. The number of veins is then found automatically from the number of intersection.

The diameter of each ostium and the diameters of the veins at specific distances from the corresponding ostium (5, 10 and 15 mm) are then measured. If a vein is branching before the distance of measurement is reached, then the diameters of all the new branches are measured. To account for the total blood flow, the cumulative PV size is computed by adding the diameters of all PV and their branches at the chosen distance from the atrium. To address the variation of the PV size and blood flow with the size of the patient, the cumulative diameter of the veins diameters was normalized by the body mass index (BMI) and the body surface area (BSA).

The Wilcoxon signed-rank test was used to test the significance of the size difference in PV diameter between SCD patients and negative controls. The Spearman correlation coefficient and its significance were computed between the non-invasive measurements of PV size and hemodynamics.
3. RESULTS

3.1 Segmentation and Quantification

Figure 1 shows examples of the segmentation of PV and left heart atrium. Maps of diameter sizes can be found in Figure 2. Results indicate that the sum of the diameters of PV is significantly larger in SCD patients as compared to controls when measured either at the ostia or at a distance of 5, 10 or 15 mm from ostia (see Table 1). Results show consistently a significant size difference between patients and control with the normalization by BMI and BSA.

Table 1: Significance (p-values) of the measurements of PV cumulative diameters between patients and controls, as non-invasive PH indicators. BMI and BSA indicate the normalization factors.

<table>
<thead>
<tr>
<th>Measure / Distance from ostia</th>
<th>0 mm</th>
<th>5 mm</th>
<th>10 mm</th>
<th>15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Diameter</td>
<td>0.007</td>
<td>0.002</td>
<td>0.002</td>
<td>0.007</td>
</tr>
<tr>
<td>Cumulative Diameter/BMI</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Cumulative Diameter/BSA</td>
<td>0.003</td>
<td>0.001</td>
<td>0.001</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Many different patterns of pulmonary venous drainage were detected. Five PV were found in four (20%) patients and one (5%) control. The superior and inferior veins shared one common ostium either on the left or on the right side in one (5%) patient and two (10%) controls. Neither patients nor controls presented common ostia both in the left and right side simultaneously. The remaining patients exhibited more typical anatomy for PV with four ostia for the left superior, left inferior, right superior and right inferior PV, as shown in Figure 3.

Table 2 shows the average (and standard deviations) PV cumulative diameters in patients and controls.

<table>
<thead>
<tr>
<th>Group / Distance from ostia</th>
<th>0 mm</th>
<th>5 mm</th>
<th>10 mm</th>
<th>15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>43.0±9.0 mm</td>
<td>41.4±8.0 mm</td>
<td>38.5±10.7 mm</td>
<td>36.2±11.5 mm</td>
</tr>
<tr>
<td>Controls</td>
<td>31.0±9.3 mm</td>
<td>28.1±8.6 mm</td>
<td>25.1±8.8 mm</td>
<td>22.1±9.1 mm</td>
</tr>
</tbody>
</table>
3.2 Manual Measurements

An observer determined manually the location of the PV ostia in each image. There were 81 true ostia in the dataset and our method identified correctly 78 of them or 96.3%. The method output 4 additional ostia that could not be matched with any ostia point found by the observer.

The observer determined manually the radii of PV at the ostia in the axial plane, as in clinical practice. These are approximated two-dimensional measurements from projection images. The resulting correlation between these 2D measurements and the values found by our method for the radii of ostia was 0.6 (p<0.001).

Table 3: Correlation and significance of the PV size markers at 15mm from the ostia with central venous (CVP), systolic pulmonary artery (PAS), diastolic pulmonary artery (PAD) and mean pulmonary artery (PAM) pressures. Corr indicates the Spearman correlation and p its significance. BMI and BSA are the normalization factors.

<table>
<thead>
<tr>
<th>PV size/ Hemodynamics</th>
<th>CVP</th>
<th>PAS</th>
<th>PAM</th>
<th>PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Diameter</td>
<td>Corr 0.89</td>
<td>0.78</td>
<td>0.84</td>
<td>0.79</td>
</tr>
<tr>
<td>p</td>
<td>0.91</td>
<td>0.91</td>
<td>0.89</td>
<td>0.78</td>
</tr>
<tr>
<td>Cumulative Diameter/BMI</td>
<td>Corr 0.77</td>
<td>0.73</td>
<td>0.71</td>
<td>0.66</td>
</tr>
</tbody>
</table>

4. DISCUSSION

A method was presented for the segmentation and quantification of pulmonary veins from 3D CT-Angiography using levels sets and active contours. The left heart atrium and the pulmonary veins were segmented and the diameter of the latter quantified to better understand the pathophysiology of pulmonary hypertension in sickle cell disease and discriminate between sickle cell patients and controls. Results showed that the cumulative diameters of the pulmonary veins at the ostia, and at 5, 10 or 15 mm from the ostia is significantly larger in the patient population as compared to controls. Additionally, the measurements taken at 15 mm from ostia are shown to have a high and significant correlation with hemodynamic indicators used to invasively diagnose pulmonary hypertension. The method is robust to variations in anatomy (such as variable number of veins) and low contrast in the veins. 96.3% of the pulmonary veins ostia were detected correctly. The results found the method correlated significantly with manual clinical measurements. In conclusion, this 3D evaluation of pulmonary veins shows great promise as a noninvasive assessment tool for pulmonary hypertension.

5. ACKNOWLEDGEMENT

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6. REFERENCES


