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CT and Image Processing Non-invasive Indicators of Sick Cell Secondary Pulmonary Hypertension

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Abstract

This retrospective study investigates the potential of image analysis to quantify for the presence and extent of pulmonary hypertension secondary to sickle cell disease (SCD). A combination of fast marching and geodesic active contours level sets were employed to segment the pulmonary artery from smoothed CT-Angiography images from 16 SCD patients and 16 matching controls. An algorithm based on fast marching methods was used to compute the centerline of the segmented arteries to measure automatically the diameters of the pulmonary trunk and first branches of the pulmonary arteries. Results show that the pulmonary trunk and arterial branches are significantly larger in diameter in SCD patients as compared to controls (p-values of 0.002 for trunk and 0.0003 for branches). For validation, the results were compared with manually measured values and did not demonstrate significant difference (mean p-values 0.71). CT with image processing shows great potential as a surrogate indicator of pulmonary hemodynamics or response to therapy, which could be an important tool for drug discovery and noninvasive clinical surveillance.

I. INTRODUCTION

Pulmonary arterial hypertension is a frequent complication associated with sickle-cell disease (SCD); roughly 75% of SCD patients have pulmonary arterial hypertension at the time of death [1]. High mortality rates suggest that patients with high anemia, such as SCD, have low tolerance to pulmonary hypertension (PHT). Approximately a third of adult SCD patients present signs of PHT [8,14], often manifested by pruning or tapering of blood vessels (large arterial trunk and abrupt downstream transition between large and small caliber arteries) and leading to heart failure.

Noninvasive monitoring for the biologic effects of sickle cell anemia may facilitate drug discovery, response, prognosis and acute management. The relation between the disease and PHT is under investigation in therapeutic trials targeted toward SCD patients [5]. This method proposes the semi-automatic computer-aided quantification of PHT in SCD patients for diagnosis and assessment of prognosis.

Little work has been presented toward the automatic computer-based analysis of the pulmonary artery; there are even fewer examples using CT [6,9,17]. However, there is extensive literature for the extraction of curvilinear structures in medical images [2,4,7,15]. Recently, the quantitative analysis of airways from CT in relation to arterial size was presented in [12,13].

This application uses geodesic active contours to segment pulmonary arteries. Moreover, it combines level sets with the extraction of centerline using fast marching methods. As a result, this algorithm presents a map of diameter size (and associated blood flow) along the length of the pulmonary artery. This application shows for the first time a computer-aided quantitative association between pulmonary artery size change and hemodynamics in sickle cell patients with PHT. The validation and analysis of results demonstrate the robustness of the method to differentiate between patient and control populations. This tool could facilitate better understanding of the pathophysiology of PHT in SCD. Correlation of imaging with hemodynamic measures could eventually help develop a noninvasive tool for assessing pulmonary physiology.

II. METHODS

A. Data and Materials

Forty pulmonary CT-Angiography (CTA) studies were analyzed: 16 from patients with sickle cell anemia and related PHT ranging from mild to severe forms (proven and quantified by right heart catheterization); 16 from randomly-selected patients without SCD or PHT as negative controls; and 8 from randomly-selected patients used for the training of parameters and not included in the statistical analysis.

Scans with marked sub-optimal enhancement of the arteries in the radiological report were excluded. Controls were matched to cases on the basis of age and gender. Controls that had a primary diagnosis of lung pathology, such as tuberculosis or lung cancer, were not included in the study.

All pulmonary CTA data were collected using GE Lightspeed Ultra (GE Healthcare) and Philips Mx8000 IDT 16 (Philips Medical Systems). Image resolution ranged from $0.66 \times 0.66 \times 1.0$ to $0.89 \times 0.89 \times 1.25$. The implementation used Visual C++ 8.0 (Microsoft), OpenGL (SGI) and the Insight Segmentation and Registration Toolkit (ITK) 2.4.

B. Segmentation

CT data were smoothed using anisotropic diffusion to enhance the homogeneity of abdominal structures and ensure boundary preservation. The classic Perona-Malik anisotropy model was employed [13]. During the diffusion process, smoother versions of the image (I) were computed iteratively. The resulting image (I_s) provided stable edges over a large number of iterations based on a rapidly decreasing diffusivity function [13].

The second stage of the method is the segmentation of pulmonary arteries and this approach used a combination of fast marching and geodesic active contour level sets [3,12,18]. Level sets are surfaces that expand or contract, split or merge in the direction orthonormal to the surface. Their definition allows level sets to be adapted to the image conditions and by using

knowledge of shape, curvature and edge to segment incomplete data. Like other types of iso-surfaces, level sets are expressed as time-crossing maps.

A fast marching level set was used to initialize the segmentation [18]. The fast marching method assumes that the surface can only expand starting from the seed points provided by the user. The speed of expansion is constant and along the surface normal. The smoothed CT scan (I_s) provides the feature image, while the sigmoid of the gradient of I_s supplies an edge image (or speed function) I_e , with α and β computed from ∇I_s

$$I_e = 1 - \frac{1}{1 + \exp \left[-\frac{\nabla I_s - (\alpha + \beta)}{3(\alpha - \beta)} \right]}$$

A better-adapted level set based on geodesic active contours is used to refine the fast marching segmentation [3]. In deformable models there are two types of forces that govern the evolution of the active contour: the internal forces within the surface, which keep the model smooth during the deformation, and the external forces from the image data, which attract the model towards edges. To initialize the model, we used the fast marching segmentation as input level image (zero-level) into a geodesic active contour.

C. Skeletonization

The method used to automatically calculate the arterial distention consisted of two steps [19]. The first step was calculating the Euclidean distance map for the arteries and the second step was computing the centerline of the arteries. From the level set segmentation, the subvoxel accurate Euclidean distance transform was computed in multiple passes using linear interpolation at the boundary voxels to determine the distance to the boundary followed by a previously presented algorithm similar to the Saito-Toriwaki distance transform method [16]. The first pass was along the x -axis of the segmentation dataset, where the voxels were traversed in scanline order. All subsequent voxels that were inside the object are assigned values that increment the previous scanline voxel value by the x -spacing. Upon completion, the scanline was again traversed in the opposite direction, now incrementally computing distance from the opposite boundary's zero-crossing. The minimum of the forward and backward scanline passes was assigned to each voxel. Next, the dataset was traversed in y -axis scanline order. For each voxel in the scanline, the true Euclidean distance cannot be larger than the distance recorded in the x -axis pass. For each buffer entry in the range $\pm(x\text{-distance})$, the distance between the boundary intersection point and the circle center was computed using the Pythagorean theorem. The value assigned in the distance dataset at the current voxel was the minimum of all of these computed distances and the previously assigned x -distance at the current voxel. The arteries were processed in the same way by repeating this procedure with the minimum distance from the xy -plane (xy -distance) and the distances assigned at the voxels within the sphere of radius $\pm(xy\text{-distance})$.

To compute the centerline, a subvoxel accurate skeletonization was used [19]. The calculated distance transform was used as a speed image in the fast marching propagation. The fast marching method is an efficient way to numerically evaluate the solution to the Eikonal equation. The algorithm processes the voxels in a sorted order based on increasing values of T , while maintaining the candidates in a heap. This causes the algorithm to require a computation time of $O(n \log(n))$. The implementation used in this paper is a discretization of the Eikonal equation:

$$\max(D^{-X}_{i,j,k}, 0)^2 + \min(D^{+X}_{i,j,k}, 0)^2 + \max(D^{-Y}_{i,j,k}, 0)^2 + \min(D^{+Y}_{i,j,k}, 0)^2 + \max(D^{-Z}_{i,j,k}, 0)^2 + \min(D^{+Z}_{i,j,k}, 0)^2 = F_{i,j,k}^{-2},$$

where $D^{-X}_{i,j,k}$ and $D^{+X}_{i,j,k}$ are values resulting from backward and forward difference calculations at point (i,j,k) , respectively.

By solving the minimum-cost path problem, the path $C(t) : [0, \infty) \rightarrow R^n$ that minimizes the cumulative cost, from the start point, S , to the end point, E , in R^n can be calculated. When the cost is solely a function of the position $\vec{x}$ in the object domain, the minimum cumulative cost is defined as

$$T(\vec{x}) = \min_{C_{sx}} \int_0^L H(C(t)) dt$$

where C_{sx} is the set of all paths from S to $\vec{x}$, L is the distance from E to S along C , and H is the cost function. The solution for T also satisfies the Eikonal equation with $F(\vec{x}) = 1/H(\vec{x})$. By using the distance field, a new cost function can be calculated such that a minimum cost path exists between two points on the centerline

$$H(\vec{x}) = \left(\frac{d(\vec{x})}{D} \right)^2$$

where $d(\vec{x})$ is the distance value at position $\vec{x}$ and D is the maximum value in the distance field dataset.

The resulting cost function is used as a speed image in the fast marching method propagation starting at the point with the largest distance from the boundary of the arteries, the global maximum point of the distance field. The fast marching method propagation had been augmented to calculate the geodesic distance from the starting point in addition to the time that is required for the propagation front to pass each point in the arteries' segmentation, the time crossing map. The furthest geodesic point resulting from this fast marching method propagation is used as a start point of the centerline. The gradient descent method is used on the time crossing map. The remaining points of the centerline are determined by taking subvoxel steps along the path of the gradient descent. This process is repeated for each branch of the skeleton, but rather than using the single point of the global maximum distance from the object's boundary as the start point for the augmented fast marching method, all points in the previously calculated branches are used as start points along with the original distance field.

From the centerline and distance transform, the distention of the arteries at each step in the subvoxel accurate centerline was determined by linear interpolation of the values stored at the voxel locations in the distance transform field.

A simplified model based on Poiseuille's law was used to compute the blood flow in the pulmonary artery for the estimation of cardiopulmonary hemodynamics.

III. RESULTS

Figure 1 shows an example of the segmentation steps employed by the algorithm, from the smoothed CTA image, continuing with a first estimate of PA by fast marching level sets and the final segmentation of PA by geodesic active contours. 3D rendering of the segmentation was visualized using VolView (Kitware, Inc.) The skeletonization is exemplified in Figure 2, along with the quantification of PA distention using Euclidean maps of subvoxel precision.

To validate the segmentation algorithm, an observer measured manually the diameters of the pulmonary trunk and branches at their maximum distension for all data. The measurements were repeated twice in a blinded manner to assess intra-observer variability. Table 1 presents the statistical analysis of the intra-observer and observer versus computer-aided diagnosis (CAD) tool measurement variability of the maximum diameter of the pulmonary branches. p-values of the paired t-test show no statistical significance between the three sets of measurements. The mean measurement error for the pulmonary branches and trunk are $1.66 \pm 1.36\text{mm}$ (7.05%) and $2.22 \pm 1.77\text{mm}$ (6.99%) respectively.

Results indicate that the pulmonary trunk (t-test p-value = 0.033) and PA branches (p-value = 0.007) are significantly in diameter in SCD larger patients as compared to controls. mean maximum diameter of the pulmonary trunk of SCD patients is $32.83 \pm 4.34\text{mm}$, while that of controls is of $28.68 \pm 4.11\text{mm}$. The mean maximum diameter along the first branches of PA of SCD patients is $26.12 \pm 3.36\text{mm}$, while that of controls is of $21.73 \pm 4.2\text{mm}$.

To address the variation of PA size and blood flow with size of the patient, the PA diameters were normalized to thoracic cavity width, body weight, and body surface T-tests between sickle-cell patients area. T-tests between sickle-cell patients and controls were on normalized data sets. Box-plots were performed generated using R-2.5.1 and are presented in Figure 3 along with the corresponding p-values.

As expected, data normalized by the width of the thoracic offers the cavity offers the best discrimination between SCD patients non-SCD patients, as the body weight and surface are less correlated to the pulmonary blood flow. The maximum radius of the PA branches after the first junction was taken to the fourth power and then normalized to thoracic cavity width to account for blood flow. A comparison between sickle cell-anemia and control data revealed significantly increased blood flow in SCD patients compared to controls (p-value = 0.003). The mean relative in blood flow is of 184% in the pulmonary trunk 251% in the branches.

IV. DISCUSSION

This retrospective study investigates whether a size change in the pulmonary arteries (PA) of sickle cell disease (SCD) patients can be linked to sickle-cell associated pulmonary hypertension (PHT). A semi-automatic method was developed and is presented for the segmentation of pulmonary arteries from 3D CT-Angiography (CTA) using levels sets and fast marching methods. The arteries are segmented and their size and associated blood flow are quantified to better understand the pathophysiology of PHT in SCD and discriminate between SCD patients and controls. The validation of the segmentation and quantification algorithm shows no significant difference when compared to manual measurements. Results illustrate that the PA trunk and PA branches are significantly larger in diameter in sickle-cell anemia patients as compared to controls.

Possible sources of error in the analysis are related to the abnormal control population, as it was selected from patients with CTA data without pulmonary pathology, due to the lack of scans from healthy volunteers. Nevertheless, statistical analysis shows significant difference between our patient and control populations. Additionally, the comparison with manual

measurements is currently performed between 2D and 3D quantifications; the manual 2D values do not account for the full 3D anatomical complexity of the arteries. However, comparative measurements do not present a significant disparity.

Direct comparison with cardiopulmonary hemodynamics was not specifically performed, but a simplified model was used. Future plans could include prospective statistical analysis of this relationship in a specific clinical setting and well defined time point during the health care cycle. Data from healthy populations will be integrated in future analysis, along with inter-observer variability. The change in blood flow patterns and pruning of the pulmonary artery will also be analyzed for further discrimination between SCD patients and controls for a more comprehensive analysis of the possible relationships of imaging findings to the degree of PHT. Future large animal and clinical studies may also analyze multiple theoretical imaging features which could have hemodynamic correlates.

CT with image processing shows great potential as a surrogate indicator of pulmonary hemodynamics or response to therapy, which could be an important tool for drug discovery and noninvasive clinical surveillance.

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Fig. 1.

The segmentation of pulmonary artery exemplified in a patient (top row) and a control (bottom row): (a) 2D slices of the 3D CTA data with enhanced PA after smoothing; (b) the 3D segmentation obtained using fast marching level sets; (c) the refined 3D segmentation using a geodesic active contour.

Fig. 2. Centerline extraction in patient (top row) and a control (bottom row): (a) the 3D skeletons for the segmented PA; (b) the distance maps of the segmented arteries (2D slices of the 3D maps); (c) the map of diameter size along the centerline (maximum intensity projections of the 3D data).

Fig. 3.

Boxplots for patient (1) versus control (2) data: (a) the largest diameter of the first pulmonary arterial branches was normalized to the thoracic cavity width (p-value = 0.0003) (b) the maximum diameter of the pulmonary trunk was normalized to the thoracic cavity width (p-value = 0.002).

TABLE I
MEASUREMENT VARIABILITY FOR THE PULMONARY BRANCH

	Correlation	R-squared	p-value
Intra-observer	0.955	0.9125	0.254
Observer1-CAD	0.878	0.7763	0.721
Observer2-CAD	0.891	0.7979	0.706

Statistical values of the comparison between observer and CAD measurements: Pearson correlation coefficient, R-squared of the best linear fit for correlated data, and p-value of the paired t-test.