Automatic Quantitative Analysis of Pulmonary Vessels in CT: Methods and Applications

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Introduction

1.1 Pulmonary anatomy and respiratory physiology

The human lungs consist of a right and left lung, located in the thoracic cavity on either side of the heart [1]. The right lung, with three lobes, is generally larger than the left, which consists of two lobes. The lungs are surrounded by a thin tissue layer called the pleura. Pulmonary blood vessels and airways pass into the lungs at the root, a central recession called the hilum [2]. Pulmonary blood vessels can be divided into arteries and veins, as shown in Figure 1.1. Pulmonary arteries deliver oxygen-poor blood from heart to the lungs, and the pulmonary veins drain oxygen-rich blood from the lung to the heart. The main pulmonary artery is connected to the right ventricle of the heart by the pulmonary trunk, and branches into the right and left pulmonary artery. There are four main pulmonary veins, two for each lung, connected to the left atrium of the heart. The pulmonary airways, called bronchi, branch out from the trachea into lungs. The bronchi divide into smaller and smaller branches, and eventually end in cluster of small sacs, called alveoli, where gasses are exchanged. The thin layer of cells between the alveoli is called the interstitium, which contains blood vessels and cells that help support the alveoli.

The lungs are the major organs of the respiratory system, and their primary function is gas exchange [1]. With each breath, air first enters the nose or mouth, passes through the larynx and the trachea, and splits into the bronchi. Within the lungs, the bronchial trees deliver the air to the terminals of the alveoli [3]. In the alveoli, oxygen from the air diffuses through the walls of the alveoli into the blood of the pulmonary capillaries. Carbon dioxide, a waste production of the metabolism, transfers from the blood to the alveoli, where it can be breathed out through the airway [4], as shown in Figure 1.2. Oxygenated blood is collected from the capillaries through the pulmonary veins back to the heart, and deoxygenated blood is carried by

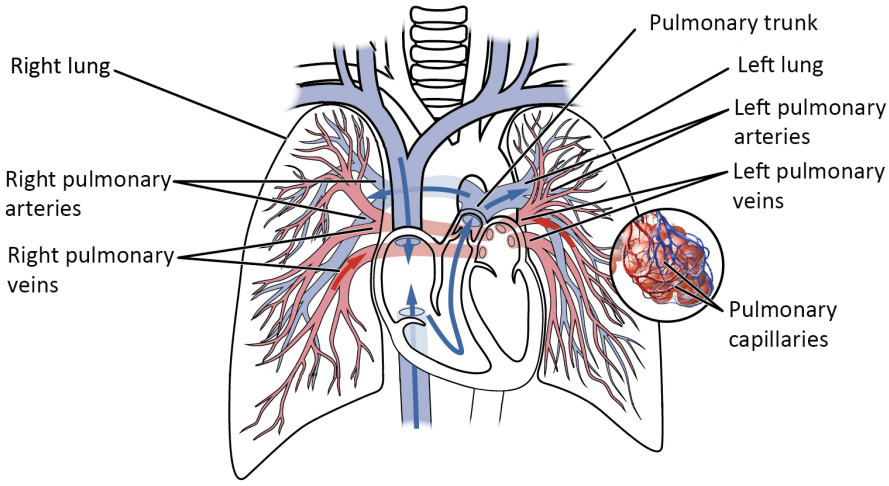

Figure 1.1: Lung anatomy which (modified and adopted from the website of `https://en.wikipedia.org/wiki/File:2119_Pulmonary_Circuit.jpg`)

the pulmonary arteries from the heart to the lungs. This makes the pulmonary blood circulation unique [5]. since blood circulation in all other organs carries oxygenated blood through the arteries and deoxygenated blood through the veins.

1.2 Pulmonary diseases

The lung is an organ with a complex structure, expanding and shrinking thousands times a day, during inhalation and exhalation [6]. The lung can be affected by a variety of diseases in specific parts of the complex system influencing its function. There are several diseases, such as asthma, bronchiectasis, bronchitis and chronic obstructive pulmonary disease, that affect the airways and obstruct gas delivery [7]. Some lung diseases, like pneumonia and asbestosis, could can cause the damage of in alveoli [8]. Various lung diseases, for example interstitial lung disease, affect the interstitium, which is the thin layer between the lungs' alveoli. Diseases, such as pulmonary embolism, pulmonary hypertension and chronic thromboembolic pulmonary hypertension, affect the pulmonary blood vessels. Gas exchange and blood circulation can be influenced by damage in any structure of the lungs. Two diseases that can affect the lungs have a special focus in this thesis: systemic sclerosis and chronic thromboembolic pulmonary hypertension.

Systemic sclerosis (SSc) is an autoimmune connective tissue disease that can involve multiple organs, including skin, musculoskeletal, pulmonary, renal and other complications [9]. Pulmonary disease, which is the leading cause of mortality in patients with SSc [10], mainly consist of interstitial lung disease (ILD) and pulmonary

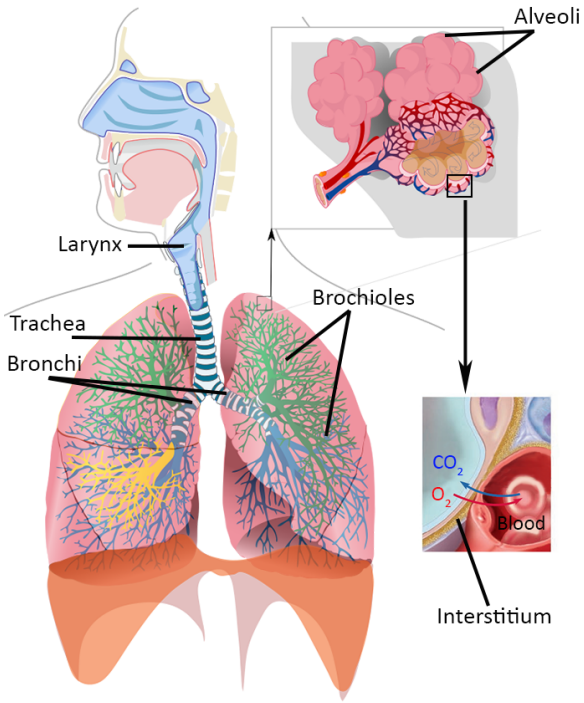

Figure 1.2: Respiratory physiology (modified and adopted from `https://commons.wikimedia.org/wiki/File:Respiratory`

hypertension (PH) [11]. In SSc-related ILD, structural changes in the parenchyma, i.e. fibrosis, is known to affect pulmonary function. For assessing ILD, pulmonary function tests, such as diffusion capacity for carbon monoxide (DLCO) and forced vital capacity, and high-resolution chest computed tomography (HRCT) are commonly used. PH is characterized by abnormally high blood pressure in the pulmonary vessels, which can cause remodeling of pulmonary arteries [12]. In SSc-related PH, DLCO decreases years before diagnosis of PH [13]. Conversely, gas transfer can be mildly or moderately impaired in the absence of detectable pulmonary fibrosis and pulmonary hypertension.

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by the occurrence of unresolved thromboembolism undergoing fibrotic organization [14], which is caused by persistent obstruction of pulmonary arteries after pulmonary embolism [15]. The mechanical obstruction of pulmonary arteries is produced by fibrotic transformation of pulmonary thrombius, which canould lead to pulmonary hypertension and increasing pulmonary vascular resistance (PVR) [16]. CTEPH patients have poor prognoses: 2-years survival rate is 20% in patients with mean

pulmonary artery pressure higher than 50 mmHg [17, 18, 19]. The prognosis can be improved by pulmonary endarterectomy [20] or balloon pulmonary angioplasty (BPA) [21], combined with optimal medication. Pulmonary endarterectomy is a curative treatment for CTEPH, leading to nearly normalized hemodynamics in the majority of patients [22]. However, for patients with inoperable CTEPH, BPA can be an alternative treatment to improve the clinical status and hemodynamics with a low mortality [23].

1.3 Clinical measurements for assessing SSc and CTEPH

Evaluation of the disease severity and assessment of treatment effects play an important role in the diagnosis and therapy of any disease. The higher risk patients, who may benefit from treatment, could be selected by accurate prognostic evaluation [11, 24]. There are several clinical measurements for evaluating the severity of diseases and response to treatment, such as 6-minute walk distance, pulmonary function tests, invasive right-sided heart catheterization (RHC) and chest computed tomography (CT).

Pulmonary function tests, such as the diffusion capacity for carbon monoxide (DLCO) and force vital capacity (FVC), are key measures for evaluating the response to treatment of interstitial lung disease [25]. DLCO is a measurement of the extent of gas transfer in the lungs. As the affinity and absorption capacity of red blood cells for carbon monoxide (CO) is strong, gas uptake by the capillaries are less dependent on cardiac output [26]. Generally DLCO is measured in 'ml/min/mmHg', which involves measuring the rate of CO uptake (ml/min) divided by the alveolar pressure (mmHg). FVC (L) which is the volume of air that can forcibly be expired after full inspiration, as demonstrate in Figure 1.3 (b) [27]. The FVC can be influenced by many factors, including body mass index (BMI), physical condition, and smoking status. FVC can be compared to the normal value standardized for age, sex, height, etc. For follow-up studies the raw FVC measurements are used to compare with previous measurements to determine whether a pulmonary condition improved or deteriorated.

Right heart catheterization (RHC) is the gold standard for measuring the pulmonary artery pressure (PAP) [28]. For monitoring the right sided pressure, a catheter is inserted into the pulmonary artery. The hemodynamic parameters are examined via RHC, including (systolic, diastolic and mean) PAP, systolic right ventricular pressure, right atrial pressure, cardiac output, cardiac index and pulmonary capillary wedge pressure [16]. According to the European society of cardiology (ESC) guideline on diagnosis and treatment of PH, RHC is the diagnostic gold standard for pulmonary hypertension (PH), defined by a mean PAP $\geq$ 25 mm Hg [29, 30]. In evaluating the severity of CTEPH and assessing treatment effects, the invasive RHC serves as the standard criterion [31].

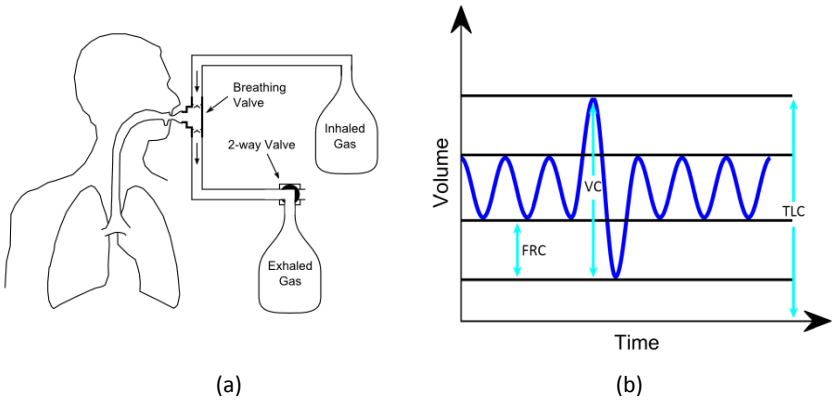

Figure 1.3: (a) DLCO test (adopted from `https://www.pftforum.com/blog/`), (b) breathing curve, VC is vital capacity, TLC is total lung capacity and FRC is functional residual capacity.

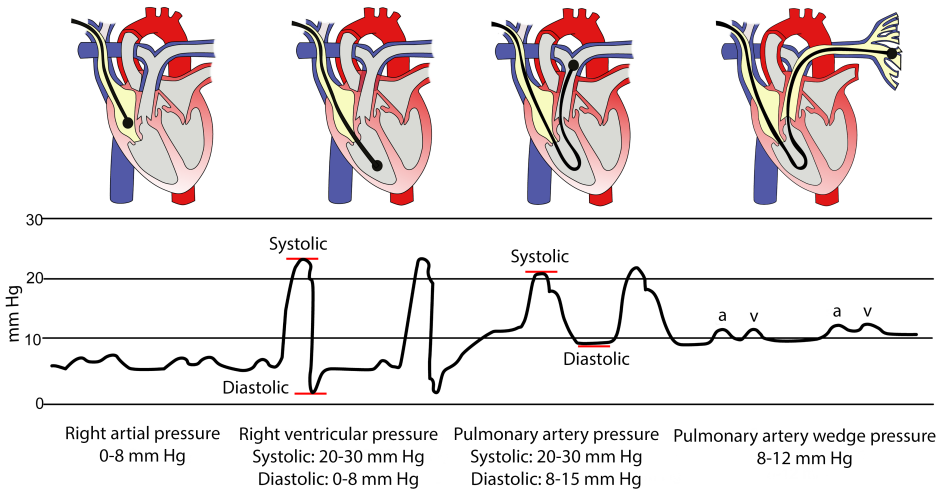

Figure 1.4: Illustration of right heart catheterization. The normal pressure waves with normal value is demonstrated, which is measured at the pulmonary artery during right heart catheterization. (adopted and modified from `https://www.pcipedia.org/wiki/Right_heart_catheterization`

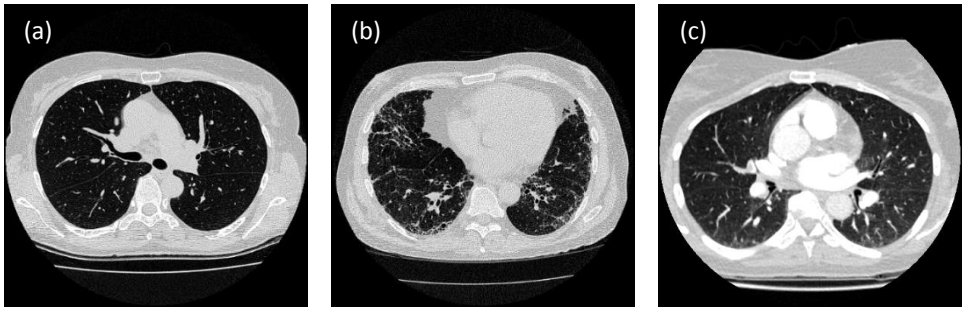

Figure 1.5: Slices of HRCT scans from a normal case (a), a patient with ILD (b), and a slice of CTPA from a patient in CTEPH.

1.4 Chest CT

Currently, non-invasive imaging techniques play a key role in both diagnosis the lung diseases and assessment of treatment effects [11, 32, 33]. High-resolution computed tomography (HRCT) of the chest is considered the most accurate imaging method for assessing ILD [25]. Computed tomography pulmonary angiography (CTPA) is used in diagnosis and evaluation the severity of CTEPH [34]. A chest CT scan, which is a more detailed type of chest X-ray, takes many projections of lungs, and a computer can combine these projections to create three-dimensional cross-sectional images to show the organs' size, shape, and structures. CT allows imaging of the entire chest during a single breath hold [35]. The multiple parallel rows of x-ray detector of CT scanners increases from 4, 16, 64 to 320.

Dual-energy CT can be performed with a dual-source scanner or with a single-source scanner with fast kilovoltage switching [36], which has ushered in the ability of material differentiation and tissue characterization beyond the traditional CT [37]. Radiographic contrast agents, such as injected iodine media or inhaled xenon gas, can be specified at two different energies, subsequently, the specific content of contrast agents in tissues can be visualized and quantified in the dual-energy CT [38]. Both anatomical and functional information about the lungs can be provided with dual-energy CT, in a variety of pulmonary diseases. Applications in the thorax, including detection and prognostication of acute or chronic pulmonary embolism (PE), and characterization of parenchymal disease, benefit from this imaging technique [37, 19, 39].

1.5 Outline of the thesis

With the development of CT scanners, nowadays, a high-resolution CT scan may contain around 500 slices, which significantly improves the accuracy of diagnosis. However, the huge amount of data from CT obviously increases the diagnostic

workload for clinicians and is difficult to interpret in some cases, e.g. SSc patients without fibrosis in CT who still suffer from impaired gas transfer, and CTEPH patients with CTPA before and after treatment are difficult to quantify objectively by clinicians. Therefore, developing automatic computer aided methods is important in order to investigate pathology of pulmonary vascular diseases and quantitatively assess treatment effects.

The aim of this thesis is to develop these methods focusing on quantifying pulmonary vascular diseases and assessing treatment effects, based on CT images. Particularly, the following objectives have been pursued in this thesis: 1) to develop an accurate lung vessel segmentation method; 2) to propose and validate an automatic method for quantifying pulmonary vascular morphology; 3) to investigate pulmonary vascular remodeling in SSc patients with impaired DLCO, but in the absence of pulmonary fibrosis; 4) to investigate changes in the pulmonary vascular densitometry and morphology in patients with CTEPH, treated with BPA. These objectives are described in this thesis, with the following structure:

Chapter 2 presents a method for extracting lung vessels, based on graph-cuts, where the appearance and shape features are combined into a newly designed cost function. To cope with memory requirements of a graph representation for voxels in chest CT, an efficient strategy was proposed by extracting sparse graphs with a low threshold and generating an adjacency matrix with diagonal vector assignments.

In **Chapter 3** an automatic method is proposed and validated, for the quantification of pulmonary vascular morphology in CT images. The proposed method consists of pulmonary vessel extraction and quantification, where the vessel extraction method from Chapter 2 was extended, by incorporating CT intensity, vesselness and the distance map to airways, and the quantification method is based on a radius histogram analysis. The proposed method was validated with a public data set, a data set of a 3D-printed vessel phantom and a clinical data set.

Chapter 4 investigates the association between pulmonary vascular morphology and gas exchange in patients in systemic sclerosis without lung fibrosis. Pulmonary vessels were detected and quantified automatically in CT images, and subsequently two images biomarkers (α and β) were calculated, where α reflects the relative contribution of small vessels compared to large vessels and β represents the vessel tree's capacity. The correlations between imaging biomarkers and gas transfer (DLCO) were evaluated with Spearman's correlation.

Chapter 5 presents a method for visualizing and quantifying changes in pulmonary perfusion by automatically comparing CTPA before and after BPA treatment. Fourteen CTEPH patients were involved in the study, who underwent CTPA and RHC, before and after BPA treatment. The quantification of perfusion changes was validated against hemodynamic changes.

In **Chapter 6** a method is proposed for quantifying morphological changes, which consists of three processing steps: constructing vascular trees from the detected pulmonary vessels, matching vascular trees with preserving local tree topology and quantifying local morphological changes based on Poiseuille's law. The vascular tree matching method was validated with a data set of synthetic trees and the relation between the quantification of morphological changes and clinical RHC parameters was investigated in CTEPH patients.

Chapter 7 summarizes and discusses the overall achievements of this thesis.