BronCare: clinical multimedia system for new therapies assessment in asthma

A. SARAGAGLIA, C. FETITA, and F. PRETEUX
ARTEMIS Project Unit, GET/INT, Evry, FRANCE
9, Rue Charles Fourier, 91011, Evry-France

Abstract: - In the framework of therapy efficiency assessment in asthma, this paper describes a clinical multimedia system, providing the appropriate tools for bronchial reactivity and wall remodeling evaluation from MDCT successive examinations conditional to a treatment. Relying on the 3D reconstruction of the bronchial tree, central axis analysis and accurate quantification capabilities, such a system makes it possible to estimate the impact of a therapeutic protocol in mild and severe asthmatics, as demonstrated by a clinical study here discussed.

Key-Words: Multimedia system, therapy assessment, bronchial reactivity, wall remodeling, 3D image processing.

1 Introduction

Asthma ranks among the most common chronic conditions all over the world. At present, its intimate mechanisms remain unknown and no cure is available. In asthma, airway hyperactivity and chronic inflammation lead to airway remodeling, responsible for bronchial wall thickening and pulmonary functional obstruction [1]. The new developing therapies for asthma try to reverse the induced airway remodeling by delivering various anti-inflammatory drugs. Evaluating the efficiency of such therapies requires appropriate *in-vivo* quantification tools. Airway remodeling may be assessed non-invasively by measuring bronchial thickening in multi-detector computed tomography (MDCT) images [2]. Recently, Niimi *et al.* [3] showed that effects of inhaled corticosteroids on airway wall thickening could be measured in patients with persistent asthma. However, the approach based on manual contouring of the internal and external perimeters of the airways, presents severe drawbacks: (1) inter and intra-observer variability, (2) absence of tilt angle estimation of the bronchus, (3) partial volume effects with 3-mm slice thickness, (4) bronchial wall thickness variability from one slice to another, and (5) high inhomogeneity of airway response to deep inspiration in asthma.

(Semi-)automatic segmentation and quantification approaches proposed in the literature [4,5,6] made it possible to overcome some (but not all) of the mentioned drawbacks; they still remain inaccurate for bronchial remodeling evaluation in asthma.

This paper describes in detail the design and implementation of a multimedia quantification system for assessing bronchial reactivity and wall thickening in mild and severe asthma. Starting from specific MDCT acquisitions of patients before/after treatment, such a system provides the interaction and quantification tools for a comparative analysis of the same target bronchi, in cross section image planes reconstructed orthogonally to each bronchus axis. Section 2 addresses the technical requirements and presents the developed system. The preliminary results obtained on clinical trials in asthma are discussed in Section 3.

2. Quantification of bronchial parameters: the proposed approach

The medical constraints discussed in Section 1 for a reliable quantification of the bronchial parameters are addressed here in terms of technical requirements.

Selecting the same bronchial segments for a comparative quantification before/after treatment imposes: (1) a reproducible MDCT acquisition protocol, (2) automatic extraction of the airways morphology from the MDCT data by means of 3D reconstruction, (3) easy interaction and sample measurement points by means of Central-Axis (CA)-based description, (4) selection of appropriate 2D sampled data generation for each selected bronchus and (5) accurate 2D quantification of cross-section bronchial parameters and comparative statistics before/after medication.
A multimedia system (Fig.1) was developed to address these issues.

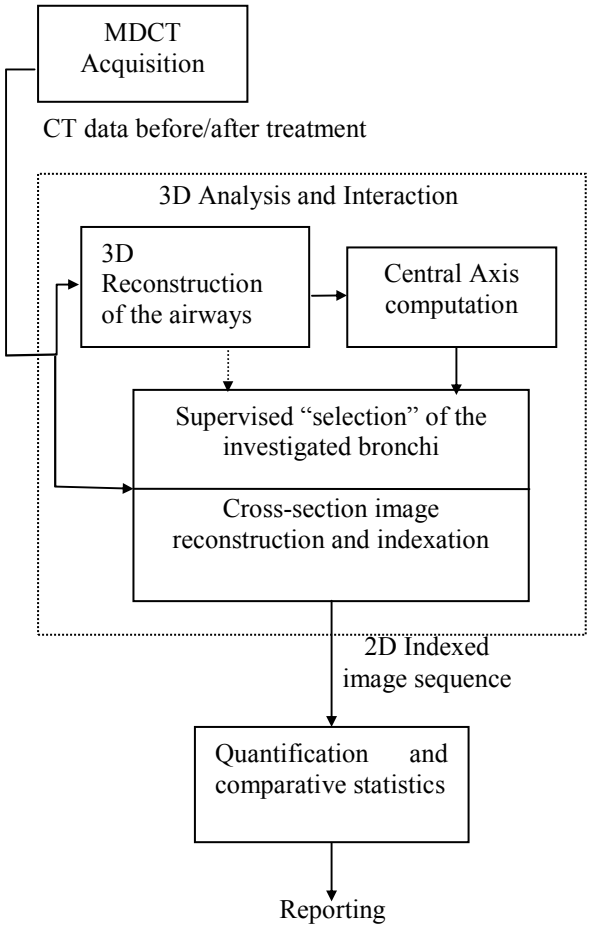


Fig.1. Synopsis of the BronCare multimedia system.

2.1 MDCT acquisition protocol

In order to ensure similar measurement conditions before and after treatment, a specific MDCT acquisition protocol was requested. Spiral acquisitions were performed at low dose radiation with 0.6 mm collimation and 0.3 mm reconstruction interval of axial images (16-row General Electric LightSpeed scanner). The field of view was set to 18-20 cm according to the patient morphology, focusing the right lung, thus providing *quasi*-isotropic data volumes free from cardiac motion artifacts. All acquisitions were made after interruption of the slow expiration phase following a deep inspiration, at 65% of total lung capacity, using a spirometric gating system (V2000; Sensormedic, Yorba Linda, USA).

2.2 3D-analysis and interaction tools

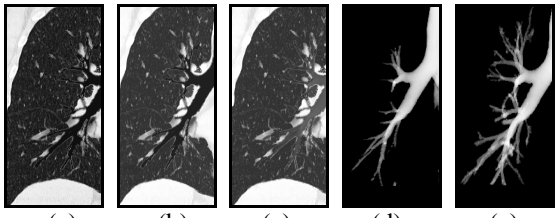
The "3D analysis and interaction" module provides the required 3D reconstruction, interaction and data sampling tools (Fig.1). It inputs the MDCT data and outputs the collection of quantification image samples, indexed according to the bronchus segment.

2.2.1 3D-reconstruction of the bronchial tree

Airway segmentation from CT images is a challenging problem due to the inhomogeneity of the bronchial lumen and bronchial wall gray-levels along different subdivision orders. The airway 3D reconstruction approach aims at overcoming the main limitations encountered in the existing 3D segmentation techniques [7] and to provide: (1) a fully-automated extraction of the airways, (2) down to the sub-sub-segmental subdivision order, (3) robust with respect to obstructive pathologies, and (4) accurately mapping the inner bronchial wall.
To achieve this goal, the proposed technique combines a robust marking procedure in order to detect a representative subset of low-order airways (even in the presence of obstructing pathologies) and an energy-based aggregation model able to reconstruct high-order bronchi.
The marking procedure has to discriminate between the airway lumens and other low density regions/noise in the lung parenchyma, and to provide an initial subset to guide the high-order bronchi reconstruction. A multiresolution approach based on a strong morphological filter, *the selective marking and depth constrained connection cost* (SMDC-CC) [7], implements the initialization scheme by combining connectivity and morphological properties of the anatomical gray-level "relief".

SMDC-CC applied at a resolution level *n*, has the property to level up all the local valleys in the relief (low density regions) having a maximal cross-section size *n*, irrespective to their shape, location and orientation.
By tuning the *n* parameter to fine and coarse resolution, the noise in the lung parenchyma can be removed and a low order airway subset extracted (Fig.2). Note that the marking subset may contain non-bronchial structures (esophagus, emphysema air pockets, etc. – Fig. 2). Such structures are disconnected from the airways and will be removed according to knowledge-based criteria.

Starting from the marking subset, the high-order bronchi are reconstructed by using an energy-based aggregation model (Fig.2). The energy functional is expressed in terms of propagation potentials which favor a radial and distal subset growth within the bronchial lumen limits.

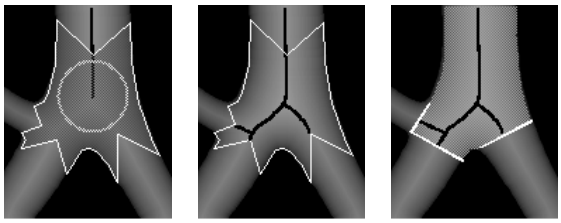


(a) (b) (c) (d) (e)

Fig.2. Principe of the 3D reconstruction of the airways. (a) Original thorax volume, (b) SMDC-CC of small size (noise filtering), (c) SMDC-CC of large size (airway selection), (d) Low-order airway subset, (e) 3D filtering and final reconstruction.

2.2.2 Central Axis computation

The bronchial tree morphology can be described as a (*quasi*)-tubular structure presenting a highly branching topology. Extracting the CA of such a structure raises several issues: besides the estimation of each segment median axis, the procedure should ensure an accurate detection of the branch subdivision and preservation of the branching hierarchy. Due to the topology complexity, the caliber variability with the bronchial order and the noisy bronchial wall irregularities, these problems appear particularly challenging. The methods presented in literature for CA extraction refer to three main classes which are Voronoï diagram-based algorithms, iterative thinning and methods relying on the distance transform. This latter type turned out to be the most appropriate one in the case of branching objects represented by volumetric data. However, existing methods applied to the bronchial tree show a common drawback related to the inaccurate branching point detection, which may lead to a wrong subdivision hierarchy.
The developed method [8] overcomes these limitations by using a 3D distance map computed with respect to the bronchial wall, which provides general information on the branching area configuration and thus ensures robust branching point detection. The CA extraction procedure combines the 3D distance map with a geodesic front propagation front initialized at the top of trachea. The CA is defined as the set union of the 3D locations of the local distance map maximum on 3D successive propagation fronts. A possible subdivision is detected when several local maxima appear inside the current propagation front. The subdivision is then confirmed or invalidated by a specific space-partitioning based criterion (Fig.3). The space partitioning first defines the maximum sphere centered on the possible branching point and inscribed in the airway tree. Then, the points situated on the sphere surface propagate toward lower values on the distance map. This propagation results in cone-shaped structures corresponding to each segment of the subdivision, irrespective to the degree of the subdivision (bifurcation, trifurcation, etc.) (Fig.3a). The information thus obtained enables to robustly manage any complex configuration of subdivision area. The geometry of the CA at the subdivision level is then reconstructed by linking the vertex of each cone-shaped structure to the subdivision point, following the maximum value path on the distance map (Fig.3b). A subdivision in sub-trees is then performed and the procedure is recursively applied to each sub-tree.



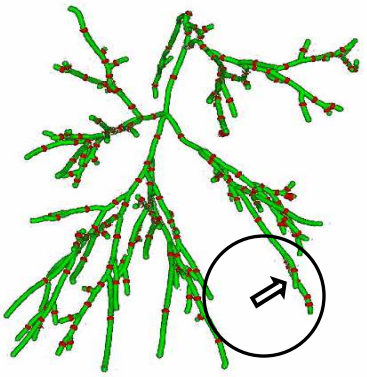
(a) (b) (c)

Fig.3. Illustration of the subdivision detection approach: (a) Space partitioning and

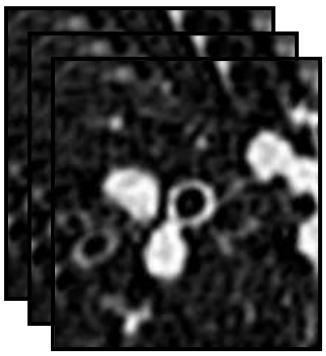
subdivision validation, (b) CA reconstruction at the subdivision level, (c) Partitioning in sub-trees and recursive procedure resumption.

2.2.3 3D interaction and data sampling

The CA-based description provides the navigation and interaction tools required for selecting the bronchi under investigation. An experienced radiologist defines the measurement zones by pointing the landmark displayed on each CA segment (Fig.4a). An automatic sampling of the MDCT data volume along planes orthogonal to the selected bronchus axis at equally-spaced points on the CA segment provides the 2D sample measurements data indexed by the bronchus label (Fig.4b). The sampling procedure allows to control the spatial resolution of the reconstructed cross-section images by means of linear interpolation.



(a)



(b)

Fig.4: 3D interaction (a) and cross-section image reconstruction perpendicular to the CA of the selected bronchus (b).

3. Bronchial parameter quantification

The quantification of the bronchial parameters is performed independently on each cross-section image series. In this respect, a fully-automated approach was developed in order to overcome the limitations of the existing techniques [9] related to the segmentation accuracy and to the robustness with respect to the adjacency degree with the homologous artery. The developed methodology relies on mathematical morphology and energy-based contour matching and is presented in the following.

3.1 Lumen extraction

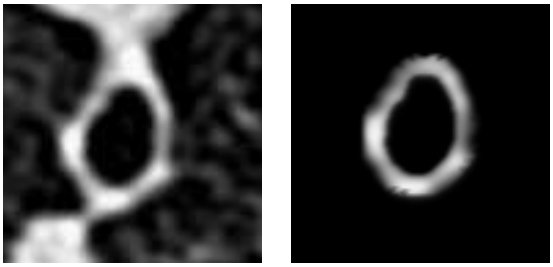
The inner wall is segmented by using a controlled propagation starting from an initial lumen set obtained with the SMDC-CC operator described in §2.2.1. The propagation uses gradient and gray level information in order to regularize the inner wall contour.

3.2 Wall extraction

The outer wall location (Co) of the bronchus is detected using a contour matching technique. The outer wall contour is initialized at the level of the inner contour in order to coarsely impose the lumen shape during the propagation. The propagation is controlled by an energy functional relying on antagonist forces, externals vs. internal. The external force $\vec{F}ext$ tends to dilate the contour while the internal force $\vec{F}in$ tries to reach an equilibrium at the level of the outer bronchial contour.
The external force is defined at a point $x \in \Re^2$ as the sum between the image gray level value, $h(x)$ and the approximate reliable wall value $Arw(x)$,(Fig.5):

$$\vec{F}ext = h(x) + Arw(x) \quad , \qquad (1)$$

Arw enhances $\vec{F}ext$ for a correct matching of eventual wall irregularities, without penetrating within the contact zone between the bronchus and the vessel. Arw information is extracted from the original image by using a mathematical morphology-based approach.



(a) (b)

Fig.5: Elements defining $\vec{F}ext$: (a) Original image of the bronchus, $h(x)$ and (b) the approximate reliable wall value, $Arw(x)$.

In order to equilibrate $\vec{F}ext$, the internal force $\vec{F}in$ will be defined as an elastic force, which linearly depends on the distance to the inner wall contour (Ci) and to a local gradient value computed with respect to the average gray level value on the external and internal neighborhood:

$$\vec{F}in(x) = FdistIc(x) + FIntExt(x), \quad (2)$$

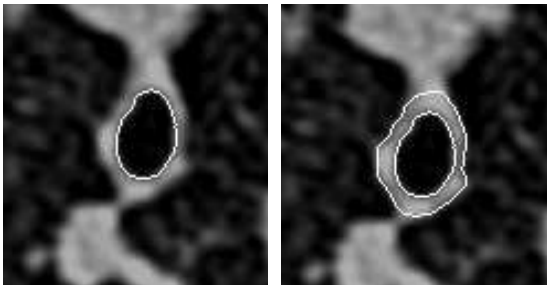
where,

$$FIntExt(x) = \frac{\sum ExtNeigh(x)/nExt}{\sum IntNeigh(x)/nInt}, \quad (3)$$

with $ExtNeigh(x)$ / $IntNeigh(x)$ denoting the average grey level value on the external/internal neighborhood of x and $nExt$, $nInt$ their respective cardinality, and

$$FdistIc(x) = \left(1 + 2 \times \frac{d(x, Ci)}{d(Co, Ci)}\right) \times K, \quad (4)$$

with K denoting the minimum acceptable gray level value for the bronchial wall and $d(\cdot,\cdot)$ the Euclidean distance function.



(a) (b)

Fig.6: Result of bronchial wall segmentation: (a) Inner wall contour initializing the matching procedure, (b) Bronchial wall contour obtained.

The outer contour evolves until $\vec{F}in$ equilibrates $\vec{F}ext$. Fig.6 shows an example of inner and outer wall segmentation. Lumen and wall areas are estimated for each indexed sample data before and after treatment, and computation statistics are provided.

3.3 Validation

The 2D bronchial quantification was validated with respect to a 3D image model simulating a tubular bronchus-vessel pair of different calibers and lumen/wall textures. In all cases, the estimation errors were less than 5%.

4. Clinical Application

The developed multimedia system was applied to a clinical study in order to evaluate the necessary criteria for bronchi inclusion in bronchial reactivity and wall remodeling assessment in mild asthmatics [10].

Ten mild asthmatic patients were included in this study with the approval of the local ethics committee. CT acquisitions were performed with the described protocol before and twelve weeks after treatment.

The objective was to evaluate the pertinence of a bronchial analysis in successive examinations, using the developed system, that is to check if the number of correctly quantified samples is enough to assess therapy efficiency for asthma. The study focused on segmental and subsegmental bronchi of the right middle and lower lobes. From 222 bronchi in our database, 174 were correctly matched after the 3D reconstruction and CA extraction. The matching errors (3D reconstruction failure in at least one of the pair exams) had three main causes: Orthogonal departure of the bronchus from the bronchial tree (n=18), small size of the bronchus (n=24), and airway wall hernia (n=4). Among the matched bronchi, only those providing reliable quantifications of bronchial parameters on at least 10 contiguous cross-section images were taken into account. The quantification was considered as reliable for bronchi with lumen area greater than 4mm^2 and a confidence index (defined as the percentage of the bronchial wall contour which was not abutted by vessels or other bronchi) greater than 55%. Using

these criteria, 133 among the 222 candidate bronchi could be selected for evaluation, which demonstrates the efficiency of the developed system for assessing new therapies in asthma.

5. Conclusion

This paper developed an original multimedia system for new therapies assessment in asthma based on MDCT acquisitions. Such a system is able to produce, manipulate and analyze 2D and 3D anatomical contents extracted from clinical data in order to quantitatively assess the bronchial reactivity and wall remodeling in successive examinations, before and after a therapeutic protocol.
Our future work will address on the one hand the clinical validation of measures reproducibility, and on the other hand, the development of a fully-3D bronchial wall segmentation and quantification procedure in order to eliminate the dependency between 2D bronchial parameter estimation and the accuracy of central axis computation.

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