Construction of a 3D coronary map to assess geometrical information in-vivo from coronary patients

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Abstract. Traditional risk factors are involved in the development of coronary artery disease (CAD), but geometrical risk factors have also proved to be determinant. In this work we present a new method to construct a 3D map of the left coronary artery tree using CT image processing and skeletonization techniques. We computed cumulative length-volume functions through the coronary tree bifurcations and also the relationships between total tree volumes, total length, number of segments and bifurcations with respect to the presence and severity of atherosclerotic plaques. A total of 65 patients, 40 with and 20 without CAD were recruited. We found more vascular segments and bifurcations per patient in the CAD group. Accordingly, total cumulative length was longer in CAD patients (p<0.01) whereas total cumulative volume was similar between groups. Cumulative length-volume (L-V) relationships conformed to an allometric function L= K_v V^β. The allometric slope β=0.75 did not change with disease, whereas the allometric constant K_v was lower in the healthy group (p<0.05) consistent with the literature. These results suggest that CAD patients follow a compensatory mechanism, dilating the vessels to maintain a normal coronary flow. The 3D coronary map offers useful quantitative information of the coronary morphometry.

1. Introduction

Traditional risk factors (age, gender, smoking, sedentary habits, etc) are involved in the development of coronary artery disease (CAD). Recently, geometrical risk factors proved to be determinant to explaining the lesions location and inherent risk of atherosclerotic plaques [1]-[4]. It is well known that bifurcations and curvatures condition blood flow and might create turbulences or low shear stress regions that might promote plaque proliferation [2]-[4]. At the same time, coronary geometry reconstruction has been improved by new imaging techniques such as planar reconstruction using angiography (AngioCT) and intravascular ultrasound (IVUS). Multislice computed tomography (MSCT) is being also widely employed [5]-[9]. In some of those works, allometric functions relating arterial diameter, length, volume and bifurcation angles were proposed to detect pathological patterns in the coronary tree [10], [11]. The logic behind this idea is that some geometric rules that determine the coronary architecture to ensure a reliable blood transport to the myocardium might have been reached through evolution of blood transport systems. The best known example is Murray’s Law describing the optimal relationship between parent and daughter vessel diameters and bifurcation angles to minimize metabolic and functional cost in the organism [12], [13]. This Law, local in nature, was generalized to determine the relationship between cumulative lengths and volumes of the
coronary tree, resulting in an allometric potential relationship to predict coronary geometry, relying on the fractal nature of the circulatory tree [15]. To evaluate this potential function the coronary tree must be divided in a stem-crown way [19] to define cumulative magnitudes (figure 1). Stems are defined as the vessel segments between two bifurcation points (nodes) or a node and a distal point of the coronary tree. Crowns are defined as the group of vessels distal to a certain stem.

![Figure 1](image_url)

Figure 1. Division of a tree segment in a stem-crown way. Stems are the vessels between two successive bifurcation points, or between a bifurcation point and the end of the tree. Crowns are defined as the group of vessels distal to a certain stem (image reproduced from [19]).

Allometric functions were verified in the past on porcine heart casts and human autopsies [5]. Precise information of the porcine coronary tree in vivo was also obtained through MSCT [11]. Recently we published a work where this same technology was used to verify the same allometric relationships for human patients in vivo [16] verifying that the left coronary tree morphology adjusts to the potential function:

\[ L = K V^\beta \]  \hspace{1cm} (1)

where \( V \) [mm\(^3\)] and \( L \) [mm] stand for cumulative length and volume in each node, respectively. Allometric constants \( K \) and \( \beta \) determine the geometry of the coronary tree [19] and can be obtained for each patient though least squares fitting of equation (1) in log scale.

In this work we present the methods to construct a 3D map of the left coronary artery tree using tomographic reconstructions of patients with and without CAD. We use this map to obtain morphometrical parameters of the left coronary circulation: vessel lengths and volumes, total amount of reconstructed segments and bifurcations, among others. This quantitative anatomical information is used to verify allometric length-volume functions and to study the relationships between total tree volumes, total length, number of segments and bifurcations with the presence and severity of CAD.

2. Methods

2.1. Population

Studies used in this work belong to consecutive patients of the MSCT Department of the Favaloro Foundation arriving in one month of 2011. Selected subjects were referred due to suspected coronary artery disease. Patients with previous coronary surgeries were excluded. Signed informed consents were obtained from each patient according to the good clinical practices of the Institution. Patients were separated in 2 groups according to the presence or absence of CAD.
2.2. Computed tomography scanning
All scans were performed using a 64-row MSCT scanner (Aquilion 64, Toshiba, Japan). Details of the scanning process can be found in a recent publication of the group [14]. Briefly, each subject received a bolus of ionated contrast material injected through an arm vein, followed by 50 mL of saline infusion at the same injection speed. Heart rate was controlled to remain below 60 bpm. The scan parameters were: a collimator detector of 64x0.5 mm, a rotation time of 0.4 s, tube voltage 120-135 KV and mAs of 320-440 depending on patient weight. Images were acquired during diastole using ECG-gating in order to reduce motion facts. Transaxial images were reconstructed with 0.5 mm slice thickness and 0.3 mm increments. An experienced technician measured Calcium Score Coefficient (CAC) using Agatston method [17] in studies where calcified plaques were found. For each CAD patient, the amount, type, degree of stenosis and localization of every plaque was registered.

2.3. 3D reconstruction
All digital imaging processes were done using a custom software designed in the Favaloro University. DICOM sequences of 350 to 400 images (512 by 512 pixels) were imported from each scan. First, the user selects a volume of interest (VOI) where the whole heart remains inside. Next, the user initiates an automatic process to create a coronary map. This process can be separated in 3 stages: 1) Heart isolation, 2) artery segmentation and 3) skeletonization for the estimation of the length-volume relation (L-V).

2.3.1. Heart Isolation
Heart isolation begins with a k-means clustering process inside the VOI [18] where 3 groups are discriminated: lungs, myocardial mass and blood pools (including coronary arteries, ventricles and atriums). The voxel representing the center of gravity of the whole volume is determined and is considered as the initial seed point for a slice-by-slice region growing segmentation process:
   a) Region growing from i-seed point in the ith-slice, grouping all pixels belonging to myocardial mass or blood pool, and excluding all points belonging to lungs.
   b) From the region segmented in a), a new center of gravity is calculated. This point is the i+1 seeding point for the (ith+1)-slice segmentation process.
   c) Steps a) and b) are subsequently repeated until all slices in the VOI are segmented. This requires the procedure to be split in two parts: the first one is the segmentation of all slices below the initial seed point i=0, and the second one the segmentation of all the slices below the initial seed point.
   d) All regions segmented in a) for each slice are merged as Heart-Region (HR). Every voxel not belonging to HR is considered as Not Heart Region (NHR), and its value is set to the minimum pixel value of the whole volume in Hounsfield Units (HU). The result is a fast partial isolation of the heart (processing time is below 10 seconds) where all lung tissue and lung vessels are completely removed (figure 2).
2.3.2. Coronary artery segmentation

The procedure to segment coronary arteries inside the heart-isolated VOI is an adaptation for TC from other reports [19], [20] and is described hereafter:

- Three-dimensional median filtering using a 5x5x5 mask to suppress noise and improve tissue extraction (figure 3a).
- Three-dimensional morphological opening filtering, where a spherical structuring element with a radius slightly greater than the radius of the biggest coronary segment (usually belonging to the left main trunk) is used. This radius is manually selected by the user, and is often between 6 and 8 pixels. The result of this step is a volume in which every spherical/cylindrical structure with a lesser radius than that of the structuring element is removed. Consequently, large blood pools and myocardial mass are enhanced (figure 3b).
- The volume obtained in the previous step is subtracted from the heart-isolated volume. Thus, all structures removed by the morphological filter are enhanced, including coronary arteries, coronary veins and cone-shaped blood pools near to papillary muscles of the ventricles (figure 3c).
- Contrast is doubled in order to enlarge the difference between coronary veins and arteries in HU.
- A windowing process follows in order to visualize coronary arteries and to neglect coronary veins. Threshold values were typically C:-700HU and W: 700HU (C=Center and W=Width). This empirically selected window performs a double function: in one hand it neglects all the voxels corresponding to coronary veins (lower HU values), and in the other hand it neglects all calcified plaques around coronary vessels (higher HU values).
- To select left coronary arteries and neglect all spurious structures inside the VOI that may have survived the windowing process, the user is required to manually select a voxel belonging to the left coronary tree. This point is the initial point for a volumetric region growing segmentation, where each voxel 26-connected to the seed-point and with HU values between the interval [C-W; C+W] is iteratively merged (figure 3d).
- Manual correction of the result is performed using a custom 3D erasing tool, where traces of coronary veins, ventricle blood pools regions near papillary muscles or spurious noise connected to coronary arteries are removed.
2.3.3. Skeletonization and length-volume Measurements
Medial axis skeleton of the segmented coronary artery tree is obtained by a simple-point identification approach using a template matching 12-Steps subiteration algorithm [21]. Skeleton clustered regions are eliminated and approximated by straight lines connecting exit-points to the center of mass of the clustered regions (generally belonging to stenotic portions of arteries with plaque deposition) [22] (figure 4). The coronary skeleton obtained is manually pruned and labeled, where all spurious branches not representing real bifurcations are deleted. All real branches resulting from pruning are smoothed with B-Splines for branch length calculations (L). Each voxel of the coronary tree is associated to the nearest branch by a least squares distance approach (figure 5: left). Branch volume (V) is calculated as the amount of voxels belonging to the branch times the voxel volume, typically $5.4 \times 10^3 \text{ mm}^3$. Every bifurcation point is labeled as a Node. Data from each stem and crown is assigned to its corresponding node and a coronary map is constructed (figure 5, right). This map is used to calculate $L$-$V$ measurements [11], [19], [20].

2.4. Statistical analysis
Values were expressed as mean±SD. Cumulative Log(Length)-Log(volume) correlations were plotted for each patient and the allometric constants, $\beta$ and $K_V$, were calculated from linear regression models (equation 1). Comparisons between groups were made using a t-test with significant levels when $p<0.05$. 

Figure 3. Left coronary artery segmentation: (a) Representative case of the heart isolation process in an arbitrary slice. (b) Morphological opening filter. (c) Images a) and b) are subtracted for vessel enhancement. (d) Three-dimensional result after volumetric region-growing segmentation. In every case, the arrow points to the seed-point selected by the user over the main trunk of the left coronary artery.

Figure 4. Coronary skeleton cluster elimination. a) 3D reconstruction of the coronary tree. b) Skeletonization of (a) where clusters appear around atheromatous plaque formations. c) Cluster are eliminated and replaced by the center of mass. d) Linear interpolation of clusters exit points and center of mass.
3. Results

The total number of subjects was 65, divided into 2 groups. As expected in this kind of study, we found more atherosclerotic than healthy patients. Group 1 (healthy): subjects without plaques (n=25, age 54±8 y.o., male gender 48%). Group 2 (CAD): subjects with at least one plaque in the left coronary tree (n=40, age 59±10 y.o., male gender 57%). We found an average of 4±2 plaques in the second group with a median value of coronary calcium score (CAC) of 233 [quartiles 63-690]. Plaques were 85% calcified. A high correlation was found between Log(CAC+1) and the number of plaques as shown in figure 6.

The morphometric results are presented in Table 1. We detected more vascular segments and bifurcations in CAD group. Accordingly, total cumulative length was longer in CAD patients (p<0.01) whereas total cumulative volume was similar between groups. The allometric slopes did not change with disease, whereas the allometric constant Kv was lower in the healthy group (p<0.05).

Table 1. Morphometric results.

|                         | 1. Healthy subjects (n=25) | 2. CAD subjects (n=40) |
|-------------------------|----------------------------|------------------------|
| Number of segments      | 16±6                       | 22±8††                 |
| Number of bifurcations  | 7±3                        | 10±4††                 |
| Total cumulative length, cm | 38.5±11.8                 | 47.3±10.8††            |
| Total cumulative volume, ml | 2.4±1.1                   | 2.7±1.0                |
| Allometric slope β      | 0.77±0.08                  | 0.74±0.07              |
| Allometric constant Kv  | 1.11±0.53                  | 1.48±0.74†             |

Values are expressed as mean±SD. †p<0.05, ††p<0.01. CAD = coronary artery disease.

4. Discussion

In this work we present an original method to reconstruct in 3D the left coronary tree of healthy and CAD patients using MSCT images in vivo. Previous works, where the coronary tree geometry was assessed with tomography to study allometric relations, were reported in autopsies from pigs [23] and humans [5,24]. We found also in vivo studies but only in pigs [11]. When human patients were
involved, invasive methods were employed [6], [7]. As far as we know, this is the first time human patients are tested in vivo with this kind of methodology.

We divided each coronary segment in the left tree and estimated its length and volume. Our main findings were that CAD subjects had a similar cumulative volume and a longer cumulative length than healthy patients. In other words, the presence of atheromatous plaques did not change the volume of the coronary arteries but increased the detected length. Accordingly, the numbers of segments (and bifurcations) were significantly more in the CAD group. We can explain these results with 2 hypotheses: i) Volume did not change due to a compensatory mechanism that self-regulates blood flow. Accordingly, coronary flow reserve is defined as the ability to reduce resistance in the coronary vascular bed to recover a normal blood circulation. When a lesion obstructs a branch, a distal dilating effect is expected to increases the branch perfusion within the coronary flow reserve limits. This dilation might explain the similar cumulative volumes found in both group. ii) The number of detected segments increased in CAD subjects because these dilated vessels became visible to the tomography study. When distal arteries dilate, they enhance blood circulation and might turn visible to the CT detectors. Usually, CT images can capture only arteries with a diameter >1mm. In fact, this first limitation has to be taken into account when this in vivo study is compared with other reports [5,23,24]. We cannot disregard the idea that CAD patients may also promote collateral circulation and the formation of new vessels to recover a proper coronary blood flow. These two mechanisms could also contribute to increase the number of detected segments. Further studies with more patients and detailed hemodynamic information should be addressed to corroborate these hypotheses.

Recently, our group analyzed the allometric relations between cumulative length and volume in the coronary arteries [16]. The idea behind this work was to identify if the coronary geometrical configuration of certain patients could induce the formation of plaques. We found that the allometric slope in patients with focal lesions in the left coronary tree did not differ from healthy patients. In other words, the cumulative length and volume in each bifurcation thought the coronary tree kept a constant allometric relation. In this work, we decided to include patients with a more advanced diffuse CAD. Again, the allometric slope did not change between groups (Table 1). Values of $\beta=0.75$ are similar to results from pigs and humans [10,11,20,25]. However, the allometric constant was significantly higher in CAD patients. If the allometric slopes are considered to be invariable, the cumulative Log(L)-Log(V) lines would represent parallel lines [16], [25]. In this scheme, a higher allometric constant would imply that for the same cumulative length, CAD patients have lower cumulative volume due to the presence of lesions. Moreover, this idea is coherent with the lesions simulations introduced in other allometric models [26].
The skeletonization method proved to be efficient even with patients presenting diffuse coronary disease. In spite of the reduced number of patients, our results show that the allometric relation did not change between subjects with and without CAD. This result confirms the existence of an allometric length-volume relationship in the coronary tree. More importantly, this relationship was verified in human patients and with CT techniques \textit{in vivo}. As mentioned before, MSCT technique has an intrinsic limitation to reconstruct vessels with diameters below 1mm$^2$ due to cardiac movement artifacts and resolution, not present in ex vivo studies that can go far below this limit [11]. Results obtained in this work could be improved with additional morphometrical information of the vascular tree (tortuosity, bifurcation angles, etc) that could be used to identify geometrical risk factors explaining the location and proliferation of atheromatous plaque [14].

Although the algorithm presented in this work could effectively reproduce the coronary artery tree with minimum intervention, the user still required to select the VOI, to select a seed-point for the region growing segmentation, and to perform a manual pruning of spurious skeleton branches. All these interventions require 3 to 6 minutes per study. A higher amount of spurious branches that need to be manually removed increment this time. The presence of diffuse coronary arteries might also introduce errors in vessel length measurements because of the topology preserving algorithms used to skeletonize the arterial tree. This algorithms cannot fill the holes that surround a plaque, thus introduces clustered regions in the artery skeleton which must be manually erased and linearly interpolated. In this process, the real curvature of vessels may also be altered. Once the arterial map is complete, allometric measuring is automatic. Further efforts are made to reduce user interventions and improve repeatability. In spite of these limitations, the combination of CT technology and image processing techniques are reliable tools for assessing quantitative information of the human coronary tree. They state the basis to develop new diagnostic tools to be applied in clinical practice.

\textbf{Figure 6.} Correlation between coronary calcium score (CAC) in logarithmic scale and the number of plaques in the left coronary tree.
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6. References

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