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Estimation of regional myocardial mass at risk based on distal arterial lumen volume and length using 3D micro-CT images

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Abstract

The determination of regional myocardial mass at risk distal to a coronary occlusion provides valuable prognostic information for a patient with coronary artery disease. The coronary arterial system follows a design rule which allows for the use of arterial branch length and lumen volume to estimate regional myocardial mass at risk. Image processing techniques, such as segmentation, skeletonization, and arterial network tracking, are presented for extracting anatomical details of the coronary arterial system using micro-computed tomography (CT). Moreover, a method of assigning tissue voxels to their corresponding arterial branches is presented to determine the dependent myocardial region. The proposed micro-CT technique was utilized to investigate the relationship between the sum of the distal coronary arterial branch lengths and volumes to the dependent regional myocardial mass using a polymer cast of a porcine heart. The correlations of the logarithm of the total distal arterial lengths (L) to the logarithm of the regional myocardial mass (M) for the left anterior descending (LAD), left circumflex (LCX) and right coronary (RCA) arteries were $\log(L) = 0.73\log(M) + 0.09$ ($R = 0.78$), $\log(L) = 0.82\log(M) + 0.05$ ($R = 0.77$), and $\log(L) = 0.85\log(M) + 0.05$ ($R = 0.87$), respectively. The correlation of the logarithm of the total distal arterial lumen volumes (V) to the logarithm of the regional myocardial mass for the LAD, LCX and RCA were $\log(V) = 0.93\log(M) - 1.65$ ($R = 0.81$), $\log(V) = 1.02\log(M) - 1.79$ ($R = 0.78$), and $\log(V) = 1.17\log(M) - 2.10$ ($R = 0.82$), respectively. These morphological relations did not change appreciably for diameter truncations of 600 to 1400 μm . The results indicate that the image processing procedures successfully extracted information from a large 3D dataset of the coronary arterial tree to provide prognostic indications in the form of arterial tree parameters and anatomical area at risk.

Keywords

Vessel segmentation; arterial length; lumen volume; coronary arteries; simulation

1. Introduction

Occlusion or partial occlusion of coronary arteries frequently occurs in man while imparting high morbidity and mortality. Previous studies have shown that the most important determinant of infarct size for a given coronary artery occlusion is the size of myocardium that the artery perfuses [1–5]. Therefore, information about the perfusion territory, or myocardial mass at risk, can be used to determine the potential infarct severity of an occluded artery. Current

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clinical applications of radionuclide perfusion imaging and contrast echocardiography utilize this concept by identifying inadequately perfused regions with a radiopharmaceutical tracer or contrast material, respectively, to estimate the potential infarct size. Alternatively, previous studies have indicated that morphological surrogates for myocardial mass measurements may exist [6–9]. For example, the sum of arterial branch lengths distal to the point of occlusion has been proposed for estimating the corresponding regional myocardial mass at risk [6]. Moreover, the total volume of blood in mammals have been found to scale proportionately with their body mass [7–9]. More recently, a study using a computer grown coronary arterial tree has suggested that the blood volume in coronary arteries scales proportionately with the tissue volume they supply through a power-law relation with an exponent of 1.2 [10]. However, the calculation of arterial branch lengths in the former study were made from three-dimensionally (3D) reconstructed arterial trees using biplane coronary angiograms. 3D reconstruction from biplane projections is known to be limited by vessel overlap [11]. In addition, existing experimental data that gives rise to blood volume-body mass relation is global in nature. Other studies have reported on the relationships between the length [12], volume [13], and the cross-sectional area [14] of the main feeder arterial branch versus the perfused myocardial volume. The current investigation provides experimental data that compares the total distal regional coronary arterial lumen volumes, lengths, and myocardial mass. These relations parallel Zhou et al's relationship between the sum of distal branch lengths and the sum of distal branch volumes [15].

In the current study, a method for quantifying morphological parameters of coronary arterial trees and analyzing the relationships between them was developed using micro-computed tomography (micro-CT) and several image processing techniques. Micro-CT can obtain 3D anatomical data of biological specimens with a spatial resolution as high as 50 μm [16]. Combined with a contrast enhancing agent, micro-CT has been successfully used for imaging the vasculatures of a rat kidney [17,18], heart [19], liver [20] and swine heart [21,22]. However, vascular imaging with micro-CT produces 3D images of the arterial tree that contains hundreds of branches spanning many generations. Methods for analyzing micro-CT images of the rat's coronary system have been developed [23]. While these methods provide valuable insight into the extraction and representation of an arterial tree, further improvements in the methodology are needed in order to reconstruct a more complete coronary arterial tree. In the current study, methods for vascular analysis from micro-CTs involve four principle steps: 1) segmenting arteries from the background anatomy; 2) labeling the segmented branches and storing their diameters and lengths; 3) mapping the connectivity between branches; and 4) partitioning myocardial voxels into separate perfusion beds supplied by different arterial branches. The methodology for casting the heart, imaging, segmentation, and quantification of morphological parameters are also presented.

In addition to the quantification of parameters, the current study also evaluates the relationships between total distal branch lengths and total lumen volume with respect to regional myocardial mass using a volumetric image dataset from a pig's coronary arterial tree. Morphological data obtained from micro-CT has not been previously used to investigate these relationships. These relationships can potentially provide valuable insight into the prognostic significance of an acute myocardial infarction due to an arterial occlusion and aid in the decision-making of treatment options.

2. Material and methods

In order to study the relationships between arterial branch length, lumen volume, and myocardial mass at risk, methods for obtaining accurate measurements of these parameters were developed and tested on a porcine heart. 60 cc of saturated KCL solution was injected into the right jugular vein of a 35 kg swine to arrest its heart and keep it in a relaxed state. The

heart was then excised with the ascending aorta clamped to keep air bubbles from entering the coronary vessels. The coronary vessels were immediately perfused with an iso-osmotic, cardioplegic solution to keep the vasculature vasodilated. The excised heart was then casted with a radio-opaque polymer and imaged with a micro-CT. After image acquisition and reconstruction, numerous post-acquisition image processing techniques were used to determine arterial branch lengths, lumen volumes, and myocardial mass of different arterial perfusion beds. Briefly, the process begins with differentiating voxels belonging to the myocardium versus those belonging to the arterial branches. The extracted arterial branches are then thinned until only their skeletal centerlines remain. These centerlines are used for calculating arterial branch lengths. Moreover, with the density of the myocardium known, the myocardial mass of perfusion beds can be determined from the total volume of the extracted myocardial voxels. The procedure includes the following steps (fig. 1):

1. median filtering to suppress noise and improve the extraction of tissue voxels,
2. thresholding to extract tissue voxels,
3. morphological filtering of the original image to enhance coronary vessels,
4. region growing to extract continuous vessels,
5. 3D thinning to determine vessel centerlines while preserving shape and topology,
6. tree tracking to database individual branches for further processing,
7. B-spline fitting to determine arterial branch lengths more accurately,
8. tissue voxel assignment to divide the myocardium according to different perfusion beds.

The details of casting, image acquisition, image processing, and analysis are given in the following sections.

Polymer cast of coronary arterial tree

The arterial trees of the left anterior descending (LAD), left circumflex (LCX), and right coronary arteries were casted with Microfil (Flow Tech, Inc. Caver, MA, USA), which is a liquid polymer that provides complete filling with minimal shrinkage in volume after curing. A previous study has reported on the casting method, which is summarized here with some modifications for this particular application [24]. The LAD, LCX and RCA of the excised porcine heart were cannulated under saline to avoid air bubbles. Three 60 cc syringes connected to the main pressure source were used for injecting cardioplegic and casting solutions into the cannulated arteries. Cardioplegic solution was initially used to perfuse the LAD, LCX, and RCA in order to wash out remnant blood and to maintain the arteries in a dilated state. Microfil was then used to make a cast of the coronary vasculature. The Microfil solution solidifies in a specific period of time after it has been catalyzed with 6% stannous 2-ethylhexoate and 3.0% ethyl silicate. The catalyzed Microfil solution was stirred and degassed under vacuum to remove air bubbles. After degassing, perfusion with the cardioplegic solution was stopped. The LAD, LCX and RCA were then simultaneously perfused with the Microfil solution. Each of the three main coronary arteries was perfused with Microfil of different color. The coloring enabled the three perfusion beds to be dissected and weighed. The perfusion pressure was maintained at 100 mm Hg until the elastomer hardened. Saline and residual casting material that leaked into the ventricles were purged to allow better contrast of the chambers during imaging.

Image acquisition and processing

Images of the casted porcine heart were acquired using a Micro-CT scanner (XSPECT, Gamma-Medica, Northridge, CA, USA). The X-ray parameters for volume imaging were 80 kVp, 150 mA, and 10 ms. The source-to-origin and source-to-detector distances were 225 and 311 mm, respectively. The casted heart was placed inside a cylindrical container for easy placement in the center of the detector's field of view. The heart was carefully positioned to insure that all vessels were inside the field of view. A total of 256 projections spanning 360 degrees were acquired. Images were reconstructed with commercially available software designed for cone-beam reconstruction using a modified Feldkamp algorithm (Exxim COBRA). The reconstructed volume was $512 \times 512 \times 512$ voxels, with a voxel size of $0.145 \times 0.145 \times 0.145$ mm.

Tissue and vessel segmentation

The reconstructed CT volumes have dimensions of $512 \times 512 \times 512$ voxels, and each voxel was encoded by 8 bits. A median filter with a radius of 2-pixel was used to reduce the image noise [25]. The volume was then thresholded to separate the myocardium from vessels and background. A new, binary dataset was generated where only the myocardium was in the foreground. A cross-platform java image processing application was used for the procedure (ImageJ, NIH).

A 3D gray-scale morphological filter was used for vessel segmentation. Morphological filters are often used to eliminate or enhance information that conforms to certain shapes called structuring elements [26]. Since the coronary vasculature in volumetric images can be approximated as cylinders, a spherical structuring element with a diameter slightly larger than the diameter of the largest vessel was used to remove all the vessels. The vessels were removed by using the open operator of the morphological filter, which eliminated structures smaller than or the same size as the structuring element. The resultant vessel-free volume was then subtracted from the original volume, leaving an enhanced reconstruction of only the vessels.

Vessel segmentation was performed by using a locally adaptive region growing algorithm. The procedure combined the concept of local cubes [48] and symmetric region growing [49]. The algorithm started with a user determined seed point. Beginning with the seed point the surrounding voxels were analyzed to determine the mean standard deviation of the gray level intensity inside the object. An $80 \times 80 \times 80$ cube was created with the seed point as the center. The symmetric region growing algorithm, described below, was performed locally in this cube with the given mean and standard deviation of the voxel intensities. After the data inside the cube was segmented, the six faces of the cube were examined to locate the position of the next cube(s). A connected-component algorithm was used to locate the end point of the branches on the faces of the cube. For each of the component found, a new cube was created for the next segmentation. If more than one component was present then the new cubes were stored in a queue and waited for their turn to be analyzed. The process was repeated until the local cube had zero connected components. When no connected components were found, the end of the branch was reached. Ideally, the cube must be of the right size to completely contain the segmented vessels. If the cube was too small then the segmentation might not contain useful information since the cube might be completely circumscribed by the vessels. To check if the size of the cube was adequate, a condition was imposed on the connected components where each component must not span opposite faces of the cube. If this test failed then the size of the cube was doubled and the segmentation was repeated.

A symmetric region growing [49] algorithm was implemented to segment the vessels within a local cube. This algorithm is a one-pass procedure that does not rely on recursions to grow one voxel into the next. The fundamental concept is to segment in one dimension and

subsequently builds up to two and three dimensions. The algorithm began by segmenting one line of voxels according to the parameters (mean and standard deviation of gray level intensities inside the vessels) of the region growing procedure. Then the next line was segmented and the two regions were merged. The process continued until a whole slice was analyzed. After one slice was segmented, the next slice was analyzed and merged to the previous one until the whole 3D dataset was segmented. Since this process was one-pass, the segmentation information could be stored directly onto the image being analyzed, therefore saving memory. Also, computational efficiency was achieved because each voxel was visited only once as opposed to recursive methods where voxels might be visited more than once.

Centerline extraction

The next step is vessel skeletonization for branch tracking and length computation. Skeletonization, otherwise known as medial axis transform, can usually be achieved in two primary ways. One method calculates the distance transform of the image where the value of each voxel belonging to the object is replaced by its distance to the nearest edge of the object [28]. The medial axis transform follows the ridges of the distance transform, where the values are higher than their surroundings. The other method morphologically thins the object by repeatedly eroding boundary voxels until the object cannot be thinned any further, at which point only the skeleton is left [29]. For this study, the latter method was chosen for its robustness in preserving topology and shape [30]. Vessel centerlines were extracted from the binary vessel dataset using a 3D parallel thinning approach as reported by Palagyi et al [30]. Briefly, this skeletonization technique builds on the concept of simple points. Simple points are defined as voxels that can be deleted without changing the topology of the objects. The skeletonization algorithm examines each voxel and determines if it is a simple point that can be deleted. A simple point is deleted if its neighborhood matches a set of $3 \times 3 \times 3$ templates. On the other hand, a simple point is not deleted if it is an endpoint so that the shape of the object is preserved. The algorithm is divided into 12 sub-iterations, with each sub-iteration corresponding to a direction relative to a particular point. The 12 directions are up-north, up-east, up-south, up-west, north-east, north-west, north-down, east-south, east-down, south-west, south-down, and west-down. Each direction consists of 14 matching templates. Each of the 12 sub-iterations can be operated in parallel, which means the order of directions analyzed do not affect the results. The algorithm operates on the image repeatedly until no additional point can be deleted.

Tree tracking

The resulting skeleton of the coronary arterial tree was used to track each of the coronary arteries from its root branch to the most distal branches. The tree was broken down into individual branches for the computation of lengths and diameters. First, a seed voxel at the beginning of the root branch was visually chosen. Then the voxel's $3 \times 3 \times 3$ neighborhood was examined to search for other skeleton points. The search for additional skeleton points continued until no other skeleton points existed in the neighborhood, then the current voxel was considered an endpoint. If exactly one other point was present in the neighborhood, then this point was added to the branch. If more than one point were found, then the algorithm tentatively assumed the existence of a multiple branch point (e.g bifurcation or trifurcation). A chain of voxels was defined as a branch if its length was greater than 5 voxels. A threshold of 5 voxels was determined by comparing the images of the tracked branches and the segmented vessels. A series of voxels shorter than 5 voxels was treated as a false branch and deleted. Each new point was checked to determine if it was part of a new branch. Once a new branch was found, it was tracked to its endpoint and assigned as the left or right child of its parent branch. If a trifurcation was encountered, the three children branches were divided into two tandem bifurcations that were connected by an artificial branch of length 0. This artificial branch along with one real branch made up the first bifurcation. The second bifurcation was composed of the remaining two children branches with the artificial branch acting as their parent branch.

After the branches were tracked, a B-spline was fitted to each branch before their lengths were computed. A cubic smoothing B-spline was utilized to smooth the centerline by taking every third point as a node for the algorithm.

Tissue voxel assignment

An important characteristic of an arterial tree is the spatial distribution of its terminal arteriole branches that connect to the capillaries. These terminal arterial branches define the area of the myocardium that the larger proximal arterial branches perfuse. If the locations of the terminating arterial branches are not known, then an estimate of their location and the corresponding myocardium they perfuse have to be obtained from the existing location of the proximal branches. The two main approaches for determining the spatial distribution of terminal arterioles are the nearest neighbor method [31] and the fractal method [32]. For determining the region of myocardium that a terminal arteriole supplies, Karch et al[10] used voronoi polyhedrals to associate tissue regions to their supplying arterioles. However, their arteriole-tissue assignment was based on a simulated arterial tree that was fully grown to the pre-capillary level using a method of constrained constructive optimization. In the current study, pre-capillary arterioles were not available because only arteries with diameters larger than 500 microns were segmented. Segmentation of smaller arteries was hampered by low contrast to noise ratio. Using the concept of minimized transport cost, regions occupied by pre-capillary arteriole branches can be assumed to arise from the nearest terminal arterial branch, which in turn arises from the nearest conducting arterial branch. Thus the source of blood for different regions of the myocardium can be assumed to arise from the nearest reconstructed terminal arterial branches. Based on these assumptions, every reconstructed tissue voxel was assigned to a specific branch from one of the coronary arterial trees. This assignment of tissue-branch pairs began with calculating each voxel's distance to every terminal branch. Then a search for a minimum distance was performed to find the appropriate blood source for a particular voxel.

Diameter measurement validation

The region growing algorithm requires a range of voxel intensities in which it operates. The low threshold value is more important than the high threshold value because it defines the cutoff intensity below which voxels are considered to be outside the vessel. To obtain segmented vessels with the most accurate diameter, an optimal low threshold value must be chosen. Values that are too high or too low will cause the segmentation process to underestimate or overestimate vessel diameters, respectively. Choosing the thresholds for the region growing algorithm is, therefore, critical for subsequent calculations of vessel volumes. Appropriate threshold values can be chosen from an analysis of voxel intensity profiles along vessel edges. Edges were defined from an analysis of the first and second derivatives of intensity profiles as described in the tissue and vessel segmentation section. A validation procedure was used to compare the accuracy of measuring diameters from using the first derivative only versus using a combination of the first and second derivatives for determining vessel edges. The validation procedure is described below.

Five plastic tubes (Silastic, Laboratory Tubing, Midland, Michigan) of 10 cm in length and varying diameters were used for the validation process. The inner diameters of the tubes were 2.64 mm, 1.98 mm, 1.57 mm, 1.02 mm, and 0.76 mm. They were filled with the Microfil polymer. The plastic tubes were anchored onto the inner wall of a styrofoam cup, conforming to its curvature, to simulate the curvature of the coronary vessels as they curve along the epicardium. The cup was then filled with water before it was imaged. Water was used to simulate cardiac tissue because the densities of the two are similar. After the volume dataset of the diameter was acquired, the segmentation procedure was applied and the diameters of the plastic tubes were calculated. Diameters were computed by utilizing the centerline binary

image and the segmented-vessel image. Starting from the root branch, for each of the skeleton points in each branch, a plane perpendicular to the direction of the branch was calculated. The cross-sectional area of the vessel at this point was determined by computing the area of intersection between the plane and vessel dataset. The diameter was calculated by assuming that the cross-sectional area of the arteries is circular. Since each of the skeleton points was associated with a diameter value, the branch diameter was the average of the individual centerline-point diameters. The methods were compared for their accuracy in diameter calculation. The method that produced the most accurate diameters was used for the quantification of arterial tree properties.

Length measurement validation

Figure 2(d) shows the extracted centerlines from the parallel thinning algorithm. Using the centerline data, the location of bifurcation points and the boundaries of branches were determined by tracking the tree voxel by voxel. The length of each branch was determined by summing the Euclidean distances between consecutive points along the branch. As can be seen in the figure 3, the noise in the original segmented vessel dataset caused the centerline to have a zig-zag pattern. The zig-zag pattern will produce an overestimation in the length of the vessel. Thus the extracted centerlines were fitted with a cubic smoothing B-spline in order to minimize the effect of noise and to obtain a more accurate representation of true vessel centerlines. The B-spline fit was determined by choosing appropriately spaced points along the segments to serve as control points.

To compare the B-spline lengths and non-B-spline lengths, a set of plastic tubes with diameter of 1.57mm and lengths of 2, 4, 6, 8 and 10 cm were used. The tubes were filled with the Microfil casting material. The elastic polymer, mixed with the curing catalyst, was injected through a long tube with a syringe. Once the liquid began to exit the other end, a stopcock was used to close off the opening. A pressure of 100 mmHg held the polymer in place until the casting material solidified. After that, the tubes were cut into segments with the aforementioned lengths. Random curvatures were applied to the tubes before imaging.

Morphological relationships

The morphological relationships in a coronary artery tree have previously been reported [33] [15] [34]. A coronary artery tree can be recursively broken down into a stem and crown system. A stem is a vessel segment between any two bifurcations. A crown is defined as the collection of all distal branches to a stem with the same terminal diameter. With L , V , and M representing the cumulative arterial branch length of a crown, the cumulative arterial lumen volume of a crown and the total mass perfused by the crown, respectively. Some of the previously reported morphological relationships are as follows:

$$L = k_V V^{\beta_V}, \quad (1)$$

$$L = k_M M^{\beta_M}, \quad (2)$$

where k_V and k_M are the proportionality constants that relate the total crown length to the total crown volume and total perfused myocardial mass, respectively. β_V and β_M are the exponents characterizing the power relations. Since previous studies have found β_V and β_M to be 0.75, V and M can be related linearly as follows:

$$V = k_{VM} M^{\beta_{VM}}, \quad (3)$$

where k_{VM} is the proportionality constants and β_{VM} is the power exponent that should ideally be equal to 1. These relationships were tested in one swine heart for the three principle arterial

trees of the coronary system—the left anterior descending (LAD), and left circumflex (LCX) and the right (RCA) coronary artery trees.

The morphological relationships were also examined for the three trees at different levels of diameter truncations to determine the impact of imaging system spatial resolution on the observed morphological relationships. Truncation levels of 600, 800, 1000, 1200, and 1400 μm were studied in order to approximately include spatial resolutions of coronary angiography and CT angiography. The cumulative lengths and volumes were recalculated for each truncation. Moreover, tissue voxel assignment was performed on remaining arterial branches for each truncation level. The CT regional mass of the LAD, LCX and RCA were compared to values obtained from the dissected perfusion beds for each arterial tree.

3. Results

Tissue and vessel segmentation

Starting from the micro-CT images of the casted heart, the myocardium and coronary vessels were segmented. Figure 2 shows the maximum intensity projections of the original raw data (a), the segmented tissue (b), and the segmented vessels (c) and the resulting skeleton (d). The smallest coronary branches that could be segmented were approximately 400 μm .

Centerline extraction

The parallel thinning algorithm produced the image shown in Fig. 2d. As seen in the image, the topology of the skeleton was rough, in contrast to the smooth coronary vessels in Fig. 2a. This centerline was then pruned and fitted with a B-spline smoothing fit so that the topology of the skeleton more faithfully represents the smoothness of the original vessels.

Tissue voxel assignment

Figure 3 shows the 3D visualization of the coronary arteries with their corresponding perfusion beds. In figure 3 (a), the myocardium belonging to the LAD is transparent, that belonging to the RCA is transparent blue, and that belonging to the LCX is green. The demarcation between the LCX myocardium and the RCA myocardium can be seen. In figure 3 (b), a cross section of the myocardium shows the demarcation between the three myocardial beds in an axial plane.

Diameter measurement validation

Figure 4 shows the linear regression of the computed diameters and the true diameters of the tubing phantoms. Diameters computed from only the first derivative (figure 4a), a combination of the first and second derivative with inner maximums (figure 4b), and combined first and second derivative with outer maximums (figure 4c) are shown. The fits for figure 4a, figure 4b and figure 4c are $D_M = 0.50D_K + 0.37$ ($R=0.95$), $D_M = 0.60D_K + 0.13$ ($R=0.99$) and $D_M = 0.83D_K + 0.09$ ($R=0.99$), respectively—where D_M is the computed diameter and D_K is the known diameter. The average errors in diameter measurements for methods in figure 4a, figure 4b and figure 4c are 22.8%, 29.4% and 11.2%, respectively. The dotted line represents the line of identity.

Length measurement validation

Figure 5 shows the linear regressions of the measured lengths (L_M) and the known lengths (L_K) of the tubing phantoms. In figure 5(a), the length was computed before applying the B-spline smoothing algorithm. On the other hand, the length in figure 5(b) was computed after B-spline smoothing. The fits for figure 5(a) and figure 5(b) are $L_M = 1.19L_K - 10.52$ ($R=1.00$) and $L_M = 1.07L_K - 7.47$ ($R=1.00$), respectively. The errors in length measurements for methods without and with cubic B-spline smoothing are 12.9% and 10.9%, respectively. For longer

segments (>50mm), more accurate length measurements were made with the B-spline smoothing. However, lengths obtained with and without B-spline were similar for shorter segments (<50mm). Also, lengths computed with B-spline smoothing were usually underestimated, whereas lengths computed without B-spline smoothing were often overestimated.

Relation of distal branch lengths and lumen volumes to regional myocardial mass

Figure 6 shows the log-log plots of the total distal coronary branch lengths (L) and total distal lumen volume (V) for the LAD ($\log(L) = 0.76\log(V) + 1.46$, $R = 0.99$), LCX ($\log(L) = 0.78\log(V) + 1.53$, $R = 0.99$), and RCA ($\log(L) = 0.74\log(V) + 1.45$, $R = 0.98$). Figure 7 shows the log-log plots of total distal coronary branch length (L) and myocardial mass (M) for the LAD ($\log(L) = 0.73\log(M) + 0.09$, $R = 0.78$), LCX ($\log(L) = 0.82\log(M) + 0.06$, $R = 0.77$), and RCA ($\log(L) = 0.85\log(M) + 0.05$, $R = 0.87$). Figure 8 shows the log-log plots of total distal arterial lumen volume (V) and myocardial mass (M) for the LAD ($\log(V) = 0.93\log(M) - 1.66$, $R = 0.81$), LCX ($\log(V) = 1.02\log(M) - 1.79$, $R = 0.78$), and RCA ($\log(V) = 1.17\log(M) - 2.10$, $R = 0.82$). The correlation between total distal branch length and regional myocardial mass as well as between total distal lumen volume and regional myocardial mass were good. Table 1 tabulates the exponents of the morphological relationships for the 600 μm truncation. The average values of the exponents of the relationships were 0.76, 0.80 and 1.04 for β_V , β_M and β_{VM} , respectively. Table 2 provides a summary of length, volume, and mass measurements from the CT image. The measured regional myocardial masses perfused by the LAD, LCX, and RCA were 67.90 g, 58.67 g, and 64.48 g, respectively. Similarly, the CT computed masses assigned to the LAD, LCX, and RCA at 600 μm truncation were 70.19 g, 55.71 g, and 63.54 g, respectively. The relative error in CT computed masses are tabulated in Table 2. In addition, the total computed mass of 189.44 g compared well with the measured mass of 191.05 g (relative error of 0.84%).

Figure 9 to Figure 11 compare the different levels of diameter truncations for β_V , β_M and β_{VM} , respectively. The errors in β_M and β_{VM} increased with increasing truncation level. However, the errors in β_V were small and remained relatively constant for different truncations. Errors in β_V , β_M and β_{VM} introduced by truncation ranged from 1.13–1.98%, 4.76–12.74%, and 4.38–10.59%, respectively. Figure 12 to Figure 14 compare the different levels of diameter truncations for $\log(k_V)$, $\log(k_M)$, and $\log(k_{VM})$, respectively. These figures show that errors for $\log(k_M)$ and $\log(k_{VM})$ increased with increasing truncation level while errors for $\log(k_V)$ slightly decreased. Figure 15 shows the error between the CT computed mass and the measured mass for different levels of truncations. The range of errors were 1.46–5.05%, 1.01–5.06%, 2.71–5.92%, 5.10–18.35%, and 11.18–29.03 for truncations of 600, 800, 1000, 1200, and 1400 μm , respectively. The errors were calculated relative to the measured regional mass for each coronary arterial bed.

4. Discussion

The methodology presented has enabled the analysis of the volumetric micro-CT dataset of a swine heart. A previous study has reported a technique to analyze the micro-CT of a rat heart [23]. However, this study was limited in reconstructing all branches in different generations of the coronary arterial tree. In the current technique, the reconstruction of the coronary arterial tree was improved by using of a 3D morphological filter to enhance the vessels before segmentation. Furthermore, the current technique was used to quantify coronary arterial length and lumen volume and relating them to regional myocardial mass. This study represents an application of various well established image processing algorithms for the purpose of extracting the coronary arterial tree information from micro-CT data and validating the morphological relationships. Our aim was to determine the sequence of image processing algorithms that can be easily implemented in order to to extract information from a CT dataset

accurately. In this regard, the four primary algorithms that were chosen were region growing, 3D topological thinning, voxel-based tree tracking and shortest-distance tissue voxel assignment. The results of the morphological relationships showed that these methods accurately extracted parameters such as lengths and diameters from the 3D dataset. However, there are more sophisticated image processing techniques that can potentially improve upon the current methods of data analysis. Specifically, improvements can be made to segment the tree down to the scanner's resolution and to assign the myocardial voxel to the supplying arterial branch more accurately. Segmentation of the vessels is the most critical step because all subsequent vessel processing steps depend on its quality. Region growing is an efficient method for segmenting a large dataset with fairly uniform image regions, but it cannot segment complex volumes. For this study, a locally adaptive method was used, and the region growing algorithm could segment vessels as small as 400 μm . A limitation of the region growing method is its inability to compensate for the roughness of the anatomical surface caused by image noise and artifacts. Because the skeletonization entirely depends on the quality of the initial segmentation, rough surfaces cause the algorithm to produce spurious branches. Compensating for the surface imperfections requires the use of deformable contours for segmentation [36]. These contours, or snakes, are given various constraints to deform until their shapes coincide to that of the vessel.

The assignment of tissue voxels to the supplying arterial branch is straightforward but not as intuitive. Since the vessels were not segmented to the pre-capillary arterioles, it is difficult to assign tissue voxel to the arterial branch that supplies it with blood. If the locations of pre-capillary arterioles are known, then it is more accurate to assume that the myocardial mass closest to a particular arteriole is supplied by the corresponding parent arterial branch. This mass region can be determined by computing the voronoi polyhedra surrounding the arterioles [10]. With the tree truncated at 400 μm , the alternative is to computationally grow the tree to the pre-capillary level with a set of statistical constraints and mathematical rules [37]. Subsequently, the tissue assignment can proceed naturally with the knowledge of the spatial coordinates of all terminating arterioles. The relationships between total distal volumes and lengths versus regional myocardial mass can potentially improve with a tree grown to the pre-capillary level. Implementation of more sophisticated vessel extraction techniques, tree-growing to the pre-capillary level and assignment of mass based on voronoi polyhedra are the subjects of future investigations.

The computation of branch properties such as diameters and lengths using volumetric micro-CT data were validated with phantoms. The validation showed good agreement with the known diameters and lengths. The best method for choosing the low threshold value in the region growing algorithm, as revealed by the diameter validation results, was utilization of both the first and second derivative where the outer maximums of the second derivative were used. For length computations, cubic smoothing B-spline improved the results. Computed lengths without B-spline smoothing were often overestimated. Moreover, longer branches with higher degrees of curvature have a greater probability of deviating from the true medial axis and having their lengths overestimated if B-spline smoothing is not applied.

Previous studies have shown that regional myocardial mass was closely and linearly related to the total coronary branch lengths distal to any point in the coronary arterial tree [6,38]. A linear relation between lengths and mass were found in dogs [6]. However, a recent report [34] has indicated that there is a power law relationship between lengths and mass. Specifically, total distal branch lengths is proportional to the total perfused mass raised to the power of 0.75. The present study also found a 0.75 power law between arterial lengths and regional myocardial mass in swine—the average value of the exponents for the three coronary trees was $\beta_V = 0.76$. Previous studies [15,33] have also found a 0.75 power relationship between vessel lengths and lumen volumes. Accordingly, the current investigation closely agrees with these past results

with an average value of $\beta_M = 0.80$. Since the lengths are related to lumen volumes and mass with the same power law exponent, lumen volumes should be linearly proportional to mass. Indeed, this is the case according to our results of the average of $\beta_{VM} = 1.04$. These findings suggest that quantitative information on the myocardial area at risk can potentially be obtained from coronary angiograms by measuring the total arterial lengths or lumen volumes of a crown that belongs to the stem that has segmental stenosis. By analyzing clinical angiographs, it is possible to categorize patients according to different prognostic indications suggested by the area at risk. However, it can be difficult to measure the lengths of arterial branches on coronary angiograms [39]. Tracing the tree manually is time consuming and tracking it automatically is limited by image noise, artifacts and anatomical background [40]. For biplane angiography, 3D reconstruction based on geometrical methods can be used to obtain the lengths [41–44]. However, the method requires the user to define corresponding points in the biplane images, which is also time-consuming. In the current findings, the total distal lumen volumes can also be used to estimate the regional myocardial mass at risk, which supports the theoretical derivation of the volume-mass relation by West et al [9]. The lumen volume of an arterial tree can be readily obtained from digital coronary angiogram by using a densitometry technique [45,46]. The densitometry technique is more robust than the geometric techniques because it is independent of the projection angles and makes no assumption as to the cross-section of the coronary vessels. An iodine calibration phantom is used for converting integrated gray level into volume. The implementation requires the user to draw a region of interest around an arterial tree or subtree, and then the obtained lumen volume distal to the stenosis can be used to estimate the amount of myocardium at risk.

The morphological relationships were examined at different levels of diameter truncations to investigate if a truncated coronary tree can still be used to assign regional myocardial mass accurately. Although branches with diameter of 400 μm were detected, the analysis was performed for truncation values starting at 600 μm to insure uniform diameters at the terminal vessels. The errors in β_M and β_{VM} increased as the truncation diameter increased since there were fewer data points for larger truncations. But values of approximately 0.75 and 1 (0.80 and 1.04, average for the three trees) were still found for β_M and β_{VM} at a truncation diameter of 1400 μm with maximum errors of 12.74% and 10.59%, respectively. β_V errors remained low (1.13% – 1.98%) and did not increase with truncation diameter because truncation affects both length and volume calculations. When the trees were truncated at a certain diameter, both the length and the volume of the vessels were cut off proportionately. Similar to β_M and β_{VM} the errors in k_M and k_{VM} increased as the truncation diameter increased because of fewer data points. However, the errors for k_V decreased slightly for larger truncations because smaller arteries, which are usually associated with larger length and volume measurement errors, were excluded. These results indicated that the parameters of the morphological relationships could be faithfully extracted for trees with truncation diameter as large as 1400 μm . On the other hand, β_M and β_{VM} is dependent on regional mass assignment, which can incur increased error due to the truncation. Mass assignment was validated by weighing the three main perfusion beds and comparing them to the values obtained from CT. The CT mass errors were relatively lower for truncations of 600–1000 μm (1.01–6.43% errors) than for truncations of 1200 and 1400 μm (5.10–29.03% errors). The maximum errors were 18.34% and 29.03% for truncations of 1200 and 1400 μm , respectively. These errors indicate that regional myocardial mass at risk cannot be reliably obtained from these two truncation levels. The maximum error for the lower three truncation levels was 6.43%. Therefore, relatively accurate regional masses supplied by the LAD, LCX, and RCA could be deduced from coronary arterial branches as large as 1000 μm in diameter.

An important mediating factor for coronary artery disease that was not considered in this study is collateral circulation [50]. Collaterals serve as bridges between coronary arteries to provide an alternate blood source to ischemic myocardial beds. Cardiac vulnerability depends on the

patient's ability to develop coronary collaterals. The current study utilized normal swine hearts; therefore collaterals were not visualized. By not including the collaterals, the myocardial mass at risk predicted by the morphological relationships would be overestimated since collateral perfusion is ignored. However, the effects of collaterals on the exponents and slopes of the L versus M and V versus M relationships require further investigation.

Despite the various improvements that can be made on the current methodology, results from this study provide insights into the coronary arterial tree and its perfusion bed that can potentially be clinically useful. Future studies might involve the aforementioned improvements in the methodology that can improve the accuracy of the computed branch parameters. Moreover, in combination with current advances in coronary CT angiography [47], the reported method can be used to obtain the lumen volume-mass and length-mass relationships as the patients undergo non-invasive coronary CT angiography. Thus, this additional information can potentially provide a guide for intervention.

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Figure 1.
Flow Diagram of the image processing procedure.

Figure 2. Maximum intensity images of the raw data (a), the segmented tissue (b), the segmented vessels (c) and the resulting skeleton (d).

Figure 3. Visualization of the coronary vessels with their corresponding perfusion beds (a) and with the perfusion bed truncated (b).

Figure 4.

Relationships between the measured diameters and the known diameters for the methods utilizing the first derivative (a), the combined first-second derivative using the inner maximum (b) and outer maximum (c) of the second derivative. The dotted lines are the lines of identity. The fits are $D_M = 0.50D_K + 0.37$ ($R=0.95$), $D_M = 0.60 D_K + 0.13$ ($R=0.99$) and $D_M = 0.83 D_K + 0.09$ ($R=0.99$) for (a), (b), and (c), respectively. D_K = Known Diameter, D_M = Measured Diameter.

Figure 5. Relationships between the measured lengths and the known lengths of the tubing phantoms without (a) and with (b) B-spline smoothing fit. The dotted lines are the lines of identity. The fits are $L_M = 1.19L_K - 10.52$ ($R=1.00$) and $L_M = 1.07L_K - 7.47$ ($R=1.00$) for (a) and (b), respectively. L_K = Known Length, L_M = Measured Length

Figure 6.

Relationships between the total distal branch lengths and total distal lumen volumes of the LAD (a), LCX (b), and RCA (c). The fits are $\log(L) = 0.76\log(V) + 1.46$ ($R = 0.99$), $\log(L) = 0.78\log(V) + 1.53$ ($R = 0.99$), and $\log(L) = 0.74\log(V) + 1.45$ ($R = 0.98$) for (a), (b) and (c), respectively. L = Crown Length, V = Crown Volume.

Figure 7.

Relationships between the total distal branch lengths and myocardial mass of the LAD (a), LCX (b), and RCA (c). The fits are $\log(L)=0.73\log(M)+0.09$ ($R=0.78$), $\log(L)=0.82\log(M)+0.06$ ($R=0.77$), and $\log(L)=0.85\log(M)+0.05$ ($R=0.87$) for (a), (b) and (c), respectively. L = Crown Length, M = Dependent Myocardial Mass.

Figure 8.

Relationships between the total distal vessel volumes and myocardial mass of the LAD (a), LCX (b), and RCA (c). The fits are $\log(V) = 0.93\log(M) - 1.66$ ($R = 0.81$), $\log(V) = 1.02\log(M) - 1.79$ ($R = 0.78$), and $\log(V) = 1.17\log(M) - 2.10$ ($R = 0.82$) for (a), (b) and (c), respectively. V = Crown Volume, M = Dependent Myocardial Mass.

Figure 9.

Comparison of β_V and its errors for different levels of diameter truncations. The bottom, middle and top graphs correspond to the LAD, LCX, and RCA, respectively.

Figure 10.

Comparison of β_M and its errors for different levels of diameter truncations. The bottom, middle and top graphs correspond to the LAD, LCX, and RCA, respectively.

Figure 11.

Comparison of β_{VM} and its errors for different levels of diameter truncations. The bottom, middle and top graphs correspond to the LAD, LCX, and RCA, respectively.

Figure 12.

Comparison of $\log(k_V)$ and its errors for different levels of diameter truncations. The bottom, middle and top graphs correspond to the LAD, LCX, and RCA, respectively.

Figure 13.

Comparison of $\log(k_M)$ and its errors for different levels of diameter truncations. The bottom, middle and top graphs correspond to the LAD, LCX, and RCA, respectively.

Figure 14.

Comparison of $\log(k_{VM})$ and its errors for different levels of diameter truncations. The bottom, middle and top graphs correspond to the LAD, LCX, and RCA, respectively.

Figure 15.

Errors of the CT computed masses for different levels of diameter truncations. The bottom, middle and top graphs correspond to the LAD, LCX, and RCA, respectively.

Table 1

Summary of the exponents of the morphological relationships.

	β_V	β_M	β_{VM}
LAD	0.76	0.73	0.93
LCX	0.78	0.81	1.02
RCA	0.74	0.85	1.17
Average	0.76	0.80	1.04

Table 2

Summary of micro-CT measurements. Regional myocardial masses at 600 μm are compared to the measured masses.

	LAD	LCX	RCA
Total branch length (cm)	102.60	74.84	61.25
Total lumen volume (cm ³)	4.01	2.47	2.68
Regional CT mass (g)	70.19	55.71	63.54
Regional measured mass (g)	67.90	58.67	64.48
Error of CT mass (%)	3.37	5.05	1.46