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Citation: Medical Physics 40, 091910 (2013); doi: 10.1118/1.4817577
View online: http://dx.doi.org/10.1118/1.4817577
View Table of Contents: http://scitation.aip.org/content/aapm/journal/medphys/40/9?ver=pdfcov
Published by the American Association of Physicists in Medicine

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Automatic quantification of epicardial fat volume on non-enhanced cardiac CT scans using a multi-atlas segmentation approach

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(Received 2 May 2013; revised 2 July 2013; accepted for publication 23 July 2013; published 12 August 2013)

**Purpose:** There is increasing evidence that epicardial fat (i.e., adipose tissue contained within the pericardium) plays an important role in the development of cardiovascular disease. Obtaining the epicardial fat volume from routinely performed non-enhanced cardiac CT scans is therefore of clinical interest. The purpose of this work is to investigate the feasibility of automatic pericardium segmentation and subsequent quantification of epicardial fat on non-enhanced cardiac CT scans.

**Methods:** Imaging data of 98 randomly selected subjects belonging to a larger cohort of subjects who underwent a cardiac CT scan at our medical center were retrieved. The data were acquired on two different scanners. Automatic multi-atlas based method for segmenting the pericardium and calculating the epicardial fat volume has been developed. The performance of the method was assessed by (1) comparing the automatically segmented pericardium to a manually annotated reference standard, (2) comparing the automatically obtained epicardial fat volumes to those obtained manually, and (3) comparing the accuracy of the automatic results to the inter-observer variability.
Results: Automatic segmentation of the pericardium was achieved with a Dice similarity index of 89.1 ± 2.6% with respect to Observer 1 and 89.2 ± 1.9% with respect to Observer 2. The correlation between the automatic method and the manual observers with respect to the epicardial fat volume computed as the Pearson’s correlation coefficient (R) was 0.91 (P < 0.001) for both observers. The inter-observer study resulted in a Dice similarity index of 89.0 ± 2.4% for segmenting the pericardium and a Pearson’s correlation coefficient of 0.92 (P < 0.001) for computation of the epicardial fat volume.

Conclusions: The authors developed a fully automatic method that is capable of segmenting the pericardium and quantifying epicardial fat on non-enhanced cardiac CT scans. The authors demonstrated the feasibility of using this method to replace manual annotations by showing that the automatic method performs as good as manual annotation on a large dataset. © 2013 American Association of Physicists in Medicine. [http://dx.doi.org/10.1118/1.4817577]

Key words: registration, segmentation, pericardium delineation, adipose tissue, computed tomography (CT)

1. INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death worldwide. Epicardial fat is the adipose tissue which is found between the myocardium and the visceral layer of the pericardium, and thus directly surrounds the entire heart as well as the coronary arteries. Increasing evidence implicates epicardial fat in the etiology of CVD. It is thought that through local production of inflammatory factors it may directly contribute to the formation of coronary atherosclerosis. Few studies have found that epicardial fat is associated with cardiovascular risk factors. Other studies have shown that epicardial fat is a dominant factor in case of coronary artery disease. A few population based studies have also been performed. Ding et al. investigated whether epicardial fat is an independent predictor of future heart disease events as compared to conventional risk factors on 998 individuals from the MESA study. Mahabadi et al. quantified epicardial fat volume on 4093 subjects in order to determine if epicardial fat predicts coronary events in the general population.

Several methods for epicardial fat quantification have recently been developed. Most of these methods are completely manual, which is a tedious procedure to perform. The manual methods are also prone to inter and intra-observer variability. The objective of our study is to develop and evaluate a fully automatic method, which can accurately and robustly segment the pericardium and quantify the amount of adipose tissue contained within. To the best of our knowledge, this is the first fully automatic method presented in the literature. Hence, it has the potential to be applied to large scale clinical or population based studies.

Most of the methods described previously require manual delineation of the pericardium, which is subsequently used to quantify the volume of fat. Taguchi et al. traced the epicardial, subcutaneous, and visceral fat. Wheeler et al. used landmark points to initialize the heart segmentation. Rosito et al. traced the pericardium to delineate the heart from the surrounding structures. Ding et al. used a few landmark points around the heart to enclose it in an envelope, similar to the method proposed by Wheeler et al.

More recently, a semi-automatic method was proposed by Dey et al. Their method needs two interactions. First, the user needs to select the top and the bottom slice in between which the heart is contained. Once this is done, the method uses region growing and anatomical information to segment the heart. Second, the user needs to select five to seven control points on the axial slices to pinpoint the location of the pericardium. The degree of interaction of this method is still substantial. Population and clinical studies, as well as clinical workflow, would greatly benefit from a precise and fully automatic method for epicardial fat quantification. Ultimately, findings from such studies could further establish the role of epicardial fat in the development of CVD.

In this paper, we present a method which is able of automatically segmenting the pericardium on non-enhanced cardiac CT scans and subsequently quantifying the epicardial fat volume within the pericardium. Our method uses an atlas-based segmentation approach in order to segment the pericardium. The atlas-based segmentation approach is an adaptation of our previous work, where atlas-based segmentation was evaluated with respect to segmenting the heart and its chambers in a multicenter, multivendor contrast-enhanced CT (CTA) study. Our method was evaluated on 98 CT scans with respect to (1) the accuracy of pericardium segmentation, (2) the accuracy of epicardial fat quantification, and (3) accuracy of the results with respect to the inter-observer variability. The evaluation was conducted by comparing the performance of our method to two independent manual observers.

The remaining of the paper is organized as follows. Section 2 gives details about the imaging data, overview of our method and the experiments we performed. We present our results in Sec. 3, discussion and future work in Sec. 4, and finally the conclusion is provided in Sec. 5.

2. MATERIAL AND METHODS

2.A. Study population and imaging protocol

For this study, we randomly selected 98 subjects from the population-based Rotterdam Study, who underwent a multi-detector computed tomography (MDCT) scan of the heart. This study was part of a larger MDCT-project involving
Table I. Characteristics of the subjects (n = 98). Values are mean ± SD for continuous variables and numbers (%) for dichotomous variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>46 (46.9%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.4 ± 5.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 ± 3.9</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>147.8 ± 22.3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82.2 ± 11.1</td>
</tr>
<tr>
<td>Smoking (ever)</td>
<td>69 (70.4%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (7.1%)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.8 ± 0.9</td>
</tr>
</tbody>
</table>

calcium-scoring in multiple vessel beds. The participants were scanned on two different generations of Siemens scanners [Sensation 16 (n = 55) or Sensation 64 (n = 43), Siemens Medical Solutions, Forchheim, Germany]. The cardiac scan ranged from the apex of the heart to the tracheal bifurcation. The Rotterdam Study was approved by the Institutional Review Board with additional specific approval of the CT study. All participants gave written informed consent for the CT examination.

Subject characteristics are provided in Table I. Scan settings were as follows. The scan reached from the apex of the heart to the tracheal bifurcation, no contrast material was used. On the 16-slice scanner, consecutive nonoverlapping 3.0 mm thick slices were acquired within a single breath hold. The collimation was 12 × 1.5 mm, the tube voltage was 120 kV, the effective tube current 30 mAs, and prospective ECG triggering at 50% of the cardiac cycle was used. For the 64-slice scanner, all parameters except the collimation and tube current changed. Collimation was set to 32 × 0.6 mm and the tube current was adopted with respect to the body weight (CARE DOSE, Siemens, Forchheim, Germany) with a reference value of 50, 100, and 190 mAs. The images from both scanners were reconstructed with a 3.0 mm increment and an average field of view (FOV) of 180 mm. The images were reconstructed with a matrix of 512 × 512 using a b35f (medium sharp) kernel, and contained on average 52 slices.

2.B. Method overview

The quantification method consists of two steps: (1) pericardium segmentation, and (2) epicardial fat volume quantification. For pericardium segmentation, we used a multi-atlas segmentation approach, as described in the work of Kiriçi et al.20 In this approach, manually segmented CTA scans (atlases) are registered to the subject’s CT scan. The segmentations of these atlases are mapped onto the subject’s scan to be analyzed. The mapped segmentations from each of the atlases are fused to obtain the final pericardium segmentation. This whole procedure is fully automatic. The epicardial fat is subsequently quantified by applying a threshold of −200 to −30 HU (Ref. 23) to the segmented pericardium, followed by connected component analysis. Details with respect to the atlases used, the registration approach, and the fat quantification are presented in the sections 2.C, 2.D, and 2.E. Figure 1 shows an overview of all the steps involved in the automatic method.

2.C. Atlas selection and surface computation

CTA scans were used as atlas images because of their higher resolution and the better visibility of the cardiac chambers (due to the presence of contrast material). This enables the observers to accurately delineate the pericardium.
FIG. 2. The eight pericardium atlas surfaces used for atlas-based segmentation illustrating the encountered shape and size variations in the atlas images.

FIG. 3. (a) A random axial slice showing the result of a manually obtained whole heart segmentation (with adjusted windowing level, for better visibility). (b) Corresponding slice showing the voxels containing epicardial fat.

2.D. Multi-atlas based segmentation

Multi-atlas segmentation is a process in which multiple atlas images with corresponding manually annotated label images are individually registered to the subject scans. The segmentation of the subject scans is then obtained by fusing all the resulting transformed label images. In this work, we use majority voting to fuse the label images.

Image registration is used to spatially align the atlas scans and the subjects scan. In the registration procedure, the transformation parameters $T$ that minimizes the cost function $C$ between the fixed image ($I_f$) and the a moving image ($I_m$) are determined. Detailed information on registration is provided in Refs. 27 and 28.

The registration steps and the parameters are explained in more detail in Sec. 2.H, where we also compare the performance of registration with and without masking certain areas of the image.

The resulting transformations from the registration steps are used to map each of the eight atlas surfaces onto the subject’s scan. Once this is done, the 3D surface intensities are converted to binary masks and majority voting is applied to obtain the final pericardium segmentation (see Fig. 1 for a visual representation).

2.E. Epicardial fat quantification

The automatically obtained segmented pericardium is used as a region of interest (ROI) to quantify the adipose tissue voxels. A threshold window of $-200$ to $-30$ HU is applied to obtain the adipose tissue. A connected-component analysis is subsequently applied to all adipose tissue voxels using an 18-neighborhood rule, in order to remove regions smaller than 10 voxels ($2.8$ mm$^3$) in size, which we consider to be noise.

2.F. Reference standard

Two experienced observers (D.B. and A.R.), blinded to the patient information as well as to the results of each other, manually traced the pericardium in each of the CT scans, as shown in Fig. 3(a). A dedicated tool implemented in MeVisLab (Ref. 30) was used by the observers for manual annotations. Once the pericardium was delineated, a threshold window of $-200$ to $-30$ HU was applied to the segmented region. Adipose tissue voxels were then automatically extracted using connected-component analysis and the volume of fat in milliliters (ml) was computed. The reference standard obtained this way contains both pericardium segmentations and epicardial fat volume quantifications [Fig. 3(b)].

2.G. Statistical analysis

We report the Dice similarity index and the mean surface distance error between the pericardial heart segmentation by the automatic method and each of the manually obtained segmentations. To evaluate the performance of the fat quantification method per patient, Pearson’s correlation coefficient ($R$) was calculated, linear regression was performed, and
Bland-Altman plots were created. Furthermore, the accuracy of the method was compared to the interobserver variability. The analyses were performed using MATLAB version 7.9.0. (The MathWorks, Natick, MA) and IBM SPSS Statistics version 20 (IBM Corp, Armonk, NY).

2.H. Experiments

Our method consists of segmenting nonenhanced CT scans with the help of contrast-enhanced CT atlas scans. The registration problem we face here is that the fixed image \((I_f)\) and moving image \((I_m)\) have different characteristics, both in terms of contrast and resolution. The CT scans in which we aim to quantify the epicardial fat has an average in-plane resolution of \(0.35 \times 0.35 \text{ mm}^2\) and a slice thickness of 3.0 mm, whereas the CTA atlases have an average in-plane resolution of \(0.32 \times 0.32 \text{ mm}^2\) and a slice thickness of 0.4 mm. In order to obtain the optimal parameters to register the CTA atlases and the CT subjects, we performed pilot experiments on a subset of 35 randomly selected CT datasets. Two registration strategies were investigated and the segmentation results were compared to the results of one of the observers. In both strategies, the CTA atlas was used as the fixed image \((I_f)\) and the subjects CT scan was used as the moving image \((I_m)\).

Table II. Table representing the results of the registration strategy. Values represent mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Strategy 1</th>
<th>Strategy 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dice similarity index %</td>
<td>90.0 ± 3.2</td>
<td>89.6 ± 1.9</td>
</tr>
<tr>
<td>Mean surface distance mm</td>
<td>3.4 ± 1.3</td>
<td>3.5 ± 0.8</td>
</tr>
</tbody>
</table>

Strategy 1: The similarity metric was computed by randomly sampling intensity values from the whole image.
Strategy 2: The similarity metric was computed by randomly sampling intensity values within the heart region only (by using a fixed heart mask).

For both strategies, a two-stage registration approach was used. In the first stage, an affine transformation was used. In the second stage, a non-rigid registration using a B-spline transformation was employed while using the results of the affine transformation to initialize the registration. Mutual information was used as similarity measure for the cost function. Optimization was performed using adaptive stochastic gradient descent, the number of voxels sampled in each iteration was set to 2048, and the number of iterations were set to 512 for the affine transformation and 2048 for the B-spline transformation. For further details about parameter selection and optimizations, readers are referred to our previous study. All registrations were performed using Elastix, a publicly available software package.

The heart mask was used in both stages of the registration approach. The main purpose of using the fixed mask was to prevent the registration to be affected by tissues surrounding the heart, such as the lungs, rib cage, and the vertebra. Figure 4 shows a random axial slice of one of the fixed masks used for the registration optimization. The mask was created by dilating the original manually annotated pericardium by 1 cm. The masks were created once, only for the atlas scans and not the subject scans. Hence, called the fixed mask.

Table II shows the results obtained for both the strategies. It can be observed that the average accuracy of both strategies was very similar in terms of the mean, but using the mask resulted in a smaller standard deviation. It was also confirmed visually that the accuracy of finding the pericardium using Strategy 2 was better than when using Strategy 1. Further experiments on the entire dataset were thus performed using the registration with the mask.

3. RESULTS

3.A. Agreement between the automatic method and the observers

A visual check showed that 95 out of 98 segmentations were successful. Three segmentations failed due to registration errors caused by anatomical and FOV variations. These scans were excluded from further analysis.

The subjects had an average fat volume of 101 ± 38 ml according to Observer 1 and 113 ± 43 ml according to Observer 2. The automatic method found the average fat volume to be 102 ± 34 ml. A Dice similarity index of 89.1% and 89.2% was obtained between the automatic segmentation and each of the manual segmentations, respectively. The mean surface distance between the automatically derived cardiac surface and the observer segmentations was 3.8 ± 1.1 mm and 3.5 ± 0.7 mm, respectively. A Pearson correlation \(R\) of 0.91 \((P \leq 0.001)\) was obtained for fat quantification results between the automatic segmentation and each of the manual segmentations. The mean absolute difference between the
FIG. 5. Scatter plots of automatic vs manual fat quantification methods and results from linear regression: (a) correlation between the two observers; (b) correlation between Observer 1 and the automatic method; and (c) correlation between Observer 2 and the automatic method.

automatic method and each of the manual segmentations with respect to the amount of quantified fat was 11.6 ml and 16.6 ml, respectively. The linear regression plots are shown in Fig. 5. The numbers obtained from the Bland–Altman analysis and the confidence intervals of the linear regression are shown in Table III with a graphical representation in Fig. 6. It can be noted that the bias from the Bland–Altman analysis with respect to Observer 1 is almost zero and the automatic method slightly overestimates the volume of epicardial fat as compared to Observer 2.

3.B. Interobserver agreement

An average Dice similarity coefficient of 88.9% was found between the segmentations of the observers. The mean surface distance between the two observers was 4.3 ± 1.0 mm over all datasets. With respect to the amount of quantified epicardial fat, the mean absolute difference between the two observers was 15.6 ml, and the Pearson correlation coefficient was 0.92 ($P < 0.001$). A Bland–Altman analysis of the data showed that the limits of agreement were between −45.3 and 21.3 ml and a bias of 12.1. Figures 5 and 6 show the correlation graph and the Bland–Altman analysis.

4. DISCUSSION

In this study, we presented a fully automatic method for epicardial fat quantification. The method is based on automatic pericardium segmentation. A good correlation with manual quantification was observed, with differences very similar to the inter-observer variability.

The Dice similarity index (overlap area) between the automatic pericardium segmentation and each of the manual annotations was slightly better than the inter-observer Dice similarity coefficient. The mean surface distance error between the automatic and manual segmentations corresponds to 1.5 voxels in the slice direction, which can be considered small. When the actual amount of fat volume quantified using our method was compared to each of the observers, it resulted in a mean absolute difference of 11.6 ml and 16.6 ml, respectively. This difference in volume is very close to the inter-observer agreement, which was 15.6 ml. The same conclusion can be drawn from the correlation coefficient $R$.
TABLE III. Performance of the whole heart segmentation: comparing the automatic method to each of the observers and the observers to each other.

<table>
<thead>
<tr>
<th>Segmentation measures</th>
<th>Automatic vs Observer 1</th>
<th>Automatic vs Observer 2</th>
<th>Observer 1 vs Observer 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dice similarity index (mean ± SD) %</td>
<td>89.1 ± 2.6</td>
<td>89.2 ± 1.9</td>
<td>88.9 ± 2.5</td>
</tr>
<tr>
<td>Mean surface distance (mean ± SD) mm</td>
<td>3.8 ± 1.1</td>
<td>3.5 ± 0.7</td>
<td>4.3 ± 1.0</td>
</tr>
<tr>
<td>Quantification measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation R</td>
<td>0.91</td>
<td>0.91</td>
<td>0.92</td>
</tr>
<tr>
<td>Linear regression (CI for $\beta$)</td>
<td>0.75–0.90</td>
<td>0.65–0.79</td>
<td>0.96–1.15</td>
</tr>
<tr>
<td>Bland-Altman bias (95% CI)</td>
<td>$-0.8$ (–31 to 29)</td>
<td>11.3 (–25 to 47)</td>
<td>12.1 (–21 to 45)</td>
</tr>
</tbody>
</table>

obtained with respect to the quantified fat volume of the automatic method and the manual observers.

Compared to the existing quantification methods, our method is the first that is fully automatic. The methods proposed in Refs. 8 and 13–17 either use manual tracings of the different tissue types, or a manual approach to delineate the pericardium, before quantifying the adipose tissue voxels. This is a tedious and time-consuming task to perform. The semi-automatic method proposed in Refs. 18 and 19 needs two interactions, which could limit the use of the method in processing a large number of datasets in an epidemiologic setting.

The three subjects that were excluded from the analysis had the following issues: one subject underwent pneumonectomy (removal of a lung) causing a very unusual position of the heart [see Fig. 7(a)], the other had a heart shape

![Fig. 6. Bland–Altman analysis: (a) between observers; (b) between automatic method and Observer 1; and (c) between automatic method and Observer 2.](image)
anatomically quite different from the others [see Fig. 7(b)], and the last one had a different field of view compared to the atlas scans used. The large difference between the atlas scan and the subject scan caused the registration to fail, which resulted in erroneous segmentation of the pericardium.

There has been some confusion in the literature between the nomenclatures of the adipose tissue contained within the pericardium; some studies call it epicardial fat tissue, whereas others call it pericardial fat tissue. Based on the definition provided here, we decided to denote the adipose tissue contained within the pericardium as epicardial fat. In short, in this definition epicardial fat is the adipose tissue between the myocardium and the visceral layer of the pericardium.

We did not investigate to what extent the method can be used on multiple scanner types; in this study, we only demonstrated the feasibility of using the method on two generations of Siemens scanners. However, as our method is based on multi-atlas segmentation, we are confident that the same approach would work on other scanner types, as long as the subject scans and the atlas scans have a similar field of view. It has been demonstrated in our previous study, that atlas-based segmentation of the pericardium was performed with a similar accuracy with respect to multivendor/multicenter CTA datasets. If required, the method could utilize atlas scans from the same scanner.

In the current setup, visual inspection was still required to check the accuracy of the pericardium segmentation, which resulted in discarding the three scans on which the segmentation failed. Instead of discarding these scans, or in case of small failures, manual correction before fat quantification is an option. We did not integrate this in our protocol, as the results were sufficiently accurate without adaptation.

5. CONCLUSION

We developed and evaluated an automatic method for pericardium segmentation and subsequent epicardial fat quantification. We demonstrated that our automatic approach achieved good correlation to manual quantifications. The automatic method described in this paper could potentially be used on large clinical or population studies in order to investigate the relationship between epicardial fat volume and CVD.

ACKNOWLEDGMENTS

Rahil Shahzad and Hortense Kirisli are supported by a grant from the Dutch Ministry of Economic Affairs (AgentschapNL) under the title “Het Hart in Drie Dimensies” (PID06003). Coert Metz and Theo van Walsum are supported by a grant from the Information Technology for European Advancement (ITEA), under the title “Patient Friendly Medical Intervention” (project 09039, Mediate). Stefan Klein is supported by a grant from the Netherlands Science Organisation (NWO), division of Exact Sciences (project 639.021.919).

Fig. 7. Excluded subjects: (a) subject with lung removed and (b) segmentation leaking into the ribcage due to rare anatomical variation in heart shape.


