Growth Pattern of Atherosclerotic Calcifications

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\textbf{Abstract.} We present a novel method to analyze the growth of abdominal atherosclerotic plaques based on x-ray projections. The growth analysis can aid progression monitoring in clinical trials and in population screening programs. Our results are based on a longitudinal study over 8.5 years. The annotations of the calcifications are matched longitudinally using thin plate spline registration and area overlap calculations. The growth of the calcifications is measured by the distribution of the geometry statistics of the calcifications. The method was evaluated on 135 subjects with a total number of 611 calcifications. Our results show, for instance longitudinal growth of calcifications with a mean of 2.53 mm (\(\pm 1.95\)) in the blood flow direction and correlations with pathologically related biomarkers.

\section{Introduction}

Atherosclerosis is a primary cardiovascular disease (CVD), that is the main cause of the disease burden (illness and death) in Europe. The cost of CVD is estimated to 192 billion euro per year spread out on direct health care, productivity losses and informal health care [1]. Atherosclerosis is a chronic inflammatory process that builds up plaque in the intimal wall of the arteries. Atherosclerosis starts in the childhood and progresses during adolescence as development of fatty streaks, that evolves to fibrous caps and lastly formation of calcifications, which could lead to ruptures possibly resulting in strokes and heart attacks. Calcifications are widely used as a clinical indicator of atherosclerosis [2, 3].

X-ray imaging is an attractive image modality for quantification of calcifications that can aid in large scale clinical trials and screening programs due to the low cost, fast examination and non-invasiveness. Other image modalities such as intravascular ultrasound, computed tomography and magnetic resonance imaging have also been used for studies of the atherosclerotic growth [4–6], but to a smaller extent due to the cost and the patient discomfort. Available x-ray data already exist from clinical trials and routine screening for osteoporosis, which can be used for identifying the growth pattern of calcifications.

Our hypothesis is that the growth patterns are good estimators of the progression of atherosclerosis. The gold standard severity score for atherosclerotic calcifications is the AC24 score introduced by the Framingham group. AC24 is
quantifying the amount of calcification only as the amount along the arterial wall [7, 8]. To our knowledge this is the first study that characterize the growth patterns of atherosclerotic calcifications from x-ray projections. Our region of interest is the lumbar region denoted by L1-L4. The amount of calcified deposit in L1-L4 can be an indicator of the risk of future cardiovascular events [9]. The annotations of the calcifications are registered by thin plate spline registration and then a suitable match is found using area overlap. Now we extract information of the individual calcifications about the growth patterns.

In this work we have used manual annotations of the images by radiologists, but an automated segmentation method [9] could be used instead, which would be cost-saving and minimize the degree of subjectivity.

In the next section we describe our dataset and then we give a brief overview of the thin plate spline algorithm and a description of our registration and matching process. We then describe the statistical geometry used to characterize the growth patterns. Finally we present our results and we discuss the validity of the method used in respect to well-known biomarkers of the pathology.

2 The Dataset

The dataset consists of 135 women with mean age 62.4 (± 7.0) and mean BMI 24.3 (± 4.0) at the initial scanning. The patients in our dataset had x-ray images taken twice, once in 1992 (baseline) and again in 2000/2001 (follow-up) as part of an osteoporosis study. The images are lateral x-ray projections, which were digitalized with a Vidar DosimetryPro Advantage scanner with a pixel size of 44.6 × 44.6 µ. The images were scanned at the Center for Clinical and Basic Research (CCBR) in Copenhagen. The annotations of the images were done by three trained radiologists from CCBR. The annotations include six points of each vertebrae L1-L4, the posterior and anterior aorta wall and the calcified deposits, that were included if a dense area was visible in an area parallel to the lumbar spine; an example can be seen in Fig. 1. From the dataset 103 patients had baseline calcifications with an average of 4.8 (± 8.1) calcifications.

3 The Registration

The position in the scanner and the anatomy of the patients have changed in between the x-ray images. The calibration of the scanner also differs. This causes a significant variability in the position of the vertebrae and the aorta. Due to these combined variabilities image registration is needed to be able to extract the biological information about the growth of the calcifications. The registration is used to align the aorta and thereby the calcifications in the follow-up image to the baseline image. We use thin plate splines (TPS) for the registration [10]. Thin plate splines form a class of non-rigid mapping functions that are globally smooth. This makes them desirable for registering the deformable aorta and thereby the calcifications. We want to make predictive growth patterns from the baseline information by use of the follow-up information. TPS is non-symmetric
Fig. 1. The follow-up image (right) and the baseline image (left), where the aorta from the follow-up is registered to the baseline aorta. Blue are the original annotations of the structures and green are the registered annotations of the follow-up aorta on the baseline. Note that the registered follow-up aorta is well aligned with the baseline aorta.

in source and destination, so we need to register from follow-up to baseline, see Fig. 1. TPS map the corresponding set of landmarks so they minimize the bending energy. The landmarks we have used are the intersections between the line through the vertebrae annotations and the anterior/posterior aorta wall. Since the alignment in the registration could bias the analysis of the position and growth of the calcifications, the calcifications are unsuitable as landmarks. The mapping function $f$ for the follow-up annotations $(x, y) \in \mathbb{R}^2$ is given by

$$f(x, y) = a_1 + a_x x + a_y y + \sum_{i=1}^{N} w_i U(||(x_i, y_i) - (x, y)||),$$  

(1)

where $(x_i, y_i)$ are the landmarks from baseline and $r = ||(x_i, y_i) - (x, y)||$ is the Euclidean distance. $a_1 + a_x + a_y$ are affine motion coefficients, $w_i$ are the weights for the combination of the distance measurements for the correspondence points and the thin plate splines. $U(r) = r^2 \log(r^2)$ is the radial basis function.

4 Matching

After the follow-up image is warped into the baseline image, we need to find the matching of individual calcification from the pair of images. We have matched the calcifications based on area overlap $AO$ between the baseline and follow-up.

$$AO = \frac{|A_{baseline} \cap A_{follow-up}|}{|A_{baseline} \cup A_{follow-up}|}$$  

(2)

The area overlap is a suitable method for matching, because it captures the matching calcifications without any assumptions of a certain shape of the calcifications. Alternatively we could have matched using nearest center of mass calculations. This method would need a threshold for the maximum distance
allowed between the possibly matching center of masses, which could bias the result. Ongoing research have not yet clarified how the calcifications emerge, grow together, rupture or get reabsorbed. Due to lack of knowledge of the behavior of the growth of the calcifications, more complicated matching methods with prior information about splitting, merges, creation or clearance of calcifications are likely not able to increase the quality of the matching without biasing the resulting growth pattern. We have based our growth descriptors on one-to-one correspondence; where there is only found one area overlap between the baseline and follow-up calcifications, see Fig. 2. The one-to-one correspondence ensures that no bias effect in the interpretation of how a one-to-many or many-to-one correspondence is created.

5 The Growth Measurements

The growth of the calcifications can be measured in three different biologically meaningful directions; longitudinal (in the blood flow direction), circumferential (around the aorta) and radial (the direction into the aorta).

Our hypothesis is that these directions can give good indicators of the growth pattern. The longitudinal growth would give an idea of whether the calcifications are making the aorta wall more stiff, due to calcifications occupying a longer part of the aorta wall. We have measured the longitudinal growth as the change in height of the calcifications. The x-ray attenuation makes the calcifications on the anterior/posterior sides of the aorta wall most visible in the x-ray images. This makes us capable of measuring the radial growth as the change in width of the calcifications. The area of the calcifications could give information about the overall growth of the calcifications. The area of the calcifications combines contributions from the circumferential and radial directions, due to the 2D projection. Because of the x-ray attenuation, the area will be based mainly on the radial and longitudinal direction.

To measure the overall growth direction we calculate the difference in the center of mass of the matched calcifications. This way we should get an identifier of the longitudinal growth direction. The difference in center of mass could also

![Fig. 2. An example of the matched calcifications. Blue shows the annotations of the vertebrae and the aorta wall. Red are the baseline calcifications and green are the follow-up calcifications. Note that the area overlap is a good indicator of the matching calcifications.](image)
give an indicator of the radial growth direction, but we have to keep in mind that calcifications on the anterior and posterior aorta walls both grow towards the center of the aorta; causing the mean change in the radial direction to be canceled out by the movements in opposite directions.

The knowledge of the directions in the aorta is an important indicator of the growth pattern, because the growth needs to be measured in an aorta coordinate system. We have assumed that the y-direction in the images corresponds to the longitudinal direction and the x-direction to the radial direction which is a simple approximation to the aorta coordinate system. In future work the growth patterns will be based on the shape of the aorta.

Measurements of the shape of the calcifications in any direction using shape models or moments will be hard to interpret without biasing the growth patterns due to the projections into 2D and the correspondence to the aorta coordinate system. We have chosen to use the least committed method to avoid influence of artifacts in our method. The height $H$ of a calcification is therefore simply measured as:

$$H = \max(y_1, \ldots, y_i) - \min(y_1, \ldots, y_i),$$

where $y_i$ is the y-coordinate of the $i$'th boundary point of the calcification.

We have based the width of the calcification on the local width to avoid overestimation due to the curvature of the aorta. The width calculation is based on a modified scan-line algorithm [11], that finds the width for each scan-line through the calcifications and then chooses the maximal local width as the width of the calcification. The area of a calcification [12] is measured as:

$$A = \frac{1}{2} \sum_{i=1}^{n} (x_i y_{i+1} - x_{i+1} y_i),$$

where $(x_i, y_i)$ are the $i$'th boundary point of a calcification and $n$ is the total number of annotation points. The center of mass (CM) of the calcification is calculated as the position of the calcification in the aorta. This way we can describe the growth direction based on differences in the center of mass position for the matched registered calcifications. We assume the mass density is uniform and then by use of Green’s theorem the CM is given by 5, where $A$ is the area and $(x_i, y_i)$ is the $i$'th annotation of the calcification [12]:

$$CM_x = \frac{1}{6A} \sum_{i=1}^{n} (x_i + x_{i+1})(x_i y_{i+1} - x_{i+1} y_i)$$

$$CM_y = \frac{1}{6A} \sum_{i=1}^{n} (y_i + y_{i+1})(x_i y_{i+1} - x_{i+1} y_i)$$

6 Validation of Matching

The total number of calcifications at baseline is 611 and the number increases to 1321 at follow-up. We have been able to match 32.4% of the baseline calcifications to one corresponding follow-up calcification. This is in respect to 16.4% one-to-many correspondences (the calcifications may have grown together) and to 8.7% many-to-one correspondence, and 42.4% where no correspondence were
Table 1. The mean and standard deviation of the area, height and width of the unmatched and matched calcifications in mm. †=p < 0.1, *=p < 0.05, **=p < 0.01 and ***=p < 0.001 on a unpaired t-test between the unmatched and matched calcifications and a paired t-test for the growth. Note that the matched calcifications is a little larger than the total number of calcifications and that the calcifications grows significantly in area, height and width and the position of the calcifications in the aorta is moved in the blood flow direction.

<table>
<thead>
<tr>
<th></th>
<th>Unmatched Baseline</th>
<th>Unmatched Follow-up</th>
<th>Matched Baseline</th>
<th>Matched Follow-up</th>
<th>Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area (mm²)</td>
<td>172** (± 199)</td>
<td>211*** (± 313.57)</td>
<td>205 (± 206)</td>
<td>325 (± 317)</td>
<td>120*** (± 240)</td>
</tr>
<tr>
<td>Height (mm)</td>
<td>5.02** (± 3.75)</td>
<td>5.76*** (± 4.81)</td>
<td>5.81 (± 3.55)</td>
<td>8.35 (± 5.26)</td>
<td>2.53*** (± 4.33)</td>
</tr>
<tr>
<td>Width (mm)</td>
<td>2.12† (± 1.20)</td>
<td>2.23* (± 1.35)</td>
<td>2.17 (± 1.24)</td>
<td>2.46 (± 1.45)</td>
<td>0.29** (± 1.32)</td>
</tr>
<tr>
<td>Cx (mm)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.91*** (± 0.81)</td>
</tr>
<tr>
<td>Cy (mm)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-2.02*** (± 1.95)</td>
</tr>
</tbody>
</table>

found. In an intra/inter observer study of the manual annotations, the radiologists have area overlaps of 40-60 % of the calcifications. The relative low reproducibility in the annotations could account for a large number of the non-matched calcifications. The average size of the matched calcifications is a little larger than the average baseline calcification - e.g. mean height of unmatched and matched baseline calcifications are 5.02 mm and 8.35 mm respectively. This is due to difficulties in matching the smaller registered calcifications and the increased activity in the growth of the new and smaller calcifications. Tab. 1 shows mean and standard deviations for heights, widths and areas of the unmatched and matched calcifications.

7 Characterizing the Growth of the Calcifications

The linear correlation coefficients for unmatched and matched calcifications for the height, width and area can be seen in Tab. 2. Intuitively there are correlations between growth in area and growth in height and width. Our results also show a correlation between growth in width and height, indicating that calcifications grow both longitudinally and radially.

The characteristica of the growth of the calcifications can be seen in Tab. 1, based on signed values. The results show that the matched calcifications are growing longitudinally with a mean growth of 2.53 mm (± 4.33). This is an increase of 50.4 %. The mean growth in the radial direction is 0.29 mm (± 1.70), corresponding to 13.7 %, see Fig. 3. The center of mass is moved 2.02 (± 1.95) mm in the longitudinal direction, see Fig. 3. The absolute anterior/posterior center of mass movement is 0.91 (± 0.81) mm in the absolute inside radial direction. This indicate that more calcifications are placed on the anterior wall or the calcifications are growing towards the posterior wall.
We have correlated our growth patterns with known biological risk factors [13], see Tab. 3. A high cholesterol or triglyceride level correlates with growth in width and area of the calcifications. High glucose level correlates with growth in area and height of the calcifications.

8 Discussion and Future Work

The registration and matching process is necessary to describe the growth patterns for the calcifications and especially the growth direction, measured by change in the center of mass. Our results show that the calcifications grow longitudinally and the center of mass is moved with the blood flow. The calcifications will occupy more of the aorta wall as they grow. The calcifications grows downward the aorta, which could be caused by the turbulence in the direction of the blood flow, when the aorta wall becomes non-smooth, due to the existing calcifications.

Our results show that high cholesterol and triglyceride levels correlate with growth in width of the calcifications. This could correspond to intimal calcifications that likely are related to cholesterol and lipids that induce atherosclerosis [14]. A high glucose level correlates mainly to growth in heights possibly corresponding to the elongated medial calcifications observed in diabetes patients [2]. Glucose is a main factor of growth of all types of calcifications, which

Table 2. The linear correlation coefficient of the width, height and area of the matched and non matched calcifications. The correlations are all significant with $p < 0.001$. Note that there is correlation between height and width indicating that the calcifications grow longitudinally and radially.

<table>
<thead>
<tr>
<th>Correlation coefficient</th>
<th>Width vs. Height</th>
<th>Width vs. Area</th>
<th>Height vs. Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (unmatched)</td>
<td>0.5156</td>
<td>0.7664</td>
<td>0.8587</td>
</tr>
<tr>
<td>Follow-up (unmatched)</td>
<td>0.5240</td>
<td>0.7443</td>
<td>0.8256</td>
</tr>
<tr>
<td>Baseline (matched)</td>
<td>0.3412</td>
<td>0.7391</td>
<td>0.8062</td>
</tr>
<tr>
<td>Follow-up (matched)</td>
<td>0.2701</td>
<td>0.7340</td>
<td>0.7380</td>
</tr>
<tr>
<td>Growth</td>
<td>0.2302</td>
<td>0.6753</td>
<td>0.7053</td>
</tr>
</tbody>
</table>
Table 3. The linear correlation between our growth patterns and the biological risk factors; \( * = p < 0.05, ** = p < 0.01 \) and \( *** = p < 0.001 \). Note correlation between area/width and cholesterol, area/height and glucose and area/height and triglyceride.

<table>
<thead>
<tr>
<th>Correlation coefficient and p-values</th>
<th>Cholesterol</th>
<th>Glucose</th>
<th>Triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth in area</td>
<td>0.21*</td>
<td>0.33**</td>
<td>0.21*</td>
</tr>
<tr>
<td>Growth in height</td>
<td>0.15</td>
<td>0.39**</td>
<td>0.22*</td>
</tr>
<tr>
<td>Growth in width</td>
<td>0.26**</td>
<td>0.20†</td>
<td>0.18†</td>
</tr>
</tbody>
</table>

can also be seen in the correlation.

At this point we can describe clinically meaningful growth patterns of the atherosclerotic plaques. More work will be based on modifying the growth patterns and get correlations with the different characteristic biomarkers. We will also try to further distinguish the growth pattern of medial and intimal calcifications [14] in our future growth patterns. We have shown that registration and plaque matching based on x-ray images can give a good description of the growth patterns, which indicates the ability for a simple and low cost method to measure the longitudinal progression of atherosclerosis.

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References

1. European Heart Network (EHN): http://www.ehnheart.org/content/