Quantifying Calcification in the Lumbar Aorta on X-Ray Images

Lars A. Conrad-Hansen[2], Marleen de Bruijne[1,2], François Lauze[2], László B. Tankó[3], Paola C. Pettersen[3], Qing He[3,4], Jianghong Chen[3,4], Claus Christiansen[2,3], and Mads Nielsen[1,2]

[1] Department of Computer Science, University of Copenhagen, Denmark
[2] Nordic Bioscience A/S, Herlev, Denmark
[3] Center for Clinical and Basic Research A/S, Copenhagen, Denmark
[4] Department of Radiology, Beijing Friendship Hospital, China

Abstract. In this paper we propose to use inpainting to estimate the severity of atherosclerotic plaques from X-ray projections. Inpainting allows to "remove" the plaque and estimate what the background image for an uncalcified aorta would have looked like. A measure of plaque severity can then be derived by subtracting the inpainting from the original image. In contrast to the current standard of categorical calcification scoring from X-rays, our method estimates both the size and the density of calcified areas and provides a continuous severity score, thus allowing for measurement of more subtle differences.

We discuss a class of smooth inpainting methods, compare their ability to reconstruct the original images, and compare the inpainting based calcification score to the conventional categorical score in a longitudinal study on 49 patients addressing correlations of the calcification scores with hypertension, a known cardiovascular risk factor.

1 Introduction

Atherosclerosis forms the basis of coronary-heart diseases that may culminate in myocardial infarct, stroke, and sudden death [9]. Various studies demonstrate that calcific deposits in the abdominal aorta have an independent predictive value for estimating the risk of future cardiovascular events [9,12,10] and that aortic calcification is a good indicator for the presence of atherosclerosis in coronary arteries [4]. The medical expert consensus is that vascular imaging is vital for monitoring the severity and progression of atherosclerosis in both clinical practice and clinical trials [4,9].

An attractive modality suitable for large scale clinical trials is common lateral X-ray imaging. Although several other modalities can be used for the assessment of atherosclerotic plaque, including ultrasound (US), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) [13,9], none of these seems particularly well suited for large scale studies because of the time and costs involved. In addition, common X-rays are already routinely used for the assessment of vertebral fractures in clinical trials for osteoporosis, and a large amount of "historical" data is therefore readily available (see for instance [7]).

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For the assessment of atherosclerotic plaque in the aorta, the lumbar region denoted by the L1-L4 vertebrae is a natural choice as the region of interest, since bifurcation of the lumbar aorta that is mostly located at the L4 level [13,5] is a known predilective site of atherosclerosis. Early development of plaques at this site is mainly due to the turbulent fluid dynamics, directly contributing to vascular damage and the deposition of atherogenic metabolites in the vessel wall [13]. The natural progression of atherogenesis and development of calcified deposits expands from distal to the more proximal regions (i.e. L4 to L1).

This led Witteman et al. [11] to develop a semi-quantitative scoring system measuring the longitudinal extent of the plaque areas in the L1-L4 region. This scheme was developed further in 1997 by Kauppila et al. [5], which still constitutes the current practice of assessing the amount of calcification on lateral 2-D X-ray [5,6]. In this scheme the calcifications are measured longitudinally for the posterior as well as anterior walls at each aortic segment adjacent to the first four lumbar vertebrae, using the midpoint of the intervertebral space above and below the respective vertebra as segment boundaries. Each of the eight wall segments is then scored a 0 (uncalcified), 1 (up to 1/3 of the length of the segment calcified), 2 (between 1/3 and 2/3 calcified) or 3 (completely calcified). The scores are summed into a 24-score reflecting the anterior - posterior severity which will in the course of this paper be referred to as the AC24 score (see [5] for details). The categorical nature of this AC24 score makes the detection of subtle changes of atherogenesis difficult over shorter periods of time (< 3 years).

In this paper we propose to quantify the severity of an atherosclerotic plaque by comparing the observed image intensity to the image intensity that would be expected if the aorta were uncalcified. First, all calcified areas in the L1-L4 region are segmented. In this work we have used manual annotations by radiologists, but automated segmentation methods could be used instead [1]. Subsequently, the "healthy" aorta appearance is reconstructed by interpolating the background image around the calcification using inpainting techniques. Plaque density can then be estimated by subtracting this inpainting from the original X-ray. This paper presents a more elaborate validation in a longitudinal setting of the methods previously presented in [3].

The paper is organized as follows. In the next section we present the inpainting and the resulting scoring method and in Section 3 we discuss validation of the new scoring method. In Section 4 we present results. Conclusions are drawn in Section 5.

2 Inpainting Based Calcification Scoring

Inpainting

Given an area of an X-ray where a calcification is present, can we estimate what the signal would have looked like without the calcification, i.e. at an hypothetical baseline when atherosclerosis had not started? Assuming that the plaque is superposed to the aortic wall, from the additive nature of the X-ray attenuation coefficients, subtracting the estimated signal from the original should ideally

result in the calcific deposit signal. This is illustrated in Fig. 1. The simulated non-calcified baseline image is created by inpainting the calcified areas. The hope is that such a measure not only allows for assessing minor plaque progression, but also offers a possibility to make a statement about the plaque density.

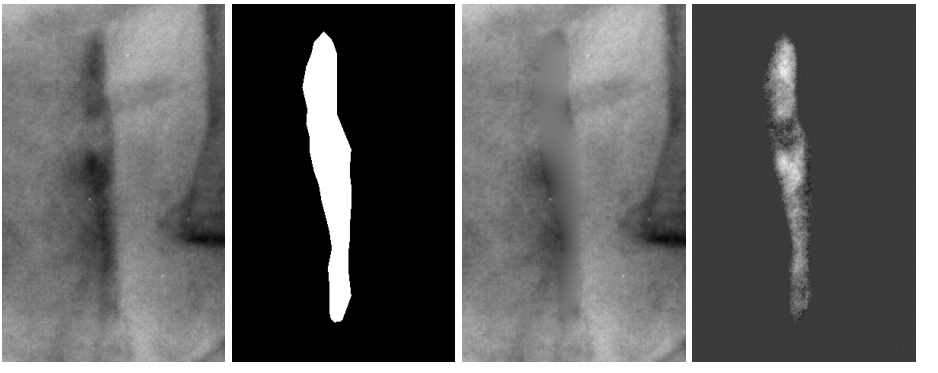

Fig. 1. Quantification methodology: Left: The original image, inverted for better visibility of the calcifications. Second-to-left: The manually delineated calcifications. Second-to-right: The inpainted result, mimicking the aorta in a healthy state. Right: The difference between the original and inpainted aorta.

We first introduce some notations. Let D denote the image domain, Ω the region encompassing the calcification, u_0 the observed X-ray signal as a function $D \to \mathbb{R}$. Then a very crude inpainting method is the simple "Average", where Ω is filled homogeneously with the *constant value* S resulting from averaging over the immediate boundary $\partial\Omega$ of Ω, in discrete settings:

$$S = \frac{1}{n} \sum_{i \in \partial\Omega} u_0(i), \tag{1}$$

where n is the number of boundary pixels.

Meanwhile the expectation that the X-ray image is piecewise smooth suggests a Bayesian approach: the probability $p(u|u_0, \Omega)$ of a candidate baseline signal u can be written

$$p(u|u_0, \Omega) \propto p(u_0|u, \Omega)p(u|\Omega) \tag{2}$$

(the denominator $p(u_0|\Omega)$ being constant is not used). We may assume independence of u and Ω (because, for instance, at our hypothetical baseline, *conditionally* to the the knowledge of the location of the aorta in the image, there would be no way to decide whether atherosclerosis would develop at a specific location from the observation of the tissues), and thus $p(u|\Omega) = p(u)$. This latter term represents the prior knowledge on the image regularity, while the first term $p(u_0|u, \Omega)$ is the likelihood of observing u_0 knowing u and Ω. As a coarse approximation, we assume that u_0 comes from the contamination of u by some

independent Gaussian white noise of variance σ on each pixel in $D\backslash\Omega$. The regularity is expressed in terms of the distribution of local variations of intensities at a given pixel location i of D. These variations are expressed as a discrete gradient and assumed to be pixelwise independent : $p(u) \approx \prod_{i\in D} e^{\frac{|\nabla u|_i^q}{\mu}}$. We'll see in the next paragraph that it is not necessary to choose values for σ and for μ.

A candidate reconstruction can thus be obtained by maximization of the posterior (MAP) following its factorization in (2). By taking $-\log$ on each side of equation 2, the MAP problem is transformed into a minimization problem that can be written (with some slight abuses in continuous setting) as minimizing the following energy

$$E(u) = \int_{D\backslash\Omega} (u - u_0)^2 \, dx + \lambda \int_D |\nabla u|^q \, dx \tag{3}$$

where $\lambda = 2\sigma^2/\mu$. As this formula shows, we don't need to worry about choices for σ and μ, it is sufficient to choose a value of λ, we chose $\lambda = 10^{-2}$, it did experimentally provide good background estimation both for $q = 1$ and $q = 2$. A numerical solution is obtained by numerically solving the Euler-Lagrange equation resulting from equation (3)

$$(u - u_o)\chi - \lambda\nabla \cdot \left(\frac{\nabla u}{|\nabla u|^{2-q}}\right) = 0$$

where $\nabla\cdot$ is the divergence and $\chi(x) = 0$ if $x \in \Omega$, $\chi(x) = 1$ otherwise. For $q = 1$ this is the well known Total Variation Inpainting/Denoising of Chan and Shen [2], (TV), while for $q = 2$, one observes from the above equation that the solution u satisfies a Laplace equation $\Delta u = 0$ in Ω, i.e. is harmonic in Ω and for that reason we call it Harmonic inpainting (although u may not be harmonic on D). In order to solve numerically the resulting equations, we use the scheme proposed by Chan and Shen in [2], verbatim for $q = 1$ and with the obvious simplification for $q = 2$.

Calcification Scoring

This is straightforward. For each image u_{0n}, and each of its calcified areas $\Omega_n^1, \ldots, \Omega_n^k$, as *annotated by radiologists*, we compute the inpainting, according to method M where M is either average, harmonic or TV inpainting, along each Ω_n^i to obtain the inpainted image u_n^{Mi} and assign as score the quantity

$$s_n^M(i) = \sum_{i=1}^{k} \int_{\Omega_n^i} (u_{0n} - u_n^{Mi}) \, dx, \quad M \in \{\text{Average, Harmonic,TV}\}.$$

3 Validation Methodology

Background Estimation

We need first to determine how well the individual inpainting techniques actually simulate the data. We apply TV, Harmonic and Average inpainting to cut-out

sections of uncalcified aortas and compare these to corresponding sections of the true image. The pixelwise differences between the inpainted and original are taken and the standard deviations, mean errors and mean absolute errors are calculated.

Due to potential differences in imaging technology we compute separate error models for baseline and follow-up images. In each group 10 healthy subjects were randomly selected. True calcification shapes were selected from the calcification annotations and the errors were then measured by placing one of these, randomly chosen, at the center of each of the seven possible sections of the aorta in order to ensure near-independent measures without spatial overlap. The area coinciding with each successfully placed template is cut out of the image and then inpainted.

Clinical Value of the New Score

Correlations of the results from the various inpainting methods with the AC24 score are computed. To investigate the clinical value of the continuous score we compare the Δ-results, which denote the respective differences between the scores at follow-up and at baseline, for the AC24 and TV scores, to Hypertension (HT), a known physiological risk factor, at baseline. HT is defined as systolic blood pressure (SBP) above 140 mm Hg or diastolic blood pressure (DBP) above 90 mm Hg. Statistical significance is assumed for $p < 0.05$, calculated according to *Mann-Whitney tests*.

4 Results

The Data Set

The data set used in the here presented study constitutes a subset of 49 patients from a 500+ patients study population investigated by Tankó *et al*. in [8]. The selection was carried out by focusing on covering as much as possible of the entire atherosclerotic spectrum; thus, the patients of the population range from 0 to 17 on the AC24 scale. The selected 49 patients were subjected to X-ray twice, once at baseline (1992) and a second time eight years later (2000/2001). Each batch also contains 10 extra images that belong to the same initial population but include healthy (uncalcified aorta) subjects only, which were used for the evaluation of background estimation errors as described in Section 3. The data set contains thus 118 X-ray images. The images were taken at different centers in the Copenhagen area, Denmark. All images were digitized with a Vidar DosimetryPro Advantage scanner with 12 bit intensity range and a resolution of 570 dpi.

In order to be able to extract the calcifications from the X-ray images, the relevant anatomical structures, which include the four corner points of each of the L1 - L4 vertebrae, the posterior as well as the anterior wall of the aorta, and the calcified regions (if any were present), where delineated manually by radiologists from CCBR.

Background Estimation

The results from the background estimation described in Section 3 are listed in Table 1. The tendency for all data sets is clear: TV inpainting produces the smallest absolute mean error per pixel and Harmonic inpainting follows closely. Average inpainting performs worst. *Wilcoxon signed rank tests* performed on both experimental sets of the background data showed significant ($p < 0.01$) performance differences for TV vs. Average inpainting, TV vs. Harmonic inpainting, and Average vs. Harmonic inpainting.

Table 1. Background estimation results. Left: The results for the baseline data; the top part of the table displays the p-values resulting from the paired *Wilcoxon signed rank test* of the mean absolute errors. The three bottom rows show the standard deviations of the pixelwise error, the mean error, and the mean absolute error for the three inpainting methods. Right: The results for the follow-up.

Baseline			
	TV	Harmonic	Average
TV	1	0.0074	<0.00001
Harmonic	0.0074	1	<0.00001
Average	<0.00001	<0.00001	1
std	0.00116	0.00125	0.00138
mean error	2.7676	3.6791	1.1335
mean abs error	24.2813	26.2639	41.0328

Follow-up			
	TV	Harmonic	Average
TV	1	0.0001	<0.00001
Harmonic	0.0001	1	<0.00001
Average	<0.00001	<0.00001	1
std	0.00141	0.00153	0.00175
mean error	0.7154	2.0805	2.7175
mean abs error	28.9577	31.8650	48.1623

Calcification Scoring

In the remainder of the experiments we focus on the TV inpainting, since it is the most accurate of the three inpainting schemes. Figure 2 shows the obtained intensity differences calculated for baseline, follow-up, and Δ (difference between

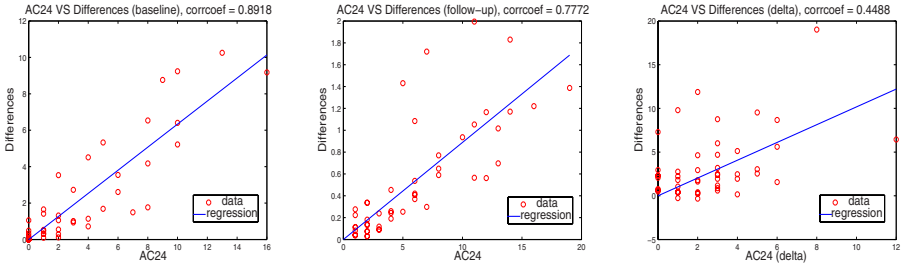

Fig. 2. The intensity difference score plotted against the AC24 score. Left: Intensity differences ($\times 10^{-6}$) versus the AC24 score at baseline. Middle: Intensity differences ($\times 10^{-7}$) versus the AC24 score at follow-up. Right: Intensity differences ($\times 10^{-6}$)versus the AC24 score for Δ.

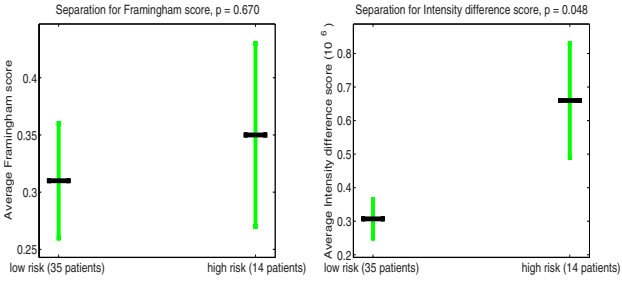

Fig. 3. Visualization of the patient stratification into low- and high-risk groups for hypertension. Left: AC24 scores. Right: intensity difference score.

baseline and follow-up) using TV inpainting correlated with the respective AC24 score. The correlation coefficients $r = 0.89$ at baseline, $r = 0.78$ at follow-up, and $r = 0.45$ for Δ reflect that our continuous score follows the trend of the AC24 score rather well.

Correlation to Hypertension

For the comparisons of different measures of atherosclerosis with relation to HT, the study population was divided into a normal group and a HT (high risk) group at baseline, according to the usual risk-thresholds for HT. Figure 3 shows the annual rate of change in the AC24 and inpainting scores for the two groups. The respective p-values were calculated using *Mann-Whitney tests*.

5 Discussion and Conclusion

In our attempt to develop a meaningful, continuous scoring system for atherosclerotic plaque we have investigated TV and Harmonic inpainting and compared them to the crude Average inpainting scheme. Results showed that TV inpainting is best suited for the task (Table 1).

The continuous intensity difference score shows a good correlation to the AC24 score. Higher r-values would not necessarily be desirable, since that would imply less room for improvement with respect to the AC24 score. The individual scatterplots in Figure 2 show many examples for which the AC24 score yields exactly the same value, whereas the inpainting score results in a larger variety of values, which indicates that the two scores carry different information.

Our continuous inpainting score significantly separates the high risk and low risk groups for hypertension($p = 0.048$), while the AC24 score does not ($p = 0.670$). This suggests that the inpainting based score may carry more relevant information than the AC24 score.

At this point we can claim that we can put clinically meaningful, continuous numbers on the severity of calcification in atherosclerotic plaque. A larger scale

study to further assess the utility and potential of this method is currently performed.

The lack of accuracy in manual segmentation may influence in the inpainting process as illustrated in Fig. 1, parts of the calcified region were missed, the effect can be seen in inpainting. This suggests in fact a method for locally correcting the annotations and we are currently experimenting it intensively.

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