Automated planning approaches for non-invasive cardiac valve replacement procedures from CT angiography

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Fully automatic volume quantification of aortic valve calcium in coronary computed tomography angiography

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Abstract

Background: Aortic valve calcium quantification has significant meaning for the prognosis of coronary and cardiovascular disease. The extent of calcium is also correlated to the occurrence of paravalvular regurgitation after the procedure of trans-catheter aortic valve replacement. In this study, we evaluated a new fully automatic approach to detect and quantify the presence and degree of aortic valve calcium.

Methods: This retrospective study consisted of 68 patients who went through computed tomography angiography because of potential coronary artery disease. The first step is the automatic detection of the aortic root. Next, double-oblique images were automatically reconstructed to properly display the aortic valve. Finally, the calcium on the valve was segmented by thresholding, and the volume score was calculated. For the validation, a reference standard was set by an experienced cardiologist using a semi-automatic method.

Results: In this study, the median of the reference standard calcium volume was 0.54 mm3 (range: 0 to 1131.23 mm3, 25th-75th percentile: 0 to 12.00 mm3). The median of the automatic calcium volume score was 0.46 mm3 (range: 0 to 1136.17 mm3, 25th-75th percentile: 0 to 11.22 mm3). The median difference was 1.82 mm3 (25th-75th percentile: 0 to 5.08 mm3), with the Spearman rank correlation coefficient of 0.81 ($p < 0.001$). The Bland-Altman analysis illustrated that the bias between the automatic result and the reference measurement was -1.1 mm3 with limits of agreement between -16.2 and +14.1 mm3. The specificity of our automatic approach was 82.4%; the sensitivity was 85.3%. The mean processing time was 90 seconds.

Conclusions: This study demonstrated that a new fully automatic approach for aortic valve calcium quantification is accurate.

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6.1 Introduction

The existence of aortic valve calcium (AVC) in contrast-enhanced computed tomography is a first indication for the presence of coronary and cardiovascular related diseases (Cueff et al. 2010; Kamperidis et al. 2014; Owens et al. 2012). AVC was found to correlate significantly with subclinical atherosclerosis (Owens et al. 2012). Furthermore, it can be used to appraise the extent of aortic stenosis (Cueff et al. 2010). In recent years, AVC has also proven to be related to paravalvular regurgitation or mortality after trans-catheter aortic valve replacement (TAVR) (Bettinger et al. 2015; Sinning et al. 2013). Therefore, the quantification of AVC has become an important indication. However, quantifying the AVC can be complicated. The direction of the aortic valve plane is usually oblique to the axial CT slices, which requires multiple steps of manual interactions to obtain a proper plane parallel to the valve. To reduce the manual interaction and improve the workflow, an automatic AVC quantification tool for contrast- enhanced CT scans would be preferred.

Therefore a new fully automatic approach to quantify calcium on the aortic valve was developed in this study. The accuracy of the method was appraised by comparing the calcium volume score with the results of an experienced cardiologist using a semi-automatic tool.

6.2 Methods

Patient cohort and CT protocol

This study used the same coronary computed tomography angiography (CCTA) image database as described in Kamperidis et al. (Kamperidis et al. 2014). The CCTA images of the patients were collected at Leiden University Medical Center in the period of November 2007 to April 2010. The patients were referred for a CCTA examination by the treating physician on the basis of standard clinical procedures to estimate the possible presence of coronary artery disease. Two different scanners were used, one was a 64-slice system with 64 × 0.5 mm collimation, and the other one a 320-slice system with 320 × 0.5 mm collimation, both from Toshiba Medical Systems, Japan. For the 64-slice scanner, the reconstruction parameters were 120kV and 300 mA, 0.3mm, reconstruction at 75% of the RR interval. For the 320-slice scanner, the reconstruction parameters were 120kV and 400 to 580 mA according to the patient's body mass index (BMI) and thoracic anatomy, 0.5 mm with 0.25 mm increment, reconstruction also at 75% phase of the R-R interval.

Automatic aortic valve calcium measurement

Automatic segmentation of aortic root

The automatic AVC measurement approach was implemented based on the algorithms that were previously developed for whole-body CT scans (Gao, Kitslaar, Budde, et al. 2016; Gao, Kitslaar, Scholte, et al. 2016). The approach follows the subsequent steps: First, the aortic root was segmented automatically using a registration-based algorithm (Kirişli et al. 2010). Second, the initial segmentation was refined according to the intensity distribution of the original images (Gao, Kitslaar, Scholte, et al. 2016).

Automatic detection of centerline and annulus plane

Figure 6.1(a) interprets the aortic root by a diagram. The aortic annulus plane was calculated from the segmentations of step 6.2.2.1. The 2D cross-sectional contours were calculated from the 3D surface of the segmentation from the ascending aorta into LVOT along the direction of the aortic annulus (Figure 6.1(b)). The area curve diagram was calculated from the 2D contours. According to Figure 6.1(a), starting from the aortic annulus plane up into the ascending aorta, the Sino-tubular junction plane is the first valley point along the area curve after the aortic annulus (Figure 6.1(c)).

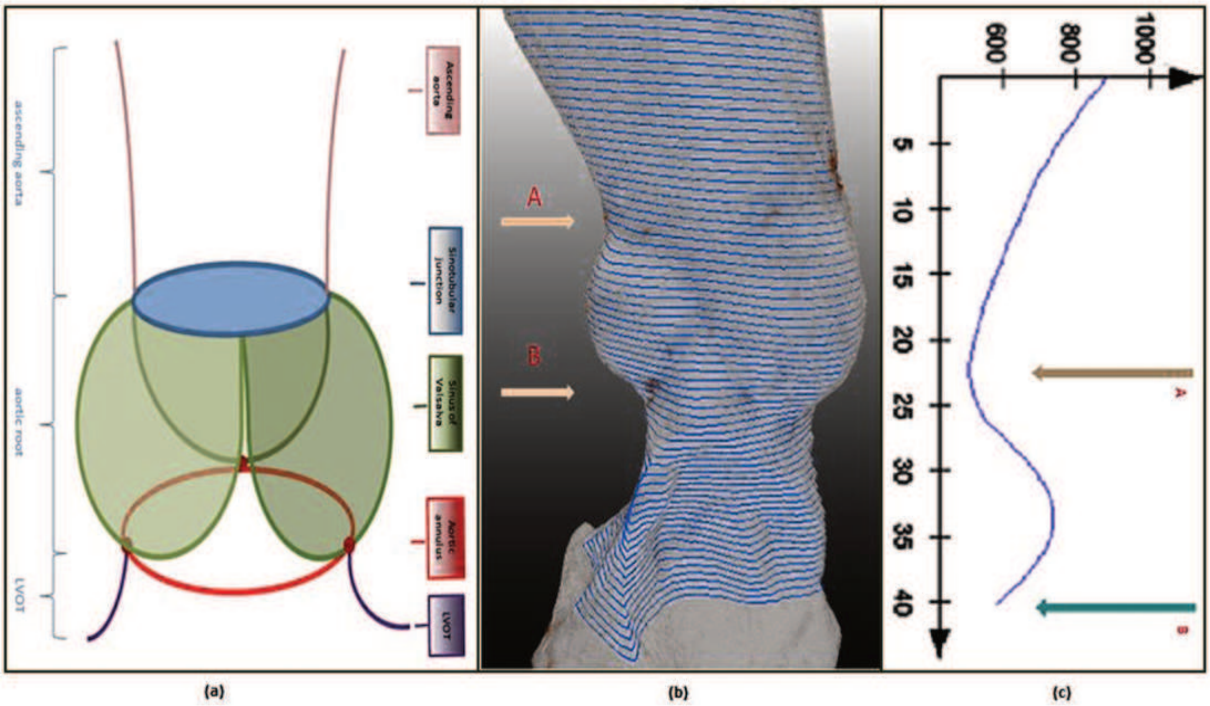

Figure 6.1 Automatic detection of annulus plane: (a) A schematic representation of the anatomical structure of the ascending aorta, aortic root and LVOT. (b) The 2D cross-sectional contours obtained from the 3D segmentation from ascending aorta into LVOT. Arrow A – sino tubular junction, arrow B – aortic annulus. (c) The area curve of 2D cross-sectional contours along the aortic root: arrow A - sino tubular junction, arrow B - aortic annulus. (y axis - mm, x axis- mm^2 , the curve range is from ascending aorta (40mm above aortic annulus) to aortic annulus.

Automatic detection of the calcium

With the aortic annulus orientation and location from the previous step, double oblique reformatted image slices (in-plane resolution 0.39mm × 0.39mm and field of view 100mm × 100 mm) parallel to the aortic annulus were created from the original image volume to clearly visualize the detailed structure of the aortic valves and the localization of the calcium in and around the aortic root (Figure 6.2). The slab thickness was set to 3 mm according to the previous study (Kamperidis et al. 2014). Within the region of the aortic root detected, a fixed threshold was used to segment the calcium. A cutoff value of 130 Hounsfield units (HU) is frequently used for the segmentation of the calcium in the coronary artery in non-contrast CT images (Agatston et al. 1990). However, in contrast images, the HU value of contrast-enhanced vascular structures can be all above the level of this value. In the work by Ewe et al. (Ewe et al. 2011) and Kamperidis et al. (Kamperidis et al. 2014), 800 HU was considered as a reasonable value for the calcium threshold in CCTA images and generated quantification results correlated to clinical outcome. In our study, 800 HU was also used as the threshold value. The volume of the voxels above this threshold in the reformatted images was used to compute the AVC volume.

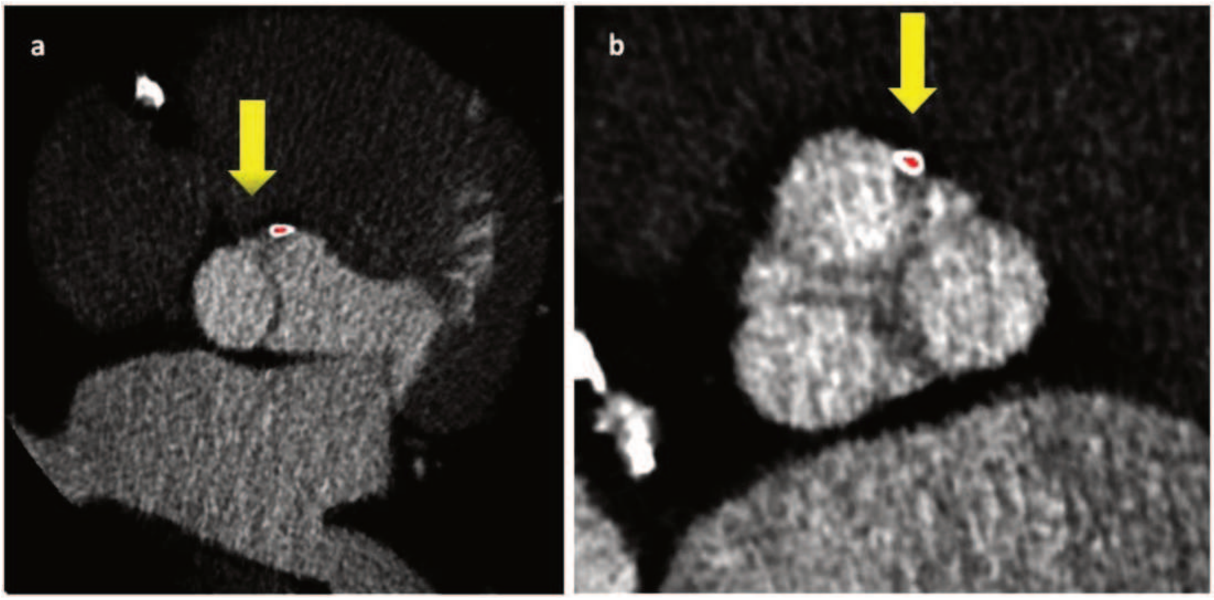

Figure 6.2. Aortic valve calcium in the same position in one patient in different views: (a) axial view (b) double oblique reformatted view. In Figure b, the location of the calcium relative to the aortic valve is much easier to determine than in Figure a.

Reference standard

In the study of Kamperidis et al. (Kamperidis et al. 2014), quantification of AVC was implemented by a semi-automatic image post processing tool (customized research version of CalcScore V1.1.1, Medis specials bv). The original image was first re-oriented manually to obtain a double oblique reformatted view. In this view, the three lowest points of the aortic valve cusps appear at the same time (according to the definition of the aortic annulus). A 3 mm slab thickness was used in this tool according to the reference standard for scoring coronary artery calcium. Next, the user manually annotated the calcium which was in the aortic valve.

Statistical analysis

If normally distributed (based on the Shapiro-Wilk test), the error of the automatic results was quantified by average difference and standard deviation, meanwhile the correlation analyzed by the Pearson correlation coefficient. Otherwise, the differences were expressed by median and interquartile range, and the correlation by Spearman rank correlation. The median difference is the median of all absolute differences. Bland-Altman plots were generated to show the deviation and the limits of agreement. P-values lower than 0.05 were deemed as statistically significant. Specificity and sensitivity were calculated for the classification of AVC and no-AVC cases with the number of true positive (TP), true negative (TN), false positive (FP) and false negative (FN) cases.

Implementation

The whole framework was implemented in the MeVisLab (version 2.7.1, MeVis Medical Solutions AG, Germany) environment.

The statistical analyses were carried out with SPSS (version 20.0, SPSS Inc., USA) along with MedCalc (version 15.6, Belgium).

6.3 Results

Patient characteristics

In total, 68 patients were included. According to the reference standard, 34 were with AVC, and 34 without AVC (selected randomly); the baseline characteristics are presented in Table 6.1.

	Total (68)
Age (years)	61 ± 11
Gender (% male)	43 (63%)
Diabetes	19 (28%)
Hypertension†	33 (49%)
Hypercholesterolemia‡	28 (41%)
Family history of CAD*	21 (315)
Smoking	14 (21%)
Obesity	17 (25%)

Table 6.1. Patient characteristics
Data are represented as mean ± SD, median (interquartile range) or as number and percentages of patients.
†Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90
mmHg or the use of antihypertensive medication.
‡Defined as serum total cholesterol ≥230 mg/dL or serum triglycerides ≥200 mg/dL or treatment with lipid lowering medication.
*Defined as the presence of coronary artery disease in first-degree family members at age <55 years in men and <65 years in women.
CAD: coronary artery disease

Aortic valve calcium score

According to the Shapiro-Wilk test, neither the results of the reference standard nor our automatic approach was normally distributed. The median calcium volume score of the reference standard was 0.54 mm3 (range: 0 to 1131.23 mm^3, 25th-75th percentile: 0 to 12.00 mm^3). The median of the automatic calcium volume score was 0.46 mm^3 (range: 0 to 1136.17 mm^3, 25th-75th percentile: 0 to 11.22 mm^3).

Automatic aortic valve calcium score evaluation

The median difference of the calcium volume between the automatic measurement and reference standard for the patient cohort in this study was 1.82 mm^3 (25th-75th percentile: 0 to 5.08 mm^3). The Spearman rank correlation coefficient between the results of the two measurements was 0.81 ($p < 0.001$). In Figure 6.3, two Bland-Altman plots of all the 68 patients are shown. Figure 6.3A shows the plot of the full range of quantified volumes (0 to 1200 mm^3). Figure 6.3B is a magnified plot of the volume range from 0 to 100 mm^3 excluding a seriously calcified AVC case whose calcium volume score greatly differs from the other patients. The Bland-Altman analysis showed that the bias between the automatic and the ground truth is -1.1 mm^3 with limits of agreement between -16.2 mm^3 and +14.1 mm^3.

Of the 34 patients without AVC, the automatic approach also did not detect any calcium in 28 patients (specificity: 82.4%). For the 34 patients with calcium on the aortic valve, the automatic approach also assigned a non-zero score to 29 patients (sensitivity: 85.3%). Table 6.2 shows the contingency table of the results.

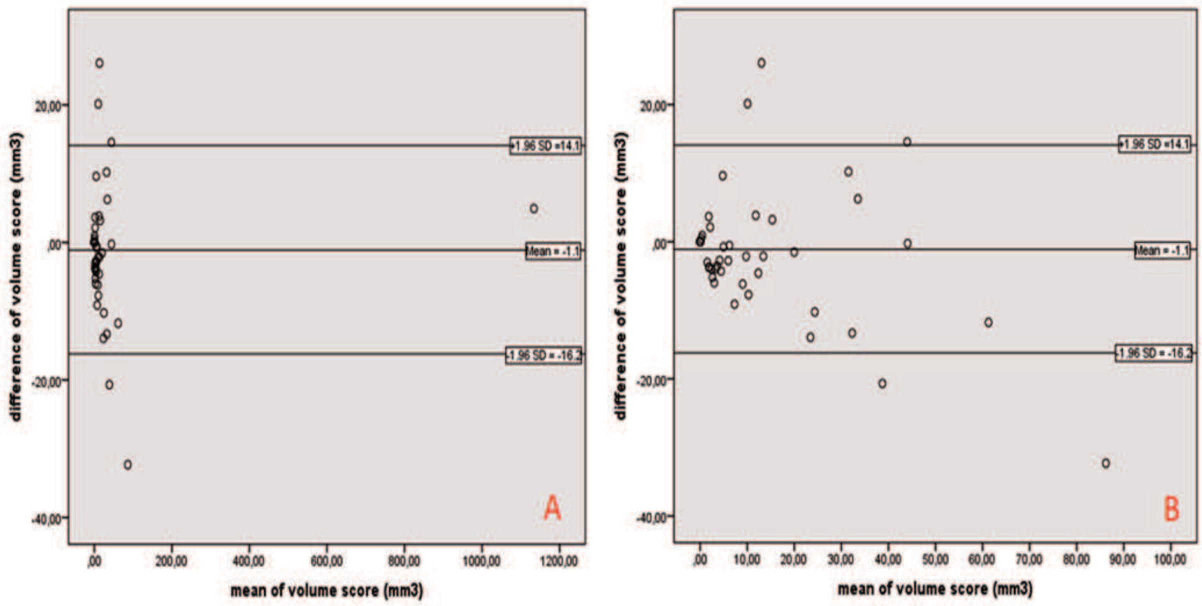

Figure 6.3. Bland-Altman plot of aortic calcium volume score. Figure A is the plot including all the results. Figure B is the plot within the magnified view of the range from 0 to 100 mm^3. Difference of volume score = automatic measurement − reference standard. Mean of volume score = (automatic measurement + reference standard)/2.

		reference standard	
		calcium	no-calcium
automatic measurement	calcium	TP = 29	FP = 6
	no-calcium	FN = 5	TN = 28

Table 6.2. The contingency table of all the patients: true positive (TP), true negative (TN), false positive (FP) and false negative (FN)

Time needed for the computation

The automatic quantification approach needs on average 90 seconds to segment and quantify the calcium in a single CCTA scan on a typical workstation.

6.4 Discussion

Two studies have been published related to the aortic valve calcium quantification, Jilaihawi et al.'s semi-automatic method (Jilaihawi et al. 2014) and Grbic et al.'s automatic methods (Grbic et al. 2013). Grbic et al. discussed an automatic method to extract the aortic valve model including calcium. The Dice Similarity Coefficient was analyzed, but the calcium scoring was not presented. Jilaihawi et al. investigated the clinical impact of a semi-automatic tool for aortic valvar calcium quantification, which proved that both leaflet and left ventricle outflow tract calcium can predict paravalvular leakage. However, no automatic quantification of calcium scoring in aortic valve has been evaluated.

In this study, a fully automatic approach to quantify aortic valve calcium scoring on CCTA scans was presented and evaluated in this study. Physicians will be able to use this to do the batch measurement in large population cohort studies.

With the same threshold set to 800 HU as the semi-automatic method, the AVC quantification results depend on the automatic detection accuracy of the aortic root. The aortic root was segmented successfully in all the patients by visual examination, which indicated that the algorithms in our previous studies (Gao, Kitslaar, Budde, et al. 2016; Gao, Kitslaar, Scholte, et al. 2016) developed especially for TAVR-related patients, can also be used in CCTA images scanned for diagnosis of CAD with different CT protocol and different anatomy.

We evaluated the automatic calcium segmentation results by comparing the median and Spearman rank correlation with semi-automatically obtained reference standard values. The correlation coefficient was excellent with the number 0.81. The left panel in Figure 6.3 showed that most of our volume scores were within a small range [0,100] with a single heavy calcified patient in the range [1000, 1200]. Bland-Altman plots show the bias between automatic measurement and reference standard. The range 0 - 1200 mm3 included all the patients. The magnified plot in range 0 - 100 mm3 enables a more detailed view of the results. In Figure 6.3A, the serious calcified patient's bias was within limits of agreement. Figure 6.3B showed that when the volume score is larger, the difference between the automatic measurement and reference standard is also larger.

The classification of AVC is important for a calcium score quantification system for risk assessment and cardiovascular disease prediction. For our system, there were 6 FP and 5 FN cases. The specificity was 82.4% and sensitivity 85.3%.

The main likely cause of the 5 FN patients and the 6 FP patients was the partial volume effect. This generated a difference between our results and the reference standard since a double oblique reconstruction of the image was used. Rutten et al. (Rutten, Isgum, and Prokop 2008) described the influence of partial volume effect on coronary artery calcium scoring and prediction of risk factors due to small variations in starting position of MPR images. With a different starting position, the calcium distribution changed. This can lead to the variation of the calcium quantification results with a fixed threshold. Similarly, in our system, first, the center and direction of the aortic annulus were detected. The positions of the MPR images were defined by the two parameters. The bias of the annulus location and orientation between our automatic approach and the reference standard can cause variations in the start positions and orientations.

In Figure 6.4, panel (a) &(c) show the multiplanar reconstruction (MPR) images in the reference standard, panel (b) & (d) show the MPR images of the same patient by the automatic approach. The locations of the calcium were different, and the intensity of the calcium changed too. This patient was considered to have no calcium in the reference standard, but had calcium in the automatic approach.

To investigate the effect of a change in orientation we applied a 5-degree orientation difference in MPR images of the same patient. The 5 degrees was chosen based on work by Tzikas et al. (Tzikas et al. 2010), where a 10-degree cut-off is used to distinguish accurate measurements while evaluating the angular difference of aortic annulus orientation. In Figure 6.5 the six MPR images show the aortic root of the same patient. The calcification distribution in the aortic valve leaflets changed when the reconstruction orientation changed for 5 degrees (top versus bottom row). This can lead to the variation of the calcium quantification results as proven by Rutten et al. (Rutten, Isgum, and Prokop 2008). The difference of the calcium volume score for these two orientations is 8.39 mm^3, which is much higher than the median and mean error of our approach.

In the ground truth measurement, the region of the aortic root was defined manually. The definition of the top of the region was different. There is no standard of the definition of AVC as far as we know. According to Hanneman et al.'s description (Hanneman et al. 2015), the sino-tubular junction is the highest level at which the aortic valve cusps and commissures are attached to the aortic wall. In order to include all the aortic valve cusps in our automatic method, we used the sino-tubular junction. In the reference standard, the coronary ostium were used. When there was calcium beyond the coronary ostium inside the aortic root, the results can be different in our automatic approach compared with the reference standard. This effect caused 2 false positive (FP) cases.

There are several aspects that can be improved in this study. Firstly, the quantification results of AVC were assessed only by comparing the quantified volumes with a manual reference standard that has shown to vary with small changes in image orientation. The clinical value of our automatic method can be further evaluated by directly analyzing the relationship between the automatic calcium measurement and risk factors of a patient. Secondly, the performance of the automatic algorithm needs to be tested on patients with a broader range of AVC. Finally, the segmentation of the calcium into separate valves, which reflects the distribution of calcium, can be realized in future based on the extension of the methods described in this study.

In conclusion, a fully automatic aortic valve calcium quantification approach was established and evaluated in this study. The evaluation proved that the approach is accurate.

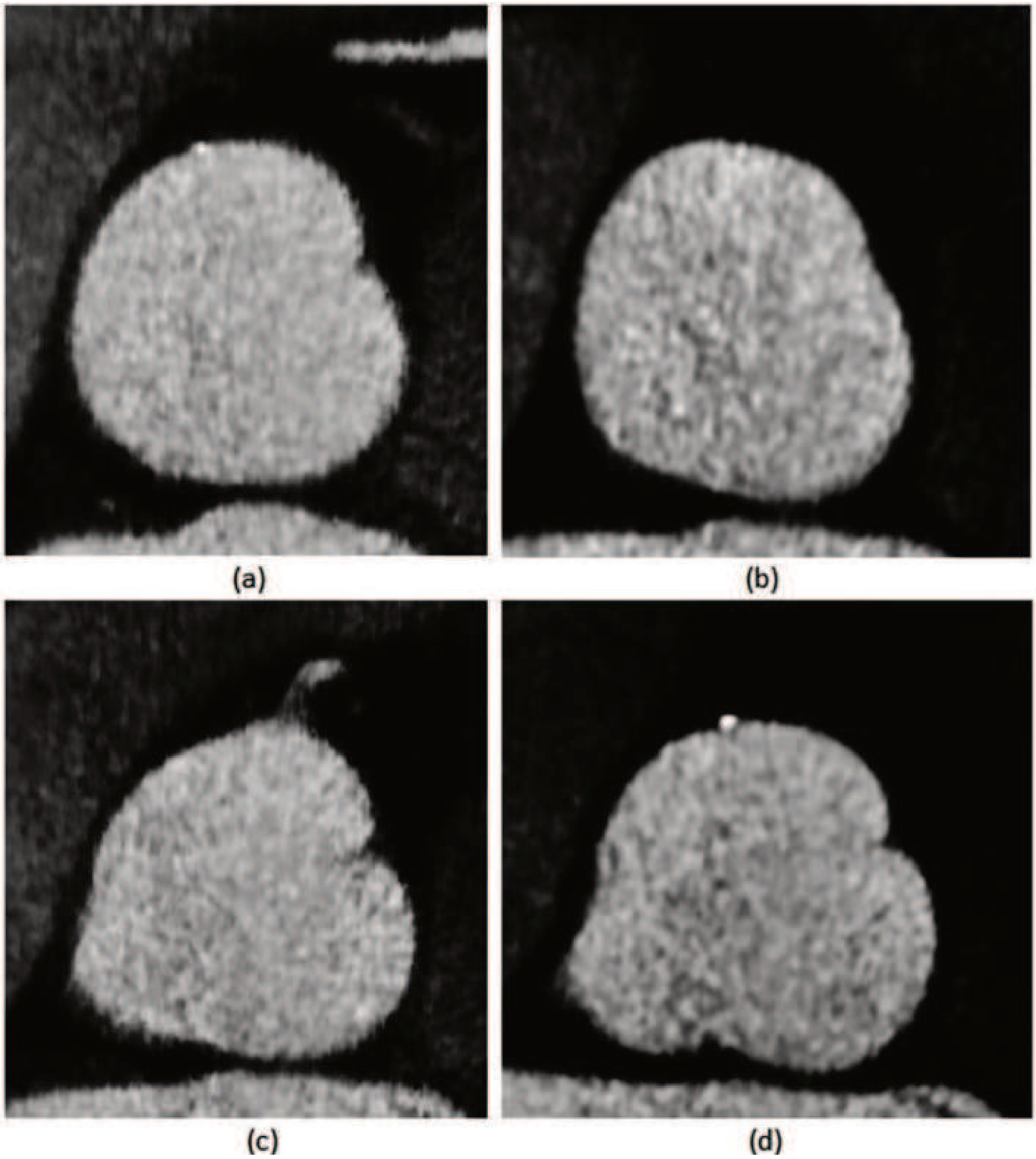

Figure 6.4. Multiplanar reconstruction (MPR) images of the same patient in reference standard and the automatic approach. (Image (a) & (c) are the reference standard, image (b) & (d) are the automatic measurement)

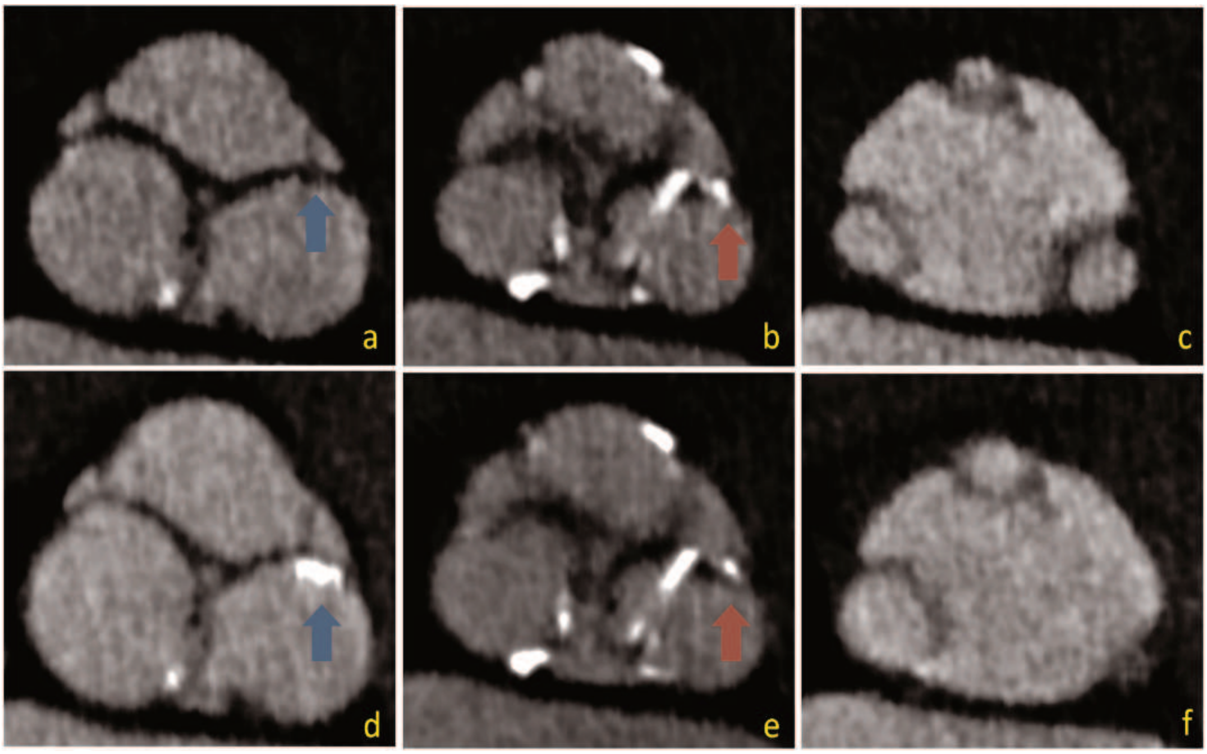

Figure 6.5. MPR images of the same CCTA image with the same slice thickness 3 mm and different reconstruction orientations. The angle between the two different orientations was 5 degrees. a. b. c. belong to one MPR image. d. e. f. belong to the MPR image of another orientation. The six different MPR images were both showing the aortic root of the same patient, the calcifications were not of the same size in the spots pointed by the arrow. The arrows of the same color denoted the same position in different MPR images of the same CCTA image.