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Atherosclerosis

Variation in Cardiac Vein System is Associated with Coronary Artery Calcium – A Venous-Atherosclerosis Paradox?

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Background: The factors that determine the different patterns of venous anatomy are not well understood. This study was designed to evaluate the relationship between variation in the cardiac vein system and the extent of coronary artery calcium score (CACS).

Methods: We reviewed the results of 64-slice CTs of 226 subjects (age 57.2 ± 11.2; 133M) enrolled in our study. The subjects were divided into 3 groups based on coronary artery calcium: 92 patients. with CACS = 0 AU (Agatston Unit, AU); 56 with CACS = 1-100 AU; and 78 patients with CACS > than 100 AU. The cardiac venous system was reconstructed during the optimal phase of the cardiac cycle in each subject.

Results: Subjects with a higher CACS had a better quality of vein images ($p < 0.01$). The number of visible veins differed between the groups. Eight subjects (8.7%) in the group with CACS = 0 AU, 7 (12.5%) in the group with CACS = 1-100 AU, and 23 (29.5%) in the group with CACS > 100 AU had five or more visible veins ($p < 0.001$), whereas the proportion of subjects with less than three visible veins was 56 (60.8%), 31 (55.4%) and 30 (38.4%), respectively ($p < 0.05$). The number of visible veins correlated with CACS ($r = 0.28$; $p < 0.05$). In a multivariate regression analysis, which included age, gender, CACS, LV ejection fraction, myocardial volume and heart rate, the CACS was found to be an independent determinant of the number of visible veins ($p < 0.05$).

Conclusions: The results of our study suggested that there is a link between a variation in the cardiac venous system and the extent of atherosclerosis.

Key Words: Coronary artery calcium score (CACS) • Computed tomography • Coronary veins

INTRODUCTION

It is well understood that there is considerable variation in the cardiac venous system in humans, especially in light of their role regarding cardiac resynchronization therapy.[1,2] However, the factors that determine the different patterns of the venous anatomy are less understood.

Current imaging techniques allow the cardiac veins to be visualized noninvasively, thus providing an opportunity to observe factors influencing their detection and anatomical patterns. One of such method is cardiac computed tomography,[3,4] which allows the coronary veins, coronary sinus and its ostium or even the Thebesian valve – often called the guardian of the coronary sinus[5,6] – to be visualized. It has also been documented that in certain diseases such as advanced coronary artery disease the coronary venous system is often extended (probably as a kind of compensation mechanism) after implantation of coronary artery bypass

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grafts (CABG) or in advanced heart failure.[7,8] Unfortunately, a computed tomography (CT) angiography examination requires a significant dose of radiation as well as a substantial volume of contrast agent. Therefore, the question of whether there is any examination that can safely provide information about the coronary venous system is still a legitimate one.

It is possible that the results of coronary artery calcium score (CACS) as a non-contrast, low-radiation marker of coronary artery disease can correlate with the anatomy of coronary veins. So the purpose of this study was to evaluate the relationship between the cardiac venous system and coronary artery calcification.

METHODS

The data for 226 consecutive patients (133 men, aged 57.2 ± 11.2) from 64-slice CT (Aquilion 64, Toshiba Medical, Japan) were studied. In these patients, multi-slice computed tomography of the heart was originally performed because their physicians suspected coronary artery disease. The subjects were divided into 3 groups based on the CACS:

- 92 (40.7%) patients with no detectable CACS: 0 (Agatston Unit – AU),
- 56 (24.8%) patients with less advanced coronary atherosclerosis CACS: 1-100 AU,
- 78 (34.5%) patients with CACS greater than 100 AU.

Patients were excluded if they had atrial fibrillation, frequent premature heartbeats, renal insufficiency (serum creatinine > 1.2 mg/dl), hyperthyreosis, a known allergy to nonionic contrast agents or a previously implanted pacemaker with unipolar leads.

The local Ethics Committee approved the study protocol and all of the participants gave their informed consent for the examination. The study protocol conformed to the version of the Helsinki Convention that was current at the time the study was designed.

CACS methods

A coronary artery calcium score protocol was performed during the same examination as the visualization of the coronary venous system during an angio-CT. Scanning with prospective electrocardiography (ECG)-gating using 64 slices with a collimated slice thickness of 3 mm was performed during a breath hold. The exact technical parameters are presented in Table 1. No contrast agent was used in the CACS protocol. Acquisition of data was performed in two stages: a localization pre-test and the proper CACS examination; the place of triggering was chosen based on the heart rhythm.

Computed tomography protocol

Scanning with retrospective ECG-gating was performed during a breath hold using 64 slice CT with a collimated slice thickness of 0.5 mm. A breath-hold examination was performed to adjust the scanner settings. On average, 100 ml of non-ionic contrast agent (Iopromide, Ultravist 370, Schering, Germany) was given to each patient during the examination at an average rate of 4.5 ml/s. The contrast agent was administered in three phases. In certain cases where the HR was higher, metoprolol succinate (Betaloc, Astra Zeneca, Sweden) at a dosage of 5-10 mg was given intravenously unless contraindicated. If the expected HR slowing did not occur, the patient was excluded from the study.

Post-processing and analysis of data

Reconstruction of all data was performed on Vitrea

Table 1. Parameters of the scan during CACS as well as CTs used in the research

	CACS	Angio CT	
Layer thickness	3 mm	0.5 mm	
Reconstruction thickness	3 mm	0.5 mm	
Helical pitch	---	12.8 (best)	
Rotating time	0.25 sec	0.4 sec	
Energy	120 kV at 300 mA	BMI < 23.9	120 kV at 330 mA
		BMI = 24.0 ~ 29.9	380 mA
		BMI > 30.0	135 kV at 430 mA
Post-processing workstations		Vital images	

BMI, body mass index; CACS, coronary artery calcium score; CT,computed tomography.

2 workstations (Vital Images, Minnetonka, MN, USA; software version 3.9.0.0 and 5.1). Calcifications in the CACS study were calculated using the Agatston scale and "2DVScore with Color" semiautomatic presets by two experts who were trained in MSCT. The coronary arteries during CACS were selected manually by experienced researchers.

For the analysis of the coronary veins, we created ten (10) axial image series as well as 3D volume rendering (VR) reconstructions from 0 to 90% R-R intervals (step 10%) using a 2.0 mm slice thickness to reduce the large amount of data in each case. Coronary veins were graded using a previously published 6-point scale by two experts[9] (Table 2). Here, a higher score indicates a better quality of visualization; a designation of "visible" was treated veins with a score of 1 or more.

Vessels were graded by 2 experts trained in MSCT and experienced in the visualization of the coronary venous system.

Statistical analysis

Continuous data are presented as mean values and corresponding standard deviations, and the Chi-square test was used for statistical comparison of visible veins between the groups. Correlations were calculated by Pearson's correlation test. For graphic purposes, raw CACS results were logarithmically changed (log CACS+1) to decrease the scatter of data. Multivariate regression analysis was used to establish an independent determinant of the number of visible veins. Those calculations were performed using the Polish version of Statistica (StatSoft, Inc., Tulsa, OK, USA). A designation of $p < 0.05$ was recognized as statistically significant.

Reproducibility of vein visualization and the determination of CACS results were evaluated using the Bland-Altman method and by calculating the inter-rater agreement coefficient kappa. Correlations between data were calculated by means of the Spearman's rank coefficient using MedCalc Software (MedCalc Softward, Ostend, Belgium).

RESULTS

Patients included into the study had a comparable cardiac function parameters evaluated by using cardiac computed tomography including ejection fraction and diastolic volume. The exact hemodynamic characteristics are presented in Table 3. In our study, the number of visible cardiac veins was highly reproducible (inter-rater agreement kappa: 1.0; standard error: 0.0), while intra-observer agreement was excellent as well (mean difference 0, inter-rater agreement kappa 1.0, standard error: 0.0). Similarly, we were also able to obtain excellent reproducibility of CACS.

There was a very satisfactory agreement between observers in the evaluation of the quality of the reconstructions (95% CI, -0.945-1.000, inter-rater agreement kappa 0.974). There were similar results in the repeated evaluation of the score by the same observer (95% CI, 0.959-1.0000 and kappa 0.983).

Quality of visualization of coronary veins and CACS

High quality coronary sinus images were obtained for all of the subjects. Visualization of veins varied between the CACS groups as noted: group CACS = 0 AU (quality: 3.82 ± 1.2); group CACS = 1-100 AU (quality: 4.32 ± 0.9); and group CACS > 100 where the average

Table 2. The scale of the quality of the visualization of the coronary venous system

Score	Description
0	No vessel(s) present*
1#	Vessel, length less than 5 mm, weakly contrasted and/or with a number of artifacts
2	Between score 1 and score 3
3	Vessel more than 1 cm long, better contrasted. Sometimes areas not visible or artifacts occurred
4	Between score 3 and score 5
5	Vessel well contrasted, clearly visible on the entire length of the vessel

* When a vein is not visualized in any of the phases, it has a grade of 0. However, this does not necessarily mean that the vein is absent – it could be, e.g., very small and therefore lower than the resolution of the CT scanner. # Grade 1 means that a vessel is present but very poorly visualized.

Table 3. Characteristics of the patients who were included, and values obtained using cardiac computed tomography

	CACS = 0 AU	CACS = 1-100 AU	CACS > 100 AU
Ejection fraction (%)	62.6 ± 7.7	62.7 ± 8.2	60.3 ± 13.6
EDV (ml)	144.5 ± 43.0	141.3 ± 37.1	151.6 ± 57.6
ESD (ml)	55.1 ± 23.2	54.2 ± 25.7	65.8 ± 58.3
Stroke volume (ml)	88.2 ± 20.8	87.6 ± 18.6	85.9 ± 20.7
Cardiac output (L/min)	5.6 ± 1.9	5.3 ± 1.4	5.2 ± 1.3
Myocardial mass (g)	129.6 ± 43.4	137.2 ± 44.5	151.2 ± 50.1
Myocardial volume (ml)	119.7 ± 40.0	130.6 ± 42.8	143.6 ± 48.5
Heart rRate (bpm)	62.9 ± 13.4	60.9 ± 8.9	60.2 ± 6.8

CACS, coronary artery calcium score; EDV, end diastolic volume; ESD, end systolic diameter.

quality was 4.28 ± 0.9. Those with higher CACS (group 3) had better quality vein images (ANOVA F = 5.916; p = 0.003).

Number of coronary veins and CACS

The number of visible veins differed between the groups. Eight subjects (8.7%) were in the CACS = 0 AU group, seven (12.5%) were in the CACS = 1-100 AU group, and 23 (29.5%) were in the CACS > 100 AU group, with five or more visible veins (chi-squared = 14.037; p < 0.0008); the proportion of subjects with fewer than three visible veins was 56 (60.8%), 31 (55.4%) and 30 (38.4%), respectively (chi-squared = 8.872; p = 0.0118). The exact number of visible coronary veins according to the CACS is presented in Table 4.

The number of visible veins correlated statistically with CACS (Pearson's r = 0.28; p < 0.05), and after reduction of extreme data (Pearson's r = 0.17; p < 0.05) (Figure 1).

In the multivariate regression analysis, which included age, gender, CACS, LV ejection fraction, myocardial volume and heart rate, the CACS was found to be an independent determinant of the number of visible veins (t = 3.019; p = 0.002).

An examples of coronary venous system with calcium score in patients with high and low CACS according to the visible veins are presented in the Figures 2.

Table 4. Number of visible veins according to the CACS group

	CACS = 0 AU	CACS = 1-100 AU	CACS > 100 AU
1 vein	9 (9.78%)	3 (5.36%)	2 (2.56%)
2 veins	20 (21.74%)	12 (21.43%)	9 (11.54%)
3 veins	27 (29.35%)	16 (28.57%)	19 (24.36%)
4 veins	27 (29.35%)	17 (30.36%)	24 (30.77%)
5 veins	8 (8.69%)	7 (12.5%)	14 (17.95%)
6 or more veins	0	0	9 (11.54%)

DISCUSSION

Computed tomography of the heart is one of the methods that is used to visualize the heart including the coronary arteries and coronary veins.[10] However, heart anatomy can only be recognized during a full cardiac examination that is performed with a contrast agent. An examination typically starts with the coronary artery calcium score protocol, which can only visualize the number of calcifications in the coronary arteries. The CACS is a test that does not requires contrast agent, with a low dose of radiation that allows the amount of calcium in the coronary arteries to be ascertained. It can also permit coronary artery disease to be found in an non-invasive way.[11,12] Actually, this examination is recommended in the guidelines for asymptomatic patients

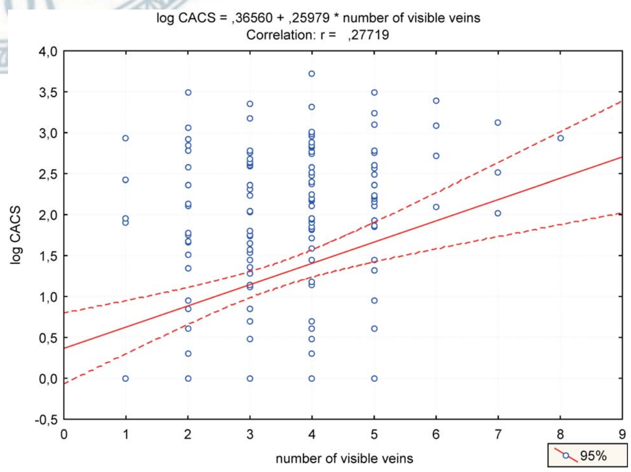

Figure 1. *Correlation of the CACS results with the number of visible veins. Raw CACS results were logarithmically changed (log CACS) to decrease the scatter of data. Only for graphical purposes.*

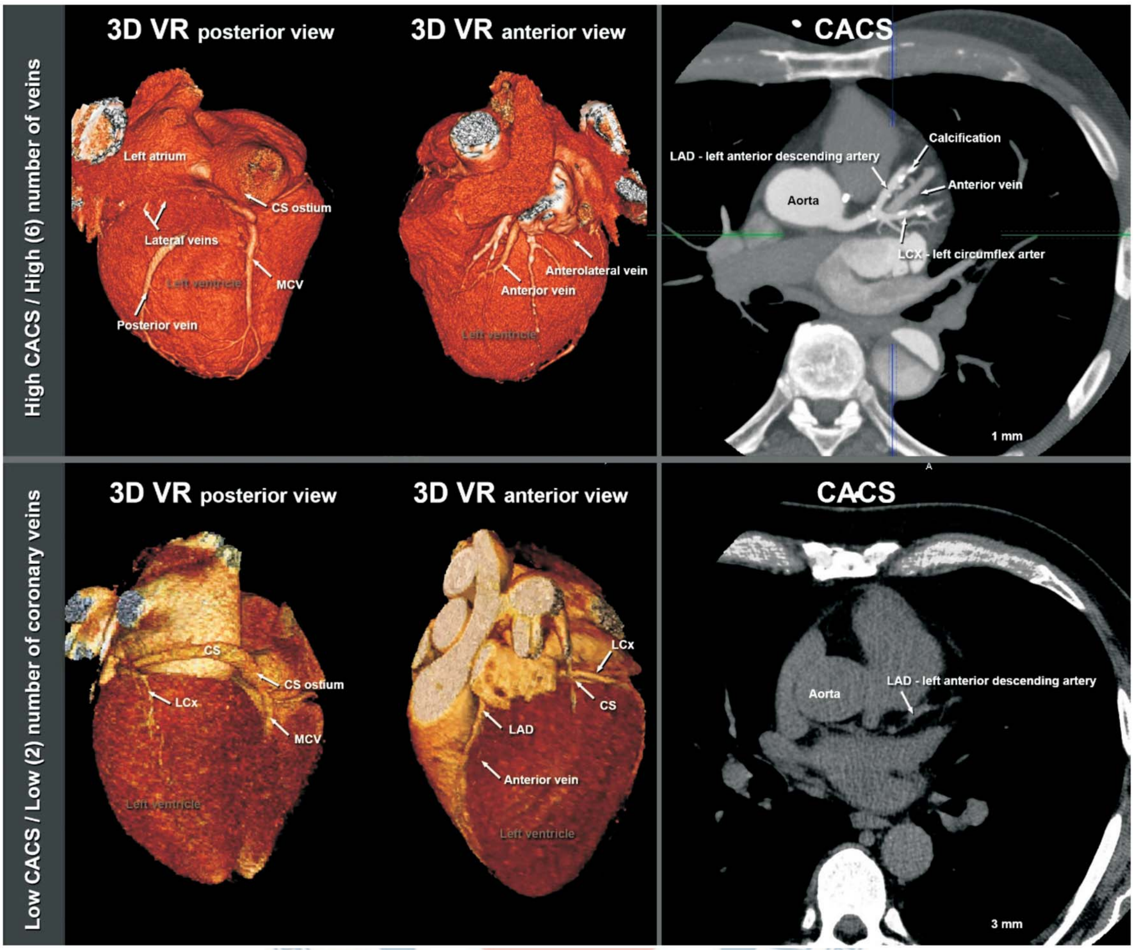

Figure 2. *A comparison of coronary venous system with coronary artery calcium score in patients with high and low values of CACS. CACS, coronary artery calcium score; CS, coronary sinus; MCV, middle cardiac vein; VR, volume rendering.*

with a moderate risk.[13] Sometimes during the CACS process, the coronary sinus and its ostium can be visualized and measured; however, this is not a part of routine clinical practice. A comparison of CACS images with an angio CT is presented in Figure 3.

Based on earlier literature, we hypothesized that calcifications in the coronary arteries might correlate with the extension of the coronary venous system, which is the basis of this study. In our earlier projects, we documented that selected cardiac diseases including heart failure and advanced coronary artery disease significantly influence the coronary venous system.[8,14]

We have to remember that coronary artery disease is often a pre- disease for heart failure, so the results from this paper should be, though not directly, in accordance with earlier research.

In a previously published paper, we found that the average number of visible coronary veins was statistically higher (3.44 $\pm$ 1.34) in the heart failure group as compared to that (2.72 $\pm$ 1.05) in the normal ejection fraction group.[8] The statistical correlation between the reduction of the ejection fraction and the increase in the number of veins was also found. We concluded that this may be evidence of coronary venous retention understand it could be responsible for high right sided (atrial) pressure and slower transit of venous return.[8]

Similar results were obtained by Chen et al., who concluded that the diameters of all of the coronary venous tributaries were higher in the heart failure group.[15] Also, the results were comparable to Cubuk et al., who demonstrated an increase in the diameters and lengths of the coronary veins in patients with systolic heart failure.[16] The studies for both papers were performed using

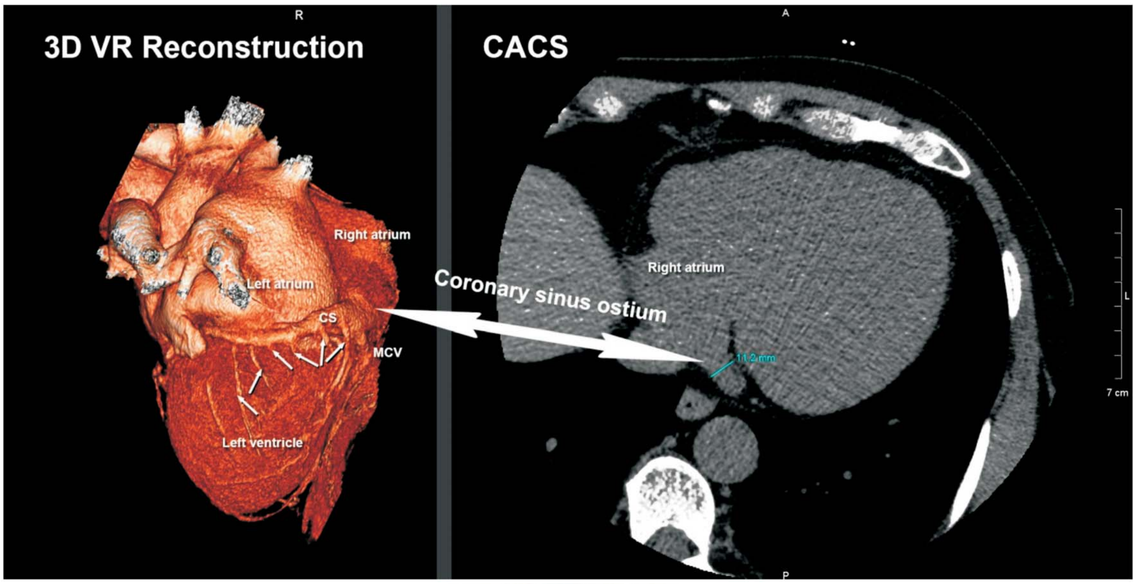

Figure 3. *Comparison of cardiac computed tomography in 3D volume rendering with a CACS examination. CACS, coronary artery calcium score; CS, coronary sinus; MCV, middle cardiac vein.*

computed tomography images without CACS images. On the other hand, Yuce et al. found that the ejection fraction was an independent predictor of the diameter of the coronary sinus in the echocardiography.[17]

Most of the authors believe that the capacity of the coronary sinus (usually measured as its diameter) is probably a part of the entire process of cardiac remodeling and can predict the severity of chronic heart failure and poor functional class.

In our study, the coronary artery calcium score was found to be an independent determinant of the number of visible veins. Those results confirmed the observation that the coronary venous system plays the role of a kind of buffer in different heart diseases.

The final question is – what is the practical meaning of the results of this study? Patients who have a significantly elevated calcium score can have more coronary veins available, which can influence the optimal placement of left ventricle lead. Of course, the CACS examination will not permit the diameters or angles of veins, their tracts or any obstacles such as valves to be measured. It can only be an indirect indication of the state of the coronary veins. Needless to say, we are not recommending that CACS should be performed in all patients before cardiac resynchronization; we are only suggesting a kind of physiological mechanism that should be described in detail in the near future.

CONCLUSIONS

Subjects with a higher amount of coronary artery calcium were more likely to have a greater number of visible coronary veins. The results suggest that there is a link between a variation in the cardiac venous system and the extent of atherosclerosis; however, further investigation is necessary to provide an explanation for this paradox. These results may have clinical implications for cardiac resynchronization therapy.

CONFLICTS OF INTEREST

None.

ACKNOWLEDGMENTS

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CLARIFICATION

The aim of the study was not to prove that the CACS examination can influence the decision about CRT implantation. In fact, the results of the study only document a correlation between CACS and the anatomy of coronary veins. We can only expect that when a patient has a high CACS, we can expect a greater number of coronary veins.

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