Subclinical Burden of Coronary Artery Calcium in Patients With Coarctation of the Aorta

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Coronary computed tomography (CT) angiography is often performed in adults with coarctation of the aorta (CoA) for anatomic assessment. As this population ages, assessment of atherosclerotic cardiovascular disease burden is important. Thus, quantitative and qualitative coronary artery calcium (CAC) scores were assessed for patients with CoA $\geq$ 16 years of age, who were seen at a referral center. CoA patients had either coronary CT angiography or chest CT with interpretable coronary information performed for clinical indications (follow-up, preoperative, or for symptoms) from 2004 to 2017. Qualitative CAC was determined based on low-dose CT and lung cancer screening protocols. Quantitative CAC scores were compared with an age- and gender-matched control cohort of patients chosen from an emergency department database of patients who received coronary CT angiography for chest pain evaluation. Atherosclerotic cardiovascular disease 10-year predicted risk scores were calculated for both cohorts. Out of 131 patients with CoA (mean age 46.1 ± 15.3 years), 22 patients (17%) had multivessel atherosclerotic disease on qualitative assessment. In the subgroup of patients $\geq$ 40 years, those with CoA were more likely to have a quantitative CAC score $\geq$ 400 compared with those without CoA (14% vs 4%, p = 0.02). Median atherosclerotic cardiovascular disease risk score was 8% (interquartile range 2% to 12%) for CoA patients $\geq$ 40 years, and 5% (interquartile range 2% to 9%) for patient without CoA $\geq$ 40 years. In conclusion, we determined that CoA patients have subclinical atherosclerosis identifiable on CT in high rates when compared with patients without CoA. Atherosclerotic cardiovascular disease should be assessed in these patients for prevention and treatment.   © 2018 Published by Elsevier Inc. (Am J Cardiol 2019;123:323−328)

Coarctation of the Aorta (CoA) is a common congenital heart defect.[1,2] Despite repair, morbidity and mortality is higher in this patient population compared with the general population, with coronary artery disease as the leading cause.[3] This risk of coronary artery disease is thought to be due, in part, to abnormal vascular reactivity, as well as residual hypertension, endothelial dysfunction, and increased proinflammatory cytokines all of which may persist after repair.[4−8] Thus, atherosclerotic cardiovascular disease risk prediction in this patient population is important. Several mechanisms have been utilized to assess atherosclerotic cardiovascular disease in the general population as well as high-risk subgroups.[9−12] Coronary artery calcium (CAC) is an independent predictor of incident coronary heart disease that has been validated in a few specialized populations.[13] Its use in atherosclerotic cardiovascular disease risk stratification for patients with CoA has not been thoroughly explored.[14−16] In this study, we not only assessed traditional cardiovascular risk burden and atherosclerotic cardiovascular disease 10-year predicted risk scores for patients with CoA, but specifically sought to characterize the subclinical atherosclerotic burden in this population using quantitative and qualitative CAC scores based on clinically indicated computed tomography (CT) during routine care.

Methods

Patients with CoA followed at a single, tertiary care, academic referral center were included in this study. Patients $\geq$ 16 years of age were retrospectively chosen for this study if they had either a coronary CT angiography or chest CT with interpretable coronary information from 2004 to 2017 (Figure 1). Patient characteristics, laboratory information, imaging results, and clinical outcomes data were collected and managed using an institutional database. Our Institutional Review Board's approval and waiver of consent was granted for this retrospective study.

A control cohort of patients without known CoA was developed from an emergency department database of
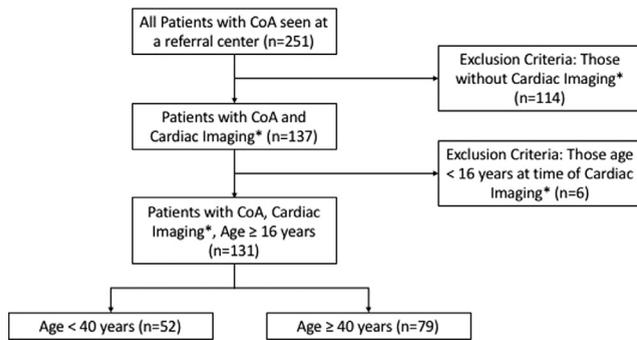
Figure 1. **Patient selection flowchart.** Patient selection flowchart that shows inclusion and exclusion criteria to result in a final study population of 131 patients. CoA = coarctation of the aorta. *Either coronary computed tomography angiography or chest computed tomography with interpretable coronary information.

patients from the same institution who had a coronary CT angiography for chest pain. These patients were deemed low to intermediate risk for acute coronary syndrome at time of their emergency department presentation by the clinician who ordered the coronary CT angiography. For each patient with CoA, 2 control patients were matched individually for age (±2 years) and gender, except 2 patients, for whom 2 matched controls could not be found. Atherosclerotic cardiovascular disease 10-year predicted risk scores were calculated for patients with and without CoA ≥ 40 years of age using the 2013 American College of Cardiology and American Heart Association pooled risk equations.[10]

All patients included in this study underwent either coronary CT angiography or chest CT performed for various indications. The interpretations of images were all performed at the study institution. The scans were reviewed by a dedicated subspecialty imaging fellow-in-training in cardiac CT with an attending imager with over 5 years of clinical experience, all of whom were blinded to diagnosis and outcome.

Patients who underwent coronary CT angiography had a preceding electrocardiography-gated noncontrast scan, from which quantitative CAC scores were derived using a dedicated workstation and the Agatston method. Patients were placed into 4 categories based on calcified atherosclerotic burden as follows: quantitative CAC score 0; quantitative CAC score > 0 and < 100; quantitative CAC score ≥ 100 and < 400; quantitative CAC score ≥ 400.

For patients with CoA, qualitative CAC scores were estimated based on validated protocols derived from patients receiving a low-dose CT for lung cancer screening.[17,18] Each of the 4 main arteries was identified (left main, left anterior descending, left circumflex, and right coronary). For qualitative assessment, calcium in each artery was categorized as absent, mild, moderate, or severe, and scored as 0, 1, 2, or 3, respectively. Calcium was classified as mild when 1/3 of the length of the artery or less showed calcium, moderate when 1/3 to 2/3 of the artery showed calcium, and severe when more than 2/3 of the artery showed calcium. Each patient received a qualitative CAC score ranging from 0 to 12 (the sum of each individual artery's score). For the purposes of this analysis, the 4 categories of CAC were as follows: normal, 0; minimal, 1 to 3; moderate, 4 to 6; severe, 7 to 12.[18]

Baseline characteristics of CoA patients were summarized using medians and twenty-fifth to seventy-fifth percentiles or means and standard deviations for continuous variables. Frequencies and percentages were used for categorical variables. Characteristics and CAC scores were compared between patients with and without CoA using Pearson chi-square tests for categorical variables and Welch 2-sample t test or Wilcoxon rank sum test for continuous variables. Similar methods were used to compare characteristics between patients with CoA who were < 40 years of age or ≥ 40 years of age, as well as quantitative CAC scores and qualitative CAC scores between the 2 age groups. A p value < 0.05 was considered to be significant. All analyses were carried out using R Statistical Software (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

There were 131 patients identified with CoA, who had either a coronary CT angiography or chest CT from 2004 to 2017. There were 259 patients included in the age- and gender-matched control cohort. Demographics and clinical characteristics of the CoA and control population are shown in Table 1. In the overall CoA population, 77% of patients had hypertension, and 10% had a diagnosis of diabetes mellitus. Hypertension was significantly less prevalent in the control cohort (77% vs 38%, p < 0.001). The median atherosclerotic cardiovascular disease 10-year predicted risk score was 8% in those with CoA compared with 5% in those without CoA. The median quantitative CAC score was 65 (interquartile range 17 to 622) for CoA patients who had a nonzero quantitative CAC score. In comparison, the median nonzero quantitative CAC score was 32 (interquartile range 6 to 161) for patients without CoA (p = 0.22). Clinical characteristics for the CoA cohort by age are described in Table 2. CoA patients aged ≥ 40 years were more likely to be older at first repair (20.3 ± 15.7 vs 12.4 ± 13.7, p = 0.006), carry a diagnosis of hypertension (83% vs 67%, p = 0.03), and be prescribed a statin (47% vs 4%, p < 0.001) compared with those age < 40 years.

Quantitative CAC scores for patients with CoA by age are shown in Table 3. Quantitative CAC scores of 0 were identified in 77% of the CoA cohort, and scores ≥ 400 were identified in 8% of the CoA cohort. Those aged ≥ 40 years were more likely to have a quantitative CAC score ≥ 400 (14% vs 0%, p = 0.04). Patients with CoA ≥ 40 years of age were more likely to have a quantitative CAC score ≥ 400 compared with controls (14% vs 4%, p = 0.02; Table 4). When the overall CoA population was compared with the age- and gender-matched control cohort, the rate of patients with quantitative CAC scores ≥ 400 in the CoA cohort was higher than in the cohort without CoA (8% vs 2%, p = 0.03).

Normal appearing coronary arteries (qualitative calcium score of 0) were found in 72% of CoA patients who underwent a nongated chest CT (Table 5). Those age ≥ 40 years were more likely to have minimal or moderate (CAC score 1 to 6) qualitative CAC scores (30% vs 2%, p < 0.001; 11% vs 0%, p = 0.01, respectively) as well as multivessel disease (27% vs 2%, p < 0.001) compared with younger CoA patients.

Table 1
Clinical characteristics of patients with and without coarctation of the aorta

Variable	Total n	Coarctation of the aorta		p value
		Yes (n = 131)	No (n = 259)	
Age (years)*	390	46.1 ± 15.3	46.6 ± 14.9	p = 0.75
Female*	390	60 (46%)	117 (45%)	p = 0.91
White	390	102 (78%)	175 (68%)	p = 0.03
Black	390	2 (2%)	33 (13%)	p < 0.001
Other/Unknown race	390	27 (21%)	51 (20%)	p = 0.83
Systolic blood pressure (mm Hg)*	384	128.2 ± 17.4	127.5 ± 19.0	p = 0.73
Hypertension*	389	100 (77%)	97 (38%)	p < 0.001
Diabetes mellitus*	383	12 (10%)	26 (10%)	p = 0.91
Total cholesterol (mg/dl)*	294	175.5 ± 33.8	187.1 ± 38.8	p < 0.001
High-density lipoprotein (mg/dl)*	294	54.6 ± 17.3	50.8 ± 17.9	p = 0.08
Current smoker*	381	3 (3%)	30 (12%)	p = 0.003
Body mass index (kg/m^2)	354	27.2 ± 6.2	30.1 ± 7.1	p < 0.001
Body mass index ≥ 25 kg/m^2	354	69 (62%)	183 (76%)	p = 0.007
Atherosclerotic cardiovascular disease 10-year predicted risk score (%)	209	8 (2-12)	5 (2-9)	
Agatston score[†]	104	65 (17-622)	32 (6-161)	p = 0.22

Values are mean ± standard deviation, n (%), or median (interquartile range).

* Variables included in atherosclerotic cardiovascular disease 10-year predicted risk score calculator.

[†] In patients with Agatston (quantitative coronary artery calcium) score > 0; for distribution of all scores, see Tables 3 and 4.

Discussion

Our analysis highlights several findings that have important clinical implications for prevention and treatment of atherosclerotic cardiovascular disease in patients with CoA. Patients with CoA have high rates of co-morbidities including diabetes mellitus, hypertension, and high body mass index. A significant number of patients with CoA have subclinical atherosclerosis as demonstrated by both quantitative CAC scores and qualitative CAC scores. Patients with CoA over the age of 40 have a higher

Table 2
Clinical characteristics of patients with coarctation of the aorta by age

Variable	Total n	Age (years)		p value
		< 40 (n = 52)	≥ 40 (n = 79)	
Age (years)*	131	30.8 ± 6.0	56.2 ± 10.5	p < 0.001
Female*	131	26 (50%)	34 (43%)	p = 0.43
White	131	36 (70%)	66 (84%)	p = 0.05
Black	131	1 (2%)	1 (1%)	p = 0.76
Other/Unknown race	131	15 (29%)	12 (15%)	p = 0.06
Age of first repair (years)	111	12.4 ± 13.7	20.3 ± 15.7	p = 0.006
Surgical first repair	114	36 (77%)	54 (81%)	p = 0.61
Catheter-based first repair	114	8 (17%)	9 (13%)	p = 0.60
Unknown type of first repair	114	3 (6%)	4 (6%)	p = 0.86
Systolic blood pressure (mm Hg)*	130	127.6 ± 17.0	128.6 ± 17.7	p = 0.74
Diastolic blood pressure (mm Hg)	130	72.8 ± 15.5	73.6 ± 8.8	p = 0.74
Hypertension	130	35 (67%)	65 (83%)	p = 0.03
Prescribed any antihypertensive medication*	130	34 (65%)	63 (81%)	p = 0.05
Prescribed beta blocker	130	25 (48%)	49 (63%)	p = 0.10
Prescribed ace-inhibitor	130	15 (29%)	21 (27%)	p = 0.81
Prescribed angiotensin receptor blocker	130	6 (12%)	18 (23%)	p = 0.11
Prescribed other antihypertensive	130	7 (14%)	27 (35%)	p = 0.007
Body mass index (kg/m^2)	112	28.3 ± 6.8	26.6 ± 5.8	p = 0.19
Body mass index ≥ 25 kg/m^2	112	29 (73%)	40 (56%)	p = 0.40
Diabetes mellitus*	124	3 (6%)	9 (12%)	p = 0.28
Total cholesterol (mg/dl)*	96	172.5 ± 32.5	176.8 ± 34.7	p = 0.57
High-density lipoprotein (mg/dl)*	96	49.1 ± 12.9	57.3 ± 18.0	p = 0.01
Low-density lipoprotein (mg/dl)	95	102.3 ± 30.0	99.2 ± 30.1	p = 0.645
Prescribed statin	130	2 (4%)	37 (47%)	p < 0.001
Prescribed aspirin	130	20 (39%)	38 (49%)	p = 0.25
Current smoker*	122	1 (2%)	2 (3%)	p = 0.87
Former smoker	122	6 (13%)	24 (32%)	p=0.02

Values are mean ± standard deviation or n (%).

* Variables included in atherosclerotic cardiovascular disease 10-year predicted risk score calculator.

Table 3
Quantitative calcium scores (Agatston) from gated computed tomography in patients with coarctation of the aorta by age group

Quantitative calcium scores	Overall Cohort (n = 64)	Age (years)		p value
		< 40 (n = 28)	≥ 40 (n = 36)	
0	49 (77%)	28 (100%)	21 (58%)	p < 0.001
> 0 and < 100	8 (13%)	0	8 (22%)	p = 0.008
≥ 100 and < 400	2 (3%)	0	2 (6%)	p = 0.21
≥ 400	5 (8%)	0	5 (14%)	p = 0.04

Values are n (%).

prevalence of atherosclerosis on imaging compared with age- and gender-matched controls.

Risk factors for atherosclerotic cardiovascular disease were common in this cohort of CoA patients even in those of young age.[11,12,19−21] Systemic hypertension, overweight or obese body habitus, and diabetes were the most prevalent risk factors for our study population. The prevalence of systemic hypertension in this CoA cohort (77%) was high compared with the general adult US population (29%) as well as our age- and gender-matched cohort (38%). This increased prevalence of hypertension persists across age groups.[22] The high rate of hypertension in CoA patients is well-described and is likely in part due to reduced systemic arterial compliance that persists, or even worsens, despite repair, as well as potential residual lesions.[8,23] Hypertension likely contributes to the prevalence of subclinical atherosclerosis in CoA patients; however, it is unlikely to be the sole driver of atherosclerosis.

The high prevalence of other modifiable risk factors is crucial to address in this CoA population who is at risk for atherosclerotic disease, despite their young age. This population may historically have been encouraged to restrict exercise or had symptomatic limitations due to claudication or other associated heart disease. Additionally, the optimal management of dyslipidemia is particularly challenging, as this patient group is predominantly young, and therefore, falls outside the current guideline-recommended use of the atherosclerotic cardiovascular disease 10-year predicted risk score for assessment of lipid-lowering drug therapy. We show that the CoA population is at higher risk of atherosclerosis compared with their age- and gender-matched peers, and thus may benefit from drug therapy initiation at an earlier age. However, the risks and benefits of lipid-lowering medications in this young group, who despite their elevated risk of atherosclerosis remain at a low-absolute risk of clinical atherosclerotic events until their sixth decade, are still not well defined. It is clear, however, that discussion of lifestyle modification, diet, and exercise, is beneficial at any age, and an important part of their adult congenital specialized care.

A significant number of patients with CoA were found to have subclinical atherosclerosis as identified by CAC scores. A high burden of calcified atherosclerosis was identified in 8% of the overall CoA cohort, and 14% of those age ≥ 40 years. Compared with age- and gender-matched peers, our CoA population had higher rates of subclinical atherosclerosis. Their CAC scores were also higher than healthy controls in large published cohorts from outside our institution. For example, in 2,084 patients included in the Dallas

Table 4
Quantitative calcium scores (Agatston) from gated computed tomography in patients with and without coarctation of the aorta by age group

Quantitative calcium scores	Age <40 years			Age ≥40 years			Overall cohort		
	With coarctation of the aorta (n = 28)	Without coarctation of the aorta (n = 99)	p value	With coarctation of the aorta (n = 36)	Without coarctation of the aorta (n = 160)	p value	With coarctation of the aorta (n = 64)	Without coarctation of the aorta (n = 259)	p value
0	28 (100%)	87 (88%)	0.053	21 (58%)	83 (52%)	0.48	49 (77%)	170 (66%)	0.094
> 0 and < 100	0	12 (12%)	0.053	8 (22%)	50 (31%)	0.28	8 (13%)	62 (24%)	0.05
≥ 100 and < 400	0	0 (0.0)		2 (6%)	21 (13%)	0.20	2 (3%)	21 (8%)	0.165
≥ 400	0	0 (0.0)		5 (14%)	6 (4%)	0.017	5 (8%)	6 (2%)	0.03

Values are n (%).

Table 5
Qualitative calcium scores (total calcium visualized) in nongated chest computed tomography in patients with coarctation of the aorta by age

Qualitative calcium scores	Overall (n = 130)	Age (years)		p value
		< 40 (n = 51)	≥ 40 (n = 79)	
Normal (0)	93 (72%)	50 (98%)	43 (54%)	p < 0.001
Minimal (1-3)	25 (19%)	1 (2%)	24 (30%)	p < 0.001
Moderate (4-6)	9 (7%)	0	9 (11%)	p = 0.01
Severe (7-12)	3 (2%)	0	3 (4%)	p = 0.16
≥ 2 vessels with any calcium visualized	22 (17%)	1 (2%)	21 (27%)	p < 0.001

Values are n (%).

Heart Study, the rate of patients with quantitative CAC scores >400 was 2% for average age 44.4 ± 9.0 years and 5% for average age 56.4 ± 4.0 years.[24] The increased prevalence of subclinical atherosclerosis in our study cohort compared with the Dallas Heart Study is likely multifactorial, as patients with diabetes were excluded from their study.

We recognize the association between low-dose ionizing radiation from cardiac procedures and incident cancer in the adult congenital heart disease population, and that this association, in addition to the ability to assess aortic gradients, leads many of us to utilize magnetic resonance imaging over CT.[25] If coronary CT angiography or a chest CT is performed clinically in the CoA population (cardiac procedural planning, assessment of lung pathology, contraindications to magnetic resonance imaging, or institutional preference), subclinical atherosclerosis should be assessed, as this information can guide clinical decision-making. This is particularly relevant to CoA patients' age ≥ 40 years given the increased incidence of subclinical atherosclerosis in this age group. Importantly, groups including our own have demonstrated that median radiation dose for coronary CT angiography can be greatly reduced from 13.1 milliSieverts to 3.3 milliSieverts using protocols and scanner technology aimed at limiting radiation exposure.[26] More recently, we have lowered doses to a median of 1.6 milliSieverts in women of normal body mass index with improved protocols and technology.[27]

This study has limitations. This was a single-center retrospective study of a small number of individuals with CoA seen at a tertiary institution; therefore, we bear the limitations of a convenience sample. For example, our study also found a higher rate of subclinical atherosclerosis by quantitative CAC scores compared with qualitative calcium scores. We hypothesize that patients who had a coronary CT angiography performed were more likely to have presented with symptoms that required assessment of coronary artery disease, and thus a selection bias may exist within the study cohort. Additionally, the age- and gender-matched cohort without CoA was derived from patients who presented to an emergency department with cardiac symptoms, thus subclinical atherosclerosis may be higher in our control cohort than in a healthy population; this could have minimized the difference seen between our CoA cohort and the controls. Regardless, this study of patients with CoA demonstrates that there is a reasonable prevalence of subclinical atherosclerosis which can be identified in the CoA population when coronary CT angiography or chest CT with interpretable coronary information is available.

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