Journal of Cardiovascular Computed Tomography xxx (2016) 1–5

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.JournalofCardiovascularCT.com

Research paper

Coronary artery anomalies in Turner Syndrome

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ARTICLE INFO

Article history:
Received 18 July 2016
Received in revised form
30 July 2016
Accepted 3 August 2016
Available online xxx

Keywords:
Anatomy
Embryology
Coronary artery disease
Pathology
Abnormal karyotype

ABSTRACT

Background: Congenital heart disease, primarily involving the left-sided structures, is often seen in patients with Turner Syndrome. Moreover, a few case reports have indicated that coronary anomalies may be more prevalent in Turner Syndrome than in the normal population. We therefore set out to systematically investigate coronary arterial anatomy by computed tomographic coronary angiography (coronary CTA) in Turner Syndrome patients.
Methods: Fifty consecutive women with Turner Syndrome (mean age 47 years [17–71]) underwent coronary CTA. Patients were compared with 25 gender-matched controls.
Results: Coronary anomaly was more frequent in patients with Turner Syndrome than in healthy controls [20% vs. 4% ($p = 0.043$)]. Nine out of ten abnormal cases had an anomalous left coronary artery anatomy (absent left main trunk, $n = 7$; circumflex artery originating from the right aortic sinus, $n = 2$). One case had a tubular origin of the right coronary artery above the aortic sinus. There was no correlation between the presence of coronary arterial anomalies and karyotype, bicuspid aortic valve, or other congenital heart defects.
Conclusion: Coronary anomalies are highly prevalent in Turner Syndrome. The left coronary artery is predominantly affected, with an absent left main coronary artery being the most common anomaly. No hemodynamically relevant coronary anomalies were found.

1. Introduction

Turner Syndrome is a condition in which females lack an entire X chromosome or parts thereof. A range of congenital cardiovascular malformations are associated, potentially necessitating medical and surgical treatment.[1] The most frequent malformations include bicuspid aortic valve, aortic coarctation, and/or partial anomalous pulmonary venous return. The aorta is often aneurysmal, may have abnormal branching vessels, and the risk of aortic dissection is high as 40 per 100,000 person years compared to 6 per 100,000 person years in the general population.[2,3]

These abnormalities and the associated morbidity explain part of the increased mortality in Turner Syndrome.[4,5] However, case reports also describe anomalous coronary arteries in Turner Syndrome, which may also contribute to increased morbidity and mortality.[6] In our own clinical experience, we have also frequently encountered abnormal courses or origins of one or both coronary arteries, so awareness of the risk of coronary artery anomalies is crucial. Individuals who require aortic root replacement at young age where coronary artery disease was not expected and dedicated coronary imaging was not recommended may experience surgical

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http://dx.doi.org/10.1016/j.jcct.2016.08.004
1934-5925/

complications and mortality as a result.[7,8]

The genetic background for congenital cardiovascular malformations in Turner Syndrome is unknown, but recent data suggest an association to genetic abnormalities on the short arm of the X chromosome (Xp).[9] However, a number of other genes have also been linked to the development of congenital cardiac anomalies but a causal relationship has yet to be established. Recently, the European Society of Cardiology published a position statement on congenital coronary artery anomalies,[10] presenting views on both normal and abnormal coronary embryogenesis and pathophysiology. This inspired us to examine if women with Turner Syndrome had a high prevalence of coronary anomalies.

We therefore set out to systematically investigate coronary arterial anatomy by computed tomographic coronary angiography (Coronary CTA) in Turner Syndrome patients and relate the findings to the presence of other congenital cardiovascular anomalies and karyotype.

2. Methods

2.1. Study population

Fifty females with karyotypically proven Turner Syndrome were examined with a computed tomography coronary angiography (coronary CTA) over two-year period. Forty-five participants were recruited from a cohort study of cardiovascular health in Turner Syndrome. Non-coronary findings from this cohort study have previously been published.[11–13] An additional five Turner Syndrome women had a coronary CTA performed due to considerations regarding aortic root replacement. All participants were asymptomatic and without known coronary artery disease. A group of 25 females served as controls (Table 1).

2.2. Computed tomography coronary angiography

Computed tomography coronary angiography (Coronary CTA) was performed using a dual-source CT scanner (SOMATOM Definition Flash; Siemens, Forchheim, Germany) with prospective electrocardiographic triggering acquisition performed in all patients and controls. In the event of a heart rate $\leq$65/min or >65/min, the RR scan intervals were 65%–75% and 40%–70%, respectively. Data acquisition was performed using 100 or 120 kV tube voltage in patients weighing $\leq$70 or >70 kg, respectively. The imaging studies were evaluated by two coronary CTA experts, who were blinded to all clinical data.

The coronary artery anatomy was classified according to the ESC position paper into the following subgroups[9]: A) Anomalies of coronary artery connection; B) Anomalies to the aorta/systemic circulation; C) Anomalous coronary artery ostium location within or near the proper aortic sinus; D) Anomalous coronary artery ostium location at improper aortic sinus–wrong sinus; E) Single coronary artery; F) Anomalous coronary artery ostium location outside sino-tubular aorta; G) Anomalies of intrinsic coronary artery anatomy; H) Anomalous coronary artery ramification; and I) Anomalous myocardial/coronary artery interaction. The coronary arterial system was classified as right dominant when the posterior descending artery originated from the right coronary artery (RCA). Left dominance was defined when the posterior descending artery originated from the left circumflex artery (LCx). A balanced dominant coronary system was categorized when the posterior descending artery originated from the RCA in combination with a large posterolateral branch originating from the LCx entering the posterior interventricular groove.[14]

Table 1
Demographics of participants.

	Controls n = 25	Turner syndrome n = 50
Age (years)	53 (26–70)	47 (17–71)
Weight (kg)	71 (47–99)	57 (40–84)
Height (cm)	170 ± 7	148 ± 7
BMI (kg/m^2)	25.0 ± 4	26.5 ± 4

2.3. Aortic valve morphology

In most cases, the morphology was determined by echocardiography or MRI. Two cases had an aortic valve prosthesis. In these cases, the surgical notes were retrieved for assessment of valve morphology.

2.4. Ethics

Informed consent was obtained from all participants, and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki and is approved by Aarhus County Ethical Scientific Committee (Denmark) (#2012-500-12).

3. Statistical methods

Mathematical computations were performed using Stata Statistical Software: Release 12.1 (College Station, TX: StataCorp LP) and R 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Normality was assessed by Q-Q-plots of absolute or log-transformed values and box-plots were scrutinized for outliers. Comparisons of continuous variables were performed using Student's independent *t*-test (mean ± SD or for transformed values, as median with range) or Mann–Whitney *U* test (median with range) as appropriate. Comparison of nominal variables were performed using the likelihood ratio test for 2 × 2 tables[15] or Fisher's exact test if one or more cells contained zero counts. Contingency tables larger than 2 × 2 were analyzed with the exact test for multinomial data. A p-value <0.05 was considered significant.

4. Results

Demographic data are summarized in Table 1. The patient's karyotypes were 45, X in 28 cases, with 20 cases having other karyotypes compatible with Turner Syndrome (Supplementary Table 1).

Seventeen Turner Syndrome patients had a bicuspid aortic valve (34%) and nine (18%) were diagnosed with aortic coarctation. The two patients with mechanical valve prostheses had bicuspid aortic valves prior to operation. Four women had partial abnormal pulmonary venous drainage. One of these four patients also had aortic coarctation and a bicuspid aortic valve. Fig. 1 displays an overview of the different congenital heart defects related to the presence of a coronary anomaly and karyotype.

Detailed and conclusive coronary CTA images were obtained in all cases (Figs. 2–3). Compared to the control group, Turner Syndrome women had a significantly different coronary arterial distribution with a higher prevalence of left dominant coronary anatomy: Right dominance Turner Syndrome: 60% vs. Controls: 76%; left dominance, Turner Syndrome: 28% vs. Controls: 20%; and balanced dominance, Turner Syndrome: 12% vs. Controls: 4% (overall, p = 0.01).

Abnormal coronary arterial anatomy was found in 20% in Turner Syndrome (Table 2). In 9 out of 10 abnormal cases, the left coronary artery was involved with either an absent left main (LM) (Fig. 2A) or LCx originating from the right aortic sinus (Fig. 2B). In only one case,

Please cite this article in press as: Viuff MH, et al., Coronary artery anomalies in Turner Syndrome, Journal of Cardiovascular Computed Tomography (2016), http://dx.doi.org/10.1016/j.jcct.2016.08.004

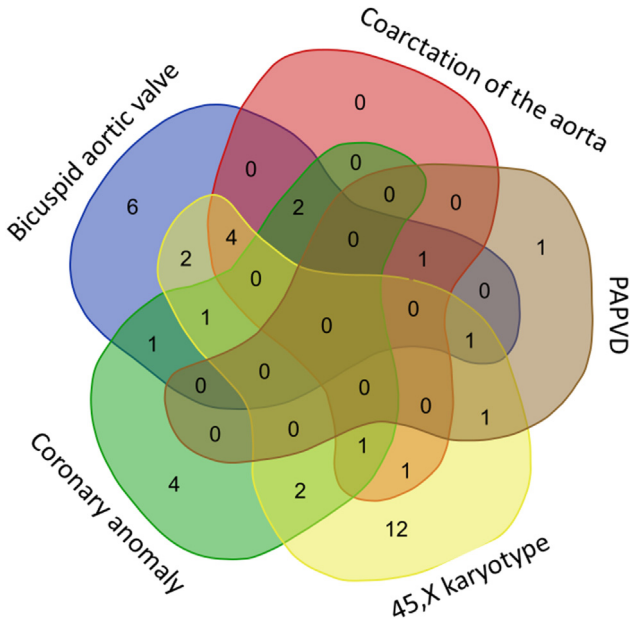

Fig. 1. Venn diagram illustrating the overlap between congenital heart defects and the 45, X karyotype. PAPVD=Partial Anomalous Pulmonary Venous Drainage.

the RCA was involved in the form of a high 'tubular' origin above the aortic sinus (Fig. 3A). This latter patient also had a bicuspid aortic valve, aortic coarctation, and aortic dilation.

There was no association between the presence of a bicuspid aortic valve and coronary artery anatomy (bicuspid valve, n = 5 (29%) versus tricuspid valve, n = 7 (21%) (n = 7), p = 0.5). Also, there was even distribution of coronary anomalies in karyotype 45, X compared with other karyotypes, 16% vs. 25% (p = 0.4).

5. Discussion

This first systematic study of congenital coronary arterial anomalies in Turner Syndrome showed a remarkably high prevalence of coronary anomalies, primarily involving the left coronary artery. In the general population, the prevalence of coronary anomalies approximates 5%,[16] compared to more than 20% of the present cohort of patients with Turner Syndrome. Interestingly, anomalies of the RCA are most common in the normal population,[17] whereas anomaly of the left coronary arteries seem to be more frequent in Turner Syndrome patients.

Absent LM was the most frequent finding in this study. In the general population, this anomaly is seen in less than one percent and is considered benign and without clinical implications.[16] One patient in this study had a high origin of the RCA, previously shown in a single case report regarding a Turner Syndrome patient.[8] In isolation, this anomaly is not associated with increased risk, but is important to visualize by coronary CTA before embarking on aortic root surgery or revascularization in patients with Turner Syndrome.[18] This is irrespective of age, risk of coronary atherosclerosis, or symptoms, which are conventional indications for undertaking preoperative coronary arterial angiograms.

In this report, the LCx was noted to have an anomalous origin from the opposing sinus in two cases. This anomaly is normally seen in less than 1% of the normal population, and is not suspected to cause myocardial ischemia in contrast to anomalies that have an interarterial course.[19] However, it may be hypothesized that the potentially lethal anomalies with either the LAD or the RCA arising from the opposite sinus and an interarterial course could exist with

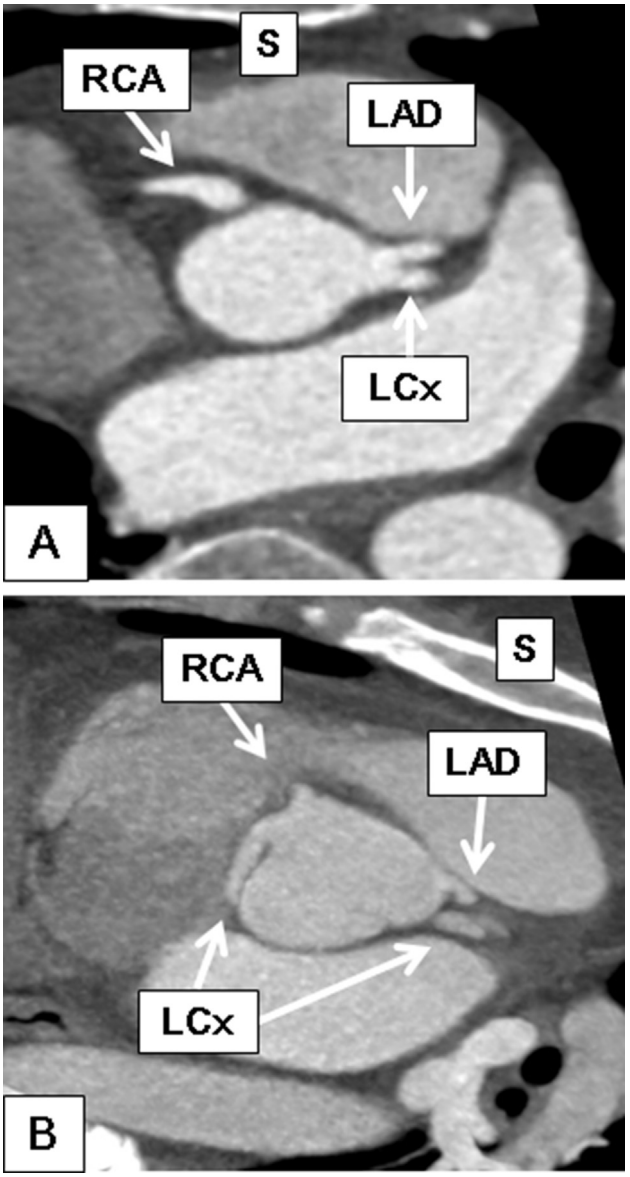

Fig. 2. . Computed tomography coronary angiography of two different coronary anomalies: A) Absent left main, B) LCx from opposite sinus. Figure annotations: S: Sternum; RCA: Right coronary artery; LAD: Left anterior descending coronary artery; LCx: Left circumflex coronary artery.

a higher frequency in Turner Syndrome. Such anomalies could contribute to the increased risk of sudden cardiovascular death in Turner Syndrome.[4] For this reason, coronary arterial anatomy should be visualized at the first encounter with a Turner Syndrome patient either by an echocardiogram in newborns and infants, or by coronary CTA[20] or magnetic resonance imaging[21] in the asymptomatic adult population, if not readily seen by echocardiography.

In our own center (Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark), a 25-year old TS with the LCx originating from the opposing sinus, died from cardiogenic shock immediately after aortic root replacement. The patient suffered from a massive infarct in the left ventricle due to occlusion of the circumflex artery after the aortic root prosthesis was put in. This was probably caused either by spacing problems or a suture through the vessel (See Fig. 2B). This experience emphasizes that aortic root or aortic valve replacement should be done with caution in these cases.

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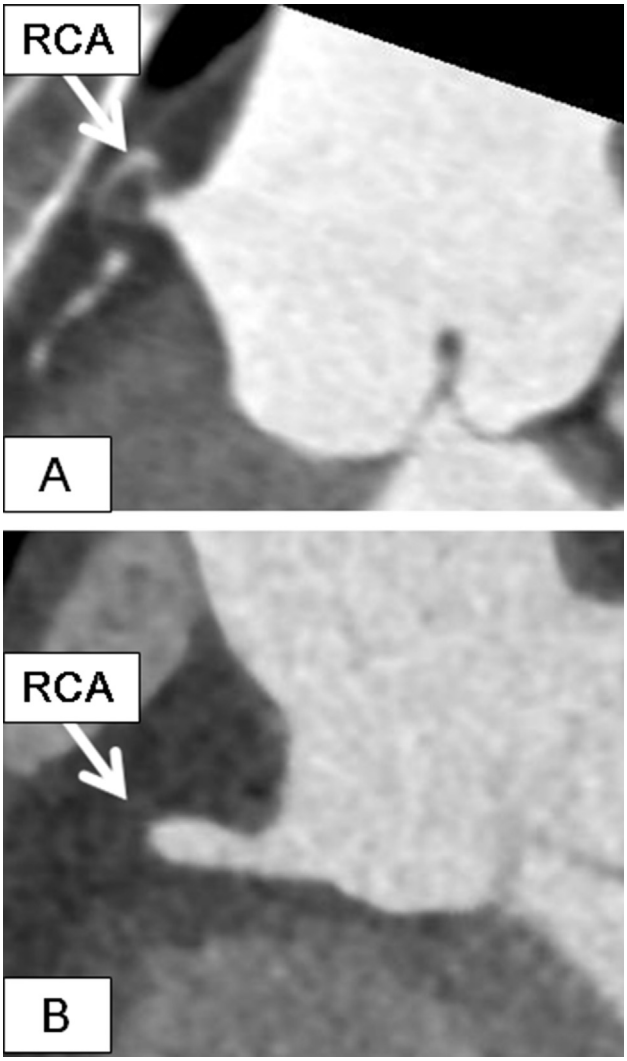

Fig. 3. . Two images of the right coronary artery take-off from the aortic root. Panel A. High origin above the aortic sinus. Panel B. Normal origin from the aortic sinus.

The etiology behind the high prevalence of coronary arterial anomaly in Turner Syndrome is unclear. The left coronary artery was more frequently involved than the RCA, which is in accordance with other types of left sided congenital anomalies found in Turner Syndrome, including mitral and aortic valve disease, hypoplastic left heart syndrome, and anomalous pulmonary vein drainage.[22] However, there does not seem to be any connection to bicuspid aortic valve morphology since we did not find any clear co-segregation between the presence of coronary artery anomalies and bicuspid aortic valves. We also found a similar number of coronary anomalies in patients with other congenital cardiac anomalies. Moreover, there was no relationship between the karyotype and the frequency of coronary anomaly, indicating that TS mosaic females may have the same risk of having abnormal coronary arterial anatomy as the classical 45, X monosomy. However, it should be acknowledged that the present findings were based on a relatively small sample size, thus larger studies are needed for further delineation of these issues.

Table 2
Coronary arterial anomalies in Turner Syndrome.

Coronary arterial anatomy	Healthy controls n = 25	Turner syndrome[a] n = 50
Normal	96% (24/25)	80% (40/50)
Absent left main trunk	4% (1/25)	14% (7/50)
LCx from opposite sinus	0% (0/25)	4% (2/50)
High origin of RCA	0% (0/25)	2% (1/50)

[a] p = 0.043 for the comparison coronary anomaly vs. normal coronary anatomy.

Importantly, the present observational report leaves us without an explanation for why coronary anomalies are more frequent in Turner Syndrome. The embryonic development of the coronary arteries has been under some debate over recent decades, but it seems that the origin of the coronary arteries occurs by outward budding from the aorta.[23] Angiogenic cells are thought to be necessary for the establishment of the coronary vessels and VEGF-C expression throughout the aorta suggests that it plays an important part in the early coronary angiogenesis. However, the specific mechanism determining the exact location of the coronary vessel origin remains unknown.[24] Interference with this development can result in misaligned coronary artery origins and course. Understanding how this process is influenced by the function of the X chromosome will not only shed light on cardiac disease in Turner Syndrome, but may also help in the understanding of the molecular mechanisms behind coronary vessel development.

The current findings clearly imply that it is important to recognise that coronary artery disease in Turner Syndrome is not solely atherosclerosis but also a congenital issue with implications beyond the presence of a bicuspid aortic valves or a coarctation of the aorta.

6. Limitations

The number of included cases in this report is relatively low. However, this is the first study of its kind and as such has relevance beyond the few available case reports that have heretofore been published. Importantly, we performed this study without having an index case, thus issues related to selection bias were negligible.

7. Conclusions

Coronary anomaly is prevalent in Turner Syndrome, and involves mainly the left coronary arterial system with absence of the left main coronary artery being the most commonly encountered anomaly. No hemodynamically relevant coronary anomalies were found.

All individuals with Turner Syndrome should be screened for coronary anomaly using echocardiography and coronary CTA in the surgical planning stage before aortic root replacement even in the absence of clinical symptoms.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcct.2016.08.004.

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