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Coronary computed tomography angiography and echocardiography in children with homozygous familial hypercholesterolemia

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HIGHLIGHTS

- Low-dose computed tomography angiography (cCTA) enables early detection of subclinical atherosclerosis in homozygous familial hypercholesterolemia (hoFH).
- Low-dose cCTA seems superior to echocardiography in assessing atherosclerosis.
- Adjusting therapy on atherosclerosis detection might impact outcome in hoFH children.
- Low-dose cCTA should be routinely performed in hoFH children.

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ABSTRACT

Background and aims: Homozygous familial hypercholesterolemia (hoFH) is a rare genetic disease, hallmarked by a lifelong exposure to very high levels of low-density lipoprotein cholesterol (LDL-C). Untreated, patients can experience a cardiovascular event in the first decade of life. Early detection and monitoring of subclinical atherosclerosis in these patients is therefore extremely important. We set out to assess the diagnostic yield of low-dose coronary computed tomography angiography (cCTA) compared to echocardiography in detecting subclinical atherosclerosis.

Methods: For this single-center cross-sectional study, we included all pediatric hoFH patients treated with lipoprotein-apheresis (LA) in Amsterdam UMC. We performed both cCTA and echocardiography in all patients as part of routine follow-up.

Results: Six hoFH patients were included. Median ages at diagnosis, onset of LA and cardiovascular assessment (cCTA and echocardiography) were 2.6, 6.5, 10.8 and 11.1 years, respectively. Echocardiography revealed no signs of atherosclerosis in any of the six patients. In two patients, mild dilatation of the cardiac chambers was detected and two patients showed signs of mitral or aortic insufficiency. On cCTA, however, non-calcified plaques without stenosis were detected in four patients. In two patients calcified coronary plaques were found at the ostia of the right coronary artery or the left main coronary artery. Aortic root calcifications were found in two patients.

Conclusions: Our findings suggest that in hoFH children, low-dose cCTA is superior to echocardiography for the detection of subclinical coronary and aortic root atherosclerosis and should therefore be considered in the routine cardiovascular monitoring of these high-risk children.

1. Introduction

Homozygous familial hypercholesterolemia (hoFH) is a rare genetic disease caused by mutations in both alleles of the low-density lipoprotein (LDL) receptor gene or other genes encoding key proteins involved in LDL-cholesterol (LDL-C) metabolism. The disease is characterized by extremely elevated circulating LDL-C, leading to premature atherosclerotic cardiovascular disease (CVD). Due to the

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Table 1
Demographic and clinical characteristics of the six hoFH patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)						
At diagnosis	1.9	0.9	0.3	3.3	7.2	9.4
At start medication	1.7	2.2	1.0	4.3	7.2	8.5
At start LA	3.4	5.5	6.2	6.8	10.3	11.5
At last echo	4.1	9.5	9.2	12.7	16.3	18.0
At last cCTA	3.1	8.1	9.0	12.4	15.3	16.6
Gender	Female	Male	Female	Female	Male	Female
Mutations						
Name	W23X D206E	dupl exon11-12 dupl exon11-12	314–1 S285L	313 + 1/2 (intron 3) 313 + 1/2 (intron 3)	2417insG exon 17 D283 N exon 6	dupl exon11-12 dupl exon11-12
Type	Null/Defective	Null/Null	Null/Defective	Null/Null	Null/Defective	Null/Null
Xanthoma at diagnosis	Yes	Yes	No	Yes	Yes	Yes
Treatment						
Medication	Rosuvastatin 5 mg Ezetimibe 10 mg	Rosuvastatin 20 mg Ezetimibe 10 mg	Rosuvastatin 20 mg Ezetimibe 10 mg	Rosuvastatin 20 mg Ezetimibe 10 mg	Rosuvastatin 20 mg Ezetimibe 10 mg	Rosuvastatin 20 mg Ezetimibe 10 mg
Frequency LA	1/week	1/week	1/week	1/week	1/week	1/week
Lipid levels (mmol/L)						
LDL-C at diagnosis	16.50	14.18	14.15	20.82	16.89	18.8
LDL-C on medication	9.72	9.87	8.08	13.25	9.14	11.15
Mean LDL-C on LA	4.65	3.6	2.90	3.81	4.50	3.06

cCTA = coronary computed tomography angiography, LA = lipoprotein apheresis, LDL-C = low-density lipoprotein cholesterol.

severity of the disease, untreated patients with hoFH can experience their first cardiovascular event in the first decade of life and generally do not survive past 30 years of age [1–3].

Since the extent of atherosclerosis is directly associated with the cholesterol-year score [4], which is an integrated measure of the severity and the duration of elevated LDL-C levels, treatment of children with hoFH is targeted at lowering LDL-C. In most patients statin therapy does not sufficiently lower LDL-C and all guidelines for treatment of hoFH patients therefore suggest initiation of lipoprotein-apheresis (LA) as early as possible [4,5]. Although LA has shown to be highly effective in removing LDL-C, there is debate about the target LDL-C level for these children and the indicated intensity of this stressful therapy in terms of frequency. This makes an adequate monitoring of atherosclerosis extraordinary important for these children.

The accelerated atherosclerosis typically affects the aortic root, the coronary ostia and the aortic valve. Diagnosis and monitoring of accelerated atherosclerosis is critical in these patients in order to prevent clinical CVD [6,7]. Since conventional coronary angiography is an invasive procedure and can even be dangerous in children with hoFH [8], there is an urgent need for reliable noninvasive imaging techniques to monitor the development of atherosclerosis.

Therefore, in a recent position paper of Cuchel et al. [8], annual echocardiographic evaluation of the heart and aorta is recommended, and, if available, coronary computed tomography angiography (cCTA) every 5 years. In children however, the high radiation exposure of standard cCTA made routine assessment not desirable. With the introduction of next generation CT scanners with low-dose radiation, imaging by cCTA has become more acceptable for regular use in children. However, the added value of cCTA to echocardiography in monitoring atherosclerosis in hoFH children has not been evaluated so far.

The aim of the current study was therefore to assess the diagnostic yield of low-dose cCTA, compared to echocardiography in determining plaque and/or calcification of the aortic root and the coronary arteries of hoFH children on LA.

2. Materials and methods

2.1. Study population

For this single-center cross-sectional study we included all pediatric hoFH patients that were treated with LA in Amsterdam UMC, the Netherlands and had undergone a complete routine cardiac screening including an assessment of medical history, physical examination, electrocardiography, echocardiography and cCTA.

2.2. Echocardiographic measurements

All patients were studied using the Vivid E95 ultrasound system (GE Medical Systems, USA) using a standardized protocol that includes M-mode echocardiography and two-dimensional gray scale images. Off-line analysis was done using the EchoPac workstation (GE Medical Systems, USA). Echocardiography and all other analyses were done by two pediatric cardiologists (IMK and AB). Analysis was performed in accordance with the guidelines of the American Society of Echocardiography (ASE) [9].

To assess the aortic root diameter, the following parameters were analyzed in two-dimensional mode: aortic valve annulus, sinus of Valsalva, and sinotubular junction. Valve abnormalities (mitral valve and aortic valve) were graded using the guidelines and standards of the ASE [10].

The ostia and proximal segments of the coronary arteries were subjectively assessed for luminal narrowing.

To investigate left ventricular function, the left ventricular ejection fraction (LVEF) was determined according to the Simpson method. For children an EF > 50% was considered normal.

Also, M-mode echocardiography was performed from parasternal long axis views to analyze fractional shortening (FS) as another measure for left ventricular (LV) systolic function. For children an FS between 28 and 44% was considered normal.

Table 2
Results of the echocardiographic examinations.

Patient	LVEF 2Ch	LVEF 4Ch	LVEF BiP	%FS	MI	AI	Atria	Ventricles	Origo coronary	Ao Valve	Ao Root
1	63.3%	58.7%	61.8%	33.1%	–	–	Mild dilatation (right), some indication for restriction	–	NA	NA	NA
2	52.5%	49.7%	51.1%	30.6%	–	–	–	–	NA	NA	NA
3	57.7%	51.1%	54.1%	37.8%	Mild MI	Mild AI	–	–	NA	NA	v
4	61.0%	50.8%	55.9%	37.1%	–	–	Mild dilatation (left)	Mild dilatation (left)	NA	NA	NA
5	54.2%	55.6%	55.2%	32.2%	–	Mild AI	–	Hyper trabe-cularisation of both ventricles	NA	Cloverleaf Ao valve	Slightly dilated Ao root
6	41.9%	61.6%	51.9%	34.8%	Mild MI	–	–	–	NA	NA	NA

LVEF = left ventricular ejection fraction, 2CH = 2 chamber view, 4CH = 4 chamber view, FS = fractional shortening, MI = mitral insufficiency, AI = aortic insufficiency, Ao = aortic, NA = no abnormalities.

Fig. 1. Coronary computed tomographic angiography of the left anterior descending artery (LAD).
Two yellow lines indicate non-calcified plaque in patient 6. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.3. Coronary computed tomography angiography

From June 2015, a third generation dual source CT-scanner (Siemens Somatom Force, Germany) was used for cCTA in our hospital. A prospective ECG-triggered high-pitch spiral scan sequence was applied for patients in sinus rhythm and a heartrate below 70 beats per minute. A prospective ECG-triggered sequential step and shoot sequence was used for patients with an irregular heartrate or heartrate above 70 beats per minute. The lowest feasible tube voltage was selected by using care-kV (range 70–120 kV). Intravenous iodine-based contrast medium (Ultravist 300 mg/ml, Bayer Healthcare Pharmaceuticals, Berlin, Germany) was administered via venous access at the antecubital fossa with an injection speed adjusted to body weight and ranging from 0.3 (0.5 kg body weight) tot 4 ml/s (44 kg body weight). Scans were analyzed and reported by an experienced cardiovascular radiologist using dedicated coronary post-processing software (SyngoVia, Siemens). Coronary anatomy, vessel wall irregularities by calcified plaque, mixed plaque or non-calcified plaque and luminal stenosis was assessed.

Table 3
Results of the coronary computed tomography angiography.

Patient	RCA	LMCA	LAD	Cx	Ao Valve	Ao Root	DLP	Dosis	Scan
1	NA	NA	NA	NA	NA	NA	39	0.7	SeqSys
2	Non-calcified plaque[a]	NA	Non-calcified plaque[a]	NA	NA	NA	108	1.9	SeqSys
3	NA	NA	NA	NA	NA	NA	156	2.8	SeqSys
4	NA	Calcified plaque[a]	Non-calcified plaque[a]	NA	NA	Calcification	63	1.1	SeqSys
5	Calcifications at ostia with non-calcified plaque[a]	Calcifications at ostia[a]	NA	NA	NA	Calcification	85	1.5	TfDia
6	Non-calcified plaque[a]	NA	Non-calcified plaque[a]	NA	NA	NA	176	3.2	TfSys & SeqSys

RCA = right coronary artery, LMCA = left main coronary artery, LAD = left anterior descending artery, Cx = circumflex artery, Ao = aortic, DLP = dose-length product, NA = no abnormalities.
[a] All calcified and non-calcified plaques are eccentric with outward remodeling and without luminal stenosis.

2.4. Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of patients, outcome of echocardiography and outcome of cCTA. The Statistical Package for Social Sciences (SPSS) version 23.0 for windows (version 23.0, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

3. Results

3.1. Study population

The single center study cohort included six children with hoFH who needed LA, diagnosed between 2008 and 2016. All patients were homozygous or compound heterozygous for LDL receptor mutations. In all children LA was performed via an AV-fistula in the left arm.

Patient demographics, type of mutation, and lipid levels at onset of disease, under medication and under chronic weekly LA, are presented in Table 1. Age at diagnoses ranged from 0.3 to 9.4 years and age at starting LA ranged from 3.4 to 11.5 years. Mean (standard deviation [SD]) LDL-C at diagnosis was 16.9 (2.6) mmol/L with a range of 14.2–20.8 mmol/L. On LA, mean (SD) LDL-C was 3.8 (0.7) mmol/l. Other risk factors for CVD (smoking, hypertension and diabetes) were not present in this cohort. None of the patients had ever experienced clinical signs of a cardiovascular event.

3.2. Echocardiography

Echocardiography revealed no signs of calcifications or thickening of the aortic valve or the aortic root in any of the six hoFH patients. In one patient, a cloverleaf aortic valve was detected, along with a slightly dilated aortic root with subsequent mild aortic insufficiency (AI) (Table 2). In a second patient, both a mild mitral insufficiency (MI) and a mild AI were present. A third patient showed a mild MI. Dilatation of the left atrium as well as the left ventricle was detected in a fourth patient. Right atrial dilatation was seen in a fifth patient (Table 2).

No luminal narrowing was observed in the right or left coronary artery in any of the patients.

In all patients the mean LVEF was within normal range. Shortening fraction was also normal in all hoFH children.

3.3. Coronary computed tomography angiography

The median irradiation exposure with the low-dose CT-scanner was 105 DLP (range 39–176).

Non-calcified plaques without stenosis were detected in four patients and all lesions were eccentric without narrowing or major luminal stenosis. An example of a non-calcified plaque is shown in Fig. 1. In two patients, calcified coronary plaques were found at the ostia of the right coronary artery (RCA) or the left main coronary artery (LMCA) (Table 3 and Fig. 2A). Aortic root calcifications were found in two

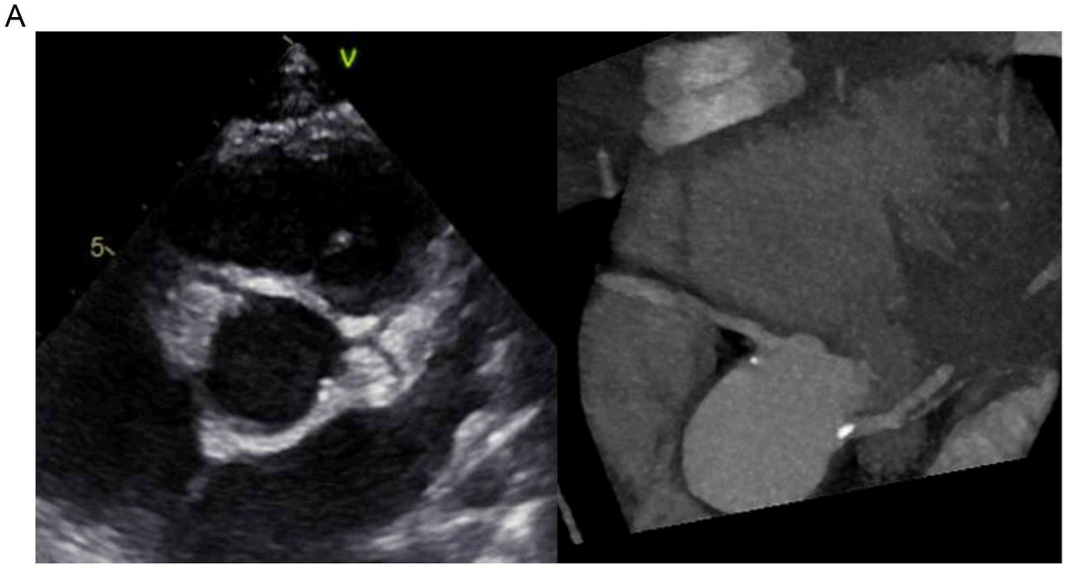

Fig. 2. (A) Images of the aortic root by echocardiography in short-axis view (left panel) and with corresponding coronary computed tomography angiography (cCTA) maximum intensity projection (MIP) reconstructions (right panel). cCTA reveals calcifications at the coronary origin and aortic root that were not detected by echocardiography (patient 5). (B) Echocardiography (left panel) and corresponding coronary computed tomographic angiography (cCTA) maximum intensity projection (right panel). On echocardiography no signs of atherosclerosis were seen, while using cCTA aortic root calcifications were shown (patient 4).

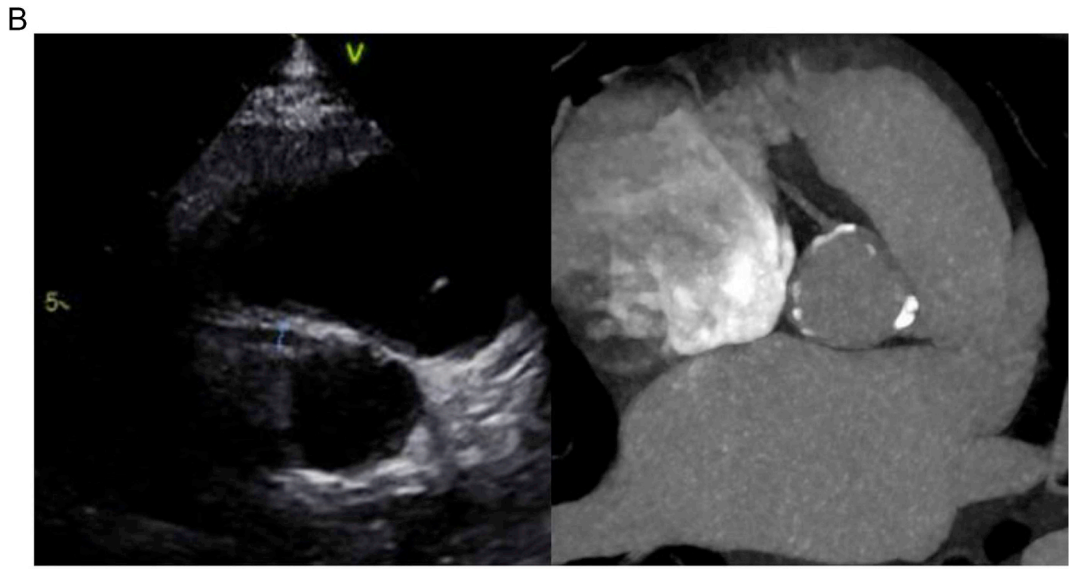

Fig. 2. (*continued*)

patients (Fig. 2B) and no abnormalities of the aortic valve were visible with cCTA. Two out of the six patients showed no abnormalities on cCTA.

4. Discussion

We found significant signs of atherosclerosis in four out of six pediatric hoFH patients by low-dose cCTA, which were not detected in any of these patients by echocardiography. These abnormalities consisted of both calcified and non-calcified plaques of the coronary arteries and the aortic root. Echocardiography revealed a cloverleaf aortic valve in one patient, along with a slightly dilated aortic root with subsequent mild AI and dilatation of atria and/or ventricles in two other patients and mild MI.

To our knowledge, this study is the first to compare echocardiography and low-dose cCTA to determine the cardiovascular status of children with hoFH. Several studies have reported on the use of cCTA in patients with familial hypercholesterolemia (FH), but none of these studies targeted the pediatric population specifically. Santos et al. performed cCTA in five hoFH patients, the youngest being 15 years of age [11], and found atherosclerotic plaques in the aorta as well as in the coronary ostia in all five patients. No echocardiography results were reported, but all subjects had negative exercise stress tests and myocardial scintigraphy examinations. Miname et al. found significantly more signs of coronary atherosclerosis in FH patients compared to healthy controls as assessed by cCTA, but no echocardiographic results were reported [12].

The premature atherosclerosis typically affects the aortic root, the coronary ostia and the aortic valves. Often these manifestations occur in the first two decades of life [7]. Multiple studies established that once valvular and supra-valvular aortic disease is present, this can further progress even if cholesterol levels are effectively reduced by medication and LA [13,14]. Furthermore, depending on the severity of the phenotype, impaired cardiac function can develop in pediatric hoFH patients as a result of left ventricular hypertrophy due to left ventricular outflow obstruction associated with aortic valve stenosis. Given the high risk of cardiovascular events in children with hoFH, early detection of subclinical aortic and/or coronary atherosclerosis and impaired cardiac function is of pivotal importance and should start at a young age.

Although echocardiography seems to be inferior to cCTA in detecting subclinical atherosclerosis, it still may have additional value in the monitoring of cardiac function of hoFH children on LA. Echocardiography revealed discrete functional abnormalities, like valve insufficiencies and dilatation of the cardiac chambers. The latter could be the direct result of the application of an AV-fistula in patients on LA. There are no data on the effects of AV fistula in hoFH or other non-renal patients, but in renal patients, an AV-shunt has indeed been associated with increased cardiac output and dilatation of cardiac chambers [15,16]. Yet, the application of an AV-shunt may be advantageous to the patient as it may reduce the LA session time from over 3 to less than 1.5 h with the same efficacy, due to the possibility to increase the blood flow, which is an important improvement in quality of life. Careful monitoring of potential detrimental (and reversible) effects on the cardiac function by echocardiography is essential for these patients.

Some limitations of our study merit discussion. First, we could only include six pediatric hoFH patients on LA, and this small sample may limit extrapolation of our results to the entire population of hoFH children. The paucity of patients made a more solid study design impossible, reason why we performed an observational study. However, due to the rare nature of the disease we did include all pediatric hoFH on LA in the Netherlands. Since the outcomes were so different between both methods, we believe that our observations are important and warrant the conclusion that our data indeed suggest that cCTA is importantly superior to echocardiography Further research in pediatric hoFH populations from other countries, might establish the robustness of our findings.

Furthermore, cCTA and echocardiography were not performed on the same day. Still, we believe that our conclusions are valid since echocardiography was performed after the cCTA in all patients.

In conclusion, our findings suggest that in children with hoFH, low-dose cCTA is superior to echocardiography for the detection of subclinical coronary and aortic root atherosclerosis. Therefore, on top of echocardiography for monitoring cardiac function, low-dose cCTA should be considered in the routine follow-up of children with hoFH to detect and monitor subclinical atherosclerosis.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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