SYSTEMATIC REVIEW

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# Optical coherence tomography of the pulmonary arteries in children with congenital heart diseases: A systematic review

Ling Sun | Qiuping Jiang | Yumei Xie | Shushui Wang | Zhiwei Zhang

Department of Pediatric Cardiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong Cardiovascular Institute, Guangdong Provincial Key Laboratory of South China Structural Heart Disease, Guangzhou, Guangdong, China

**Correspondence**
Zhiwei Zhang, Department of Pediatric Cardiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong Cardiovascular Institute, Guangdong Provincial Key Laboratory of South China Structural Heart Disease, Guangzhou 510080, Guangdong, China.
Email: drzhangzhiwei@sina.com

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## ABSTRACT

**Importance:** Optical coherence tomography (OCT) is a high-resolution intravascular imaging tool and has shown promise for providing real-time quantitative and qualitative descriptions of pulmonary vascular structures *in vivo* in adult pulmonary hypertension (PH), while not popular in pediatric patients with congenital heart diseases (CHD).

**Objective:** The aim of this review is to summarize all the available evidence on the use of OCT for imaging pulmonary vascular remodeling in pediatric patients.

**Methods:** We conducted the systematic literature resources (Cochran Library database, Medline via PubMed, EMBASE, and Web of Knowledge) from January 2010 to December 2021 and the search terms were "PH", "child", "children", "pediatric", "OCT", "CHD", "pulmonary vessels", "pulmonary artery wall". Studies in which OCT was used to image the pulmonary vessels in pediatric patients with CHD were considered for inclusion.

**Results:** Five studies met the inclusion criteria. These five papers discussed the study of OCT in the pulmonary vasculature of different types of CHD, including common simple CHD, complex cyanotic CHD, and Williams-Beuren syndrome. In biventricular anatomy, pulmonary vascular remodeling was primarily reflected by pulmonary intima thickening from two-dimensional OCT. In single-ventricle anatomy, due to the state of hypoxia, the morphology of pulmonary vessels was indirectly reflected by the number and shape of nourishing vessels from three-dimensional OCT.

**Interpretation:** OCT may be an adequate imaging procedure for the demonstration of pulmonary vascular structures and provide additional information in pediatric patients.

## KEYWORDS

Children, Congenital heart diseases, Optical coherence tomography, Pulmonary hypertension, Pulmonary vessels

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## INTRODUCTION

Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure (mPAP) ≥20 mmHg at rest, which can only be assessed using right heart catheterization (RHC).[1] Despite advances that have been achieved in understanding its etiology, pathophysiology, management, and prognosis, PH-related morbidity and mortality remain high in pediatric patients.[2–4] Many cardiopulmonary diseases associated with PH are unique to pediatric patients, and the exact causes of PH remain unclear.[5] Congenital heart diseases (CHD) are a common etiology of PH in pediatric patients. Left to right shunt causes volume and pressure overload on the pulmonary vascular bed, resulting in vascular remodeling, including neointimal formation, intimal fibrosis, and medial thickening. Subsequently, concentric intimal fibrosis, plexiform and dilatation lesions lead to an increase in pulmonary vascular resistance (PVR).[6,7] As to univentricular anatomy, the creation of the Fontan circulation results in elevated systemic venous pressure and loss of pulmonary artery (PA) pulsatile flow from the Glenn stage to Fontan completion. This can induce vascular and ventricular remodeling plus angiogenesis in the pulmonary circulation, with subsequent elevation in PVR.[8,9] Most children with PH are not diagnosed timely due to a lack of significant clinical manifestations at an early stage, which causes the development of Eisenmenger's syndrome. Therefore, it is important to prevent and diagnose PH timely.

It is widely recognized that the hallmark of PH is structural alterations of the pulmonary vascular wall,[10] but a direct morphological assessment of the pulmonary vessel is limited to pulmonary angiography and lung biopsy.[11] Most information regarding alterations in pulmonary vasculature is primarily obtained from postmortem or postoperative specimens.[12] With the rapid development of intravascular imaging modalities, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have demonstrated promise for providing a real-time quantitative and qualitative assessment of pulmonary vascular structures *in vivo*.[13–16] IVUS can explore pulmonary arteries ranging from 2 to 5 mm in diameter and has been validated to be a reliable method, but it remains insufficient for accurate assessment of pulmonary vessel changes.[17,18] OCT is a high-resolution (10 microns) intravascular imaging tool, which is 10-fold greater than that achieved by IVUS.[19,20] Recent studies in OCT have reported some important findings of the pulmonary vasculature in adult PH patients.[21] However, few reports have described the assessment of pulmonary vasculature in pediatric patients with CHD.

Herein, we conducted a systematic review to assess the early signs of pulmonary vascular changes using OCT for pediatric patients with CHD.

## METHODS

Literature published between January 2010 and December 2021 was searched in the Cochran Library database (Cochran Central Register of Controlled Trials), Medline via Pubmed, EMBASE, Web of Knowledge, and references cited in other studies. The following search terms were used for the search: PH, child, children, pediatric, OCT, CHD, pulmonary vessels, and PA wall.

### Study selection and outcome estimation

Studies in which OCT was used to image the pulmonary vessels in pediatric patients with CHD were considered for inclusion. Publications that report adult pulmonary vessels with OCT were excluded. Conference abstracts and results posted in trial registries were excluded. No search of the gray literature was performed. The search was limited to English-language articles.

### Grading the quality of evidence of included studies

We use the Effective Public Health Practice Project (EPHPP)[22] to rate the quality of evidence in the reviewed studies. Each study was assigned a grade of strong, moderate, or weak value.

## RESULTS

### Study selections

Seventy-five papers were retrieved, and 70 papers were excluded because of non-CHD or the study participants were not children. Five studies met the inclusion criteria. The feasibility of PA imaging with OCT in an adult patient with severe PH and with normal pulmonary pressure was first reported by Hou et al. in 2010.[18] This technique has been used mainly in the adult population but it is at the beginning in children in 2015. The literature on children's OCT studies was relatively limited. This is a promising technology and a lack of studies to support this technology in pediatrics has been found. We summarized the studies in children (Table 1). All studies were observational. According to the EPHPP score, the quality of included studies was weak. The main findings were that pulmonary vascular remodeling was reflected by pulmonary intima thickening and the number and shape of nourishing vessels from OCT.

**TABLE 1** Summary of the studies on OCT imaging of the pulmonary arteries in children with congenital heart diseases

| Reference | EPHPP category | Patient | PA wall thickness (mm) | PA diameter (mm) | mPAP (mmHg) | PVRi (Wood Units/m$^2$) | PA VV | Pulmonary vessels morphology | Main findings |
|---|---|---|---|---|---|---|---|---|---|
| Homma et al.[7] | Weak | 27 VSD; four ASD; three PDA; one VSD+PDA; one VSD+ ASD+PDA; two VSD+CoA; one IAA | 0.19 ± 0.06 | 1.3–5.0 | 21.6 ± 8.2 | 1.6 ± 0.8 | – | A three-layered appearance was delineated in 29 of 80 pulmonary vessels | PA wall thickness in the 2.0–<3.0 mm subgroup was the most frequently delineated and correlated significantly with mPAP and PVRi. The three-layered delineation appearance had no significant correlation with pulmonary hemodynamics. |
| McGovern et al.[23] | Weak | 12 Fontan | 0.12 (0.10–0.14) | – | – | 1.8 (1.6–2.0) | – | All control patients and only four of 12 Fontan patients had a three-layered wall | There was no difference in wall thickness between both groups. There was no association between wall thickness and PAP and PVRi. |
| | | 11 Control | 0.11 (0.10–0.12) | – | – | – | – | | |
| Hayabuchi et al.[24] | Weak | Two WBS | 0.29 and 0.33 | – | – | – | PA VV was abundant in the dense adventitial layer. | All children had a single-layered wall | The wall thickness was increased in WBS. Vascular diseases are frequently accompanied by the prominent development of VV, which contributes to vascular remodeling. |
| | | 20 Control | 0.14 ± 0.30 | – | – | | | | |
| Hayabuchi et al.[25] | Weak | Eight BCPC | 0.12 ± 0.03 | 2.0–2.5 | 10.4 ± 2.6 | – | The PA VV area ratio was significantly greater in the BCPC group | – | There was no significant difference in PA wall thickness between the BCPC and control groups. Visualization of the PA using OCT can be clinically useful to assess pathological remodeling and therapeutic effects in patients after BCPC. |
| | | 20 Control | 0.12 ± 0.02 | | 12.5 ± 3.3 | | | | |
| Hayabuchi et al.[26] | Weak | 10 BDG stage | 0.12 (0.10–0.15) | 2.61 (2.40–2.78) | 10.2 ± 1.8 | – | PA VV number and diameter were significantly higher and curved and torturous-shaped VV were more frequently observed in the BDG and Fontan groups | – | Three-dimensional OCT is a novel method that can be used to evaluate adventitial PA VV. |
| | | 10 Fontan stage | 0.12 (0.11–0.15) | 2.66 (2.50–2.84) | 12.2 ± 0.9 | | | | |
| | | 20 Control | 0.12 (0.10–0.15) | 2.60 (2.40–2.79) | 12.4 ± 2.6 | | | | |

Abbreviations: ASD, atrial septal defect; BCPC, bidirectional cavopulmonary connections; BDG, bidirectional Glenn; CoA, coarctation of the aorta; EPHPP, Effective Public Health Practice Project; IAA, interrupted aortic arch; mPAP, mean pulmonary arterial pressure; OCT, optical coherence tomography; PA, pulmonary artery; PDA, patent ductus arteriosus; PVRi, pulmonary arterial resistance indexed to body surface area; VSD, ventricular septal defect; VV, vasa vasorum; WBS, Williams–Beuren syndrome.

### OCT image of morphology in pulmonary vessels

OCT images were obtained from one or more segmental pulmonary arteries of the right or left inferior lobe with a diameter of 2.0–3.0 mm because this size of PA was the most easily and distinctly observed. Whether the PA vessel is three-layer or single-layer is undetermined. Three studies have reported PA wall dimensions. McGovern et al.[23] employed OCT to evaluate structural changes within the pulmonary arteries of 12 Fontan patients and 11 individuals with normal pulmonary circulation. The authors reported vessel media in all control patients and only four of 12 Fontan patients. It means that pulmonary arteries were not often visualized as a single-layered wall. Control patients and only four Fontan patients were delineated three-layer structures, while other Fontan patients were not. Hayabuchi et al.[24] for the first time reported the pathological findings of PA in a 3-year-old girl and a 9-year-old boy with Williams-Beuren syndrome (WBS). The images showed that the PA wall comprised a single layer with homogeneous signal-rich bands in WBS patients and 20 normal children. Homma et al.[7] enrolled 39 children with CHD to evaluate pulmonary vessels using OCT. They observed three layers in 29/80 PA walls, which were considered as the intima-media layer because the three-layer smoothly continued into the single intima-media layer.

### OCT parameters and the relationships with pulmonary hemodynamics

Five studies measured the PA wall thickness by OCT and evaluated the correlations with pulmonary hemodynamics in children. Homma et al.[7] studied 39 infants and children with CHD. They measured PA wall thickness (0.19 ± 0.06 mm), PA diameter (1.31–5.00 mm), mPAP (21.6 ± 8.2 mmHg), PVR indexed to body surface area (PVRi; 1.6 ± 0.8 Wood Units/$m^2$) and pulmonary-to-systemic blood flow ratio (Qp/Qs; 2.0 ± 0.8). The results indicated that PA wall thickness correlated significantly with mPAP, PVRi, and Qp/Qs and OCT might represent a promising tool for evaluating the PA wall in children with CHD. McGovern et al.[23] measured PA wall thickness, PA pressure, and PVRi in Fontan and control patients. They found no significant difference in wall thickness between both groups and no association between wall thickness and PA pressure or PVRi. Hayabuchi et al.[24] measured PA wall thickness in a 3-year-old girl and a 9-year-old boy with WBS and 20 normal children by OCT. The PA wall thickness in normal children was 0.14 ± 0.30 mm and the wall thickness was increased in WBS patients (0.29 and 0.33 mm, respectively). Then Hayabuchi et al.[25] conducted a single-center, prospective, observational study in 2019. They measured PA wall thickness in the distal PA of eight consecutive patients after bidirectional cavopulmonary connection (BCPC) and 20 age-matched children with normal PA morphology and pressure. No significant difference in PA wall thickness was found between the BCPC and control groups (0.12 ± 0.03 mm vs. 0.12 ± 0.02 mm, respectively). In 2020, they prospectively assessed the distal PA of 10 patients with bidirectional Glenn circulation (BDG group) and Fontan circulation (Fontan group) and 20 children with normal PA hemodynamics and morphology (control group). The PA wall thickness was not significantly different among the three groups.[26]

### Imaging of pulmonary arterial vasa vasorum using OCT

Three studies reported the imaging of pulmonary arterial vasa vasorum (VV). Hayabuchi et al.[24] first reported that PA VV was abundant in the dense adventitial layer in WBS patients. The authors thought that vascular diseases were frequently accompanied by prominent development of the VV, which contributes to vascular remodeling. Then the author reported the development of PA VV in Glenn and Fontan circulation in cyanotic CHD from the two-dimensional cross-sectional, multi-planar reconstruction, and volume rendering imaging of OCT.[25,26] Development of the VV was evaluated by the VV area ratio, defined as the VV area divided by the adventitial area in cross-sectional images. The number, morphology, and volume of adventitial VV were significantly altered due to pulmonary hemodynamic conditions that occur with Glenn or Fontan circulation. They observed PA VV number, diameter, and VV area ratio were significantly higher, and the curve or torturous-shaped VV was more frequent in Glenn or Fontan groups compared to control groups. And after the Fontan production, the VV area ratio decreased but remained higher than the control groups.

## DISCUSSION

### OCT image of morphology in pulmonary vessels

Whether OCT can clearly discriminate the intima from the media of pulmonary vessels is controversial. The pulmonary vessel is different from the coronary artery which is characterized by three layers of OCT image that is brightness, darkness, and brightness. Li et al.[27] reported the normal pulmonary arterial wall has a single-layered structure from 11 cadavers in 2012. Unlike coronary arteries, which had a media consisting of 10–20 layers of vascular smooth muscle cells, the PA media was rich in elastic fibers with strong reflected light in OCT image, which was difficult to distinguish between intima and media. According to five studies on children with different CHD, the results seem to vary due to the different pathophysiological status of these patients, including simple or complex CHD. The reasons for this may be due to technical aspects of the

catheter procedure in OCT or pathological alterations in the vessel itself. The position of the OCT guidewire, the distance between the wire and the PA wall, and the degree of blood flushing are all factors that influence the delineation of the three-layer structure of the pulmonary vessel wall.[7] However, besides these factors, it was thought that loss of the media may reflect an early sign of vascular change or the hallmark of pulmonary vascular disease in CHD pediatric patients which presents with a single-layered vascular wall and homogeneous signal-rich bands.[23,28] But others thought that the three-layered appearance may reflect pathological changes. Further studies are needed to confirm early PA structural changes in CHD children with or without PH.

## Correlation between PA wall thickness and pulmonary hemodynamics

The feasibility of PA imaging in a patient with severe PH and with normal pulmonary pressure was first reported by Hou et al. in 2010.[18] The intima of distal PA was more than twice in thickness in a patient with PH compared with a patient with normal pulmonary pressure. In adult patients with PH, OCT may provide a method to study the pulmonary remodeling process. Some parameters can be measured: lumen diameter, intimal thickness, intimal thickness/lumen diameter, lumen area, intimal area, percentage intimal area (intimal area/lumen area), and so on. Some studies have shown a significant correlation between PA wall thickness and PAP using OCT in an adult with PH,[21,29] but few studies have evaluated PA wall thickness in pediatric patients with CHD and the results were controversial. In simple CHD for biventricular circulations, like a ventricular septal defect, atrial septal defect, and patent ductus arteriosus, the PA wall thickness correlated significantly with mPAP and PVRi.[7] Other studies have also verified the strong correlation between histological and OCT measurements of PA wall thickness in patients with pulmonary arterial hypertension.[27] However, in complex CHD that has undergone a Glenn or Fontan circulation, the PA wall thickness had no correlation with mPAP and PVRi.[23] It might be due to a small sample size or different pulmonary circulation conditions. Ridderbos et al.[30] noted less marked medial layer thickening in univentricular patients with good outcomes. It also indirectly indicated that Glenn or Fontan patients had no pulmonary arterial hypertension when less medial layer thickened. It is well known that PAH is associated with medial or intimal hypertrophy, and several studies have supported endothelial dysfunction in the pulmonary arteries of univentricular or biventricular patients.[9,23,30] If PA wall thickness measured using OCT served as an alternative indicator of the very early stages of PAH and can be used to identify the development of PA remodeling among Eisenmenger's syndrome, cyanotic heart disease or Fontan patients, it may be a useful tool for prognostication and assessing response to PAH therapy or medical decision-making during follow-up.

## OCT image of pulmonary arterial VV

VV is defined as arterial micro-vessels that supply nutrients and oxygen to the adventitia and outer media of the vessels. The structure of VV is different between diseased and non-diseased arteries.[31] Hypoxic conditions can stimulate the development of VV neovascularization. It has been proved that VV neovascularization plays an important role in atherosclerosis,[32–34] and assessment of coronary artery adventitial VV may predict the progression of the coronary lesion.[35,36] In the pulmonary circulation of hypoxic conditions, VV expansion also exists and is related to vascular remodeling and angiogenesis, especially the pathogenesis of pulmonary arterial hypertension.[37–39] We can use micro-computerized tomography to evaluate the adventitial VV, but it is limited to *in vitro* assessments.[40] OCT has enabled precise examination of PA morphology *in vivo*, and 3D assessment of OCT images of PA VV in children is feasible. Although advances in pediatric PH therapy have been achieved, some severe pediatric PH with CHD is refractory and children with Eisenmenger's, Glenn, and Fontan circulation remain poorly in response to therapy. Hayabuchi et al.[24] first showed that OCT can be used to identify the development of PA VV. The number, morphology, and volume of adventitial VV were significantly altered due to pulmonary hemodynamic conditions that occur with Glenn or Fontan circulation, which may predict the therapeutic effects.[26] They found that PA VV expansion was greater in Glenn circulation than that of Fontan circulation or control groups. This phenomenon may be linked to the development of systemic-to-pulmonary collateral arteries in cyanotic CHD, leading to increased PA flow and oxygen.[41,42] From this respect, with future studies it would be interesting to document VV morphology by OCT in the Glenn circulation versus Fontan and to investigate whether there is any correlation to adverse clinical outcomes. In the healthy control group, the morphology of PA VV is mostly straight and the diameter is normal, while in hypoxic conditions, the morphology of PA VV is commonly curved and tortuous, and the diameter is increased. However, there is no report on PA VV in patients with simple left-to-right shunt CHD. We hypothesize that from the hemodynamic PH to obstructive PH, the PA VV may be altered and this needs to be further investigated. OCT may be a useful tool to demonstrate the development of PA VV in pediatric patients with simple and complex CHD.

## Current clinical applications and future perspectives

Currently, the potential application for OCT imaging of the pulmonary vessels may include evaluating progression,

assessing response to medical therapy, predicting prognosis, and guiding medical decision-making during follow-up. OCT is an emerging tool for guiding clinical practice, and the technology still needs to be improved to obtain higher frame rates and deeper penetration images.

### Conclusions

OCT has become a promising tool for the *in vivo* study of PA morphology and may provide additional information in the assessment of pediatric patients with CHD. Further prospective high-quality studies in pediatric patients are needed to confirm the safety, validity, and clinical impact of OCT imaging to evaluate pulmonary vessels.

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## CONFLICT OF INTEREST

None.

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