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Histopathology of the great vessels in patients with pulmonary arterial hypertension in association with congenital heart disease: Large pulmonary arteries matter too ☆

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) is considered primarily a disease of the distal pulmonary arteries whereas little is known on the effect of long-standing pulmonary hypertension on the larger proximal pulmonary arteries. This study aims to investigate the structural changes in the great arteries of adults who developed PAH in association with congenital heart disease (CHD), with severe cases termed Eisenmenger syndrome.
Methods: We performed macroscopic and light microscopy analyses on the great arteries of 10 formalin-fixed human hearts from patients with PAH/CHD and compared them to age-matched healthy controls. A detailed histology grading score was used to assess the severity of medial wall abnormalities.
Results: Severe atherosclerotic lesions were found macroscopically in the elastic pulmonary arteries of 4 PAH/CHD specimens and organised thrombi in 3; none were present in the controls. Significant medial wall abnormalities were present in the pulmonary trunk (PT), including fibrosis (80%), and atypical elastic pattern (80%). Cyst-like formations were present in less than one third of patients and were severe in a single case leading to wall rupture. The cumulative PT histology grading score was significantly higher in PAH/CHD cases compared to controls ($p<0.0001$) and correlated positively with larger PT diameters ($\rho=0.812$, $p<0.0001$) and the degree of medial wall hypertrophy ($\rho=0.749$, $p<0.0001$).
Conclusions: Chronic PAH in association with CHD results in marked macroscopic and histological abnormalities in the large pulmonary arteries. These abnormalities are likely to affect haemodynamics and contribute to morbidity and mortality in this cohort.

1. Introduction

Approximately 5% to 10% of adults with congenital heart disease (CHD) develop pulmonary arterial hypertension (PAH) of variable severity [1]. Eisenmenger syndrome represents the extreme manifestation of PAH in association with CHD, characterised by the presence of reversed or bidirectional shunting and cyanosis [2]. Treatment strategies for PAH/CHD and PAH in general focus primarily on the small muscular distal pulmonary arteries (PAs). Current targeted PAH therapies in fact aim at attenuation of pulmonary vascular remodelling accompanied by reduction of pulmonary arterial pressure [1]. However, the large elastic PAs are also affected in the setting of PAH, with previous reports of aneurysmal dilatation, atherosclerosis and thrombosis [3–5].

It remains unknown whether structural changes in the greater PA vessels of patients with PAH/CHD are purely the result of distal pulmonary vascular disease and PAH or whether there is an additional contribution from intrinsic abnormalities relating to the underlying cardiac defect [6,7]. The morphology and mechanical characteristics of large PAs dictate not only the risk of major complications, such as PA dissection or rupture, but also have an impact on right ventricular function. In fact, recent non-invasive imaging techniques have highlighted the clinical importance of arterial stiffness of the proximal PAs as a predictor of mortality in non-congenital PAH [8]. Reduced proximal PA compliance has also been exhibited in patients with PAH/CHD [9,10] with increased stiffness being a predictor of poor functional capacity [11]. Increased stiffness of the proximal PAs is thought to independently affect the pulsatile load of the right

Abbreviations: CHD, congenital heart disease; ETC, elastic tissue configuration; HGS, histology grading score; LPA, left pulmonary artery; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PT, pulmonary trunk; PT/Ao MT, pulmonary trunk-to-aortic media thickness; RPA, right pulmonary artery; STJ, sinutubular junction.

☆ The above authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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ventricle, whilst stiff, conduit-like PAs lead to further distal arterial damage through increased flow pulsatility [12].

The aim of this study was to assess the morphological and histological features of the large elastic PAs and aorta in adult patients with PAH/CHD, using macroscopic criteria and light microscopy examination, focusing particularly on structural characteristics that may affect vessel mechanical properties and predisposition to rupture.

2. Methods

Human heart specimens from adult PAH/CHD patients, who died between 1975 and 1999, were retrieved from our cardiac morphology archive (Royal Brompton Hospital, London, UK) of formalin-fixed hearts. For the control group, we retrieved age-matched structurally normal hearts from patients who were not known to have suffered from any congenital heart abnormality and had not died from cardiovascular disease. Ethical approval for this study was obtained as per institutional guidelines conforming to the ethical guidelines of the 1975 Declaration of Helsinki. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.1. Macroscopic analysis

Direct measurements of the luminal circumference of the pulmonary trunk (PT) and aorta were made manually 5 mm above the sinutubular junction (STJ). Additional measurement of the internal circumference of the right and left main pulmonary artery (RPA and LPA) was obtained, just above the PT bifurcation. All circumference measurements were indexed to the length of the left ventricle, measured as the distance from the left atrioventricular junction to the left ventricular apex, to account for differences in age/patient size and presence of a rudimentary morphological right ventricle in 3 CHD patients. Both of the great arteries were inspected for presence of atherosclerotic lesions and thrombus. The severity of the atheroma was categorised in 4 grades according to a macroscopic classification [3]; grade 0 denoted absence of atheroma, grade A sparse, superficial atheroma, grade B distinct raised plaques of moderate number and ≥3 mm in diameter and grade C indicated confluent atheroma (Fig. 1). All measurements and inspections were performed by a single investigator on two separate occasions who obtained a mean score for each case.

2.2. Microscopic analyses

Full thickness sections of the PT and aorta were dissected 5 mm distally to the STJ. Sections from the RPA and LPA were taken directly above the bifurcation level and from sites where thrombus was detected. Sections of 6 μm in thickness were cut from paraffin blocks and studied via light microscopy using alcian blue, haematoxylin & eosin and elastic van Gieson stains. All sections were examined separately by two observers, with repeat evaluation by a blinded third observer in cases of discrepancy.

2.3. Aorta

Sections of the aorta were examined for presence of medionecrosis, fibrosis, cyst-like formation (basophilia of the media) and elastic fragmentation. Medial wall abnormalities were categorised in 4 distinct grades (0–3) according to the criteria proposed by Schlatmann and Becker [13] adapted from our group [14]: grade 0 denoted absence of lesions and grades 1–3 were used according to severity of processes.

2.4. Elastic pulmonary arteries

Sections of the PT, RPA, and LPA were assessed for medionecrosis, fibrosis, and cystic-like formation, applying histological criteria adopted for the pulmonary artery (grades 0–3) [15,16].

Normally, the PT structure loses its foetal characteristics and resemblance to the aorta by the second year of life [17]. Thereafter, the elastic tissue configuration (ETC) of the PT acquires its adult pattern with short fragmented fibrils and sparser elastic tissue and the media becomes thinner with a pulmonary trunk-to-aortic media thickness (PT/Ao MT) ratio of 0.4 to 0.7 [17]. The PT ETC was examined using the Heath classification and the PT to aortic media thickness (PT/Ao MT) ratio was calculated [17]. To evaluate the presence of elastic fragmentation in the pulmonary arteries we used an 'inversed' grading score compared to that of the aorta, termed as "atypical elastic pattern" which describes absence/presence and severity of elastic fragmentation. Thus, specimens with the normal pulmonary pattern of short, overlapping and fragmented lamellae were graded 0 whereas those with complete absence of elastic

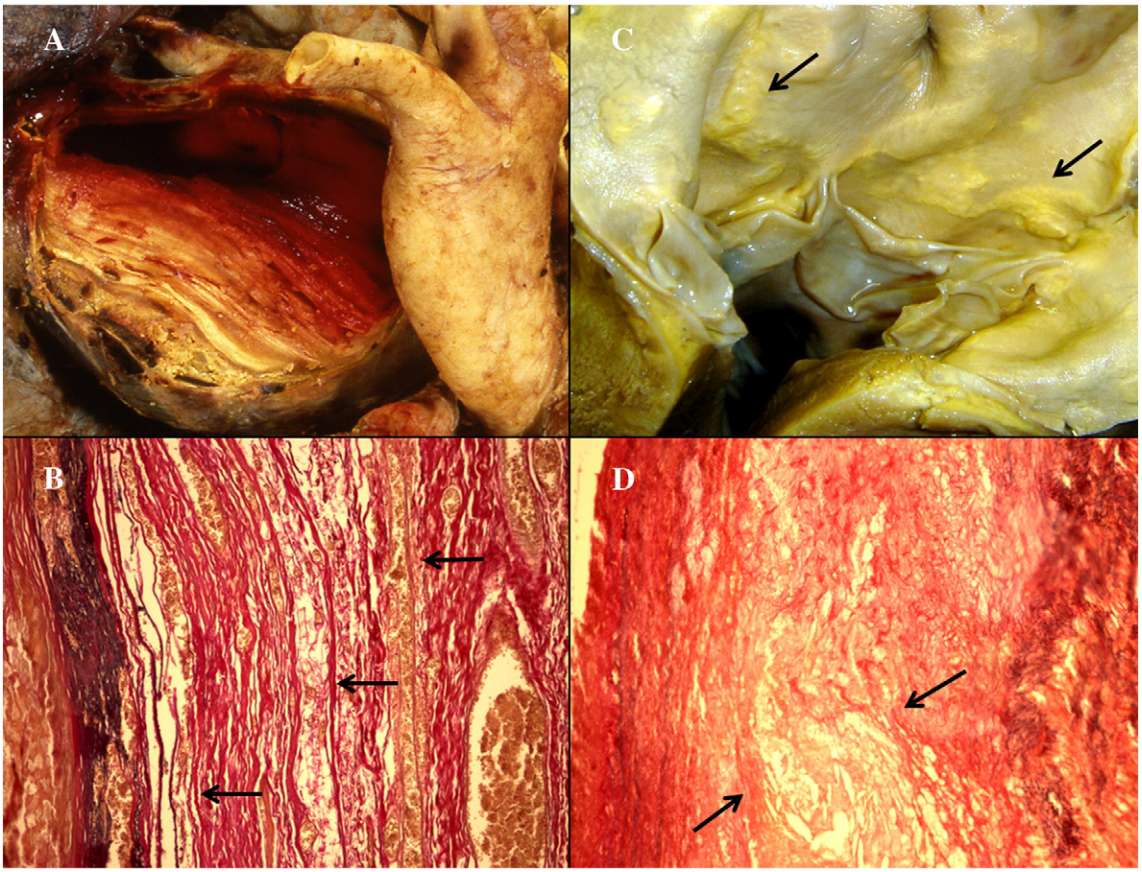

Fig. 1. A 55 year old female with Eisenmenger patent ductus arteriosus had a spherical aneurysm of the right pulmonary artery with thrombus formation (A) and multiple well organised layers on histology (B, x200 magnification, black arrows). Severe atherosclerosis (C, black arrows) was present in the pulmonary trunk and early stages of atheroma were also seen microscopically (D, x200 magnification, black arrows).