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Prevalence and prognostic significance of pulmonary artery aneurysms in adults with congenital heart disease

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ABSTRACT

Background: Prevalence and prognostic significance of pulmonary artery (PA) dilatation in congenital heart disease (CHD) have never been studied systematically.
Methods: Chest X-rays of 1192 consecutive adults with CHD were reviewed. Major diameter of the PA was determined by imaging techniques in those with PA dilatation. A value >29 mm was considered abnormal. Data on anatomy, hemodynamics, residual lesions and outcomes were retrospectively collected.
Results: Overall prevalence of PA dilatation was 18%. A minority of patients (5.5%) reached 40 mm (aneurysm; PAA) and 1.8% exceeded 50 mm. The most common PAA underlying malformations were pulmonary stenosis (21%), and shunts (55%). Significantly larger diameters were observed in hypertensive shunts (40 mm; IQR 36.7–45 mm vs. 34 mm; IQR 32–36 mm) ($p < 0.0001$). However, the largest diameters were found in conotruncal anomalies. There was no significant correlation between PA dimensions and systolic pulmonary pressure ($r = -0.196$), trans-pulmonary gradient ($r = -0.203$), pulmonary regurgitation (PR) ($r = 0.071$) or magnitude of shunt ($r = 0.137$) ($p > 0.05$ for all). Over follow-up, 1 sudden death (SD) occurred in one Eisenmenger patient. Complications included coronary (3), recurrent laryngeal nerve (1) and airway (1) compressions, progressive PR (1), and PA thrombosis (1). Coronary compression and SD were strongly associated (univariate analysis) with pulmonary hypertension (120 vs. 55 mm Hg; $p = 0.002$) but not with extreme PA dilatation (range: 40–65 mm).
Conclusions: PA dilatation in CHD is common but only a small percentage of patients have PAA. Clinical impact on outcomes is low. Complications occurred almost exclusively in patients with pulmonary hypertension whereas PA diameter alone was not associated with adverse outcomes.

1. Introduction

Pulmonary artery (PA) dilatation is detected increasingly in patients with congenital heart diseases (CHD) due to the frequent utilization of imaging techniques [1, 2]. In these patients, PA dilatation is considered a consequence of hemodynamic alterations [3], but its prevalence and prognosis have not been studied systematically. Pulmonary artery aneurysm (PAA), defined as a PA dilatation to a diameter of at least 1.5 times the normal dimension, is less frequently seen and its clinical significance also remains uncertain [3, 4]. This is likely due to several reasons. Although gender-specific reference values for main PA dimensions have been reported in an asymptomatic community-based population [5, 6], the diagnosis is still challenging and existing definitions do not relate the diagnostic thresholds to body dimensions or to the diameter of other vessels [2, 3]. Cut-off values to define PAA vary between studies and most of the information available in the literature is based on case reports and small series [2, 3, 7], what limit external validity and generalizability of the published studies. Occasionally, PAA causes severe complications such as pulmonary artery dissection - an extremely rare entity of difficult diagnosis with non-specific symptoms [8–10]. Until recently, sudden cardiac death was often the first manifestation and PA dissection was typically diagnosed at post-mortem examination rather than during

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life [9, 11]. As a consequence of the rarity of the disease and the multiple publication bias, there are no clear guidelines for risk stratification and best therapeutic approach.

The aim of the present study was to address the prevalence of PA dilatation and PAA in a contemporary cohort of adult patients with CHD and to evaluate the prognostic impact of PA dilatation by analysing the outcomes of patients with PA aneurysms, which could include life-threatening mechanical complications.

2. Methods

2.1. Patients and study design

We systematically reviewed chest X-rays of 1587 consecutive adult patients with CHD (median age 29 years; IQR 22–41 years; 52% males) visited at our unit between January 2011 and April 2012. Given that previous studies in other populations have found chest X-ray to be more sensitive than echocardiogram for the screening [12], PA dilatation was initially assessed by visual estimation on chest X-ray. Chest X-ray was taken in postero-anterior view and standing position in near deep inspiration. Enlarged main PA was defined as a bulge at the second curve of left cardiac border or as a bulging of left pulmonary mediastinal margin with prominent main right or left branches of the PA. For this study, the most recent radiographs preceding the initial visit in 2011–2012, and performed no >3 years before the imaging studies, were requested. Three hundred and ninety five patients were excluded, as their X-rays were not available at the time of this retrospective analysis. Thus, a total of 1192 patients comprised the study cohort (Fig. 1S. Supplementary Material Online). Over a median follow up time of 5 years (IQR 3–8), the majority of patients (90%) had at least 2 clinical visits separated by an interval of 1 to 5 years.

For the present study, CHD was defined according to the criteria of Mitchell et al. [13]. According to complexity, 28% had simple, 50% moderate, and 22% severe defects. Patients were classified based on the major underlying defect, and those with combinations of lesions were assigned to the highest complexity group. This study was approved by our institutional research ethics committee.

2.2. Pulmonary artery imaging

In this retrospective study, we used images that were part of the routine clinical evaluation of the patients. Echocardiographic examinations were performed with Vivid 7 (GE Healthcare, Frankfurt, Germany) or iE33 (Philips, Andover, Massachusetts). The major diameter of the main PA was measured by transthoracic echocardiography at end-diastole from parasternal short axis view just before the bifurcation using the inner-edge-to-inner-edge convention. All echocardiographic measurements were retrospectiveely performed by the same referent operator in patients with PA dilatation.

Contrast enhanced computed tomography (CT) scan imaging of the chest was also used to image PA using a Toshiba Aquilion 64 CT machine with a prospectively electrocardiographically gated axial technique initiated at 50% of the R-R interval in mild inspiration. Cardiac magnetic resonance (CMR) was performed on 1.5T Philips Achieva system and PA dimensions were measured based on magnitude images used for phase contrast imaging at end-diastole. Experienced readers, blinded to the echo measurements, using a dedicated offline cardiac workstation, read the CT and CMR scans independently. Specifically, the transverse axial internal diameter of the main pulmonary trunk at the level of the bifurcation was measured. Although accurate measurements of the pulmonary diameters were possible in many patients by echocardiography, it can sometimes be difficult to optimize visualization of the PA. As described by Bland and Altman [14], limits of agreement (95% confidence interval) between imaging techniques were estimated as mean difference ± 2 SD of the differences.

In 248 patients with an enlarged PA on chest radiography, the major PA diameter was determined by both CT/CMR scan and echo in 156 and only by echo in 92. Of them, only 2 cases had incomplete follow-up (0.8%). A PA diameter by CT, MRI or echo was also obtained from medical records in >50% of patients without PA dilatation on X-ray (Fig. 1S. Supplementary Material Online). For the purpose of the study, a value of PA diameter above 29 mm for males and 27 for female [5] was considered abnormal and PAA was defined as a PA diameter over 40 mm. In those cases where multimodality imaging measurements of the PA was available, the largest diameter was chosen for the analysis.

2.3. Data collection

Data on demographics, anatomy, surgical or percutaneous repairs and palliations, clinical status, residual lesions and complications were collected from medical records. Findings on 2-dimensional echocardiography, CMR and cardiac catheterization were also collected. The transpulmonic pressure gradient was evaluated by using continuous wave Doppler or at cardiac catherization [12]. Severe pulmonary outflow tract stenosis was defined as Doppler or catheter peak pressure gradient >50 mmHg at valvular, subvalvular, or supravalvular level (or > 30 mmHg in the setting of severe pulmonary ventricular dysfunction) and aortic outflow tract stenosis as Doppler or catheter mean systolic pressure gradient >40 mmHg. Echocardiographic estimate of pulmonary artery systolic pressure was calculated as the sum of the peak systolic pressure gradient of the pulmonary atrio-ventricular regurgitation jet and a right atrial pressure of 10 mm Hg. Severe pulmonary hypertension (PH) was assumed to exist when a maximum velocity jet >3.5 m/s was measured by continuous Doppler in the absence of pulmonary stenosis. Pulmonary-to-systemic blood flow ratio (Qp/Qs) was obtained at cardiac catheterization or non-invasively by echocardiography or CMR. Moderate-to-severe systemic or pulmonary ventricular systolic dysfunction was qualitatively or quantitatively assessed by imaging techniques. Valvular dysfunction was graded as mild, moderate, or severe from Doppler color flow mapping and continuous wave tracings.

2.4. Follow-up

In the study cohort, mortality and PAA-related complications at follow-up were analyzed. The causes of death were classified into cardiovascular (CV) or non-CV deaths. According to previous publications [15], the cause of CV death was then classified as heart failure, sudden death (SD), perioperative, and other CV deaths. Other CV deaths included myocardial infarction, aortic dissection or rupture, stroke, pulmonary or systemic thromboembolism, infective endocarditis or severe hemoptysis. The presence of mechanical complications was determined on the basis of symptoms and findings on imaging scans and classified as follows: severe pulmonary regurgitation (PR), left main coronary artery (LMCA) compression, bronchial compression, nerve compression, PA thrombosis or dissection.

2.5. Statistical analysis

Continuous variables are given as mean, standard deviation, or median, interquartile range, where appropriate. Categorical data are expressed as numbers and proportions. Normality of distributions was tested with the Shapiro-Wilk test. Chi-square or Fisher's exact tests were used to analyze categorical data. Unrelated two-group comparisons were done with unpaired two-tailed *t*-tests or Mann-Whitney *U* test for non-normally distributed variables. PA diameters and hemodynamic parameters (both normally distributed) were correlated using Spearman's rank correlation coefficient. We performed univariate analysis of variables retrospectively collected from patients' medical records using binary logistic regression to identify predictors of mechanical complications. Because of the presumed bias of this retrospective analysis and the very low number of events we refrained from carrying out complex statistical analysis to identify independent predictors for mechanical complications. A two-sided $P < 0.05$ was considered statistically significant. For all calculations, SPSS 22.0 for Windows (SPSS, Inc., Chicago, Illinois) was used.

3. Results

3.1. PA measurements

Fig. 1A shows the distribution of all available PA diameters obtained from imaging techniques in the entire study population of patients with enlargement of the PA on chest X ray. Of the total of 248 patients (20.8% of the study cohort) with PA dilatation on chest X ray, 208 (18% of the study cohort) had PA diameters >29 mm. The median PA diameter was 35 mm, the minimum was 14 mm and the maximum 75 mm. Only a minority of patients (66 of the 248; 5.5% of the total cohort) reached a diameter above 40 mm and very few of these (21 of the 66; 1.8% of the total cohort) reached >50 mm. The median PA diameter in patients with PAA was 44 mm (IQR 40–50 mm).

Five hundred and ninety eight patients had both CT or CMR and echocardiographic measurements of PA diameter. The correlation coefficient between those measurements was highly significant ($r = 0.95$; $p < 0.001$) and the limits of agreement (95% CI) were −2.3 to +1.8 mm, acceptable for the present study.

3.2. Characteristics of patients with PA aneurysms

Patients with PAA were older (median age 39 years; IQR: 29–54 years) and the prevalence of females (52% vs. 48%) and PH (22% vs. 5%) was higher compared to patients without PA dilatation. With regard to complexity, the distribution was similar to that of the entire cohort and the development of PAA was not more frequently associated with complex CHD compared to simple CHD (29% simple, 46% moderate, and 25% severe defects).

3.3. Prevalence of aneurysms in congenital lesions

Remarkably, the percentages of subjects with PAA in the overall study population with CHD and distributed by cardiac lesion were, in general, very low (Fig. 1B). In the best scenario, and although

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