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Haemodynamic characterisation and heart catheterisation complications in children with pulmonary hypertension: Insights from the Global TOPP Registry (tracking outcomes and practice in paediatric pulmonary hypertension)

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ABSTRACT

Background: The TOPP Registry has been designed to provide epidemiologic, diagnostic, clinical, and outcome data on children with pulmonary hypertension (PH) confirmed by heart catheterisation (HC). This study aims to identify important characteristics of the haemodynamic profile at diagnosis and HC complications of paediatric patients presenting with PH.

Methods and results: HC data sets underwent a blinded review for confirmation of PH (defined as mean pulmonary arterial pressure ≥25 mm Hg, pulmonary capillary wedge pressure ≤12 mm Hg and pulmonary vascular resistance index [PVRI] of >3 WU × m^2). Of 568 patients enrolled, 472 who fulfilled the inclusion criteria and had sufficient data from HC were analysed. A total of 908 diagnostic and follow-up HCs were performed and complications occurred in 5.9% of all HCs including five (0.6%) deaths. General anaesthesia (GA) was used in 53%, and conscious sedation in 47%. Complications at diagnosis were more likely to occur if GA was used ($p = 0.04$) and with higher functional class ($p = 0.02$). Mean cardiac index (CI) was within normal limits at diagnosis when analysed for the entire group (3.7 L/min/m^2; 95% confidence interval 3.4–4.1), as was right atrial pressure despite a severely increased PVRI (16.6 WU × m^2, 95% confidence interval 15.6–17.76). However, 24% of the patients had a CI of <2.5 L/min/m^2 at diagnosis. A progressive increase in PVRI and decrease in CI was observed with age ($p < 0.001$).

Conclusion: In TOPP, haemodynamic assessment was remarkable for preserved CI in the majority of patients despite severely elevated PVRI. HC-related complication incidence was 5.9%, and was associated with GA and higher functional class.

1. Introduction

Pulmonary hypertension (PH) remains an important cause of mortality and morbidity [1]. It is characterised by a progressive increase in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) that ultimately leads to right ventricular dysfunction and death. The definition of pulmonary arterial hypertension (PAH) is based on haemodynamics using the same criteria for children as for adult patients [1,2].

Non-invasive tests are useful for screening suspected PH but haemodynamic assessment with invasive heart catheterisation (HC) remains the gold standard to confirm diagnosis and to assess disease severity [2–4]. Haemodynamics (PVR and right atrial pressure) are recognised as risk factors at baseline and important for therapeutic decisions [1, 5–7]. The recent statement of the AHA on the indications for HC in paediatrics recommends HC to assess PVR and reversibility of PH in patients with congenital heart disease (CHD) or idiopathic PAH (iPAH) when accurate assessment of PVR is needed to make therapeutic decisions [8]. The majority of children with PH enrolled in current registries have iPAH or CHD–PAH, underscoring the need to perform HC at diagnosis in this population [9,10]. Multi-centre studies have been published describing the complication rate of HC in paediatrics but no large studies have focused on a pure population of PH [11,12]. Controversial opinions challenge the use of invasive haemodynamics and are mainly focused on the potential risks of HC [1]. With increasing treatment options, accurate characterisation of the disease is needed to provide optimal care as, until now, targeted therapies have not shown efficacy in other forms of PH than PAH [2]. The haemodynamic profile for the PH population enrolled in TOPP as well as HC-related complications of 908 diagnostic and follow-up HCs performed are reported.

2. Methods

The Registry was designed as a multi-centre, prospective observational cohort study at 31 centres in 19 countries. Patients underwent clinical assessment and received treatment and follow-up according to the sole judgement of their local physician and were not on TOPP-related specific diagnostic and therapeutic protocols. Enrolment began in January 2008. All eligible patients with complete HC data available on 27th February 2012 were included in the analysis.

The study was designed and supervised by an Executive Board (EB). Data management and analyses were performed by contract organisations working with the EB. The protocol was approved by the relevant Institutional Review Boards and/or Ethics Committees; the study complies with the Declaration of Helsinki; and informed consent has been obtained from all patients and/or their legal guardians.

Consecutive patients between 3 months and 18 years of age at the time of diagnosis with PH confirmed by HC were eligible for enrolment in the TOPP Registry. Both newly diagnosed (incident, within 3 months of enrolment in the registry) patients and previously diagnosed (prevalent, more than 3 months prior to enrolment) patients were eligible.

Patients were eligible if they had PH belonging to Venice Groups 1, 3, 4, or 5 according to the Venice 2003 clinical classification [13], as this was the actual classification at the time of registry design.

The diagnosis of "PH-confirmed" required HC confirmation (defined as mPAP ≥ 25 mm Hg, PVRI ≥ 3 WU × m^2, and PCWP ≤ 12 mm Hg). The EB reviewed all cardiac catheterisation data sets and recalculated PVRI and cardiac output by the Fick method using a single assumed oxygen consumption table [14] or the recorded cardiac output as measured by thermodilution (if performed and physiology permitted). Following this review, patients not fulfilling the above-mentioned definition of PH were excluded from the analysis of the haemodynamic parameters. Patients for whom a diagnostic HC could not be performed because of clinical reasons, could be included based on a confirmatory echocardiography and/or histopathology as they may have a follow-up HC.

Overall data on general anaesthesia (GA) and conscious sedation to perform HC was collected but information on specific drugs was not collected.

Acute vasodilatory response testing (AVRT) was recorded, where the interpretation of a positive or absent response to AVRT was left with the local physician following the rules of a non-interventional registry.

Predefined HC-related complications were recorded but were not adjudicated by the EB. For the purpose of this analysis all diagnostic and follow-up HCs were pooled together.

2.1. Statistical analysis

A statistical analysis plan was written to specify the initial descriptive analysis, and was completed prior to data finalisation. After team review of the descriptive results, evaluation of specific hypotheses (ANOVA) was executed. No formal sample size calculation was performed, and hence the sample was not powered a priori for specific comparisons. The analysis population for haemodynamic parameters was the PH-confirmed cohort, which included only patients who met all enrolment criteria, but all patients were analysed for HC complications. Continuous data was summarised using descriptive statistics (mean, SD, 95% confidence interval, median, min/max and 25th and 75th percentiles) and 95% confidence intervals where relevant. Age was grouped for descriptive summaries (3–24 months, 2–6 years, 7–11 years and 12–18 years). Categorical data was summarised using counts and percentages. Unless stated otherwise, the denominator for percentages was the total number of patients with non-missing data for each variable analysed. All eCRFs were individually reviewed and assessed by EB members. Post-review values were used in the analyses, unless there was insufficient data for review in which case the original eCRF data was used. The association between key haemodynamic parameters and age at diagnosis (years), aetiology and NYHA functional class (FC) was investigated using an ANCOVA model including all 3 variables. Cardiac index (CI), PVRI and PVRI/SVRI were log-transformed to improve the assumption of normality.

In order to investigate the potential risk factors for HC complications at diagnosis, logistic regression analyses were performed. The risk factors investigated were age at diagnosis (years), NYHA FC (trend over classes I–IV), aetiology and sedation method, with all variables retained in the final model. All analyses were performed using SAS statistical software package (version 8.2 or higher).

3. Results

At the data cut on February 2012, 568 patients were enrolled and 480 fulfilled the inclusion criteria, i.e., are patients for whom PH has