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ORIGINAL RESEARCH

Monitoring of Hemodynamics With Right Heart Catheterization in Children With Pulmonary Arterial Hypertension

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BACKGROUND: Right heart catheterization (RHC) is a high-risk procedure in children with pulmonary arterial hypertension without clear guidelines for the indications and targets of invasive reassessment. Our objectives are to define the aims of repeated RHC and evaluate the correlation between noninvasive criteria and hemodynamic parameters.

METHODS AND RESULTS: Clinical and hemodynamic characteristics from 71 incident treatment-naïve children (median age 6.2 years) with pulmonary arterial hypertension who had a baseline and reevaluation RHC were analyzed. Correlations between noninvasive predictors and hemodynamic parameters were tested. Adverse outcomes were defined as death, lung transplantation, or Potts shunt. At baseline, pulmonary vascular resistance index (hazard ratio [HR] 1.07 per 1 WU·m^2 increase [95% CI, 1.02–1.12], P=0.002), stroke volume index (HR 0.95 per 1 L·min^{-1}·m^{-2} increase [95% CI, 0.91–0.99], P=0.012), pulmonary artery compliance index (HR 0.16 per 1 mL·mm Hg^{-1}·m^{-2} increase [95% CI, 0.051–0.52], P=0.002), and right atrial pressure (HR, 1.31 per 1 mm Hg increase [95% CI, 1.01–1.71], P=0.043) were associated with adverse outcomes. Pulmonary vascular resistance index, pulmonary artery compliance index, and right atrial pressure were still associated with a worse outcome at second RHC. Noninvasive criteria accurately predicted hemodynamic evolution; however, 70% of the patients who had improved based on noninvasive criteria still presented at least 1 "at risk" hemodynamics at second RHC.

CONCLUSIONS: Pulmonary vascular resistance index, pulmonary artery compliance index, and right atrial pressure are solid predictors of adverse outcomes in pediatric pulmonary arterial hypertension and potential therapeutic targets. Noninvasive criteria accurately predict the evolution of hemodynamic parameters, but insufficiently. Repeated RHC are helpful to identify children with persistent higher risk after treatment introduction.

Key Words: outcome ■ pediatric ■ pulmonary arterial hypertension ■ pulmonary hypertension ■ right heart catheterization

Pulmonary arterial hypertension (PAH) is a rare disease characterized by a progressive obstruction of the small pulmonary vessels leading to an increase in pulmonary vascular resistance (PVR), right heart failure, and death. It is a form of precapillary pulmonary hypertension (PH) with an estimated incidence ranging from 0.47 to 2 cases per million children.[1–5]

The definition and diagnosis of PAH is the same as in adults and relies on hemodynamic assessment by right heart catheterization (RHC). RHC is also a useful tool for risk stratification, and hemodynamic parameters including stroke volume index (SVI), right atrial pressure (RAP), and pulmonary arterial compliance (PAC) have proven to be accurate markers of severity

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CLINICAL PERSPECTIVE

What Is New?

- Correlation between clinical and hemodynamic parameters in children with pulmonary arterial hypertension (PAH) are unknown, while new prognosis hemodynamic factors such as stroke volume index or pulmonary artery compliance index have been scarcely tested.
- Pulmonary vascular resistance index, pulmonary arterial compliance index, right atrial pressure, and stroke volume index are independent prognosis factors at baseline evaluation in children with PAH.

What Are the Clinical Implications?

- Hemodynamic variables remain an essential part of the follow-up in children with PAH at diagnosis but also at reevaluation.
- There is a strong correlation between noninvasive and hemodynamic parameters. However, children who improved after the introduction of a specific PAH therapy would still benefit from an invasive assessment by right heart catheterization because they may present "at risk" values. Children who did not improve despite specific PAH therapy would benefit from a therapeutic intensification before invasive reassessment, since they will systematically present an "at risk" value at right heart catheterization, suggesting they would benefit from a therapeutic intensification before undergoing hemodynamic reassessment.

Nonstandard Abbreviations and Acronyms

CI	cardiac index
HR	heart rate
mPAP	mean pulmonary arterial pressure
NYHA-Fc	New York Heart Association-functional class
PACi	pulmonary arterial compliance index
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
PVRi	pulmonary vascular resistance index
RAP	right atrial pressure
RHC	right heart catheterization
SVI	stroke volume index

at diagnosis and during the follow-up in adult patients, while being scantily tested in the pediatric population. Additionally, although RHC holds a central place in the care of children with PAH, it is associated with a relatively high probability of complications with an estimated risk of major adverse events ranging from 3.5% to 6.2% and a risk of death estimated between 0.2% and 1.4% in experimented centers.[6–10]

There are currently no clear guidelines for the indication of repeated RHC in children with PAH. This lack of recommendation, associated with the limited knowledge regarding the relevance of new hemodynamic parameters in the pediatric population, potentially leads to an underestimation of the gravity of the condition of the patients, while exposing them to unnecessary invasive investigation. To try to alleviate this problem, we aimed to define relevant hemodynamic parameters at diagnosis and reevaluation. In addition, we sought to evaluate the correlation between noninvasive characteristics and those hemodynamic parameters, allowing us to eventually draw conclusions on the necessity of performing monitoring RHC as well as the complementarity of hemodynamics and noninvasive parameters in a cohort of incident cases of children with PAH.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

From January 2000 to October 31, 2021, we retrospectively analyzed data from incident patients diagnosed with PAH at our institution (Necker-enfants-malades Hospital). Patients were included if they were <18 years old, treatment-naïve for PAH-specific drugs at first RHC, and had at least a second RHC during their follow-up. Patients with PAH associated with open cardiac shunts, postcapillary PH, and with a persistent response to calcium channel blockers, were excluded. Only children with PAH associated with atrial septal defect were included in the present study. All patients underwent a full-scale genetic analysis as previously reported.[11,12] Patient assents were collected if they were able to give it and parents signed an informed consent. Patients with atrial septal defect and PAH who had a mutation in 1 of the PAH genes were classified as heritable PAH. The study was approved by our institution ethics committee (MR004 n°20 220 729 172 242).

Therapeutic decision after first RHC was based on the clinical, biological, and echocardiographic status of the patient. Triple therapy was indicated from the outset in case of pericardial effusion, right heart failure, multiple syncope at rest, or after nonimprovement in the clinical status despite oral combination therapy.

Clinical, Biological, and Hemodynamic Data

Before 2019, patients were diagnosed with PAH if mPAP was >25 mm Hg, associated with PVR >3 WU and pulmonary arterial wedge pressure <15 mm Hg; after 2019, we used a mPAP value of 20 mm Hg as an inclusion criterion.[13,14] During sequential noninvasive evaluations, 3 noninvasive factors were collected: New York Heart Association-functional class (NYHA-Fc), echocardiographic assessment, and brain natriuretic peptide (BNP)/ NT-proBNP (N-terminal pro-B-type natriuretic peptide) value. The measurement of BNP level was replaced by the measurement of NT-proBNP level during the period of the study; BNP value >100 pg/mL and NT-proBNP value >300 pg/mL were classified as abnormal otherwise. Echocardiographic improvement was defined as a decrease of 0.5 m/s of the tricuspid velocity, an increase of 2 mm in the absolute tricuspid annular plane systolic excursion value, or an absence of right cavities dilatation in patients with previously dilated cavities.

All patients with a diagnosis of PAH undergo a second RHC in the year following PAH treatment introduction. We retrospectively analyzed every report preceding the second RHC. Patients undergoing a second RHC were classified as worsened or not improved if the patient was still in NYHA-Fc III or IV, worsened or did not improve its echocardiographic assessment, and had an abnormal value of BNP/NT-proBNP when available. In case of missing BNP/NT-proBNP values, the conclusion was solely based on clinical status and echocardiographic data.

Cardiac output was measured using the thermodilution method and the Fick method in case of atrial shunting. Cardiac index was calculated by the formula cardiac output/body surface area (BSA), pulmonary vascular resistances were calculated by the formula: (mPAP–pulmonary arterial wedge pressure)/ cardiac output, pulmonary vascular resistance index (PVRi) were calculated using the following formula: PVR/BSA. SVI was calculated from the cardiac index divided by heart rate (HR) at time of RHC, and pulmonary artery compliance index (PACi) was calculated by SVI divided by pulse pressure (difference between systolic and diastolic PAP). Acute vasodilatation testing was performed and analyzed according to current recommendations.[15,16]

Statistical Analysis

To present the demographic variables and biological parameters and measurements, descriptive analyses were made at every RHC (a total of 4). Quantitative variables were synthetized as mean and SD and as median, range (extreme values) and quartiles (first and third). Statistical comparisons between values at different catheterizations were done using ANOVA (if normal distributions were assumed) or nonparametric Kruskal–Wallis test. Qualitative variables were summarized as counts and percentage (calculated on the number of available data). The number of missing data was counted for every variable if any. To observe the evolution of the biological parameters of each patient, they were compared pairwise from 1 catheterization to the next one until the fourth catheterization. Quantitative variables were compared with paired *t* test if the value differences between catheterizations were normally distributed or with the rank-signed Wilcoxon test otherwise. Qualitative variables were compared pairwise according to the McNemar test. These pairwise analyses were done on the global population and in the 2 subgroups "catheterization after improvement" and "catheterization after worsening." To avoid a potential immortal bias, the event-free survival since the second catheterization has been modelized, where the

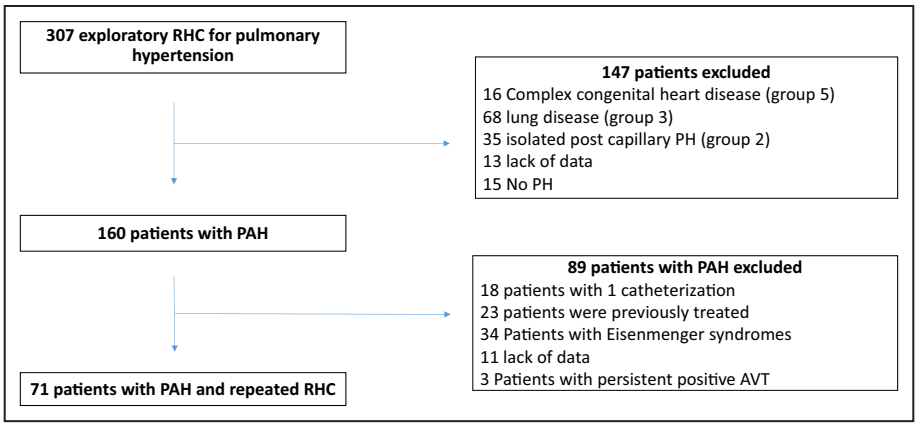

Figure 1. Flow chart of the population.
AVT indicates acute vasoreactivity testing; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; and RHC, right heart catheterization.

Table 1. Clinical and Hemodynamics Parameters of Patients at Baseline Evaluation Showing No Significant Differences Before PAH Treatment Introduction

	Total (n=71)	First RHC in patients who worsened (n=14)	First RHC in patients who improved (n=57)	*P* value
Clinical characteristics				
Age, y (Q1–Q3)	6.2 (2.8–12.1)	3.5 (1.9–8.3)	6.5 (3.2–12.2)	0.201
M/F	18/53	5/10	13/43	0.511
BMI	15.63	14.86	15.87	0.086
NYHA-Fc (%)				
I-II	41 (58)	8 (57)	33 (57)	0.277
III-IV	30 (42)	6 (43)	24 (43)	
Clinical presentation				
Right heart failure (%)	2 (2.82)	0 (0)	2 (3.57)	
Cough (%)	2 (2.82)	0 (0)	2 (3.57)	
Fatigue (%)	27 (38.03)	5 (33.33)	22 (39.29)	
Chest pain (%)	2 (2.82)	0 (0)	2 (3.57)	
Dizziness (%)	8 (11.27)	2 (13.33)	6 (10.71)	
Cyanosis at rest (%)	27 (38.03)	4 (26.67)	23 (41.07)	
Cyanosis at effort (%)	15 (21.13)	4 (26.67)	11 (19.64)	
Syncope (%)	27 (38.03)	7 (46.67)	20 (35.71)	
Hemodynamics values				
sPAP, mm Hg (Q1–Q3)	74.5 (61.25–97.5)	85 (69.5–91.5)	82 (65–93)	0.737
mPAP, mm Hg (Q1–Q3)	56 (46.5–70.5)	56 (45.23–75)	56 (47–70)	0.868
dPAP, mm Hg (Q1–Q3)	39 (28–55)	31 (26–55.5)	40 (29.5–54)	0.429
PVR, WU (Q1–Q3)	14.5 (11.12–21.2)	18.9 (10–20)	14 (11.55–21.7)	0.838
PVRi, WU·m^2 (Q1–Q3)	13.15 (8.7–18.85)	12.3 (8.3–24.9)	13.2 (8.7–18.7)	0.965
CI, L·min^{-1}·m^{-2} (Q1–Q3)	3.53 (2.6–4.43)	3.17 (2.16–5.35)	3.53 (2.67–4.4)	0.914
RAP, mm Hg (Q1–Q3)	6 (4.5–7.5)	7 (4–8)	6 (5–7)	0.736
SVI, mL·m^{-2} (Q1–Q3)	40.93 (32.25–48.55)	39.05 (26.32–67.82)	41.18 (33.98–48.55)	0.517
PACi, mL·mm Hg^{-1}·m^{-2} (Q1–Q3)	1.14 (0.71–1.58)	0.83 (0.55–1.34)	1.21 (0.81–1.61)	0.187
HR, beats per minute (Q1–Q3)	100 (83–112)	96.5 (83.75–103.25)	100 (83–118)	0.463

BMI indicates body mass index; CI, cardiac index; dPAP, diastolic pulmonary arterial pressure; F, female; HR, heart rate; M, male; mPAP, mean pulmonary arterial pressure; NYHA-Fc, New York Heart Association-functional class; PACi, pulmonary arterial compliance index; PAH, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; RHC, right heart catheterization; sPAP, systolic pulmonary arterial pressure; and SVI, stroke volume index.

first event was defined as Potts, transplant, or death. Otherwise, patients were censored at their last follow-up or at 5 years. Survival curves were illustrated with the Kaplan–Meier method, completed with a log-rank test to compare curves.

Associations with biological parameters at the first and second catheterizations have been analyzed through univariate Cox regressions. Proportion hazards tests based on Schoenfeld residuals were performed systematically beforehand. To illustrate the significant results based on quantitative variables, the maximum AUC estimated over time-dependent receiver operating characteristic curves at 24 and 36 months since the second catheterization have been used to find the best threshold value with the "closest top-left" method. The level of significance was set at 5%; consequently estimations of odds ratios, hazard ratios, and probabilities were presented with their 95% bilateral CIs. No correction of *P* values has been done for multiple testing. Statistical analyses and graphics were computed with R v4.1.2, with the help of "survival," "timeROC," and "ggplot2" packages.

RESULTS

Population Description

Over the study period, 307 patients were referred at our institution for RHC to confirm pulmonary hypertension; 147 were excluded because they were part of group 2, 3, and 5 of the current PH classification, and had no PH or missing data (Figure 1).

One hundred sixty patients had a diagnosis of PAH; 89 were excluded, because of previous treatment with PAH drugs (n=23), lack of RHC during follow-up (n=18),

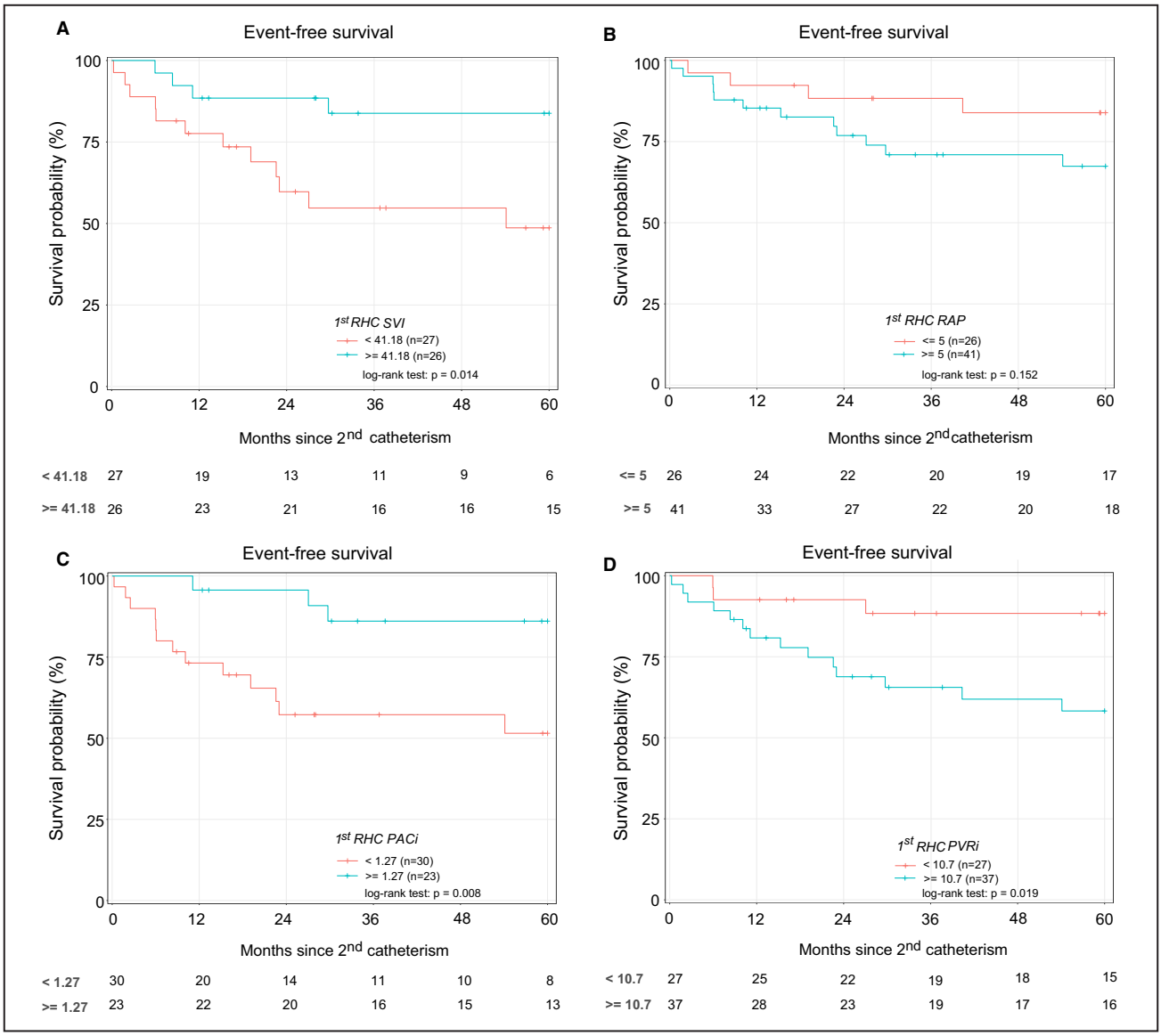

Figure 2. Survival curves of significant hemodynamic parameters at first RHC.
Relevant hemodynamic parameters at first RHC in our cohort included PVRi (n=64 available data), PACi (n=53 available data), SVI (n=53 available data), and RAP (n=67 available data). We determined that threshold values for PVRi, SVI, and PACi were 10.7 WU·m^{-2}, 41.18 mL·m^{-2}, and 1.27 mL·mm Hg^{-1}·m^{-2}, respectively. Cath indicates right heart catheterization; PACi, pulmonary arterial compliance index; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; RHC, right heart catheterization; and SVI, stroke volume index.

PAH with open cardiac shunt other than atrial septal defect (n=34), long-term responders to calcium channel blockers (n=3), or missing data (n=11). We analyzed data from 71 incident patients with a diagnosis of PAH and treatment-naïve: 25 heritable PAH (35.2%), 23 idiopathic PAH (32.4%), 14 PAH associated with a congenital heart disease (19.7%) amidst 3 patients with an opened atrial septal defect, and 10 patients who developed PAH after closure of simple lesions, 3 pulmonary veno-occlusive disease (4.2%), 4 connective tissue disease–associated PAH (5.6%), 2 drugs, and toxin-induced PAH (2.8%). There were 53 women and 18 men, and the median age at diagnosis was 6.2 years (min. 31 days–max. 17.4 years). Clinical presentation and baseline hemodynamics values are presented in Table 1. Thirty patients (42%) were in NYHA-Fc III-IV at diagnosis, the median tricuspid annular plane systolic excursion value was 18 mm. BNP and NT-proBNP values were available for 56 patients and were considered abnormal in 26 patients. The median mPAP value was 56 mm Hg (25–103), 15 patients had a PVRi value >20 WU·m^2, 3 patients had a RAP value >10 mm Hg, 11 patients had a CI <2.5 L·min^{-1}·m^{-2}; the median value for SVI, PACi, and HR were 40.93 mL·m^{-2}, 1.14 mL ·mm Hg^{-1}, and 100

Table 2. Univariable Cox Proportional Hazards Regression Showing Clinical and Hemodynamic Variables Associated With Lung Transplantation, Death, or Potts Shunt at Baseline and Reevaluation

Variable (%)	Hazard ratio	95% CI	Cox *P* value
First RHC			
Sex (100)	1.72	0.63–4.68	0.288
Age at diagnosis (100)	1.00	1.00–1.00	0.939
BMI (100)	1.01	0.85–1.19	0.938
Cyanosis at effort (100)	3.22	1.25–8.32	0.016
Cyanosis at rest (100)	3.97	1.49–10.55	0.006
Syncope (100)	1.39	0.56–3.48	0.477
Dizziness (100)	3.57	1.36–9.38	0.010
Right heart failure (100)	2.79	0.26–30.00	0.398
NYHA-Fc I-II/III-IV (100)	2.42	0.94–6.20	0.067
mPAP (100)	1.02	1.00–1.05	0.025
sPAP (100)	1.02	1.00–1.03	0.019
dPAP (100)	1.03	1.00–1.06	0.029
Time between first RHC and diagnosis, d (100)	1.00	1.00–1.00	0.990
BNP, by 100 units (31)	1.00	1.00–1.00	0.001
NT-proBNP, by 100 units (46.5)	1.00	1.00–1.00	0.001
Positive AVT (92)	0.15	0.018–1.2	0.073
PVRi (90)	1.07	1.02–1.12	<0.001
SVI (75)	0.95	0.91–0.99	0.003
HR (75)	1.01	0.99–1.03	0.418
PACi (75)	0.16	0.051–0.52	0.001
RAP (94)	1.31	1.01–1.71	0.043
CI (75)	0.68	0.43–1.08	0.086
Second RHC			
PVRi (96)	1.11	1.07–1.16	<0.001
SVI (76)	0.96	0.91–1.01	0.126
HR (79)	1.01	0.98–1.03	0.502
PACi (76)	0.11	0.031–0.42	0.001
RAP (96)	1.25	1.07–1.45	0.002
CI (76)	0.73	0.47–1.14	0.085
TAPSE (79)	0.9	0.81–1.00	0.046
BNP/NT proBNP (77)	0.15	0.05–0.44	0.001

Relevant hemodynamic parameters at first RHC included PVRi, SVI, PACi, and RAP, and only PVRi, RAP, and PACi at second RHC, suggesting those parameters are not only relevant prognosis factors but also potential therapeutic targets. AVT indicates acute vasoreactivity testing; BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; dPAP, diastolic pulmonary arterial pressure; HR, heart rate; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA-Fc, New York Heart Association-functional class; PACi, pulmonary arterial compliance index; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; RHC, right heart catheterization; sPAP, systolic pulmonary arterial pressure; SVI, stroke volume index; and TAPSE, tricuspid annular plane systolic excursion.

bpm, respectively, and 18 patients (27.7%) were considered responders (Sitbon's criteria) during vasodilatation testing.

Effects of PAH Treatment on the Hemodynamic Parameters at Second RHC

At second RHC, 7 patients (9.9%) did not receive any treatment, 32 patients (45.1%) received oral monotherapy, 20 patients (28.2%) were treated with oral dual therapy, and 12 patients (16.9%) were treated with a triple therapy including a prostacyclin analog. The median delay between first and second RHC was 7.4 months (min. 0.5–max. 59.4). At second RHC, 61 patients (86%) were in NYHA-Fc I-II versus 41 at baseline (58%; $P<0.001$), and 41 patients (74%) had a normal BNP/NT-proBNP value versus 25 (49%) at baseline ($P=0.009$) (Figures Tables S1–S4 and S2). There was a significant improvement in the tricuspid annular plane systolic excursion value whether as an absolute value or in the *Z* score ($P=0.001$ and $P=0.017$). Overall, first-line PAH treatment led to a decrease of ≈15% in mPAP ($P<0.001$) with a mean decrease in PVRi of 24% (3.19 WU·m^{-2}), 18% (2.49 WU·m^{-2}), 68% (9.13 WU·m^{-2}), and in mPAP of 16% (9.1 mm Hg), 9% (5.1 mm Hg), 27% (15.08 mm Hg) with oral monotherapy (endothelin receptor antagonist or phosphodiesterase 5 inhibitor), dual oral therapy (endothelin receptor antagonist + phosphodiesterase 5 inhibitor), and triple therapy (endothelin receptor antagonist + phosphodiesterase 5 inhibitor+prostacycline analogue intravenous or subcutaneous), respectively. Among patients treated with triple therapy, 6 of them had a triple therapy right after the first RHC, and 5 were initially treated with dual oral therapy, and then escalated because of insufficient response after the first clinical evaluation. PACi and SVI significantly increased ($P<0.001$ and $P=0.005$, respectively) with no significant changes in the RAP or the HR. Supplementary Table S1 summarize the changes in the patients' characteristics and in hemodynamics.

Hemodynamic Parameters Associated With Adverse Outcomes

Univariate analysis at first RHC showed that PVRi (HR 1.07 per 1 WU·m^2 increase [95% CI, 1.02–1.12], $P<0.001$), SVI (HR 0.95 per 1 L·min^{-1}·m^{-2} increase [95% CI, 0.91–0.99], $P=0.003$), PACi (HR 0.16 per 1 mL/mm Hg increase [95% CI, 0.051–0.52], $P=0.001$), and RAP (HR 1.31 per 1 mm Hg increase [95% CI, 1.01–1.71], $P=0.043$) were associated with adverse outcomes, while CI and HR were not. We determined threshold values at baseline of 10.7 WU·m^{-2} (AUC, 0.716; $P=0.002$), 1.27 mL·mm Hg^{-1}·m^{-2} (AUC, 0.816; $P=0.008$), and 41.18 mL·m^{-2} (AUC, 0.636; $P=0.014$) for PVRi, PACi, and SVI, respectively, with predicted survival curves shown in Figure 2.

At second RHC, PVRi (HR 1.11 per 1 WU·m^{-2} increase, [95% CI, 1.07–1.16], $P<0.001$), PACi (HR 0.11 per

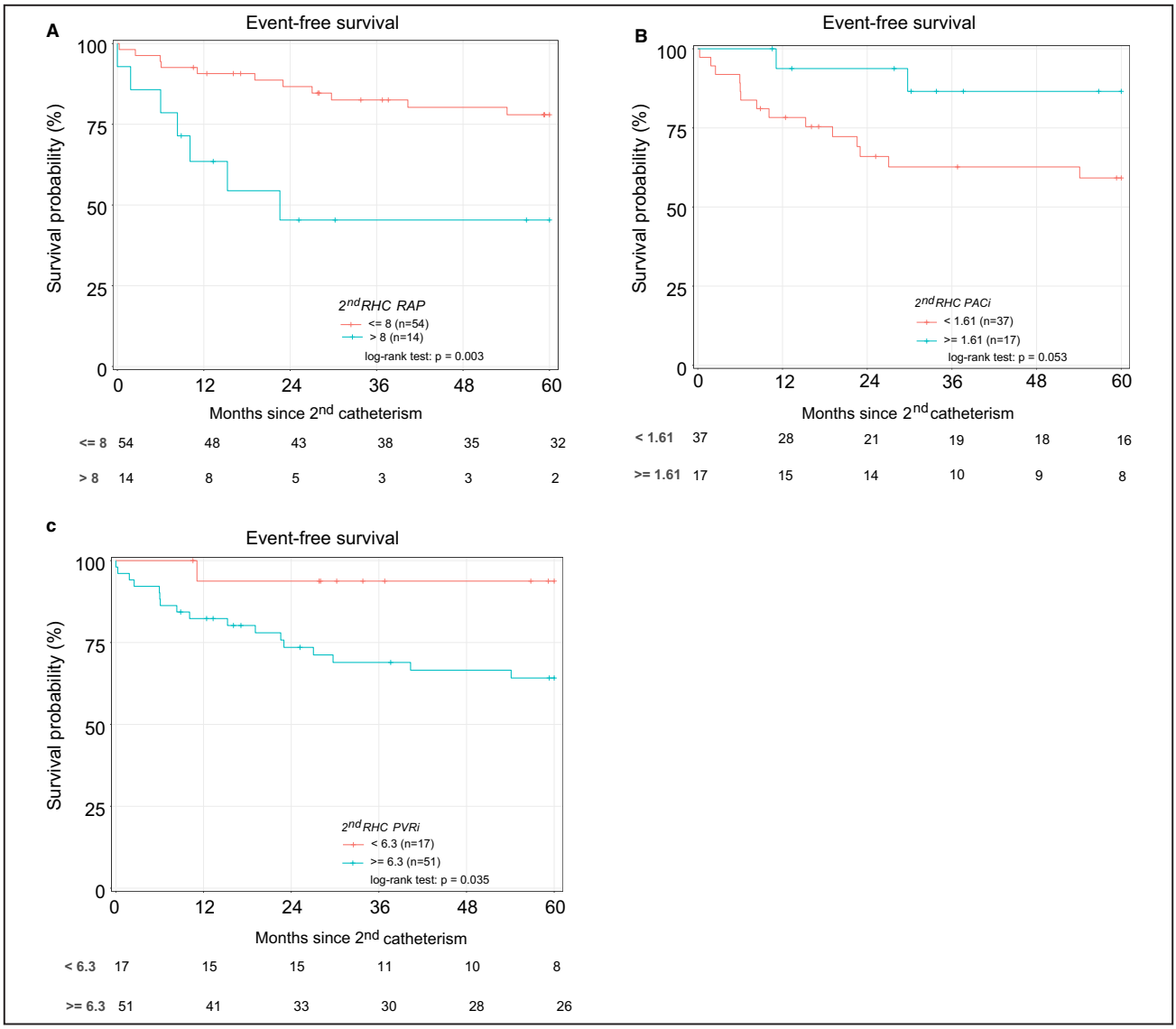

Figure 3. Survival curves of hemodynamic parameters associated with adverse outcomes at second RHC.
Threshold values for PVRi (n=68 available data), PACi (n=54 available data), and RAP (n=68 available data) in our cohort were 6.3 WU·m^{-2}, 1.61 mL·mm Hg^{-1}·m^{-2}, and 8 mm Hg, respectively. Cath indicates right heart catheterization; PACi, pulmonary arterial compliance index; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; and RHC, right heart catheterization.

1 mL/mm Hg increase [95% CI, 0.031–0.42] *P*=0.001), and RAP (HR 1.25 per 1 mm Hg increase, [95% CI, 1.07–1.45], *P*=0.004) were significantly associated with adverse outcomes; SVI, CI, and HR were not. Cutoff values at second RHC were 6.3 WU·m^{-2} (AUC, 0.849, *P*<0.001) for PVRi, 1.61 mL·mm Hg^{-1}·m^{-2} (AUC, 0.816, *P*=0.053) for PACi, and 8 mm Hg (AUC, 0.746; *P*=0.003) for RAP. Predictors of adverse outcomes (death, lung transplantation, or Potts shunt) at first and at second RHC are listed in Table 2. Kaplan–Meier curves showing the absolute values and their associated survival at second RHC and combined values at first and second RHC are shown in Figures 3 and 4.

Correlation Between Clinical and Hemodynamic Parameters

When analyzing noninvasive parameters collected at the last clinic before the second RHC, we sought to evaluate the correlation between the clinical and the hemodynamic parameters. Fifty-seven patients had a second RHC after a clinical improvement and 14 patients had a second RHC after clinical worsening as defined above. Detailed treatment for each group is listed in Table S2. There was no significant difference between those 2 groups in the clinical or hemodynamic status at baseline (Table 1). In the group undergoing a second RHC after clinical improvement, there

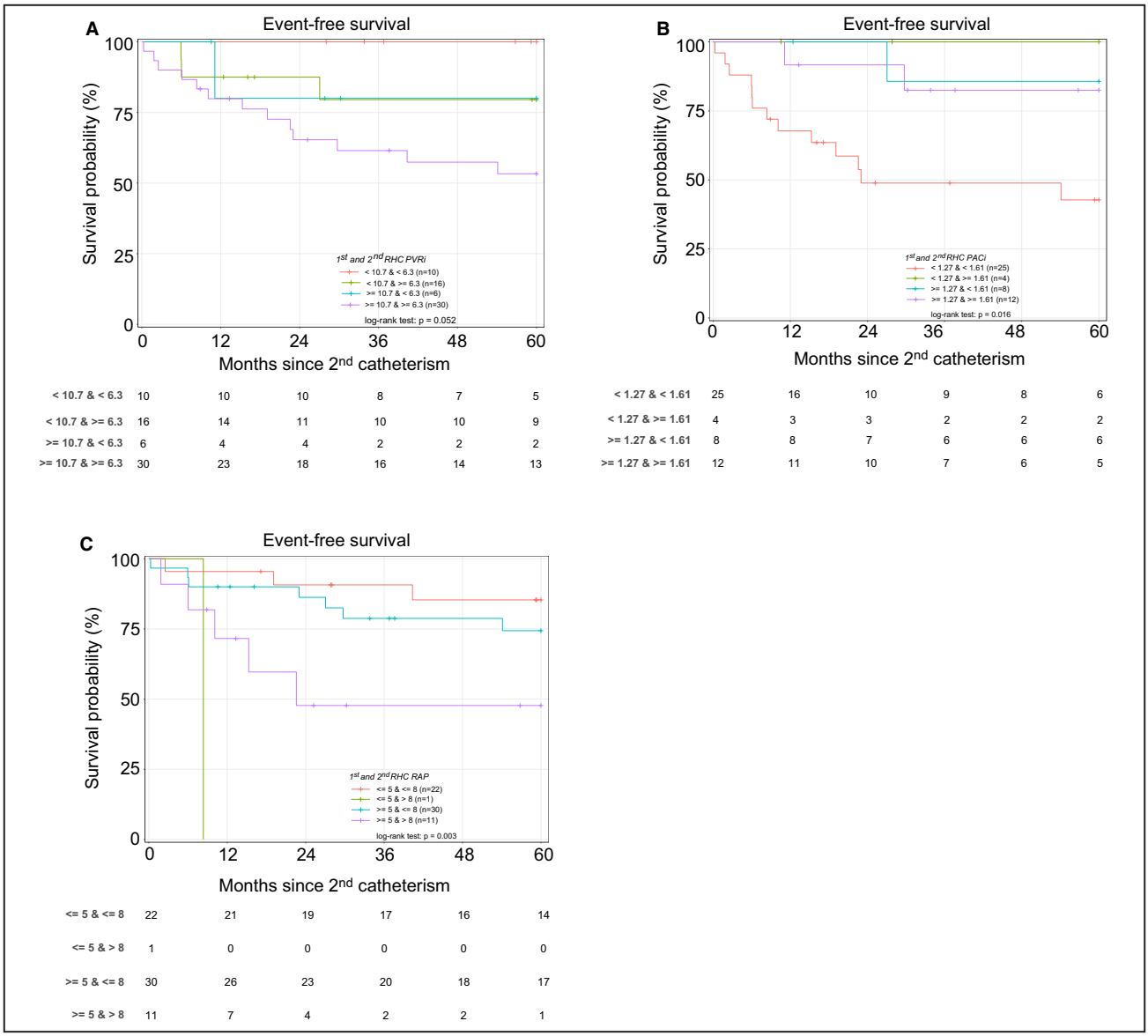

Figure 4. Survival curves of patients at first and second RHC with predetermined threshold values in our cohort.
Cath indicates right heart catheterization, PACi, pulmonary arterial compliance index; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; and RHC, right heart catheterization.

was a significant improvement in the mPAP, the PVRi, the SVI, and the PACi values, while there was no difference in the RAP, HR, and CI values (Table 3). In the group undergoing a second RHC after clinical worsening or no status change despite introduction of PAH treatment, we did not find any significant improvement in any of the hemodynamic parameters (Table 4). Patients who had a second RHC after a clinical improvement had significantly lower mPAP and PVRi values, and higher SVI and PACi values compared with patients who had a second RHC for worsening (Table S2).

Necessity Assessment of Hemodynamic Reevaluation

To assess the necessity for a second RHC, we evaluated the hemodynamic parameters based on the evolution of the patients. We hypothesized that patients with a significant clinical improvement after introduction of PAH treatment would necessitate a reevaluation RHC, while patients who did not improve should not undergo a second RHC, given their clinical status and the likely absence of improvement. Detailed clinical characteristics and hemodynamic characteristics of patients from both groups are listed in Tables 3 and 4. Among patients who had a second RHC after a clinical

Table 3. Clinical and Hemodynamic Parameters of Patients Undergoing a Second RHC After Improvement Based on Noninvasive Criteria

	Baseline RHC 1	RHC 2 after improvement	*P* value
Noninvasive characteristics			
NYHA-Fc			
I-II	33	57	<0.001
III-IV	24	0	
BNP or NT-proBNP			
Abnormal (%)	23 (53)	10 (22.7)	0.009
Normal (%)	20 (46.5)	34 (77.3)	
TAPSE, mm (Q1–Q3)	17 (14.8–20) (n=36)	21 (18–23) (n=45)	<0.001
TAPSE/sPAP, mm/mm Hg (Q1–Q3)	0.2 (0.16–0.28)	0.48 (0.31–0.6)	<0.001
TR peak velocity, m/s (Q1–Q3)	4.3 (3.85–4.6)	3.3 (2.95–3.8)	<0.001
Hemodynamic parameters			
sPAP, mm Hg (Q1–Q3)	85 (69.5–91.5)	65 (49.8–82)	<0.001
mPAP, mm Hg (Q1–Q3)	56 (47–70)	45 (34–60)	<0.001
dPAP, mm Hg (Q1–Q3)	40 (29.5–54)	29 (23–44)	0.001
PVR (WU) (Q1–Q3)	14 (11.55–21.7)	8.1 (5.43–11.5)	<0.001
PVRi (WU·m^{-2}) (Q1–Q3)	14 (8.8–18.6)	8.3 (5.6–11.79)	<0.001
CI (L·min^{-1}·m^{-2}) (Q1–Q3)	3.53 (2.67–4.4)	4.3 (3.05–5.38)	0.069
RAP (mm Hg) (Q1–Q3)	6 (5–7)	6 (4–8)	0.959
SVI (mL·m^{-2}) (Q1–Q3)	41.18 (33.98–48.55)	46.81 (39.11–52.56)	0.001
PACi (mL·mm Hg^{-1}·m^{-2}) (Q1–Q3)	1.21 (0.81–1.61) (n=45)	1.35 (1.03–1.88) (n=45)	<0.001
HR (beats/min) (Q1–Q3)	100 (83–118)	95 (85–112)	0.322
Positive AVT	14	0	<0.001

There was a significant improvement in those patients in most of the hemodynamic parameters, proving the correlation between noninvasive criteria and hemodynamic parameters. AVT indicates acute vasoreactivity testing; BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; dPAP, diastolic pulmonary arterial pressure; HR, heart rate; mPAP, mean pulmonary arterial pressure; NYHA-Fc, New York Heart Association functional class; PACi, pulmonary arterial compliance index; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; RHC, right heart catheterization; sPAP, systolic pulmonary arterial pressure; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; and TR, tricuspid regurgitation.

improvement, 40 (74%) still had 1 parameter that could be considered as higher risk: 38 (69%) had a PVRi value ≥6.3 WU·m^{-2}, 28 (62%) had a PACi value <1.61 mL·mm Hg^{-1}·m^{-2}, and 10 (18.5%) had a RAP value >8 mm Hg. Considering patients who underwent a second RHC after a clinical worsening, all of them had at least 1 hemodynamic parameter at higher risk based on the values we defined as predictors of outcome at second RHC. To further explore the correlation between clinical and hemodynamics parameters, we evaluated 34 patients who had a third RHC study; 16 could be considered as "systematic" RHC, while in 18 the third RHC was performed for worsening. The median delay between second and third RHC was 17.51 months. We found no significant differences in the hemodynamics values between second and third RHC of patients who had a RHC despite their stable status, while patients who had a third invasive exploration because of clinical worsening had significantly worsened mPAP, PVR, and PVRi values (Tables S3 and S4).

DISCUSSION

This study analyzes for the first time the correlation and potential discrepancies between clinical and hemodynamic findings in children with PAH, while implementing new relevant hemodynamic parameters at baseline and follow-up after treatment initiation.

We confirmed that PVRi, PACi, SVI, and RAP are robust predictors of worse outcomes at baseline and at reevaluation after PAH treatment introduction. We found lower threshold values for PVRi (10.7 WU·m^{-2}) and higher cutoff values for PACi (1.14 mL·mm Hg^{-1}·m^{-2}) and SVI (41.18 mL·m^{-2}) than previously described in the pediatric population.[17-19] CI was not a predictor of outcome in our series. This may be explained by the inclusion of patients with open shunts and Eisenmenger syndrome in previous studies,[17,18] which we deliberately excluded. This difference in pathophysiology will irremediably lead to different results for data directly depending on the CI. Furthermore, patients undergoing Potts shunt as a worse outcome were not included in any of the survival

Table 4. Clinical and Hemodynamic Parameters of Patients Undergoing a Second RHC After Worsening

	Baseline RHC1	RHC2 after worsening	*P* value
Noninvasive characteristics			
NYHA-Fc			
I-II	8	5	0.371
III-IV	6	9	
BNP or NT-proBNP			
Abnormal	3	4	1.000
Normal	5	7	
TAPSE	13.5	17	0.309
TR	4.15	4.5	0.363
TAPSE/sPAP	0.15	0.15	0.782
Hemodynamic parameters			
sPAP, mm Hg (Q1–Q3)	85 (61.25–97.5)	88.5 (80–103)	0.307
mPAP, mm Hg (Q1–Q3)	56 (45.3–75)	59 (52–64.75)	0.358
dPAP, mm Hg (Q1–Q3)	31 (26–55.5)	40 (29.75–47.75)	0.434
PVRi, WU·m^{-2} (Q1–Q3)	12.3 (8.3–24.9)	17.7 (8.9–23)	0.524
CI, L·min^{-1}·m^{-2} (Q1–Q3)	3.17 (2.16–5.35)	2.99 (2.51–3.7)	1
RAP, mm Hg (Q1–Q3)	7 (4–8)	5 (4.3–9.5)	0.826
SVI mL·m^{-2} (Q1–Q3)	39.05 (26.32–67.82)	36.39 (27.97–41.67)	0.809
PACi, mL·mm Hg^{-1}·m^{-2} (Q1–Q3)	0.83 (0.55–1.34)	0.93 (0.49–1.14)	0.962
HR, beats/min (Q1–Q3)	96.5 (83.75–103.25)	95 (87–102)	0.962
Positive AVT	4	0	<0.001

There was no significant difference between the hemodynamic parameters between baseline and reevaluation despite specific pulmonary arterial hypertension treatment introduction, suggesting that the second RHC should instead be performed after a therapeutic intensification in those patients.

AVT indicates acute vasoreactivity testing; BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; dPAP, diastolic pulmonary arterial pressure; HR, heart rate; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA-Fc, New York Heart Association functional class; PACi, pulmonary arterial compliance index; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; RHC, right heart catheterization; sPAP, systolic pulmonary arterial pressure; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; and TR, tricuspid regurgitation.

curves of those preceding studies.[20,21] HR alone was not associated in any good or bad outcome in our study, this is in accordance with the Weatherald et al study.[22] Although 2 pediatric studies found resting HR associated with worse outcome in children with PAH, the groups were heterogeneous, with ≈20% of the patients in the Moledina et al study who had a miscellaneous cause of PH and a shorter follow-up duration (3 years), and an important difference in patients' age in both cohorts.[18,23]

To further explore the importance of those parameters, we analyzed data from the second RHC and found that PVRi, PACi, and RAP could not only be considered as prognosis factors but also as potential therapeutic targets since their changes with treatment were associated with changes in outcomes (Figures 2 and 3).

Sequential noninvasive evaluation/risk stratification during follow-up accurately predicts the improvement in hemodynamic parameters. Given this significant improvement in all the main hemodynamic values, the second RHC may seem unnecessary; nonetheless those improvements are not sufficient. Indeed, in patients who had a second RHC after clinical improvement, an important proportion was still at higher risk if we consider the threshold values of PVRi (69%), PACi (37%), and RAP (18%). Those patients may benefit from a therapeutic escalation, which would not have been detected if the evaluation was solely based on noninvasive parameters. To confirm the importance of a standardized second RHC in the year after the baseline RHC, we found that 13 of our patients who had an initial positive acute vasoreactivity testing had a clinical improvement despite "losing" their vasoreactivity at reevaluation. Notwithstanding, invasive measurements after the second RHC in clinically stabilized patients do not seem necessary, given their hemodynamic status did not significantly vary from second to third RHC. To reinforce this idea, we performed the same analysis on 16 patients who underwent a fourth RHC despite being stable and found the same outcome (data not shown). Contrastingly, all patients who underwent a second RHC after clinical worsening did have higher risk hemodynamic

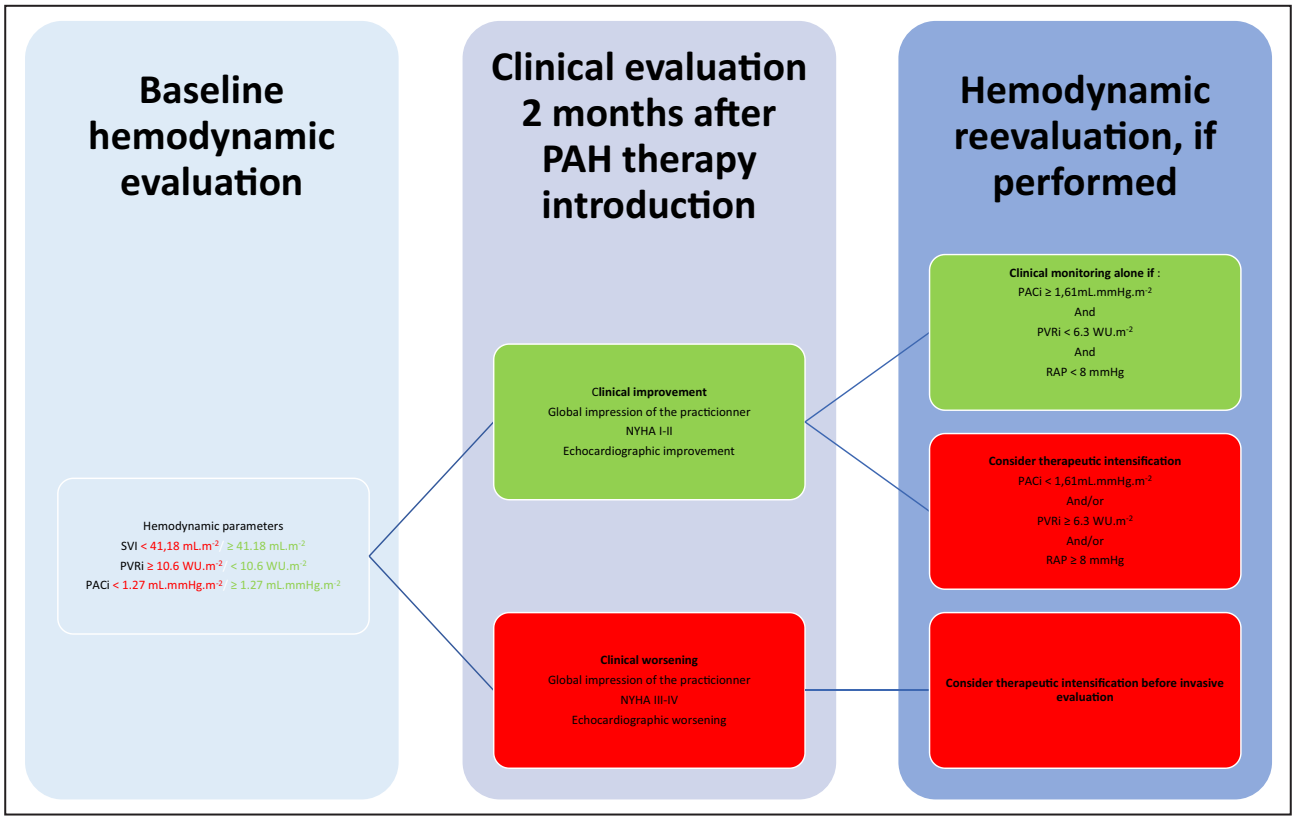

Figure 5. Algorithm presenting prognosis factors and indications of RHC in children with PAH.
This algorithm shows the hemodynamic values we found at first and second RHC, and the indications of reassessment. Based on our results, patients with a clinical worsening despite PAH therapy introduction should not undergo a second RHC; instead an intensification in the therapeutics should be made before the invasive reevaluation. On the other hand, reevaluation of patients who improved after treatment introduction should be performed in order to validate this improvement. NYHA indicates New York Heart Association; PAH, pulmonary arterial hypertension; PACi, pulmonary arterial compliance index; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; and RHC, right heart catheterization.

values of PVRi (100%), PACi (100%), and RAP (71%), while at third RHC there was a significant worsening in hemodynamic parameters of worsened patients. Overall, this suggests—counterintuitively—that a second RHC should be systematically performed in patients with a clinical improvement after PAH treatment introduction, while it ought not to be carried out in clinically stabilized patients, and rather be executed after a therapeutic adjustment in clinically worsened patients (Figure 5). Our results confirm the idea that RHC still holds a central place in the care of patients with PAH[24]; however, given the risk engendered by this invasive tool in the pediatric population, children should be carefully screened before undergoing hemodynamic evaluation.

The collecting and evaluation of our data are made over a 20-year period, and changes in therapeutic strategy during this period may affect the outcomes of our patients. However, the main innovations in the care of children with PAH during those years were the introduction of Potts Shunt and the introduction of triple therapy with addition of subcutaneous treatment; also, the Potts procedure was included in our survival curves, while triple therapy was introduced in 1998 intravenously and in 2005 subcutaneously at our unit,[25] and only 2 patients (2.7%) underwent RHC before this date. The retrospective and monocentric collection of the data added to the inclusion of Potts shunt as a major end point may limit the generalization of the threshold values found in our cohort. Nevertheless, our results are in accordance with the most recent recommendations in the adult population. Although those new hemodynamic parameters seem promising, we were not able to evaluate the effect of specific PAH therapeutics on those parameters, since they were not systematically analyzed in our unit or in the pediatric population in general. Therefore, further studies are needed to validate the use of those new hemodynamic parameters and their possible use as therapeutic targets.

CONCLUSIONS

Hemodynamic variables are valid tools to appreciate the severity of PAH in children at first and at

second catheterization, suggesting they may be used as prognostic factors and therapeutic targets. The clinical evaluation can predict the trend of hemodynamic changes at repeated RHC, but its accuracy is not sufficient to precisely adapt treatments and predict outcomes. Further studies are needed to confirm our findings and accurately define threshold values.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S2

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Supplemental Material

Table S1. Clinical and hemodynamic characteristics of patients before and after initiation of specific PAH therapy.

	Before treatment (n=71)	After treatment (n=71)	P value
Treatment			
Oral monotherapy (%)	0	20 (28.2)	
Oral dual bitherapy (%)	0	32 (45.1)	
Tritherapy (%)	0	12 (16.9)	
Noninvasive parameters			
NYHA-Fc			
I-II	41 (57.7)	61 (86)	<0.001
III-IV	30 (42.2)	10 (14)	<0.001
BNP and NT pro BNP			
Normal	25 (	14	0.009
Abnormal	26	41	
TAPSE (mm) (Q1-Q3)	18 (14-20.25) (n=40)	19.3 (17-22.25) (n=56)	0.071
TAPSE/sPAP (Q1-Q3)	0.2 (0.15-0.24) (n=30)	0.43 (0.26-0.58) (n=36)	<0.001
TR (Q1-Q3)	4.3 (3.77-4.62) (n=30)	3.4 (3-4.3) (n=36)	<0.001
Hemodynamics values			
sPAP (mmHg) (Q1-Q3)	74.5 (61.25-97.5)	50 (39-80)	0.004
mPAP (mmHg) (Q1-Q3)	56 (46.5-70.5)	47 (36.5-61)	0.004
dPAP (mmHg) (Q1-Q3)	39 (28-55)	30 (24-44)	0.009
PVR (WU) (Q1-Q3)	14.5 (11.12-21.2)	8.3 (6.05-12.65)	<0.001
PVRi (WU.m²) (Q1-Q3)	13.15 (8.7-18.85) (n=64)	8.9 (6.27-13.2) (n=68)	0.003
RAP (mmHg) (Q1-Q3)	6 (4.5-7.5) (n=67)	6 (4-8) (n=68)	0.849
SVI ($mL.m^{-2}$) (Q1-Q3)	40.93 (32.25-48.55) (n=53)	43.81 (38.5-51.6) (n=54)	0.008
PACi ($mL.mmHg^{-1}.m^{-2}$) (Q1-Q3)	1.14 (0.71-1.58) (n=53)	1.33 (0.94-1.8) (n=54)	<0.001
HR (beats per minute) (Q1-Q3)	100 (83-112) (n=53)	95 (85-112) (n=56)	0.404
Positive AVT	18	0	<0.001

Abbreviations: AVT – Acute vasoreactivity testing; BNP – Brain natriuretic peptide; dPAP – diastolic pulmonary arterial pressure; HR – Heart rate; mPAP – mean pulmonary arterial pressure; PACi – indexed pulmonary arterial compliance; PVR – Pulmonary vascular resistance; PVRi – indexed pulmonary vascular resistance; RAP – right atrial pressure; sPAP – Systolic pulmonary arterial pressure; SVI – stroke volume index; NYHA-Fc – New York Heart Association-functional class.

Table S2. Comparison of noninvasive and hemodynamic parameters in patients who underwent a 2nd RHC after worsening or after improvement.

	2nd RHC after worsening (n=14)	2nd RHC after improvement (n=57)	P value
Treatment strategy			0.011
Monotherapy (%)	3 (21.4)	29 (50.9)	
Oral dual bitherapy (%)	9 (64.3)	11 (19.3)	
Tritherapy (%)	1 (7.1)	11 (19.3)	
Noninvasive characteristics			
WHO FC			
I-II (%)	5 (	57	<0.001
III-IV (%)	9	0	
BNP or NT pro BNP			
Abnormal	4	10	0.427
Normal	6	34	
TAPSE (Q1-Q3)	17	21	0.008
TR (Q1-Q3)	4.5	3.3	<0.001
TAPSE/ sPAP (Q1-Q3)	0.15	0.48	0.015
Hemodynamic parameters			
sPAP (mmHg) (Q1-Q3)	88.5 (80-103)	65 (49.8-82)	<0.001
mPAP (mmHg) (Q1-Q3)	59 (52-64.75)	45 (34-60)	0.004
PVRi (WU.m^{-2}) (Q1-Q3)	17.7 (8.9-23)	8.3 (5.6-11.79)	0.002
CI (L.min^{-1}.m^{-2}) (Q1-Q3)	2.99 (2.51-3.7)	4.3 (3.05-5.38)	0.161
RAP (mmHg) (Q1-Q3)	5 (4.3-9.5)	6 (4-8)	0.825
SVI (mL.m^{-2}) (Q1-Q3)	36.39 (27.97-41.67)	46.81 (39.1-52.6)	0.013
PACi (mL.mmHg^{-1}.m^{-2}) (Q1-Q3)	0.93 (0.49-1.14)	1.35 (1.03-1.88) (n=45)	0.004
HR (Q1-Q3)	95 (87-102)	95 (85-112)	0.973
Positive AVT	0	0	1.000

There was a significant difference in the treatment strategy. Patients undergoing a 2nd RHC after clinical improvement were significantly more treated with oral monotherapy or tritherapy, while patients undergoing a 2nd RHC were significantly more treated with bitherapy.

Abbreviations: AVT – Acute vasoreactivity testing; BNP – Brain natriuretic peptide; dPAP – diastolic pulmonary arterial pressure; HR – Heart rate; mPAP – mean pulmonary arterial pressure; PACi – indexed pulmonary arterial compliance; PVR – Pulmonary vascular resistance; PVRi – indexed pulmonary vascular resistance; RAP – right atrial pressure; sPAP – Systolic pulmonary arterial pressure; SVI – stroke volume index; NYHA-Fc – New York Heart Association-functional class.

Table S3. Clinical and hemodynamic parameters for patients undergoing a 3rd RHC after clinical deterioration.

	RHC 2 after worsening (n=18)	RHC 3 after worsening (n=18)	P value
Noninvasive characteristics			
WHO-Fc			0.404
I-II	16	13	
III-IV	2	5	
BNP or NT pro BNP			0.409
Abnormal	2	6	
Normal	11	11	
TAPSE (Q1-Q3)	18 (17-21)	17 (15.25-20.45)	0.474
Invasive parameters			
sPAP mmHg (Q1-Q3)	72.5 (62.5-84.25)	87 (76.25-92.5)	<0.001
mPAP mmHg (Q1-Q3)	49.5 (45-59)	63.5 (53-70.75)	<0.001
PVRi WU.m² (Q1-Q3)	9.2 (8.03-11.02)	13.5 (10.9-18)	<0.001
CI $L.min^{-1}.m^{-2}$ (Q1-Q3)	4.93 (3.5-5.17)	3.83 (3.55-4.4)	0.113
RAP mmHg (Q1-Q3)	5 (4-8)	7 (5-8)	0.060
SVI $mL.m^{-2}$ (Q1-Q3)	47.81 (35.44-51.41)	45.75 (36.51-50.08)	0.893
PACi $mL.mmHg^{-1}$ (Q1-Q3)	1.24 (0.84-1.51)	1.3 (0.71-1.51)	0.405
HR beats per minute (Q1-Q3)	97 (90-113)	85 (74-97)	0.015

There is a significant worsening in mPAP, sPAP, and PVRi in those patients.

Abbreviations: AVT – Acute vasoreactivity testing; BNP – Brain natriuretic peptide; dPAP – diastolic pulmonary arterial pressure; HR – Heart rate; mPAP – mean pulmonary arterial pressure; PACi – indexed pulmonary arterial compliance; PVR – Pulmonary vascular resistance; PVRi – indexed pulmonary vascular resistance; RAP – right atrial pressure; sPAP – Systolic pulmonary arterial pressure; SVI – stroke volume index; NYHA-Fc – New York Heart Association-functional class.

Table S4. Hemodynamic parameters in clinically stable patients.

	RHC 2 in stable patients(n=16)	RHC 3 in stable patients (n=16)	P value
Noninvasive characteristics			
WHO-Fc			
I-II	14	16	1.000
III-IV	2	0	
BNP or NT pro BNP			
Abnormal	2	6	0.231
Normal	10	9	
TAPSE	20 (16.5-23.5)	21 (19.5-22.5)	0.387
Invasive parameters			
sPAP mmHg (Q1-Q3)	72.5 (69.5-75.25)	64 (52-103)	0.352
mPAP mmHg (Q1-Q3)	50.5 (40.25-62)	50.5 (39-71.5)	0.648
PVR WU (Q1-Q3)	12.9 (10.2-16.3)	10.7 (6-14.6)	0.634
PVRi WU.m² (Q1-Q3)	9.2 (6.4-13.8)	10.7 (6.6-15.8)	0.820
CI $L.min^{-1}.m^{-2}$ (Q1-Q3)	2.8 (2.55-4.5)	4.03 (3.25-5.1)	0.788
RAP mmHg (Q1-Q3)	7 (5-8.3)	7 (6.8-8)	0.672
SVI $mL.m^{-2}$ (Q1-Q3)	45.26 (38.7-53.3)	43.3 (39.1-51.9)	0.979
PACi $mL.mmHg^{-1}$ (Q1-Q3)	1.27 (0.94-1.42)	1.33 (0.99-1.6)	0.709
HR beats per minute (Q1-Q3)	92.5 (85.5-110)	87 (83-99)	0.023

There was no significant difference in any of the relevant hemodynamic data between the 2nd and 3rd RHC.

Abbreviations: AVT – Acute vasoreactivity testing; BNP – Brain natriuretic peptide; dPAP – diastolic pulmonary arterial pressure; HR – Heart rate; mPAP – mean pulmonary arterial pressure; PACi – indexed pulmonary arterial compliance; PVR – Pulmonary vascular resistance; PVRi – indexed pulmonary vascular resistance; RAP – right atrial pressure; sPAP – Systolic pulmonary arterial pressure; SVI – stroke volume index; NYHA-Fc – New York Heart Association-functional class.

Figure S1. Evolution of BNP after treatment introduction, introduction of treatment led to a significant improvement in BNP absolute value (p=0.037).

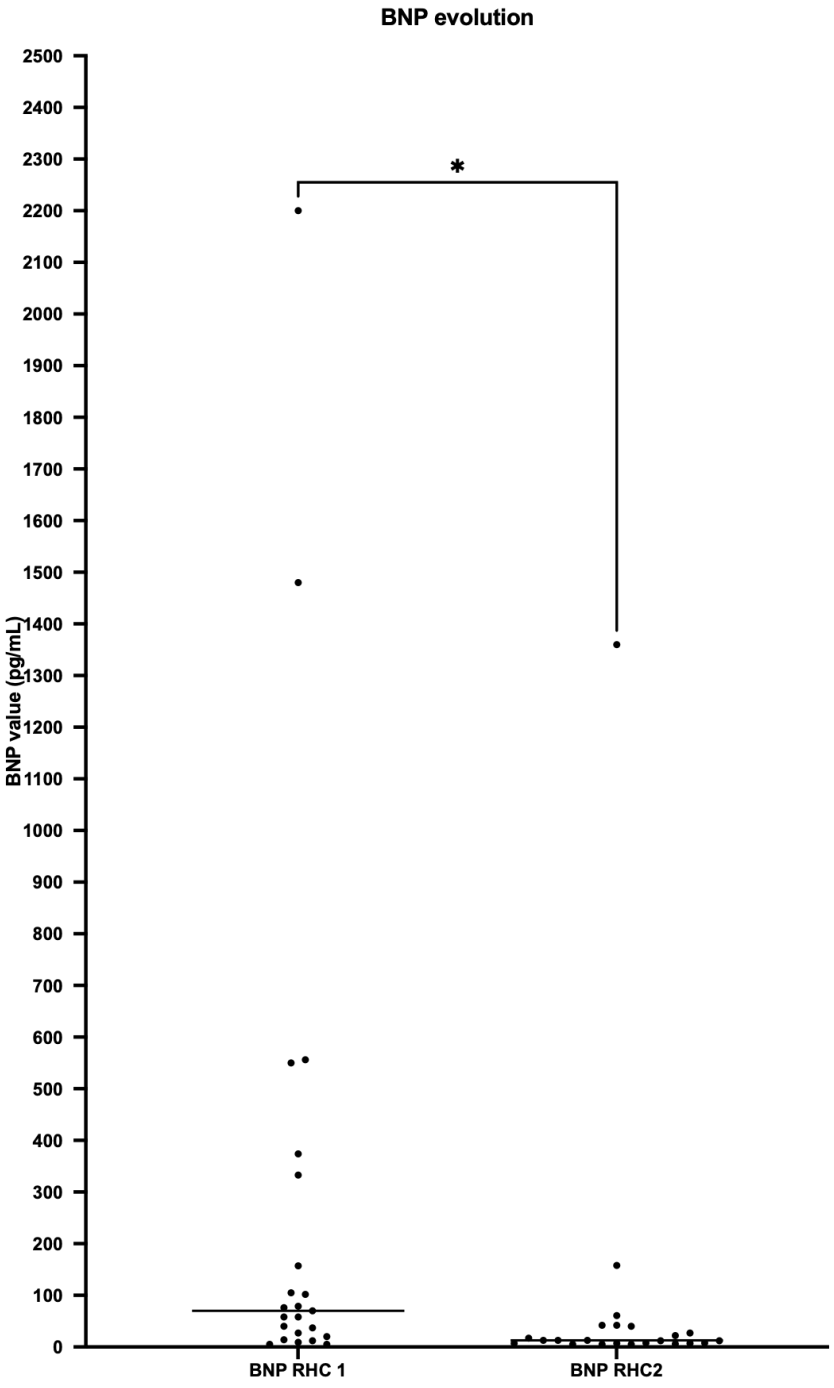

Figure S2. Evolution of NT pro BNP after treatment introduction, introduction of treatment led to a significant improvement in NT pro BNP absolute value (p=0.032).