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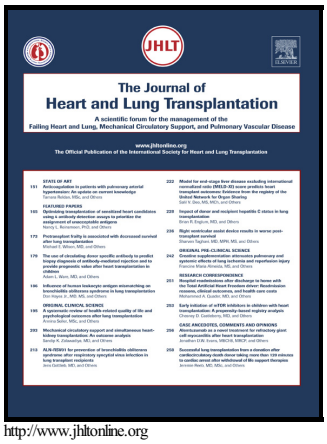

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LONG-TERM OUTCOMES OF PULMONARY ARTERIAL HYPERTENSION UNDER SPECIFIC DRUG THERAPY IN EISENMENGER SYNDROME

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ABSTRACT

BACKGROUND. The long-term effectiveness of pulmonary artery hypertension-specific drug therapy (PAH-SDT) in Eisenmenger syndrome is controversial. We investigated short- and long-term hemodynamic changes under PAH-SDT and their associations with outcomes in a bicentric cohort.

METHODS. Over 20 years, we included 69 patients with congenital heart disease, an indexed pulmonary vascular resistance (PVRi) >8 WU·m², and a total of 292 standardized catheterizations at baseline and after PAH-SDT initiation or intensification. Oxygen consumption (VO_2) was measured and the Fick principle applied to calculate indexed pulmonary output (Qpi) and PVRi.

RESULTS. After PAH-SDT initiation or intensification, median [interquartile range] PVRi decrease was 5.1 WU·m² [-1.4; -12.6] (*P*<0.0001). Median Qpi and 6-minute walking test (6'WT) increases were +0.4 $L \cdot min^{-1} \cdot m^{-2}$ [0.0; +0.9] (*P*<0.0001) and +49 m [+15; +93] (*P*=0.0003), respectively. A hemodynamic response combining increased Qpi with decreases in transpulmonary gradient and PVRi occurred in 68.0% of patients. After a median of 4.9 years, PVRi and Qpi changes were no longer significant. Over a median of 7.2 years, 23 (33.3%) patients met a composite criterion (death, n=8; heart-lung transplantation or listing for transplantation, n=15). The 15-year cumulative event rate was 49.2%. By multivariate analysis, independent predictors of events were superior vena cava O_2 saturation and hemodynamic response (*P*=0.048 and *P*<0.0001).

CONCLUSIONS. In Eisenmenger syndrome, PAH-SDT induces early hemodynamic improvements, which decline over time. Hemodynamic changes under PAH-SDT vary across patients. Hemodynamic parameters at baseline and under PAH-SDT are associated with events. PAH-SDT may deserve to be individualized based on hemodynamic changes.

Introduction

Eisenmenger syndrome (ES) develops when pulmonary hypertension due to an unrepaired congenital left-to-right shunt becomes sufficiently severe to reverse the direction of the shunt, causing peripheral desaturation.(1) ES develops in 3.5 to 12.0% of adults with congenital heart disease (CHD).(2)

PAH specific drug therapies (PAH-SDTs) are designed to induce vasodilation of the pulmonary microvascular tree. Beneficial effects of PAH-SDTs on functional class (FC) have been reported in patients with ES.(3, 4) The PAH-SDT bosentan is approved in Europe for patients with a World Health Organization-FC (WHO-FC) of III or IV.(5) Evidence supporting the use of other PAH-SDTs in ES is less substantial.(5) More specifically, long-term effects and associations with mortality are unclear.(4, 6-9)

The objective of this large prospective cohort study in patients with ES was to assess short- and long-term changes in multiple invasive hemodynamic parameters under PAH-SDT, as well as their associations with outcomes including exercise capacity and clinical events.

Methods

We performed a bicentric observational cohort study in consecutive patients with CHD and an indexed pulmonary vascular resistance (PVRi) >8 Wood Units·m² (WU) indicating either ES or non-correctable prevalent systemic-to-pulmonary shunt according to the NICE classification (5, 10). Exclusion criteria were PAH with a closed defect, coincidental small cardiac defect, or patent foramen ovale. The two participating centers were referral centers for PAH and used the same standard-of-care protocol. Each included patient had at least one standardized right heart catheterization (RHC). All RHCs were done at the same laboratory. Data were collected prospectively in incident patients starting in 1994, by a single investigator (AC).

The study database was reported to the French data protection authority (CNIL n°1154338, April 27, 2006). The study was approved by our institutional review board (n°CCML 2015-4). Written informed consent was obtained from each patient.

WHO-FC and the 6-minute walking test (6'WT) were assessed during the index hospitalization using a standardized method.(11) Blood was collected during RHC for hemoglobin concentration and hematocrit determination using multimodality techniques (ABX Pentra DX 120, Horiba, Kyoto, Japan). Follow-up information was obtained by telephone calls to patients, relatives, and/or general practitioners.

RHCs were performed in hemodynamically stable and spontaneously breathing patients, under local anesthesia, without oxygen support. **Appendix 1** describes the catheterization method. Briefly, pressures were measured in cardiac chambers and vessels and averaged over several respiratory cycles.(12) Left atrial pressure (LAP) was measured directly if there was a pre-tricuspid defect and estimated from the pulmonary wedge pressure (PWP) otherwise. Oxygen consumption (VO_2) was measured using an indirect calorimeter that collected expired gas in a canopy hood (13) (Deltatrac II™, Datex, Helsinki, Finland in 1994-2012 and Quark RMR® Cosmed, Roma, Italy, thereafter). Blood samples for staged oxygen saturation measurements were obtained (ABL80 FLEX CO-OX,

Radiometer, Copenhagen, Denmark). Pulmonary output (Qp) was calculated using the Fick principle then indexed (Qpi) to body surface area (Boyd formula).(14)

The following hemodynamic data were collected: right atrial pressure (RAP); superior vena cava (SVC) oxygen saturation; pulsed peripheral arterial oxygen saturation (SaO_2); mean, diastolic, and systolic pulmonary artery pressures (mPAP, dPAP, and sPAP); pulmonary artery oxygen saturation; mean and systolic aortic pressures (mAP and sAP), PWP, LAP, VO_2, and transpulmonary pressure gradient (TPG). PVRi was calculated as the ratio of TPG/Qpi.

Statistical methods

Statistical analyses were performed using Stata® 11.2 software (StataCorp, College Station, TX). Data are described as mean±standard deviation for normally distributed variables, median [interquartile range] for skewed continuous variables, and number (%) for categorical variables. Categorical variables were compared with the χ^2 statistic or Fisher exact statistic. Comparisons of continuous variables were with Student's *t* test for independent samples if its basic assumptions were satisfied (Shapiro-Wilks and Levene tests) and the Wilcoxon-Mann-Whitney U test otherwise. When continuous variables were distributed among more than two groups, the Kruskal-Wallis test was applied. Reported *P* values are two-sided. *P* values <0.05 were considered statistically significant.

We defined a treatment step as initiation or intensification of PAH-SDT (initiation of PAH-SDT with one or two drugs; or addition of a drug in a patient already taking one or two drugs). Changes between two time points in TPG, PVR, PVRi, Qpi, indexed pulmonary power input (PPIi), and 6'WT were calculated after each treatment step as the difference (Δ) in median (IQR) values. PVR, PVRi, Qpi, and 6'WT were compared before and after each step using the Wilcoxon matched-pairs signed ranks test. Changes following each step were evaluated after a few months then again at last follow-up before the next step. Spearman's coefficients were computed to assess correlations between changes in 6'WT and in hemodynamic parameters after each step.

Assumptions were made to estimate the significance threshold for hemodynamic data changes and to take into account variability due to the measurement methods before the assessment of

pressure-flow relationships (Appendix 1). ΔQpi, ΔTPG, and ΔPVRi values below the threshold were considered nonsignificant and replaced by zero. Changes in corrected TPG were displayed according to corrected Qp on a polar diagram (**Figure 1**).(15) We distinguished three patterns of hemodynamic change over time: improvement, defined as a significant Qpi increase and/or a significant TPG decrease; deterioration, defined as a significant Qpi decrease and/or a significant TPG increase; and stability, defined as no significant change in Qpi or TPG.

We used a composite criterion including four clinical events: death, heart-lung transplantation, lung transplantation, and listing for transplantation. Selection for listing was based on an assessment of each individual patient during a multidisciplinary discussion that focused on FC and right heart failure parameters, without considering pulmonary pressures or PVR obtained during RHC.(16) Kaplan-Meier cumulative events curves were plotted using years since first RHC as the time scale. Differences in cumulative events curves according to hemodynamic data were assessed using the Log rank test.

Associations between baseline variables and outcome were assessed using a Cox proportional hazards model. Proportionality of hazards was evaluated by applying a test for correlation between the scaled Schoenfeld residuals and the logarithmic transformation of time.(17) Variables associated with $P<0.15$ by univariate analysis were introduced into a multivariate model then subjected to stepwise backward selection. A significant interaction was observed between WHO-FC or 6'WT and the pattern of hemodynamic change; therefore, 6'WT and WHO-FC were excluded from the first model. A second model was built without the pattern of hemodynamic change but with WHO-FC and 6'WT. The interaction with WHO-FC tested by adding the interaction term to the model was not significant.

Results

1) Study population

We included 69 patients with 292 RHCs (median, 3 per patient; range 1-14); 10 patients had a single RHC. **Table 1** reports the demographic and hemodynamic data in the overall population and the two subgroups defined by defect location.

Atrial septal defects (ASD) predominated (n=43, 62.3%, including 39 ostium secundum [OS], 2 sinus venosus, and 2 ostium primum), followed by ventricular septal defects (VSD) (n=13, 18.8%), patent ductus arteriosus (PDA) (n=6, 8.7%), and aorto-pulmonary window (n=2, 2.9%); the remaining 5 (7.2%) patients had combined defects (1 case each of PDA+ASD, OS ASD+ abnormal pulmonary venous return (APVR), and VSD+PDA and 2 cases of VSD+ASD). RHC was followed by major adverse events in 2 cases (0.7%; 95%CI, 0.1-2.5%).

At the time of the first RHC, 54 (78.3%) patients were not taking PAH-SDT; 12 (17.4%) were taking a single PAH drug and 3 (4.3%) two PAH- drugs. Of the 59 patients who had two or more RHCs, at the last RHC, 3 (5.1%) were taking no PAH-SDT; 11 (18.6%) were taking a single PAH drug, 32 (54.3%) two PAH drugs, and 13 (22.0%) three PAH drugs. **Appendix 2** describes the treatments in detail.

2) Changes in hemodynamic and functional parameters after treatment steps

a) Hemodynamic parameters

We analyzed 69 treatment steps in 50 patients, Overall, after each step, median PVRi decreased significantly, from 24.4 [18.8-36.5] to 21.2 [14.6-26.2] WU·m² (*P*<0.0001); median Qpi increased from 2.2 [1.8-2.9] to 2.6 [2.1-3.4] $L \cdot min^{-1} \cdot m^{-2}$ (*P*<0.0001). The early hemodynamic changes varied across patients. An improvement with an increase in Qpi and decreases in TPG and PVRi was observed in 66.7% of cases (95%CI, 54.3-77.6%). After each step (**Table 2, Figure 2**), PVRi decreased significantly

and Qpi increased in the patients taking one or two PAH drugs but not in the small group (n=13) taking three PAH drugs.

After a median follow-up of 4.9 years, no significant PVRi decrease or Qpi increase was observed compared to baseline and only 37.4% of patients met our definition of hemodynamic improvement (increased Qpi and decreased TPG and PVRi). The patients taking three PAH drugs had a distinctive long-term profile with a persistent significant PVRi decrease.

Table 3 shows the comparison of clinical and hemodynamic parameters in 50 patients stratified according to the hemodynamic pattern after the first treatment step with available RHC data. Distribution of treatment step types in these 50 patients was as follows: starting a first single drug, n=25; adding a second drug, n=11; adding a third drug, n=3; and starting PAH-SDT with two drugs simultaneously, n=11. A hemodynamic improvement occurred in 34 (68.0%; 95%CI, 53.3-80.5) patients, including the 6 patients with persistent left-to-right shunts (**Figure 1**). Hemodynamic stability was more common in patients with post-tricuspid shunts. Patients with hemodynamic improvement (n=34, 68%) or stability (n=8, 16%) had worse baseline features with more dyspnea, higher PVRi, and lower Qpi compared to the patients with hemodynamic deterioration. Patients with hemodynamic improvement had the largest PVRi decrease and largest Qpi increase, so that their hemodynamic parameters at the second RHC were better than in the patients with hemodynamic stability or deterioration. Patients with hemodynamic deterioration had milder symptoms, lower PVRi, and higher Qpi despite similar pulmonary pressures at baseline. Decreases in both Qpi and TPG occurred in only 2 (4.0%) patients, who had compromised function and died during follow-up. This pattern was characterized by decreases in Qpi, systemic output, and TPG with no significant change in PVRi.

Table 4 shows that the short- and long-term changes in hemodynamic parameters were not significantly different in the subgroups defined by defect location. Only the pattern of hemodynamic change was related to defect location in the short term, with a hemodynamic improvement being more common in the group with pre-tricuspid defects (*P*=0.008).

b) Functional parameters

An overall increase in 6'WT (+44 m [+6; +80]) was observed. After each treatment step (**Table 2**), 6'WT improved significantly in three treatment-step groups, the exception being the group given a third PAH-SDT. However, in this last group, ∆6'WT correlated significantly with ∆PVRi (r=-0.94, *P*<0.005) and ∆Qpi (r=0.83, *P*<0.05). After a median follow-up of 59.1 months [41.6-82.4], ∆6'WT correlated significantly with ∆Qpi (r=1.0, *P*<0.0001). No correlations were found between 6'WT and hemodynamic parameter changes in patients taking one or more PAH drugs.

3) Clinical events (death, transplantation, and listing for transplantation)

Follow-up data on cardiovascular events were available for 68 (98.6%) patients, 4.2 months to 19.7 years after the first RHC (median, 7.2 years). Median age at last follow-up was 45.3 years [38.9; 54.6].

Events occurred in 23 patients (33.3%; 95%CI: 22.4%-45.7%): 8 patients died, 8 received transplants, and 7 were listed for transplantation (**Figure 3**). Median time to event was 8.1 years (range, 7.2 months to 13.6 years) after the first RHC and 2.6 years (range, 2 days to 8.8 years) after the last RHC. Age at events ranged from 18 to 62 years (median, 43.1 years [35.4 - 50.2]) with no significant difference according to defect location (*P*=0.75). The cumulative event rate 15 years after the first RHC was 49.2% (**Figure 4 A**).

Table 5 reports the results of the bivariate analysis comparing patients with and without events. **Figure 4** shows the Kaplan-Meier curves of cumulative events according to clinical and hemodynamic parameters.

Functional parameters at baseline were associated with events and all-cause mortality. Mortality was higher in patients with a shorter 6'WT and higher WHO-FC (*P*=0.015 and *P*<0.001, respectively).

Patients with events had worse hemodynamic characteristics at baseline. By Cox univariate analysis, significant predictors of events were PVRi >30 WU·m² (HR, 2.4; 95%CI, 1.1-5.5; *P*=0.048), RAP>4 mmHg (HR, 3.0; 95%CI, 1.2-7.2; *P*=0.017), SVC oxygen saturation <65% (HR, 8.2; 95%CI, 1.9-35.4; *P*=0.005), and PA oxygen saturation <70% (HR, 4.2; 95%CI, 1.7-10.0; *P*=0.001). Nonsignificant trends were found for the other hemodynamic parameters. After adjustment for defect location, gender, PAH type in the NICE classification, and number of antihypertensive drugs, in the first model (without 6'WT or WHO-FC), SVC oxygen saturation and pattern of hemodynamic change were significantly associated with the outcome (*P*=0.048 and *P*<0.0001, respectively). In the second model (with 6'WT and WHO-FC but without the pattern of hemodynamic change), 6'WT and SVC oxygen saturation were significantly associated with events (*P*=0.038 and *P*=0.005, respectively). Each 1% decrease in SVC oxygen saturation was associated with a 9.8% increase in the HR for events (95%CI, 3.2%-26.1%).

Early patterns of hemodynamic change were significantly associated with events (*P*=0.008) and all-cause mortality (*P*=0.01). Events were more common in patients with the stable or deterioration patterns compared to those with the improvement pattern (HR, 3.8; 95%CI, 1.1-13.5; *P*=0.038) after adjustment for defect location, gender, PAH type (NICE), and number of antihypertensive drugs.

Discussion

In this large cohort of 69 patients with ES, we assessed hemodynamics using a standardized method over a 20-year period. This standardization is a major strength of our study, as it provides reliable data to evaluate the long-term effects of PAH-SDT. PAH-SDT initiation or intensification was associated with early hemodynamic improvements. Nevertheless, the hemodynamic effects of PAH-SDT varied across patients and declined over time. Hemodynamic parameter values at baseline and during PAH-SDT were associated with clinical events.

Methods used to investigate hemodynamics in Eisenmenger syndrome (ES)

Some studies of PAH-SDT effects in ES failed to collect hemodynamic data.(8, 9) Echocardiography provides an assessment of right ventricle function but does not accurately investigate Qp and PVR.(18) In contemporary clinical practice, cardiac output measurement still relies on thermodilution or the Fick method, both of which are invasive.(19) In patients with CHD, thermodilution is inaccurate because the injected cold solution undergoes early recirculation or is lost through septal defects, and the Fick method is therefore the reference standard. VO_2 must be determined to compute cardiac output using the Fick method.(5, 20) Because direct VO_2 measurement is complex and requires sophisticated equipment, VO_2 is often estimated instead, not only in clinical practice but also in studies of ES (3), (21, 22). However, the equations used to estimate VO_2 have been proven inaccurate in both adults and children.(20, 23, 24) We therefore measured VO_2 directly.(13) Furthermore, when assessing hemodynamic changes over time, we took the variability related to the measurement method into account.

Changes in hemodynamics and functional capacity induced by PAH-SDT

Overall, the short-term improvements in PVRi, Qpi, and functional capacity observed under PAH-SDT were consistent with those in previously reported placebo-controlled trials such as

BREATHE-5.(3) However, the hemodynamic effects of PAH-SDT varied across patients. Thus, hemodynamics improved in only about two-thirds of patients.

PAH-SDT in idiopathic PAH is prescribed according to a stepwise strategy.(5) Few data are available on combination PAH-SDT in ES. The analysis of hemodynamic data in patients with ES given combination PAH-SDT is thus a strength of our study. Combination therapy with bosentan and sildenafil failed to improve hemodynamic and functional parameters in a randomized, placebo-controlled, double-blind trial in patients with ES.(25) However, sildenafil was added routinely after 3 months on bosentan.(25) In our cohort and in other studies of everyday clinical practice, stepwise treatment intensification with addition of a PAH drug when the previous treatment became inadequately effective was associated with a significant PVRi decrease and with significant increases in Qpi and 6'WT.(6) Furthermore, our data suggest that initiating PAH-SDT with two drugs in combination may provide greater hemodynamic improvements than a single initial drug.

In the long-term, after a median of nearly 5 years, the effects of PAH-SDT had lessened considerably, with only one-third of patients still exhibiting the hemodynamic improvement pattern of Qpi increase and RVPi decrease. The 6'WT remained higher than at baseline (6) but the size of the difference was similar to that reported previously during placebo therapy.(26) However, the study design did not allow us to determine whether the waning of PAH-SDT effects over time was related to PAH progression or to PAH-SDT escape phenomenon. In particular, we were not able to assess whether PAH-SDT slowed disease progression. In keeping with our data, a study of bosentan showed that the exercise parameters returned to baseline within 2 years.(7)

The pattern of hemodynamic change was associated with the baseline data. The group with the hemodynamic improvement pattern had worse symptoms and higher PVRi at baseline compared to the other groups. In contrast, the hemodynamic deterioration pattern was associated with milder baseline symptoms and lower PVRi values compared to the other groups. PAH-SDT is recommended in patients with idiopathic PAH whose WHO-FC is II, III, or IV.(5) In ES, the effectiveness of PAH-SDT may be greatest in the WHO-FC III and IV classes.(5) Furthermore, differences in clinical phenotype

and echocardiographic parameters exist between patients with pre-tricuspid and post-tricuspid defects.(27) In our cohort, post-tricuspid defects were associated with worse hemodynamic parameter values.(28, 29) Overall, hemodynamic changes induced by PAH-SDT were not significantly different between these two groups, in keeping with a sub-group analysis of data from BREATHE-5.(29) However, in the patient-by-patient analysis, the hemodynamic improvement pattern was noted in only half the patients with post-tricuspid defects compared to three-fourths of those with pre-tricuspid defects. Thus, the response to PAH-SDT may differ according to defect location.(28)

Association between hemodynamics and outcome

Our study confirms the severity of ES, with one-third of patients dying or requiring lung transplantation at a median age of 44.2 years. Similar severity was found in a large single-center study in which most patients had complex shunts.(8) Despite intensive PAH-SDT in our cohort, which included patients classified WHO-FC II, the incidence of major events was high. The absence of a PAH-SDT-naive group limits our ability to assess the impact of PAH-SDT on outcome. The above-mentioned retrospective single-center observational study (8) and a German registry study (9) suggested better survival with PAH-SDT, but neither study collected hemodynamic data. In our population, in addition to WHO-FC, several hemodynamic parameters predicted events, including PVRi, aortic oxygen saturation,(8, 27) RAP, PA oxygen saturation, and SVC oxygen saturation. By multivariate analysis, low SVC oxygen saturation was independently associated with events. In ES, low SVC oxygen saturation reflects both aortic oxygen desaturation and decreased systemic output. We also found that hemodynamic changes during PAH-SDT were strongly associated with events, whereas defect location was not.(27) However, immortal time bias may have occurred in the group with post-tricuspid defects. Unfortunately, our patients did not routinely undergo an accurate echocardiographic assessment of ventricular function, which strongly predicts outcome (18), and we were therefore unable to determine whether invasive hemodynamic parameters provided additional predictive power.

Conclusion:

In ES, the hemodynamic changes under PAH-SDT vary across patients and are associated with clinical events. The PAH-SDT strategy may deserve to be tailored to the hemodynamic changes.

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Figure 1

Polar diagram displaying changes in transpulmonary gradient (TPG) according to changes in pulmonary output index (Qpi) under PAH-SDT. On this pressure-flow diagram, a TPG increase with a Qpi decrease (red area) indicates hemodynamic deterioration with an increase in indexed pulmonary vascular resistance (PVRi). A TPG decrease with a Qpi increase (green area) indicates hemodynamic improvement with a decrease in PVRi. A TPG decrease with a Qpi decrease (gray area) indicates uncertainty. Absence of significant changes in TPG and Qpi defined the hemodynamic stability pattern.

Abbreviations: mPAP, mean pulmonary artery pressure; LAP, left atrial pressure; PVRi, indexed pulmonary vascular resistance; TPG, transpulmonary gradient; Qpi, indexed pulmonary output

Figure 2

Changes in indexed pulmonary vascular resistance (A), transpulmonary gradient (B), indexed pulmonary output (C) and six-minute walking test (D) after each PAH-SDT step.

Abbreviations: PAH-SDT, pulmonary arterial hypertension specific drug therapy; PVRi, indexed pulmonary vascular resistance; Qpi, indexed pulmonary output; TPG, transpulmonary gradient; 6'WT= six-minute walking test.

Figure 3

Distribution of events in the study population (n=69). The data are numbers and percentages.

Figure 4

Kaplan-Meier cumulative event curves in the overall population (A) and in subgroups according to WHO status (B), pulmonary artery oxygen saturation (C), right atrial pressure (D), indexed pulmonary vascular resistance (E), aortic oxygen saturation (F), superior vena cava oxygen saturation (G), and pattern of hemodynamic change under PAH-SDT (H).

Abbreviations: CI, confidence interval; PAH-SDT, pulmonary arterial hypertension specific drug therapy

TABLE 1 Demographic and hemodynamic data of the overall population and subgroups based on defect location

TABLE 2 Short- and long-term changes in hemodynamic parameters and 6-minute walking test after each PAH-SDT step

TABLE 3 Clinical and hemodynamic parameters in 50 patients stratified according to pattern of hemodynamic change after the first PAH-SDT step

Table 4 Changes in hemodynamic parameters under PAH-SDT in patient subgroups defined by defect location

TABLE 5 Bivariate analysis comparing distributions of variables in patients with versus without events during follow-up

TABLE 1 Demographic and hemodynamic data of the overall population and subgroups based on defect location

		Total population	Pre-tricuspid shunt		Post-tricuspid shunt		
		n=69	n=44 (63.8%)		n=23 (33.3%)		P *value*
1.Eisenmenger Syndrome		63 (91.3%)	39	88.6%	22	95.7%	*p=0.656*
2.Left-to-right shunt		6 (8.7%)	5	11.4%	1	4.3%	
Female gender		56 (81.2%)	40	90.9%	15	65.2%	***0.017***
Age at PAH diagnosis (years)		30.8±15.3	33 [28; 41]	14; 64	20 [5; 35]	1; 61	***0.0025***
First RHC							
Age (years)		38.4±13.3	39 [30; 49]	14; 64	35 [22; 47]	14; 76	*0.4090*
6' walking test (m) (n=49)		375±95	396 [318; 432]	140; 505	365 [292; 436]	148; 600	*0.9001*
WHO-FC (n=69)	**1**	0 (0.0%)	0	0.0%	0	0.0%	
	2	25 (36.2%)	16	36.4%	9	39.1%	*1.000*
	3	41 (59.4%)	26	59.1%	13	56.5%	
	4	3 (4.3%)	2	4.6%	1	4.4%	
Pulmonary Vascular Resistance		16.0 [11.4-23.8]	13.7 [10.2; 19.6]	5.9; 43.2	21.7 [16.5; 30.6]	10.8; 65.8	***0.0005***
Pulmonary Vascular Resistance index (WU.m²)		26.0 [19.9-38.3]	23.0 [16.0; 32.1]	10.6 ; 66.1	36.1 [24.1; 43.6]	18.4; 91.5	***0.001***
Pulmonary output ($L.min^{-1}$)		3.8±1.3	3.9 [3.1; 4.9]	1.3; 6.5	3.1 [2.1; 4.3]	1.4; 5.7	***0.0413***
Pulmonary output index ($L.min^{-1}.m^{-2}$)		2.2 [1.6-2.7]	2.2 [1.9; 3.1]	0.8; 4.3	2.0 [1.5; 2.4]	1.0; 3.6	*0.0663*
Systemic output ($L.min^{-1}$)		3.6 [3.0-4.0]	3.6 [2.9; 4.0]	1.9; 8.1	3.4 [3.1; 3.9]	1.5; 9.8	*0.7721*
Systemic output index ($L.min^{-1}.m^{-2}$) (n=65)		2.2 [1.9-2.5]	2.1 [1.8; 2.5]	1.3; 4.5	2.2 [1.9; 2.3]	1.1; 4.8	*0.7227*
Systemic Vascular Resistance index (WU.m²)		38.6 [31.3-48.1]	39.4 [32.8; 52.7]	19.9; 64.6	39.0 [27.7; 45.6]	17.2; 109.4	*0.3058*
Systolic Pulm. Artery Pressure		96 [88-114]	91 [80; 103]	60; 130	113 [103; 133]	75; 210	***0.0001***
Diastolic Pulm. Artery Pressure		40 [35-50]	37 [30; 41]	24; 60	56 [40; 64]	31; 100	***<0.0001***
Mean Pum.Artery Pressure		62 [53-75]	57 [51; 64]	42; 91	78 [65; 86]	52; 122	***<0.0001***
Mean Right Atrial pressure		3 |2-5]	3 [2; 5]	0; 9	3 [1; 6]	0; 20	*0.7434*
Trans Pulmonary Gradient		57 [49-70]	55 [47; 61]	38; 90	70 [61; 79]	38; 116	***0.0002***
Qp/Qs		1.0 [0.8-1.3]	1.1 [0.8; 1.4]	0.3; 1.9	0.8 [0.6; 1.2]	0.5; 1.8	***0.0093***
Pulm. To System. Vascular res. ratio		0.7 [0.5-1.1]	0.5 [0.4; 1.0]	0.3; 2.3	1.1 [0.7; 1.4]	0.4; 2.0	***0.0006***
Pulmonary Artery Oxygen Saturation (%)		71 [67-75]	71 [69; 75]	37; 85	70 [60; 73]	39; 80	*0.1278*
Aortic Oxygen Saturation (%)		87 [83-92]	90 [86; 93]	56; 98	83 [77; 84]	67; 96	***<0.0001***
Superior Vena Cava Oxygen Saturation (%)		63 [58-68]	63 [58; 69]	36; 76	61 [54; 66]	42; 71	*0.1149*
Pulmonary Power Input index ($Watt.m^{-2}$)		0.30 [0.25-0.39]	0.29 [0.25; 0.38]	0.11; 0.58	0.34 [0.23; 0.41]	0.19; 0.62	*0.3274*
Last RHC							
Pulmonary Vascular Resistance		14.0 [9.7-19.8]	11.0 [7.8; 16.5]	4.5; 42.1	19.9 [16.0; 27.3]	10.8; 51.5	***<0.0001***

Pulmonary Vascular Resistance index (WU.m²)	22.6 [16.0-29.8]	19.2 [14.1; 24.9]	6.2; 66.1	30.0 [26.1; 42.9]	17.9; 75.7	***<0.0001***
Pulmonary output (L.min^{-1})	4.1±1.3	4.2 [3.2; 5.4]	1.3; 7.4	3.6 [2.1; 4.0]	1.7; 5.7	***0.0110***
Pulmonary output index (L.min^{-1}.m^{-2})	2.4 [1.9-2.8]	2.6 [2.0; 3.2]	0.8; 5.3	2.2 [1.4; 2.4]	1.1; 2.8	***0.0035***
Systemic output (L.min^{-1})	3.7 [3.1-4.2]	3.6 [3.1; 4.4]	2.0; 7.9	3.7 [3.0; 4.2]	2.0; 9.8	*0.8486*
Systemic output index (L.min^{-1}.m^{-2}) (n=65)	2.3 [2.0-2.6]	2.3 [2.0; 2.6]	1.3; 5.4	2.3 [1.8; 2.6]	1.4; 4.8	*0.7776*

RHC=right heart catheterization; Qp/Qs= pulmonary output / systemic output; FC=functional class; WU=Wood Unit

Pressure unit: mmHg; Resistance unit: Wood Unit (mmHg.L-1.min)

TABLE 2 Short- and long-term changes in hemodynamic parameters and 6-minute walking test after each PAH-SDT step

Early change (post- pre)

	Delay (m.)	**Delta PVR** (WU)	**Delta PVRindex** (WU.m²)	**Delta Qp index** (l.min^{-1}.m^{-2})	**6'WT** (m)	**Stability**	**↘Qpi-↗TPG**	**↘TPG-↗Qpi**	**↗TPG-↗Qpi**	**↘TPG-↘Qpi**
	med. [IQR]	med. [QR]	med. [IQR]	med. [IQR]	med. [IQR]					
Single PAH-SDT n=25	6 [5-11]	-3.1 [-10.2 ; +0.0] p<0.01	-4.5 [-15.8 ; +0.3] p<0.01	+0.5 [-0.1 ; +0.8] p<0.01	+37 [+13 ; +88] p<0.01	5 (20.0%)	3 (12.0%)	16 (64.0%)	0	1 (4.0%)
First-line double PAH-SDT n=11	4 [3-5]	-4.0 [-9.4;-2.1] p=0.02	-8.5 [-16.7; -2.6] p=0.01	+1.0 [-0.2; +1.5] p=0.06	+70.0 [+15.0 ; +137.0] p=0.03	0	1 (9.1%)	9 (81.8%)	0	1 (9.1%)
From single to double PAH-SDT n=23	6 [5-13]	-2.0 [-4.7 ; -0.7] p=0.01	-2.5 [-7.7 ; -0.9] p=0.02	+0.3 [+0.0; +0.6] p=0.02	+20.0 [-9 : +67] p=0.07	5 (21.7%)	3 (13.0%)	14 (60.9%)	0	1 (4.4%)
From double to triple PAH-SDT n=10	5.5 [5-10]	-2.7 [-5.4 ; +1.0] p=0.18	- 4.8 [-11.2 ; +1.6] p=0.20	+0.3 [-0.3 ; +0.9] p=0.28	+61 [-58; +80] p=0.25	0	4 (40.0%)	6 (60.0%)	0	0

Late change (post- pre)

	Delay (m.)	**Delta PVR** (WU)	**Delta PVRindex** (WU.m²)	**Delta Qp index** (l.min^{-1}.m^{-2})	**6'WT** (m)	**"no-change pattern"**	**↘Qpi-↗TPG**	**↘TPG-↗Qpi**	**↗TPG-↗Qpi**	**↘TPG-↘Qpi**
	med. [IQR]	med. [IQR]	med. [IQR]	med. [IQR]	med. [IQR]					
from 1st to last RHC n=59	65 [43-109]	-2.0 [-6.3 ; +1.1] p<0.01	-5.0 [-11.1 ; +2.9] p<0.01	+0.1 [-0.3 ; +0.6] p=0.10	+40.0 [-7.0 ; +71.0] p<0.01					
Single PAH-SDT n=17	48 [30-83]	+0.4 [-2.4; 2.1] p=0.98	+1.1 [-4.8; +3.3] p=0.98	+0.0 [-0.5 ; 0.4] p=0.52	+58.5 [0.0 ; +100.5] p=0.03	4 (23.5%)	4 (23.5%)	5 (29.4%)	1 (5.9%)	3 (17.7%)

First-line double PAH-SDT n=9	57 [54-59]	-0.6 [-4.9; +0.7] p=0.31	-0.4 [-6.5; +0.1] p=0.14	+0.0 [-0.3 ; +0.2] p=0.68	+32.0 [-25.0 ; +103.0] p=0.25	2 (22.2 %)	1 (11.1 %)	n=2 (22.2%)	0	4 (44.4 %)
From single to double PAH-SDT n=21	48 [36-63]	-0.7 [-4.0; 1.5] p=0.40	-2.3 [-6.0 ; +2.3] p=0.37	-0.1 [-0.5 ; +0.3] p=0.79	+3.5 [-22.0 ; +40.0] p=0.80	4 (19.1 %)	2 (9.5 %)	11 (52.4%)	0	4 (19.1 %)
From double to triple PAH-SDT n=6	57 [41-78]	-6.1 [-8.3;-0.3] p=0.07	-8.0 [-16.9 ; -0.6] p=0.03	+0.5 [+0.0 ; +2.4] p=0.17	+20.5 [-64.5 ; +100.0] p=0.47	2 (33.3 %)	0	n=3 (50.0%)	0	1 (16.7 %)

Data are median [interquartile range] Abbreviations: RHC=right heart catheterization; PAH= Pulmonary Artery Hypertension; SDT= Specific Drug Therapy; PVR=Pulmonary Vascular Resistance; WT= walking test; Qpi=indexed pulmonary output; TPG=trans-pulmonary gradient; med=mediane; ITQ= interquartile; WU=Wood Unit Unit $mmHg.L^{-1}.min$

TABLE 3 Clinical and hemodynamic parameters in 50 patients stratified according to pattern of hemodynamic change after the first PAH-SDT step

Pattern of hemodynamic change		"no-change pattern"	↘Qpi-↗TPG	↘TPG-↗Qpi	↘TPG-↘Qpi	
n=50		n=8 (16%)	n=6 (12%)	n=34 (68%)	n=2 (4%)	***P value***
Events		5 (62.5%)	0 (100%)	9 (26.5%)	2 (100%)	***0.008***
Eisenmenger Syndrome		8 (100%)	6 (100%)	28 (82.4%)	2 (100%)	*0.615*
Pre-tricuspid shunt		2 (25.0%)	4 (66.7%)	28 (82.4%)	2 (100%)	***0.003***
Gender	Female	6 (75.0%)	5 (83.3%)	28 (82.4%)	2 (100%)	*1.000*
RHC before PAH-SDT step						
Pulmonary Vascular Resistance		19.6 [13.5; 27.6]	11.5 [11.0; 12.4]	15.8 [11.2; 24.2]	5.9; 9.9	***0.016***
Pulmonary Vascular Resistance index (WU.m²)		31.5 [23.4; 41.4]	18.1 [14.5; 21.4]	28.1 [19.2; 39.5]	15.5; 11.8	***0.0074***
Age (y)		34 [32; 41]	33 [30; 46]	40 [31; 49]	29; 59	*0.8016*
6'Walking Test (m)		320 [275; 424]	399 [339; 419]	389 [357; 434]	200; 240	*0.1306*
WHO-FC	1	0	1 (16.7%)	0	0	***0.004***
	2	4 (50.0%)	4 (66.6%)	9 (26.5%)	0	
	3	4 (50.0%)	1 (16.7%)	25 (73.5%)	1 (50.0%)	
	4	0	0	0	1 (50.0%)	
Pulmonary output index ($L.min^{-1}.m^{-2}$)		2.0 [1.5; 2.4]	3.6 [3.0; 3.6]	2.1 [1.6; 2.6]	2.7; 3.2	***0.004***
Systemic output index ($L.min^{-1}.m^{-2}$)		1.9 [1.8; 2.3]	2.7 [2.1; 3.1]	2.0 [1.7; 2.4]	2.0; 2.7	*0.1028*
Systemic Vascular Resistance index (WU.m²)		33.0 [24.5; 52.7]	32.3 [28.1; 36.5]	40.5 [34.3; 55.2]	32.8; 46.7	*0.2661*
Mean Pulmonary Artery Pressure		68 [57; 86]	64 [62; 77]	59 [52; 71]	42; 47	*0.083*
Mean Right Atrial Pressure		4 [2; 6]	5 [3; 9]	3 [2; 6]	4; 5	*0.6770*
Transpulmonary Gradient		59 [52; 82]	59 [53; 67]	56 [47; 65]	38; 42	*0.1182*
Qp/Qs		1.1 [0.6; 1.2]	1.4 [1.0; 1.6]	1.0 [0.8; 1.3]	1.0; 1.6	*0.2081*
Pulm. To System. Vascular res. ratio		0.8 [0.6; 1.4]	0.5 [0.5; 0.7]	0.6 [0.5; 1.1]	0.3; 0.5	*0.1161*
Aortic Oxygen Saturation (%)		81 [76; 91]	89 [84; 93]	88 [83; 94]	89; 92	*0.2936*
Superior Vena Cava Oxygen Saturation (%)		62 [57; 65]	61 [58; 68]	62 [57; 66]	60; 70	*0.8835*
Pulmonary Power Input index ($Watt.m^{-2}$)		0.32 [0.24; 0.35]	0.49 [0.39; 0.62]	0.26 [0.23; 0.32]	0.28; 0.30	***0.0119***
early RHC after PAH-SDT step						
Delay (months)		5.5 [3; 10]	12 [3; 14]	5 [4; 9]	4; 5	*0.8169*
Pulmonary Vascular Resistance		20.0 [13.4-27.7]	12.9 [11.4-15.8]	9.5 [7.8-15.4]	6.1; 10.0	***0.0108***
Pulmonary Vascular Resistance index (WU.m²)		31.4 [23.5-41.8]	22.2 [18.6-23.4]	16.8 [12.9-24.7]	12.4; 15.3	***0.0099***
6'Walking Test (m)		366 [329; 375]	464 [431; 495]	450 [389; 500]	293; 331	***0.0269***
WHO-FC	1	1 (12.5%)	1 (16.7%)	2 (4.8%)	0	***0.383***
	2	4 (50.0%)	4 (66.6%)	21 (61.8%)	0	
	3	2 (25.0%)	1 (16.7%)	10 (29.4%)	2 (100%)	
	4	1 (12.5%)	0	1 (2.9%)	0	
Pulmonary output index ($L.min^{-1}.m^{-2}$)		2.1 [1.9; 2.3]	2.8 [2.4; 3.4]	2.9 [2.3; 3.7]	2.4; 2.6	***0.0245***
Systemic output index ($L.min^{-1}.m^{-2}$)		2.1 [1.8; 2.5]	2.5 [2.2; 3.0]	2.5 [2.1; 2.8]	1.3; 1.8	*0.1376*
Systemic Vascular Resistance index (WU.m²)		34.6 [26.4; 46.2]	31.3 [27.3; 38.9]	32.3 [26.8; 42.1]	42.9; 62.6	*0.2995*
Mean Pulmonary Artery Pressure		76 [62; 90]	63 [62; 69]	52 [48; 67]	37; 41	***0.0032***
Mean Right Atrial Pressure		5 [4; 6]	3 [1; 7]	5 [3; 6]	5; 5	*0.8368*

Trans Pulmonary Gradient	68 [53; 85]	59 [56; 63]	49 [43; 61]	32; 36	***0.007***
Qp/Qs	1.0 [0.7; 1.2]	1.2 [0.9; 1.4]	1.2 [0.9; 1.5]	1.3; 2.0	*0.1725*
Pulm. To System. Vascular res. ratio	1.0 [0.7; 1.3]	0.7 [0.6; 0.8]	0.5 [0.3; 0.7]	0.2; 0.4	***0.0144***
Aortic Oxygen Saturation (%)	84 [77; 91]	92 [83; 94]	89 [87; 93]	88; 98	*0.2481*
Superior Vena Cava Oxygen Saturation (%)	56 [54; 65]	63 [56; 69]	65 [60; 71]	54; 61	*0.1239*
Pulmonary Power Input index ($Watt.m^{-2}$)	0.37 [0.25; 0.39]	0.39 [0.34; 0.49]	0.34 [0.29; 0.43]	0.21; 0.21	*0.0919*
Changes between the 2 RHCs (1st -2nd value)					
Δ 6'Walking Test (m)	-20 [0; -49]	-82 [-17; -110]	-45 [-15; -88]	-53; -131	*0.4469*
Δ Trans Pulmonary Gradient (mmHg)	-3.0 [-7.0; 0.0]	0.0 [-3.0; 2.0]	6.5 [1.0-12.0]	6; 6	***0.0036***
Δ Pulmonary output index ($L.min^{-1}.m^{-2}$)	-0.2 [-0.3; 0.0]	0.6 [0.4; 0.9]	-0.7 [-1.0; -0.5]	0.5; 0.4	***0.0001***
Δ Pulmonary Vascular Resistance index ($WU.m^2$)	0.0 [0.0; 0.0]	-4.8 [-5.6; -2.6]	8.6 [5.0; 17.4]	0.0; 0.0	***0.0001***
Δ Pulmonary Power Input index ($Watt.m^{-2}$)	-0.02 [-0.09;0.00]	0.08 [0.04; 0.16]	-0.07 [-0.13; -0.02]	0.08; 0.07	***0.0018***

RHC=right heart catheterization; PAH= Pulmonary Artery Hypertension; SDT= Specific Drug Therapy; Qpi=indexed pulmonary output; TPG=transpulmonary gradient; FC=functional class; WU=Wood Unit Unit $mmHg.l^{-1}.min$

Pressure unit: mmHg; Resistance unit: Wood Unit (mmHg.L-1.min)

TABLE 4 Changes in hemodynamic parameters under PAH-SDT in patient subgroups defined by defect location

		pre-tricuspid shunt		post-tricuspid shunt		
Change between first and last RHC		n=40		n=18		*P value*
First value - last value		med [itq]	min.; max.	med [IQR]	min.; max.	
Time from first to last RHC (months)		63 [46; 105]	4; 180	67 [24; 109]	3; 229	*0.9464*
Δ Qpi ($l.min^{-1}.m^{-2}$)		-0.1 [-0.9; 0.3]	-3.1; 1.6	0.0 [-0.4; 0.2]	-0.8; 0.8	*0.4824*
Δ PVR index ($WU.m^2$)		5.6 [0.0; 11.2]	-13.3; 36.2	0.0 [-4.9; 8.9]	-13.9; 43.4	*0.2210*
Δ TPG (mmHg)		6 [0; 13]	-16; 90	0 [0; 8]	-35; 30	*0.1984*
Δ PPIi ($Watt.m^{-2}$)		0.00 [-0.05; 0.08]	-0.27; 0.17	0.01 [-0.04; 0.07]	-0.26; 0.25	*0.5823*
Δ 6'WT (meters)		-24 [-71; 18]	-232; 106	-48 [-74; -20]	-159; 25	*0.2583*
Change after a treatment step		n=36		n=13		*P value*
Value before step - value after step						
Time interval (months)		5 [4; 8]	2; 14	5 [3; 12]	3; 24	*0.9346*
Δ Qpi ($l.min^{-1}.m^{-2}$)		-0.6 [-1.0; 0.0]	[-2.4; 0.8]	-0.2 [-0.5; 0.0]	-2.3; 1.3	*0.2477*
Δ PVR index ($WU.m^2$)		5.2 [0.0; 10.7]	-18.5; 21.7	5.5 [0.0; 15.8]	- 8.4 ; 37.4	*0.8376*
Δ TPG (mmHg)		3 [0; 10]	-11; 23	0 [0; 12]	-12; 38	*0.8235*
Δ PPIi ($Watt.m^{-2}$)		-0.05 [-0.12; 0.02]	-0.22; 0.09	-0.05 [-0.09; 0.00]	-0.30; 0.26	*0.5938*
Δ 6'WT (meters)		-49 [-100; -15]	-148; 104	-24 [-59; -13]	-88; 0	*0.4446*
pattern of early post-step change	**stability**	2	5.6%	6	46.2%	***0.008***
	↘Qpi-↗TPG	4	11.1%	1	7.7%	
	↘TPG-↗Qpi	28	77.8%	6	46.2%	
	↗TPG-↗Qpi	0	0.0%	0	0.0%	
	↘TPG-↘Qpi	2	5.6%	0	0.0%	

PAH= Pulmonary Artery Hypertension; SDT= Specific Drug Therapy; Qpi=indexed pulmonary output; TPG=trans-pulmonary gradient; PVT= Pulponary Vascular Resistance; PPIi = Pulmonary Power Input index; WT= Walking Test; WU=Wood Unit Unit $mmHg.l^{-1}.min$

TABLE 5 Bivariate analysis comparing distributions of variables in patients with versus without events during follow-up

		Events (transplantation / death)	No events	*P* value
		n=23 (33.3%)	**n=46 (66.7%)**	
Female gender		20 (87.0%)	36 (78.3%)	*0.52*
1.Eisenmenger Syndrome		23 (100.0%)	40 (87.0%)	*0.168*
Pre-tricuspid shunt		14 (60.9%)	30 (65.2%)	*0.634*
Age at PAH diagnosis (y)		33.2±12.0	29.6±16.7	*0.371*
First RHC				
Number of PAH drugs at 1st RHC	**0**	18 (78.2%)	36 (78.3%)	*1.000*
	1	4 (17.4%)	8 (17.4%)	
	2	1 (4.4%)	2 (4.4%)	
WHO-FC (n=69)	**1**	0 (0.0%)	0 (0.0%)	***0.005***
	2	4 (17.4%)	21 (45.7%)	
	3	16 (69.6%)	25 (54.3%)	
	4	3 (13.0%)	0 (0.0%)	
6' walking test (m) (n=49)		302±95	407±75	***<0.001***
Pulmonary Vascular Resistance (WU)		21.0 [13.4-25.4]	14.9 [11.0-21.5]	*0.080*
Pulmonary Vascular Resistance index ≥30 WU.m²		13 (56.5%)	15 (32.6%)	***0.035***
Pulmonary output index ($l.min^{-1}.m^{-2}$)		2.0 [1.5-2.5]	2.3 [1.9-2.8]	*0.104*
Systemic output index ($l.min^{-1}.m^{-2}$) (n=65)		2.1 [1.9-2.3]	2.2 [1.8-2.7]	*0.537*
Mean Right Atrial Pressure		4 [3-6]	3 [2-5]	***0.024***
Mean Right Atrial Pressure ≥4		16 (69.6%)	16 (34.8%)	***0.006***
Mean Pulmonary Artery Pressure		67 [52-75]	62 [54-75]	*0.679*
Diastolic Pulmonary Artery Pressure		45 [35-55]	38 [33-46]	*0.122*
Diastolic Pulmonary Artery Pressure≥45		12 (52.2%)	13 (28.9%)	*0.060*
Superior Vena Cava oxygen saturation (%)		60 [55-63]	64 [58-69]	***0.011***
Superior vena cava oxygen saturation ≤65%		21 (91.3%)	26 (56.5%)	***0.005***
Aortic oxygen saturation (%)		84 [79-89]	88 [84-93]	***<0.010***
Pulmonary Artery oxygen saturation (%)		69 [60-73]	72 [69-77]	***0.007***
Pulmonary Artery oxygen saturation >70%		8 (34.8%)	32 (69.6%)	***0.006***
VO2 index ($ml.min^{-1}.m^{-2}$)		123.3±17.9	126.0±17.2	*0.564*
Hemoglobin ($g.dL^{-1}$)		15.9 [14.2-18.7]	16.6 [14.8-18.1]	*0.651*
Pulm. To System. Vascular resistance ratio		0.8 [0.5-1.1]	0.7 [0.5-1.1]	*0.5329*
Pulmonary Power Input index ($Watt.m^{-2}$)		0.28 [0.23-0.35]	0.31 [0.26-0.40]	*0.203*
Transpulmonary Gradient (mmHg)		61 [47-70]	57 [50-70]	*0.964*
Early hemodynamic change after PAH-SDT step (n=50)				***0.008***
Stability		5 (31.3%)	3 (8.8%)	
↘Qpi-↗TPG		0 (0.0%)	6 (17.7%)	
↘TPG-↗Qpi		9 (56.3%)	25 (73.5%)	
↘TPG-↘Qpi		2 (12.5%)	0 (0.0%)	

PAH= Pulmonary Artery Hypertension; SDT= Specific Drug Therapy; Qpi=indexed pulmonary output; TPG=transpulmonary gradient; FC=functional class; WU=Wood Unit mmHg.L^{-1}.min

Pressure unit: mmHg