Original Article

Vasoreactive testing prevalence and characteristics in patients with idiopathic pulmonary arterial hypertension

Goncharova Natalia, Kirill Lapshin[1], Aelita Berezina[2], Irina Zlobina[2], Anton Ryzhkov[3], Zhaneta Matakaeva[1], Elizaveta Andreeva, Olga Moiseeva

Departments of Noncoronary Disease, [1]Intensive Care Unit, [2]Cardiorespiratory Testing and [3]Magnetic Resonance Imaging, Almazov National Medical Research Center, Saint-Petersburg, Russia

Address for correspondence:
Dr. Goncharova Natalia, Akkuratova Street, 2, Saint-Petersburg 197341, Russia.
E-mail: ns.goncharova@gmail.com

Submission: 26-08-2024
Revised: 18-09-2024
Accepted: 26-09-2024
Published: 11-01-2025

Abstract:

INTRODUCTION: The choice of treatment strategy in patients with idiopathic pulmonary arterial hypertension (IPAH)/HPAH/DPAH (Hereditary pulmonary arterial hypertension/ Drug-induced pulmonary arterial hypertension) II-III functional class (FC) (WHO) based on an acute vasoreactive testing result (VRT). Positive VRT (VRT+) is an indication for calcium channel blockers therapy. Long-term vasoresponders demonstrate sustained low-risk status and the highest survival among all PH subtypes.

THE STUDY AIMED: To characterize VRT performance in IPAH patients and differences in presentation between patients with positive, negative VRT, and patients with not done VRT due to physicians' decision.

METHODS: One hundred and sixty-six adult IPAH patients (44.2 ± 15.3 years, 34 males) comprised into prospective single-center study between 2008 and 2023 years. Inhaled iloprost was used for VRT. Positive VRT was defined with established Sitbon criteria. Standard baseline pulmonary arterial hypertension (PAH) evaluation including cardiopulmonary exercise test (CPET) was performed. Risk status was evaluated using ESC/ERS (European Society of Cardiology/European Respiratory Society) risk scale 2015. Survival was assessed with the Kaplan–Mayer method.

RESULTS: Eighty-five (51.2%) patients underwent VRT. VRT not done (ND VRT) due to the physicians' decision in 26.7% patients, due to the technical inability in 15.4% and IV FC (WHO) in 16.2% patients. Positive VRT registered in 26 (15.6%) patients. Patients with negative VRT demonstrated worse hemodynamics and exercise tolerance, higher N-terminal pro-brain-type natriuretic peptide (NT-proBNP) level, and right heart dilatation compared with VRT+. Patients with ND VRT due to the physicians decision were often older than 60 years, had higher body mass index, symptoms of right heart failure, hemoptysis, arrhythmias, high NT-proBNP, and hemodynamic criteria of high risk in comparison with patients with done VRT. Some CPET parameters were similar between VRT + group and patients ND VRT group. Loss of vasoreactivity and PAH worsening were detected in 50% of VRT + patients in a 1.76 year of follow-up. Patients with vasoreactivity loss exhibited the criteria of intermediate risk at a baseline. Five-year survival was 97% in VRT + group in comparison with 61% in VRT – and 53% in ND VRT group.

CONCLUSIONS: Physicians' decision was the most common reason for not doing VRT in IPAH patients. Intermediate high-risk criteria presence at a baseline were associated with not done VRT due to physicians decision, negative VRT, and the vasoreactivity loss during the follow-up. CPET should be used more widely to detect the early signs of PAH progression in low risk or VRT + patients.

Keywords:

Cardiopulmonary exercise test, idiopathic pulmonary arterial hypertension, vasoreactive testing, vasoreactivity loss

Access this article online

Quick Response Code:

Website: https://journals.lww.com/aotm

DOI: 10.4103/atm.atm_189_24

How to cite this article: Natalia G, Lapshin K, Berezina A, Zlobina I, Ryzhkov A, Matakaeva Z, *et al*. Vasoreactive testing prevalence and characteristics in patients with idiopathic pulmonary arterial hypertension. Ann Thorac Med 2025;20:62-70.

Idiopathic pulmonary arterial hypertension (IPAH) is a rare disease, with the incidence of 48–55 cases and prevalence of 6 cases per 1 million adult population a year.[1] The mortality rate remains comparable to oncological diseases and reaches 55% within 3 years even with pulmonary arterial hypertension (PAH) specific therapy.[2] The choice of treatment strategy in patients with IPAH/heritable PAH/drugs and toxin-induced PAH II-III FC (WHO) based on an acute vasoreactive tesing result (VRT).[1] Positive VRT is an indication for the high-dose calcium channel blockers (CCB) therapy.[1] Long-term CCB vasoresponders exhibit 5-year survival of 98%, which is the highest survival among all PH types.[3] Moreover, CCB therapy might be more beneficial in true long-term vasoresponders compared to PAH-specific therapy.[4] The annual cost of PAH-specific therapy varies between 5647 and 87,058 $ per year per patient, which is a heavy burden for the healthcare system.[5] While CCB therapy cost ranges from 56 to 214 $ per year per patient.[6] Unrecognized vasoresponders might lose an opportunity for highly effective CCB therapy.[7] Therefore, identification of IPAH/HPAH/FPAH patients with positive VRT is of a paramount importance for the healthcare system.

Low incidence of long-term vasoresponders (<10%)[8] and the broad prescription of PAH-specific therapy have led to a significant decrease of VRT performance. The only 22.4% of IPAH patients underwent VRT in the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) registry.[9] However, the reasons for not done VRT in IPAH patients remained unknown.

The study aimed to characterize VRT performance in IPAH patients, reasons for not done VRT, and differences in presentation between patients with positive, negative VRT and patients with not done VRT due to physicians' decision.

Methods

Study population

The study population comprised 166 adult IPAH Caucasian patients (≥18 years old) prospectively recruited in a single-PH referral center between 2008 and February 2023. The inclusion criteria into the study were the following: A mean pulmonary arterial pressure (mean PAP) ≥25 mmHg, pulmonary capillary wedge pressure (PCWP) <15 mmHg, and pulmonary vascular resistance (PVR) ≥3 Wood units. The exclusion criteria for the study were the following: PAH other etiologies than IPAH, moderate-to-severe lung disease or left heart disease, established malignancies with an expected survival <12 months, and mental disorders. IPAH patients were divided on to three groups: I Group – VRT+, II Group – VRT−, and III Group – VRT not done due to physicians' decision (ND VRT group). IPAH patients without VRT due to the IV FC (WHO) and technical inability or prevalent patients diagnosed at another reference center with PAH therapy were not included into the further analysis [Figure 1].

Data collection

Demographics, symptoms, 6-min walk test (6MWT) distance, cardiac magnetic resonance imaging (MRI), laboratory variables (hemoglobin, creatinine with estimated glomerular filtration rate (eGFR), and N-terminal pro-brain-type natriuretic peptide [NT-proBNP]) were collected at a baseline in a period of 1 month, when the right heart catheterization (RHC) was performed. eGFR was calculated according to the Chronic kidney disease epidemiology collaboration (CKD-EPI) equation. Vasoreactive testing (VRT) with inhaled Iloprost (Bayer, Germany) was done in 85 patients. Positive VRT was defined as previously described.[1,10,11] Repeat RHC was done in 22 VRT + patients with CCB therapy in the center.

Cardiopulmonary exercise test (CPET) was performed in 89 patients on a cycle ergometer with an incremental workload 10 W/min (RAMP-protocol) up to the patient maximum tolerance using Ebike (GI, USA). Gas exchange was measured breath-by-breath method using the calibrated Oxycon Pro equipment (Cardinal Health, Germany).

Cardiac MRI was done using MAGNETOM Trio A Tim System 3 Tesla (Siemens, Germany) in 44 patients. MRI data for all VRT + patients were used for the analyses.

Baseline risk stratification was performed using 2015 ESC/ERS risk stratification (https://www.pahinitiative.com/hcp/risk-assessment/calculators) (URL accessed on June, 01 2024).

The start date of follow-up was the date of the first RHC at the center and the last date of follow-up was the date of death, last patient visit, or telephone contact within 3 months to May 2024. The last patient was included into the study on February 2023 to have 12 months' follow-up period for an appropriate long-term CCB responders definition.[12]

The study reflects daily clinical practice within the Guidelines for the management of patients with PAH.[1,10,11] Identifiable patient information was not presented in the study.

Statistical analysis

Demography, clinical data including comorbidity, PAH functional class (FC) (WHO), hemodynamic

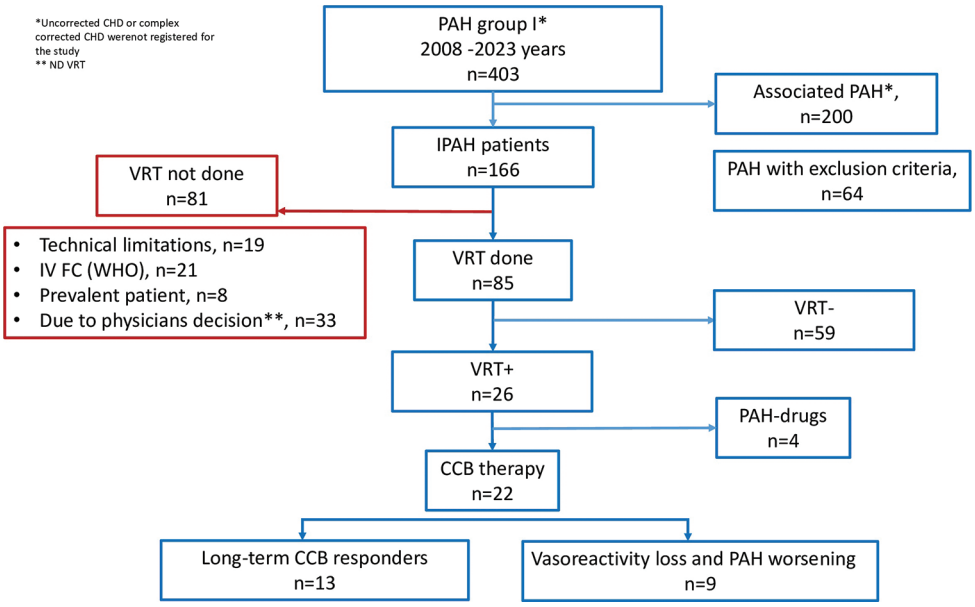


Figure 1: Study population. IPAH: Idiopathic pulmonary arterial hypertension, CCB: Calcium channel blockers, CHD: Congenital heart defects, FC: Functional class, ND: Not done, VRT: Vasoreactive testing, −: Negative; +: Positive

data, laboratory and lung function test parameters, echocardiography variables, and exercise tests, obtained at baseline, were compared in three groups (VRT+, VRT − and ND VRT) and in patients long-term vasoresponders and patients with vasoreactivity loss. Patients without VRT due to the IV FC (WHO), technical limitations, and prevalent IPAH patient were not included in further analyses. Numerical parameters with a normal distribution were presented as mean ± standard deviation, and numerical parameters with an abnormal distribution were presented as median and interquartile range (IQR; M ± 25%, 75%). Categorical variables were described as absolute numbers and percentages and compared using Fisher exact or Pearson M-L Chi-square tests, as appropriate. The continous variables among the groups were compared using the one-way ANOVA. Survival analyses performed using Kaplan–Meier curves and log-rank test to compare the survival distribution between three groups. A statistically significant difference was determined as a two-tailed $P < 0.05$. The statistical analyses of the data were carried out using Statistica for Windows, version 10.0 (StatSoft: Tulsa, Okla, USA).

Results

VRT was performed in 85 (51.2%) patients. Positive VRT registered in 26 (30.58%) patients with CCB prescription in 22 patients. VRT was not carried out in 81 patients due to the technical reason in 15.4% cases (n = 19); in IV FC (WHO) patients in 16.2% (n = 21); in 8 prevalent patients with PAH specific therapy prescription in another PH center and in 26.7% (n = 33) IPAH patients due to the decision of two PH center physicians. Physicians' decision of not doing VRT was based on subjective assumption the disease severity and low probability of positive effect of CCB therapy in a particular patient. Technical limitation for VRT performance was associated with the absence of iloprost or nitric oxide at the time of PH referral center establishment.

Vasoreactive testing-positive group

VRT + patients were significantly younger, often with body mass index (BMI) <30 kg/m^2, without hemoptysis and rhythm disturbances in comparison with VRT − or ND VRT group [Table 1] at the time of diagnosis. VRT + patients demonstrated better exercise tolerance in 6MWT and CPET, rare symptoms of right heart failure (RHF) and III FC (WHO), and lower NT-proBNP concentration, as well.

Mean PAP was significantly lower in VRT + compared with VRT − patients (P = 0.0002) but did not reach significant difference with ND VRT group (P = 0.08). Right atrial pressure was the lowest in VRT + patients in comparison to ND VRT group and VRT − patients (P = 0.01). VRT + and VRT − patients did not differ in PCWP (P = 0.1), whereas PCWP was significantly higher (P = 0.04) in ND VRT group compared to VRT + patients. Cardiac index (CI) was the highest in VRT + group in comparison with VRT− (P = 0.00001) patients and ND VRT group (P = 0.00006). Arterial blood ($SatO_2$) and mixed venous oxygen saturations (SvO_2) were significantly higher in VRT + groups compared with others.

Right atrial square, the ratio of RV/LV diameters were smaller and RV ejection fraction was higher in

Table 1: Characteristic of idiopathic pulmonary arterial hypertension patients with positive, negative vasoreactive testing and in not done vasoreactive testing group due to physician's decision

Parameters, *n* (%); mean±SD; median (IQR 25%–75%)	All patients (*n*=118)	Group I (VRT+) (*n*=26)	Group II (VRT–) (*n*=59)	Group III (ND VRT) (*n*=33)	*P*
Age (years)	44.1±15.5	38.7±16.1	42.7±13.8	50.9±16.2	0.006
>60 years	28 (23.7)	4 (15.4)	8 (13.6)	16 (50)	0.0003
Male*	26 (22)	3 (11.5)	15 (25.4)	8 (24.2)	0.3
Symptoms					
Edema*	53 (44.9)	5 (19.2)	25 (42.4)	23 (69.7)	0.0005
Chest pain*	34 (28.8)	8 (30.7)	17 (28.8)	9 (27.3)	0.9
Syncope*	46 (38.9)	14 (53.8)	23 (38.9)	9 (27.3)	0.1
Arrhythmia**	10 (8.5)	0	3 (5.1)	7 (21.2)	0.006
Hemoptysis*	4 (3.4)	0	0	4 (12.2)	0.005
6MWT (m)	338.7±123.3	422.6±113.6	322.2±125.5	302.2±96.7	0.0002
III FC PAH*	90 (76.3)	13 (50)	48 (81.4)	29 (87.9)	0.001
Comorbidity					
Hypertension	52 (44.1)	9 (34.6)	25 (42.4)	18 (54.5)	0.3
IHD	10 (8.5)	1 (3.8)	4 (6.8)	5 (15.2)	0.2
COPD	12 (10.2)	1 (3.8)	7 (11.6)	4 (12.1)	0.5
Diabetes	18 (15.2)	3 (11.5)	13 (22)	2 (6.1)	0.1
BMI (kg/m^2)	27.3±5.9	25.1±4.5	27.8±6.5	28.2±5.4	0.08
BMI >30 (kg/m^2)	41 (34.7)	4 (15.4)	23 (38.9)	14 (42.4)	0.06
Smoking	24 (20.3)	3 (11.5)	12 (20.3)	9 (27.3)	0.3
Laboratory					
NT-proBNP (pg/mL)	1014 (385–2600)	460 (96–811)	1549 (612–2835)	1092 (341–1092)	0.008
Creatinine (µmol/L)	85.9±19.8	82.9±16.5	86.7±19.2	86.8±23.3	0.6
eGFR (mL/min/1.73 m^2)	84.8±24.8	91.5±22.7	87.4±23.7	74.8±26.1	0.017
Hemoglobin (g/L)	147.6±20.1	139.6±17.9	141.8±20.1	147.8±19.8	0.01
Hemodynamics					
HR (bpm)	80.7±14.3	74.8±13.4	83.3±12.9	80.5±16.0	0.04
mBP (mmHg)	89.5±13.5	88.2±12.1	87.5±12.9	94.2±14.7	0.06
mPAP (mmHg)	56.3±14.9	49.3±11.8	59.7±14.9	55.7±15.4	0.01
RAP (mmHg)	7.5±5.3	5.4±4.1	7.5±4.9	9.0±6.4	0.03
PAWP (mmHg)	7.69±3.6	6.5±3.25	7.7±3.7	8.45±3.5	0.1
CI (L/min/m2)	2.16±0.67	2.4±0.7	1.8±0.6	1.8±0.5	0.000006
PVR (WU)	14.1±7.8	9.5±3.7	15.9±8.4	14.3±7.8	0.002
$SatO_2$ (%)	94.6±3.4	96.3±2.7	94.4±3.1	93.6±3.9	0.01
SvO_2 (%)	61.6±9.7	68.9±6.3	58.7±9.9	61.1±8.4	0.00001
Echocardiography					
LAVI (mL/m^2)	26.6±8.9	26.1±6.6	25.3±8.9	29.4±11.6	0.09
EDD LV (mm)	40.8±10.5	42.3±4.9	40.9±13.2	39.7±7.9	0.6
MMI LV (g/m^2)	73.3±26.1	73.5±22.6	71.3±25.1	76.6±30.6	0.6
RA size (cm^2)	28.9±8.1	23.1±6.1	29.9±7.8	31.7±8.1	0.00006
RV base. A4C (mm)	47.3±6.4	45.1±6.8	47.6±5.9	48.6±6.5	0.09
TASV (cm/s)	9.26±2.6	10.7±2.1	8.7±2.4	9.1±3.1	0.005
EDD RV/EDD LV	1.2±0.3	1.07±0.2	1.28±0.27	1.28±0.3	0.005
IVC (mm)	20.7±4.5	18.7±4.4	21.1±4.7	21.7±4.2	0.04
Pulmonary function test (%)					
FVC	91.6±16.9	95.5±14.8	91.4±18.6	88.7±15.4	0.3
FEV_1	84.5±14.2	89.5±9.7	83.2±15.3	82.9±14.3	0.1
DLCO	64.3±16.3	69.6±14.2	62.9±16.9	61.1±16.4	0.1
ESC/ERS 2015 risk status and mortality					
Score	2.12±0.45	1.7±0.38	2.2±0.43	2.2±0.34	0.00000001
Low risk	17 (14.4)	10 (38.5)	6 (10.2)	1 (3.0)	0.05
Intermediate risk	64 (54.2)	16 (61.5)	30 (50.8)	18 (54.6)	1.0
High risk	37 (31.4)	0	23 (38.9)	14 (42.4)	0.0005

Contd...

Table 1: Contd...

Parameters, *n* (%); mean±SD; median (IQR 25%–75%)	All patients (*n*=118)	Group I (VRT+) (*n*=26)	Group II (VRT–) (*n*=59)	Group III (ND VRT) (*n*=33)	*P*
Death*	43 (36.4)	4 (15.3)	18 (30.5)	21 (63.6)	0.0003

*Fisher's *t*-test, **Atrial flutter and atrial fibrillation were taken into account. 6MWT=6-min walk test, BMI=Body mass index, CI=Cardiac index, LV=Left ventricle, COPD=Chronic obstructive pulmonary disease, DLCO=Diffusion capacity of the lungs for carbon monoxide, EDD LV=End-diastolic dimension of LV, EDD RV/EDD LV=The ratio of the end-diastolic dimension of the right ventricle to the EDD LV, CKD-EPI=Chronic kidney disease epidemiology collaboration, eGFR=Estimated glomerular filtration rate (the eGFR was calculated according to the CKD-EPI equation), FC=Functional class, FEV_1=Forced expiratory volume in 1 s, FVC=Forced vital capacity, HR=Heart rate, IHD=Ischemic heart disease (included patients with revascularized status), IVC=Inferior vena cava, IQR=Interquartile range, LAVI=Left atrium volume index, mBP=Mean blood pressure, MMI=Myocardial mass index, mPAP=Mean pulmonary artery pressure, NT-proBNP=N-terminal fragment of B-type brain natriuretic peptide, PAH=Pulmonary arterial hypertension, PVR=Pulmonary vascular resistance, RA=Right atrial, RAP=RA pressure, RV=Right ventricle, $SatO_2$=Arterial blood saturation, SvO_2=Mixed venous oxygen saturation, VRT+=Positive vasoreactive testing, VRT−=Negative vasoreactive testing, ND VRT=Vasoreactive testing not done, SD=Standard deviation, PAWP=Pulmonary artery wedge pressure, ePAP=Estimated pulmonary artery pressure, IPAH=Idiopathic pulmonary arterial hypertension, LVEF=Left ventricular ejection fraction, PCWP=Pulmonary capillary wedge pressure, RHC=Right heart catheterization, SV=Stroke volume, SVi=Stroke volume index, TAPSE=Tricuspid annulus plane systolic excursion, TASV=Tricuspid annular systolic velocity, ESC=European society of cardiology, ERS=European respiratory society

VRT + patients in comparison with VRT – and ND VRT groups. Diffusion capacity to monoxide and pulmonary function test results did not differ between the groups.

VRT + patients demonstrated a significantly higher level of physical performance in terms of the workload and peak oxygen consumption in absolute values (peak VO_2) compared to VRT – and ND VRT groups [Table 2]. However, when analyzing the percentage of predicted peak oxygen consumption (VO_2 peak predicted %), no difference between VRT + and ND VRT groups was revealed. Percent of VO_2 peak predicted was the lowest in VRT – patients and significantly differed even from ND VRT group. The same correlations were observed for oxygen consumption at anaerobic threshold (VO_2/kg AT) with the lowest value in patients with negative VRT. Percent of predicted oxygen pulse (VO_2/HR Predicted, %) was significantly higher in VRT + group in comparison with VRT – patients but did not differ with ND VRT group. Carbon dioxide equivalents at peak (VE/VCO_2) and at anaerobic threshold (VE/VCO_2 AT) were significantly lower in VRT + group in comparison with VRT – patients. VRT + patients demonstrated more effective ventilation pattern in comparison with VRT – and ND VRT group: The difference between dead space ventilation at rest and peak physical exertion (ΔVD/VT) was the lowest in VRT+.

There were no high-risk patients in VRT + group. Low-risk status was associated with positive VRT [Table 1].

Vasoreactive testing negative group

VRT – patients were comparable in age with VRT + group (P = 0.25) but were significantly younger than patients with ND VRT. Hemodynamic parameters, right heart size, and function were significantly worsened, and NT-proBNP concentration elevated in VRT – group in comparison with VRT + patients [Table 1].

VRT – patients exhibited the lowest distance in 6MWT, peak VO_2 in absolute and in predicted value, percent of VO_2/AT predicted and VO_2/HR predicted; and the highest heat rate acceleration (HR/Vkg) in comparison with VRT + patients and ND VRT group. VE/VCO_2 was significantly higher in comparison with VRT + and ND VRT group. However, the difference in VE/VCO_2 was lost between VRT – and VN VRT group at anaerobic threshold. Aerobic work efficiency ($\Delta VO_2/\Delta WR$) was the lowest in VRT – patients in comparison with other groups, but $\Delta VO_2/\Delta WR$ did not differ between VRT + and ND VRT group [Table 2].

The number of low-risk patients was significantly lower in VRT – group in comparison with VRT+. Risk groups distribution in VRT – patients was comparable with ND VRT.

Not done vasoreactive testing group due to physicians decision

ND VRT group characterized with a significantly higher number of patients older than 60 years, with BMI > 30 kg/m^2 and lower eGFR in comparison with VRT + and VRT – groups. Nevertheless, no significant difference registered in terms of comorbidity between the three groups. This observation could be explained with a low number of patients older than 60 years in the entire cohort (n = 28) and strict exclusion criteria.

NT-proBNP concentration did not differ between VRT – patients and ND VRT group (P = 0.5). ND VRT patients demonstrated similar to VRT – group hemodynamics and heart remodeling negative changes. No significant differences registered in mean PAP, CI, PVR, $SatO_2$, right atrial square, the ratio of RV/LV diameters, and RV systolic function between VRT – and ND VRT groups [Table 1].

Six min walk distance did not differ between VRT – and ND VRT group (P = 0.2). Nevertheless, peak VO_2, VO_2 Predicted (%), VO_2AT were significantly higher in ND VRT patients in comparison to VRT – group [Table 2]. Oxygen pulse was significantly higher in ND VRT group in comparison to VRT – patients and did not differ with VRT + group. Ventilatory equivalent to CO_2 was significantly lower in ND VRT in comparison to VRT – group, but the correlation significance was lost on anaerobic threshold achievement between these two groups. Aerobic work efficiency ($\Delta VO_2/\Delta WR$) did not

Table 2: Cardiopulmonary exercise testing in idiopathic pulmonary arterial hypertension patients with positive, negative vasoreactive testing, and in group with not done vasoreactive testing due to physicians decision

Parameters, *n* (%); mean±SD; median (IQR 25%–75%)	Entire cohort (*n*=118)	Group I (VRT+) (*n*=26)	Group II (VRT–) (*n*=59)	*P* (Group I and II)	Group III (ND VRT) (*n*=33)	*P* (Groups I and III)	*P* (Groups II and III)	*P* (Groups I, II, III)
CPET parameters (*n*)	89	17	25		47			
Load (W)	60 (50–80)	80 (70–90)	60 (50–80)	0.002	60 (60–80)	0.056	0.5	0.004
VE max predicted (%)	63.5±19.1	60.5±16.9	63.5±18.1	0.5	67.9±24.4	0.2	0.4	0.5
Desaturation (%)	4.9±9.4	3.9±3.2	5.6±12.4	0.5	4.3±4.9	0.7	0.7	0.7
VO_2 peak (mL/min/kg)	12.2 (10.6–16.8)	17.2 (12.1–22)	11.2 (9.1–14.6)	0.000006	13.5 (11.4–16.8)	0.057	0.03	0.00001
VO_2 peak predicted (%)	51 (40–66)	62 (53–72)	44 (35–53)	0.00002	62 (42–71)	0.8	0.001	0.00005
VO_2/kg AT predicted (mL/kg/min)	47 (38–63)	59.5 (45–73.5)	40 (31–57)	0.0005	59 (49–64)	0.1	0.02	0.0004
$\Delta VO_2/\Delta WR$ (mL/min/W)	8.8±2.2	9.4±1.8	8.2±2.4	0.04	9.8±1.7	0.5	0.02	0.02
VO_2/HR predicted (%)	64 (49–72)	68 (59–80)	54 (46–67)	0.0004	69 (63–82)	0.6	0.0003	0.00006
HR/Vkg (L/mL/kg)	10.7 (8.8–12.7)	10 (7.4–11.3)	11.5 (10.5–13.5)	0.02	9.6 (8.4–11.5)	0.6	0.01	0.006
ΔVD/VT (%)	19 (15–24)	17 (12–19)	21 (17–24)	0.055	22 (17–24)	0.3	0.4	0.1
BR predicted (%, L)	3 (–2–7)	3 (0–9)	–1 (–6––7)	0.6	3 (0–7)	0.8	0.4	0.7
VE/VCO_2	49.9±13.7	41.6±10.3	55.2±12.8	0.00002	47.4±14.2	0.1	0.04	0.0001
VE/VCO_2 AT	43.8 (34.6–54.6)	34.4 (30.8–44.7)	48.3 (38.8–55.9)	0.002	44.3 (32.7–57.0)	0.03	0.6	0.01

AT=Anaerobic threshold, BR=Breathing reserve, CPET=Cardiopulmonary exercise test, IQR=Interquartile range, HR/V kg=Heart rate slope, $\Delta VO_2/\Delta WR$=Relationship between oxygen consumption and workload (anaerobic work efficiency), ΔVD/VT=Delta peak to rest of the ratio of the dead space volume to the tidal volume, VO_2/HR=Oxygen pulse; VE=Ventilator equivalent, VE/VCO_2=The ratio of minute ventilation to carbon dioxide production, VO_2 peak=Peak oxygen consumption, VO2/kg AT=VO2 peak at anaerobic threshold, VE/VCO_2=Minute ventilation per unit carbon dioxide production, SD=Standard deviation, VRT+=Positive vasoreactive testing, VRT–=Negative vasoreactive testing, ND VRT=Vasoreactive testing not done

differ between ND VRT and VRT + patients but was the lowest in VRT – group even in comparison to ND VRT patients.

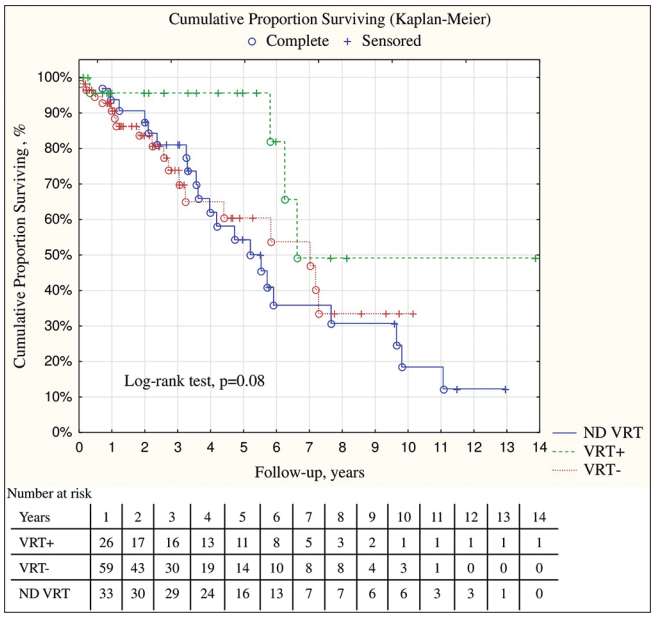
Vasoreactivity loss

High-dose CCB therapy prescribed in 24 from 26 VRT + patients. PAH specific therapy was initiated in 2 VRT+ (male and female) patients based on recurrent syncope, high mean PAP, severe right heart dilatation, and systolic dysfunction confirmed with MRI. Both patients experienced severe PAH worsening to the high-risk status on 397 and 435 days of follow-up despite PAH specific therapy. Another two cases with initial PAH therapy with sildenafil were women with IPAH manifestation during pregnancy. VRT was performed after delivery with sildenafil withdrawn. Both females had positive VRT. CCB therapy was prescribed in one female, and further, the patient reached and maintained low-risk status with positive VRT and near normalized hemodynamic for several years, being long-term vasoresponder. In another patient, CCB therapy was initiated and sildenafil was resumed. The decision on combination of CCB and sildenafil is based on the right heart dilatation and RV systolic dysfunction presence. The patient achieved low-risk status and confirmed VRT + at follow-up.

Repeat VRT was performed in 22 patients on CCB therapy: In all patients with symptomatic PAH worsening ($n = 13$) and in 9 low-risk patients, repeat VRT was not done in two patients, as they achieved low-risk status with completely normalized right heart size and function according to MRI, high exercise tolerance and normal VE/VCO_2 on CPET, estimated systolic PAP below 40 mmHg on Doppler evaluation, and NT-proBNP concentration in a reference range being on a high-dose CCB therapy.

Half of VRT + patients (50%) experienced PAH worsening in 1.76 years (6.6 months; 4.4 years) of follow-up. Decreased exercise tolerance, edema, NT-proBNP elevation, and right heart dilatation were the most common manifestations of vasoreactivity loss, which was confirmed with negative VRT in all 13 patients. PAH specific therapy has been started in patients in all VRT – patients.

Patients with vasoreactivity loss were older than long-term vasoresponders (44.7 ± 18.3 vs. 32.8 ± 11.3 years, $P = 0.05$), had history of edema ($\chi^2 = 6.2$, $P = 0.01$), tendency to RA dilatation (54.5 ± 10.4 vs. 44.3 ± 5.1 mm, $P = 0.05$), significantly enlarged RV end systolic volume (110.8 ± 20 vs. 77 ± 27.4 ml, $P = 0.02$), and the ratio of end diastolic volumes RV/LV (1.58 ± 0.43 vs. 1.01 ± 0.14, $P = 0.01$) according to MRI data and tendency to a higher PVR (10.8 ± 3.6 vs. 8.3 ± 3.5 WU, $P = 0.08$) at a baseline. No differences in 6MWT distance were noticed in patients with vasoreactivity loss and long-term vasoresponders. Nevertheless, peakVO_2 was significantly lower in patients with vasoreactivity loss in comparison with long-term vasoresponders at a baseline (12.7; [11.8] vs. 21.5 [17.5; 22.8] ml/min/kg, $P = 0.03$). Higher ESC/ERS 2015 risk score was observed in patients with vasoreactivity loss in comparison with long-term vasoresponders at a baseline (1.9 ± 0.2 vs. 1.5 ± 0.4, $P = 0.005$), which numerically corresponded to the intermediate ESC/ERS risk.



Number at risk

Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14
VRT+	26	17	16	13	11	8	5	3	2	1	1	1	1	1
VRT-	59	43	30	19	14	10	8	8	4	3	1	0	0	0
ND VRT	33	30	29	24	16	13	7	7	6	6	3	3	1	0

Figure 2: Survival in idiopathic pulmonary arterial hypertension patients with vasoreactive testing (VRT) positive, VRT negative and not done VRT due to physicians' decision

Survival in entire cohort

Seventy-one (42.7%) patients dead during 3.29 years (1.34; 5.9 years) of follow-up in the entire cohort of patients ($n = 166$). The majority of dead patients belonged to ND VRT group ($n = 49$, 60.5%) in comparison with VRT+ ($n = 4$, 15.3%) and VRT − group ($n = 30$, 18.5%) ($\chi^2 = 21.9$, $P = 0.00001$). The same significant correlation also maintained when removing from the analyses patients with FC IV (WHO), patients with not done VRT due to the technical reasons and prevalent IPAH patients [Figure 2]. The survival curves were similar in VRT − and ND VRT groups. VRT + patients demonstrated the highest 5-year survival of 97% in comparison with 61% in VRT − and 53% in ND VRT group. The greatest discrepancy in survival curves between VRT + and VRT−/ND VRT groups observed during the first 6 years; subsequently, with the loss of vasoreactivity, the survival of patients with initially VRT + approached that of the other groups.

Discussion

The main result of this study was the demonstration of the low frequency of VRT performance (58.6%) in patients with II-III FC (WHO) IPAH in PH reference center. The PHSANZ (Pulmonary Hypertension Society of Australia and New Zealand) registry showed even lower rate of VRT (22.4%),[9] with only 16.6% of tests adequate for interpretation. The reasons for the low incidence of VRT performance in IPAH patients in the PHSANZ registry remained unexplained. It might assume that the rare occurrence of long-term responders to CCB therapy, and the widespread prescription of PAH-specific medicines resulted in a low VRT performance.

In the present study, the main reason for not doing VRT was the physicians' decision in 26.7% patients, technical problems in 15.4%, and IV FC (WHO) in 16.2% cases at the time of diagnosis. At present, there are no criteria, when VRT carrying out is not reasonable in II-II FC (WHO) IPAH patients. We found, that the decision of not doing VRT was associated with age over 60 years, obesity, RHF symptoms, hemoptysis, and rhythm disturbances. Severe right heart dilatation, high NT-proBNP concentration, and an unfavorable hemodynamic profile (high mean PAP and low CI) contributed to the gestalt of the futility of CCB therapy and, accordingly, the uselessness of VRT. VRT was performed significantly more often in young patients with satisfactory exercise tolerance, without signs of right ventricular heart failure, moderate remodeling of the right heart, and with a slight CI decrease. The absence of difference in oxygen consumption and oxygen pulse in VRT positive and ND VRT group was the only observation, that raised concerns about a possible misconception in some patients, who might have positive VRT or better risk profile indeed.

The number of VRT positive patients was 15.6% in entire cohort, with only 7.8% long-term vasoresponders to CCB therapy, which did not differ from the others studies [8; 12]. VRT positive patients were younger (38.7 ± 16.1 years), without significant comorbidity and obesity, had satisfactory physical performance with a mean peak VO_2 17.2 ml/min/kg and few symptoms of PAH. Overall, patients with positive VRT were more likely to have low-risk criteria at the time of diagnosis. Other studies presented the same trend of symptoms and hemodynamics attributed to the mild to moderate pulmonary vascular disease in VRT + patients.[3,13] CPET parameters in VRT + patients demonstrated minimal involvement of compensatory reserves of the cardiovascular system and normal response of the respiratory system. It seems that CPET has been unfairly forgotten in the last 2022 ERS/ESC Guideline,[1] despite the high correlation of CPET parameters with the main hemodynamics determinants of prognosis, NT-proBNP and heart remodeling.[14] In a present study, the elevation of ventilatory equivalent of CO_2 was an earliest manifestation of cardiopulmonary insufficiency in VRT positive group. Therefore, CPET might discover the early signs of PAH progression in low-risk patients or VRT + patients.

Other important observation of the study was vasoreactivity loss in 50% of VRT + patients in a 1.76 year of follow-up. At present, there are no predictors of vasoreactivity loss and mortality in patients with initially positive VRT.[15] We did not know how VRT changes in time or whether PAH drugs could modify vasoreactivity itself.[16-18] In our study, patients with vasoreactivity loss exhibited ESC/ERS

criteria of intermediate risk at a baseline and were older than long-term vasoresponders. We did not find significant difference in NT-proBNP level in patients with the loss of vasoreactivity and long-term vasoresponders at a baseline. This might be due to the low numbers of VRT + patients in our study. Gerhardt *et al*. noted a significantly lower concentration of NT-proBNP in long-term vasoresponders, a larger number of patients with initially low risk compared to patients who lost the vasoreactive response.[3] Five-year survival was 97% in VRT + patients, which was considerably superior over VRT negative patients with 61% and ND VRT patients with 53%. With the loss of vasoreactivity, survival significantly decreased and became comparable to that in patients with negative VRT or with ND VRT group after 6 years from the diagnosis. Current ESC/ERS 2015 and 2022 recommendations [1; 11] oblige to perform VRT in 3 months after CCB therapy initiation in VRT + patients with IPAH/HPAH/DPAH II-III FC (WHO). In fact, repeat VRT carried out at least in 50% of cases.[9] Moreover, the possibility of performing multiple repeat VRT procedures in a patient limited by the high cost, invasiveness of the procedure, and patient reluctance. Everyday, clinical practice raises the question of using sophisticated, highly informative diagnostic tools, such as cardiac MRI and CPET, for the early noninvasive detection of PAH progression or inadequate response to CCB therapy in patients with positive VRT. This approach might help to select patients for repeat VRT during the long-term follow-up.

Conclusions

1. VRT was not performed in almost half of IPAH II-III FC (WHO) patients
2. Symptoms of the RHF, right heart dilatation, high PVR and NT-proBNP, in combination with age over 60 years, were associated with negative VRT or loss of response to CCB therapy and PAH worsening on follow-up
3. VRT-positive patients demonstrated the highest 5-year survival. With loss of vasoreactivity, the survival approaches that of patients with initially negative VRT
4. Careful monitoring of the effectiveness of CCB therapy is necessary in VRT positive patients with intermediate-high risk parameters at a baseline. CPET should be used more widely to detect the early signs of PAH progression in low-risk or VRT + patients.

Limitations

Predictors of survival and the loss of vasoreactivity were not assessed given the small number of VRT + patients.

Financial support and sponsorship

This study was financially supported by the Russian Science Foundation, agreement number 23-15-00318.

Conflicts of interest

There are no conflicts of interest.

References

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RM, Brida M, *et al.* 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61:9.
2. Chang KY, Duval S, Badesch DB, Bull TM, Chakinala MM, De Marco T, *et al.* Mortality in pulmonary arterial hypertension in the modern era: Early insights from the pulmonary hypertension association registry. J Am Heart Assoc 2022;11:e024969.
3. Gerhardt F, Fiessler E, Olsson KM, Kayser MZ, Kovacs G, Gall H, *et al.* Positive vasoreactivity testing in pulmonary arterial hypertension: Therapeutic consequences, treatment patterns, and outcomes in the modern management era. Circulation 2024;149:1549-64.
4. Hirakawa K, Asano R, Ueda J, Aoki T, Tsuji A, Ogo T. Calcium channel blockers in patients with pulmonary arterial hypertension receiving PAH-specific treatment. Int J Cardiol 2024;406:132043.
5. Zakiev VD, Martynyuk TV, Vedernikov AA, Petrenko DA, Korkach-Romanov SV. Socio-economic burden of newly diagnosed pulmonary arterial hypertension and early specific treatment initiation impact on the costs in real clinical practice in Russia. Med Technol Assess Choice 2023;1:99-113. (In Russ.).
6. Saint Petersburg: Online-Pharmacy Resource. Available from: https://www.eapteka.ru. [Last accessed on 2024 Jun 01].
7. Sharma A, Obiagwu C, Mezue K, Garg A, Mukherjee D, Haythe J, *et al.* Role of vasodilator testing in pulmonary hypertension. Prog Cardiovasc Dis 2016;58:425-33.
8. Naranjo M, Rosenzweig EB, Hemnes AR, Jacob M, Desai A, Hill NS, *et al.* Frequency of acute vasodilator response (AVR) in incident and prevalent patients with pulmonary arterial hypertension: Results from the pulmonary vascular disease phenomics study. Pulm Circ 2023;13:e12281.
9. Chandrasekara S, Lau EM, Anderson J, Collins N, Cordina R, Corrigan C, *et al.* Acute vasoreactivity testing and outcomes in pulmonary arterial hypertension: A call for increased testing. Heart Lung Circ 2023;32:156-65.
10. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension: The task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493-537.
11. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
12. Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, *et al.* Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105-11.
13. Kiani A, Omidvar R, Naderi N, Taghavi S, Mirtajaddini M. The long-term response to treatment with calcium channel blockers in patients with idiopathic pulmonary arterial hypertension. J Tehran Heart Cent 2023;18:62-7.
14. Pezzuto B, Agostoni P. The current role of cardiopulmonary exercise test in the diagnosis and management of pulmonary hypertension. J Clin Med 2023;12:5465.

15. Piloto B, Fernandes CJ, Jardim C, Castro M, Alves JL Jr., Souza R. Loss of response to calcium channel blockers after long-term follow-up treatment in patients with idiopathic pulmonary arterial hypertension. J Bras Pneumol 2023;49:e20220337.
16. Tooba R, Almoushref A, Tonelli AR. Is there value in repeating inhaled nitric oxide vasoreactivity tests in patients with pulmonary arterial hypertension? Lung 2020;198:87-94.
17. Evers PD, Quinn P, Critser PJ, Frank BS, Alnoor M, Armsby LB. Prognostic value of longitudinal vasoreactivity in pediatric pulmonary hypertension. Pulm Circ 2022;12:e12152.
18. Ishii S, Hatano M, Maki H, Minatsuki S, Saito A, Yagi H, *et al.* Prognostic value of follow-up vasoreactivity test in pulmonary arterial hypertension. J Cardiol 2023;82:69-75.