Am J Transl Res 2020;12(3):959-973
www.ajtr.org /ISSN:1943-8141/AJTR0104364

Original Article

Changed hemodynamics in acute vasoreactivity testing: prognostic predictors in chronic thromboembolic pulmonary hypertension

Yan-Zhe Yu[1,2*], Ping Yuan[4*], Yi-Lan Yang[4*], Yuan-Yuan Sun[4], Qin-Hua Zhao[4], Lan Wang[4], Rong Jiang[4], Wen-Hui Wu[4], Jing He[4], Jing-Hong Dai[1], Yuan Li[4], Bigyan Pudasaini[5], Jin-Ling Li[4], Su-Gang Gong[4], Wei-Ping Xie[3], Jin-Ming Liu[4]

[1]Department of Respiratory Medicine, Nanjing Drum Tower Hospital, Nanjing, Jiangsu, China; Departments of [2]Respiratory and Critical Care Medicine, [3]Respiratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China; [4]Department of Cardio-Pulmonary Circulation, Shanghai Pulmonary Hospital, Tongji University, School of Medicine, Shanghai, China; [5]Department of Internal Medicine, Columbia Bainuo Clinic, Shanghai, China. [*]Equal contributors.

Received November 2, 2019; Accepted February 20, 2020; Epub March 15, 2020; Published March 30, 2020

Abstract: Chronic thromboembolic pulmonary hypertension (CTEPH) is similar to pulmonary arterial hypertension (PAH) in its pathogenesis. Changed hemodynamic parameters in acute vasoreactivity testing (AVT) have proved to be prognostic predictors of PAH. We wanted to determine whether these changed indices also impacted the prognosis of CTEPH. Data was retrieved for 86 CTEPH patients who underwent right heart catheterization (RHC) with AVT at Shanghai Pulmonary Hospital from 2009 to 2018 and following up for 20 ± 15 months for event. Cox proportional hazards models were performed to determine the predictors of independent event-free survival. Receiver operating characteristic curve was plotted to determine the cut-off value of independent parameters in CTEPH. Kaplan-Meier method and log-rank test were used to perform the Survival analyses. Forty seven patients had an event. Many hemodynamic indices improved after AVT. The event-free group had better mean right atrial pressure, mean pulmonary arterial pressure, pulmonary vascular resistance (PVR) and oxygen saturation of mixed venous blood (SvO2) both at baseline and after AVT. The event-free group also showed higher cardiac output (CO) and cardiac index (CI) after AVT. Among the changed hemodynamic parameters during the AVT, ΔCO, ΔCO/baseline CO, ΔCI, ΔCI/baseline CI and ΔPVR/baseline PVR were significantly higher in the event-free group. Foremost, ΔPVR/baseline PVR, PVR after AVT and baseline SvO2 were independent predictors for event-free survival. Patients with SvO2 ≥ 61.65% at baseline or PVR < 8.09 WU after AVT or ΔPVR/baseline PVR ≥ 0.054 had significantly better survival. Hemodynamic indices both at baseline and after AVT as well as the changes in these indices reflected the severity of CTEPH. Baseline SvO2, PVR after AVT, and ΔPVR/baseline PVR could be used as independent predictors to estimate the outcomes of CTEPH patients.

Keywords: Chronic thromboembolic pulmonary hypertension, right heart catheterization, acute vasoreactivity testing, pulmonary vascular resistance, oxygen saturation of mixed venous blood, event-free survival

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by persistent thromboembolic obstruction of the pulmonary arteries, eventually leading to pulmonary hypertension (PH) and right heart failure. CTEPH is also viewed as a potentially curable disease when treated with pulmonary endarterectomy (PEA) [1]. Balloon pulmonary angioplasty (BPA), as a percutaneous approach for the treatment of CTEPH has gained increased attention. As per the latest guidelines PH-specific medications are recommended for CTEPH patients for whom surgical therapy and BPA is not an option [1]. However, varied treatment responses of these patients increased the uncertainty of their prognosis. Therefore, indices especially acquired during the first diagnosis that help precisely predict the prognosis are urgently needed for nonsurgical CTEPH patients.

Right heart catheterization (RHC) provides accurate and direct measurements of hemody-

namics of the pulmonary circulation in CTEPH. Acute vasoreactivity testing (AVT) is performed in some patients to evaluate the reversibility of hypertension in the pulmonary vasculature [2-5]. AVT is recommended in PAH to identify a small group of positive response to AVT patients with favorable long-term response to high dose calcium channel blockers (CCBs) and better survival [6]. The changed hemodynamics during AVT is also relevant to the prognosis of PAH patients not meeting the current definitions of positive responses [7]. A previous study demonstrated the similar rates of positive responses to AVT between the CTEPH and PAH. Positive responses to AVT in the CTEPH patients was significantly correlated with better survival [8]. Yet the exact relationship between the changed hemodynamics during AVT and prognosis of nonsurgical CTEPH patients is yet to be clearly elucidated.

Therefore, the primary aim of the present study was to investigate whether if the changed hemodynamic parameters were associated with clinical outcomes of inoperable patients with CTEPH and to estimate the prognostic value of these indices.

Materials and methods

Population study

Eighty six CTEPH patients (38 males and 48 females) aged more than 18 years were recruited at Shanghai Pulmonary Hospital, Shanghai, China from May 2009 to Feb 2018. The diagnosis of CTEPH was established according to the latest guidelines for the diagnosis and treatment of PH [9]. The diagnosis of pre-capillary PH was defined based on the right heart catheterization (RHC) (mean pulmonary artery pressure ≥ 25 mmHg and mean pulmonary arterial wedge pressure ≤ 15 mmHg) in the presence of mismatched perfusion defects on lung scans and distinctive signs for CTEPH seen by multi-detector computed tomography, magnetic resonance imaging, or conventional pulmonary cine-angiography, such as ring-like stenosis, chronic total occlusions (pouch lesions or tapered lesions), and webs/slits, even after at least 3 months of effective anticoagulation, which can be used to discriminate it from "subacute" pulmonary embolism. Patients with PH due to chronic lung diseases or left heart disease were excluded. Either at the time of the study or in the past, patients with acute or chronic illnesses that might influence hormonal metabolism (i.e., acute or chronic infections, chronic autoimmune diseases, and previously established primary endocrine disorders) and patients receiving any treatment with hormones (thyroid hormones, anabolic steroids, and corticosteroids) or drugs that markedly inhibit hormone production were also excluded [10, 11]. Meanwhile, all patients in the present study were not treated with PEA or BPA.

The study protocol was reviewed and approved by the local Ethics Committee of Shanghai Pulmonary Hospital. Each patient gave written informed consent for inclusion into the study and prior to the performance of any study-related procedures.

Assessment of patients

Demographic variables such as sex, age, body surface area (BSA), 6-minute walk distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP) and world health organization functional classification (WHO FC) were obtained at baseline. The 6MWD test was performed according to the guidelines of the American Thoracic Society and a Borg dyspnea score was determined immediately after the 6MWD test.

RHC was performed for all the patients in the present study by using the Swan-Ganz Catheter (Edwards Inc, USA). Patients stopped anticoagulant therapy before the procedure without bridging and started again after 6 h, if no complications occurred. Vital signs including blood pressure and heart rate were monitored during the entire course. Mean right atrium pressure (mRAP), mean pulmonary artery pressure (mPAP), and mean pulmonary capillary wedge pressure (mPAWP) were obtained after catheter balloon inflation at the end of expiration. Cardiac output (CO) was measured with thermodilution with cold saline, whereas the cardiac index (CI) and pulmonary vascular resistance (PVR) were calculated based on previous measurements. Mixed venous blood and peripheral arterial blood were also collected for blood gas analysis. AVT was performed by inhaling 5 μg of iloprost within 10 minutes. Hemodynamic variables were recorded immediately after stopping the iloprost inhalation. The positive criteria of AVT for PH were as fol-

Table 1. Baseline characteristics of CTEPH

	Event-free (n = 39)	Event (n = 47)	*P*-value
Age, yrs	58.66 ± 12.78	59.29 ± 12.87	0.820
BSA	1.67 ± 0.16	1.70 ± 0.16	0.827
6MWD, m	371.53 ± 116.64	325.26 ± 125.76	0.193
NT-pro-BNP, pg/ml	652.50 (98.25, 1294.25)	1302.50 (226.00, 2757.50)	0.038
WHO FC, n (%)			0.025
I-II	19 (48.72)	12 (25.53)	
III-IV	20 (51.28)	35 (74.47)	
Specific therapy, n (%)			0.201
PDE-5 inhibitors	18 (46.15)	11 (23.40)	
ERAs	3 (7.68)	4 (8.51)	
Prostacyclin anlogs	1 (2.56)	4 (8.51)	
combination	12 (30.76)	22 (46.80)	
Nonspecific medication	5 (12.82)	6 (12.77)	

6MWD, indicates 6-minute walk distance; BSA, body surface area; ERA, endothelin receptor antagonist; PDE-5, phosphodiesterase 5; WHO FC, WHO functional class.

lows: mPAP decrease of at least 10 mmHg and below 40 mmHg with increased or unchanged CO.

Outcomes assessment

The primary outcome was clinical worsening, including death, hospitalization or initiation of a new active therapy because of worsening disease. Event-free survival was estimated from the date of confirmation to 20 Feb 2018. Patients lost during follow-up were censored as alive on the last day of contact.

Statistical analysis

All results were expressed as mean ± SD or medians (and inter-quartile range) for continuous variables and as the absolute number for categorical variables. Comparisons were performed using the independent-sample t-test, paired t-test or Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Cox proportional hazards models were performed to determine the associations between the hemodynamic indices and event-free survival with or without covariate adjustment. Receiver operating characteristic curves were used to select the cut-off values for independent predictors with the maximum sensitivity and specificity. Kaplan-Meier method and log-rank test were used to perform the survival analyses. *P*-value < 0.05 was considered significant. The main analysis was performed using SPSS (Statistic Package for Social Science, Chicago, IL, USA) version 19.0.

Results

Patient population

A total of 86 CTEPH patients were included in our present study and 38 (44%) were women. The mean duration of follow-up was 19.7 ± 15.0 months. Forty seven patients had an event: 6 patients died, 28 patients required rehospitalization due to clinical worsening and 13 patients required additional PH-active medication or switched from oral PH-active therapy to parenteral therapy. No patient was lost during the follow-up, giving us a follow-up rate of 100%. Moreover, two patients met the criteria of AVT as "responder". The mean age was 58.7 ± 12.8 for patients with an event, 59.3 ± 12.9 for event-free patients and 59.4 ± 12.7 for all the patients. There were no differences in age, BSA and 6MWD between the event and event-free groups. Both NT-proBNP and WHO FC were significantly higher in the event group of CTEPH patients than in the event-free group (**Table 1**).

Target medications including phosphodiesterase type 5 inhibitors (sildenail, tadalafil and vadenafil), oral endothelial receptor antagonists (ambrisentan and bosentan), and prostacyclin analogs (beraprost, iloprost, and iloprost), as well as combination therapy and nonspecific medications were used by the CTEPH patients in the present study. There were no apparent differences in the use of medications between the event and event-free groups (**Table 1**).

Table 2. Comparisons of hemodynamics between baseline and after AVT in patients with CTEPH

	Baseline (n = 86)	After AVT (n = 86)	*P*-value
HR, bpm	84.00 ± 15.72	83.00 ± 15.19	0.323
SBP, mmHg	129.66 ± 20.49	125.41 ± 21.16	< 0.001
DBP, mmHg	77.60 ± 11.27	74.12 ± 12.31	0.001
Hemodynamics			
mRAP, mmHg	5.79 ± 4.24	5.37 ± 4.58	0.010
mPAP, mmHg	47.35 ± 10.87	44.48 ± 11.64	< 0.001
mPAWP, mmHg	7.63 ± 3.23	7.37 ± 3.14	0.358
PVR, Wood units	9.23 ± 4.21	7.62 ± 3.32	< 0.001
CO, L/min	4.71 ± 1.35	5.28 ± 1.62	< 0.001
CI, L/min/m^2	2.78 ± 0.75	3.11 ± 0.91	< 0.001
SvO2, %	62.65 ± 7.66	61.56 ± 8.15	0.013
SaO2, %	90.65 ± 3.65	90.14 ± 4.03	0.164

AVT, acute vasoreactivity testing; CI, cardiac index; CO, cardiac output; DBP, diastolic blood pressure; HR, indicates heart rate; mPAP, mean pulmonary arterial pressure; mPAWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; SaO2, oxygen saturation of peripheral arterial blood; SBP, systolic blood pressure; SvO2, oxygen saturation of mixed venous blood.

Comparison of hemodynamic indices between baseline and after the AVT

There were a number of differences observed in the case of hemodynamic indices between the baseline and after the AVT in CTEPH patients (**Table 2**). Except for the HR, PAWP and oxygen saturation of peripheral arterial blood (SaO2), the majority of the indices including the mPAP, mRAP, PVR, CO and CI were significantly improved by implement the AVT ($P < 0.05$). Meanwhile, oxygen saturation of mixed venous blood (SvO2) and BP decreased after the AVT ($P < 0.05$).

Hemodynamic comparison between event-free and event groups

In the present study, there were no significant differences in HR, SBP, DBP, mPAWP, CO, CI and SaO2 between the two groups of CTEPH patients at baseline. The event-free group had better hemodynamic indices in mRAP, mPAP, PVR, and SvO2 compared with the event group ($P < 0.05$, **Table 3**). With regard to the hemodynamic indices after the AVT (**Table 3**), significant differences were found in more indices between the two groups. The event-free group showed higher CO, CI, SvO2 and lower mRAP, mPAP and PVR compared with the event group ($P < 0.05$). No statistical difference was found in HR, SBP, DBP, mPAWP and SaO2 between the two groups. We also performed a comparison between event and event-free groups in terms of the change of the hemodynamic indices during the AVT as shown in **Table 4**. ΔCO, ΔCO/baseline CO, ΔCI, ΔCI/baseline CI along with ΔPVR/baseline PVR were significantly higher in the event-free group compared with the event group ($P < 0.05$).

Factors influencing event-free survival

In the univariate Cox proportional hazards analysis, baseline PVR, DBP, mPAP and SvO2 values were related to the event-free survival ($P < 0.1$). After the AVT, mRAP, mPAP, PVR, CO, CI and SvO2 were related to event-free survival ($P < 0.1$). In regard to the changed hemodynamic indices, ΔmRAP/baseline mRAP, ΔPVR/baseline PVR, ΔSvO2, ΔCO, ΔCI along with ΔCI/baseline CI were related to event-free survival ($P < 0.1$). However, age, sex, and BSA were not predictors of event-free survival.

In the multivariate forward stepwise analysis, model was adjusted by age, sex and BSA. Among all baseline hemodynamic indices, SvO2 was an independent predictor of event-free survival ($P < 0.05$, **Table 5**). Among hemodynamic indices after the AVT, PVR was also found to be an independent predictor of event-free survival ($P < 0.01$, **Table 5**). With regard to the indices of changed hemodynamics during the AVT, ΔPVR/baseline PVR was proved to be an independent predictor of event-free survival ($P < 0.05$, **Table 6**).

Receiver-operating characteristics

Receiver-operating characteristic curves were plotted for baseline SvO2, PVR after AVT and ΔPVR/baseline PVR (**Table 7**). Baseline SvO2 < 61.90 mmHg showed a sensitivity of 79.5% and a specificity of 57.4% in predicting an event ($P < 0.05$). While PVR after AVT < 8.09 WU showed a sensitivity of 61.7% and a specificity of 79.5% in predicting an event ($P < 0.01$). In addition, the cut-off value for ΔPVR/baseline PVR was 0.054 with a sensitivity of 84.6% and a specificity of 64.4% ($P < 0.05$).

Table 3. Comparisons of hemodynamics between event-free and event groups in patients with CTEPH at baseline and after AVT

	Event-free (n = 39)	Event (n = 47)	*P*-value
Vital signs at baseline			
HR, bpm	83.64 ± 13.20	84.30 ± 17.36	0.848
SBP, mmHg	130.74 ± 19.34	128.77 ± 21.57	0.659
DBP, mmHg	75.67 ± 11.92	79.21 ± 10.55	0.148
Hemodynamics at baseline			
mRAP, mmHg	4.59 ± 3.63	6.79 ± 4.48	0.016
mPAP, mmHg	44.46 ± 11.44	49.74 ± 9.87	0.024
mPAWP, mmHg	7.85 ± 3.42	7.45 ± 3.08	0.571
PVR, Wood units	8.12 ± 3.59	10.13 ± 4.49	0.026
CO, L/min	4.89 ± 1.44	4.55 ± 1.27	0.253
CI, L/min/m^2	2.89 ± 0.82	2.68 ± 0.68	0.208
SvO2 (%)	64.65 ± 4.93	60.98 ± 9.06	0.020
SaO2 (%)	90.63 ± 3.23	90.65 ± 3.99	0.978
Vital signs after AVT			
HR, bpm	83.90 ± 13.14	82.26 ± 16.80	0.621
SBP, mmHg	125.79 ± 17.66	125.09 ± 23.87	0.878
DBP, mmHg	73.72 ± 11.42	74.45 ± 13.11	0.786
Hemodynamics after AVT			
mRAP, mmHg	3.95 ± 3.64	6.55 ± 4.97	0.006
mPAP, mmHg	41.13 ± 12.27	47.26 ± 10.42	0.016
mPAWP, mmHg	7.74 ± 3.31	7.06 ± 3.00	0.321
PVR, Wood units	6.32 ± 2.77	8.69 ± 3.37	0.001
CO, L/min	5.47 ± 1.72	4.87 ± 3.50	0.026
CI, L/min/m^2	3.29 ± 0.99	2.87 ± 0.76	0.016
SvO2, %	64.15 ± 5.74	59.42 ± 9.23	0.005
SaO2, %	90.34 ± 4.03	89.97 ± 4.06	0.674

AVT, acute vasoreactivity testing; CI, cardiac index; CO, cardiac output; DBP, diastolic blood pressure; HR, indicates heart rate; mPAP, mean pulmonary arterial pressure; mPAWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; SaO2, oxygen saturation of peripheral arterial blood; SBP, systolic blood pressure; SvO2, oxygen saturation of mixed venous blood.

Kaplan-Meier event-free survival analysis

Kaplan-Meier event-free survival curves were plotted based on the cut-off values of ΔPVR/baseline PVR, PVR after AVT, and baseline SvO2 by receiver-operating characteristic analysis. Patients with baseline SvO2 ≥ 61.90% had a significantly better prognosis than those with SvO2 < 61.90% ($P < 0.01$, **Figure 1A**). **Figure 1B** revealed that patients with PVR < 8.09 WU after AVT had significantly better event-free survival ($P < 0.001$), similar findings were observed in the patients with ΔPVR/baseline PVR ≥ 0.054 ($P < 0.001$, **Figure 1C**).

The combination of these independent predictors identified subgroups with a significantly different probabilities of events. There were significant differences in event-free survival among the groups according to the cut-off value of baseline SvO2, PVR after AVT and ΔPVR/baseline PVR ($P < 0.001$, **Figure 1D-F**). When combined with PVR after AVT, the group with baseline SvO2 ≥ 61.9% and PVR after AVT < 8.09 WU had better event-free survival than the other three groups. While the group with SvO2 < 61.9% and PVR after AVT ≥ 8.09 WU had the worst event-free survival among these four groups (**Figure 1D**). Similar results were also observed in **Figure 1F**. The group with PVR after AVT < 8.09 WU and ΔPVR/baseline PVR ≥ 0.054 had the best survival, whereas the group with PVR after AVT ≥ 8.09 WU and ΔPVR/baseline PVR < 0.054 had the worst survival respectively. The third type of combination as shown in **Figure 1E** demonstrated that the group with baseline SvO2 ≥ 61.9% and ΔPVR/baseline PVR ≥ 0.054 had significantly better prognosis than the other groups, while the group with baseline SvO2 < 61.9% and ΔPVR/baseline PVR < 0.054 had the worst survival among these four groups.

Impact of the three independent predictors on NT-proBNP and WHO FC in CTEPH

To further validate the important role of baseline SvO2, PVR after AVT, ΔPVR/baseline PVR in this cohort, we analyzed the correlation between baseline SvO2, PVR after AVT, ΔPVR/baseline PVR and NT-proBNP, WHO FC in CTEPH patients (**Figure 2**). It was shown that baseline SvO2 had significantly severe and moderate negative correlation with NT-proBNP and WHO FC in CTEPH, respectively ($P < 0.001$).

Table 4. Comparisons of changed hemodynamics during AVT between event-free and event groups in patients with CTEPH

	Event-free (n = 39)	Event (n = 47)	*P*-value
Vital signs			
ΔHR, bpm	0.00 (-4.00, 3.00)	1.00 (-2.00, 4.00)	0.327
ΔHR/baseline	0.00 (-0.05, 0.03)	0.01 (-0.03, 0.06)	0.260
ΔSBP, mmHg	4.00 (-1.00, 9.00)	1.00 (-3.00, 10.00)	0.230
ΔSBP/baseline	0.03 (-0.01, 0.07)	0.01 (-0.02, 0.08)	0.521
ΔDBP, mmHg	0.00 (-3.00, 4.00)	2.00 (-1.00, 8.00)	0.182
ΔDBP/baseline	0.00 (-0.04, 0.05)	0.03 (-0.01, 0.11)	0.437
Hemodynamics			
ΔmRAP, mmHg	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.389
ΔmRAP/baseline mRAP	0.00 (0.00, 0.33)	1.00 (-2.00, 4.00)	0.182
ΔmPAP, mmHg	0.00 (2.00, 7.00)	1.00 (0.00, 5.00)	0.368
ΔmPAP/baseline mPAP	0.05 (0.00, 0.17)	0.02 (0.00, 0.10)	0.271
ΔmPAWP, mmHg	0.00 (-1.00, 1.00)	0.00 (0.00, 1.00)	0.142
ΔmPAWP/baseline mPAWP	0.00 (-0.21, 0.08)	0.00 (0.00, 0.13)	0.108
ΔPVR, Wood units	1.09 (0.77, 2.42)	0.96 (-0.03, 2.51)	0.218
ΔPVR/baseline PVR	0.20 (0.08, 0.28)	0.12 (-0.01, 0.96)	0.022
ΔCO, L/min	-0.55 (-1.00, -0.20)	-0.25 (-0.77, 0.00)	0.016
ΔCO/baseline CO	-0.12 (-0.20, -0.04)	-0.05 (-0.19, 0.03)	0.049
ΔCI, L/min.m^2	-0.34 (-0.58, -0.13)	-0.16 (-0.48, 0.00)	0.014
ΔCI/baseline CI	-0.11 (-0.17, -0.04)	-0.05 (-0.16, 0.00)	0.045
ΔSvO2, %	0.00 (-0.80, 2.70)	2.00 (0.00, 4.80)	0.072
ΔSvO2/baseline SvO2	0.00 (-0.01, 0.04)	0.03 (0.00, 0.08)	0.089
ΔSaO2, %	-0.10 (-8.00, 2.30)	0.10 (-0.90, 1.70)	0.440
ΔSaO2/baseline SaO2	0.00 (-0.01, 0.03)	0.00 (-0.01, 0.02)	0.442

AVT, acute vasoreactivity testing; CI, cardiac index; CO, cardiac output; DBP, diastolic blood pressure; HR, indicates heart rate; mPAP, mean pulmonary arterial pressure; mPAWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; SaO2, oxygen saturation of peripheral arterial blood; SBP, systolic blood pressure; SvO2, oxygen saturation of mixed venous blood.

PVR after AVT had markedly severe and moderate positive correlation with NT-proBNP and WHO FC respectively in CTEPH ($P < 0.001$). ΔPVR/baseline PVR had moderate negative correlation with NT-proBNP in CTEPH ($P < 0.001$). No significant relationship between ΔPVR/baseline PVR and WHO FC noted in this cohort. In addition, we also analyzed the differences of NT-proBNP and WHO FC in CTEPH patients grouped by the cut-off values of the three independent predictors in CTEPH (**Figure 3A-F**). Patients with baseline SvO2 ≥ 61.9% had significantly lower NT-proBNP levels and WHO FC compared to patients with baseline SvO2 < 61.9% ($P < 0.001$, **Figure 3A** and **3B**). Patients with PVR after AVT < 8.09 WU and ΔPVR/baseline PVR ≥ 0.054 showed similar results ($P < 0.001$, **Figure 3C-F**).

Discussion

This is the first study to reveal the relationship between the changes in hemodynamic indices during AVT and the prognosis of inoperable CTEPH patients when positive results of AVT were not necessarily involved. We compared the hemodynamic indices accessed before and after the AVT. Meanwhile, the discrepancies of hemodynamic indices between the event and event-free groups were also illustrated. It is clear that the event group showed more severe hemodynamic abnormities both at baseline and after the AVT, whereas more improvement was observed in the event-free group. Among ΔPVR/baseline PVR, PVR after AVT, and SvO2 at baseline, each of was an independent predictor of event-free survival in CTEPH patients.

The baseline characteristics of the present study showed that the mean age was 59.4, in line with the previous registries [12-18]. NT-proBNP represents myocardial dysfunction and provides prognostic information at the time of diagnosis or during follow-up [19-21]. As expected, our study demonstrated that the level of NT-proBNP was higher in the event group compared to the event-free group which revealed that worse cardiac function heralded more events in CTEPH patients. A couple of previous studies have revealed the correlation between a deteriorating WHO FC and progression of disease [22, 23]. The present study reconfirmed that patients in the event group had worse WHO FC than the patients in the event-free group. No differences were observed with regards to 6MWD and specific medications

Table 5. Univariate and multivariate analysis results relating event-free survival to selected hemodynamics at baseline and after AVT in CTEPH

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.01 (0.98-1.03)	0.669		
Sex	0.63 (0.35-1.13)	0.121		
BSA	1.27 (0.24-6.65)	0.775		
At baseline				
HR	1.00 (0.98-1.02)	0.895		
SBP	1.00 (0.99-1.02)	0.926		
DBP	1.02 (1.00-1.05)	0.068		
mRAP	1.04 (0.98-1.10)	0.198		
mPAP	1.02 (1.00-1.05)	0.096		
mPAWP	0.97 (0.88-1.07)	0.534		
PVR	1.05 (1.00-1.12)	0.065		
CO	0.85 (0.67-1.08)	0.192		
CI	0.72 (0.46-1.12)	0.146		
SvO2	0.96 (0.93-1.00)	0.046	0.96 (0.92-0.99)	0.049*
SaO2	1.01 (0.93-1.09)	0.867		
After AVT				
HR	1.00 (0.98-1.02)	0.984		
SBP	1.00 (0.99-1.02)	0.622		
DBP	1.01 (0.99-1.04)	0.283		
mRAP	1.05 (0.99-1.10)	0.097		
mPAP	1.03 (1.00-1.05)	0.054		
mPAWP	0.93 (0.85-1.02)	0.144		
PVR	1.14 (1.05-1.24)	0.002	1.13 (1.04-1.23)	0.003*
CO	0.79 (0.63-0.99)	0.042		
CI	0.62 (0.40-0.94)	0.026		
SvO2	0.95 (0.92-0.99)	0.008		
SaO2	0.98 (0.92-1.05)	0.559		

BSA, body surface area; CO, cardiac output; CI, cardiac index; DBP, diastolic blood pressure; HR, heart rate; mPAP, mean pulmonary arterial pressure; mPAWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; SaO2, oxygen saturation of peripheral arterial blood; SBP, systolic blood pressure; SvO2, oxygen saturation of mixed venous blood. *adjusted for Age, Sex, BSA and WHO FC in the multivariate analysis.

between the two groups, which were in accordance with the result of our previous research [24].

AVT was routinely performed in our hospital to assess the changes in hemodynamics. mPAP is one of the most important hemodynamic indices in CTEPH. Decrease in mPAP is also an indispensable criterion for the positive result of AVT. As expected, mPAP improved with the inhalation of the 5 ug iloprost during the AVT, which was in accordance with previous studies [7, 8]. However, other studies demonstrated that mPAP provided little prognostic information in PH even if higher mPAP indicated more severe disease [22, 23]. Consistent with these studies, the present study showed that the CTEPH patients with higher mPAP exhibited more events. However, neither the mPAP at baseline as well as after AVT nor the changes in mPAP were not relevant to the event-free survival.

SvO2, a parameter related to oxygen consumption and oxygen delivery, was also thought to be a robust indicator of RV function, provided very important prognostic information in many subsets of PH [25-28]. As expected, both SvO2 at baseline and after AVT were higher in the event-free groups. Moreover, SvO2 at baseline was identified as an independent predictor of event-free survival. Interestingly, SvO2 declined mildly during AVT possible due to the acute vasodilation during AVT, which potentially deteriorated the imbalance of the V/Q ratio resulting in the decrease of oxygenation [29]. The non-uniform change in SvO2 during the AVT may also decrease the prognostic value of SvO2 after the AVT as well as the changed SvO2 during the AVT.

PVR is another significant hemodynamic index acquired in RHC since CTEPH is characterized by increased PVR during its progression. We chose to observe the differences of PVR both at baseline and after AVT, noting the change of PVR during the AVT between the event and event-free groups in order to find possible associations between these indices and event-free survival. We found that PVR both at baseline and after AVT was higher in patients with events, which was in consistent with our previous finding in CTEPH [18]. Moreover, the event-free patients had higher ΔPVR/baseline PVR, indicating that the patients with better improvement in PVR during the AVT will

Table 6. Uivariate and multivariate analysis results relating event-free survival to selected changed hemodynamics during AVT in CTEPH

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ΔHR	1.00 (0.98-1.03)	0.850		
ΔHR/baseling HR	1.57 (0.08-30.33)	0.764		
ΔSBP	0.99 (0.96-1.02)	0.396		
ΔSBP/baseline SBP	0.32 (0.01-10.54)	0.523		
ΔDBP	0.99 (0.96-1.02)	0.459		
ΔDBP/baseline DBP	0.34 (0.03-3.46)	0.365		
ΔmRAP	0.85 (0.69-1042.00)	0.119		
ΔmRAP/baseline mRAP	0.39 (0.14-1.12)	0.080		
ΔmPAP	0.97 (0.91-1.04)	0.417		
ΔmPAP/baseline mPAP	0.19 (0.01-4.65)	0.312		
ΔmPAWP	1.06 (0.95-1.17)	0.287		
ΔmPAWP/baseline mPAWP	1.86 (0.82-4.24)	0.138		
ΔPVR	0.95 (0.82-1.11)	0.509		
ΔPVR/baseline PVR	0.08 (0.01-0.53)	0.009	0.08 (0.01-0.63)	0.016*
ΔCO	1.65 (1.01-2.71)	0.046		
ΔCO/baseline CO	3.03 (0.47-19.47)	0.243		
ΔCI	0.28 (0.01-5.19)	0.049		
ΔCI/baseline CI	11.28 (0.77-164.60)	0.076		
ΔSvO2	0.92 (0.84-1.00)	0.042		
ΔSvO2/baseline SvO2	38.29 (0.30-4916.51)	0.141		
ΔSaO2	0.93 (0.85-1.02)	0.140		
ΔSaO2/baseline SaO2	0.02 (0.00-94.00)	0.365		

BSA, body surface area; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; mPAP, mean pulmonary arterial pressure; mPAWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; CO, cardiac output, CI, cardiac index; SvO2, oxygen saturation of mixed venous blood; SaO2, oxygen saturation of peripheral arterial blood. *adjusted for Age, Sex, BSA and WHO FC in the multivariate analysis.

Table 7. Area under ROC curve and cut-off value for the independent predictors in patients with CTEPH

Variables	Cut-off value	Sensitivity	Specificity	AUC	95% CI	*P*-value
SvO2 (%)	61.90	0.795	0.574	0.639	0.527~0758	0.027
PVR after AVT (WU)	8.09	0.617	0.795	0.717	0.607~0.827	0.001
ΔPVR/baseline PVR	0.054	0.846	0.404	0.644	0.527~0.760	0.022

AUC indicates area under curve; AVT, acute vasoreactivity testing; CI, confidence interval; PVR, pulmonary vascular resistance; SvO2, oxygen saturation of mixed venous blood.

have fewer events. Furthermore, the PVR after AVT and ΔPVR/baseline PVR, rather than the PVR at baseline, were identified as independent predictors of event-free survival. These intricate results not noted previous perhaps needs to be explored further.

The true nature of CTEPH pathogenesis was increasingly illustrated in recent studies. Various factors including cancer, inflammation, infection or other specific clinical conditions underlie the failure of thrombus resolution. These thrombotic materials (described as "bands and webs" on pulmonary angiography) impairs blood flow, and ultimately leads to the development of CTEPH [30-32]. A number of studies have highlight similarities between PAH and CTEPH with regards to the small-vessel pathology such as intimal thickening, remodeling of pulmonary resistance vessels, eccentric inti-

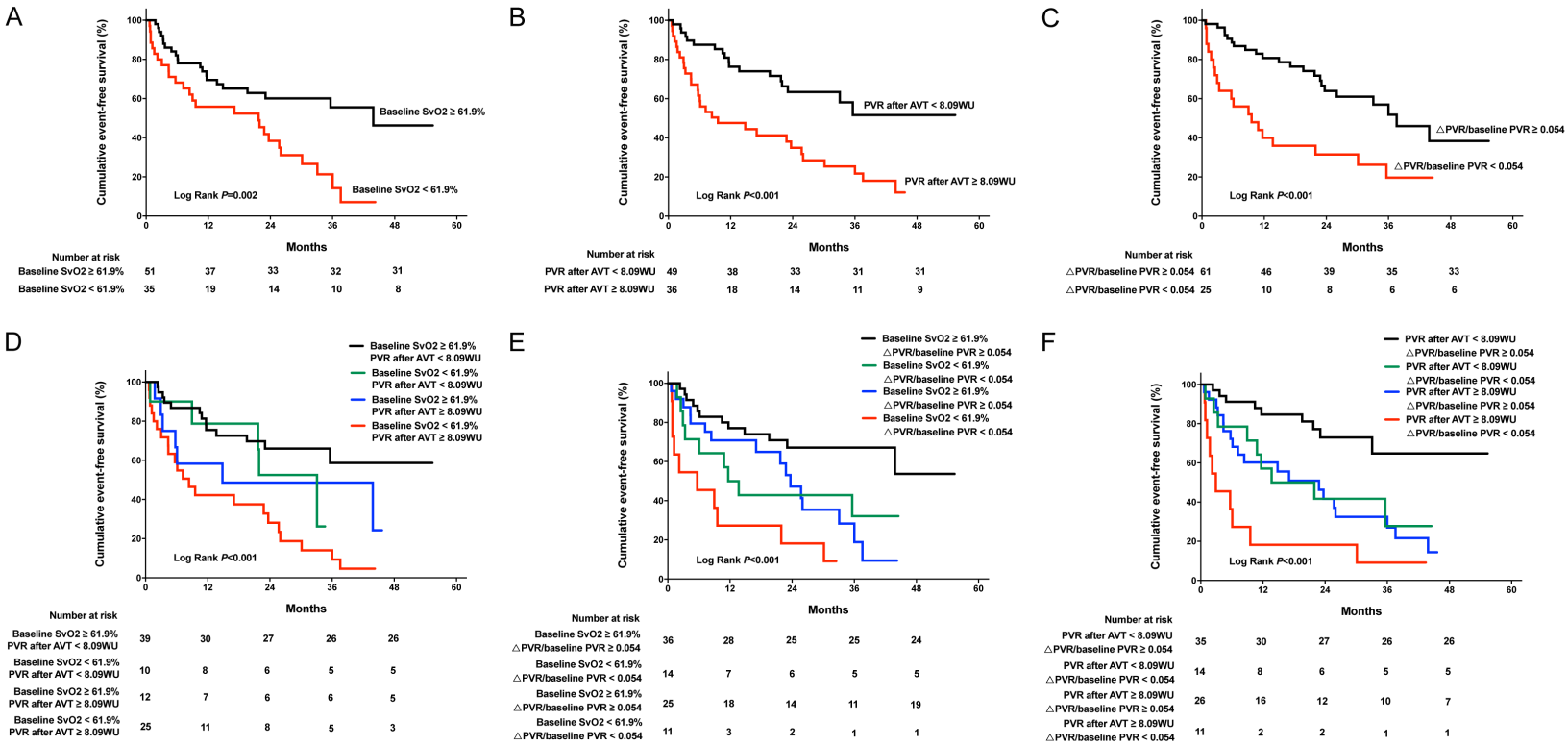

Figure 1. Kaplan-Meier analysis in CTEPH patients based on baseline SvO2, PVR after AVT and ΔPVR/baseline PVR. The median follow-up period was 19.7 months. A. The event-free survival in CTEPH patients according to the cut-off value of baseline SvO2 (n = 86). Patients with higher baseline SvO2 ≥ 61.9% had significantly better survival. B. The event- free survival in CTEPH patients based on the cut-off value of PVR after AVT (n = 86). Patients with PVR after AVT < 8.09 WU had significantly better survival. C. The event-free survival in CTEPH patients based on the cut-off values of ΔPVR/baseline PVR (n = 86). Patients with higher ΔPVR/baseline PVR ≥ 0.054 had significantly better survival. D. The event-free survival in CTEPH patients according to the combined cut-off value of baseline SvO2 and ΔPVR/baseline PVR (n = 86). Patients with baseline SvO2 ≥ 61.9% and PVR after AVT < 8.09 WU had the significantly best survival, and patients with baseline SvO2 < 61.9% and PVR after AVT ≥ 8.09 WU had the significantly worst survival among these four groups. E. The event-free survival in CTEPH patients based on the combined cut off values of baseline SvO2 and PVR after AVT (n = 86). Patients with baseline SvO2 ≥ 61.9% and PVR after AVT < 8.09 WU had the significantly best survival, and patients with baseline SvO2 < 61.9% and PVR after AVT ≥ 8.09 WU had the significantly worst survival among these four groups. F. The event-free survival in CTEPH patients according to the combined cut-off values of ΔPVR/baseline PVR and PVR after AVT (n = 86). Patients with PVR after AVT < 8.09 WU and ΔPVR/baseline PVR ≥ 0.054 had the significantly best survival, and patients with PVR after AVT ≥ 8.09 WU with ΔPVR/baseline PVR < 0.054 had the significantly worst survival among these four groups. Survival analyses were compared by log-rank test.

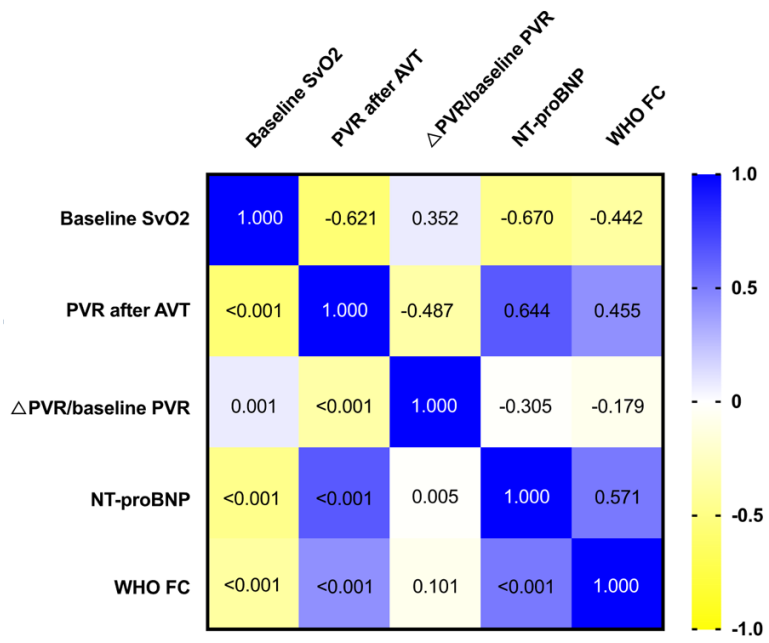

Figure 2. Correlation matrix of baseline SvO2, PVR after AVT, ΔPVR/baseline PVR and NT-proBNP, WHO FC in CTEPH. Data are presented as rho correlation coefficient of Spearman (n = 86). The upper right half indicated are the correlation coefficients and the lower left half indicates the associated *P* values.

mal fibrosis and fibromuscular proliferation along with plexiform lesions [30, 33-34]. Although few studies had deliberately illustrated the effect of pulmonary vasoconstriction in the pathogenesis of CTEPH as in PAH, vasodilator responders who demonstrate positive AVT results exist in CTEPH both in the present and previous studies [8]. In the present study, the hemodynamics improved after the AVT. Novel specific therapies for CTEPH play a major role in regulating vasodilation [35, 36]. Therefore, it is very likely that pulmonary vasoconstriction also mediates the pathogenesis of CTEPH. Some of these features such as pulmonary vasoconstrictions are reversible in response to the vasodilators, while chronic remodeling processes perhaps are not. Different reversibility of pulmonary vasculature was closely related to their severity. Therefore, different outcomes of the disease may develop depending on the reversibility of pulmonary vasculature which was directly reflected by AVT. Better prognosis was observed in CTEPH patients with better hemodynamic improvement in AVT. Similar results were reported in PAH. Hanno et al [7] demonstrated that more improvement of hemodynamics during AVT predicted a better outcome of PAH even in vasodilator non-responders. Moreover, improved survival was observed in CTEPH patients with positive responses during AVT [8]. Our present study reconfirmed these previous results and for the first time authenticated that, ΔPVR/baseline PVR which represented the reversible part of hemodynamics could be used to predict the outcome of CTEPH without regards to AVT being positive or negative. This also applies to PVR after AVT, which perhaps more precisely reflected the irreversible aspect of the hemodynamics compared to the PVR at baseline.

The interpretation of the results of PVR may also partially explain the results of CO and CI in the present study. We did not find any statistical difference regarding CO and CI between the two groups at baseline. The event-free group showed more improvement during the AVT and better results after AVT with regards to these two indices. CTEPH is not a uniform disease and different pathophysiological aspects may be involved to different extents resulting in the different reversibility of hemodynamics. Improvement of CO and CI during AVT reflected better reversibility, which results in fewer events in CTEPH. Meanwhile, CO and CI after AVT reflected more "authentic" hemodynamics compared to those at baseline.

The cut-off values of the three independent predictors were determined by the receiver operating characteristic curve and as expected, marked differences in event-free survival were observed between subgroups divided by these cut-off values. ΔPVR/baseline PVR was found to be the prognostic predictor of survival in PAH, but no specific cut-off values were given regarding AVT [7]. In the present study for the first time, the specific cut-off value of ΔPVR/baseline PVR was provided in order to better evaluate the event-free survival. In addition, more subgroups were formed by combing the two different independent predictors to further evaluate the influence of predictors of progno-

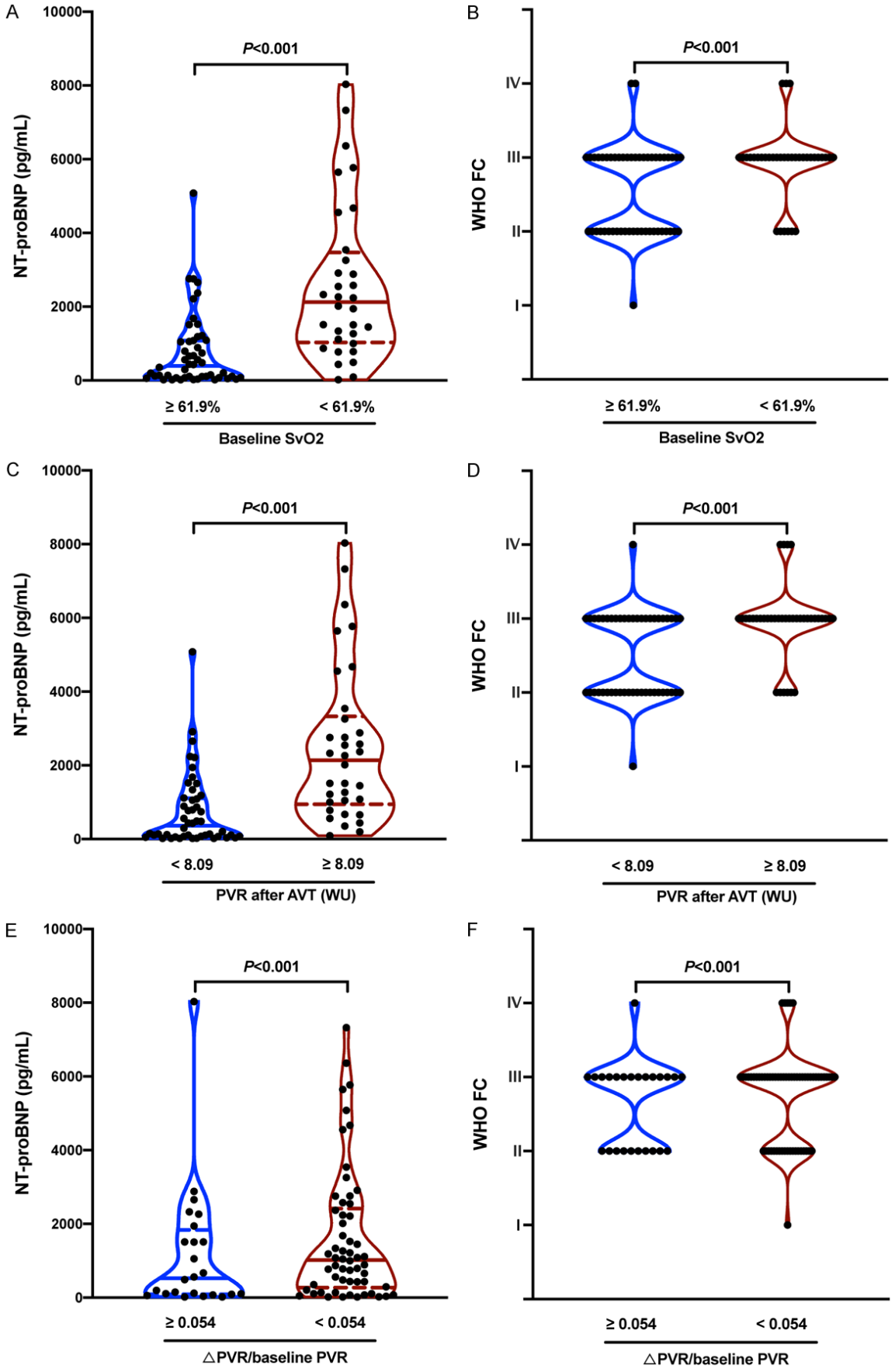
A
NT-proBNP (pg/mL)
10000
8000
6000
4000
2000
0
P<0.001
≥ 61.9%
< 61.9%
Baseline SvO2
B
WHO FC
IV
III
II
I
P<0.001
≥ 61.9%
< 61.9%
Baseline SvO2
C
NT-proBNP (pg/mL)
P<0.001
< 8.09
≥ 8.09
PVR after AVT (WU)
D
WHO FC
P<0.001
< 8.09
≥ 8.09
PVR after AVT (WU)
E
NT-proBNP (pg/mL)
P<0.001
≥ 0.054
< 0.054
△PVR/baseline PVR
F
WHO FC
P<0.001
≥ 0.054
< 0.054
△PVR/baseline PVR

Figure 3. Comparisons of NT-proBNP and WHO FC in CTEPH patients grouped by the cut-off values of baseline SvO2, PVR after AVT and ΔPVR/baseline PVR. Concentrations of NT-proBNP are expressed using the median interquartile range and compared by Mann-Whitney U test (n = 86). Results of WHO FC are expressed in numbers and compared by Chi square test (n = 86).

sis in CTEPH patients. They perhaps will provide some more clues to evaluate the outcome of such patients in clinical practice. We suggest AVT be routinely performed for patients with CTEPH to precisely estimate the prognosis in the future, despite significance or necessity of AVT in CTEPH not yet mentioned by the latest guidelines.

The major limitation of the present study is that the patient sample size is relatively small compared with the other subsets of PH, which prevented us from dividing the patients into more subgroups by combining three different independent predictors. Based on latest recommendations [37-40], iloprost was chosen for AVT in our study. The 5 mg iloprost approach has been used in several settings before especially by Jing and colleges [4] in AVT. The changes of hemodynamics may be varied if different substances or higher doses of iloprost were used, potentially impacting the value of the prognosis predictors reported by our current study. Moreover, therapeutic options for CTEPH patients have expanded with the development BPA. The safety and efficacy of this treatment have been demonstrated in many previous studies [41-44] and receives a class IIb recommendation for inoperable CTEPH. As this treatment was developed in our pulmonary center recently, this group of patients is not enrolled in our studies which may influenced the results of this study to some extent. Nevertheless, patients with poor prognosis in our study reflected the poor response to the PH-specific medications, making BPA a more appropriate modality of treatment for such patients. Additionally, the changed hemodynamics in AVT may be used to estimate the value and necessity of BPA in non-surgical CTEPH patients.

Conclusion

CTEPH stands out as the only subset of PH that can potentially be cured. However, the prognosis is still very poor in nonsurgical CTEPH patients. Our study for the first time reported the hemodynamic indices in AVT can be used to predict the event-free survival in nonsurgical CTEPH patients, which could potentially be used to estimate the prognosis of CTEPH.

Acknowledgements

This study was supported by the Program of National Natural Science Foundation of China (81870042, 81700045 and 81900050), National Science and Technology Information System of the People's Republic of China (2018-YFC1313603).

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Jin-Ming Liu and Su-Gang Gong, Department of Cardio-Pulmonary Circulation, Shanghai Pulmonary Hospital Affiliated to Tongji University, No. 507 Zhengmin Road, Shanghai 200433, China. Tel: +86-21-65115006-3121; Fax: +86-21-55662767; E-mail: jinmingliu@tongji.edu.cn (JML); gongsugang1999@sohu.com (SGG); Dr. Wei-Ping Xie, Department of Respiratory Medicine, The First Affiliated Hospital of Nanjing Medical University, No. 300 Guangzhou Road, Nanjing 210029, Jiangsu, China. E-mail: wpxie@njmu.edu.cn

References

[1] Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M and Hoeper M; ESC Scientific Document Group. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016; 37: 67-119.

[2] Costard-Jackle A and Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high-risk group. J Am Coll Cardiol 1992; 19: 48-54.

[3] Torres-Macho J, Delgado-Jimenez JF, Sanz-Salvo J, Gonzalez-Mansilla A, Sanchez-Sanchez V, Gamez-Diez S, Escribano-Subias P and Saenz-de-la-Calzada C. Effect of different pharmaco-

logic agents to reverse severe pulmonary hypertension among end-stage heart failure patients. Transplant Proc 2009; 41: 2477-2479.
[4] Jing ZC, Jiang X, Han ZY, Xu XQ, Wang Y, Wu Y, Lv H, Ma CR, Yang YJ and Pu JL. Iloprost for pulmonary vasodilator testing in idiopathic pulmonary arterial hypertension. Eur Respir J 2009; 33: 1354-1360.
[5] Semigran MJ, Cockrill BA, Kacmarek R, Thompson BT, Zapol WM, Dec GW and Fifer MA. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol 1994; 24: 982-988.
[6] Kurzyna M, Araszkiewicz A, Błaszczak P, Grabka M, Hawranek M, Kopeć G, Mroczek E, Zembala M, Torbicki A and Ochała A. Summary of recommendations for the haemodynamic and angiographic assessment of the pulmonary circulation. Joint statement of the Polish Cardiac Society's Working Group on pulmonary circulation and association of cardiovascular interventions. Kardiol Pol 2015; 73: 63-68.
[7] Leuchte HH, Baezner C, Baumgartner RA, Muehling O, Neurohr C and Behr J. Residual pulmonary vasodilative reserve predicts outcome in idiopathic pulmonary hypertension. Heart 2015; 101: 972-976.
[8] Xu QX, Yang YH, Geng J, Zhai ZG, Gong JN, Li JF, Tang X and Wang C. Clinical study of acute vasoreactivity testing in patients with chronic thromboembolic pulmonary hypertension. Chin Med J 2017; 130: 382-391.
[9] Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk-Noordegraaf A, Beghetti M, Ghofrani A, Gomez-Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M and Hoeper M. 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 Respir J 2015; 46: 903-975.
[10] Yuan P, Chen TX, Pudasaini B, Zhang J, Guo J, Zhang SJ, Wang L, Zhao QH, Gong SG, Jiang R, Wu WH, He J, Liu JM and Hu QH. Sex-specific cardiopulmonary exercise testing indices related to hemodynamics in idiopathic pulmonary arterial hypertension. Ther Adv Respir Dis 2017; 11: 135-145.
[11] Yuan P, Ni HJ, Chen TX, Pudasaini B, Jiang R, Liu H, Zhao QH, Wang L, Gong SG and Liu JM. Sex-specifc cardiopulmonary exercise testing parameters as predictors in patients with idiopathic pulmonary arterial hypertension. Hypertens Res 2017; 40: 868-875.
[12] Giusca S, Popa E, Amzulescu MS, Ghiorghiu I, Coman IM, Popescu BA, Delcroix M, Voigt JU, Ginghina C and Jurcut R. Is right ventricular remodeling in pulmonary hypertension dependent on etiology? An echocardiographic study. Echocardiography 2016; 33: 546-554.
[13] Escribano-Subias P, Blanco I, López-Meseguer M, Lopez-Guarch CJ, Roman A, Morales P, Castillo-Palma MJ, Segovia J, Gómez-Sanchez MA and Barberà JA; REHAP investigators. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. Eur Respir J 2012; 40: 596-603.
[14] Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jaïs X and Simonneau G. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011; 124: 1973-1981.
[15] Ascione R, Talpahewa S, Rajakaruna C, Reeves BC, Lovell AT, Cohen A and Angelini GD. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. Ann Thorac Surg 2012; 94: 97-103.
[16] Gall H, Felix JF, Schneck FK, Milger K, Sommer N, Voswinckel R, Franco OH, Hofman A, Schermuly RT, Weissmann N, Grimminger F, Seeger W and Ghofrani HA. The Giessen pulmonary hypertension registry: survival in pulmonary hypertension subgroups. J Heart Lung Transplant 2017; 36: 957-967.
[17] Tanabe N, Sugiura T and Tatsumi K. Recent progress in the diagnosis and management of chronic thromboembolic pulmonary hypertension. Respir Investig 2013; 51: 134-146.
[18] Al-Naamani N, Espitia HG, Velazquez-Moreno H, Macuil-Chazaro B, Serrano-Lopez A, Vega-Barrientos RS, Hill NS and Preston IR. Chronic thromboembolic pulmonary hypertension: experience from a single center in Mexico. Lung 2016; 194: 315-323.
[19] Leuchte HH, El-Nounou M, Tuerpe JC, Hartmann B, Baumgartner RA, Vogeser M, Muehling O and Behr J. N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension. Chest 2007; 131: 402-409.
[20] Guérin L, Couturaud F, Parent F, Revel MP, Gillaizeau F, Planquette B, Pontal D, Guégan M, Simonneau G, Meyer G and Sanchez O. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmo-

nary embolism. Thromb Haemost 2014; 112: 598-605.
[21] Klok FA, Dzikowska-Diduch O, Kostrubiec M, Vliegen HW, Pruszczyk P, Hasenfuß G, Huisman MV, Konstantinides S and Lankeit M. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2016; 14: 121-128.
[22] Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, Welte T and Hoeper MM. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2012; 39: 589-596.
[23] Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG and McGoon MD. Predicting survival in pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation 2010; 122: 164-172.
[24] Chen TX, Pudasaini B, Guo J, Gong SG, Jiang R, Wang L, Zhao QH, Wu WH, Yuan P and Liu JM. Sex-specific cardiopulmonary exercise testing indices to estimate the severity of inoperable chronic thromboembolic pulmonary hypertension. Int J Chron Obstruct Pulmon Dis 2018; 13: 385-397.
[25] Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, Rainisio M and Simonneau G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002; 40: 780-788.
[26] McLaughlin VV, Sitbon O, Badesch DB, Barst RJ, Black C, Galiè N, Rainisio M, Simonneau G and Rubin LJ. Survival with first line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005; 25: 244-249.
[27] Sitbon O, McLaughlin VV, Badesch DB, Barst RJ, Black C, Galiè N, Humbert M, Rainisio M, Rubin LJ and Simonneau G. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. Thorax 2005; 60: 1025-1030.
[28] Simonneau G, Torbicki A, Dorfmüller P and Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017; 26: 112-160.
[29] Olschewski H, Simonneau G, Galiè N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, Winkler J, Sitbon O, Popov W, Ghofrani HA, Manes A, Kiely DG, Ewert R, Meyer A, Corris PA, Delcroix M, Gomez-Sanchez M, Siedentop H and Seeger W; Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002; 347: 322-329.
[30] Lang IM, Dorfmüller P and Vonk Noordegraaf A. The pathobiology of chronic thromboembolic pulmonary hypertension. Ann Am Thorac Soc 2016; 13: S215-221.
[31] Lang IM, Dorfmüller P and Vonk Noordegraaf A. Pulmonary endarterectomy: part I. Pathophysiology, clinical manifestations, and diagnostic evaluation of chronic thromboembolic pulmonary hypertension. Semin Cardiothorac Vasc Anesth 2014; 18: 319-330.
[32] Wagenvoort CA. Pathology of pulmonary thromboembolism. Chest 1995; 107: 10S-17S.
[33] Moser KM and Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 1993; 103: 685-692.
[34] Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, Reid LM and Tuder RM. Pathologic assessment of vasculopathies in pulmonary hypertension. J Am Coll Cardiol 2004; 43: 25S-32S.
[35] Guha M. First-in-class guanylate cyclase stimulator approved for PAH. Nat Biotech 2013; 31: 1064-1068.
[36] Donda K, Zambrano R, Moon Y, Percival J, Vaidya R, Dapaah-Siakwan F, Luo S, Duncan MR, Bao Y, Wang L, Qin L, Benny M, Young K and Wu S. Riociguat prevents hyperoxia-induced lung injury and pulmonary hypertension in neonatal rats without effects on long bone growth. PLoS One 2018; 13: e0199927.
[37] Zhang HL, Liu ZH, Wang Y, Xiong CM, Ni XH, He JG, Luo Q, Zhao ZH, Zhao Q and Sun XG. Acute responses to inhalation of Iloprost in patients with pulmonary hypertension. Chin Med J 2012; 125: 2826-2831.
[38] Reichenberger F, Mainwood A, Doughty N, Fineberg A, Morrell NW and Pepke-Zaba J. Effects of nebulised iloprost on pulmonary function and gas exchange in severe pulmonary hypertension. Respir Med 2007; 101: 217-222.
[39] Leuchte HH, Baezner CJ, Baumgartner RA, Mernitz P, Neurohr C and Behr J. Acute hemodynamic responses to supplemental oxygen and their prognostic implications in pulmonary hypertension. Respiration 2013; 85: 400-407.
[40] Ulrich S, Fischler M, Speich R, Popov V and Maggiorini M. Chronic thromboembolic and pulmonary arterial hypertension share acute vasoreactivity properties. Chest 2006; 130: 841-846.
[41] Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H and Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hy-

pertension. Circ Cardiovasc Interv 2012; 5: 748-755.
[42] Dimopoulos K, Kempny A, Alonso-Gonzalez R and Wort SJ. Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv 2012; 5: 756-762.
[43] Sugimura K, Fukumoto Y, Satoh K, Nochioka K, Miura Y, Aoki T, Tatebe S, Miyamichi-Yamamoto S and Shimokawa H. Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. Circ J 2012; 76: 485-488.
[44] Kataoka M, Inami T, Kawakami T, Fukuda K and Satoh T. Balloon pulmonary angioplasty (percutaneous transluminal pulmonary angioplasty) for chronic thromboembolic pulmonary hypertension: a Japanese perspective. JACC Cardiovasc Interv 2019; 12: 1382-1388.