The spectrum and prevalence of arrhythmia in different clinical pulmonary hypertension groups in Chinese population

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Abstract

Background: Arrhythmia is not uncommon among pulmonary hypertension (PH) population, and may be associated with disease severity.

Hypothesis: To investigate different spectrums and prevalence of arrhythmias in different clinical PH groups in Chinese population.

Methods: Patients diagnosed with PH between April 15, 2019, and August 2, 2021, were enrolled prospectively. The prevalence of different types of arrhythmias in PH patients were calculated. Logistic regression analyses were conducted to determine independent predictors for arrhythmia.

Results: One thousand patients were enrolled. The prevalence of any arrhythmia, sinus node dysfunction, sinus tachycardia, atrial fibrillation, atrial flutter, other types of atrial tachycardia, atrioventricular block, and ventricular tachycardia is 44.4%, 12.2%, 15.2%, 8.1%, 4.1%, 10.2%, 7.1%, and 2.5%. Logistic regression analyses revealed that older age and larger right ventricle (odds ratio: 1.111 and 1.095, p < .05) were independently related with higher probability of supraventricular arrhythmia; Complicating with coronary artery disease, larger right ventricle, and increased left ventricular end-diastolic diameter (odds ratio: 19.540, 1.106, and 1.085, p < .05) were independently correlated with sinus node dysfunction/atrioventricular block in patients with pulmonary arterial hypertension.

Conclusions: Nearly half of PH patients experienced at least one type of arrhythmia. The most common seen arrhythmias were supraventricular arrhythmia, sinus tachycardia, and sinus node dysfunction. Older age and larger right ventricle were independently related with higher probability of supraventricular arrhythmia; Complicating with coronary artery disease, larger right ventricle and increased left ventricular end-diastolic diameter were independently correlated with higher probability of sinus node dysfunction/atrioventricular block in patients with pulmonary arterial hypertension.

Keywords
atrioventricular block, prevalence of arrhythmia, pulmonary arterial hypertension, pulmonary hypertension, sinus node dysfunction, supraventricular arrhythmia
1 | INTRODUCTION

Pulmonary hypertension (PH) is a pathophysiological disorder defined as a mean pulmonary arterial pressure (mPAP) ≥25 mm Hg measured by right heart catheterization (RHC) in the supine position at rest. According to clinical presentation, pathological, and hemodynamic characteristics, PH is categorized into five clinical groups.1 Regardless of different etiology and clinical classification, PH is associated with progressive impaired right heart function and poor prognosis. Current targeted treatment for pulmonary arterial hypertension (PAH) appears to improve clinical outcomes in modern registries compared to historical controls,2–7 but the mortality of PH patients is still relatively high.

Arrhythmia is not uncommon among PH population, and may be associated with disease severity. Several previous studies indicated certain arrhythmias, such as atrial fibrillation (AF) and atrial flutter (AFL), were associated with clinical deterioration or even increased mortality in PH/PAH patients.8–13 While other recent studies did not find any association between arrhythmias and mortality.14,15

However, the prevalence of arrhythmias in PH patients, and the clinical relevance of arrhythmias with right ventricular dysfunction have not been well evaluated among Chinese population. Moreover, studies suggested the spectrum and prevalence of arrhythmia may differ according to the etiology of PH.13 Therefore, our study aimed to investigate different spectrums and prevalence of arrhythmias in different clinical PH groups in Chinese population.

2 | MATERIALS AND METHODS

2.1 | Study population

The study was approved by the ethics committee of Fuwai Hospital. Patients diagnosed with PH and discharged from the Department of Pulmonary Vascular Diseases between April 15, 2019, and August 2, 2021, were enrolled prospectively. The inclusion criteria were as follows: (1) patients confirmed PH by RHC; (2) patients who had at least one electrocardiograph (ECG) or 24-h Holter electrocardiogram during hospitalization; and (3) no age restriction. The exclusion criterion was: mPAP (measured by RHC) <25 mm Hg before targeted therapy.

2.2 | Study protocol and procedure

Every patient’s ECGs and Holter (if applicable) during hospitalization or provided by them were collected. All ECGs and Holter electrocardiograms were carefully reviewed and all arrhythmias were adjudicated by an experienced cardiologist. All detected arrhythmias (except for arrhythmias within 72 h after RHC procedure) of the participants before the end of enrollment were taken into account. Arrhythmias indicated by diagnoses of patients’ medical records were also taken into account.

We subcategorized different arrhythmias into sinus node dysfunction (SND), sinus tachycardia, AF, AFL, other types of atrial tachycardia (AT) (consisting of atrial ectopic tachycardia, atrioventricular reentry tachycardia, atrioventricular nodal reentry tachycardia), atrioventricular block (AVB), ventricular tachycardia (VT) (including non-sustained VT, NSVT) and ventricular fibrillation/flutter (VF). In our study, supraventricular arrhythmia (SVA) consisted of AF, AFL, and other AT. The prevalence of different types of arrhythmias in PH patients were calculated.

Baseline demographic and clinical parameters, including gender, age, body mass index, comorbidities, World Health Organization functional class (WHO-FC), six-minute walk distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, parameters of echocardiography, hemodynamic parameters and medications, were recorded and compared.

2.3 | Statistical analysis

Statistical analyses were conducted using the SPSS system software, version 20.0.0. Continuous variables were presented as mean with standard deviation or median with interquartile ranges after testing for normality, and were compared using the Student t-test or the Mann–Whitney rank-sum test, as appropriate. Categorical variables were expressed as counts (percentages) and were compared using the chi-square or Fisher’s exact test. A p value <.05 was considered statistically significant. Multivariable analysis was performed using binary logistic regression to determine independent predictors for arrhythmias.

3 | RESULTS

3.1 | Spectrum and prevalence of arrhythmias in different clinical PH groups

A total of 1000 patients (median age 41 years, 29.9% males) were enrolled. Among the patients, 725 (72.5%) were diagnosed with PAH (Group 1 PH), 18 (1.8%) were PH due to left heart disease (Group 2 PH), 32 (3.2%) were PH due to lung diseases and/or hypoxia (Group 3 PH), 216 (21.6%) were chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions (Group 4 PH), and the last 9 (0.9%) were PH with unclear and/or multifactorial mechanisms (Group 5 PH). At the time of inclusion, the median time since PH diagnoses was 0.20 (0.11–17.03) months.

In our relatively large PH population, 44.4% patients experienced at least one type of arrhythmia in their lifetime before enrollment. The prevalence of SND, sinus tachycardia, AF, AFL, other types of AT, AVB, and VT is 12.2%, 15.2%, 8.1%, 4.1%, 10.2%, 7.1%, and 2.5%. The spectrum and prevalence of arrhythmias in different clinical PH groups are shown in Table 1. Patients of Group 5 PH had the highest prevalence of Sinus tachycardia (18.2%, p = .012) and other AT (22.2%, p = .027); Patients of Group 2 PH had the highest prevalence...
**Table 1** Spectrum and prevalence of arrhythmias in different clinical PH groups according to clinical classification

|                        | Total (n = 1000) | Group 1 PH, n = 725 | Group 2 PH, n = 32 | Group 3 PH, n = 32 | Group 4 PH, n = 216 | Group 5 PH, n = 9 | p      |
|------------------------|------------------|---------------------|-------------------|-------------------|-------------------|------------------|--------|
| **Any arrhythmia, n (%)** | 444 (44.4)       | 309 (42.6)          | 144 (44.3)        | 25 (33.8)         | 140 (42.9)        | 16 (50.0)        | .037   |
| **SSS, n (%)**       | 121 (12.1)       | 81 (11.2)           | 34 (10.5)         | 5 (6.8)           | 42 (12.9)         | 3 (16.7)         | .222   |
| **Sinus tachycardia, n (%)** | 152 (15.2)       | 126 (17.4)          | 48 (14.8)         | 15 (20.3)         | 63 (19.3)         | 0 (0.0)          | .012   |
| **SVA**              |                  |                     |                   |                   |                   |                  |        |
| Total, n (%)         | 185 (18.5)       | 113 (15.6)          | 67 (20.6)         | 6 (8.1)           | 40 (12.3)         | 11 (61.1)        |        |
| AF, n (%)            | 81 (8.1)         | 48 (6.6)            | 31 (9.5)          | 1 (1.4)           | 16 (4.9)          | 8 (44.4)         | <.001  |
| AFL, n (%)           | 41 (4.1)         | 28 (3.9)            | 15 (4.6)          | 1 (1.4)           | 12 (3.7)          | 4 (22.2)         | <.001  |
| Other ATa, n (%)     | 102 (10.2)       | 62 (8.6)            | 37 (11.4)         | 4 (5.4)           | 21 (6.4)          | 3 (16.7)         | .027   |
| AVB, n (%)           | 71 (7.1)         | 49 (6.8)            | 28 (8.6)          | 2 (2.7)           | 19 (5.8)          | 2 (11.1)         | .325   |
| VTb, n (%)           | 25 (2.5)         | 17 (2.3)            | 11 (3.4)          | 0 (0.0)           | 6 (1.8)           | 3 (16.7)         | 1 (3.1) |

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; AVB, atrioventricular block; CHD, congenital heart disease; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SSS, sick sinus syndrome; SVA, supraventricular arrhythmia; VT, ventricular tachycardia.

*Consisting of atrial ectopic tachycardia, atrioventricular reentry tachycardia, and atrioventricular nodal reentry tachycardia.

bIncluding non-sustained VT.
| TABLE 2 | Baseline characteristics of PAH patients with SVA versus PAH patients without SVA |
|---------|-------------------------------------------------------------------------|
|         | All PAH patients (n = 725) | PAH with SVA (n = 113) | PAH without SVA (n = 612) | p     |
| Male gender, n (%) | 177 (24.4) | 37 (32.7) | 140 (22.9) | .025 |
| Age, years | 35.00 (28.00–46.00) | 48.00 (37.00–60.50) | 33.00 (27.00–42.00) | <.001 |
| BMI, kg/m² | 21.48 (19.01–24.08) | 21.15 (18.49–24.55) | 21.48 (19.05–24.02) | .618 |
| Time since PH diagnoses, months | 0.233 (0.133–20.90) | 0.17 (0.10–8.20) | 0.30 (0.13–21.58) | .033 |
| WHO-FC | | | | .001 |
| WHO-FC I, n (%) | 23 (3.2) | 1 (0.9) | 22 (3.6) | |
| WHO-FC II, n (%) | 421 (58.1) | 50 (44.2) | 371 (60.6) | |
| WHO-FC III, n (%) | 248 (34.2) | 52 (46.0) | 196 (32.0) | |
| WHO-FC IV, n (%) | 33 (4.6) | 10 (8.8) | 23 (3.8) | |
| Comorbidities | | | | |
| CAD, n (%) | 13 (1.8) | 5 (4.4) | 8 (1.3) | .056 |
| Arterial hypertension, n (%) | 83 (11.4) | 24 (21.2) | 59 (9.6) | <.001 |
| OSA, n (%) | 132 (26.1) | 31 (41.3) | 101 (23.5) | <.001 |
| Diabetes mellitus, n (%) | 35 (4.8) | 13 (11.5) | 22 (3.6) | <.001 |
| 6MWD, m | 420 (357–480) | 317 (291–422) | 428 (360–480) | <.001 |
| NT-proBNP | 510.30 (146.73–1621.25) | 1410.00 (663.90–3144.50) | 419.00 (135.80–1358.50) | <.001 |
| Parameters of echocardiography | | | | |
| RV in PLAX, mm | 32 (27–37) | 35 (30–43) | 31 (27–36) | <.001 |
| Decreased TAPSE*, n (%) | 329 (45.4) | 69 (61.6) | 260 (42.5) | <.001 |
| LVEDD in PLAX, mm | 39.00 (34.00–44.00) | 40.00 (34.25–48.00) | 39.00 (34.00–44.00) | .063 |
| LVEF, % | 65 (60–70) | 62 (60–66) | 65 (60–70) | .001 |
| Parameters of CPET | | | | |
| VO₂peak ml/min/kg | 13.40 (10.70–16.40) | 11.80 (9.50–15.40) | 13.70 (11.10–16.40) | <.001 |
| VO₂peak %pred, % | 42.00 (33.00–52.00) | 39.00 (30.50–55.50) | 42.00 (33.75–52.00) | .414 |
| METmax, mets | 5.70 (4.80–6.40) | 5.10 (4.35–5.70) | 5.70 (4.90–6.50) | <.001 |
| Parameters of RHC | | | | |
| RAP, mm Hg | 5 (3–8) | 7 (5–11) | 5 (3–8) | <.001 |
| mPAP, mm Hg | 56.00 (45.00–72.00) | 52.00 (39.00–68.50) | 57.00 (47.00–73.00) | .005 |
| PAWP, mm Hg | 8.00 (5.00–10.00) | 9.50 (6.00–13.00) | 7.00 (5.00–9.00) | <.001 |
| PVR, WU | 10.73 (6.67–15.26) | 9.24 (3.62–18.80) | 10.93 (7.40–15.10) | .079 |
| CI, L/(min·m²) | 2.87 (2.36–3.54) | 2.65 (2.03–3.13) | 2.93 (2.41–3.57) | <.001 |
| Targeted therapy | | | | |
| ERA, n (%) | 524 (72.3) | 60 (53.1) | 464 (75.8) | <.001 |
| PDE5i, n (%) | 582 (80.3) | 81 (71.7) | 501 (81.9) | .012 |
| Oral PCA, n (%) | 30 (4.1) | 2 (1.8) | 28 (4.6) | .263 |
| Intravenous/subcutaneous/ inhaled PCA, n (%) | 81 (11.2) | 13 (11.5) | 68 (11.1) | .903 |
| sGC, n (%) | 25 (3.4) | 3 (2.7) | 22 (3.6) | .824 |
3.2 Characteristics of PAH patients with SVA versus PAH patients without SVA

As different clinical PH groups differ in etiology, we focused on PAH population in following analyses. SVA consisted of AF, AFL, and other AT in our study. The baseline clinical and hemodynamic characteristics of all PAH patients, PAH patients with SVA, and PAH patients without SVA are summarized in Table 2. In this PAH subgroup, patients with SVA were elder and had worse WHO-FC, 6MWD, NT-proBNP, peak oxygen uptake (VO2peak), and maximum metabolic equivalent (METmax), had higher proportion of males, shorter course of disease, and larger right ventricle (RV) than patients without SVA. More patients with SVA had decreased tricuspid annular plane systolic excursion (TAPSE) and comorbidities (such as systemic hypertension, obstructive sleep apnea, and diabetes mellitus) than patients without SVA. Patients without SVA tended to have greater proportion of combined targeted therapy (dual, 68.3% or triple, 6.4%) than patients with SVA (dual, 55.8% or triple combination, 3.5%).

After adjusting potential confounders (including all factors for which \( p < .2 \) on previous univariate analysis), logistic regression analysis revealed that age and RV diameter (measured by echocardiography) were independently related with SVA in PAH patients (Table 3). For PAH patients, the probability of having SVA increased by 11.1% (95% confidence interval [CI] = 1.069–1.156, \( p < .001 \)) for each additional year of age; The probability of having SVA increased by 9.5% (95% CI = 1.023–1.172, \( p = .009 \)) as their RV diameter increased by 1 mm.

3.3 Characteristics of PAH patients with SND/AVB versus PAH patients without SND/AVB

Besides SVA, the baseline characteristics of PAH patients with bradyarrhythmia (consisting of SND and AVB in our study) versus PAH patients without bradyarrhythmia were also analyzed (Table S1). Logistic regression analysis was also conducted to determine the predictors of SND/AVB in PAH patients (Table S2). In the PAH subgroup, the probability of having SND/AVB of patients with coronary artery disease (CAD) was 18.540 times higher than that of patients without CAD (95% CI = 2.117–180.404, \( p = .009 \)). The probability of having SND/AVB increased by 10.6% (95% CI = 1.012–1.208, \( p = .027 \)) or 8.5% (95% CI = 1.010–1.167, \( p = .026 \)) as their RV diameter or left ventricular end-diastolic diameter (LVEDD) increased by 1 mm.

4 DISCUSSION

4.1 Previous studies focused on Chinese population

In 2014, Wen et al. analyzed 280 patients with idiopathic pulmonary arterial hypertension (IPAH) and the result showed the cumulative 6-year incidence of SVA for IPAH patients was 15.8%. In 2018, Zhang et al. investigated the influence of PAH on the recurrence of AF after catheter ablation and found that PAH was independently correlated to late recurrence of paroxysmal AF. In the study of Zhang et al., the pulmonary arterial pressure was estimated by echocardiography other than measured by RHC. This measurement of pulmonary arterial pressure may have reduced the credibility of the results, because echocardiography is useful for screening for PH but is not precise enough for an individual diagnosis of PAH.
None of the above-mentioned studies described the spectrum and prevalence of arrhythmia in different clinical PH groups. To the best of our knowledge, our study is the first one describing the spectrum and prevalence of arrhythmia in five different clinical PH groups in Chinese population. The diagnosis of PH for each participant in our study was confirmed by RHC. In our relatively large and real-world PH population, nearly half of them (44.4%) experienced at least one kind of arrhythmias in their lifetime before enrollment. The most common seen arrhythmias in our population were SVA, sinus tachycardia, and SND.

### 4.2 Prevalence of arrhythmias

AF was seen in 8.1% patients in our overall PH population (6.6% for PAH patients), which is markedly higher than the prevalence of AF (1.03%) in general Chinese population. For patients with PH, a long-standing elevated pulmonary pressure results in impaired RV function and the enlargement of right atrium. Chronic pressure overload of right heart might lead to electrophysiologic and structural change, including generalized conduction slowing, reduced tissue voltage, and electrical silence. Ultimately, as modulating the autonomic activity, some related arrhythmia may be triggered and perpetuated. This may explain the relative high prevalence of both tachyarrhythmia and bradyarrhythmia in our study population.

The prevalence of SVA (18.5%) in our overall PH population was lower than that of two recent studies (29%) and our study, early post-PEA arrhythmia was also taken into account, which might be the reason of high prevalence of AF/AT. The prevalence of AF/AT before PEA was 20% in their study, and was close to our result (18.5%). In the study of Fingrova et al., supraventricular tachycardia (SVT), the definition of SVT in their study was the same with that of SVA in our study, occurred during follow-up was also counted, which differs from our study design and could result in higher prevalence of SVT. Earlier studies have reported a prevalence of SVA ranging from 12.3% to 46.4% in patients with PAH; Complicating with CAD, larger RV and increased LVEDD were independently correlated with higher probability of SND/AVB in patients with PAH.

Wen et al. also identified age and increased RV diameter as risk factors for developing SVA in patients with IPAH, which is in accordance with our result. The mechanism by which enlargement and dysfunction of the right heart might lead to and trigger brady- and tachy-arrhythmia was discussed above. Increased LVEDD could be the result of worse cardiac function, which might explain its relationship with the increased risk of arrhythmia.

After adjusting potential confounders (including β-blocker intake), complicating with CAD was still a strong independent risk factor for SND/AVB in PAH patients. SND/AVB is common in acute myocardial infarction, but the relationship between SND/AVB with stable CAD is not well investigated yet. Chronic myocardial ischemia resulting from long-standing CAD might play a role.

### 4.4 Study limitations

First, our results are limited due to the study design—a single-center study, which raises the possibility of selection bias. Additionally, without long-term continuous monitoring, clinically silent arrhythmia episodes might have been missed.

This study described the spectrum and prevalence of arrhythmia in different clinical PH groups in Chinese population, and risk factors of SVA and SND/AVB for PAH. New-onset arrhythmias and other long-term prognoses of our population will be detected and analyzed during follow-up. The relationship between arrhythmia (mostly atrial arrhythmia) and clinical deterioration in PH patients (mostly PAH and CTEPH) was investigated mainly in western countries before. More studies concerning the correlation of different types of arrhythmias and mortalities in different clinical PH groups, especially for the Asian population, are needed.

### 5 Conclusion

The prevalence of arrhythmia is 44.4% in our participants. The spectrum and prevalence of arrhythmia differ by different clinical PH groups. The most common seen arrhythmias were SVA (consisted of AF, AFL, and other AT), sinus tachycardia, and SND. The prevalence of AF in PH patients was markedly higher than that in general Chinese population. Older age and larger RV were independently related with higher probability of SVA in patients with PAH; Complicating with CAD, larger RV and increased LVEDD were independently correlated with higher probability of SND/AVB in patients with PAH.

### Table 3 Predictors of SVA in PAH patients

|        | β   | SE  | p      | OR      |
|--------|-----|-----|--------|---------|
| Age, years | .106 | .020 | <.001 | 1.111 (1.069–1.156) |
| RV in PLAX, mm | .091 | .035 | .009 | 1.095 (1.023–1.172) |

Abbreviations: OR, odds ratio; PAH, pulmonary arterial hypertension; PLAX, parasternal long-axis view; RV, right ventricle; SE, standard error; SVA, supraventricular arrhythmia.
related to higher probability of SVA in PAH patients. Complicating with CAD, larger RV and increased LVEDD were independently correlated with higher probability of SND/AVB in PAH patients.

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CONFLICT OF INTERESTS
The authors declare no conflict of interest.

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

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