Pulmonary arterial hypertension in Saudi Arabia: Patients’ clinical and physiological characteristics and hemodynamic parameters. A single center experience

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Abstract:
AIMS: The main objective of this study is to describe patients’ clinical characteristics and physiological and hemodynamic parameters at the time of diagnosis in a pulmonary hypertension center in Saudi Arabia.

MATERIALS AND METHODS: This study reports the results from a single pulmonary hypertension specialized center in Riyadh, Saudi Arabia, namely Prince Sultan Medical Military City/Cardiac Center (PSMMC & CC). Both newly diagnosed (incidence) and referred (prevalence) cases of pulmonary arterial hypertension are included. All characteristics, including clinical, physiological, and hemodynamic parameters at the time of diagnosis are described.

RESULTS: A total of 107 patients were identified as having pulmonary arterial hypertension as diagnosed by right heart catheterization. The mean age at diagnosis was 36 (± 9) years, and there was a female preponderance of 62.6%. The mean duration between symptom onset and diagnosis was 27.8 (± 9.0) months. At the time of enrollment, 56.1% of patients were in functional class III and 16.8% were in functional class IV. Fifty five patients (51.4%) were diagnosed as idiopathic pulmonary arterial hypertension, 29 patients (27.1%) as congenital heart disease associated with pulmonary arterial hypertension, 16 patients (15.0%) as connective tissue diseases associated with pulmonary arterial hypertension, 4 patients (3.7%) as heritable pulmonary arterial hypertension, and 3 patients (2.8%) as portopulmonary hypertension.

CONCLUSION: This data highlights the current situation of pulmonary arterial hypertension in Saudi Arabia. Our patients are much younger than patients described in other international registries but still detected as late in the course of the disease. A majority of patients displays severe functional and hemodynamic compromise.

Key words: Hemodynamics, pulmonary arterial hypertension, registry, Saudi Arabia, Saudi association for pulmonary hypertension, six minute walk test

Introduction
Pulmonary arterial hypertension (PAH) is characterized by progressive increase in pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) that can lead to right heart failure and death.[1] The understanding of PAH pathobiology and the management of the disease have undergone significant advances during the last decade. Despite such improvement, PAH remains progressive and often fatal.

The National Institutes of Health (NIH) conducted the first registry of primary pulmonary hypertension (now known as idiopathic PAH [IPAH]) in the early 1980s.[2] Subsequently, a number of registries have been published to describe the natural history of PAH in different countries.[3,4] These registries have significantly improved our understanding on many aspects of PAH. The French registry of 674 adults with PAH has described the prevalence and incidence of the disease as well as the clinical and hemodynamic characteristics of IPAH patients.[3] Other surveys from America have focused mainly on the association between the environmental factors, particularly appetite suppressive drugs, and PAH.[5] A large prospective study (REVEAL Registry) in USA has described the characteristics of the demographics, clinical course, hemodynamic features, and disease management of PAH patients.[4]

The prognostic markers in PAH include a composite of measures that includes clinical...
characteristics and physiological and hemodynamic parameters. The modified New York Heart Association (NYHA) functional class has been recognized as an important prognostic measure. Furthermore, exercise tolerance and biochemical and hemodynamic markers are also essential tools for categorizing PAH patients from both prognostic and therapeutic aspects.

The true burden of PAH in the Middle East and Saudi Arabia remains unknown, and the disease characteristics are yet to be determined. In the present study, we described the characteristics of PAH patients at the time of diagnosis in one center in Saudi Arabia.

Materials and Methods

The present study describes the results of prospectively collected and longitudinally followed cohort of patients diagnosed with PAH (both incidence and prevalence cases) in one tertiary specialized pulmonary hypertension (PH) center, Prince Sultan Medical Military City and Cardiac Center (PSMMCC&CC), in Saudi Arabia over a 3-year period.

Between December 2009 and November 2012, all patients referred to the pulmonary hypertension unit with suspected or confirmed diagnosis of WHO group I disease (PAH) were screened by using echocardiograph.

The diagnostic right heart catheterization (RHC) was necessary to meet the study inclusion criteria. RHC was performed in resting position using the Saudi Association for Pulmonary Hypertension (SAPH) RHC protocol. If appropriate wedging was not possible, left ventricular end-diastolic pressure (LVEDP) was directly measured.

The study protocol was reviewed and approved by the Registry and Research Taskforce of the Saudi Association of Pulmonary Hypertension and by the Research and Ethics Committee of Prince Sultan Medical Military City.

Participants

Patients with newly diagnosed (incidence case) or previously diagnosed (prevalence case) PAH were eligible for enrollment if they fulfilled the definition of pulmonary hypertension (PH) group I PAH, as per the Nice 5th PH World Congress. This includes patients with PAH that is idiopathic, heritable, or associated with congenital systemic-to-pulmonary shunts, connective tissue diseases, portal hypertension, drugs or toxins, HIV infection, or schistosomiasis.

The inclusion criteria were:
1. Age ≥ 14
2. PAH group 1 diseases (as described above)
3. Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) or LVEDP ≤ 15 mmHg, as measured by RHC.

Patients with splenectomy or hemoglobinopathies were excluded as this group has been moved from PAH group I diseases to PH group V diseases as per the Nice 5th PH World recommendation.

Data was collected using the SAPH-modified diagnostic and treatment protocol. The baseline assessment includes medical and drugs history, onset of symptoms, time of diagnosis, modified NYHA functional class at time of diagnosis, tests used to diagnose PAH that include pulmonary function test (PFT) including diffusion capacity, high resolution chest computerized tomography scan (HRCT), CT pulmonary angiography, V/Q scan, abdominal ultrasound, hepatic vireology screen and liver function tests, immune screening, Schistosoma titer, and HIV serology. PHA group I disease category was also identified at this stage.

Physiological assessment at the time of diagnosis includes six-minute walk test (6MWT), NT pro BNP level, and echocardiographic evaluation for pericardial effusion and right ventricular function (TAPSE score).

RHC for hemodynamic parameters was performed in all patients (except 2) and included mPAP, right atrial pressure (RAP), cardiac index (CI), PAWP or LVEDP, and PVR. Only idiopathic and congenital heart diseases patients underwent vasoreactive testing using intravenous or inhaled iloprost as per the protocol. The positive vasoreactive response is defined as a drop in mPAP by more than 10 mmHg to reach an absolute value of less than 40 mmHg in response to administration of acute vasodilator agent.

Statistical analysis

Descriptive statistics in terms of mean, standard deviations and percentages were used to describe characteristics of the studied patients. Comparison of categorical variables was conducted by Chi-Square test or Fisher’s exact test accordingly. After assessment of normality distribution of variables, Student t-test and ANOVA test were used if data had normal distribution whilst Mann–Whitney and Kruskal–Wallis test were used in skewed data. A P-value less than 0.05 was considered a significant test. SPSS version 17 was used for all statistical analysis.

Results

A total of 128 patients with clinically suspected WHO group I PAH were evaluated. Of these, 107 patients (83.6%) met the study entry criteria and are described in this study [95 (89%) incidence cases and 12 (11%) prevalence cases]. Of those excluded, 2 patients had a normal RHC despite abnormal echocardiography (one patient had systemic sclerosis, SSc) and the other had pulmonary fibrosis with suspected “out of proportion” PAH; 4 patients had a high PAWP with normal transpulmonary gradient compatible with left-ventricular diastolic dysfunction; nine patients had WHO group IV chronic thromboembolic pulmonary hypertension (CTEPH); 3 patients had veno-occlusive disease (group I'), and 3 patients had WHO group III diseases. Figure 1 illustrates the distribution of the study population.

Demographics

The mean age at diagnosis was 36 (± 9) years. Out of the 107 patients, 67 (62.6%) were female. Three patients (2.8%) were non-Saudi in origin (1 Sudanese, 1 Jordanian, and 1 Yemeni). Eighty-four patients (78.5%) were referred to the pulmonary hypertension unit with suspected PAH and 85 (78.6%) were referred to the pulmonary hypertension unit with suspected PAH.

Eighty-four patients (78.5%) were referred to the pulmonary hypertension unit with suspected PAH in one tertiary specialized pulmonary hypertension (PH) center in Saudi Arabia.
Table 1: Demography, clinical, and physiological characteristics of all patients

| Variables                  | IPAH (n = 55) | HPAH (n = 4) | CHD-APAH (n = 29) | CTD-APAH (n = 16) | Po-APAH (n = 3) | P value |
|----------------------------|---------------|-------------|-------------------|-------------------|----------------|---------|
| Age, years ±SD             | 38 ± 6        | 19 ± 2      | 27 ± 4            | 49 ± 5            | 39 ± 7         | <0.001  |
| Female, n (%)              | 36 (65.5%)    | 1 (25%)     | 18 (62.1%)        | 12 (75%)          | 0 (0%)         | 0.07    |
| NYHA FC: II/III/IV         | 12/35/38      | 1/2/1       | 14/12/3           | 2/9/5             | 0/2/1          | 0.08    |
| Symptoms duration, months  | 25.3 ± 6.6    | 15.2 ± 2.0  | 29.9 ± 8.6        | 38.1 ± 6.9        | 14.1 ± 6.2     | <0.001  |
| Baseline 6MWT, meter       | 305 ± 73      | 307 ± 132   | 345 ± 67          | 232 ± 57          | 316 ± 111      | <0.001  |
| Baseline NT-pro BNP        | 1274.9 ± 735.9| 2376.6 ± 1936.2| 980.4 ± 744.5     | 2353.2 ± 1583.4   | 1071.5 ± 744.6| 0.001   |
| Echocardiography, TAPSE, mm| 17.5 ± 2.4    | 15.5 ± 2.5  | 18.5 ± 3.1        | 16.6 ± 1.9        | 17.7 ± 2.3     | 0.08    |

IPAH = Idiopathic pulmonary arterial hypertension, CHD-APAH = Congenital heart disease-associated pulmonary arterial hypertension, CTD-APAH = Connective tissue disease-associated pulmonary arterial hypertension, HPAH = Heritable pulmonary arterial hypertension, Po-APAH = Portal hypertension-associated pulmonary arterial hypertension (portopulmonary hypertension), NYHA = Modified New York Hear Association, 6 MWT = 6-minute walk test, TAPSE = Tricuspid annular plane systolic excursion

Figure 1: The distribution of the study cohort

RHC = Right heart catheterization, PAH = Pulmonary arterial hypertension, Pts., patients, WHO = World Health Organization, IPAH = Idiopathic pulmonary arterial hypertension, PAH-ACHD = Congenital heart disease-associated pulmonary arterial hypertension, PAH-ACTD = Connective tissue disease-associated pulmonary arterial hypertension, HPAH = Heritable pulmonary arterial hypertension, Po-APAH = Portal hypertension-associated pulmonary arterial hypertension (portopulmonary hypertension)

Baseline clinical characteristics

At the time of diagnosis, 29 patients (27.1%) were in modified NYHA functional class II, 60 patients (56.1%) were in functional class III, and 18 patients (16.8%) were in functional class IV. In the whole cohort of patients, the mean (± SE) time from symptoms onset to diagnosis was 27.8 (± 9.0) months. Fifty-five patients (51.4%) were diagnosed as IPAH, 29 patients (27.1%) as PAH associated with congenital heart disease (PAH-ACHD), 16 patients (14.9%) as PAH associated with connective tissue disease (PAH-ACTD) [systemic sclerosis (n = 11), mixed connective tissue disease (n = 4), systemic lupus erythematosus (n = 1)], 4 patients (3.7%) as heritable pulmonary arterial hypertension (HPAH) [based on strong family history but genetic testing was not performed], and 3 patients (2.9%) as portopulmonary hypertension (PoPH) [all with hepatitis B virus and portal hypertension]. The HPAH subgroup patients were younger than the other subgroups (mean age 19 (± 2) years), while the PAH-ACTD patients subgroup were the eldest (mean age 49 (± 5) years) and had more severe symptoms at diagnosis. Table 1 illustrates the baseline characteristics of the patients enrolled in the study.

Physiological and hemodynamic characteristics

The results of the physiological characteristics are shown in Table 1. Exercise capacity had been evaluated at the time of diagnosis in 104 patients (97.1%) by 6MWT. Cardiopulmonary exercise test was not performed in any patient. Echocardiographic results were available for all patients (100%) at the time of diagnosis. Systolic pulmonary arterial pressure estimation, TAPSE scoring, presence of pericardial effusion, and evaluation of diastolic and systolic function of the left ventricle were included in echocardiographic evaluation. Blood NT-pro BNP level was available in 80 patients (74.8%) at the time of diagnosis.

Diagnostic RHC was available in 105 patients (98.1%) at the time of diagnosis. Two patients were diagnosed as a very complex PAH-ACHD (complex single ventricle physiology with Eisenmenger), and both had previous cardiac cath done by their congenital heart disease specialist. The treating physician considered repeat RHC unnecessary and probably risky, and so the evaluation was made by echocardiography only.

The results of hemodynamics measurement are shown in Table 2.

Acute vasodilator challenge was performed in all 55 IPAH patients (100%) and in 17 patients (58.6%) of those diagnosed with PAH-ACHD. As per SAPH protocol, PAH-ACTD, HPAH, and PoPH patients were not tested for vasodilator challenge. Intravenous prostacyclin was used as the testing agent in 48 patients (66.5%), while inhaled Iloprost was used in 14 patients (19.4%) and IV adenosine in 10 patients (14.1%). The rate of positive acute vasodilator response was overall low and reported in 5 patients (6.9%) only.

Incidence versus prevalence cases

Incident cases were those newly diagnosed patients for whom diagnosis was first made during the recruitment phase of the study, while prevalent cases were those patients with a known diagnosis of PAH and referred to our center for further management.

Ninety-five (89%) incidence cases were diagnosed during the recruitment period, while 12 (11%) cases were referred to our center with an established diagnosis of PAH (prevalent cases). All prevalence cases had a repeat RHC at enrollment for complete hemodynamic study and confirmation of the diagnosis. Clinical and hemodynamic data for incidence versus prevalent cases are shown in Table 3.

Finally, the correlation between the modified NYHA functional class and both physiological and hemodynamic parameters at the time of diagnosis is illustrated in Table 4.
Discussion

PAH is a disease characterized by progressive increase in PVR and PAP secondary to progressive narrowing of the pulmonary arteries lumen. Such abnormality is caused in part by smooth muscle contraction secondary to the imbalance between the vasoconstrictive and vasodilator mediators produced by the injured endothelial cells. More importantly, vascular remodeling caused by abnormal proliferation of all layers of the pulmonary arteries combined with a state of apoptosis resistance have been recently recognized as the main cause behind the abnormal rise in PVR in PAH.

The first recognizable work on pulmonary hypertension was in year 1981, when NIH created a national registry of 187 patients with "primary" pulmonary hypertension. Such early effort has led to major advances in the understanding of this disease. More recently, it has been recognized that several

Table 2: Hemodynamic measurements of all patients

| Variables          | IPAH   | HPAH   | CHD-APAH | CTD-APAH | Po-APAH | P value  |
|--------------------|--------|--------|----------|----------|---------|----------|
| mPAP, mmHg         | 54±10  | 55±8   | 52±8     | 41±6     | 49±9    | <0.001   |
| RAP, mmHg          | 13±3   | 13±3   | 9±3      | 9±1      | 10±2    | <0.001   |
| PAWP/LVEDP, mmHg   | 8±1    | 9±1    | 10±1     | 12±1     | 11±2    | <0.001   |
| PVR, Wood unit     | 19±6   | 22±8   | 14±6     | 11±4     | 13±5    | <0.001   |
| CI, L/min/m²       | 2.2±0.6| 1.9±0.7| 2.8±0.7  | 2.4±0.7  | 2.7±0.8 | 0.001    |

Vasoreactivity, n (%)  4 (7.3%)  ND  1 (3.4%)  ND  ND  0.79

Done in all IPAH patients, *Done in 17/29 CHD-APAH patients, IPAH = Idiopathic pulmonary arterial hypertension, HPAH = Congenital heart disease-associated pulmonary arterial hypertension, CHD-APAH = Congenital heart disease-associated pulmonary arterial hypertension, CTD-APAH = Connective tissue disease-associated pulmonary arterial hypertension, Po-APAH = Portal hypertension-associated pulmonary arterial hypertension (portopulmonary hypertension), NYHA = Modified New York Heart Association, 6 MWT = 6-minute walk test, TAPSE = Tricuspid annular plane systolic excursion, mPAP = Mean pulmonary artery pressure, RAP = Right atrial pressure, PAWP = Pulmonary arterial wedge pressure, LVEDP = Left ventricular end diastolic pressure, PVR = Pulmonary vascular resistance, CI = Cardiac index, ND = Not done

Table 3: Clinical and hemodynamic data for incidence versus prevalence cases

| Variables          | All cases (n = 107) | Incident cases (n = 95) | Prevalent cases (n = 12) | P value |
|--------------------|---------------------|------------------------|-------------------------|---------|
| Age, year (range)  | 36.5±9.7            | 36.5±9.7               | 36.5±9.9                | 0.9     |
| Female (%)         | 67 (62.6%)          | 62 (65.3%)             | 5 (41.7%)               | 0.1     |
| NYHA, II/III/IV (%)| 29/60/18            | 25/54/16               | 4/6/2                   |         |
| Symptoms duration/month | 27.8±9.0       | 27.8±9.3               | 27.4±6.5                | 0.9     |
| 6 MWT, meter       | 306.7±79.7          | 305.6±78.3             | 315.2±92.9              | 0.7     |
| NT-pro BNP         | 1405.7±1076.6       | 1394.2±1004.5          | 1486.2±1558.8           | 0.9     |
| TAPSE              | 17.5±2.6            | 17.5±2.6               | 17.8±2.9                | 0.7     |

Table 4: Physiological & hemodynamic parameters according to NYHA FC at the time of diagnosis

| Variables          | NYHA FC II | NYHA FC III | NYHA FC IV | P value |
|--------------------|------------|-------------|------------|---------|
| Number             | 29         | 60          | 18         |         |
| Age, year          | 32.9±6.2   | 37.5±9.8    | 39.1±10.6  | 0.05    |
| Female, %          | 18 (62.1%) | 39 (65.0%)  | 10 (55.6%) | 0.7     |
| Symptoms duration, m | 28.2±9.7   | 27.7±9.4    | 27.4±6.8   | 0.9     |
| 6MWT, m            | 400.9±38.0 | 294.4±44.1  | 193.8±23.5 | <0.001  |
| NT-pro BNP         | 264.6±205.9| 1312.7±525.8| 3052.3±1150.9| <0.001  |
| TAPSE, mm          | 21.5±1.8   | 16.7±1.1    | 14.7±0.9   | <0.001  |
| RAP, mmHg          | 8.5±1.8    | 12.6±2.8    | 14.1±2.7   | <0.001  |
| mPAP, mmHg         | 41.5±5.7   | 52.3±8.3    | 60.8±9.1   | <0.001  |
| PVR, Wood unit     | 8.8±1.9    | 18.5±4.8    | 24.3±6.8   | <0.001  |
| CI, L/min/m²       | 3.3±0.3    | 2.1±0.4     | 1.7±0.2    | <0.001  |

NYHA = Modified New York Heart Association, FC = Functional class, 6MWT = Six minute walk test, NT-pro BNP = N-terminal pro brain natriuretic peptide, RAP = Right atrial pressure, mPAP = Mean pulmonary artery pressure, PVR = Pulmonary vascular resistance, CI = Cardiac index

PAH is a disease characterized by progressive increase in PVR and PAP secondary to progressive narrowing of the pulmonary arteries lumen. Such abnormality is caused in part by smooth muscle contraction secondary to the imbalance between the vasoconstrictive and vasodilator mediators produced by the injured endothelial cells. More importantly, vascular remodeling caused by abnormal proliferation of all layers of the pulmonary arteries combined with a state of apoptosis resistance have been recently recognized as the main cause behind the abnormal rise in PVR in PAH. Such early effort has led to major advances in the understanding of this disease. More recently, it has been recognized that several
diseases or conditions could be associated with PAH. These diseases share similar clinical and pathobiological features with IPAH. During the last PH World congress 2013 in Nice, the classification of PH group was updated and PAH continues to be categorized as Group I diseases. This group includes IPAH, HPAH, drug- and toxin-induced PAH, and PAH associated with CHD, CTD, HIV, portopulmonary, and schistosomiasis. Despite a relatively long duration of symptoms, those patients were more likely to be in modified NYHA functional class II compared to other group, although this did not reach the statistically significant level ($P = 0.08$ between the groups). Nevertheless, PAH-ACHD patients showed a significantly better physiological profile when compared to other PAH groups.

The present study describes the characteristics of PAH in the largest population of patients in Saudi Arabia to date. The clinical characteristics used in this study was limited to the modified NYHA functional class since this clinical parameter was found to have prognostic significance both at baseline and follow up. The physiological characteristics included 6 MWT, NT-pro BNP biomarker level, and TAPSE scoring as measured by echocardiography. 6MWT is a straightforward, safe, and reproducible test, which measures the distance walked in 6 minutes. It has been found to have a prognostic measure in PAH patients. Similarly, both NT-pro BNP and TAPSE scoring have also been found to carry prognostic values. Finally, hemodynamically characteristics included both diagnostic (mPAP and PAWP) and prognostic (RAP, CI, PVR, and vasoreactivity) parameters.

In the current study, 107 adult PAH patients (95 incident cases and 12 prevalent cases; Table 1) were included. The mean age of the whole cohort at the time of diagnosis was significantly lower than the mean age reported by other registries. This can probably be explained by the young age of the Saudi Arabian population, as more than 50% of the whole Saudi population is younger than 20 years of age. The mean duration between symptom onset and diagnosis was unacceptable long ($27.8 \pm 9.0$ months). As a result, $72.8\%$ of the patients were in functional class III or IV at presentation. This delayed diagnosis is consistent with similar findings reported in many studies. Because baseline modified NYHA functional class is a well-recognized predictor of outcome in PAH patients, the long duration of symptoms before establishing the diagnosis indicates insufficient awareness about the disease in Saudi Arabia. Alhamad et al., have recently published a single-center experience in managing PH in Saudi Arabia. In his cohort of 112 PH patients, only 12 (10.7\%) belonged to group IPAH, and almost all of them were related to IPAH and PAH-ACTD. Of interest, the reported symptoms duration before establishing the diagnosis was significantly shorter ($7.3 \pm 5.7$ months) in that cohort.

IPAH was the most common subtype of PAH in our study. This observation has been recognized by other international registries. Our IPAH patients were predominantly female and significantly older than the HPAH and PAH-ACHD patients but younger than PAH-ACTD ($P < 0.001$ between the groups). Similar to other registries, the majority of patients were at functional class III or IV at the time of diagnosis. PAH-ACHD patients were the second most common PAH subgroup and had the best physiological parameters compared to other groups. The high prevalence of PAH-ACHD in this cohort probably reflects the current practice of late detection of CHD patients in Saudi Arabia and delayed surgical corrections.
Finally, there were no distinctive features between the incidence and the prevalence cases in regard to clinical, physiological, or hemodynamic parameters [Table 3]. This could in part be related to the small number of prevalence cases in this study but may also be related to the recent time of diagnosis in some prevalent cases, which put them in a similar category as the incident cases. Traditionally, it is believed that the incidence cases have a worse prognosis when compared with prevalence cases. [34] Prevalence and incidence of PAH in Saudi Arabia cannot be calculated based on this early study and will be determined once the data from other centers involved in Pulmonary Arterial Hypertension in Saudi Arabia (PATENTS) registry conducted by the Saudi Association of Pulmonary Hypertension (SAPH) becomes available.

In conclusion, this descriptive study confirmed many characteristics similarities between Saudi PAH patients and the international data. Our patients still present very late in the course of the disease, and the majority of them display severe physiological and hemodynamic compromise. Of note, our patients are much younger when compared to the international registries.

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