

# Multiprofessional and Intrahospital Experience for Diagnosis and Treatment of Pulmonary Arterial Hypertension

## *Esperienza multiprofessionale intraospedaliera nella diagnosi e nel trattamento dell'ipertensione polmonare*

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**ABSTRACT:** *Multiprofessional and Intrahospital Experience for Diagnosis and Treatment of Pulmonary Arterial Hypertension. M. Correale, D. Montrone, D. Lacedonia, R. Ieva, R. Bucci, A. Corrado, F.P. Cantatore, C.A. Greco, M. Concilio, G. Serviddio, M.P. Foschino Barbaro, M. Di Biase, N.D. Brunetti.*

**Background.** Referral centres for pulmonary hypertension will provide care by a multiprofessional team, which should as a minimum comprise: consultant physicians with a special interest in PH, clinical nurse specialist, radiologist, cardiologist with expertise in echocardiography.

**Aims.** this study sought to determine whether the experience of the establishment of a clinic for pulmonary arterial hypertension, initially created only for the treatment and diagnosis of heart failure, may be considered positive.

**Methods.** From 1 July 2008 to January 1, 2012 we evaluated 80 patients in our ambulatory dedicated to the diagnosis and treatment of PAH. All patients were performed to clinical evaluation, ECG, and echocardiography with estimation of the sPAP. Then we evaluated the functional capacity through cardiopulmonary exercise testing or six minute walking test (6MWT). RHC was required to confirm the diagnosis of pulmonary arterial hypertension.

**Results.** 80 patients (mean age: 50.9 ± 18.68 years, 31 males) were evaluated in our center; the largest groups subjected to screening were thalassemia (21 subjects), rheumatologic patients (18 patients), respirators, suspected of "out-of Proportion" (12 patients) and 4 patients with OSAS. 8 adult congenital heart patients. A diagnosis of PAH after right heart catheterization was possible in 25 cases. In particular, among patients with pulmonary arterial hypertension, 8 had a rheumatic etiology (systemic sclerosis), 2 post-thromboembolic disease, 5 patients had congenital heart disease, 1 patient with HIV infection, 1 patient with thalassemia major, 1 chronic lymphocytic leukemia and 1 with myelodysplasia.

**Conclusions.** The initial experience of our center and network within our hospital may be considered positive, because it permitted to patients easy access to hospital services, to undertake a comprehensive prognostic stratification and to recognize the early signs of worsening in subsequent tests.

**Keywords:** *pulmonary arterial hypertension, pulmonary hypertension, right heart failure.*

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## Introduction

In the last European Guidelines for the diagnosis and treatment of pulmonary hypertension (PH), PH has been defined as hemodynamic and pathological condition with an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest as assessed by right heart catheterization [1].

PH can be subdivided in: "pre-capillary PH" that can be pulmonary arterial hypertension (PAH - group 1), PH due to lung diseases (group 3), Chronic thromboembolic PH (CTEPH group 4), PH with unclear and/or Multifactorial mechanisms (group 5); and "post-capillary PH", due to left heart Disease

(group 2), that can be passive or reactive (out of proportion) [1].

The PAH (group 1), may be subdivided in "idiopathic" when it is not possible to recognize any cause; "heritable" because specific gene mutations have been identified in sporadic cases with no family history. More frequent forms in group 1 are indeed situations in which PH is associated (APHA) with other disorders such as connective tissue diseases (scleroderma, lupus), liver (portal hypertension), viral infections (HIV), congenital heart disease, and less frequently, schistosomiasis and chronic haemolytic anaemia. The persistent pulmonary hypertension of the newborn belong to this group [1].

For diagnosis, echocardiography is an important tool for screening of PH [2]. It allows to obtain various parameters that correlate with the right cardiac catheterization (RHC), including systolic pulmonary artery pressure (sPAP), which is obtained by the maximum speed tricuspid and right atrial pressure, evaluated according to the collapsibility (absent, > or <50%) and the expansion or less of the VCI. According to these criteria, PH can be defined unlikely, possible or likely. PH unlikely is characterized by a tricuspid regurgitation velocity  $\leq 2.8$  m/s, PA systolic pressure  $\leq 36$  mmHg, and no additional echocardiographic variables suggestive of PH. PH possible is characterized by a tricuspid regurgitation velocity  $\leq 2.8$  m/s, PA systolic pressure  $\leq 36$  mmHg, but presence of additional echocardiographic variables suggestive of PH; alternatively tricuspid regurgitation velocity between 2.9 m/s and 3.4 m/s and PA systolic pressure between 37 mmHg and 50 mmHg with/without additional echocardiographic variables suggestive of PH. Finally PH likely is characterized by tricuspid regurgitation velocity  $> 3.4$  m/s and PA systolic pressure  $> 50$  mmHg with/ without additional echocardiographic variables suggestive of PH [1].

Finally, RHC is required to confirm the diagnosis of PAH, to assess the severity of the haemodynamic impairment, and to test the vasoreactivity of the pulmonary circulation [1].

The purpose of a referral centre is to undertake assessment and investigation of all causes of PH, routinely manage appropriate patients with PAH-specific drug therapy. Referral centres will provide care by a multiprofessional team, which should as a minimum comprise: consultant physicians (normally from either or both of cardiology and respiratory medicine) with a special interest in PH, clinical nurse specialist, radiologist, cardiologist with expertise in echocardiography, access to psychological and social work support. It is important to have a ward where staff have special expertise in PH, an intensive therapy unit, a specialist outpatient service, emergency care, echocardiography, CT scanning, nuclear scanning, magnetic resonance imaging, ultrasound, exercise testing, lung function testing, and catheterization laboratory access to the full range of specific PAH drug therapy in their country [3].

We report our intrahospital experience where a network has been created with different professional figures (internists, cardiologists, pulmonologists, rheumatologists, haematologists) for diagnosis and treatment of PH.

## Methods

From 1 July 2008 to January 1, 2012 we evaluated 80 patients in our ambulatory dedicated to the diagnosis and treatment of PAH. The patients were affected by rheumatic disease (almost exclusively systemic sclerosis), or had a previous diagnosis of pulmonary embolism, or were affected by a congenital heart defect treated surgically or native, also there were patients with thalassemia. We also evaluated patients affected by HIV or by portal hypertension, with occasional high values of sPAP by Doppler echocardiography, during hospitalization in internal medicine.

Patients were sent from the following departments: Internal Medicine, Institute of Respiratory Disease, Center for Thalassemia, Rheumatology, other Cardiology Departments.

The non invasive cardiac evaluation included: clinical evaluation (medical history, home therapy, heart rate, blood pressure, weight, height, BMI), ECG, and echocardiography, with estimation of the sPAP. The right sectional size, the possible presence of pericardial effusion and the value of TAPSE were then also assessed. Transthoracic echocardiography was performed with the use of iE33 (Philips Medical Systems, Andover, MA, USA). All echocardiographic studies were performed and interpreted by experienced physicians.

Then we evaluated the functional capacity through cardiopulmonary exercise testing or six minute walking test (6MWT). Patients able to perform a more prolonged physical activity, performed a cardiopulmonary test. These tests were performed using the 29S VMax Spectra Sensor Medics using the bicycle ergometer Ergometrics Lode Medical Technology-Corival. All tests were conducted with working loads ranging from 4 to 15 Watts. It was used a run mode to ramp by a continuous increase in the workload in time, every second, with a computer control, trying to reach a peak  $VO_2$  in about 10 minutes. The result was indicated as the absolute value of peak  $VO_2$  and  $VO_2$  max as a percentage of predicted, changed in accordance of the overweight. The metabolic and cardiopulmonary parameters were obtained by the method of breath by breath analysis. The anaerobic threshold was calculated by the calculation of the "V Slope" (ratio of  $VCO_2$  and  $VO_2$ ). Patients not able to perform prolonged physical activity, were performed to 6MWT.

In the 6MWT, in addition to distance walked, dyspnoea on exertion (Borg scale) and finger  $O_2$  saturation are recorded. Finally, RHC was required to confirm the diagnosis of PAH, to assess the severity of the haemodynamic impairment, and to test the vasoreactivity of the pulmonary circulation in the cases suggested by the European Guidelines [1].

## Results

80 patients (mean age:  $50.9 \pm 18.68$  years, 31 males) were evaluated in our center, the characteristics are present in Table 1. Of 80 patients, 32 patients had WHO class III-IV and 48 WHO class I-II.

The largest groups subjected to screening were thalassemia (21 subjects, because the center also sought in these patients even early signs of heart failure), rheumatologic patients (18 patients), respirators, suspected of "out-of Proportion" (12 patients) and 4 patients with OSAS. 8 adult congenital heart patients (including 2 patients with tetralogy of Fallot, 1 operated for complete atrioventricular canal and Down's syndrome, 2 patients with secundum ASD, which underwent percutaneous closure with "device").

A diagnosis of PAH after right heart catheterization (PAPm  $\geq 25$  mmHg, PCWP  $< 15$  mmHg) was possible in 25 cases. The characteristics of 25 patients (mean age:  $61.62 \pm 13.95$  years, 9 males) are reported in Table 2. In particular, among patients with pulmonary arterial hypertension, 8 had a rheumatic etiology (systemic

Table 1. - Total population characteristics

Variables	Values
Patients	80
Age (years)	50,9 ± 18,68
Male	31
WHO class I-II	48
WHO class III-IV	32
Rheumatologic	18
Post-thromboembolic disease	12
Congenital heart disease	8
HIV	1
Thalassemia / hematomol.	23
Porto-pulmonary hypertension	2
Respirators	12
OSAS	4
PAPs (mmHg)	49,8 ± 25,66

sclerosis), 2 post-thromboembolic disease, 5 patients had congenital heart disease, 1 patient with HIV infection, 1 patient with thalassemia major, 1 chronic lymphocytic leukemia and 1 with myelodysplasia.

To the patients with a history of pulmonary embolism and detection of pulmonary arterial hypertension were recommended cardiac surgery for thrombectomy. Only 1 patient has consented to the intervention, and has since remained asymptomatic, with no need for specific therapy for pulmonary arterial hypertension.

12 patients were sent by the pulmonologist, all for under disproportion between the spirometric restrictive or obstructive syndrome and the degree of dyspnea, 4 of these had a previous diagnosis of OSAS. Of the 12 patients, after right heart catheterization in 4 patients was possible to make diagnosis of pulmonary arterial hypertension, 1 of which was suffering from OSAS.

3 patients had liver cirrhosis, the former died shortly before receiving a liver transplant, the last patient had also HIV infection, died after voluntary suspension of specific therapy (Sildenafil). The other patient is alive.

Another dead patient was a 65-years-old woman with systemic sclerosis, admitted to our department for effort dyspnea (*WHO functional class III*), already in therapy with bosentan for digital ulcers by another centre; we then discontinued the bosentan for finding the right heart catheterization in post-capillary pulmonary hypertension (PAPm: 30 mmHg, PCWP: 20 mmHg, CI: 2.3 l (min/m<sup>2</sup>)).

Patients with thalassemia were 21 (mean age 33.36 ± 11.30, 10 male), including 2 pediatric subjects (6 and 7 years, respectively), only 1 of them was suffering from pulmonary arterial hypertension.

About the therapy, patients performed loop diuretics, digitalis, and warfarin as the first step, after the confirmation hemodynamics of pulmonary arterial hypertension, in case of non-responders to the test of reversibility, outlined a specific therapy for hypertension pulmonary artery [1]. These drugs are: Endothelin receptor antagonists (bosentan, ambrisentan, sitaxsentan), phosphodiesterase type 5 inhibitors (sildenafil, tadalafil), and prostacyclin (epoprostenol,

iloprost, treprostinil, beraprost) represent the different classes of medications that are currently used in monotherapy and in combination to treat PAH [4].

Patients on monotherapy were: 12 (9 patients with bosentan and 3 patients with sildenafil), of these is to report the case of a patient aged 38 with a history of thalassemia and septic embolism, previously treated with sildenafil 60 mg daily, that as a result of a considerable worsening of the PAPs (82 mmHg) and dyspnea (class III WHO) and for the presence of HCV-related liver disease evolved, was treated with progressive increase of the first dose of sildenafil to 80 mg daily, and then 100 then 120 mg daily, with reduction of PAPs (50 mmHg) and dyspnea (WHO class I-II). The patient had an accident during a previous cardiac catheterization, and would not done this procedure. The degree of liver disease not indicated the use of endothelin inhibitors (ERA).

3 patients had combination therapy with 2 specific drugs (2 with 100 mg daily ambrisentan and sildenafil 60 mg daily). In this regard, 1 of these patients (as post-thromboembolic) diagnosed with severe pulmonary hypertension, right heart catheterization, previously treated with bosentan (250 mg daily) for occurrence of significant edema, that replaced the drug with the sitaxetan, and despite the good clinical response to the reduction of dyspnea and an increase of meters walked at 6MWT, the re-

Tabella 2. - Patients with PAH

Variables	Values
Patients	25
Age (years)	61,62 ± 13,95
Male	9
WHO class II	7
WHO class III-IV	18
Rheumatologic	8
Post-thromboembolic disease	2
Congenital heart disease	5
HIV	1
Thalassemia / hematomol.	3
Porto-pulmonary hypertension	2
Respirators	4
OSAS	1
PAPs (mmHg)	77,62 ± 22,91
6-MWT (m)	315,2 ± 140,07
PAPm (mmHg)	46,66 ± 18,53
PCWP (mmHg)	15,8 ± 4,9
Monotherapy	12
Bosentan	9
Sildenafil	3
Combination therapy	5
Two drugs	
Ambrisentan + Sildenafil	2
Ambrisentan + Iloprost	1
Three drugs	2
Bosentan + sildenafil + Iloprost	
Ivabradina	6

duction of edema and the absence of side effects, had to discontinue this treatment because the drug was withdrawn from sale by the company and go to ambrisentan.

The third patient (adult with surgically corrected congenital heart disease) with dual therapy took ambrisentan and iloprost, however, had previously taken sildenafil 60 mg and then tadalafil, with the development of intolerance (abdominal pain) for whom treatment has been replaced.

Triple combination was prescribed in 2 female patients, both rheumatic (systemic sclerosis), initially treated only with bosentan 250 mg daily and iloprost (iv) before arriving at our center, then with the worsening of dyspnea and reduction of meters 6MWT, was associated with treatment with sildenafil 60 mg first day with stabilization of dyspnea, and worsening again during the dosage of sildenafil was increased to 80 mg daily with the achievement of stabilization of dysphonic symptoms.

8 patients with pulmonary arterial hypertension of mild, did not practice specific therapy due to side effects (both with sildenafil than with bosentan) or because they controlled the disease with the only non-specific therapy (diuretics, digital).

Given the contraindication to therapy with beta blockers, patients with electrocardiographic finding of sinus tachycardia and symptomatic episodes of palpitations (6 subjects, mainly women with systemic sclerosis) were treated with ivabradine 10 mg daily, with reported improvement in symptoms and quality of life. Recently we reported the first of these patients with ivabradine therapy, in this 60-year-old woman with systemic sclerosis and interstitial pulmonary with radiological pattern non specific interstitial pneumonia, long term treatment with ivabradine was safe and well tolerated, without pharmacological interaction (bosentan, sildenafil, iloprost, coumadin). Selective heart rate reduction improved symptoms, above all, palpitation and exercise tolerance [5].

## Discussion

We report the experience that began in July 2008, the establishment of a clinic, which was initially created only for the treatment and diagnosis of heart failure, has also deployed its expertise to meet even in patients with pulmonary arterial hypertension. We have now created a network with other elements of an enterprise (Internal Medicine, Respiratory Diseases, Center for Thalassemia, rheumatology, cardiology clinics other) with their referents, placing patients at screening echocardiography and functional evaluation.

The presence in each of these structures, however, an expert person who is interested in the problem has simplified the communication between the cardiac center and other centers of the company, limiting the dispersion data of patients in inappropriate wards and especially the excessive mobilization to the large cities national. Moreover, the establishment of the surgery allowed by qualified people, the titration of specific drugs, the investigation of possible side effects and a reference point

for patients when they come from centers outside the region and require different treatment plans for these specific drugs.

Furthermore, the dedicated clinic, day-by day-hospital or services, allowing these patients rapid access to the department.

The presence of dedicated nursing staff, for the telephone follow-up or for the preparation and execution of the test cardiopulmonary, spirometry or 6MWT, has allowed to improve the care of these patients.

The low number of patients in combination therapy (5 of 17 total pts who were receiving specific therapy) may be partly explained because symptom onset recent for many patients in monotherapy enrolled in the study.

Another feature of our experience demonstrates the safety and handling of ivabradine in these patients, especially those with systemic sclerosis. This molecule has reduced the palpitations and has improved exercise tolerance as measured by the 6MWT distance. Especially as a therapy is better tolerated than atenolol, first used by some patients.

## Conclusions

The initial experience of our center and network within our hospital may be considered positive, because it permitted to patients easy access to hospital services, to undertake a comprehensive prognostic stratification and to recognize the early signs of worsening in subsequent tests. Specific drugs for PAH can be handled by expert hands, and associated with confidence to other therapy. However, it is necessary to invited other colleagues so that patients are increasingly to analyze. Each centre for diagnosis and treatment of PAH must make a specific network with multiprofessional team.

## Limitations

Main limitation of the study is the small number of patients enrolled. These preliminary results need to be confirmed in larger cohorts of patients.

## Riassunto

*Background.* I centri di riferimento per la diagnosi e cura dell'ipertensione arteriosa polmonare garantiscono assistenza con un team multiprofessionale, che comprende: medici ed infermieri specializzati per la cura di questi pazienti, radiologi, cardiologi specializzati in ecocardiografia.

*Scopo.* questo studio vuole valutare se è positiva la realizzazione di un ambulatorio per l'ipertensione arteriosa polmonare, laddove era inizialmente istituito solo un centro per il trattamento dei pazienti con scompenso cardiaco.

*Metodi.* Dal 1° Luglio 2008 al 1° Gennaio, 2012 noi abbiamo valutato 80 pazienti in un nostro ambulatorio dedicato all'ipertensione arteriosa polmonare. Tutti I pazienti furono sottoposti a valutazione clinica, ECG, ed ecocardiografia con la stima della PAPs. Valutammo anche la capacità funzionale con

il test cardiopolmonare o “six minute walking test” (6MWT). Il cateterismo cardiaco destro confermò la diagnosi di ipertensione arteriosa polmonare.

**Risultati.** 80 pazienti (età media:  $50.9 \pm 18.68$  anni, 31 maschi) furono valutati nel nostro centro; il gruppo più grande di pazienti sottoposti a screening furono i talassemici (21), pazienti reumatologici (18), respiratori, sospetti di “out-of Proportion” (12) e 4 pazienti con OSAS. 8 adulti con cardiopatie congenite. Una diagnosi di PAH fu possibile dopo cateterismo cardiaco destro in 25 cases. In particolare, tra i pazienti con PAH, 8 avevano una eziologia reumatica, 2 post-thromboembolica, 5 con cardiopatia congenita, 1 con infezione da HIV, 1 con talassemia major, 1 con leucemia linfatica cronica e 1 con mielodisplasia.

**Conclusioni.** L'esperienza iniziale del centro e la rete intraospedaliera possono essere considerate positive, perché permettono ai pazienti un facile accesso ai servizi degli ospedali, per una completa stratificazione prognostica e per cogliere precocemente segni di peggioramento.

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