Original Research

Pulmonary Arterial Hypertension: Many Years' Experience and Modern Approach to a Malignant Disease in a Pulmonary Hypertension Centre

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Key words: **Right ventricle, pulmonary vascular resistance, pulmonary heart diseases.**

Introduction: The aim of this study was to record the results from a modern diagnostic and therapeutic approach to patients with pulmonary arterial hypertension.

Methods: We studied the clinical characteristics and the treatment of 69 patients (50 women, 72.5%), aged 44 ± 17 years, who were diagnosed with pulmonary hypertension (World Health Organisation categories I, IV and V). The patients' outcomes were recorded over 14 years' operation of our Pulmonary Hypertension Unit.

Results: Twenty-seven patients (39.1%) suffered from idiopathic pulmonary hypertension, 12 (17.4%) from thromboembolic obstructive disease, 14 (20.3%) from congenital heart diseases, 11 (15.9%) from connective tissue diseases, 3 (4.3%) from portal hypertension, 2 (2.9%) from sarcoidosis, and 1 (1.4%) from pulmonary veno-occlusive disease. Six patients (8.7%) were in New York Heart Association (NYHA) functional class I, 28 (40.6%) were in class II, 30 (43.5%) were in class III, and 5 (7.2%) were in class IV. Thirty-four patients completed a 6-minute walk test and covered a mean distance of 352 ± 137 m. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured in 18 patients, with a mean value of 1665 ± 1935 pg/ml. A vasoreactivity test in 41 patients had a positive response in 10 (24.4%). Twenty-six patients (37.7%) were treated with combination therapy, whereas 16 (23.2%) either did not comply with or were not given specific medication. The mortality over a mean follow-up period of 5 ± 4 years was 26%, significantly lower than that reported before the introduction of new drugs. An advanced NYHA class was an independent predictor of mortality (p=0.004), while elevated NT-proBNP levels were also associated with poor survival (p=0.013).

Conclusions: Pulmonary arterial hypertension is a severe disease that leads to right heart failure and death. Despite the latest advances, vigilance and continuous investigation are needed in order to achieve a prompt diagnosis and the most suitable treatment.

Manuscript received:
April 21, 2009;
Accepted:
July 10, 2009.

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Pulmonary arterial hypertension, regardless of its aetiology, is an extremely severe and life-threatening disease that is difficult to identify in its first stages because of the non-specific early symptoms.[1] A high level of alertness to patients who are at risk, as well as the recognition of the early manifestations of the condition, are essential for prompt diagnosis, before significant and irreversible pathophysiological changes occur.

The diagnostic approach, using an algorithm that includes various tests,[2] is focused on ruling out other causes of pulmonary hypertension that are much more common and have a more favourable prognosis. A better understanding of the pathogenic mechanisms underlying the disease has led to the discovery and use in treatment of new specific drugs that appear to alter its natural history.

In the most recently published clinical

classification of pulmonary hypertension (Venice 2003)[3] 5 forms are recognised: I) pulmonary arterial hypertension; II) venous pulmonary hypertension; III) hypertension related to diseases of the pulmonary parenchyma or to hypoxaemia; IV) hypertension due to chronic thrombotic or embolic disease; and V) hypertension due to various diseases, such as sarcoidosis. This classification is very important, since each category involves different pathogenetic mechanisms, natural history, treatment and prognosis, with the most malignant being categories I and IV.[4-6]

In the present study we describe the results from 67 patients who were diagnosed with pulmonary hypertension class I or IV, as well as 2 who suffered from sarcoidosis (class V).

Methods

Over a period of 14 years (1993-2007), the diagnosis of pulmonary hypertension was made in 69 patients (classes I, IV and V). The examination of choice for the detection of these patients, always taking into account the history (symptoms, family history, risk factors), was the echocardiogram. Patients with a tricuspid regurgitation Doppler flow velocity >3 m/s in successive measurements with a 6 month interval between them, and with no indications of systolic or diastolic left heart disease, underwent a thorough investigation with haematological and imaging examinations, check of pulmonary function indexes (spirometry, diffusing **c**apacity of the lung for carbon monoxide), and eventually right cardiac catheterisation to determine the aetiology and confirm the diagnosis.

The haematological examinations included a general blood test, N-terminal pro-brain natriuretic peptide (NT-proBNP), immunological examinations to rule out autoimmune disorders, HIV antibodies, tests of liver function, and various prognostic indexes, such as C-reactive protein (CRP), uric acid, and troponin.

Imaging modalities included simple chest X-ray, transoesophageal echocardiography if there was suspicion of a congenital anomaly, pulmonary ventilation-perfusion scintigraphy, and depending on the clinical suspicion, high resolution computed tomography (CT) of the chest, spiral chest CT, CT or magnetic resonance angiography, and standard pulmonary angiography.

During right heart catheterisation, pressures and resistances were measured, as well as cardiac output and cardiac index using the Fick method. In the majority of cases (84%), it was combined with the vasoreactivity test, in which rapid-action vasodilators of the pulmonary circulation, such as nitric oxide (NO) and/or inhaled or intravenous prostanoids, were administered. Patients were considered vasoreactive if they showed a drop in mean pulmonary artery pressure (mPAP) ≥10 mmHg reaching a final value of mPAP ≤40 mmHg, without a reduction in cardiac output.[2]

A lack of response to treatment was defined as a combination of various parameters, such as the patient remaining in functional class III or IV, a reduction in 6-minute walk distance >15% in relation to the previous test, as well as a deterioration in echocardiographic indexes (tissue Doppler imaging, eccentricity index, cardiac output, pericardial effusion).[7]

Patients were followed in the outpatients' department, and specifically in our Pulmonary Hypertension Unit, whose staff consists of two cardiologists and one nurse with training and specialisation in the disease, and which provides 24-hour coverage. The frequency of visits depended on the severity of the disease, with the most severely affected patients being examined once every month or every three months, depending on the stability of their condition, while the remainder were re-evaluated every six months. On re-evaluation, apart from the history, and clinical and echocardiographic examinations, the patients underwent a 6-minute walk test and measurement of NT-proBNP. It should be noted that these latter procedures were only started after 2002, when the 6-minute walk test became the endpoint for various multi-centre studies and when measurement of NT-proBNP became feasible in the hospital.

Statistical analysis

For continuous variables, the mean, standard deviation and median values were determined, while for categorical variables frequency distributions over the categories and percentiles were calculated for the whole study population. Categorical variables were compared using Pearson's χ^2 test in cases where we did not have cell cohesion with expected values <5 in the tables. For the cases with expected values <5, Fisher's exact test was used. For continuous variables, we first checked for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed variables were compared using the t-test, while non-normal distributions were analysed using the non-parametric Mann-Whitney test for comparison of medians. Kaplan-Meier survival curves

Table 1. Clinical characteristics of 69 patients with pulmonary hypertension.

Age (years)	44 ± 17
Sex (M/F)	19/50
Aetiology of pulmonary hypertension:	
Idiopathic	27 (39.1%)
Congenital heart diseases:	14 (20.3%)
Atrial septal defect*	10
Ventricular septal defect	2
Tetralogy of Fallot	1
Patent *ductus arteriosus*	1
Autoimmune diseases:	11 (15.9%)
Scleroderma	6
Lupus	3
Other	2
Chronic thromboembolic disease	12 (17.4%)
Portal hypertension	3 (4.3%)
Sarcoidosis	2 (2.9%)
Pulmonary veno-occlusive disease	1 (1.4%)
NYHA functional class:	
I	6 (8.7%)
II	28 (40.6%)
III	30 (43.5%)
IV	5 (7.2%)
Six-minute walk distance (m) (n=34)	352 ± 137
NT-proBNP (pg/ml) (n=18)	1665 ± 1935

NT-proBNP – N-terminal pro-brain natriuretic peptide.
*One patient with an atrial septal defect also suffered from scleroderma.

were plotted and compared using the log-rank test (Mantel-Cox). The prognostic value of several parameters was examined using Cox regression analysis. The criterion of statistical significance was a p-value <0.05.

Results

Investigation and diagnosis

The diagnosis of pulmonary hypertension was made in 69 patients, mean age 44 ± 17 years (range 12-79), of whom 50 (72.5%) were women. Their principal symptom was dyspnoea on effort and at the time of diagnosis 6 patients (8.7%) were in New York Heart Association (NYHA) functional class I, with 28 (40.6%), 30 (43.5%) and 5 (7.2%) in classes II, III and IV, respectively. Thirty-four patients completed a 6-minute walk test and covered a mean distance of 352 ± 137 m. NT-proBNP levels were measured in 18 patients, with a mean value of 1665 ± 1935 pg/ml (range 36-7237 pg/ml). The aetiology of pulmonary hypertension and the patients' clinical characteristics are given in Table 1, while echocardiographic and haemodynamic parameters are shown in Table 2.

Forty-one patients (59.4%) underwent a vasoreactivity test and 10 of them (24.4%) had a positive response. There was no significant difference between responders and non-responders in initial functional class or the aetiology of pulmonary hypertension (Table 3); however, the mortality of the non-responders was triple that of the responders, while regression analysis showed that a positive vasoreactivity test was a negative prognostic factor for death (hazard ratio, HR 0.01, 95% confidence interval, CI: 0-0.8, p=0.04, Table 4). In addition, of those patients with a positive vasoreactivity test, only 1 (10%) continued to be a responder, in functional class I, while on monotherapy with calcium channel blockers.

Treatment

For the treatment of the disease, apart from the standard conventional treatment for heart failure (O_2, diuretics, anticoagulants), drugs specific to pulmonary hypertension were also administered, including the non-selective endothelin receptor antagonist bosentan, sildenafil, and calcium channel blockers for the vasoreactive patients, intravenous prostacyclin and inhaled or subcutaneous prostanoid analogues (Table 5). For the patients who received parenteral compounds (prostacyclin, prostanoid analogue) the route of administration and the duration of treatment are shown in Table 6. Of those patients, 1 woman received intravenous prostacyclin for 60 months, followed by inhaled prostanoid for 16 months, and has since been on subcutaneous treprostinil. One male patient took prostacyclin, inhaled for 8 months then intravenous for 37

Table 2. Haemodynamic and echocardiographic parameters, given as mean ± standard deviation (range).

Mean pulmonary artery pressure (mmHg)	n=49	59 ± 13.8	(32-105)
Systolic pulmonary artery pressure (mmHg)	n=49	91.3 ± 20.5	(52-150)
Diastolic pulmonary artery pressure (mmHg)	n=49	37.5 ± 11.7	(16-85)
Cardiac index (L/min/m^2)	n=37	2.2 ± 0.8	(0.75-5.3)
Right atrial pressure (mmHg)	n=43	12.3 ± 4.7	(3-24)
Pulmonary artery resistances (Woods units)	n=40	13.4 ± 9.2	(2.8-57.3)
Pulmonary artery pressure (echo) (mmHg)	n=69	87.8 ± 24.7	(40-160)

Table 3. Clinical parameters and vasoreactivity test.

Parameter	Vasoreactivity test		Total	p-value
	Positive	Negative		
	N (%)	N (%)	N (%)	
NYHA:				
I	0	2 (6)	2 (5)	
II	7 (70)	12 (39)	19 (46)	
III	2 (20)	13 (42)	15 (37)	NS
IV	1 (10)	4 (13)	5 (12)	
Total	10	31	41	
Female sex	8 (80)	24 (77)	32 (78)	NS
Mortality	1 (10)	10 (32)	11	0.2
Aetiology of pulmonary hypertension:				
Idiopathic	6 (60)	17 (55)	23 (56)	
Scleroderma	0	1 (3)	1 (2)	
Lupus	3 (30)	0	3 (7)	
Congenital heart disease	0	6 (19)	6 (15)	NS
Thromboembolic disease	1 (10)	5 (16)	6 (15)	
Sarcoidosis	0	1 (3)	1 (2)	
Veno-occlusive disease	0	1 (3)	1 (2)	
Total	10	31	41	

Table 4. Cox regression analysis.

	p	HR	95% CI
Age	0.080	1.061	0.99-1.13
NYHA IV	0.004	45.243	3.45-592.06
Responders	0.042	0.013	0.00-0.85

HR – hazard ratio; CI confidence interval.

Table 5. Specific drugs administered for pulmonary hypertension.

Drugs	Number of patients (%)
Calcium channel blockers	7 (10)
Endothelin receptor antagonists	47 (68.1)
Intravenous prostacyclin	11 (15.9)
Inhaled prostanoid	12 (17.4)
Subcutaneous prostanoid	3 (4.3)
Sildenafil	16 (23.2)
No specific therapy / non compliance	16 (23.2)

Table 6. Route of administration of parenteral compounds and duration of treatment, given as mean ± standard deviation (range).

Administration route	n	Duration of therapy (months).	Deaths*
Intravenous	11	39 ± 25 (2-77)	4
Inhaled	12	22 ± 13 (1-48)	0
Subcutaneous	3	33 ± 7 (25-38)	1

*Deaths are reported according to the drug last taken by the patient.

months, then subcutaneous prostanoid for 36 months until he died; while another female patient received prostanoid, inhaled for 18 months and then subcutaneously.

Twenty-seven patients (39.1%) were treated with monotherapy, while 26 (37.7%) ultimately received a combination of drugs, as shown in Table 7. Of the latter, 19 (73%) were treated with a combination of 2 drugs, 6 (23%) with 3, and 1 patient (4%) with a combination of 4 drugs. Sixteen patients (23%) either did not receive specific drug therapy or did not comply with the treatment regimen. Half of these were taking calcium channel blockers, although they did not fulfil the necessary criteria and were mainly patients who

Table 7. Types of combined therapy.

Combination	Patients (%)
Ca blocker + endothelin antagonist	3 (11.5)
Endothelin antagonist + sildenafil	5 (19.2)
Endothelin antagonist + prostanoid	10 (38.4)
Sildenafil + prostanoid	1 (3.9)
Endothelin antagonist + sildenafil + prostanoid	6 (23.1)
Ca blocker + endothelin antagonist + sildenafil + prostanoid	1 (3.9)

were diagnosed before the publication of the 2003 guidelines. One female patient who did not receive specific therapy suffered from a complex congenital heart disease and underwent successful surgical repair that resulted in a significant pressure reduction in the pulmonary circulation. In the remainder, there were no statistically significant differences in relation to the aetiology of pulmonary hypertension compared to the patients who received specific medication, but a significantly smaller number of the latter were in NYHA class I at diagnosis (3.7% vs. 26.7%, p=0.018). Of the 53 patients who were given specific drugs, 12 died (22%), compared to 6 (40%) of those not taking specific therapy (p=0.026).

Concerning complications resulting from therapy, no significant complications were observed in the patients who were given sildenafil. In the patients who were taking endothelin antagonists, 5 (10.6%) showed a reversible and dose-dependent increase in transaminases (≥2 × upper normal limit), while all the patients who received inhaled prostanoid reported dryness of the mucous membrane and a dry cough. Also, all patients taking subcutaneous prostanoid reported local irritation and pain at the injection sites. Of the patients taking intravenous prostacyclin, 7 (63.6%) showed line-related infections, which led in 1 case to subclavian vein thrombosis. In the latter patient and in 2 others with catheter-related bacteraemia, intravenous administration was stopped and in 2 patients was replaced by subcutaneous administration of treprostinil.

Mortality during a follow up of 5 ± 4 years was 26% (Figure 1). A regression model including age at diagnosis, sex, idiopathic pulmonary hypertension, NYHA class IV, mean pulmonary artery pressure, pulmonary arterial resistances, right atrial pressure, cardiac index, and response to vasoreactivity test, found that NYHA class IV was an independent risk factor for death (HR 45.2, 95%CI 3.4-592, p=0.004; Table 4 & Figure 2). In addition, patients with elevated NT-proBNP levels (>1400 pg/ml) had significantly worse survival compared to those with lower levels (p=0.013; Figure 3).

Discussion

In this study we present the results from 69 patients with pulmonary hypertension, who were treated during 14 years' operation of our Pulmonary Hypertension Unit. The survival of these patients was significantly better when compared to the time before specific drugs were introduced, since >70% of our patients survived for a period ≥5 years, in contrast to the results of the National Institutes of Health (NIH) registry, where the 5-year survival rate of patients with primary pulmonary hypertension was 34%.[4] The related conditions that may cause the disease affect the prognosis, with those suffering from HIV infection or those with systemic sclerosis having the worst outcomes, with a mean survival of about 1 year in the latter group.[5]

The term "pulmonary arterial hypertension" was proposed by the World Health Organisation, placing primary and some forms of secondary pulmonary hypertension in the same category, since the pulmonary vascular changes observed are similar in these conditions and reflect almost the same pathological process.[3]

Pulmonary hypertension due to chronic thromboembolic disease has a poor prognosis, and if left untreated has a 5-year survival rate of 10% when mPAP is >50 mmHg.[6,8] At the histopathological level, the

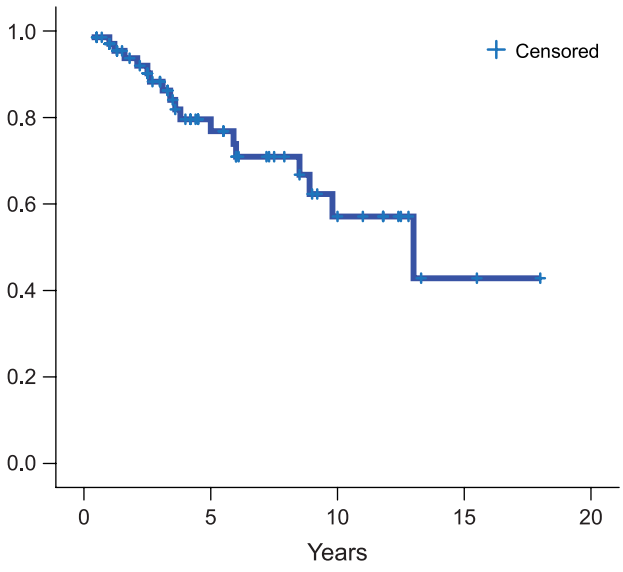

Figure 1. Survival curve for the patients of the study.

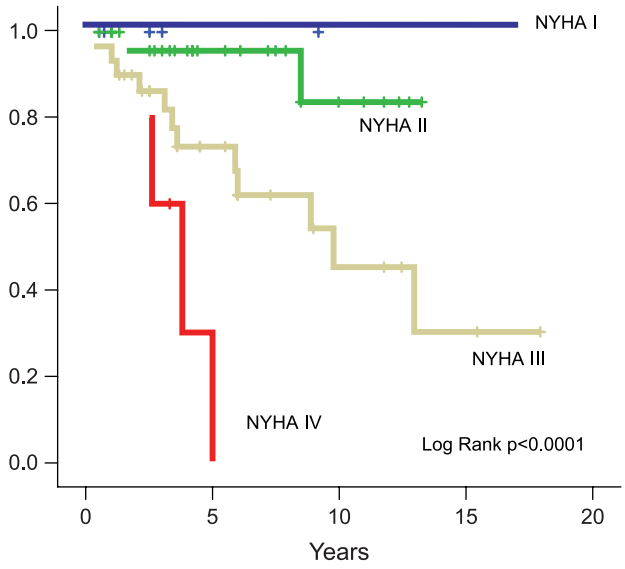

Figure 2. Survival curve according to New York Heart Association (NYHA) functional class.

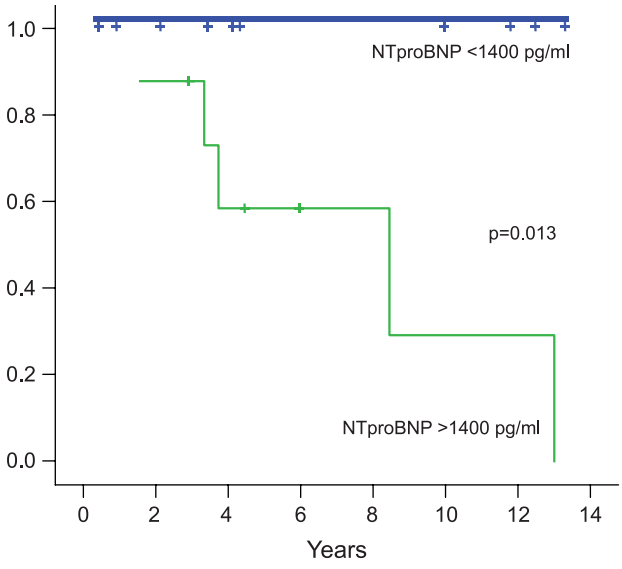

Figure 3. Survival curve according to level of N-terminal pro-brain natriuretic peptide (NT-proBNP).

changes seen in the pulmonary microcirculation closely resemble those found in other forms of severe, non-thromboembolic pulmonary arterial hypertension, which explains why the same medication is given in both categories (I and IV), when patients with chronic thromboembolic disease are not eligible for pulmonary endarterectomy.[9,10] In the present study, the patients with chronic thromboembolic disease had similar outcomes to the other patients, with a mortality of 25% versus 26.3% (p=0.87).

Before 1996, pulmonary hypertension was a fatal illness for which there was no effective treatment. The introduction of new, specific drugs has helped patients to live better and longer. Thus, three epoprostenol registries show survival at 1 year 85-88%, at 2 years 70-76%, at 3 years 63-71%, and at 5 years 55-57%,[11-13] in contrast to the survival rates of patients in the NIH registry who were under conventional treatment. Treprostinil appears to have similar 3-year results.[14] A significant effect on survival is also seen following administration of the non-selective endothelin antagonist bosentan, where the survival of patients with primary pulmonary hypertension under monotherapy ranges from 70-75% at 2 years, with a rate of 71% in the case of patients with systemic sclerosis.[15-17] An even better prognosis has been reported in patients treated with bosentan who suffer from chronic thromboembolic disease.[18]

Around 38% of the patients in this study eventually received treatment with a combination of specific drugs, either because they did not respond to monotherapy, or because of clinical deterioration. In a recent retrospective study that included only patients who had idiopathic pulmonary arterial hypertension and were in NYHA classes III/IV, under monotherapy with bosentan, it was necessary to add prostacyclin to the regimen in around 44% of patients.[19] Patients whose functional class improves to I or II in response to treatment have a significantly better prognosis than those who remain in classes III/IV.[11,12] Similarly, patients who cover ≥380 m on a 6-minute walk test after 3 months' intravenous epoprostenol had better long-term outcomes than those who did not manage this distance.[12] Failure to achieve or maintain these targets with monotherapy may be an indication for combined therapy.

Three major pathways play an important role in the course of pulmonary hypertension: the prostacyclin pathway, the nitric oxide pathway – NO-cyclic guanosine monophosphate (cGMP)-phosphodiesterase (PDE) 5 – and the endothelin pathway.[20] A disturbance of the balance between the vasodilatory/antihyperplastic action of the NO systems and the vasoconstrictive/hyperplastic action of the endothelin system seems to be the key to the onset and progression of the disease. Thus, the modern therapeutic approach targets these three pathways in order to promote the effects of the two former systems and to inhibit the action of endothelin. Based on this pathophysiology, using combined therapy may offer additional benefit by successively targeting the main path-

ways of the disease. Moreover, apart from the additive benefit, specific combinations also have a synergistic effect. The combination of a PDE-5 inhibitor and a prostanoid has shown such an effect via the inhibitory action of sildenafil on both PDE-1 and PDE-5, which mediates the hydrolysis of both cyclic adenosine monophosphate and cGMP.[21] These data suggest that different classes of drugs could beneficially be combined, aiming at different pathophysiological pathways in an attempt to increase the efficacy and improve the outcome.

A number of studies have examined some combinations and others are in progress. The PACES study examined the combination of sildenafil with epoprostenol compared to epoprostenol alone and found an improvement in 6-minute walk performance with the combined therapy.[22] Another study (STEP) compared the combination of bosentan and an inhaled prostanoid (iloprost) with bosentan monotherapy and also found an improvement in 6-minute walk as well as a delay in the clinical deterioration.[23,24] The COMPASS-1 study was the first to examine in detail the haemodynamic effects of the combination of bosentan with sildenafil and showed that the acute administration of oral sildenafil combined with long-term bosentan therapy resulted in a significant reduction in pulmonary vascular resistances.[25] The only study so far of combined therapy that aims to investigate morbidity and mortality is COMPASS-2, which is expected to be completed during 2009 and compares the combination of bosentan and sildenafil with sildenafil monotherapy.

In the present study, patients with an advanced NYHA class, as well as those with elevated NT-proBNP levels, were at increased risk of death. Especially in the case of patients with NT-proBNP levels >1400 pg/ml, their survival was statistically significantly shorter than in those patients with lower levels. The same findings were reported in a recent study, where NT-proBNP levels >1400 pg/ml were a marker of poor prognosis.[26] Brain natriuretic peptide is increased under conditions of right ventricular pressure load and is related to the severity of right ventricular dysfunction, as well as to the mortality of pulmonary arterial hypertension.[27,28] These prognostic indexes —along with others, such as haemodynamic parameters— reflect right ventricular function.

In the NIH registry, the mean survival of patients in NYHA classes I and II was about 6 years, compared with 2.5 years for patients in class III and 6 months for those in class IV.[4] Two large retrospective series have also confirmed the importance of functional class as a prognostic parameter, even during treatment. In addition, in both series, the patients who improved to functional class I or II after 3-17 months of intravenous epoprostenol treatment had a better prognosis than those who remained in classes III and IV.[11,12] All these findings make it clear that emphasis must be placed on early diagnosis of the disease, which will lead to the prompt commencement of therapy. In the early stages, the symptoms are either absent or non-specific, common to other cardiac or pulmonary diseases. This can lead to delays of more than 2 years before diagnosis and the start of therapy.[29] In a recent analysis by the National French Registry it was found that the majority of patients with pulmonary arterial hypertension are diagnosed at advanced stages, since 63% and 12%, respectively, were in NYHA classes III and IV.[30] Similarly, >50% of our patients were in classes III and IV.

Since the 1990s, it has been shown that patients who undergo a vasoreactivity test and have a positive response have a very good prognosis and are eligible for administration of high doses of calcium blockers.[31] In such patients, a 5-year survival rate of 95% has been noted, compared to those who had a negative response to the test and had 55% 5-year survival.[32] Unfortunately, the number of patients who show vasoreactivity is small (~12%)[33] and of those, less than 10% have a stable response to and benefit from the administration of calcium blockers.[34] Similar findings arose from the patients in our own study.

Limitations of the study

This was a retrospective study of patients who suffered from a relatively rare disease. Despite that, the regular follow up in the outpatients' department and the very frequent telephone contacts kept to a minimum the errors that arise in such kinds of study. As stated above, the thorough and complete examination of the patients started after 2002, when the 6-minute walk test became the endpoint for multi-centre studies and when measurement of NT-proBNP became feasible in the hospital. Therefore, the lack of these tests in patients who were diagnosed prior to 2002 could have affected our results. Finally, the drugs used specifically for treating pulmonary hypertension became available in Greece after 1998, in the case of intravenous prostacyclin, and after 2001, in the case of oral endothelin antagonists, with the result that some patients were given medications such as calcium channel blockers without there being any indication ac-

cording to our current state of knowledge; this also may have affected our results.

Conclusions

Pulmonary hypertension is a malignant disease and, despite the significant progress that has been made with respect to our understanding of its pathophysiological mechanisms and treatment, we still have some distance to go before we reach a satisfactory situation. Vigilance is needed, with prompt diagnosis, close monitoring, and on a wider scale, large clinical trials that will help us choose the most suitable kind of therapy in each case, as well as the timing of each treatment administered.

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