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Pulmonary artery pressure matters – how to efficiently improve survival in pulmonary arterial hypertension (RCD code: II-1A.1)

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Abstract

Pulmonary arterial hypertension is a disease characterized by poor prognosis despite treatment. Even in a modern era of pharmacotherapy there is a strong need to further improve survival of patients. The current therapeutic strategies do not offer a real break-through in terms of reducing mortality. In a search for better efficacy of treatment we discuss a strategy based on lowering pulmonary artery pressure as much as possible with epoprostenol in monotherapy or in combination. Epoprostenol with bosentan is an effective tool in achieving this goal. A rapid up-titration regardless of maximum epoprostenol dose achieved gives additional long-term benefit. Practical issues related to such modality of treatment are also discussed. JRCD 2017; 3 (4): 110–115

Key words: pulmonary arterial hypertension, treatment, epoprostenol, outcome

Introduction

Pulmonary arterial hypertension (PAH) (RCD code: II-1A.1–4) [1] is a progressive disease of pulmonary arterial circulation, leading to progressive increase in pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) and results in end-stage right heart failure and death. Decompensated right ventricular (RV) failure carries very high risk of unfavorable outcome and is associated with higher mortality than decompensated left heart failure [2]. Chronically, right ventricle that challenges growing static and pulsatile afterload is a subject of adaptation. This adaptation may take form of compensatory, adaptive remodeling or maladaptive one. The second phenomenon with its mechanical and metabolic phenotype inevitably results in progressive RV dysfunction [3]. Two main factors play an important role in triggering maladaptive changes in RV morphology: hypoxia and increased vascular and perivascular stiffness. A mechanical stimulus in experimental models proves to be one of the key factors, by which cellular proliferation and migration is induced in pulmonary arterial wall imposing subsequently on RV [4]. Vascular and extracellular stiffness is directly linked with pulmonary arterial compliance, a measure of flow volume and pressure in pulmonary circulation that describes pulsatile component of afterload [5]. Indirectly, elevated PAP is responsible for changes in afterload, vascular stiffness and produce excessive proliferation of pulmonary arterial vascular cells [6].

PAH carries a poor prognosis when not treated [7,8]. Enormous progress have been made in the pharmacological treatment of the disease since mid '90s when a prostacyclin-analogue epoprostenol was first introduced [9,10]. Since then, a number of other treatment modalities became available targeting specific pathophysiological pathways involved in disease progression. Current treatment options and strategies are described in 2015 European Society of Cardiology (ESC) / European Respiratory Society (ERS) guidelines for diagnosis and treatment of PAH [11]. In the modern era of pharmacotherapy, the disease became a chronic condition rather than rapidly progressive cureless illness but still, five-year survival rate of the patients is about only 60% [13]. This survival cannot satisfy either patients, their families or physicians. There is an urgent need to redefine treatment strategies or to modify treatment goals in order to improve long-term results even with currently available drugs. To improve the patients' long-term survival,

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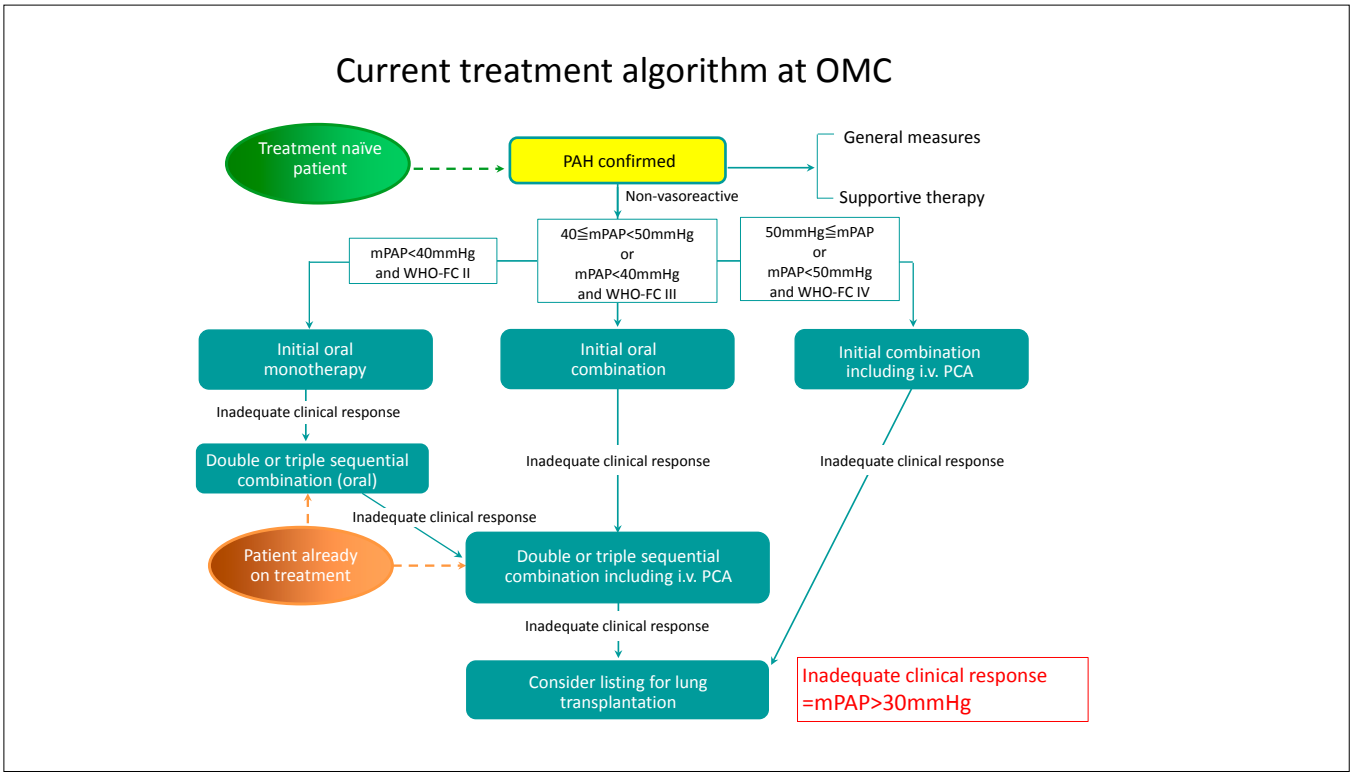

Figure 1. Strategy of pharmacotherapy focused on mean pulmonary artery pressure reduction

suppression of disease progress by lowering mechanical stimulus caused by high pressure to the pulmonary artery would be essential. A focus on how to efficiently minimize afterload not only by reducing PVR but also by substantially lowering PAP in order to improve outcome is an interesting and promising concept.

Treatment goals of PAH

When applying pharmacotherapy, one should take into account pre-specified parameters, so called "treatment goals", that guide therapy and judge it as efficient. These treatment goals, according to current stratification allow to allocate the patient into one of the three groups: of low-, intermediate- and high risk of deterioration with 1-year mortality risk of less than 5%, 5–10% and more than 10% respectively [11]. Currently, treatment goals that itself constitute determinants of prognosis are divided into four main categories: clinical and functional, biochemical, echocardiographic and hemodynamic. These include: clinical signs of right heart failure, a rate of progression of symptoms, absence of syncope, the World Health Organization functional class (WHO-FC), a distance of 6-minute walk test, a result of cardiopulmonary exercise test, N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels, right atrium area, presence of pericardial effusion (echocardiography/cardiac magnetic resonance), right atrial pressure (RAP), cardiac index and mixed-venous saturation taken from right heart catheterization. It is of note, that most of the variables and their cut-off values were chosen based on expert opinion and were only validated for idiopathic-PAH (IPAH) patients. These variables are subject of change and they evolve as the history of PAH treatment evolves and new drugs and strategies are being developed. In 2009 ESC/ERS guidelines [14], hemodynamic prognostic indices included only RAP and CI and echocardiographic prognostic indices included only tricuspid annular plane systolic excursion (TAPSE) and right atrial 2-D area. Similarly, ventilatory equivalent for carbon dioxide has been recently added as an index of unfavorable prognosis obtained from cardiopulmonary exercise test [11].

With growing efficacy of pharmacotherapy, treatment strategies has evolved during last decades from just bridging the patient to lung transplantation (LTx) as the only treatment with acceptable long term survival as was in late twentieth century [15, 16, 17, 18] to more "optimistic" targets, both from the patient's and the clinicians perspective. With the development of new drugs targeting not only prostacyclin pathway but also phosphodiesterase inhibition, endothelin receptor antagonism and activation of guanylate cyclase, this "bridging" strategy was displaced by improving patients' symptoms for as long as possible and maintaining patients' exercise capacity using mono-, sequential combination, up-front combination pharmacotherapy [14, 11]. Nowadays, considering the fact that in real-life population, access for LTx is still limited as well as the long-term survival after LTx has not improved much, being still not satisfactory [19], there is a strong need for alternative strategy to prolong patient's life. Outstanding outcome in a population of patients with IPAH and heritable PAH (HPAH) treated with high doses of epoprostenol, either as monotherapy or in combination with phosphodiesterase inhibitors and/or endothelin-receptor antagonists gives some hope for the future [26]. In this patients' cohort, decrease in PAP was the independent determinant of more than ten years survival. PAP, as the therapeutic target, emerges as

Table 1. Suggested epoprostenol dosage regimen proven to lower PAP

schedule of treatment	dosing considerations	additional comments
initiation of epo	0.2 – 2.0 ng/kg/min. 0.2 – 1.0 ng/kg/min/day depending on the impairment of patient's hemodynamics after achieving the stabilization of hemodynamics, increment of epoprostenol could be increased to 1ng/kg/min/day until the dosage reaches 20 ng/kg/min.	dobutamine should be used to keep venous saturation > 60%.
initial hospitalization dose at discharge	20 ng/kg/min.	
further up-titration within 1 year of therapy	8 ng/kg/min/month for the first month 4–6 ng/kg/min./month for following three to four months 2 ng/kg/min/month until mPAP becomes less than 30 mmHg	
upper-limit of dose	65 ng/kg/min at 1 year 90 ng/kg/min at 2 year	in most patients, 65 to 85ng/kg/min of epoprostenol is enough to decrease mPAP

an interesting and hopeful parameter to focus on, when planning and realizing treatment strategy.

Epoprostenol as the key drug to decrease pulmonary artery pressure

There is no consensus on recommended dose-regimen of epoprostenol, although several algorithms have been proposed. Oudiz and Farber reported mean maintenance dose of epoprostenol being 30–39 ng/kg/min in PAH patients [20]. Sitbon et al. utilized even smaller doses of epoprostenol (mean 19.6 ng/kg/min) as a part of the triple-combination strategy [21] and recommended dose of epoprostenol according to Mc Laughlin et al. was 25–40 ng/kg/min [22]. It is noteworthy, that all the algorithms mentioned above recommend not more than moderate doses of the drug to be administered chronically while there are data supporting higher doses and also more aggressive dose-escalation. It was already reported, that treatment with 100 ng/kg/min of epoprostenol for an average of almost 4 years in patients with IPAH/HPAH was associated with a pronounced reduction in mean PAP and PVR by 29% and 68%, respectively [23]. Although this was a retrospective analysis of a single center experience, it provided for the first time an insight into the potency, effectiveness and tolerance of high doses of epoprostenol. This dose-regimen was in counter position to the experience of the others. Side-effects of the drug were acceptable, as well as long-term adherence to therapy. This high-dose experience shows not only a perspective for achieving more than a short or middle-term reduction in severity of symptoms followed by a substantially better improvement in long-term prognosis but also a true break-through in the fight with the disease from the perspective of long-term survival.

High doses of epoprostenol may induce too high cardiac output (CO) state with excessive increase of mixed-venous saturation. This phenomenon was described earlier by Rich and McLaughlin [24] and according to the authors, it was associated with the necessity to stop the therapy with the drug. This adverse effect of epoprostenol has been well recognized. However, according to the authors' experience, occurrence of high CO failure is very rare. The key strategy to avoid high CO state according to our experience is to up-titrate at first quickly and then slowly and to follow-up patients closely in order to adjust doses of epoprostenol individually. When CO is elevated too much, the pace of up-titration should be decreased. Within those precautions the phenomenon of hyperkinetic circulation is no longer clinically significant.

Endotelin receptor antagonist bosentan proved to have important synergistic effect to epoprostenol in terms of decrease of PAP and PVR [25]. Significant reduction of dose of epoprostenol is obtainable without compromising the hemodynamic effect of therapy when adding bosentan. It is interesting, that the acute hemodynamic effect of bosentan on top of epoprostenol is detectable as early as in 48 hours [25]. Bosentan is a very convenient drug as an add-on therapy in achieving further substantial decrease in PAP in PAH patients treated with epoprostenol.

Lowering PAP to improve survival

To achieve an excellent long-term survival it is crucial to start treatment before severe RV failure develops. The risk factors for mortality in univariate analysis are B-type natriuretic peptide (BNP), RAP, and arterial blood saturation (SpO_2) [26]. Patients with a BNP level ≥ 350 pg/mL and SpO_2 ≤ 96% at baseline had a significantly worse prognosis. Also, the cut-off value for RAP of 10 mmHg in receiver operating characteristic (ROC) curves analysis is of importance but it cannot be used as a predictor of prognosis [26]. All these data suggest, that patients with IPAH/HPAH cannot be treated successfully after development of severe heart failure, even at a referral center and with a use of parenteral prostanoids. Regarding the treatment effect, a decrease in mean PAP (mPAP) below 42.5 mmHg during treatment is a most important determinant of good prognosis in epoprostenol treated individuals [26]. In a population treated to achieve as low PAP as possible, unexpectedly good long-term survival of IPAH/HPAH patients were observed. 1-, 5-, and 10-year survival rates of these patients were: 98%, 96%, and 78%, respectively. In this study cohort, 75% of

Evolving perspectives of treatment goals in pulmonary arterial hypertension
- bridging to lung transplantation
- maintaining patient's exercise capacity as long as possible
- obtaining sufficient decrease of pulmonary artery pressure

Figure 2. The evolution of treatment goals in pulmonary arterial hypertension

patients received epoprostenol and the average epoprostenol dose at the time of hemodynamic improvement was 80 ng/kg/min. A substantial decrease of mean PAP and PVR by 44% and 67% respectively was noted [26]. It is worth mentioning, that a 10-year survival of patients in whom a decrease in mPAP < 42.5mmHg was achieved was 100%. This cut-off value could probably serve as a "goal" of therapy from a hemodynamic point of view and this goal should be reached as soon as possible.

To achieve the decrease in mPAP efficiently, it seems to be crucial to avoid exertional rises in PAP. Physical activity would promote elevation of PAP and the exertional rise in PAP might be proportional to baseline pulmonary pressure. During the initial phase of treatment, PAP is not yet decreased and every transient rise in pressure promotes further vascular remodeling, which might inhibit the achievement of the treatment goal. Patients should be advised to avoid exercise. Exactly this strategy was implemented in cohorts of patients described herein [27,23,26].

The second issue is combination therapy with oral drugs. Bosentan is very effective in lowering epoprostenol dose needed to achieve desired low level of PAP instead of the strategy utilizing high doses of epoprostenol as monotherapy [25]. Moreover the retrospective study of 141 patients with IPAH/HPAH showed, that the use of endothelin receptor antagonists and intravenous epoprostenol was related to better survival in the univariate analysis [28]. On the contrary, phosphodiesterase 5-inhibitors did not prove to add any effect to epoprostenol in terms of survival so their role when combining with epoprostenol is of less importance.

Obtaining near normal PAP as soon as possible

The significance of lowering PAP in guiding pharmacotherapy has not been widely described so far. On the contrary, long-term follow-up data show significant impact of therapy on PVR and CI rather than on PAP. The same applies when assessing the prognostic impact of changes in these parameters after initiation of targeted therapy [29]. Possibly, this reflects suboptimal dosing and/or timing of escalation of therapy. PVR and CO are more prone to modification with targeted therapy and PAP decreases with a delay and along with further escalation of therapy. However, a magnitude of decrease in PAP and time needed to reach this goal seems to be important. In the recent report, excellent survival of cohort of patients in whom a substantial decrease in PAP was achieved with a rapid escalation of dose of epoprostenol [27]. The rapid increase was defined as escalation of the dose of epoprostenol to greater than 20 ng/kg/min during initial 3 months of treatment and to at least 40 ng/kg/min within the first 12 months. This treatment regimen resulted in statistically significant reduction of average mean PAP (51.6 vs 40.7, $p<0.05$) when compared with slow-increase regimen patients. As a result, the 9.5-year survival rate was significantly better in patients in the rapid increase group compared with the slow increase group (100% vs 64%, $p=0.022$). There were no deaths in the rapid increase group (0/16 pts) but 39% of patients from slow-increase group died during observational period (9/23 pts). The dose of epoprostenol was significantly higher in survivors compared to non-survivors at 3 months after initiation of therapy and remained so till 1.5 year [27] but both groups were similar in terms of maximum dose of epoprostenol. A pace of up-titration of epoprostenol is of importance but not the final dose reached. There was also no difference in a use of concomitant medications and baseline mean PAP. Also baseline parameters: age, gender, etiology of PAH (IPAH or HPAH), WHO functional class, heart rate, 6-min walking distance, plasma BNP level, hemodynamics and interval between diagnosis and treatment initiation were not different between groups. These result would indicate, that the acute impact of potent pulmonary vasodilator/vasodilators is necessary to stabilize naive patients during short term and it would help to obtain good follow-up results either on mono- and combination therapy. In the early phase of treatment a simple vasodilatory property of the drug might be of main importance. Rapid and sufficient vasodilation caused by increasing doses of epoprostenol would allow to diminish deleterious impact of high PAP, that would promote pulmonary remodeling and right ventricular pressure overload.

How to use epoprostenol efficiently – practical issues

Although the rate of up-titration with epoprostenol varies from patient to patient, it is possible to settle some general rules. The starting dose of epoprostenol ranges 0.2 – 2.0 ng/kg/min, and dosage is up-titrated with daily increment of 0.2 – 1.0 ng/kg/min depending on the patient's hemodynamics. If mixed venous saturation drops below 60%, usage of dobutamine support should not be hesitated. After achieving the stabilization of hemodynamics, daily increment of epoprostenol could be increased to 1.0 ng/kg/min until the dosage reaches 20 ng/kg/min. A recommended dose of epoprostenol at discharge is about 20 ng/kg/min. Increment of epoprostenol after discharge is 8 ng/kg/min/month for the first month and 4-6 ng/kg/min/month for the following three to four months. Then, an increase of 2 ng/kg/min/month until mPAP becomes less than 30 mmHg is advised. A dose of about 65 ng/kg/min of epoprostenol at 1 year after the initiation of therapy is usually reached. In most patients, 65 to 85 ng/kg/min of epoprostenol is enough to sufficiently decrease mPAP (see Table 1).

A caution might be needed when up-titrating epoprostenol in order to detect signs of hyperkinetic circulation. Too much elevated mixed venous saturation is a good marker of the condition and

thus, regular measurement of venous saturation during up-titrating the dose of epoprostenol would be recommended.

The strategy of introducing pharmacotherapy, that is focused on the reduction of PAP should be based on baseline mean PAP and patient's functional status. In naive patient with relatively mild elevation in PAP and preserved functional capacity (mPAP not more than 40 mmHg and WHO-FC II), initial oral monotherapy would be recommended. If a naive patient is in WHO-FC III and/or his mean PAP is between 40 and 50 mmHg, upfront oral combination therapy would be recommended. In treatment of naive patients, in whom mean PAP reaches or exceeds 50 mmHg or functional status is in class IV, parenteral prostanoids should be the first-line treatment in combination with oral drugs, preferably with bosentan or macitentan. With this strategy a close monitoring of therapeutic effect is mandatory in order not to delay further escalation of treatment. A bed-side analysis of changes in PAP with echocardiography might be useful as a surrogate for direct hemodynamic measurements. Patients not responding in short-term with a reduction of PAP by oral therapy should then be treated with double or triple therapy including parenteral prostanoids. Early introduction of parenteral prostanoids after only one week trial of oral mono or combination therapy in patients primarily allocated to oral therapy would be recommended, if oral therapy is not successful in reducing mPAP below 30 mmHg in patients with baseline mPAP between 40 and 50 mmHg (see Figure 1).

Management of side effects of epoprostenol and general measures

Escalation of epoprostenol dose is often associated with side-effects related to vasodilatory properties of the drug like flushing and headache. This happens relatively often when epoprostenol is combined with phosphodiesterase inhibitors. In order to alleviate these complications, it is sometimes necessary to decrease or stop phosphodiesterase inhibitors.

Patients exposed to epoprostenol are prone to a spectrum of skin reactions like rush, subcutaneous oedema, dermatitis or eczema localized at different areas of the body. These reactions are usually localized at thorax, abdomen and extremities with various manifestations. Treatment with antihistaminic drugs and with topical ointments are helpful in relieving the symptoms.

Epoprostenol treatment is relatively often related with drop in platelet count. Initial drop in platelet count usually starts in one week following introduction of the drug but usually does not necessitate a modification of up-titration procedure. This usually happens at the beginning of treatment and it may be of clinical importance when the platelet count drops below 30 000/µl. In most cases a return to near-normal values occur spontaneously and patients present acceptable values of platelets on discharge. During long-term follow-up, platelet count may decrease again, especially when further up-titration is needed. In general values of 100 000/µl are expected in this population and hemostasis is well preserved. Up-titration of epoprostenol should not be hesitated even if low platelet count is present. A need for interruption of up-titration or even down-titration is a rare occasion except of patients with porto-pulmonary hypertension. A different strategy should be taken into account in cases with a positive result of the test for a presence of antiplatelet antibodies. Methylprednisolone treatment is sometimes necessary to prevent further drop in platelet count. Occasionally, there is a need to replace epoprostenol with treprostinil in order to achieve a normalization of the platelet count.

Anticoagulants are not advised to combine with epoprostenol, that possesses itself a strong antiplatelet activity. There are data showing worse survival when patients treated with epoprostenol are chronically anticoagulated [28].

Oxygen therapy is recommended for at least first 6 weeks of treatment assuming the fact that the nocturnal deoxygenation is common in PAH patients. Desaturation promotes rise in PAP.

A strong recommendation of avoiding excessive physical activity should be given to patients especially at the beginning of therapy. This strategy helps obtain a sufficient reduction in PAP. A prolonged hospitalization covering the whole period of initial up-titration of epoprostenol is useful in efficiently reducing patient's daily-life physical activity. Females rather than males seem to comply with this recommendation more effectively.

Summary

PAH has been a devastating disease with poor prognosis. In a modern era of pharmacotherapy there is a strong need to further improve survival of patients. The current therapeutic strategies do not offer a real break-through in terms of reducing mortality. Treatment algorithms and treatment goals need to be redefined in a search for better efficacy. The strategy to lower PAP as much as possible with available drugs proves to be efficient. The cut-off value for better prognosis could be set up at 42.5 mmHg regarding to our experience. Epoprostenol with bosentan are an effective tool in achieving this goal. There is strong evidence that this strategy should be implemented if mPAP reaches 50 mmHg regardless of functional status of the patient and even with lower values in severely deteriorated individuals. Addition of parenteral prostanoids should be implemented shortly after failure of oral therapy and the up-titration of epoprostenol proved to give better long-term results with rapid rather than slow increase strategy regardless of maximal dose achieved. A further, substantial reduction in 10-years mortality could be achieved when applying rules of treatment allocation and escalation as described above.

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