Medical therapy of pulmonary arterial hypertension

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Primary pulmonary hypertension (PPH) has been categorized in the diagnostic classification of the World Health Organization[1] together with other conditions with similar pathologic and clinical findings like pulmonary hypertension associated with connective tissue diseases, HIV infection, portal hypertension, and congenital systemic-to-pulmonary shunts[2]. All these conditions, defined as pulmonary arterial hypertension (PAH), share a similar therapeutic strategy that is aimed at two related pathophysiologic targets: a) the progression of the pulmonary vascular disease, and b) the progression of right heart failure. The therapeutic options available for PAH patients are: 1) oral anticoagulation, 2) Ca^{++} channel blockers, 3) diuretics and digoxin, 4) prostanoids, 5) balloon atrial septostomy, 6) transplantation. In general, the first two resources are indicated in NYHA functional class I-II patients while the resources 3) to 6) are progressively utilized in the more advanced cases (NYHA functional class III-IV).

Oral anticoagulation is the first treatment that has proved to increase survival in PPH patients in both retrospective and prospective clinical trials[3,4]. The suggested INR is in the range of 1.5 to 3.0. All patients with PAH should start oral anticoagulation as soon as the diagnosis is made provided the exclusion of the usual contraindications. In particular, oral anticoagulation is contraindicated in the case of a low platelet count (< 100 000/mm^3), frequent and uncontrollable hemoptysis and advanced esophageal varices.

Ca^{++} channel blocker drugs are indicated only in the minority of patients with PAH (15-30%) that show a positive response to acute pharmacological challenge. This test should be performed in all PAH patients to identify subjects with residual pulmonary vasoreactivity[5] assessed by a reduction of 15-20% of mean pulmonary artery pressure. Tests should be performed in experienced centers by the administration of increasing doses of one of the following compounds: adenosine, prostacyclin, nitric oxide. Chronic treatment with high doses of Ca^{++} channel blockers has proven to be effective only in acute vasoreactive patients[4] while it may be harmful in the other cases (70-85% of all patients).

Diuretics are indicated in the presence of increased jugular venous pressure that is usually associated with liver tenderness and enlargement and sometimes with ascitis and ankle edema. The dose of loop diuretics should be titrated to maintain an ideal body weight; the addition of an antialdosteronic drug can reduce the rate of ipokaliemia occurrence. Digoxin improves hemodynamics and neurohormonal activation in PPH patients[6] and it is usually indicated in the presence of sinus tachycardia, supraventricular arrhythmias and concomitant use of Ca^{++} channel blockers. Oxygen treatment is indicated in cases of hypoxemia at rest, on exercise or during sleep.

The use of prostanoids in PPH patients started almost 20 years ago but only in 1996 the results of a randomized clinical trial were published, showing an improvement of survival after 12 weeks in NYHA functional class III-IV patients treated with continuous intravenous administration of epoprostenol added to conventional treatment[7]. The survival benefit is persistent even after 3 years[8] and it is accompanied by an improvement of hemodynamics, quality of life and functional capacity[7,8]. Also the comparison with lung transplantation seems to

favor prostacyclin treatment[9]. The continuous intravenous administration of prostacyclin requires tunnelized catheters and portable pumps and it is very expensive. Possible side effects are sepsis and occlusion of the infusion line.

A controlled clinical trial on the use of subcutaneous prostacyclin analogue (UT-15) administered by small portable pumps has recently been concluded and the definitive data will be presented in Autumn 2000. Preliminary reports show positive results on hemodynamics and functional capacity when compared to placebo. Currently, two additional controlled clinical trials with inhaled (iloprost) and oral (beraprost) prostacyclin analogues are ongoing and results will be available in Autumn 2001.

The use of balloon atrial septostomy is based on the demonstration that an intra-atrial defect, allowing right-to-left shunting in the setting of severe pulmonary hypertension, might be of benefit[10]. The procedure is performed under mild sedation in centers experienced in both transseptal catheterization and pulmonary hypertension. Balloon atrial septostomy is indicated as a palliative procedure in the case of failure or unavailability of prostacyclin treatment in NYHA functional class III-IV patients.

The results of lung and heart-lung transplantation in PPH patients are still not optimal. In fact, the overall survival after lung transplantation for all indications is 70, 62 and 55% after 1, 2 and 3 years, respectively[11]. Moreover, PPH diagnosis represents an additional risk for 1-year mortality and the length of the waiting list further reduces the chance of benefiting from this procedure. For these reasons double lung and heart-lung transplantation are indicated in the case of failure of maximal medical therapy including prostacyclin.

Future perspectives on the treatment of PHA are based on the results of ongoing trials on subcutaneous, inhaled and oral prostacyclin analogues. Endothelin receptor antagonists are also being actively investigated by recently started controlled clinical trials in PAH patients. Other substances like pulsed nitric oxide treatment, L-arginine, elastase inhibitors and Kv-channel openers are in an earlier stage of study.

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