The Cardirlogy 2(1) : 29-32, 2006
© Medwell Online, 2006

Management of Pulmonary Arterial Hypertension Secondary to Ventricular Septal Defect in Adults: Role of Combination Therapy

Imren Yildirim and Erer Dilek
Department of Cardiovascular Surgery Medical Faculty Gazi University
Gazi Hospital Besevler 06500 Ankara Turkey

Abstract: Pulmonary hypertension due to left to right shunts is a challenging problem in decision making for corrective surgery. Pre-operative cardiac data evaluation with proper medication convey better outcomes in those patients. We describe a succesful combination therapy in a paient with severe pulmonary hypertension prior , during and following ventricular septal defect closure.

Key words: Pulmonary arterial, ventricular septal, combination therapy

INTRODUCTION

Ventricular Septal Defects (VSD) are very common in children but much rarer in adults because the majority either close spontaneously or are operated. The persistent VSD are usually membranous with a small or moderate shunt without pulmonary hypertension.

Closure of a large Ventricular Septal Defect (VSD) in adults with elevated pulmonary vascular resistance is also associated with significant morbidity and mortality. The natural history of large, non-restrictive VSD with PHT after surgical closure has been documented[1]. The demonstration of reversibility of PHT using inhaled (hyperoxia) or intravenous vasodilators during cardiac catheterization has remained the cornerstone in the selection of adults for surgical repair. Furthermore, a positive response in terms of decrease of pulmonary vascular resistance in the catheterization laboratory serves the dual purpose of selecting the patients who will most likely still benefit from repair and offering a valuable therapeutic tool to manage rebound crises of postoperative PHT in the same patients (responders to vasodilatators), should these occur.

Various pharmacologic agents including prostocyclin analogs, adenosine, calcium channel blockers (CCB), Sildenafil, endothelin receptor antagonists (ERA), phosphodiesterase inhibitors and nitric oxide (NO) have been shown to reduce pulmonary artery pressure in pulmonary hypertensive patients[2,3,4]. There are several possible future treatment concepts that may warrant clinical investigations (serotonin transport inhibitors, potassium channel blockers, etc.)[5,6].

Iloprost, which is a stable prostacyclin analogue, seems to be an alternative promising approach in addressing the problem of post-cardiopulmonary by-pass right ventricular decompensation, particularly in pulmonary hypertensive cases due to congenital heart defects. It is available for intravenous, oral and aerosolized administration. Inhaled therapy delivers drugs to ventilated alveolar units where local pulmonary arteries vasodilate, thereby enhancing ventilation-perfusion matching. Iloprost improves functional class, exercise capacity and pulmonary hemodynamics in open and randomized studies, with side effects of flushing, headache and cough in some patients[2]. Either inhaled and intravenous forms have been shown to have an equally pulmonary vasodilatoreffect in primary pulmonary hypertension in a study conducted by Opitz *et al.*[7].

Sildenafil inhibits a particular phosphodiesterase present in lung tissue. This leads to increased intracellular concentrations of the second messenger cyclic GMP. This presumably accounts for its ability to reduce pulmonary pressure and vascular resistance in patients with pulmonary hypertension. In addition, sildenafil potentiates the pulmonary vasodilation from inhaled nitric oxide or from prostacyclin analogues[8].

Studies have shown that inhaled NO is a vasodilator in a variety of pulmonary hypertensive states, supporting its use in pulmonary vasodilator testing and acute pulmonary hypertensive states post-operatively[2]. Beck and associates concluded that inhaled NO induces substantial reductions in mPAP and increases in both cardiac index and systemic blood pressure in patients displaying elevated pulmonary hemodynamics after high-risk cardiac surgery. NO is, therefore, a useful adjunct in these patients in whom acute pulmonary hypertension threatens right ventricular function and hemodynamic stability[9].

Corresponding Author: Imren Yildirim, Department of Cardiovascular Surgery Medical Faculty Gazi University Gazi Hospital Besevler 06500 Ankara Turkey

Table 1: Pre-operative catheterization data on admission

	PAP*	PCWP*	Aortic P*	Qp**	Qs**	Qp/Qs	PVR***	SVR***
Admission	105/45	12.5	100/55	2.6	1	2.6	6.32	13.62

Table 2 : Results of oxygen challenge test

	PAP*	PCWP*	Aortic P*	Qp**	Qs**	Qp/Qs	PVR***	SVR***
Challenge test	91/36	10,6	95/60	2,3	1	2.3	5.96	12.56

* : mmHg ** : lt/min/m^2 *** : wood unit

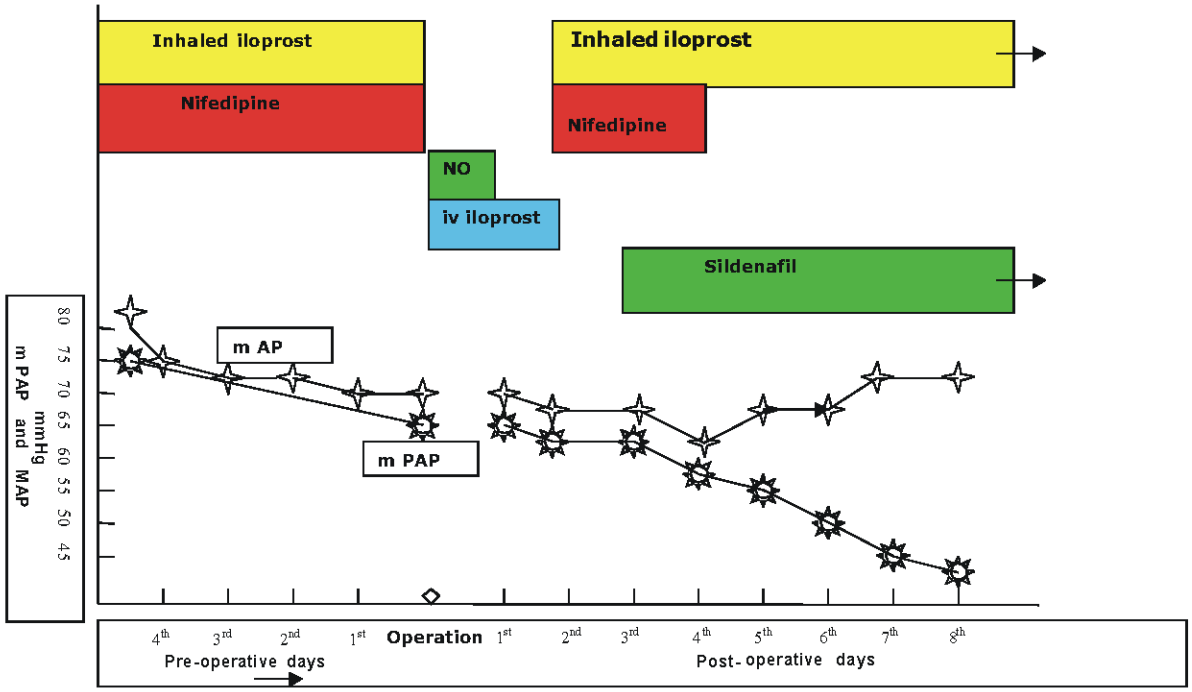

Fig. 1: Drug and mPAP relations

We describe a successful combination therapy in a high risk adult patient with elevated PAP due to VSD He recieved pre-operative; inhaled iloprost, CCB (Nifedipine), intra-operative ; inhaled NO and intravenous iloprost , early in post-operative ; inhaled NO, intravenous iloprost and CCB , inhaled iloprost and Sildenafil in late post-operative period. Therapy went on with inhaled iloprost and Sildenafil.

Case: A 31 years old man with symptoms of fatigue and dyspnea (NYHA class III) admitted for VSD closure. Cardiac catheterization revealed a perimembranous inlet VSD, elevated PAP, PCWP, Qp/Qs ratio and PVR. PAP and PVR responded to oxygen therapy during catheterization. Data was shown in Table 1 and Table 2. His hematocrit level on admission was 45 %.

Inhaled iloprost and Nifedipine were initiated prior to surgery (5 days) with doses of 100 mcq/day , 60 mg/day, respectively.

During operation a catheter was advanced into pulmonary artery for either delivering i.v. iloprost and continous PAP measurement. Initial measurements were found to be lower (90/52/67 mmHg) compared with those of catheterization. NO (10 ppm) and i.v.iloprost (2 ng/kg/min) were initiated before cardiopulmonary by-pass (CPB) and continued through operation. The operation was carried out with standart fashion and VSD was closed with endo-patch via right atriotomy.

Weaning from CPB was uneventful and intraoperative TEE proved adequecy of VSD closure.

In early post-operative period, the pateint recieved NO and i.v. iloprost at same doses until extubation. Following operation, NO was discontinued 24 hours later and the patient was extubated. Methaemoglobinaemia was screened closely and no clinical evidence of toxicity was observed. He recieved i.v. iloprost for 48 hours which was substituted with inhaled form. At the same time, Nifedipine (60 mg/day) was initiated again. Since , the

pulmonary artery pressure catheter was withdrawn in 3rd post-operative day, PAP measurements were done with echocardiography daily. Sildenafil (50 mg/day) was started in 3rd post-operative day. CCB was discontinued in 5th post-operative day because the patient developed hypotensive attacks. Drug and mPAP relations were demonstrated in Fig. 1. The post-operative follow-up was uneventful and the patient was discharged from the hospital within the normal timeframe and prescribed inhaled iloprost 100 mg/day and sildenafil 50 mg/day. Consequent mPAP was measured 40 mmHg.

DISCUSSION

Combination therapy is an attractive option to address the multiple pathophysiological mechanisms that are present in pulmonary hypertension. Combination therapy can be pursued by the simultaneous initiation of two (or more) treatments or by the addition of a second (or third) treatment to a previous therapy that may be considered insufficient. A combination of drugs with distinct mechanisms of action may have additive or synergistic effects in severe PAH. Acute haemodynamical effects of combined therapies have been reported[10].

It is usually accepted that a vasoconstrictive factor is involved in PAH. However, pure vasodilators, such as calcium channel blockers, have so far provided little or no beneficial effects on survival in the vast majority of patients, presumably because the pulmonary arteriopathy characteristic of PAH includes fibrotic and proliferative changes that predominate over vasoconstriction[10]. So far, side effects such as hypotension can develop and deteriorate clinical condition, particularly in combined therapy of PAH. Same was observed in our patient in 4th post-operative day where sildenafil was added to combination. Previously, since our patient manifested an acute response to vasodilatator challenge, we thought that CCB might have reduced PAP and PVR with inhaled iloprost. As further mPAP measurements and clinical discomforts were found to be lower with sildenafil , we decided to go on with it.

Treatment of postoperative pulmonary hypertension with IV pulmonary vasodilators is hampered by the lack of selectivity. Vasodilator therapy is difficult owing to systemic side effects and pulmonary ventilation-perfusion mismatch. Inhaled iloprost appears to be a selective pulmonary vasodilator and may be effective in the initial treatment of PH and the improvement of RV performance in the pre and post-operative operative settings[11].

Inhaled iloprost has been well tolerated in our patient and made prominent reduction with sildenafil combination following VSD closure, unlike pre-operative period where it had been initiated with CCB treatment.

Oral phosphodiesterase type-5 inhibitor sildenafil increases and prolongs the vasodilatory action of inhaled nitric oxide and aerosolised iloprost. These promising acute effects have encouraged us to use chronic combination therapy in PAH secondary to left to right shunt.

Inhaled nitric oxide, even in a low dosage, was a potent and selective pulmonary vasodilator in patients with congenital heart disease complicated with pulmonary hypertension. However it has some side-effects such as methaemoglobinaemia which should be screened closely. No clinical evidence of toxicity was seen with the administration of the inhaled nitric oxide in our patient. Long-term infusion of nitric oxide solution is technically feasible but does not effectively reverse chronic pulmonary hypertension. The failure of infused NO to reduce pulmonary hypertension is explained by the fact that the inactivation of NO by haemoglobin is much faster than anticipated[12]. NO and combination with i.v. iloprost during mechanical ventilation of our patient yielded uneventful weaning from cardiopulmonary by-pass.

Opitz *et al.*[7] concluded that both forms of inhaled and intravenous iloprost have been shown to have an equally pulmonary vasodilator effect in primary pulmonary hypertension. We believed that optimum iloprost delivery during operation and mechanical ventilation could be achieved with intravenous route because of technical difficulties with NO delivery.

Most experts recommend that severe NYHA functional class IV patients in an unstable condition should receive continuous intravenous epoprostenol. Aside from this dramatic situation, first-line therapy in NYHA functional class III patients may include endothelin-receptor antagonists or less invasive prostacyclin analogues. Since ERAs are not avaliable in our country, we could not use this class of therapy but a reasonable reduction in mPAP has been achieved with avaliable ones.

We suggest that any patient who responded to challenge test should be treated with currently approved therapies prior to surgery as long as possible, at least 5 days (as it was proved in our study). Such conservative medication will lower the risk for surgery and provide better outcome for total correction of left to right shunts with pulmonary hypertension. Our patient was strictly advised to come controls weekly and we will decide on therapy which we will go with in future. As need for combination decreases, we think to discontinue inhaled iloprost initially because of difficult administration (time consuming and patient discomfort) and cost.

As head-to-head comparisons of currently approved therapies are not available, the choice of initial treatment will depend on local experiences, underlying causes and administrative regulations, as well as on the clinical context and patient's preference. We described our successful experience with combination therapy in an adult patient who had challenged pulmonary hypertension developed secondary to VSD. However, both initial or adjunct combined therapy provides additional clinical benefits to patients with severe pulmonary arterial hypertension warrants further investigation.

REFERENCES

1. Blackstone, R.E., J.W. Kirklin, E.L. Bradley, J.W. Du Shane and A. Applebaum, 1976. Optimal age and results in repair of large ventricular septal defects. J. Thorac Cardiovasc Surg., 72: 661-679.
2. Micheal D McGoon, 2004. Medical treatment of pulmonary hypertension in 2004. Business briefing: US Cardiology, pp: 1-7.
3. Morgan, J.M., D.G. McCormack, M.J. Griffiths, C.J. Morgan, P.J. Barnes and T.W. Evans, Adenosine as a vasodilator in primary pulmonary hypertension. Circulation, 84: 1145-1149.
4. Rich, S., E. Kaufmann and P.S. Levy, 1992. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J. Med., 327: 76-81.
5. Marcos, E., S. Adnot, M.H. Pham, A. Nosjean, B. Raffestin, M. Hamon and S. Eddahibi, 2003. Serotonin transporter inhibitors protect against hypoxic pulmonary hypertension. American Journal of Respiratory and Critical Care Medicine, 168: 487-493.
6. Fukuse, T., T. Hirata, M. Omasa and H. Wada, 2002. Effect of adenosine triphosphate-sensitive potassium channel openers on lung preservation. Am J Respir Crit Care Med., 165: 1511-5.
7. Opitz, C.F., R. Wensel, M. Bettmann, R. Schaffarczyk, M. Linscheid, R. Hetzer and R. Ewert, 2003. Assessment of the vasodilator response in primary pulmonary hypertension. Comparing prostacyclin and iloprost administered by either infusion or inhalation. European Heart J., 24: 356-365.
8. Trachte, A.L., E.B. Lobato, F. Urdaneta, P.J. Hess, C.T. Klodell, T.D. Martin, E.D. Staples and T.M. Beaver, 2005. Oral sildenafil reduces pulmonary hypertension after cardiac surgery. Ann Thorac Surg., 79: 194-7.
9. Beck, J.R., L.B. Mongero, R.M. Kroslowitz, A.F. Choudhri, J.M. Chen, J.J. DeRose, M. Argenziano, A.J. Smerling and M.C. Oz, 1999. Inhaled nitric oxide improves hemodynamics in patients with acute pulmonary hypertension after high-risk cardiac surgery. Perfusion, 14: 37-42.
10. Humbert, M., O. Sitbon and G. Simonneau, 2003. Novel therapeutic perspectives in pulmonary arterial hypertension. Eur Respir J., 22: 193-194.
11. Theodoraki, K., P. Rellia, A. Thanopoulos, L. Tsourelis, D. Zarkalis, P. Sfyrakis and T. Antoniou, 2002. Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass. Can J. Anaesth, 49: 963-7.
12. Hampl, V., M. Tristani-Firouzi, D.P. Nelson and S.L. Archer, 1996. Chronic infusion of nitric oxide in experimental pulmonary hypertension: Pulmonary pressure-flow analysis. Eur Respir J., 9: 1475-1481.