Eur Respir J 1998; 12: 263–264
DOI: 10.1183/09031936.98.12020263



European Respiratory Journal
ISSN 0903 - 1936

***EDITORIAL***

# Vasodilators in the treatment of primary pulmonary hypertension

E.K. Weir, B. Schremmer

The use of vasodilators to reduce vascular resistance is over a hundred years old. BALFOUR [1] recommends the use of nitrites as vascular stimulants "which dilate the peripheral vessels (arterioles) and so promote the flow blood". In the case of primary pulmonary hypertension (PPH), vasoconstriction is one of three factors that combine to increase resistance to blood flow through the lungs. The other two being thrombosis *in situ* and intimal proliferation of the small pulmonary arteries. In the absence of contra-indications, anticoagulation is appropriate in PPH patients [2, 3]. Although intimal proliferation is probably the most important element in PPH, our ignorance of the pathophysiology has, to this point, prevented the development of an effective treatment directed against cellular proliferation. Any success that there has been in this regard has been secondary to the use of agents thought primarily to be vasodilators.

Vasodilators have been tried in the management of PPH since the use of tolazoline in 1951 [4]. The recent resurgence of interest started with reports of the efficacy of diazoxide [5] in 1978 and hydralazine [6] in 1980. At the time of the National Institute of Health (NIH) Registry on PPH (1981–1985), 12 different vasodilators were reported to have been used acutely to try to determine how much vasoconstriction contributed to the pulmonary hypertension [7]. Fortunately, the number of agents administered acutely as a trial of responsiveness has diminished considerably. In most centres the choice now is between adenosine (*i.v.*), prostacyclin (*i.v.*), calcium channel blockers (CCB; *p.o.*), and inhaled nitric oxide.

At present, long-term "vasodilator" treatment options are CCB (*p.o.*) or constant infusion of prostacyclin (*i.v.*). Experience with CCB dates back to 1983 [8]. Subsequent work by RICH and coworkers [9, 10] indicates that rather less than one-third of PPH patients will have an acute response to CCB (>20% reduction in pulmonary artery pressure and resistance). The majority of these responders will maintain the haemodynamic improvement during long-term follow-up. Those who do not respond acutely are best treated with prostacyclin or lung transplantation. Prostacyclin treatment carries the risk of septicaemia and accidental interruption of infusion, but has been remarkably effective, even in patients who showed no initial, acute vasodilator response [11–13]. It seems likely that prostacyclin is having effects in addition to vasodilatation, possibly through inhibition of cellular proliferation or of platelet activation.

Given the relative ease of treating those patients who respond acutely to vasodilators with CCB, how can they be identified? There is nothing in the duration of their symptoms, clinical presentation or baseline haemodynamics to indicate which patients will respond. In a paper in this issue of the European Respiratory Journal, SITBON *et al.* [14] report a comparison of the acute haemodynamic responses to inhaled nitric oxide and to high-dose oral CCB (nifedipine or diltiazem) in 33 consecutive PPH patients. Of these patients, ten showed a fall in both mean pulmonary artery pressure and total pulmonary resistance of >20% after inhaled nitric oxide. Nine of the 10 patients also responded acutely to CCB. The other 23 patients failed to respond to either nitric oxide or CCB. Consequently in this series, there were no patients who responded to CCB who did not also respond to nitric oxide. If this is confirmed in a larger series, nitric oxide will be the agent of choice to determine which patients would be candidates for long-term CCB treatment. The administration of nitric oxide (10 parts per million (ppm)) is fast and relatively inexpensive compared to prostacyclin. The same group has reported that the acute responses of pulmonary artery pressure and resistance to nitric oxide and prostacyclin are closely correlated [15]. In that study of 35 PPH patients, 13 patients (37%) had a fall in total pulmonary resistance >30% in response to both drugs, while 22 were nonresponders to both. Although occasional patients who respond to prostacyclin may fail to respond to nitric oxide, the key conclusion from the present paper [14] is that nitric oxide testing identifies most, or possibly all, of those who might benefit from long-term oral CCB. If nitric oxide can be relied upon to do this, then an acute trial with high-dose oral CCB, which carries the greatest risk of side-effects in nonresponders, will not be necessary.

It is interesting that 38% of the nonresponders suffered serious side-effects from the acute trial of CCB (shock, prolonged hypotension or severe vomiting), compared to 6% in an earlier study [10]. It is possible that the preceding trial of nitric oxide initiated some longer-lasting changes in vascular smooth muscle physiology, which rendered the patients more susceptible to CCB-induced hypotension. The problem with CCB is that they are not selective for the voltage-gated, L-type calcium channels in pulmonary vascular smooth muscle and consequently can precipitate systemic hypotension. Potassium channels are largely responsible for the control of vascular smooth muscle membrane potential and thus can determine the gating of the L-type calcium channel. Given the greater number of potassium channels and the diversity of their expression in different blood vessels [16, 17], it may be possible to develop potassium channel agonists that cause only pulmonary vasodilatation.

Other new approaches to the treatment of PPH include nebulizing prostacyclin or its stable analogue iloprost [18]. This mode of delivery may be more convenient, induce

Correspondence: E.K. Weir, Dept of Medicine, VA Medical Center and University of Minnesota, One Veterans Drive, Minneapolis, MN 55417, USA. Fax: 1 612 7275668.

less systemic hypotension and, in patients with parenchymal lung disease, cause less hypoxaemia. Similarly, the nebulization of nitric oxide donors may be effective [19]. Nitric oxide causes pulmonary vasodilatation, at least in part, by increasing cyclic guanosine monophosphate (cGMP) [20]. The concomitant use of a phosphodiesterase inhibitor to further enhance cGMP levels is worth investigating. In animal studies, the relatively nonspecific phosphodiesterase inhibitor, dipyridamole, causes pulmonary vasodilation [21, 22] and enhances the vasodilation induced by nitric oxide [22]. In addition, phosphodiesterase inhibitors reduce the proliferation and migration of vascular smooth muscle cells [23, 24], a property that might be advantageous in PPH. Endothelium-dependent pulmonary vasodilatation is impaired in PPH patients [25] and an alternative approach to providing exogenous nitric oxide would be to use molecular biological techniques to enhance nitric oxide production by the vascular endothelium. In one experiment a recombinant adenovirus containing the constitutive endothelial nitric oxide synthase gene was aerosolized into the lungs of rats [26]. These lungs had higher cGMP levels and a decreased pulmonary vasoconstriction in response to hypoxia, demonstrating the success of the transfection.

In ten years time the use of high-dose CCB and infused prostacyclin will be seen as poorly focused and potentially dangerous treatments. At present, however, they have both been demonstrated to be effective in the management of PPH and anything that can be accomplished to more precisely identify the patients who will benefit from these treatments is a positive step. The use of a nitric oxide test instead of an acute high-dose CCB test is one such step towards the goal of logical therapy for each of the three pathophysiological elements of PPH: thrombosis, proliferation and vasoconstriction. Then, as G. Balfour stated, "the heart, no longer opposed by an obstacle it can either not overcome, or only imperfectly and with suffering, now contracts more perfectly and all its sufferings vanish" [1].

It is particularly appropriate that the authors have dedicated this paper to F. Brenot who did so much to increase our understanding of primary pulmonary hypertension.

## References


1. Balfour GW. The Senile Heart. New York, MacMillan & Co., 1894; pp. 275.
2. Rich S, Kaufman E, Levy PS. The effect of high doses of calcium channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; 327: 76–81.
3. Frank H, Mlczoch J, Huber J, *et al*. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. *Chest* 1997; 112: 714–721.
4. Dresdale DT, Schultz M, Michtom RJ. Primary pulmonary hypertension. 1. Clinical and hemodynamic study. *Am J Med* 1951; 11: 686–705.
5. Wang SWS, Pohl, JEF, Rowlands DJ, Wade EG. Diazoxide in treatment of primary pulmonary hypertension. *Br Heart J* 1978; 40: 572–577.
6. Rubin LJ, Peter PH. Oral hydralazine therapy for primary pulmonary hypertension. *N Engl J Med* 1980; 302: 69–73.
7. Weir EK, Rubin LJ, Ayres SM, *et al*. The acute administration of vasodilators in primary pulmonary hypertension. *Am Rev Respir Dis* 1989; 140: 1623–1630.
8. Rubin LJ, Nicod P, Hillis LD, Firth BG. Treatment of primary pulmonary hypertension with nifedipine. *Ann Int Med* 1983; 99: 433–437.
9. Rich S, Brundage BH. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation* 1987; 76: 135–141.
10. Rich S, Kaufman E. High dose titration of calcium channel blocking agents for primary pulmonary hypertension: guidelines for short-term drug testing. *J Am Coll Cardiol* 1991; 18: 1323–1327.
11. Barst RJ, Rubin LJ, Long WA, *et al.* A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996; 334: 296–301.
12. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 1998; 338: 273–277.
13. Shapiro SM, Oudiz RJ, Cao T, *et al.* Primary pulmonary hypertension: improvement long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol* 1997; 30: 343–349.
14. Sitbon O, Humbert M, Jagot J, *et al.* Inhaled nitric oxide as a screening agent for safely identifying responders to oral calcium-channel blockers in primary pulmonary hypertension. *Eur Respir J* 1998; 12: 265–270.
15. Sitbon O, Brenot F, Denjean A, *et al.* Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension. *Am J Respir Crit Care Med* 1995; 151: 384–389.
16. Archer S, Huang JMC, Reeve HL, *et al*. Differential distribution of electrophysiologically distinct myocytes in conduit and resistance arteries determines their response to nitric oxide and hypoxia. *Circ Res* 1996; 78: 431–442.
17. Michelakis ED, Reeve HL, Huang JMC, *et al.* Potassium channel diversity in vascular smooth muscle cells. *Can J Physiol Pharmacol* 1997; 75: 889–897.
18. Olschewski H, Walmrath D, Schermuly R, *et al*. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Int Med* 1996; 124: 820–824.
19. Martin EB, Tolarova S, Weir EK, *et al*. Aerosol delivery of detano, a nitric oxide adduct, causes selective and sustained perinatal pulmonary vasodilation. *Ped Res* 1996; 39: 339A.
20. Archer S, Huang JMC, Hampl V, *et al*. Nitric Oxide and cGMP cause vasorelaxation by activation of a charybdotoxin-sensitive K channel by cGMP-dependent protein kinase. *Proc Natl Acad Sci USA* 1994; 91: 7583–7587.
21. Mlczoch J, Weir EK, Grover RF. Inhibition of hypoxic pulmonary vasoconstriction by dipyridamole is not platelet mediated. *Can J Physiol Pharmacol* 1977; 55: 448–451.
22. Ziegler JW, Ivy DD, Fox JJ, *et al.* Dipyridamole potentiates pulmonary vasodilation induced by acetylcholine and nitric oxide in the ovine fetus. *Am J Respir Crit Care Med* 1998; 157: 1104–1110.
23. Yu S-M, Hung L-M, Lin C-C, *et al*. cGMP-elevating agents suppress proliferation of vascular smooth muscle cells by inhibiting the activation of epidermal growth factor signaling pathway. *Circulation* 1997; 95: 1269–1277.
24. Palmer D, Tsoi K, Maurice DH. Synergistic inhibition of vascular smooth muscle cell migration by phosphodiesterase 3 and phosphodiesterase 4 inhibitors. *Circ Res* 1998; 82: 852–861.
25. Brett SJ, Simon J, Gibbs R, *et al*. Impairment of endothelium-dependent pulmonary vasodilation in patients with primary pulmonary hypertension. *Thorax* 1996; 51: 89–91.
26. Janssens SP, Bloch KD, Nong Z, *et al.* Adenoviral-mediated transfer of the human endothelial nitric oxide synthase gene reduces acute hypoxic pulmonary vasoconstriction in rats. *J Clin Invest* 1996; 98: 317–324.