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 nitrates as vascular stimulants "which dilate the peripheral vessels (arterioles) and so promote the flow blood". In the case of primary pulmonary hypertension (PPH), vasodilation 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 RENI 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 sepsicaemia 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, SIMON 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
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 vasodilatation [21, 22] and enhances the vasodilatation 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
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