Recent years have witnessed a transformation in the treatments available for patients with pulmonary arterial hypertension with the development of new therapies that offer significant therapeutic benefit. While the inspiration behind them may have been based on tipping a perceived imbalance in vasoconstrictor–vasodilator activity towards vasodilation, it is emerging that the main action of these new treatments is to prevent (and possibly reverse) pulmonary vascular remodelling. Should this insight change our protocol for investigating and working up patients for treatment?

A role for both a vasoconstrictive and a gradual obliterator vascular process in the pathogenesis of pulmonary arterial hypertension was recognized by Paul Wood when he described the profound fall in pulmonary arterial pressure in response to acetylcholine in patients with primary pulmonary hypertension in 1958. Acute pulmonary vasodilator testing has since become part of routine clinical practice in the investigation of pulmonary arterial hypertension. It identifies patients in whom vasoconstriction is a major component of their disease, and whose symptoms and prognosis are improved by calcium antagonists. There are, however, a number of problems with this approach.

One problem interpreting vasodilator testing has been the use of a variety of vasodilator drugs with diverse acute haemodynamic effects. While epoprostenol, adenosine, and nitric oxide have been popular in recent years, nitric oxide is favoured because of its trivial effect on cardiac output and lack of effect on the systemic circulation. A second concern is that there is no agreement about what constitutes a minimum beneficial response. It has been proposed that the response is a reduction in mean pulmonary artery pressure of 10 mmHg associated with no change or an increase in cardiac output, or a >20% reduction in mean pulmonary artery pressure or pulmonary vascular resistance, or a fall in both pulmonary artery pressure and resistance of >30%. Patients who respond best to chronic therapy with calcium antagonists often have a fall in both pulmonary arterial pressure and resistance closer to 50% or back to the normal range. Third, it is clear that in severe forms of the primary pulmonary hypertension, non-responders to acute vasodilators still benefit from chronic epoprostenol infusion.
these agents play an essential role in the clinical improvement seen whether or not patients respond to vasodilators.

Similarly, endothelin-1 is noted for its vasoconstrictor properties but it also stimulates human pulmonary artery smooth muscle cells to proliferate, while the cyclic GMP-dependent vasodilators, nitric oxide, and the natriuretic peptides, have the opposite effect and are antitrophic. Although endothelin receptor antagonists and phosphodiesterase type 5 (PDE5) inhibitors were developed with an eye on reducing vasomotor tone, an important component of the therapeutic effect of these drugs is likely to rest with their ability to oppose structural remodelling of the pulmonary vascular bed. If this is the case then is the acute vasodilator study missing the point and does it still have a useful role? As currently employed, the acute vasodilator response is of limited value as a tool for comparing therapeutic efficacy between classes of drugs. This may even be true for agents within the same class. In this issue of the journal, Opitz et al. compare the acute haemodynamic effects of prostacyclin analogues and show how acute falls in pulmonary vascular resistance are effected by different mechanisms according to the route of administration. As far as it gives insight into their acute haemodynamic effects, this is fine. But recent data indicate that the prostacyclin analogues iloprost, cicaprost, beraprost, and treprostinil have differential effects on human pulmonary artery smooth muscle cells proliferation and cAMP production in vitro. These differences may reflect variation in the activation of prostanoid receptor subtypes coupled to distinct adenylyl cyclase isoforms or other signalling mechanisms. With this in mind, some care must be taken when extrapolating data comparing the acute haemodynamic effects of different prostacyclin analogues to the potential value from their long-term administration.

Pulmonary arterial hypertension is a heterogeneous condition and the acute response to a vasodilator might be useful for phenotyping patients, with a view of exploring subsequent phenotype–genotype relationships. As long as calcium antagonists are judged to have a role, the test will remain useful for identifying patients in whom the disease is not severe and who may get a good result from this therapeutic class. But if endothelin antagonists and PDE5 inhibitors achieve a niche in the treatment of milder disease, and as the concept of combination therapy emerges into practice, the clinical role of the acute vasodilator challenge at least in adults becomes less clear and perhaps historical. If it is to survive then data must be collected to show how it influences therapy and clinical outcomes. Other factors—such as liver function and accurate assessments of right ventricular mass and performance—may begin to determine the choice and combination of therapies; and perhaps one day the patient's genotype itself.

References