Measuring the effects of treatment in patients with PAH: should we image the right ventricle?

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Echocardiography and CMR allow noninvasive, serial examination of right ventricular function in PAH http://ow.ly/UJPq30bRO86

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Treatment for pulmonary arterial hypertension (PAH) has really only been available for the last 16 years. Progress has been extremely rapid, and both the mortality and the morbidity from this condition have been improved by the application of one or more of three groups of therapy, the endothelin receptor antagonists (ETRA), the agents promoting the nitric oxide pathway (both phosphodiesterase 5 inhibitors (PDE5i) and guanylate cyclase activators) and the prostacyclins.

More recently, however, the initial rate of progress has slowed and perhaps we are in a plateau phase where we need further new agents or new ways of using the agents we have. The new agents in the form of drugs that prevent or reduce pulmonary artery vascular remodelling have been disappointing. Our attention has therefore turned to using the agents we have in new ways. One of the new ways is to give the agents in combination on the basis that they are likely to be synergistic.

Over the past few years and in response to the European Respiratory Society/European Society of Cardiology guidelines [1], most units have adopted the technique of giving a single agent and then, if there is insufficient improvement (goal-orientated therapy), adding a second agent. This process has been challenged, however, and it is now clear that in at least one study [2], the use of upfront combination therapy (in this case, tadalafil a PDE5i, and ambrisentan, an ETRA) was better than either agent used alone in the treatment of patients with idiopathic pulmonary arterial hypertension (IPAH). This was also shown in an open study in patients with pulmonary hypertension in association with scleroderma and other combinations have been used in IPAH [3–5].

Early trials of drugs for PAH utilised the 6-min walk test and pulmonary haemodynamics as a way of determining the success or failure of the therapy. The use of trial endpoints has also moved on and, more recently, trials, including the AMBITION trial, have used time to clinical worsening or failure to improve. These are composite endpoints comprised of several variables but, while a prevention of deterioration might seem valuable, it is not as exciting a prospect as evidence of improvement that we saw with the 6-min walk. However, there have been criticisms of the 6-min walk test (ceiling effect necessity of intact musculoskeletal system etc.) and attention is now beginning to focus on measuring the function of the right ventricle in order to determine whether a treatment has been successful. The reason for this focus is that patients with PAH die from right heart failure so it is logical to measure right heart function.
It was always felt in the past that the deterioration of right ventricular function was simply a consequence of pulmonary haemodynamics and if these could be improved, then so would the right ventricular function. There are, however, at least two reasons to doubt this assumption. Firstly, some patients appear to have worse right ventricular function for the same level of pulmonary haemodynamics; for example, patients with IPAH do better than patients with systemic sclerosis despite equivalent haemodynamics. Secondly, haemodynamics can improve but there may be continuing and ongoing deterioration of right ventricular function. This was shown by the Amsterdam group [6] and has prompted an examination of the ways we look at right ventricular function in the patients with PAH.

Currently, there are really three ways to look at right ventricular function. Firstly, by invasive pulmonary haemodynamics, but most pulmonary hypertension centres feel that this should be done at diagnosis but not repeated thereafter. Secondly, by echocardiography, which is often the first test to suggest PAH. Thirdly, by cardiac magnetic resonance (CMR) imaging.

If we want to have a test that can be repeated in order to determine the benefits, short term and long term, of therapy, we really need a noninvasive imaging system. Echocardiography and CMR imaging are the two on which the most attention has been focused. Early measures of right ventricular function by echocardiography were TAPSE (tricuspid annular plane systolic excursion) [7] and right ventricular function index, the Tei index [8]. More recently, determination of right ventricular function by three-dimensional echocardiography [9] or regional determination of wall motion by speckle tracking [10] have offered promise. However, given the high resolution of CMR imaging, this has proved to be the modality best able to demonstrate changes in right ventricular function by looking at volumes of the cardiac chambers, damage to cardiac muscle, and functional variables such as ejection fraction and strain.

For reviews of echocardiography and CMR in the evaluation of pulmonary hypertension, see elsewhere [11–16].

The Amsterdam group have been at the forefront of the use of CMR to determine right ventricular function in patients with PAH and in this issue of the European Respiratory Journal, they report the use of CMR techniques to examine changes in right ventricular volumes and wall stress in pulmonary hypertension in response to upfront combination therapy [17]. In this study, they took 80 patients with incident PAH (hereditary, idiopathic or drug induced). Patients were in functional class II or III. The authors examined the benefits to these patients of either upfront combination therapy with an ETRA and a PDE5i versus each of these agents given as monotherapy.

This was an historical study so the reasons why patients were given one drug class or another are not set out in the protocol. Nevertheless, the authors sought to examine the relative benefits of upfront combination versus upfront monotherapy by using CMR-derived measures of right ventricular volumes, and right heart catheterisation at baseline and 12 months. They combined this with measurements of N-terminal pro-brain natriuretic peptide (NT-proBNP), which is a chemical indicator of right ventricular wall stress. Using magnetic resonance imaging, they measured right ventricular volumes and mass, and calculated right ventricular end-systolic stress. They found that right ventricular volumes, such as right ventricular end-diastolic volume, improved in patients with upfront combination therapy but not in patients given initial mono- and subsequent combination therapy, i.e. sequential therapy. They also found that this difference was associated with a decrease in right ventricular wall stress in the combination patients but not in those given sequential therapy and this was supported by measures of NT-proBNP, which correlated with the calculated wall stress.

This study was, of course, a retrospective study and the patients were not randomised to the two types of treatment. However, it is interesting that clinicians gave upfront combination therapy because they were concerned about the patients’ poor clinical state and yet these patients did better in terms of right ventricular function than those given monotherapy, even when this was added to by sequential combination therapy. This suggests that upfront combination therapy is better for the right ventricle in these patients and may be the reason why these patients have a better prognosis as shown by the AMBITION trial.

Very few studies have looked at right ventricular function in relation to therapy. One was the Euro MR Study [18], which looked at patients from Glasgow (UK), Rome (Italy), Graz (Austria) and Amsterdam (the Netherlands) before, and then 4 and 12 months after the institution of therapy. This found improvements in right ventricular systolic and diastolic volumes as well as stroke volume but, interestingly, also found improvements in left ventricular function due to the increased preload to the left ventricle, which is a consequence of better right ventricular function. Currently, there are studies of macitentan (REPAIR study; www.clinicaltrials.gov identifier NCT02310672) and riociguat (REPLACE study; NCT02891850) and right ventricular function.
It is now clear that right ventricular function in the face of PAH can be variable but that right ventricular dysfunction occurs early on in the disease and should therefore be considered as an early marker of disease. In addition, the progress in right ventricular function, which may deteriorate or improve separately from changes in pulmonary haemodynamics, needs to be separately and adequately examined.

At present, the two techniques that allow noninvasive, serial examination of right ventricular function are echocardiography and cardiac magnetic imaging. The high resolution of CMR means that this technique has the edge at present but there are hopes that new techniques in echocardiography, which are continuing at pace, will allow useful comparisons in the future.

References


