**Non-invasive methods for assessing pulmonary exercise haemodynamics**

Prof. Andrew Peacock  
Scottish Pulmonary Vascular Unit  
Agamemnon Street  
G81 4DY Clydebank, West Dunbartonshire  
UNITED KINGDOM  
appeacock@udcf.gla.ac.uk

**SUMMARY**

**Introduction**

When a normal person exercises, there is an increase in cardiac output which rises from approximately 5 ltrs/min at rest to up to 30 ltrs/min on exercise. This is not usually accompanied by any rise in pulmonary artery pressures or, if there is a rise in pulmonary artery pressures, these are matched by rise in left atrial pressure, i.e., transpulmonary gradient for pressure remains low. This lack of change in pulmonary pressures is due to the remarkable compliance of the pulmonary arteries which cope with the increase in flow. In pulmonary vascular disease, this compliance is lost and, as a patient with pulmonary vascular disease exercises, there is a rise in pulmonary artery pressure greater than the rise in left atrial pressure. This rise in PA pressure may eventually become fixed (pulmonary hypertension) and is associated with diminished right ventricular function and, ultimately, with death from right ventricular failure.

In the early stages of pulmonary vascular disease, resting pulmonary artery pressures may be normal. Resting cardiac output may also be normal. However, as the disease develops, a progressive increase in pulmonary vascular resistance results in a rise in resting pressure but, at this stage, the disease may not be noticed by the attending physician. However, when the RV fails (swollen ankles, raised JVP, enlarged liver, etc), the patient usually come to the attention of the doctor. Clearly, at this point, we are quite far down the track and one’s ability to treat patients, reduce the vascular resistance and improve right ventricular function is much more limited. It would therefore be of great if we could recognise abnormal pulmonary haemodynamics early before this irreversible, or only partially reversible stage, sets in.

There have been many studies of pulmonary haemodynamics on exercise. Most of these are invasive studies, either using exercise on the cardiac catheter table or ambulatory pulmonary haemodynamics using an implanted high-fidelity micromanometer catheter or an inserted pressure monitoring device. These methods of measuring pulmonary haemodynamics during activities of daily living and formal exercise have really improved our understanding of the right ventricle and the pulmonary circulation. However, they are invasive and, although useful for research, are not for widespread use and certainly could not be used for screening large populations for pulmonary vascular disease.

To screen a population and follow them up, we really need non-invasive measures of pulmonary haemodynamics and right ventricular function on rest and exercise. Pulmonary haemodynamic measurements on exercise are difficult to measure non-invasively because it is difficult to make measures of flow and pressure without the associated Right Heart Cath and transducers.

Other relevant methods are inert gas rebreathing and bioimpedance. Inert gas rebreathing relies on the fact that if you inhale two gases, one that is not absorbed and one that is absorbed, then the concentration of these two gases in the exhalate will differ by a proportion relating to the effective pulmonary blood flow. This non-invasive test is therefore a measure of pulmonary blood flow and, taking heart rate into consideration, can give a measure of stroke volume.
Bioimpedance relies on the variation in impedance to a high frequency alternating current across the chest with changes in stroke volume. It is also an interesting non-invasive measure but there is less data either in normals or patients with PH and almost none on exercise.

Most interest in non-invasive tests of pulmonary haemodynamics have focused on the right ventricle. It is assumed that the right ventricle must respond to the pulmonary vascular resistance and impedance and, since the patients with pulmonary hypertension ultimately die from RV failure, it seems relevant to measure right ventricular function in detail, if possible, non-invasively and successively, in order to get an idea of the change in right ventricular dynamics (linked to pulmonary haemodynamics) as the disease progresses or improvements in these variables when the disease is treated.

To make these measurements, most attention is focused on echocardiography and cardiac magnetic resonance imaging.

Echocardiography provides measures of pressure, flow and cardiac volumes. It therefore should be ideal to follow-up patients with pulmonary hypertension. However, imaging is not always possible, and measurements of chamber volumes, particularly the right-sided chamber volumes, are difficult and involve many assumptions. Pressures can be measured by looking at the retrograde flow across the tricuspid valve where the flow rate is a function of the RV/RA pressure difference (Bernoulli effect). This is one of the great advantages of echocardiography over cardiac magnetic resonance imaging and has been the basis of several studies, notably by Grünig of Heidelberg, who has shown that pulmonary artery pressures rise on exercise, measured by echo is a significant marker of underlying pulmonary vascular disease.

Cardiomagnetic resonance imaging is the gold standard for imaging the right ventricle because it allows clean images of all chambers in patients with or without lung disease. It also allows measures of flow (in the aorta or main pulmonary artery) and ejection fraction/volume from the changes in the volumetric measurements of the relevant chambers. There has been much less work on using CMR on exercise but studies by La Gerche on normal subjects who are extreme endurance athletes and studies by Delacroix et al in patients with pulmonary vascular disease, have shown that these exercise measurements are possible and may well be the basis for sophisticated monitoring of patients with pulmonary vascular disease in the future.

1. **Inert gas rebreathing**

Inert gas rebreathing relies on the inspired and exhaled measurements of Nitrous Oxide and Sulphur Hexafluoride given by mask at rest and when a subject exercises. Nitrous Oxide is absorbed completely and the Sulphur Hexafluoride is not absorbed at all. Thus, the separation of the concentration curves in the exhalate (See Fig 1) allows a measurement of effective pulmonary blood flow, i.e., pulmonary blood flow that sees the Nitric Oxide. This method of measuring pulmonary blood flow and hence cardiac output has been validated against more invasive methods such as thermodilution and Fick in both pulmonary hypertension and interstitial lung disease. More recently, exercise IGR measurements have been used to determine treatment response in patients with pulmonary arterial hypertension (Lee et al, Thorax 2011;66:810-814). Patients had resting measurements then underwent a constant cardiopulmonary exercise test consisting of 2 minutes of rest followed by 3 minutes of cycling at 40% of maximum work predetermined in the incremental CPET. It is expected that the stroke volume will reach its maximum at approximately 40% (V02 max). At the end of the exercise, there were significant increases in pulmonary blood flow from the resting measurements but, more importantly, after a period of treatment, exercise response in terms of pulmonary blood flow, stroke volume and cardiac output was higher in those on pulmonary vascular treatment.
2. Bioimpedance measurements

The PhysioFlowTM principle (Signal-Morphology-ICGTM) is based on the principle that variations in the impedance (DZ) to a high-frequency (75 kHz) low-magnitude (1.8 mA) alternating current across the thorax during cardiac ejection result in a specific waveform from which stroke volume (SV) can be calculated. Compared to older technologies, the development of PhysioFlow has resulted from technical improvements that enable better signal filtering and stability and better data processing. The basic equation for calculating SV has been modified profoundly in order to overcome the difficult evaluation of variables such as blood resistivity, the distance between recording electrodes, and the basal thoracic impedance [15].

3. Echocardiography

Two-dimensional echocardiography has been used to examine the exercise responses of the right heart in patients with pulmonary arterial hypertension. Echocardiography has the advantage that it is possible to make measurement of pressures (the Bernouilli theorem), i.e., the pressure difference between right atrium and right ventricle and change in these pressures with exercise.

Patients exercise on a special table tilted over to the left to allow adequate imaging of the heart during the exercise. Limitation to making measurements in exercise is heart rate; it is difficult to get decent images above a heart rate of about 100 bpm. However, providing decent images are obtained, then it is possible to get measures of change in pressure across the tricuspid valve and measures of cardiac output (see Fig 2).

4. Cardiomagnetic resonance imaging

CMR has been used by a number of centres to examine the right ventricular response of pulmonary arterial hypertension. Most of these measurements have been made at rest and have included measurements of cardiac chamber volumes, measurements of right ventricular mass and left ventricular mass (the ventricular mass index is RV mass/LV mass), measurements of stroke volume, ejection fraction and measurements of flow through the aorta or main pulmonary artery. The particular advantage of CMR is that measurements can be made in nearly all subjects. Disadvantages are occasional claustrophobia the lack of estimates of pressure and the fact that measurements must be made supine.

Recently, there have been attempts to make Exercise CMR measurements on right ventricular function in both normal subjects (endurance athletes) and patients with pulmonary arterial hypertension. It is very important that the exercise is undertaken inside the magnet so that measurements are made actually during exercise rather than just after exercise. We know that cardiac output drops very rapidly following a bout of exercise and if the measurements are not made during exercise, it is likely that these effective changes will be missed.

Making measurements during exercise is difficult because if one uses a supine bicycle, then the patients knees tend to hit the bore of the magnet, particularly if it is one of the smaller (60 cms) magnets. An innovation has been using a step machine with appropriate resistance where the knee travel is less for the same workload, thus allowing measurements to be made inside the magnet itself. (see Figs).

It is too early to say whether CMR or echocardiography measurements on exercise are going to be useful when monitoring patients with pulmonary arterial hypertension but, given that cardiac function and cardiac output are absolutely fundamental to a patient’s exertional response, it seems highly likely that these measurements will give great insight into the workings of the right heart in patients with pulmonary hypertension and will also us allows to manipulate the function of the right heart and looks non-invasively at whether the manipulation has been successful.