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EDITORIAL COMMENT

Cardiopulmonary exercise testing in thalassemia

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In this issue of International Journal of Cardiac Imaging, researchers from the Onassis Cardiac Surgery Centre and Agia Sophia Hospital in Athens report their findings of cardiopulmonary exercise testing (CPET) in relation to cardiovascular magnetic resonance (CMR) in patients with thalassemia major (TM) [1]. In support of previously available evidence, they found raised cardiac iron and low left ventricular ejection fraction in patients with heart failure. In addition, CPET indices (VO_2max, anaerobic threshold (AT), metabolic equivalents (METs) and exercise duration) were not only lower in TM patients with heart failure but were closely correlated with iron loading, measured by CMR T2*.

Inherited hemoglobinopathies affect millions of patients worldwide, mostly due to the thalassemia syndromes and sickle cell disease [2]. TM patients have a particularly severe anemia due to the absence or severe reduction in beta globin chains, and regular blood transfusions are required from soon after birth to prevent fatal complications of the anemia. Although transfusion prevents these problems, the trade-off comes at the expense of iron overload. Each unit of blood contains ~250 mg iron and additional body iron loading comes from overabsorption of iron from the gastro-intestinal tract due to hepcidin suppression. Iron accumulates in the tissues and organs of the body, predominantly to start with in the liver, and without chelation therapy, progressive cardiac iron overload leads to arrhythmias, cardiac failure and death before the age of 20. The introduction of iron-chelating agents in the 1970s has changed the natural history of the disease and survival has dramatically improved [3]. However, myocardial siderosis leading to impaired cardiac function remains the leading cause of mortality in these patients.

Understanding the pathophysiology of iron-induced cardiac dysfunction is key to the management of heart failure in these patients. When the iron transporting capacity of transferrin is exceeded, non-transferrin bound iron appears in the plasma. This labile iron is associated with the development of free radicals which cause cellular damage by affecting membrane lipids and proteins. In cardiac myocytes, the mitochondrial respiratory chain is affected and cellular dysfunction occurs, leading to impaired myocardial contractility and subsequently heart failure [4]. Unfortunately, the onset of decompensated heart failure from iron-overload cardiomyopathy is unpredictable and a long period of asymptomatic severe iron loading may be present before any clear depression of left ventricular ejection fraction is

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apparent. As a consequence, echocardiographic parameters can remain normal despite severe myocardial siderosis but once heart failure occurs, it carries a poor prognosis [5]. Early detection of cardiac iron therefore becomes important but, until recently, non-invasive assessment of cardiac iron loading has been difficult. The historical methods used, namely serum ferritin and biopsy measurements of liver iron, have proven to be poor predictors of myocardial iron content and myocardial biopsy is not only invasive but may be misleading due to patchy iron deposition [6, 7].

From our unit, we have implemented a CMR technique for the measurement of cardiac iron. This was first described in 2001 and involves measuring T2* which is a magnetic resonance parameter [6]. T2* is significantly affected by the magnetic field perturbation caused by particulate iron in the myocardium and therefore T2* falls as the amount of iron increases. These findings which have been confirmed in an animal model of iron overload [8]. The normal human T2* value (measured in milliseconds) is greater than 20 ms. When T2* falls to below 10 ms, there is a progressive and significant fall in left ventricular ejection fraction (LV EF). We have also shown that T2* is a strong prognostic indicator for the development of heart failure [9]. With intensive chelation therapy, both T2* and LV EF improve, showing that iron-related cardiomyopathy can be reversed [10]. This has been confirmed in trials of the iron-chelating agents deferoxamine and deferiprone [11–13] and improvements in cardiac mortality have been demonstrated related to the use of cardiac iron monitoring [14]. There remain some unanswered questions. First, it is not clear why some patients with high cardiac iron develop heart failure and others do not; second, whether further testing in patients with high cardiac iron could identify those most at risk; and third, why some patients have high cardiac iron with low liver iron and vice versa. The latter may be related to differences in iron kinetics and iron-handling genes but the first two issues are more challenging.

The Athens group have a longstanding interest not only in the assessment of iron loading but also of functional status in TM patients which has lead to this latest research on CPET. Initial studies on the use of CMR in cardiac iron overload using older signal intensity ratio (SIR) and T2 CMR techniques, showed that myocardial iron was inversely correlated with both SIR and T2 [15, 16]. Indeed T2 has now become easier to do and may have a clinical role in the future [17]. An evaluation of myocardial and hepatic iron in patients who had undergone successful bone-marrow transplantation revealed that T2* was more reliable than serum ferritin in monitoring iron loading and that the myocardial iron (measured using T2*) was the same as an age-matched normal population [18]. The Athens group went onto assess respiratory function in patients with thalassemia and iron overload. A restrictive ventilatory pattern on pulmonary function testing (i.e. low predicted total lung capacity (TLC)) was noted to be a common abnormality in TM patients. Although it was postulated that this might be due to iron deposition in the respiratory system, no correlation was found between reduced TLC and hepatic iron loading [19]. They have also described impaired oxygen kinetics and limited functional capacity of peripheral muscles in TM patients during cardiopulmonary exercise testing [20, 21]. This work has suggested that part of the exercise limitation in TM stems from a slower rate of high energy phosphate production and utilization with reduced oxidative capacity of myocytes.

Cardiopulmonary exercise testing (CPET) is a useful clinical technique for the assessment of exercise capacity and prognosis in patients with heart failure and other cardiovascular conditions [22]. It is non-invasive and provides information which not only combines the exercise-related responses of the lungs, heart, and skeletal muscle but also takes account of the effects of anaemia which can alter arterial or mixed venous blood oxygen levels. CPET involves an exercise protocol using a bicycle ergometer or a treadmill and can have an advantage over conventional techniques which rely mainly on the assessment of resting cardiac function. Many different protocols exist which are tailored to the patient's functional capacity. Workload is increased in stages, either by increasing the braking load on a bicycle or the slope of the treadmill ramp. A mouthpiece is used for ventilation and respiratory gas analysis with a non-rebreathe valve to prevent mixing of inspired and expired air. Respiratory volumes are calculated by integrating the airflow/time curves. Gas analysers measure inspiratory and expiratory oxygen and carbon dioxide.

Oxygen uptake (VO_2) is dependent on the product of the cardiac output and the difference between arterial oxygen and mixed venous oxygen content

($VO_2 = CO \times$ (arterial oxygen content − mixed venous oxygen content)). It is usually indexed for weight and measured in mL O_2/kg/min. In healthy subjects, VO_2 increases linearly with increasing exercise until it reaches a plateau at near-maximal exertion (VO_2max). In patients with heart failure, the level of exercise may be limited by symptoms before VO_2max is reached and therefore, peak VO_2 (PVO_2) is used instead as an estimation of maximum oxygen uptake. With worsening exercise tolerance, peak VO_2 falls. The ventilatory anaerobic threshold (AT) is a useful indicator of exercise capacity. During exercise, muscle metabolism is initially aerobic with a linear increase in ventilation and carbon dioxide production (VCO_2) as VO_2 increases. When the supply of oxygen cannot keep up with the demand for energy required by skeletal muscle, the adenosine triphosphate (ATP) production needs to be supplemented by anaerobic metabolism and hence the anaerobic threshold is reached. This leads to the production of lactic acid within the muscles which causes a rise in blood lactate and a fall in bicarbonate levels. As the switch to anaerobic metabolism results in increased CO_2 production, the anaerobic threshold can be estimated by analysing the relative rate of production of CO_2 compared to the oxygen uptake. There are a number of methods for doing this, all of which are confounded by considerable inter and intraobserver variability [23].

To be confident that PVO_2 is a good estimate of VO_2max, it is important to ensure that a test is maximal. This can be achieved by observing a rise in heart rate and blood pressure with exercise together with ensuring that the anaerobic threshold has occurred at 50–70% of PVO_2. However, a proportion of patients with heart failure will not reach the anaerobic threshold and PVO_2 results need to be interpreted with this in mind. The VE/VCO_2 slope, which represents the relationship between expired minute ventilation (VE) and carbon dioxide production is an alternative, additional prognostic indicator. Based on the results of a number of trials, a risk stratification algorithm has been suggested for use in heart failure [24]. Patients with PVO_2 >18 ml/kg/min have a good long term outcome, whereas those with PVO_2 of below 10 ml/kg/min have a high risk of cardiac events and death. With PVO_2 between 10 and 18 ml/kg/min, there is an intermediate risk unless the VE/VCO_2 slope is ≥35, indicating a high risk.

In thalassemia patients with heart failure and poor ventricular function, exercise capacity may be limited by a number of factors. The cardiac output will be unable to increase sufficiently to provide skeletal muscles with adequate perfusion and therefore anaerobic metabolism will occur early. As cardiac iron impairs mitochondrial respiratory function, a higher level of cardiac siderosis is likely to have more of an impact on cellular metabolism. The degree of anemia, albeit mild, will also affect the oxygen supply to the muscles due to reduced arterial oxygen content.

However, CPET has its limitations. CPET can be a valuable tool in expert hands, but the technique is neither simple nor widely available. It requires expert supervision and a significant amount of training. While equipment costs are undoubtedly less than CMR, the reporting and interpretation of CPET is not easy. It is however possible that CPET might have the potential to determine which patients with a low T2* are most likely to develop cardiac complications. At present, although patients with T2* less than 10 ms are known to have a greatly increased relative risk, it is impossible to predict which of these patients will progress to left ventricular dysfunction and heart failure.

Further research is needed to establish whether CPET is an independent risk stratifier. Thus, we do not yet know if CPET adds anything to the T2* or the ejection fraction. The fact that those patients with low cardiac T2* have poor CPET indices provides further evidence to support cardiac T2* as the current method of choice for monitoring cardiac iron loading in patients with transfusion-dependent thalassemia major.

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