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Oxygen uptake efficiency slope in children: Its role in exercise testing

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Cardiopulmonary exercise testing (CPET) is a useful tool to test the physiological response of the cardiovascular, pulmonary and metabolic systems to exercise. Various parameters have previously been recognised as important to predict prognosis, and many of them show correlations with health outcomes.[1,2] The simplest measures are peak work rate, heart rate (HR) increase during exercise and its decline during the recovery phase. The highest obtained HR during exercise (HR_{peak}) is related to the chronotropic competence of the heart. Especially in children, beyond moderate intensity exercise there is a strong correlation between HR and work rate. The recovery of HR after the cessation of exercise is mainly driven by the parasympathetic part of the autonomic nervous system.[3] In different studies this parameter is strongly related to outcome and prognosis. When a respiratory gas analysis system is available, ventilation (VE), oxygen uptake (VO_2) and carbon dioxide production (VCO_2) can be measured continuously. Subsequently, parameters such as maximal oxygen uptake (VO_{2max}), VE/VCO_2 slope and the oxygen uptake efficiency slope (OUES) can be obtained.

Oxygen uptake efficiency slope

In the present issue of the journal Hossri et al. present their findings relating to OUES in both healthy children and children with heart disease.[4] They found that OUES/kg can predict a VO_{2max} below or above 80% of normal with a specificity and sensitivity of approximately 80%. The population of children with heart disease included patients after correction of tetralogy of Fallot, transposition of the great arteries and patients with a univentricular heart. In previous studies the exercise capacity in paediatric patients with congenital heart disease may differ from 88% of healthy controls in patients after closure of a ventricular septal defect[3] to 74% in patients with a univentricular heart.[5] This means that many paediatric patients after correction of their congenital heart disease have a VO_{2max} below 80% of normal children. Although a cut-off value of 80% of VO_{2max} seems low for many patient groups who have undergone a total correction, it may be useful for patient groups with reduced exercise capacity as in patients with a univentricular heart. It is important to realise that OUES is age and sex dependent, even when normalised for body mass.[1] When there are significant differences in these parameters between patients and healthy controls, as in the study by Hossri et al., care has to be taken when interpreting the results.[4] A low exercise capacity might be caused just by an increased body mass, for example.

In exercise testing the use of VO_{2max} is widely recognised as the gold standard. The main issue of this measure is that it requires a true maximal exercise for its interpretation.[1,6] In certain patient groups, e.g. young children, maximal exercise during a CPET will often not be reached, because motivational aspects of the subject can play an important role. These considerations make the use of a submaximal exercise parameter potentially valuable. Parameters that are determined during submaximal exercise include the VO_2 at the ventilatory anaerobic threshold (VAT), the regression line between VE and VCO_2 (VE/VCO_2 slope) and the OUES, the rate of increase of VO_2 in response to the increase of VE during incremental exercise.[7] The use of VAT is limited, because VAT is not always identifiable in all subjects and seems to be less reproducible, while the use of the VE/VCO_2 slope seems to be less valuable in predicting outcome in cyanotic patients.[6] When the VE over the entire exercise duration is logarithmically transformed and plotted against the VO_2, the regression coefficient is the OUES.[7] This makes the OUES a dimensionless parameter. In addition, OUES can also be normalised by body weight or body surface area to correct for

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differences in anthropometrics between patients, and oxygen uptake efficiency (VO_2/VE) can be measured at a plateau phase or at the anaerobic threshold. The OUES is age and sex related. It increases from about 1400 (ml/L) in 8-year-old boys to 3500 in 18-year-old boys, and it increases from about 1250 in 8-year-old girls to 2650 in 18-year-old girls.[1]

OUES as prognostic marker

The OUES was originally developed for children with congenital heart disease (CHD),[7] and later this has been extended to adult patients. Although a variety of underlying disease states has been investigated, many studies focused on patients with heart failure and with pulmonary arterial hypertension. In a study with end-stage heart failure patients, OUES was shown to be a predictor of 2-year survival, while other CPET variables such as VO_{2max} and the VE/VCO_2 slope were unable to predict outcome.[8] A cut-off value of 1.6 was suggested to give the optimal differentiation, showing a 2-year survival rate of 55% of those with OUES less than 1.6 and 82.4% survival for those with OUES greater than 1.6. An indexed OUES (OUES/body surface area (BSA)) has been used in patients with idiopathic pulmonary arterial hypertension. In contrast to VO_{2max} and the VE/VCO_2 slope, the indexed OUES was able to discriminate between a low and high risk of mortality.[9] Patients with a OUES index less than 0.52 $(L/L)/m^2$ had an overall 5-year survival rate of 41.9%, which increased significantly to 89.8% in patients with an OUES index greater than $0.52/m^2$.

OUES in CHD

Although there are many studies investigating the correlation between parameters of CPET and outcome variables in patients with CHD, there is only a limited number of papers investigating the predictive value of the OUES in these patients. In 2006 Dimopoulos et al. investigated a large number of exercise stress tests in 560 patients with CHD.[10] They found that the VE/VCO_2 slope was the only predictor of mortality on multivariate analysis in non-cyanotic patients, while this effect was absent in cyanotic patients. A VE/VCO_2 slope of greater than 38 was associated with a 2-year mortality of 13%, while this was only 1% in patients with a VE/VCO_2 slope less than 38. More specifically, the predicted value of CPET was investigated in 321 Fontan patients by Diller et al.[11] Although they found that most CPET parameters were related to an increased risk of hospitalisation, only HR reserve was related to the risk of mortality during a short-term follow-up period. The additional value of OUES has been studied in a number of small studies. In 50 Fallot patients both VO_{2max} as well as OUES/BSA were predictive of 2-year cardiac-related hospitalization.[12] A cut-off value of the OUES/BSA of 1.029 showed a 2-year incidence of cardiac-related hospitalisation of approximately 60% in those with an OUES/BSA less than 1.029 contrasting to an incidence of approximately 20% in those with an OUES/BSA greater than 1.029. These findings were nearly similar in a group of Fontan patients.[13] Both the VE/VCO_2 slope and OUES were predictive of cardiac-related hospitalisation, while this was independent of baseline clinical information for OUES only. During a 2-year follow-up period those with an OUES less than 45% of predicted had a 33% freedom from hospitalisation, while this was 86% for those with an OUES greater than 45% of predicted.

In certain patient groups, however, OUES values have to be interpreted with caution, especially in Fontan patients. This became clear in the paper by Giardini et al.[14] In their study, OUES measured during the entire exercise duration was not linear, as OUES measured during the first 50% of the exercise duration was lower when compared to OUES measured during the second half of the exercise duration. This was only the case in cyanotic Fontan patients, while non-cyanotic patients, patients with atrial repair of transposition of the great arteries and healthy volunteers showed a linear OUES over the entire exercise duration. In the study by Hossri et al. both cyanotic and non-cyanotic patients were studied.[4] However, as no discrimination was made between these two groups, the effect of cyanosis on OUES could not be established.

In conclusion, OUES seems to have an additive value to other established CPET parameters. However, it is as yet unclear which values, absolute or indexed to weight, height, age, BSA, or percentage of predicted, can best be used. Standardisation of the normalisation, measurement units and integration of the OUES in CPET software packages is important for its implementation in the clinical care of this parameter.

Furthermore, cyanotic patients, especially Fontan patients, have an as yet incompletely understood exercise physiology. Therefore, using a single parameter cannot be used for prognostic purposes and both VO_{2max}, HR reserve, oxygen saturation and submaximal variables such as VE/VCO_2 and OUES have to be taken into account.

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