



Minute ventilation/carbon dioxide production in congenital heart disease

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Shareable abstract (@ERSpublications)

V'_E/V'_{CO_2} elevation is a common finding in patients with congenital heart disease. It can be used as a sign for right-to-left shunting, unilateral pulmonary stenosis, pulmonary hypertension and circulatory failure. It is predictive for clinical worsening. <https://bit.ly/33gj3NQ>

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Abstract

This review summarises various applications of how ventilatory equivalent (ventilatory efficiency or better still ventilatory inefficiency) and the minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) slope obtained from cardiopulmonary exercise testing (CPET) can be used in the diagnostic or prognostic workup of patients with congenital heart disease.

The field of congenital heart disease comprises not only a very heterogeneous patient group with various heart diseases, but also various conditions in different stages of repair, as well as the different residuals seen in long-term follow-up. As such, various physiologic disarrangements must be considered in the analysis of increased V'_E/V'_{CO_2} slope from CPET in patients with congenital heart disease. In addition to congestive heart failure (CHF), cyanosis, unilateral pulmonary stenosis and pulmonary hypertension (PH) provide the background for this finding. The predictive value of increased V'_E/V'_{CO_2} slope on prognosis seems to be more important in conditions where circulatory failure is associated with failure of the systemic ventricle. In cyanotic patients, those with Fontan circulation, or those with substantial mortality from arrhythmia, the impact of V'_E/V'_{CO_2} on prognosis is not that important.

Introduction

The survival of patients with congenital heart defects has improved tremendously in the past decades. Nowadays, most of them reach adulthood despite various residuals limiting exercise capacity and quality of life [1, 2]. Cardiopulmonary exercise testing (CPET) is increasingly used in the follow up of these patients in order to detect these residuals, as well as to quantify their importance. Furthermore, some variables obtained from CPET have turned out to predict survival and/or deterioration of disease.

Cardiology for congenital heart defects comprises very heterogeneous patient groups (with very different heart defects), various conditions in different stages of palliation and “repair”, and different residuals in long-term follow-up. As such, many different kinds of physiologic disarrangement must be considered in the analysis of CPET (including the minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) slope).

Physiologic background

The physiologic background of V'_E/V'_{CO_2} is best described by the Bohr equation (figure 1) that has only a few requirements, as follows: 1. there is no carbon dioxide in the inhaled air; 2. the exhaled air is fully saturated with water; 3. the barometric pressure is 760 mmHg; 4. the alveolar partial pressure of gases is



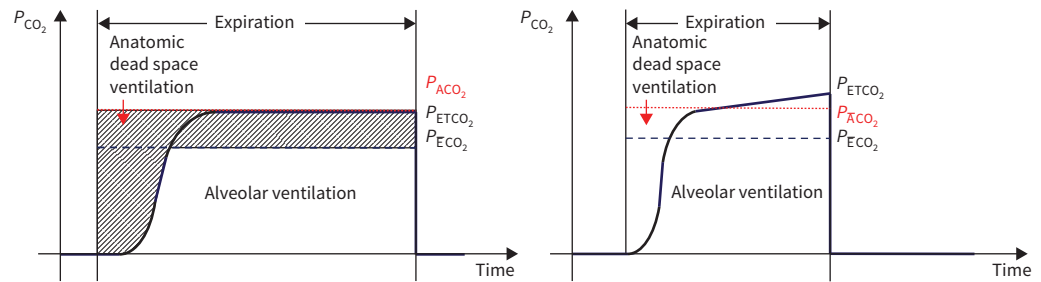


FIGURE 1 Carbon dioxide tension (P_{CO_2}) in the exhalation gas of healthy subjects at rest (left) and at exercise (right). P_{ETCO_2} : end-tidal carbon dioxide tension; P_{ECO_2} : mixed expiratory carbon dioxide tension; P_{ACO_2} : estimated alveolar carbon dioxide tension; $P_{\bar{A}CO_2}$: time-averaged alveolar carbon dioxide tension.

unique throughout the lung and does not change within the ventilatory cycle (such that equation 1 applies).

$$\frac{V'_E}{V'_{CO_2}} = \frac{863}{P_{ECO_2}} = \frac{863}{P_{ACO_2} \cdot (1 - V_D/V_T)} \quad (1)$$

Here, V'_E is under body temperature, pressure, fully saturated with water (BTPS) conditions and V'_{CO_2} is under standard temperature, pressure, dry (STPD) conditions (at 863 mmHg barometric pressure at body temperature, equivalent to 760 mmHg·(310 K/273 K)). Other parameters include mixed expiratory carbon dioxide tension (P_{ECO_2}), alveolar carbon dioxide tension (P_{ACO_2}), dead space volume (V_D) and tidal volume (V_T).

In healthy subjects at rest, P_{ACO_2} can be estimated fairly well from end-tidal carbon dioxide tension (P_{ETCO_2}) or even more easily from arterial carbon dioxide tension (P_{aCO_2}). Therefore, ENGHOFF [3] proposed substituting P_{ACO_2} with P_{aCO_2} in the Bohr equation. However, this has tremendous effects on the definition of dead space, especially when the calculation is also used in subjects without uniform ventilation and without uniform alveolar partial pressures. The new calculation of dead space is nowadays referred to as physiologic dead space and no longer resembles the anatomic dead space, as it includes all kinds of ventilation wasted in achieving a certain P_{aCO_2} . This additional alveolar dead space comprises unperfused alveoli, wasted ventilation from ventilation (V)–perfusion (Q) heterogeneity, an increased V/Q ratio (as in circulatory failure), diffusion impairment and right-to-left shunt [4].

Does end-tidal carbon dioxide tension help to differentiate the components of physiological dead space?

In healthy subjects at rest, P_{ACO_2} can be estimated fairly well from P_{ETCO_2} and the calculated Bohr dead space resembles the anatomical dead space of the conducting airways (the upper airways, larynx and the tracheobronchial tree down to but excluding the acini) reasonably well [4]. There is very little shunting by bronchial and Thebesian veins and the arterial–end-tidal carbon dioxide tension difference (P_{a-ETCO_2}) is <5 mmHg. However, P_{a-ETCO_2} increases as P_{ACO_2} starts to oscillate with breathing (even with very slow breathing and a high V_T) and P_{aCO_2} represents only mean alveolar and not end-tidal P_{ACO_2} . On the other hand, very quick and shallow breathing causes expiratory carbon dioxide tension (P_{CO_2}) to not reach the alveolar plateau [5].

At exercise there is so much carbon dioxide delivered from the working muscles to the alveoli that the oscillation of P_{ACO_2} increases. In exercising healthy subjects, P_{a-ETCO_2} exceeds P_{aCO_2} with a P_{a-ETCO_2} value of –4 mmHg (figure 2) [6, 7]. On the other hand, patients with ventilatory restriction have a high ventilatory rate together with a low V_T that reduces end-tidal P_{a-ETCO_2} . Otherwise, patients with severely obstructed and little ventilated lung units have a continuous high inflow of additional carbon dioxide to the expiratory gas. At the end of expiration there is still efflux from these poorly ventilated regions, such that P_{ETCO_2} is extraordinarily high compared to P_{ECO_2} [7, 8]. This reduced ratio of P_{ECO_2}/P_{ETCO_2} seems to be pathognomonic for severe bronchial constriction, especially at rest [7, 8].

Ventilatory inefficiency

According to the Enghoff modification of the Bohr equation, ventilatory inefficiency (elevated V'_E/V'_{CO_2}) is due either to decreased P_{aCO_2} (such as by voluntary hyperventilation or increased ventilatory drive by

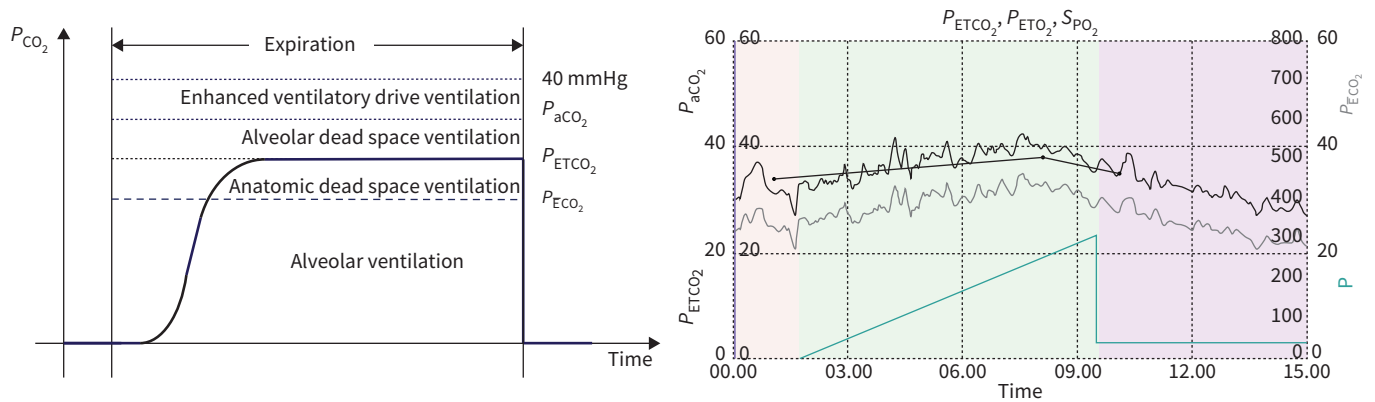


FIGURE 2 Rough interpretation of an elevated ventilatory equivalent (minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2})) with decreased mixed expiratory carbon dioxide tension ($P_{E_{CO_2}}$). The physiologic background is on the left with panel seven of a Wasserman nine-panel plot for a healthy subject on the right. P_{CO_2} : carbon dioxide tension; P_{aCO_2} : arterial carbon dioxide tension; P_{ETCO_2} : end-tidal carbon dioxide tension; P_{ETO_2} : end-tidal oxygen tension; S_{pO_2} : oxygen saturation measured by pulse oximetry.

metabolic acidosis, enhanced peripheral ergoreceptor reflex, or increased chemoreceptor sensitivity) or to elevated physiological dead space (alveolar or anatomical). However, equation 1 also shows that V'_E/V'_{CO_2} is just the reciprocal of $P_{E_{CO_2}}$ and, for a detailed analysis of the reasons for elevated V'_E/V'_{CO_2} , it seems more reasonable to have a close look at $P_{E_{CO_2}}$ and determine the reasons for the low level of this parameter. $P_{E_{CO_2}}$ resembles alveolar ventilation and must be analysed together with P_{ETCO_2} and P_{aCO_2} . The relative contribution of enhanced ventilatory drive, as well as alveolar and anatomic dead space, can be estimated roughly according to figure 2, bearing in mind the difficulties in the interpretation of end-tidal P_{ETCO_2} discussed previously.

V'_E/V'_{CO_2} versus V'_E/V'_{CO_2} slope

The V'_E/V'_{CO_2} quotient can be calculated from every single breath throughout CPET. Usually, it declines hyperbolically at the beginning of the exercise test and reaches a minimum at the ventilatory compensation point, when lactic acidosis starts to increase ventilation independent of carbon dioxide production. On the other hand, the V'_E/V'_{CO_2} slope is measured based on the whole exercise dataset, up to the ventilatory compensation point and is mathematically the asymptote of the V'_E/V'_{CO_2} versus time curve that is almost touched at the ventilatory compensation point. Despite the smallest V'_E/V'_{CO_2} value throughout the test, the V'_E/V'_{CO_2} at the ventilatory compensation point can be measured more reliably [9] and most metabolic carts already correct V'_E/V'_{CO_2} for the dead space of the face mask. The V'_E/V'_{CO_2} slope is much more extensively studied in cardiology, possibly because the slope can be measured even in incomplete exercise tests where the patient does not reach the ventilatory compensation point.

Some centres measure the V'_E/V'_{CO_2} slope over the entire exercise dataset, arguing that this excludes inter-observer variability and gives a better correlation to survival in heart failure with reduced ejection fraction [10]. However, it makes no sense physiologically to include such non-linear values after the ventilatory compensation point, as ventilatory drive is changed substantially at this moment by overt lactic acidosis. Furthermore, it makes the V'_E/V'_{CO_2} slope dependent on the grade of exhaustion at the end of exercise, as these few data points at the end of the test increase the calculated slope [7, 11].

Recently, there have also been publications on the V'_E/V'_{CO_2} intercept, which is the extrapolation of the V'_E/V'_{CO_2} line to the y-axis. This intercept resembles the grade of V'_E/V'_{CO_2} improvement at low to moderate exercise and in turn translates to the improvement in anatomic dead space due to the rise in V_T . In some patients with severe pulmonary hypertension (PH), the intercept is at zero or even has a negative value, which means that there is no improvement or even a worsening in alveolar dead space at exercise [12]. This might be due to early hyperventilation, early failure of the circulation to maintain adequate lung perfusion or increasing local ventilation perfusion heterogeneity in these patients.

V'_E/V'_{CO_2} to detect diagnostic details in congenital heart disease

Right-to-left shunt

Only a small number of all congenital heart defects are cyanotic at birth. In one group, this cyanosis is due to a shunt defect combined with a blood flow obstruction downstream to (or in) the lungs. A second group

has a malconnection on the veno-atrial level (e.g. total anomalous pulmonary venous return), the atrioventricular level (e.g. a double-inlet left ventricle), or the ventriculo-arterial level (e.g. transposition of the great arteries) that directs venous blood into the aorta. A third group consists of those patients with a univentricular heart, where one ventricle is serving both the pulmonary and systemic circulation (e.g. hypoplastic left-heart syndrome) unless Fontan circulation is established. A fourth group has intrapulmonary shunts (e.g. Osler's disease). Later in life a fifth group appears, namely Eisenmenger patients (who are born with a left-to-right shunt). The initial hyperperfusion of the lung leads to pulmonary vascular disease and finally shunt reversal. All these patients are cyanotic at rest. Oxygen saturation measured by pulse oximetry (S_{pO_2}) declines further at exercise [12, 13] when mixed venous blood (and shunting blood) becomes more desaturated and/or the pulmonary obstruction reaches a flow limitation. The nadir of S_{pO_2} is about 30 s after exercise (personal observation).

V_E/V_{CO_2} slope is strongly and inversely associated with resting S_{pO_2} in all congenital heart disease [11], as well as in cyanotic patients with and without PH [12, 13]. (Cyanosis has an additional effect on the V_E/V_{CO_2} slope in patients with PH [11]). As cyanosis is nowadays detected by pulse oximetry, the sensitivity of which has improved tremendously following the introducing of the forehead sensor and software eliminating movement artifacts, pulse oximetry should never be omitted on CPET of patients with congenital heart defects.

Exercise-induced right-to-left shunt

Shunts at the venous, atrial, ventricular or arterial level are usually left-to-right shunts. When the right heart fails or there is an extraordinary rise in pulmonary arterial pressure (PAP) (e.g. PH), a fixed right-ventricular outflow tract stenosis (e.g. pulmonary valve stenosis), or an increase in severe tricuspid regurgitation (sometimes seen in the Ebstein anomaly), these shunts flip to a right-to-left configuration. Even if there is no shunt at rest, these conditions can also open a foramen ovale (PFO) whenever right-atrial pressure exceeds left-atrial pressure [14].

In patients with Fontan circulation (e.g. a univentricular heart with direct connection of the caval veins to the pulmonary artery without the right ventricle), even small increases in PAP can lead to veno-venous fistulae with increasing right-to-left shunt.

When the exercise-induced shunt appears on CPET, there is a sudden rise in V_E/V_{CO_2} , V_E /oxygen uptake (V_{O_2}), respiratory exchange ratio (RER) and end-tidal oxygen tension (P_{ETCO_2}), combined with a sudden decrease in P_{ETCO_2} and S_{pO_2} [14]. In patients with an early-appearing shunt the findings may, with the exception of the decrease in S_{pO_2} , be similar to anxiety-induced hyperventilation [14]. In patients with a shunt only at high workload, the anaerobic threshold and ventilatory compensation point can no longer be determined and it appears, very pronouncedly, as if these two thresholds are reached at the same time point combined with the beginning of decline in S_{pO_2} . In such patients, at the end of the exercise test, all typical findings for the exercise-induced shunt return quickly to the values seen before the opening of the shunt [14].

Finally, it should be mentioned that, in young healthy subjects, heavy exercise with very high pulmonary blood flow and elevated pulmonary blood pressure itself causes alveolar capillary dilatation with a diffusion-perfusion mismatch that ends up in a decline of S_{pO_2} at the peak of exercise [15–17]. Again, cyanosis is nowadays primarily detected by pulse oximetry, but should be considered in the analysis of elevated V_E/V_{CO_2} slope with all the other changes with cyanosis.

Unilateral pulmonary stenosis

Many congenital heart defects are associated with unifocal or multifocal pulmonary artery branch stenoses. Patients with Fallot tetralogy are prone to a stenosis at the former origin of the arterial duct slightly distal to the origin of the left pulmonary artery. This is usually patched at surgical repair but might also appear later, even after retreatment by interventional balloon dilatation or stent implantation. In patients with pulmonary atresia with ventricular septal defect and multiple aorto-pulmonary collateral arteries, these aorto-pulmonary collaterals tend to become stenotic even when they are unifocalised and connected to the right-ventricular outflow tract. They often end up in multifocal central and peripheral stenoses and are difficult to treat because of their high recurrence rate.

There are also post-surgical conditions that might end up with pulmonary branch stenosis. Surgical shunts onto the pulmonary arteries are performed in many patients with complex congenital defects to stabilise pulmonary blood flow until surgical repair or to progress to a univentricular circulation according to

Fontan. When these shunts are connected to one of the pulmonary arteries, there is the risk of stenosis after surgical closure of the shunt.

Another important example is transposition of the great arteries that is nowadays treated by an early arterial switch operation with the Lecompt manoeuvre. This is a translocation of the pulmonary bifurcation anterior to the ascending aorta with the risk of future pulmonary stenosis in one or both pulmonary arteries.

In Fallot patients [18], as well as in patients subsequent to arterial switch repair for transposition [19], it has been shown that an abnormal right-to-left ratio of pulmonary blood flow (obtained by cardiac magnetic resonance) has an increased V_E/V_{CO_2} slope compared to patients with balanced pulmonary blood flow. This increased V_E/V_{CO_2} slope improves after ballooning the stenosis [20] or after stenting [21]. The decline of the V_E/V_{CO_2} slope after treatment is directly associated with improvement in pulmonary blood flow ratio [20, 21]. A stenosis of the main pulmonary artery does not cause any perfusion mismatch and, therefore, shows no elevation in V_E/V_{CO_2} slope [22].

Pulmonary hypertension

All classes of PH can occur in patients with congenital heart defects (table 1), and both diagnosis and treatment have been extensively reported upon recently [24]. From idiopathic pulmonary arterial hypertension (PAH) [25] and left-heart failure PH [26, 27], we know that V_E/V_{CO_2} and P_{ETCO_2} are closely associated with PAH and this also holds true in congenital heart disease [28]. After vasodilator therapy, V_E/V_{CO_2} improves in Eisenmenger patients [29]; however, specificity is too low to use CPET and especially V_E/V_{CO_2} slope as a screening tool for PH in patients with congenital heart defects [28].

Acyanotic patients with congenital heart disease and PH are rare, and it should be assumed that V_E/V_{CO_2} reacts similarly to elevated pulmonary vascular resistance or left-heart failure. Furthermore, it should be expected that as the number of elderly patients with congenital heart disease continues to rise, the number of patients with left-heart failure especially should also increase over the coming decades [30, 31].

Enhanced ergoreceptor/chemoreceptor reflex

In patients with acquired congestive heart failure (CHF) there are often changes in ventilation pattern. At night there might be sleep apnoea, while at exercise one can detect exercise-induced oscillatory ventilation as well as an enhanced ventilatory drive measured as low P_{aCO_2} . In congenital cardiology however, cyanotic patients without heart failure show minimal nocturnal dips in oxygen saturation (so no sleep apnoea) [32]. This might be in contrast to patients with circulatory failure, as periodic breathing is only described in two acyanotic patients with right-heart failure [33]. There are only a few descriptions of exercise oscillatory ventilation in Fontan patients [34, 35]; however, they are contradictory concerning prognostic capabilities.

Concerning the impact of ventilatory drive on elevated V_E/V_{CO_2} , there are only a few studies analysing exactly what is contributing to alveolar dead space or enhanced ventilation and most of these studies do not report an arterial blood gas analysis (*i.e.* P_{aCO_2}). Even those few that do are not consistent, as some report slightly reduced P_{aCO_2} at rest which normalises on exercise [13, 36], while others report usually lowered P_{aCO_2} in Eisenmenger patients [37], both with [36] and without [37] an impact on survival.

V_E/V_{CO_2} to estimate prognosis in congenital heart disease

Early studies looked for risk factors from CPET in the whole cohort of congenital heart disease. V_E/V_{CO_2} is associated with functional class [38] and can predict survival [38, 39] independently from New York Heart Association (NYHA) class [38], although the importance of the risk factor is low compared to resting S_{pO_2} , peak V_{O_2} , age, or heart rate reserve [39, 40]. However, these types of study do not help too much as, firstly, we already know that the patient group with the worst cyanosis, most severe PH and the least exercise capacity, which is the Eisenmenger group, has the worst prognosis compared to the other less disabled patients with congenital heart disease. Secondly, the mixture of various different diagnoses and conditions might dilute the results [40] and, as such, studies on isolated patient groups with similar conditions are needed to evaluate the additional prognostic importance of certain biomarkers (such as CPET variables) beyond simple parameters like diagnosis, age, body mass index, resting S_{pO_2} and functional class.

Cyanotic congenital heart disease and Eisenmenger's disease

In cyanotic patients with congenital heart disease, death was not only attributed to heart failure but also to sudden death (*e.g.* arrhythmia, lung haemorrhage, dissection of ascending aorta and cerebral accidents) [41, 42]

TABLE 1 Types of pulmonary hypertension (PH) according to European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines [23]; those associated with congenital heart defects are marked in bold

Classification	Description
1	PAH
1.1	Idiopathic
1.2	Heritable
1.2.1	BMPR2 mutation
1.2.2	Other mutations
1.3	Drug and toxin induced
1.4	Associated with:
1.4.1	Connective tissue disease
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart disease
1.4.4.1	Eisenmenger's syndrome
1.4.4.2	PAH associated with prevalent systemic to pulmonary shunt
1.4.4.3	PAH with small/coincidental defects
1.4.4.4	PAH after defect correction
1.4.5	Schistosomiasis
1'	Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1'.1	Idiopathic
1'.2	Heritable
1'.2.1	EIF2AK4 mutation
1'.2.2	Other mutations
1'.3	Drug, toxin and radiation induced
1'.4	Associated with:
1'.4.1	Connective tissue disease
1'.4.2	HIV infection
1''	Persistent PH of the newborn
2	PH due to left-heart disease
2.1	Left-ventricular systolic dysfunction
2.2	Left-ventricular diastolic dysfunction
2.3	Valvular disease, obstruction and congenital cardiomyopathy
2.4	Congenital/acquired left-heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5	Congenital/acquired pulmonary vein stenosis
3	PH due to lung disease and/or hypoxia
3.1	COPD
3.2	ILD
3.3	Other pulmonary diseases with mixed restrictive and obstructive patterns
3.4	SDB
3.5	Alveolar hypoventilation disorders
3.6	Chronic exposure to high altitude
3.7	Developmental lung diseases
4	CTEPH and other pulmonary artery obstructions
4.1	CTEPH
4.2	Other pulmonary artery obstructions
4.2.1	Angiosarcoma
4.2.2	Other intravascular tumours
4.2.3	Arteritis
4.2.4	Congenital pulmonary arterial stenoses
4.2.5	Parasites (hydatidosis)
5	PH with unclear and/or multifactorial mechanisms
5.1	Haematological disorders (chronic haemolytic anaemia, myeloproliferative disorders and splenectomy)
5.2	Systemic disorders (sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis and neurofibromatosis)
5.3	Metabolic disorders (glycogen storage disease, Gaucher's disease and thyroid disorders)
5.4	Others (pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis) and segmental PH)

PAH: pulmonary arterial hypertension; BMPR2: bone morphogenetic protein receptor type 2; EIF2AK4: eukaryotic translation initiation factor 2 alpha kinase 4; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; SDB: sleep disordered breathing; CTEPH: chronic thromboembolic pulmonary hypertension.

and other organ failure [24]. Despite peak V_{O_2} having an important impact on survival, V_E/V_{CO_2} was not related to outcome [39].

Univentricular heart with Fontan circulation

Exercise parameters have an important prognostic value in patients with univentricular heart and Fontan circulation [43]. Despite a substantial elevation of both V_E/V_{CO_2} slope and V_E/V_{CO_2} , these values were not predictive for survival or transplantation [44]. V_E/V_{CO_2} only predicts hospitalisation and various morbidities [44, 45].

Fallop tetralogy

In this patient group, V_E/V_{CO_2} is elevated mainly because of pulmonary branch stenosis [18] and a failing left ventricle. Possibly due to a high rate of sudden arrhythmic deaths, V_E/V_{CO_2} is not an additive risk factor for QRS duration and peak V_{O_2} in predicting survival [46]. However, it does predict event-free survival independently from QRS duration and peak V_{O_2} [46–48].

Transposition of the great arteries after atrial redirection according to Mustard or Senning

In patients with transposition of the great arteries, survival after atrial redirection depends mainly on arrhythmia or right-ventricular (systemic) failure, whereas reinterventions were performed for baffle stenosis or leakage [49]. The V_E/V_{CO_2} slope is predictive for survival without emergency hospital admissions [50].

Conclusions

It is inappropriate to summarise over various congenital heart diseases and the various conditions of such patients throughout life. The predictive value of increased V_E/V_{CO_2} slope on prognosis seems to be more important in conditions where circulatory failure is associated with failure of the systemic ventricle. In cyanotic patients, patients with Fontan circulation, or those with substantial mortality from arrhythmia, the impact of V_E/V_{CO_2} on prognosis is not that important. However, the V_E/V_{CO_2} slope is an excellent predictor of clinical deterioration, unscheduled hospitalisation or other non-fatal clinical events both independently and in addition to peak V_{O_2} .

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