Minute ventilation/carbon dioxide production in chronic heart failure

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In chronic heart failure, the V'_E *versus* V'_{CO_2} relationship gives information about V'_E/perfusion mismatch and exercise-induced dead space changes, has a relevant prognostic power, and may be modified in the presence of comorbidities https://bit.ly/2NwZWHa

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ABSTRACT In chronic heart failure, minute ventilation (V'_E) for a given carbon dioxide production (V'_{CO_2}) might be abnormally high during exercise due to increased dead space ventilation, lung stiffness, chemo- and metaboreflex sensitivity, early metabolic acidosis and abnormal pulmonary haemodynamics. The V'_E *versus* V'_{CO_2} relationship, analysed either as ratio or as slope, enables us to evaluate the causes and entity of the V'_E/perfusion mismatch. Moreover, the V'_E axis intercept, *i.e.* when V'_{CO_2} is extrapolated to 0, embeds information on exercise-induced dead space changes, while the analysis of end-tidal and arterial CO_2 pressures provides knowledge about reflex activities. The V'_E *versus* V'_{CO_2} relationship has a relevant prognostic power either alone or, better, when included within prognostic scores. The V'_E *versus* V'_{CO_2} slope is reported as an absolute number with a recognised cut-off prognostic value of 35, except for specific diseases such as hypertrophic cardiomyopathy and idiopathic cardiomyopathy, where a lower cut-off has been suggested. However, nowadays, it is more appropriate to report V'_E *versus* V'_{CO_2} slope as percentage of the predicted value, due to age and gender interferences. Relevant attention is needed in V'_E *versus* V'_{CO_2} analysis in the presence of heart failure comorbidities. Finally, V'_E *versus* V'_{CO_2} abnormalities are relevant targets for treatment in heart failure.

Physiological aspects of the V'_E *versus* V'_{CO_2} relationship and its association with heart failure prognosis

During an exercise with a progressively increasing workload, minute ventilation (V'_E) increases in four distinct domains. The first domain is aerobic carbon dioxide production (V'_{CO_2}) in parallel with oxygen

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uptake (V'_{O_2}) increase, the second is V'_{CO_2} anaerobic production with acidosis buffered by the available bicarbonate systems, the third is hydrogen (H^+) when acidosis becomes unbuffered, and the fourth, evident in a few elite athletes, is related to heat dispersion [1, 2]. The last, rarely observed in normal subjects, is the main ventilatory drive for furred animals with no or extremely limited sweat production. Hyperventilation due to heat dispersion is known as panting. In dogs, panting is associated with extreme vasodilation of the tongue, while in humans panting is exceeded by thermal dispersion through sweat, so that it seldom becomes the driving force for V'_E, and only at the very end of exercise. According to the different V'_E domains, four slopes on the V'_E *versus* workload relationship can be identified in athletes, but only three can be identified in subjects who are not athletes [2, 3] (figure 1). Consequently, up to the respiratory compensation point (RCP), which separates buffered from unbuffered acidosis, the relationship between V'_E and V'_{CO_2} is linear. The buffering capacity of the body during a short-lasting exercise mainly depends on the amount of bicarbonates available, which in turn strictly relates to pre-exercise V'_E. In case of voluntary hyperventilation, which usually takes place immediately before and/or in the early phases of exercise, or of hyperventilation related to ambient conditions or to the disease itself, the reduced capacity

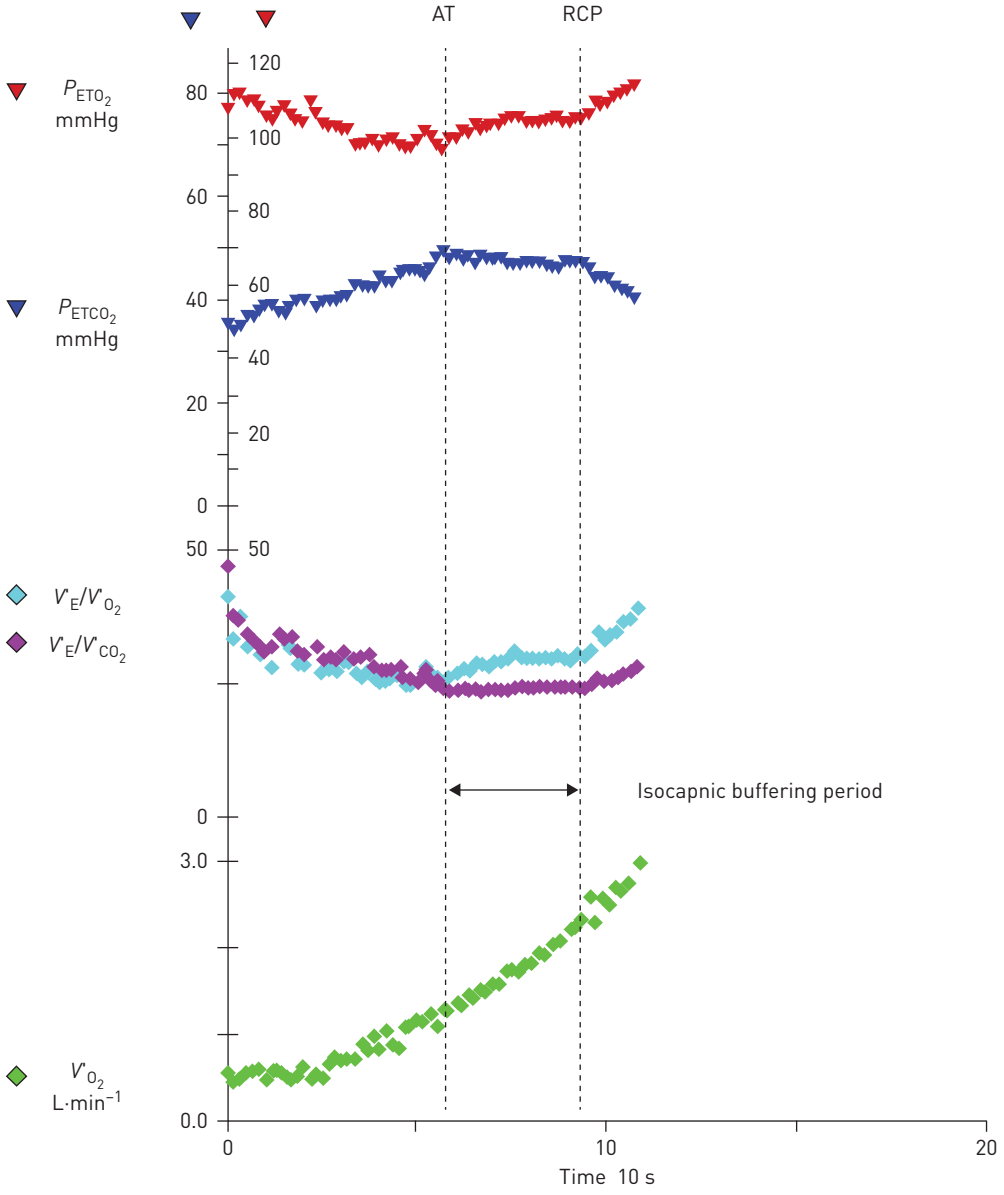

FIGURE 1 A few cardiopulmonary exercise parameters during a ramp exercise protocol. AT: anaerobic threshold; RCP: respiratory compensation point; P_{ETO_2}: end-tidal oxygen pressure; P_{ETCO_2}: end-tidal carbon dioxide pressure; V'_E: ventilation; V'_{O_2}: oxygen uptake; V'_{CO_2}: carbon dioxide production. Reproduced from [3] with permission.

of lactate buffering shortens the length of the isocapnic buffering period and reduces the V'_{O_2} therein [4, 5]. At high altitude, where hypoxia-induced hyperventilation is the norm, the isocapnic buffering period even disappears (figure 2) [6]. Of note, in heart failure, the V'_{O_2} increase during the isocapnic buffering period is directly associated with overall exercise performance [3, 7].

In heart failure patients, the mere identification of these three ventilation periods during a maximal exercise carries a relevant prognostic power [8]. The lack of identification of the ventilatory thresholds 1 and 2, as defined in the German literature [9], *i.e.* the anaerobic threshold (AT) and the RCP, respectively, can be due to several causes, such as periodic breathing, erratic breathing, uneven muscle fibre perfusion or metabolism [10]. The nonidentification of AT in an exercise where anaerobic metabolism has been reached, as suggested by a respiratory exchange ratio (V'_{CO_2}/V'_{O_2}) >1.05, is associated with a poor prognosis [11]. This happens in ≈10% of chronic heart failure patients who perform a maximal or nearly maximal cardiopulmonary exercise testing (CPET) [11]. An intermediate prognosis is that of heart failure patients with an identified AT but an unidentified RCP [8]. Figure 3, derived from the analysis of 1995 heart failure patients belonging to the Metabolic Exercise Cardiac Kidney Index score database, reports the survival of patients with identified AT and RCP (39% of cases), with identified AT and unidentified RCP (46% of cases), and with unidentified AT and RCP (15% of cases). The best prognosis was observed in patients in whom both AT and RCP were identified, whereas the risk of reaching the study end-point

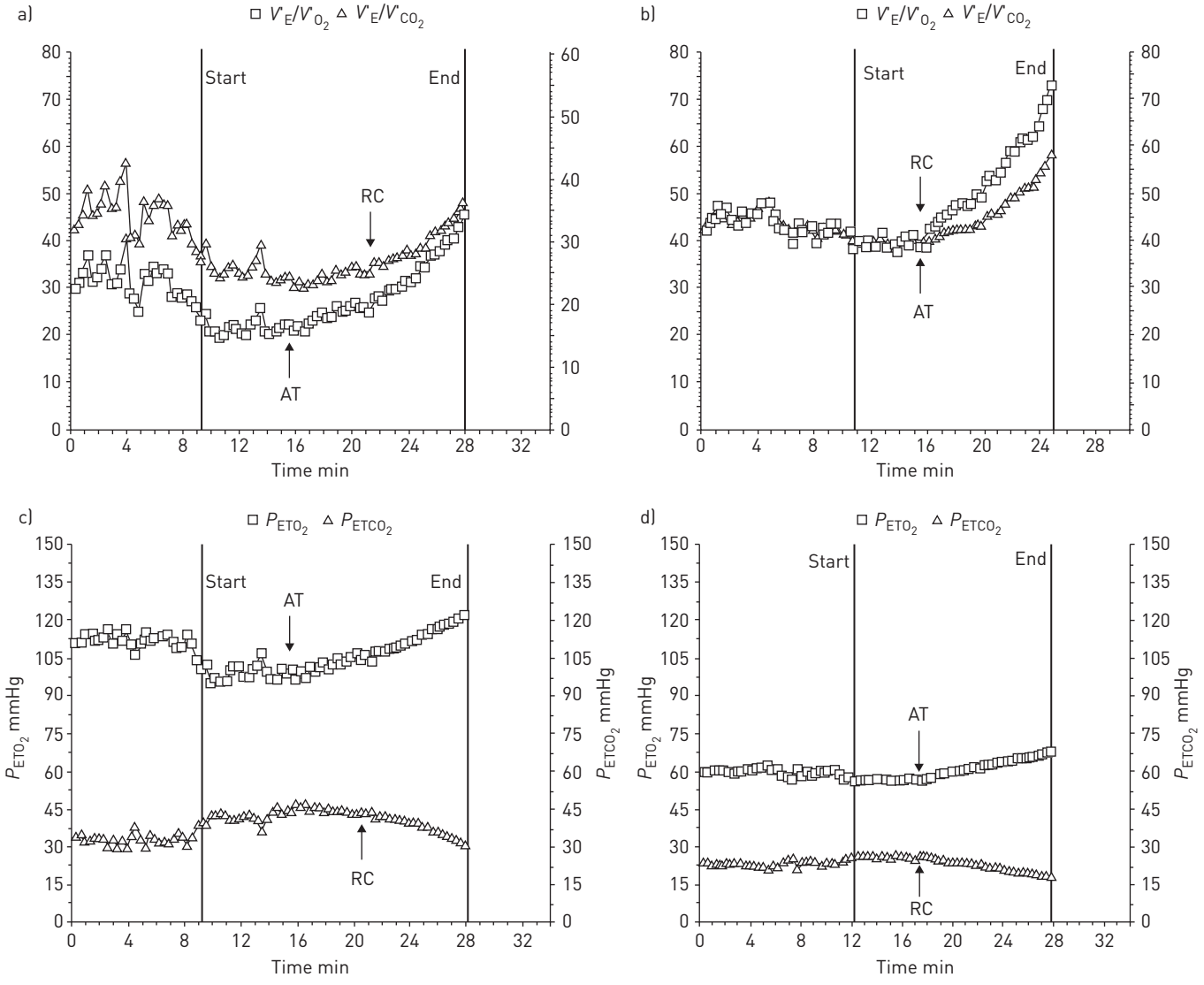

FIGURE 2 Cardiopulmonary exercise parameters during a ramp exercise protocol: oxygen uptake (V'_{O_2}) and carbon dioxide production (V'_{CO_2}) a) at sea level and b) at high altitude (Capanna Regina Margherita, Monte Rosa, Italian Alps, 4559 m) and end-tidal oxygen pressure (P_{ETO_2}) and end-tidal carbon dioxide pressure (P_{ETCO_2}) c) at sea level and d) at high altitude. V'_E: ventilation; RC: respiratory compensation point; AT: anaerobic threshold. Reproduced from [6] with permission.

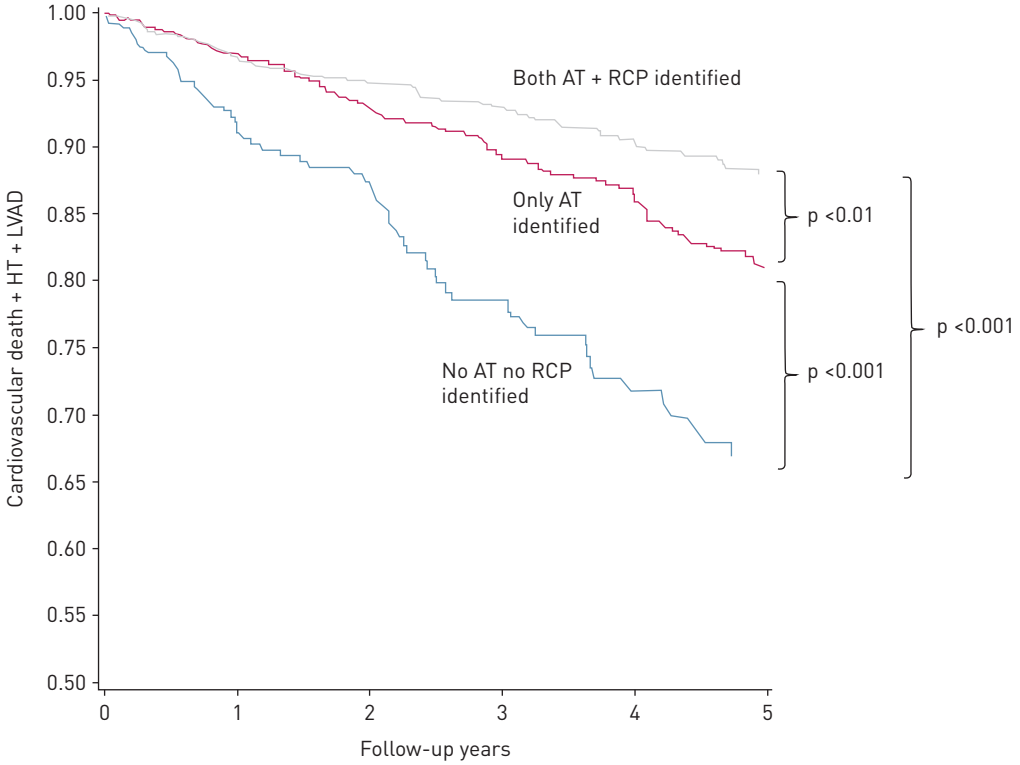

FIGURE 3 5-year survival analysis in heart failure patients in whom anaerobic threshold (AT) and respiratory compensation point (RCP) were not identified (n=292), in whom only AT was identified (n=920) and in whom both AT and RCP (n=783) were identified. HT: heart transplant; LVAD: left ventricular assist device. Reproduced from [8] with permission.

(composite of cardiovascular death, urgent heart transplant or left ventricular assist device) increased by 1.4 times in patients with AT but not RCP, and by 2.7 times in patients in whom neither AT nor RCP were identified [8]. Of note, the prognostic power of the identification of the aforementioned thresholds is independent of the V'_{O_2} value reached at the threshold. Thus, as regards heart failure patients' survival, any AT V'_{O_2} value, albeit very low, is better than an unidentified AT [11].

Ventilation is the sum of alveolar (V'_A) and dead space (V'_D) ventilation, which is the part of V'_E that does not participate in gas exchange. In normal subjects, V'_A progressively increases during exercise, while V'_D decreases, so that the linear relationship between V'_E and V'_{CO_2} has a positive intercept on the V'_E axis, *i.e.* the extrapolation of V'_E at V'_{CO_2}=0 (figure 4) [12]. Above RCP, V'_E increase is mainly due to respiratory rate increase, with a minimal further increase in tidal volume. During exercise, the end-expiratory CO_2 pressure (P_{ETCO_2}) increases up to the isocapnic buffering period, when its highest value is reached. In normal subjects, both P_{ETCO_2} and arterial CO_2 pressure (P_{aCO_2}) remain within their normal ranges up to RCP, but, above it, both P_{aCO_2} and P_{ETCO_2} decrease [10, 13]. Accordingly, during exercise, if P_{ETCO_2} is low but P_{aCO_2} is in the normal range, V'_D must be increased due to V'_E/perfusion (Q') mismatch, with a prevalence of ventilated but not perfused lung zones. Differently, if P_{aCO_2} is low, the increase in V'_E is due to other stimuli such as reflexes (chemo-, metaboreflexes), so that the observed V'_E/Q' mismatch is a consequence and not a cause of hyperventilation. These two types of V'_E increase have different denominations: hyperpnoea when P_{aCO_2} is in its normal range, and hyperventilation when P_{aCO_2} is low [14–16.] Experimentally, during exercise, a fixed increase in V'_D is associated with an upward shift of the V'_E *versus* V'_{CO_2} relationship, whereas a progressive increase in V'_D during exercise generates an increased V'_E *versus* V'_{CO_2} relationship slope (figure 4) [12, 17]. In brief, in normal subjects, the V'_E *versus* V'_{CO_2} relationship slope increase is linear up to RCP, with a positive Y-axis (V'_E axis) intercept. Remarkably, the Y-axis intercept is not an indicator of V'_D unless it has been added externally, but it provides information about V'_D changes during exercise [18, 19]. The role of Y-axis intercept evaluation in specific comorbidities such as COPD/pulmonary arterial hypertension are discussed in detail later.

Finally, the analysis of the last part of exercise, *i.e.* the part above RCP, provides useful information. Indeed, when a further increase in the slope of the V'_E *versus* V'_{CO_2} relationship slope is observed, then the increase of V'_E is only due to an increase of respiratory rate, so that V'_D increases, but no or very limited increase of V'_A is present [20]. In these cases, the $P_{ETCO_2}-P_{aCO_2}$ difference becomes significantly

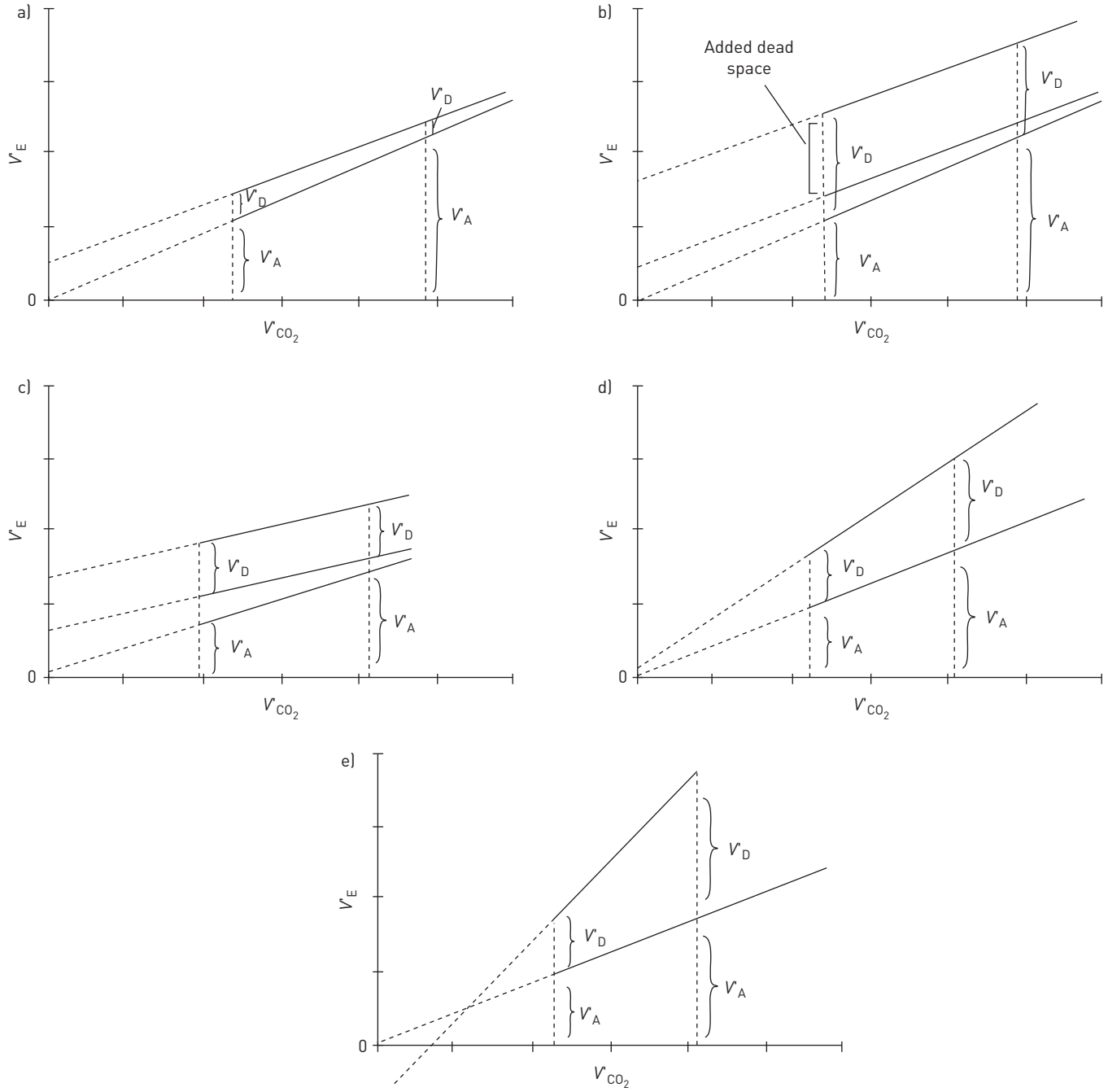

FIGURE 4 Schematic representation of ventilation (V'_E) and carbon dioxide changes (V'_{CO_2}) during exercise in five different conditions: a) normal subject; b) normal subject with added external dead space; c) COPD; d) heart failure; e) pulmonary arterial hypertension. Dead space (V'_D) and alveolar (V'_A) ventilation are also reported. Reproduced from [12] with permission.

negative. As a matter of fact, in parallel with the study of the V'_E *versus* V'_{CO_2} relationship, both as slope and as Y-intercept, attention must be dedicated to P_{ETCO_2}, P_{aCO_2} and $P_{ETCO_2}-P_{aCO_2}$ difference during workload increase, because, combined, they provide us with clear information about V'_D changes and V'_E/Q' mismatch during exercise.

How to report the V'_E *versus* V'_{CO_2} relationship

The relationship between V'_E and V'_{CO2} can be reported as the ratio or as the exercise relationship slope, but it used to be reported as V'_E at V'_{CO2}=1 L·m^{-1}. In normal subjects, the V'_E/V'_{CO2} ratio decreases at the beginning of exercise, then stays still and increases above RCP, reproducing a characteristic U shape (figure 5). However, several shapes of the V'_E/V'_{CO2} ratio can be observed in specific clinical conditions,

and looking at the shape can provide useful information, as follows. 1) In case of pre-test hyperventilation, the V'_E/V'_{CO2} ratio progressively declines during exercise; 2) in COPD, the V'_E/V'_{CO2} ratio is high and stays still or shows a limited reduction during exercise; 3) in case of heart failure, the V'_E/V'_{CO_2} ratio shifts upward, but usually maintains its U shape; 4) in case of pulmonary hypertension, V'_E/V'_{CO_2} ratio values are elevated and steady or progressively increasing in relation to the severity of pulmonary hypertension. The V'_E/V'_{CO_2} ratio has been reported at various moments of exercise, including submaximal and peak exercise [21–23.] The less variable V'_E/V'_{CO_2} ratio is probably the lowest recorded in a ramp exercise protocol, and it has been suggested as the value to consider as more clinically relevant [24–26.] In an exercise with a progressively increasing workload, the so-called ramp protocol test, the V'_E *versus* V'_{CO_2} relationship slope is physiologically measured from the beginning of exercise, usually after 1 min to avoid alteration of V'_E associated with patients' adaptation to exercise, up to the RCP, above which a second slope of the V'_E *versus* V'_{CO_2} relationship is usually present. In some laboratories, the V'_E *versus* V'_{CO_2} slope is assessed throughout the exercise, and it is consequently a little bit higher, although, when doing so, the clinical significance of the Y-axis intercept becomes at least less clear, if not lost [27, 28]. However, it is likely that both analyses can be accepted, provided that the CPET report clearly states which method has been applied, since reference values are probably different. Both the V'_E/V'_{CO_2} ratio and the V'_E *versus* V'_{CO_2} relationship slope (plus its Y-axis intercept) must be assessed in heart failure patients. Indeed, in parallel with the P_{ETCO_2} value, the V'_E/V'_{CO_2} ratio value during the isocapnic buffering period, when it is flat, gives information on the activation of the ventilation reflex [13], while the relationship slope tells more directly about the efficiency of V'_E during exercise and the development of V'_D.

Normal values of the slope of the V'_E *versus* V'_{CO_2} relationship and of V'_E/V'_{CO_2} ratio

Sex- and age-specific normal values of the V'_E/V'_{CO_2} ratio, both at AT and as the lowest value, of V'_E *versus* V'_{CO_2} relationship slope and Y-axis intercept for normal subjects have been reported by SUN *et al.* [24], with a lowest V'_E/V'_{CO_2} cut-off value for poor prognosis ⩾33 [25]. Differently, the normal values of the V'_E *versus* V'_{CO_2} relationship slope have been placed by several authors below an arbitrary value of 35, assuming that there is no influence of sex and age [29–32.] This arbitrary, "good-for-all" cut-off value has been proposed in different studies and even in guidelines [33], although the V'_E *versus* V'_{CO_2} slope increases with age and is higher in females [29]. In their pioneering work, KLEBER *et al.* [34] utilised a percentage of predicted value to define the prognostic power of the V'_E *versus* V'_{CO_2} slope in heart failure. However, the normal population was small (n=101) and included 56 females. Similarly, other

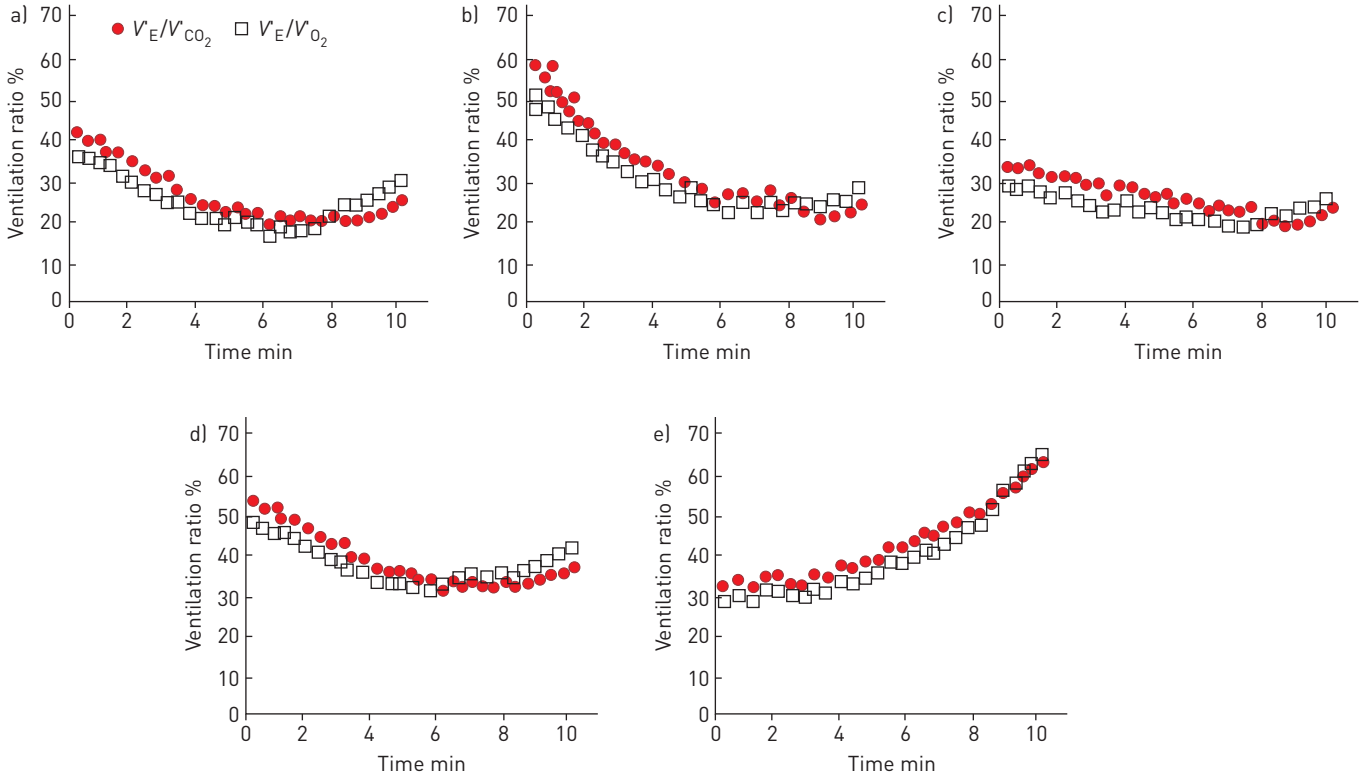

FIGURE 5 Minute ventilation (V'_E)/oxygen uptake (V'_{O_2}) and V'_E/carbon dioxide production (V'_{CO_2}) ratio behaviour in a ramp exercise protocol in a) normal subjects; b) in case of pre-test hyperventilation; c) in COPD; d) in heart failure; and e) in pulmonary arterial hypertension.

normal-value equations were proposed [24, 35, 36] but all from small samples, except very recently, when Salvioni *et al.* [29] reported normal values of a large population of both genders and all ages. Figure 6 [29] shows the regression equations of V'_E *versus* V'_{CO_2} slope relationship obtained in 1136 normal subjects (773 males and 363 females). The available regression equations to calculate the percentage of predicted V'_E/V'_{CO_2} slope are reported in table 1 [29]. Most importantly, Salvioni *et al.* [29] demonstrated that the percentage of V'_E *versus* V'_{CO_2} slope enhances the prognostic capacity of V'_E *versus* V'_{CO_2} slope in patients with severe heart failure (peak V'_{O_2} <14 mL·min^{-1}·kg^{-1}), who are more in need of a precise life expectancy estimation.

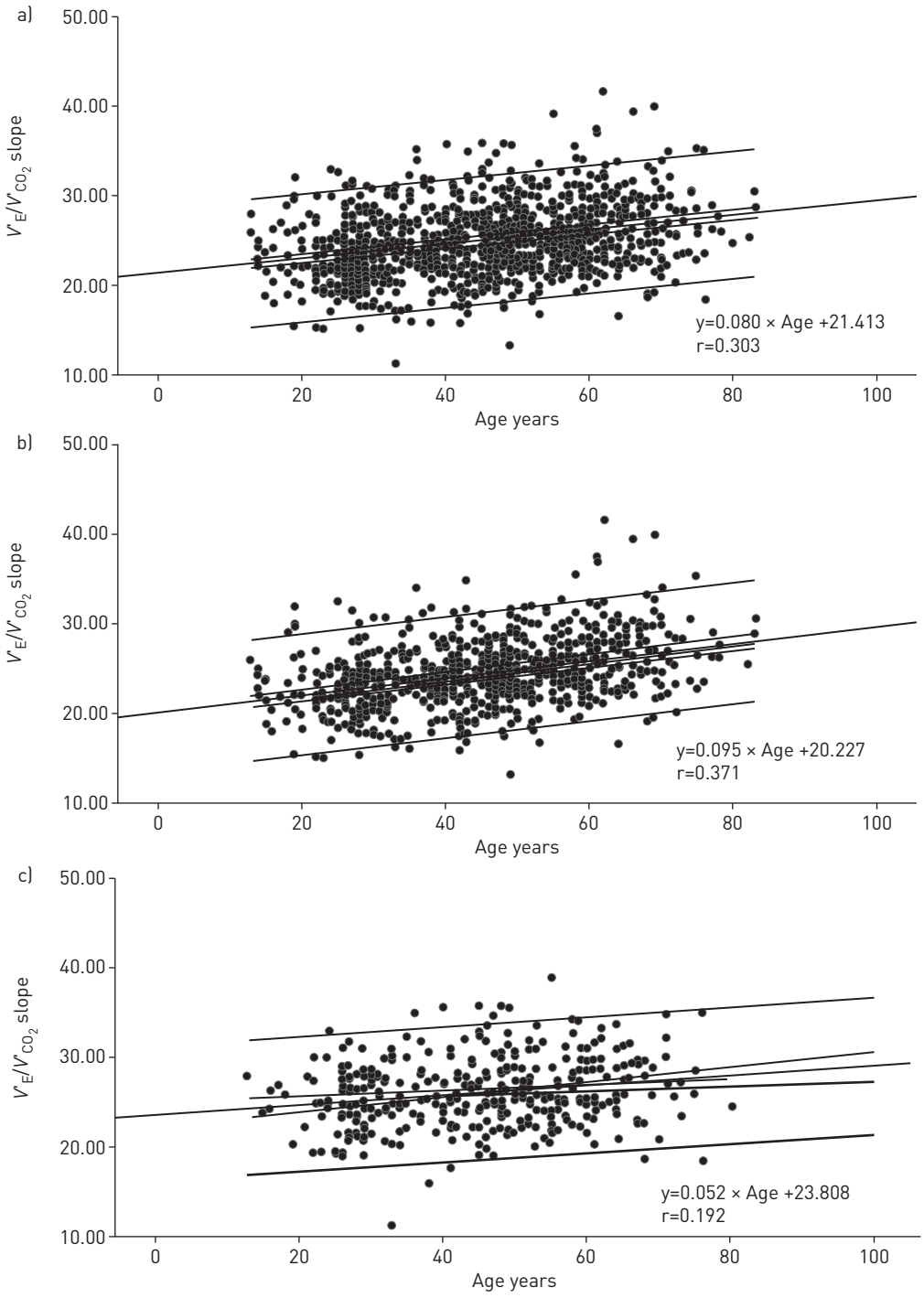

FIGURE 6 Linear regression between minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) slope and age in a) normal subjects (n=1136); b) males (n=773); and c) females (n=363). Reproduced from [29] with permission.

TABLE 1 Regressions proposed to calculate predicted ventilation/carbon dioxide production slope

First author, year (study) [reference]	Subjects (male/female)	Males	Females	Age years	Ergometer
Salvioni, 2020 [29]	1136 (773/363)	Y=0.095 * age +20.2	Y=0.052 * age +23.8	13–83	Cycle ergometer
Koch, 2009 (SHIP) [35]	534 (253/281)	Y= (−1.5*age+0.5*age2+2.5sex −0.5*age*sex)+22[#]		25–80	Cycle ergometer
Kleber, 2000 [34]	101 (45/56)	Y=0.13*age +19.9	Y=0.12*age+24.4	16–75	Treadmill
Neder, 2001 [36]	120 (60/60)	Y=0.12*age+21	Y=0.08*age+25.2	20–80	Cycle ergometer
Poulin, 1994 [37]	224 (128/96)	Y=0.29*age+7.69	Y=0.20*age+10.08	55–86	Treadmill
Sun, 2002 [24]	474 (310/164)	Y=(0.082*age−0.0723*height)+34.38		37–74	Cycle ergometer/ Treadmill

Data are presented as n or range, unless otherwise stated. Reproduced and modified from [29] with permission. [#]: age was graded in five classes (25–34, 35–44, 45–54, 55–64 and ⩾65 years) and coded for the calculation.

Mechanical and pharmacological manipulation of the V'_E *versus* V'_{CO_2} relationship

The V'_E *versus* V'_{CO_2} slope was assessed after a few manipulation manoeuvres. As mentioned earlier, an increase in external V'_D shifts the V'_E *versus* V'_{CO_2} relationship upward, but it does not affect the slope [18]. Differently, in normal volunteers, shortly after an acute saline infusion at a rate allowing an infusion ranging between 25 and 30 mL·kg^{-1} in <30 min, a significant (≈12%) increase of V'_E *versus* V'_{CO_2} relationship slope was observed [38, 39]. Noteworthy, when alveolar–capillary membrane fluid movement is hampered by alveolar β_2-receptor blockade, *i.e.* when active absorption of fluids from the alveolar space is impeded [40, 41], the V'_E *versus* V'_{CO_2} slope increase is ∼10%, with a further increase when rapid saline infusion and alveolar β_2-receptor blockade are combined [39]. Altogether, these data suggest a direct relationship between lung stiffness generated by an increased lung fluid content and V'_E inefficiency [42].

Reflex-mediated (metabo- and chemoreflex) increase in V'_E is also associated with a V'_E *versus* V'_{CO_2} slope increase. This phenomenon was shown in exercises performed during acute high-altitude exposure, *i.e.* with hypobaric hypoxia [43–46.] Conversely, at a simulated altitude of 2000 m, the V'_E *versus* V'_{CO_2} slope increases in heart failure patients. Interestingly, carvedilol in the same laboratory conditions significantly reduces the slope from 39±10 to 32±14, most likely because of a reduction of chemoreceptor stimulation by hypoxia through β_1-, β_2- and α-receptor blockade [47].

The relationship between V'_E and V'_{CO_2}, either measured as the ratio or as the relationship slope, is high in heart failure. There are several possible causes, including abnormal increased lung stiffness due to interstitial pulmonary alterations (increased intrathoracic fluids, fibrosis, *etc.*), increased chemo- and metaboreflex sensitivity, early metabolic acidosis and abnormal pulmonary haemodynamics with secondary pulmonary hypertension and high pulmonary wedge pressure. The combination of all the above mechanisms lead to V'_E/Q' mismatch, so that, for a given V'_{CO_2}, V'_E is increased. In heart failure, the elevated V'_E *versus* V'_{CO_2} relationship is associated with a low P_{ETCO_2}, which should be analysed mainly during the isocapnic buffering period (between AT and RCP) when P_{ETCO_2} most directly mirrors reflex activity [13]. In a pioneering, large, multicentre study on V'_E abnormalities in heart failure, Wasserman *et al.* [48] showed that, in heart failure patients, 8%, 47% and 45% of V'_E increase is due to P_{aCO_2}, V'_{CO_2} and V'_D volume (V_D)/tidal volume (V_T) ratio, respectively. More recently, Mezzani *et al.* [49] documented that the overactivation of reflex response is the main cause of the observed increase of V'_E/V'_{CO_2}, while haemodynamic impairment plays an additional role in more advanced stages of heart failure. As regards the comparison between heart failure patients with preserved and with reduced ejection fraction, Van Iterson *et al.* [17] showed during exercise an impaired V'_E efficiency in both groups, despite a higher V'_E *versus* V'_{CO_2} slope value in those with reduced ejection fraction as well as a different P_{aCO_2} and V_D/V_T behaviour. Indeed, in heart failure patients with preserved ejection fraction, hyperpnoea, *i.e.* low V_D/V_T and normal P_{aCO_2}, seems to be the most prevalent cause of V'_E increase, whereas in those with reduced ejection fraction, hyperventilation, *i.e.* overactivated reflexes and low P_{aCO_2}, seems to be the main cause of the increase of V'_E [17, 50]. It must be underlined that heart failure patients with preserved ejection fraction actually suffer from a hodgepodge of different diseases, so that averaging data may be misleading. Several reports have shown the relevant role of V'_E *versus* V'_{CO_2} relationship in heart failure prognosis [22, 34, 51–60] with an average cut-off value of 35 [61]. Indeed, a classification of heart failure severity based on V'_E *versus* V'_{CO_2} slope has been suggested [62] and reported in heart failure guidelines [33]. Several heart failure prognostic scores include CPET data [63–71]. Notably, V'_E *versus* V'_{CO_2} slope maintains its strong prognostic role, even in composite heart failure scores [64, 65, 68]. In heart failure, a strong correlation has been described between V'_E *versus* V'_{CO_2} relationship abnormalities and sleep apnoea,

which also has a relevant prognostic power in heart failure [72, 73]. Of note, the V'_E *versus* V'_{CO_2} relationship during exercise, regardless of how it is measured, has a relevant prognostic power both in heart failure patients with preserved and reduced ejection fraction, albeit stronger in the former [74]. Finally, the prognostic meaning of specific V'_E *versus* V'_{CO_2} slope values must be evaluated considering patients' age, date of CPET and healthcare situation. Indeed, the V'_E *versus* V'_{CO_2} slope was reported to be higher in elderly patients [75], while for CPETs performed in 1993–2000, 2000–2005, 2005–2010 and 2010–2015, for a V'_E *versus* V'_{CO_2} of 34, a progressive reduction of the risk of the composite event cardiovascular death, urgent heart transplant or left ventricular assist device at 2 years was observed from ≈20%, to ≈12%, to ≈8% and ≈8%, respectively [76]. Therefore, in chronic heart failure patients, the prognostic meaning of the V'_E *versus* V'_{CO_2} relationship slope must be contextualised for the current local healthcare situation. This is relevant when comparing previous and present survival results as well as studies done in countries with different access to healthcare facilities.

V'_E *versus* V'_{CO_2} relationship in heart failure therapy

Drugs used for heart failure treatment directly influence the V'_E *versus* V'_{CO_2} relationship [77]. Specifically, angiotensin-converting enzyme (ACE) inhibitors, but not angiotensin receptor blockers, improve both alveolar–capillary membrane diffusion and V'_E *versus* V'_{CO_2} relationship [78, 79], but the V'_E *versus* V'_{CO_2} slope improvement associated with ACE inhibitors is counteracted by the concomitant use of aspirin [78]. Accordingly, it has been suggested that the ACE inhibitor-induced V'_E *versus* V'_{CO_2} slope reduction is mediated by lung stiffness and V_D/V_T reduction, leading to V'_E/Q' improvement. Like ACE inhibitors, the long-term use of mineral receptor inhibitors, such as spironolactone or eplerenone, improves alveolar–capillary membrane diffusion and exercise performance. However, mineral receptor inhibitors do not seem to affect the V'_E *versus* V'_{CO_2} relationship, casting doubts about the true mechanisms of the action of ACE inhibitors on the V'_E *versus* V'_{CO_2} relationship [80]. In this regard, a modulating role of ACE inhibitors on chemoreflex activity has been suggested [81]. In addition, β-blockers can affect the V'_E *versus* V'_{CO_2} relationship in heart failure, although this effect is more evident with β_1-β_2-blockers such as carvedilol [77, 82, 83]. The mechanism is a direct reduction of overactivated chemoreflexes partially counteracted by a worsening of the alveolar–capillary membrane diffusion capacity [13, 39, 84]. Of note, although the reduction of V'_E response to chemoreflex stimuli is considered a beneficial effect, it may turn into a negative one under specific circumstances such as acute hypoxia [47, 77]. It has been reported that long term sacubitril–valsartan treatment reduces the V'_E *versus* V'_{CO_2} slope, but only in patients with a V'_E *versus* V'_{CO_2} value >34 [85].

V'_E *versus* V'_{CO_2} relationship in specific aetiologies

The V'_E *versus* V'_{CO_2} relationship during exercise has been studied in specific disease settings of heart failure such as hypertrophic cardiomyopathy, idiopathic cardiomyopathy and cardiac amyloidosis. In patients with hypertrophic cardiomyopathy, the V'_E *versus* V'_{CO_2} relationship is usually preserved within normal values. Nonetheless, the occasional finding of an elevated V'_E *versus* V'_{CO_2} slope value in hypertrophic cardiomyopathy patients has been associated with severe diastolic dysfunction and secondary pulmonary hypertension [86, 87]. In hypertrophic cardiomyopathy patients, a V'_E *versus* V'_{CO_2} slope value >32 has been reported as a powerful predictor of heart failure related events, and it is associated with poor prognosis and sudden cardiac death [88–90]. Of note, an even lower V'_E *versus* V'_{CO_2} slope cut-off value, 29, has been suggested by Sinagra *et al.* [91] for patients with idiopathic cardiomyopathy. The reason for the low cut-off values is probably that, in both hypertrophic cardiomyopathy and idiopathic cardiomyopathy, there is a high incidence of young patients and male sex. Conversely, in patients with heart failure due to amyloidosis, the V'_E *versus* V'_{CO_2} slope is significantly elevated and much more than in other patients with heart failure due to diastolic dysfunction of other origins [92]. The causes of the elevated V'_E *versus* V'_{CO_2} slope in these patients is likely the increase of backward pulmonary pressure. In amyloidosis, V'_E *versus* V'_{CO_2} relationship is both an indicator of therapy efficacy and a strong independent prognostic marker [92]. Specifically, the combination of V'_E *versus* V'_{CO_2} slope, C-reactive protein, sodium plasma level and serum creatinine, all independent significant prognostic indicators, leads to an AUC of 0.89 for 1-year mortality [92].

V'_E *versus* V'_{CO_2} relationship in heart failure and associated comorbidities

In some comorbidities the Y-intercept of the V'_E *versus* V'_{CO_2} relationship has a central role in the interpretation of diagnosis. If it is above its upper normal value (2.7 L), V'_D must have been high from the beginning, with a limited further increase of total V'_E during exercise, as happens in COPD [12]. Conversely, if the Y-intercept is below its normal value, it suggests a progressive increase of V'_D during exercise as is the case in heart failure, and, to a greater extent, in patients with pulmonary hypertension with and without heart failure. In these cases, the Y-intercept may even have a negative value [17, 19, 20]. Indeed, in a large multicentre study, Apostolo and co-workers [12, 93, 94] showed that, in heart failure, an

elevated Y-intercept implies the coexistence of COPD, while a Y-intercept value close to 0 or negative implies the coexistence of pulmonary hypertension.

Special attention should be dedicated to the V'_E *versus* V'_{CO_2} relationship analysis during exercise in patients with heart failure and associated comorbidities such as anxiety/depression, obesity, lung disease, kidney dysfunction and anaemia [95]. Anxiety influences the ventilatory behaviour of heart failure patients as well as that of normal subjects, but usually only in the early phase of exercise. At the beginning of exercise and even before exercise, V'_E increases, so that the CO_2 stored in the body deposits and P_{ETCO_2} decrease, while V'_E/V'_{CO_2} ratio increases. As a consequence, the capability to buffer lactic acid is reduced, and so is the length of the isocapnic buffering period; moreover, the capability to identify the AT by ventilatory equivalents is hampered, as is the physiological meaning of P_{ETCO_2} and of V'_E *versus* V'_{CO_2} relationship. Depression, which is a frequent and dangerous comorbidity of heart failure, reduces the capacity/willingness of patients to perform a maximal exercise, so that the meaning of peak V'_{O_2} is questionable in these patients. However, this does not affect the V'_E *versus* V'_{CO_2} relationship slope, which is likely to become the most powerful indicator of heart failure severity and prognosis in these patients. As regards heart failure patients with obesity, Piepoli *et al.* [96] reported a progressive reduction of the V'_E *versus* V'_{CO_2} slope in parallel with body mass index increase. However, peak V'_{O_2} and ventricular ejection fraction also increased, so that the presence of a specific behaviour of the V'_E *versus* V'_{CO_2} slope in overweight heart failure patients is still unknown**.** Lung diseases are frequently reported comorbidities of heart failure, influencing the treatment and prognosis of both heart failure and lung disease. Specifically, CPET is heavily influenced by the combination of heart failure and lung disease, so that P_{ETCO_2} can progressively increase in patients with CO_2 retention, the Y-axis intercept of V'_E *versus* V'_{CO_2} relationship slope (figure 4) is high, but, most importantly, the meaning of the V'_E *versus* V'_{CO_2} slope becomes uncertain for heart failure severity assessment and prognosis [12, 18, 93]. In addition, renal insufficiency is frequently associated with heart failure, and it is actually a part of the heart failure syndrome. Scrutinio *et al.* [97] showed, in a population of almost 3000 heart failure patients, that the V'_E *versus* V'_{CO_2} relationship slope was higher in patients with most severe renal impairment. Finally, anaemia deeply influences heart failure prognosis and directly affects peak V'_{O_2} [98–100.] As regards the V'_E *versus* V'_{CO_2} relationship in heart failure patients with anaemia, there is an unexpected but relevant finding. As a matter of fact, Cattadori *et al.* [101] showed that, in a population of almost 4000 heart failure patients, 6% of cases had very low haemoglobin levels (<11 $g{\cdot}dL^{-1}$), while 17% had a haemoglobin value >15 $g{\cdot}dL^{-1}$. In both groups, the V'_E *versus* V'_{CO_2} relationship slope lost its prognostic power. The physiological reasons behind this finding are basically unknown, although a possible role of differences in peripheral O_2 delivery and of the consequent metaboreflex on V'_E can be speculated [102]. In any case, in the presence of heart failure comorbidities, the prognostic meaning of V'_E *versus* V'_{CO_2} slope must be contextualised in each specific clinical setting.

Conclusions

In conclusion, in the complex clinical scenario of the heart failure syndrome, the ventilatory behaviour during exercise, its shape, and its relationship with V'_{CO_2} hide a variety of information useful for several features, including understanding the physiological cause of ventilatory abnormalities, assessing heart failure relationship with several comorbidities, grading heart failure severity, selecting therapy and planning heart failure follow-up. However, as frequently and erroneously done, we cannot relate to a single, good-for-all number. Indeed, we have to take into account when CPET was performed, patient's age, sex, concomitant treatments, and presence of heart failure comorbidities. Most importantly, we have to look at the V'_E *versus* V'_{CO_2} relationship by visual inspection to evaluate its shape, changes during exercise and Y-axis intercept of the relationship from the beginning of exercise to RCP, but also, separately, from RCP to peak exercise. Finally, V'_E *versus* V'_{CO_2} relationship values, regardless of how they are measured, must be integrated with several clinical and laboratory data to build the most precise mosaic of our heart failure subject with the aim of precisely tailoring their treatment.

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