Analysis of ventilatory equivalent responses for gases. Physiological significance

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Summary

Although the respiratory equivalents for the two gases are parameters provided by the software of automated devices, are of great importance in the assessment of the response to exercise in healthy and sick people. This review work analyses the evolution of these parameters in both healthy people and patients with pathologies of the cardiovascular and respiratory systems. Their considerable physiological significance lies in the formulas that express these indices of respiratory function. However, if appropriate modifications are made to the ratios $\dot{V}_E / \dot{V}O_2$ y $\dot{V}_E / \dot{V}CO_2$ allows a better physiological significance, since they are determined by F_EO_2 snd F_ECO_2, so that a modification of these variables informs about the ratio $\dot{V}_D / \dot{V}_E$ thus, indirectly, of the ratio $\dot{V}_A / \dot{Q}$. In healthy people, the response of the equivalents in the three classic phases described indicates a readjustment of the $\dot{V}_A / \dot{Q}$ ratio (phases I and II) and a "potential" mismatch (phase III). On the other hand, in patients with cardiac or pulmonary pathology, the F_EO_2 snd F_ECO_2 fractions clearly show an alteration of the $\dot{V}_A / \dot{Q}$ ratio from the start of exercise, depending, of course, on the degree of impairment. Specifically, the change in the slope of the $\frac{\dot{V}_E}{\dot{V}CO_2}$ / *intensidad* ratio has been a criterion accepted by cardiologists as a predictor of morbidity and mortality in cardiac patients with impaired ventricular function.

Key words:
Respiratory gas equivalents. Ventilation/perfusion ratio. Healthy subjects. Heart disease. Pneumopathies.

Análisis de la respuesta de los equivalentes respiratorios para los gases. Significación fisiológica

Resumen

A pesar de ser únicamente unos parámetros de la información que aportan los softwares de los aparatos automatizados, los equivalentes respiratorios para los dos gases son de gran importancia en la valoración de la respuesta al ejercicio en personas sanas y enfermas. Este trabajo de revisión analiza la evolución de estos parámetros tanto en personas sanas como enfermos con patologías del sistema cardiovascular y respiratorio. Su considerable significación fisiológica radica en las propias fórmulas que expresan estos índices de función respiratoria. Pero, si se realizan las oportunas modificaciones de los cocientes $\dot{V}_E / \dot{V}O_2$ y $\dot{V}_E / \dot{V}CO_2$ La forma de expresar los equivalentes respiratorios para los gases según las ecuaciones 3 y 5 aporta una mejor significado fisiológico, pues vienen determinados por las F_EO_2 y F_ECO_2, de manera que una modificación de estas variables informan de una modificación de la relación $\dot{V}_D / \dot{V}_E$ y por consiguiente, de forma indirecta, de la relación $\dot{V}_A / \dot{Q}$. En las personas sanas la respuesta de los equivalentes en las tres fases clásicas descritas indica un reajuste de la relación $\dot{V}_A / \dot{Q}$ (fases I y II) y un desajuste "potencial" (fase III). Por el contrario, en los enfermos con alguna patología cardiaca o pulmonar, las fracciones de las F_EO_2 y F_ECO_2 muestran claramente una alteración de la relación $\dot{V}_A / \dot{Q}$ desde el comienzo del ejercicio, naturalmente según el grado de deterioro. Concretamente, ha sido la modificación de la pendiente de la relación $\frac{\dot{V}_E}{\dot{V}CO_2}$ / *intensidad* un criterio admitido por la cardiolólogos como predictor de la morbilidad y mortalidad en cardiópatas con alteración de la función ventricular.

Palabras clave:
Equivalentes respiratorios para los gases. Relación ventilación/perfusión. Sujetos sanos. Cardiopatías. Neumopatías.

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Introduction

Among the many parameters provided by software for modern-automated appliances[1], ventilatory equivalents for gases ($\dot{V}_E / \dot{V}O_2$ y $\dot{V}_E / \dot{V}CO_2$)) are widely used in stress test assessments, both for healthy and sick persons.

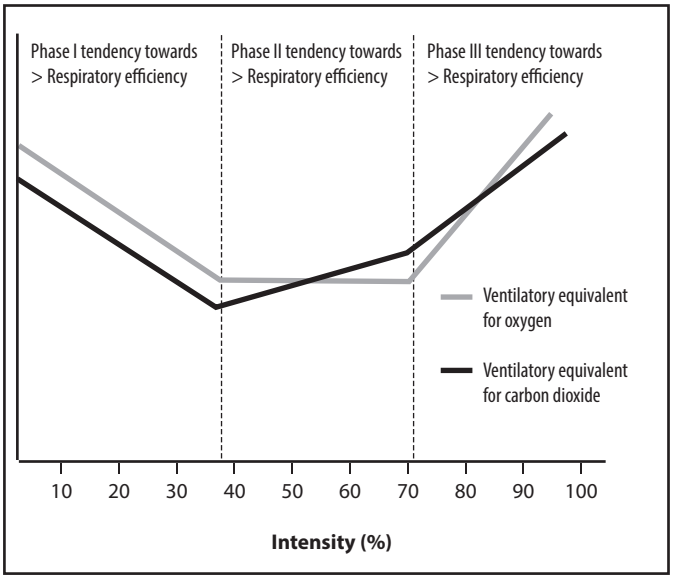
In the physiology field, for many years physiologists looked at the critical intensity which causes the accumulation of lactic acid[2,3]. Various non-invasive methods, based on continuous measurement of respiratory gases have been used to determine the "critical intensity". One of these methods involves looking at how $\dot{V}_E / \dot{V}O_2$ $\dot{V}_E / \dot{V}CO_2$ behave during increasingly intense exercise[4].

Given that ventilatory equivalents for gases are an indirect measurement of respiratory system efficiency (see physiological significance), Klebert *et al.*,[5] Guazzi *et al.*[6,7] and Shafiq A[8] proposed that the $\dot{V}_E / \dot{V}CO_2$ slope is an important morbidity and mortality predictor among heart failure patients. Specifically, the noticeable increase in the $\dot{V}_E / \dot{V}CO_2$ / *exercise intensity* ratio slope is a prognostic value for heart failure patients independently of the fraction value[6-8]. On the other hand, Dumitrescu D *et al.*[9] have demonstrated in patients with pulmonary vasculopathy, that the response changes for $PETCO_2$ and $\dot{V}_E / \dot{V}CO_2$ and other ventilatory exchange parameters make it possible to determine differences from other alterations in ventilatory exchange during exercise.

In principle, the physiological significance of $\dot{V}_E / \dot{V}O_2$ y $\dot{V}_E / \dot{V}CO_2$ is very simple. As these are dimensionless quotients, they represent a measurement of efficiency, as they indicate the quantity of air that the respiratory system mobilises in one minute ($\dot{V}_E$) to consume one litre of oxygen ($\dot{V}O_2$) or remove one litre of carbon dioxide ($\dot{V}CO_2$), for the $\dot{V}_E / \dot{V}O_2$ and $\dot{V}_E / \dot{V}CO_2$, respectively. Consequently, it seems logical to think that the larger the $\dot{V}_E$ the less efficient the respiratory system in terms of the physiological integration parameters represented by $\dot{V}O_2$ and $\dot{V}CO_2$: pulmonary, cardiovascular and muscular functions, all controlled by the nervous system.

However, the "arithmetical" consideration of the equivalents as ventilatory efficiency parameters is clearly not entirely accurate. As shown in Figure 1, the "numerical values" of the equivalents tend to gain (phase I), maintain (phase II) and lose ventilatory efficiency (phase III). Naturally, this raises an obvious question: at rest, when the equivalents' values are higher than at the end of phase I, is the respiratory system less efficient? The answer seems to be logical: the respiratory system is not less efficient at rest than during light exercise. Therefore, our aim in this review is to clarify, as far as possible, the physiological significance of the ventilatory equivalents for both gases and, from there, apply it to physiological conditions (health and performance) and pathological conditions (pathologies of the cardiovascular system and the respiratory system). As a starting point, the physiological significance is difficult to understand and so simple pulmonary function models will be used, aware of the limitations this implies.

Figure 1. Representation of the EqO2/intensity and EqCO2/intensity functions. The three phases are shown, described in the usual way, from the point of view of respiratory efficiency.



Physiological significance of the ventilatory equivalents for the gases

As the arithmetic expression of the ventilatory equivalents does not provide enough information to find out what they represent physiologically, it is advisable to express them as follows.

The oxygen consumption analysed in respiration is given by the following equation:

$$\dot{V}O_2 = (\dot{V}_I \cdot F_IO_2) - (\dot{V}_E \cdot F_EO_2) \quad \textit{(Equation 1)}$$

Where $\dot{V}_I$ and $\dot{V}_E$ are the ventilations when inhaling and exhaling and F_IO_2 y F_EO_2 are oxygen fractions in the air which is inhaled and exhaled, respectively. Unless the respiratory quotient is greater than the unit and it is necessary to apply Zunt's correction[10], wrongly attributed to Haldane, it can be considered that $\dot{V}_I$ and $\dot{V}_E$ are equal, which simplifies equation 1:

$$\dot{V}O_2 = \dot{V}_E \ (F_IO_2 - F_EO_2) \quad \textit{(Equation 2)}$$

Substituting for the oxygen equivalent in the formula gives the following equation:

$$Eq\,O_2 = \frac{\dot{V}_E}{\dot{V}_E \cdot (F_IO_2 - F_EO_2)} = \frac{1}{(F_IO_2 - F_EO_2)} \quad \textit{(Equation 3)}$$

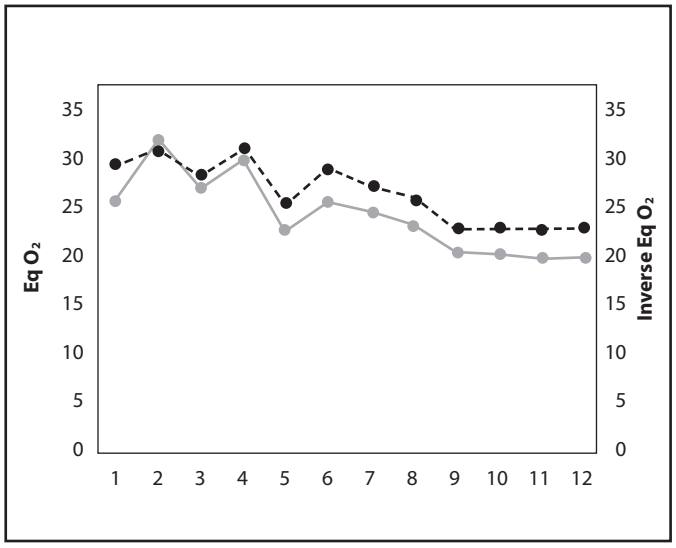
The same reasoning can be applied to carbon dioxide:

$$\dot{V}CO_2 = (\dot{V}_I \cdot F_IO_2) - (\dot{V}_E \cdot F_ECO_2) \quad \textit{(Equation 4)}$$

Given that F_IO_2 is practically zero, the ventilatory equivalent for carbon dioxide is:

$$Eq\,CO_2 = \frac{\dot{V}_E}{\dot{V}_E \cdot F_ECO_2} = \frac{1}{F_ECO_2} \quad \textit{(Equation 5)}$$

Figure 2. Representation of the ventilatory equivalent for oxygen in phase I, according to the usual expression ($EqO_2 = \dot{V}_E / \dot{V}O_2$)) and the expression corresponding to equation 3: $Eq\ O_2 = 1 / (F_I O_2 - F_E O_2)$.



As shown, this equation does not add information regarding how $\dot{V}_E/\dot{V}O_2$ behaves (Figure 2), as it is exactly the same. However, the information that it provides is important to understand it physiologically.

The behaviour of the exhaled fractions of oxygen (F_EO_2) and carbon dioxide (F_ECO_2) rreflect the variations in the ratio between the physiologic dead space (anatomic + alveolar) and the flow volume $\dot{V}_D/\dot{V}_E$[11]. When the respiratory system changes from a state of rest to light-moderate exercise, alveolar recruitment takes place, so that F_EO_2 drops slightly and F_ECO_2 rises. Consequently, the denominator of equations 3 and 5 increases, meaning that the ventilatory equivalents for the gases decrease. At this intensity, there is actually an increase in alveolar ventilation, and this produces a very slight change in the partial pressure of alveolar CO_2 (P_aCO_2) compared to pre-exercise values.

At high intensities, above 60%, there is a disproportionate increase in ventilation compared to the metabolic activity, reducing F_ECO_2 and increasing F_EO_2. This behaviour is fundamental to attempt to regulate the acid-base state, because the "acidification" effects of the carbon dioxide can be completely eliminated by compensating the metabolic acidosis associated with the increase in the concentration of arterial lactate and protein concentration[11]. The F_ECO_2 and F_EO_2 variations at high intensities are indirect data of the $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio, that can be diverted towards unbalance values greater than the unit, indicating an inappropriate cardiovascular adjustment compared to the respiratory value[12].

In summary, the way of expressing the ventilatory equivalents (equations 3 and 5) provides relevant information to understand the physiological significance for three reasons: 1) it does not represent a modification of the response of these parameters, 2) it makes it possible to centre these parameters on strictly respiratory variables (F_ECO_2 and F_EO_2) and not on an integrating variable such as oxygen consumption and 3) F_ECO_2 and F_EO_2 FEO2 are very useful parameters to estimate the $\dot{V}_D/\dot{V}_E$, ratio, an indirect parameter of the $\dot{V}_A/\dot{Q}$ ratio.

Ventilatory equivalents in healthy subjects

Among other ergospirometry parameters, ventilatory equivalents are used to determine the aerobic-anaerobic transition, a more accurate term than anaerobic threshold, as this is a process not a particular time and, the confusion regarding these terms also makes it difficult to understand it physiologically. As stated by Chicharro and Legido[13], the different denominations of the "break points" for ventilatory equivalents (Figure 1) have actually confused more than explained the physiological reasons that determine them, even more so when attempting to implement the phases determined by the variations of the equivalents in training[14]. Consequently, as one example, using Wasserman's terminology (Table 1), in intensive interval training it is not possible to qualify the intensity as an anaerobic threshold. This would be a considerable error regarding the conception of the aerobic-anaerobic transition phenomenon.

There has been wide debate around the relationship between the aerobic-anaerobic transition and the increase in concentration of lactic acid from Wasserman's description in 1986[15]. This paper does not intend to discuss this relationship, although it should be highlighted that many

Table 1. Different designations for the first increment of the ventilation.

Designation	Author
First break point	
Point of optimum efficiency	Hollman, 1959
Anaerobic threshold	Wasserman, 1964
Aerobic threshold	Kindermann, 1979; Skinner and McLellan, 1980
Individual aerobic transition	Passenhofer, 1981 Farrell, 1979
Second break point	
Aerobic-anaerobic threshold	Mader, 1976
Anaerobic threshold	Kindermann, 1981
Individual anaerobic threshold (IAT)	Stegman and Kindermann, 1981
Onset of lactate accumulation in blood	Sjodin and Jacobs, 1981
Ventilatory threshold 2	Orr, 1982
Anaerobic threshold	Skinner and McLellan, 1980

References not described in the manuscript. These are shown in reference[13].

other physiological relationships have been established such as changes in the composition of saliva, electromyographic pattern, concentration of catecholamines and variation in the heart rate/intensity slope[16]. In this respect, Peinado *et al.*[16] indicate that all the changes which occur make up the "efferent" signal managed by the command or central generator. We thereby understand that the explanation of the ventilatory equivalents' response for the gases is what is mentioned above, which we will explain succinctly and simply below.

In phase I, a readjustment of the ventilation/perfusion ratio takes place due to "alveolar recruitment" so that the ventilatory equivalents decrease. In phase II, according to elementary analysis of the equivalents, this would be the best linkage between the respiratory system and the cardiovascular system. In other words, the zone where the best health benefits are presumably obtained. Finally, the ventilation/perfusion ratio increases above the unit, suggesting that the cardiovascular system is unable to adjust[12]. In an interesting study carried out on pure-bred horses by McDonough *et al.*,[17] the ventilatory equivalent for oxygen does not increase as exercise becomes more intense. The authors attribute the response from $\dot{V}_E/\dot{V}O_2$ to a linkage between the movement pattern (length of the stride) and the regulation of the respiration (linkage between current volume and respiratory frequency) and they indicate that, when alveolar recruitment must be increased, the V_D/V_T ratio is much higher in the pure-bred horses compared to human beings.

In another respect, it is worth considering whether the variations in ventilatory equivalents for the gases with training condition might be justified by the physiological significance indicated in the previous paragraph. In a review article, Benito et al.18 indicate that the variation between different training periods among professional cyclists was under 2% and in lower-level cyclists, it was between 3 and 15%. These small differences are due to the fact the F_ECO_2 and F_EO_2 do not vary considerably according to the training condition, so that the PET CO_2 and the PET O_2 cannot show obvious changes.

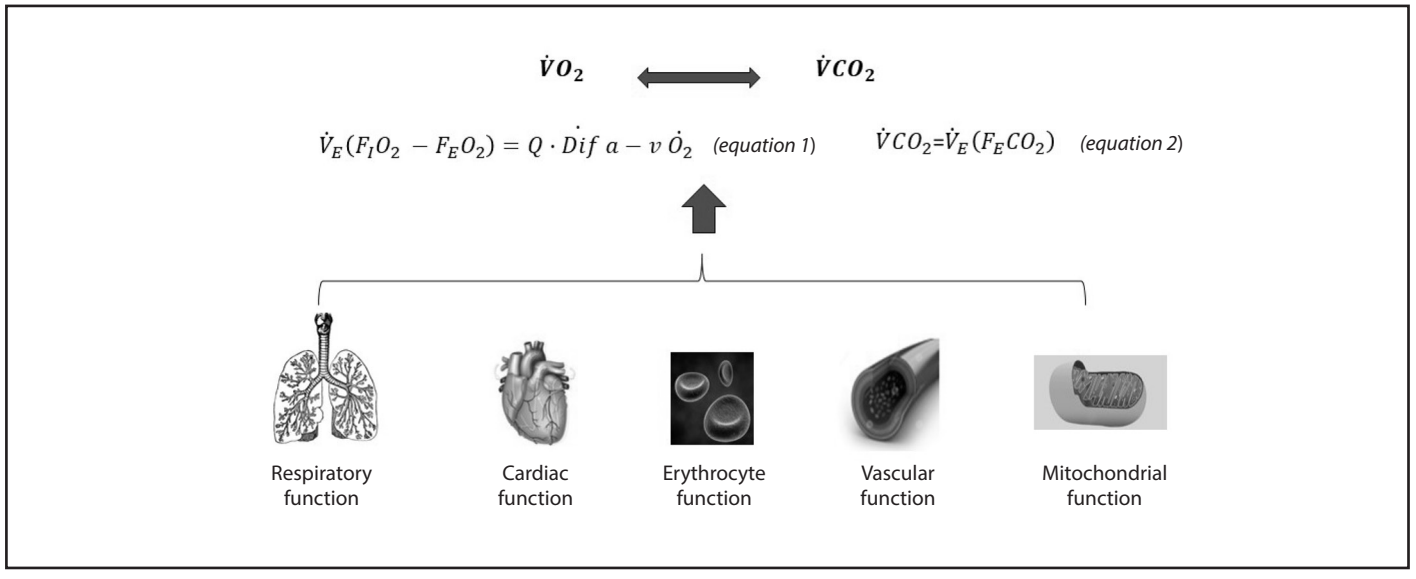
Ventilatory equivalents for the gases in persons with various pathologies

Analysis of the ventilatory equivalents for respiratory gases during exercise in persons with various pathologies is even more complex than for healthy persons. Out of all their possible pathologies which might vary the body's response to exercise, evaluated using ergospirometry, pathologies of the cardiovascular system, specifically the heart pump, and the respiratory system aroused the most interest. A careful study of the book by Wasserman and Whip[19] specifically shows that more than 80% of their practical cases focus on these pathologies.

Therefore, this section does not intend to exhaustively describe the physiological significance of these two parameters, but to analyse them from a didactic perspective. We think that with the appearance of the decree which regulates cross-cutting training for Health Science specialities, a previously-trained sports doctor or a doctor who might have trained on the job, must provide the knowledge acquired in their training to the different pathologies likely to be assessed using ergospirometry.

Figure 3 shows schematically how it is possible to impair the two central parameters of ergospirometry. A respiratory alteration lowers $\dot{V}O_2$ and $\dot{V}CO_2$ and can be explained by variations of equation 1 ($\dot{V}_E(F_IO_2 - F_EO_2)$). and equation 4 $\dot{V}\ CO_2 = (\dot{V}_I \cdot F_ICO_2) - (\dot{V}_E \cdot F_ECO_2)$, respectively. On the

Figure 3. Diagram of the organs, systems and tissues that determine oxygen consumption and carbon dioxide removal. Equation 1 is the result of equalling out the oxygen consumption by solving it in Fick's principle and the oxygen consumption according to the respiratory exchange. The carbon dioxide removal is represented according to the respiratory exchange (equation 2).



other hand, a cardiac alteration also leads to lower values of $\dot{V}O_2$ and $\dot{V}CO_2$ and can be explained by an alteration in cardiac output. Finally, a modification to the artery-vein oxygen difference (*Dif a-v* O_2) conditions lower values of $\dot{V}O_2$ and $\dot{V}CO_2$, although it is more complex to assign this term only to a cardiac or respiratory pathology.

The ventilatory equivalents for the gases in the response to exercise in respiratory system pathologies

Although it is common to divide the response to exercise in the respiratory system pathologies by the spirometry pattern (obstructive or restrictive), the contribution of the ventilatory equivalents will be analysed in general below[20,21].

Figure 4 shows the differences in the ratios

$$\frac{\dot{V}_E}{\dot{V}O_2} / intensity \qquad \frac{\dot{V}_E}{\dot{V}CO_2} / intensity$$

in a patient with obstructed airways (chronic obstructive pulmonary disease) and a healthy person. The patient's respiratory inefficiency is shown by the inability to reduce the denominator of equation 3. In other words, the patient presents difficulties to lower F_EO_2 and raise F_ECO_2 during phase I of the exercise (Figure 1) and the slope of

$$\frac{\dot{V}_E}{\dot{V}CO_2} / intensity$$

is high. This example matches the results from Dumitrescu D *et al.*,[9] who worked with patients with pulmonary vasculopathy to determine how the decrease in PET CO_2 compared to the drop in the I $\dot{V}_E/\dot{V}CO_2$ suggests a loss of blood vessels and can represent a sign of alteration of the left ventricular function, associated with this in these patients.

On the other hand, when establishing differences in the response to exercise in patients with a restrictive pattern (parenchymatous or extra-parenchymatous) compared to patients with an obstructive alteration of the airways, we consider that there is little physiopathological significance, as it is not feasible to compare the degree of damage from these pathologies that lead to modifications of the ventilatory equivalents which are difficult to differentiate. Furthermore, the possible differences do not determine clinical advantages.

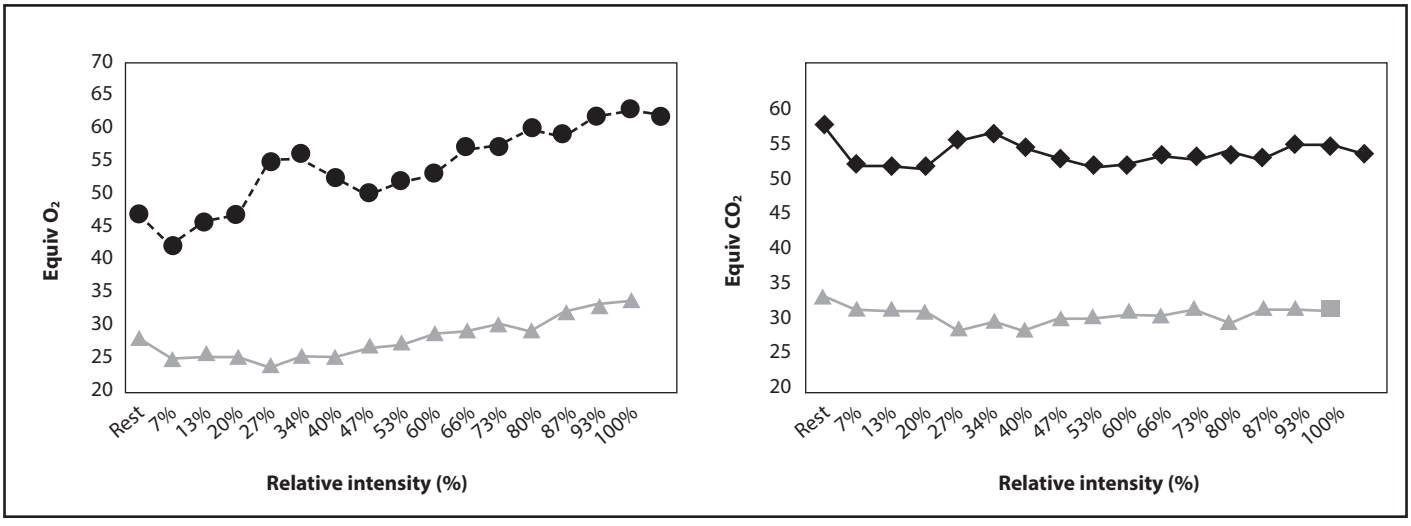
Ventilatory equivalents for the gases in the response to exercise in cardiovascular system pathologies

The "relative" problem of patients with heart failure is that the alterations in the ventricular function appear alongside alterations in the respiratory system. Consequently, the response from the ventilatory equivalents for the gases does not differ from the response corresponding to the patients with "strictly" respiratory pathologies, although according to various authors, it is one way of assessing the prognosis and evolution of the cardiac disease.

Miki *et al.*[22] assess the survival time in patients with heart failure by means of the slope of the ratio $\frac{\dot{V}_E}{\dot{V}CO_2} / intensity$

Using multivariate analysis, these authors indicate that low ventilatory efficiency, measured indirectly by $\dot{V}_E/\dot{V}CO_2$, is an important predictive morbidity and mortality factor, independently of central hemodynamic activity. Concerning the factors being studied (slope of the PaO_2, the $\dot{V}_E/\dot{V}CO_2$, oxygen pulse, maximum oxygen consumption and age), the authors of this study confirm what other authors Kleber *et al*[23] and Braga *et al.*[24] have mentioned: usefulness as survival prognosis predictors among these patients.

Figure 4. Response of the ventilatory equivalents for both gases in a healthy person and a patient with an obstructive pathology.



In the same way, in an interesting study on the possible influence of the inhibition of afferent information from the musculature on the respiratory pattern, Olson *et al*.[25] demonstrated that increased ventilation in patients with heart failure was produced by an increase in the respiratory frequency at the expense of the V_T / T_i ratio and an increase in the slope

$$\frac{\dot{V}_E}{\dot{V}CO_2} / intensity$$

plus a drop in the intensity and the peak oxygen consumption. According to these authors, they are partly due to the reduction of the information afferent to the respiration regulation centres, as when they pharmacologically cancel out the afferent inputs of the musculoskeletal system, the ventilatory response drops during exercise.

Finally, among other cardio-respiratory parameters, Takayanagi *et al*.[26] and Van Iterson[27] have raised the importance of the $\dot{V}_E / \dot{V}CO_2$ during exercise to assess patients with heart failure. The former[26] showed that during the recovery of the variations experienced by the respiratory quotient, the $\dot{V}_E / \dot{V}CO_2$ and the PET O_2 were significantly greater among people with better ventricular function. The latter[27] show that the alteration of the slope

$$\frac{\dot{V}_E}{\dot{V}CO_2} / intensity$$

during exercise is better explained by the VD/VT ratio among patients with heart failure and a low ejection fraction compared to patients with heart failure and an ejection fraction within the normal range, emphasising the need to improve interpretation of the slope

$$\frac{\dot{V}_E}{\dot{V}CO_2} / intensity$$

in heart failure, fundamentally from the clinical point of view.

Conflicts of interest

The author does not declare any conflict of interest.

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- **Patología Molecular Humana** *(2)*
- **Psicología General Sanitaria** *(1)*

(1) Presencial *(2) Semipresencial*

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