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Review Article

Ergospirometry and Respiratory Pathology

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Introduction

Ergospirometry is a diagnostic procedure that provides insight into the body's response to dynamic stress in such a way that it is used routinely in stress-test laboratories, mainly due to technological developments that have made it easier to analyze the data recorded [1]. The importance of this diagnostic test is reflected in the number of references found in PubMed by merely searching the words "gas exchange and exercise": 383 results, and 115 results when the phrase "Pulmonary diseases" is added. Likewise, numerous publications exist that address ergospirometry from other perspectives [2-5]. Finally, it should be noted that many major companies dedicated to the development of ergospirometry incorporate flow design diagrams to their software [5]. However, despite the ease with which modern devices provide information, understanding the meaning of respiratory parameters requires adequate training in respiratory function that is not always easy to achieve.

The respiratory [6] and vascular tracts [7,8] are considerably complex, in such a way that it's difficult to explain in a simplified manner how respiratory exchange occurs during exercise. For this reason, it's helpful to utilize a rather elementary model of the respiratory system: the mono-alveolar model.

The aim of this work is to present in a didactic manner the application of ergospirometry in the diagnosis of respiratory diseases that may be susceptible to this diagnostic evaluation, utilizing the mono-alveolar model for explanation purposes (Figure 1). Given the intended objective, it is presumed that the reader is familiar with the theoretical fundamentals of gas exchange analysis. However, the reader may consult any of the publications previously mentioned above [2-5] and articles on the theory of gas exchange [9-12].

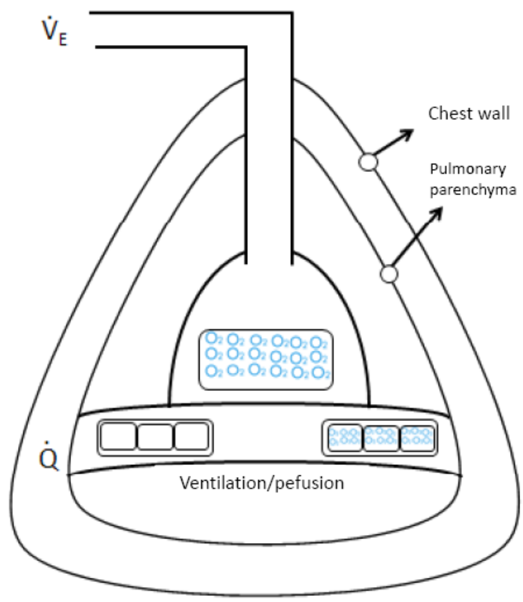


Figure 1. Mono-alveolar model of the respiratory system. The lung

is considered as a single alveolus, attached to the outside by a tube; both parts are set within a box whose pressure can be changed; the tube is a rigid element, whereas the alveolus is an elastic component.

2. The Main Ergospirometric Parameters Used in the Assessment Of Various Respiratory Diseases

Due to the incorporation of technological advances in the method of pulmonary gas exchange analysis, the number of parameters available in any commercial device can exceed 70, depending on whether they are indirect, derived or introduced by the professional in charge of the procedure. Nevertheless, despite a large amount of data, the reality is that any modern device only measures 4 parameters (change in O_2, change in CO_2, heart rate, and ventilation), while the remaining parameters are obtained from simple arithmetic operations of these four basic variables [13]. Therefore, in order to orient the reader to the practical acquisition of the information provided by modern ergospirometric devices, only the main parameters will be explained.

On the other hand, respiratory diseases susceptible to ergospirometric assessment can be divided into obstructive (Figure 2) and restrictive (Figure 3), essentially on the basis of a given pattern identified by a conventional spirometry test. As such, all pathologies that limit the ability to "introduce" or "eliminate" the air from the respiratory tract (obstructive diseases) present a characteristic pattern distinctive and different from those diseases that "limit"," restrict" or "shorten" the capacity of the thoracic cavity or the lung parenchyma itself (both alveolar and interstitial) which lead to a decrease of the effective lung compliance.

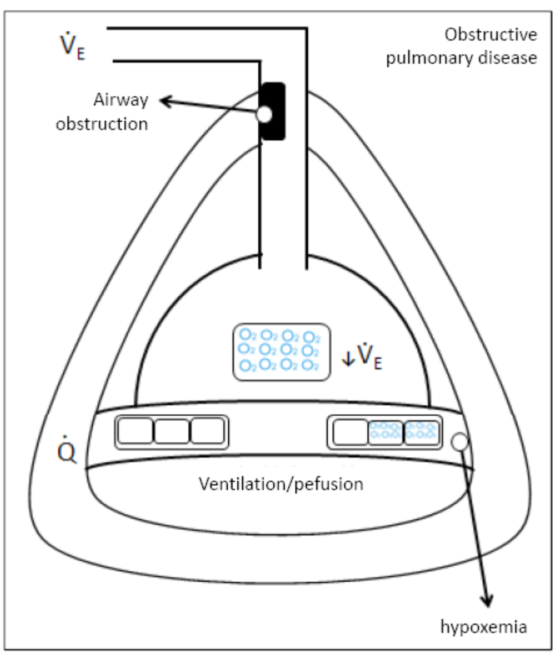


Figure 2. Obstructive condition.

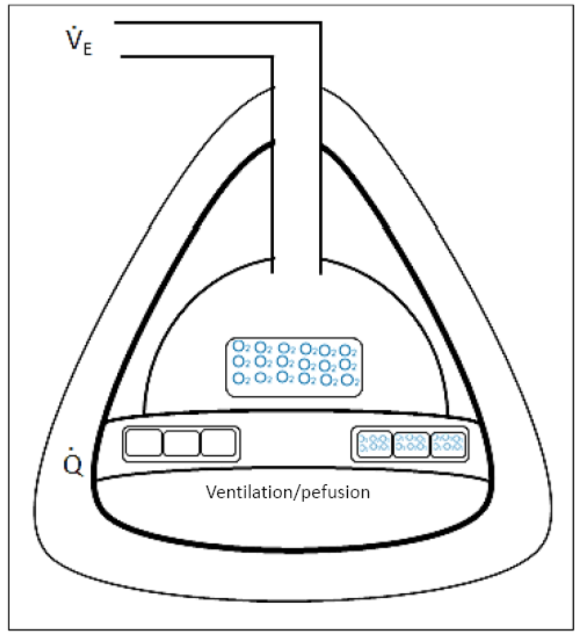


Figure 3. Restrictive condition.

It is not the aim of this work to describe the abnormal patterns of spirometry (table 1) and their etiology (table 2 and 3), even though they are shown. The interested reader may consult the texts of internal medicine or specific articles,

	TPC	RV	VC	$FEV_{1,0}$/ CVF	MIP	MEP
OBSTRUCTIVE DISEASE	N or ↑	↑	↓	↓	N	N
RESTRICTIVE DISEASE						
* Parenchymal	↓	↓	↓	N or ↑	N	N
* Extraparenchymal	↓	N or ↓	↓	N	↓ or N	N

Table 1. Abnormal spirometric patterns. TPC: total pulmonary capacity. RV: residual volume; VC: Vital capacity; $FEV_{1,0}$: forced expiratory volume in the first second of the forced expiratory maneuver; FVC: forced vital capacity; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; N: normal.

In section 2.2, the ergospirometric parameters discussed are those that provide the most information in order to differentiate obstructive pathologies from restrictive ones, without distinguishing within the latter whether they are due to parenchymal alterations (parenchymal restrictions) or due to alterations in the rib cage and its components (extraparenchymal restrictions). In addition, parameters that indirectly provide information on the ventilation/perfusion ratio are also analyzed.

Central airway obstruction	Diffuse obstructive airway disease
- Pharyngeal and laryngeal tumors - Foreign body - Extrinsic compression	- Bronchial asthma - Chronic airflow limitation - tobacco (chronic obstructive pulmonary disease - COPD)) - associated to bronchiectasis - bronchiolitis - cystic fibrosis

Table 2. Causes of obstructive spirometric patterns.

RESTRICTIVE SPIROMETRIC PATTERN. PARENCHYMAL ABNORMALITIES	RESTRICTIVE SPIROMETRIC PATTERN. CHEST WALL DISTURBANCES
Diseases with alveoli alterations - Pulmonary edema - Alveolar pneumonia - Atelectasis - Pulmonary resection	**Alterations affecting intrathoracic space** - Tumors - Cysts, bullas - Pleural effusion - Pneumothorax
Interstitial disease - Pulmonary edema - Infectious, toxic, immunological pneumonitis - Diffuse interstitial pulmonary fibrosis - Pneumoconiosis	**Diseases affecting the chest wall** - Kiphoscoliosis - Trauma - Thoracoplasties - Fibrothorax - DolorPain
	Neuromuscular diseases - Myopathies - Polyneuritis
	Extrapulmonary diseases - Obesity - Ascites

Table 3. Causes of restrictive spirometric patterns.

However, it is obvious that if there is an alteration in resting state, this will be further shown during exercise. When exercise is performed, an increase in alveolar ventilation (V_A) occurs, as shown schematically in Figure 4. If a respiratory disease is present, either obstructive or restrictive type, there is already a limitation at rest (decreased CV), and this will inevitably worsen during exercise

2.1 General parameters of Ergospirometric Assessment

Maximum Oxygen Consumption (VO_2max). This parameter significantly summarizes the body's response to exercise by providing data related to the cardiovascular system, the respiratory system, and the metabolism. The two equations that express VO_2 are important in order to understand the physiological significance of this parameter

$$VO_2 = Q \times Dif\ a - v\ O_2\ (Equation\ 1)$$

$$VO_2 = V_E (F_I O_2 - F_E O_2)\ (Equation\ 2)$$

In an elementary fashion, equation 1 indicates that the VO_2 depends on the "pumping" action of the heart (cardiac output or Q value) and oxygen transport capacity (blood and blood circulation) as well as the capacity of tissues in general, and musculature specific to extracting oxygen from the arteries (arteriovenous oxygen difference A-a DifVO_2 value). Equation 2 indicates that the VO_2 depends on the air moved by the breathing apparatus (ventilation V_E value) and the ability to extract oxygen from inhaled air. The way of expressing the second equation is only valid when inhaled volume (V_I) is equal to exhaled volume (V_E). Otherwise, it would be necessary to use the Haldane transformation (Haldane and Graham 1935), [14], but as pointed out by Poole, David C in the letter to the editor section, this idea was proposed by Geppert and Zuntz [15].

Anaerobic Threshold (AT). The term 'anaerobic threshold' was coined by Wasserman and McIlroy [16] when using the respiratory exchange ratio (RER) to detect the beginning of anaerobic metabolism in patients with heart problems performing stress tests. Later, Wasserman et al. [17] defined AT as 1) a non-linear increase in ventilation (V_E), 2) a non-linear increase in the elimination of CO_2 (VCO_2), 3) an increase in the partial pressure of O_2 during a series of breaths (Peto$_2$) with no corresponding drop in the partial pressure of CO_2 ($PetCO_2$), and 4) an increase in RER with workload (all during an incremental exercise test).

Nevertheless, despite the definition provided by Wasserman et al., the complexity of this parameter lies both in its conception [18] and varying terminology [19]. For this reason, many authors prefer the term aerobic-anaerobic transition. Here we will use VT_1 for the first increase in ventilation in response to intensity and VT_2 for the second increase in ventilation in response to intensity

2.2. Differential Diagnosis Guiding Parameters of the different pathologies susceptible to Ergospirometric Assessment.

As indicated above, modern devices provide a great number of parameters, making analysis complex. Table 4 shows all parameters used in the ergospirometric assessment that may be useful in the diagnosis for a number of respiratory pathologies, as described by Wasserman et al [5].

Upon analysis of the table, the following can be concluded:

1st) **All variables are indirect measures** of respiratory functions (ventilation, diffusion and ventilation / perfusion and gas transport). Specifically, variables 4, 5, 6 and 7 are estimates of ventilation/perfusion ratio on an overall level – not specific.

2nd) Some of the **relationships are based on estimates**. For example, the MVV variable typically isn't measured but is instead estimated from regression equations [5]. In our laboratory, MVV is measured systematically (but among a healthy population), unlike other hospital ergospirometry laboratories.

3rd) Some of the **variables require an invasive procedure for measurement.** For example, variables 5 and 6 require vessel puncture, either arterial or venous. Nevertheless, technological advances have made non-invasive assessment possible, as with pulse oximetry, in order to determine tissue oxygenation. This procedure measures the arterial oxygen saturation, but not PaO_2. Therefore, this technique has proven to be an important non-invasive assessment tool, but not without presenting errors at rest, and even more during exercise.

Pulse oximetry usefulness in different lung disease related situations has been demonstrated:

- Monitoring the improvement of pulmonary patterns after physical exercise programs in chronic pulmonary patients. Given the changes that occur in blood oxygenation during physical exercise, pulse oximetry helps assess the severity of the disease and the effect of training in pulmonary patients. The onset of increased oxygen desaturation of a 4% during regulated exercise suggests a significant desaturation, pointing to chronic lung disease, and it is used to assess the need and prescribe the use of oxygen.

- Seeking advice in patients at risk for lung resection: using pulse oximetry with standardized exercise has been demonstrated to show greater predictive power than spirometry, regarding the post-resection pulmonary outcome.

Number	Ergospirometric Variable	Description
1	Oxygen Pulse (VO_2/ HR) mL/ beat	Indirectly represents cardiac function by linking a global parameter (VO_2) with one of the determining parameters of cardiac output (heart rate or HR)
2	Respiratory reserve (MVV - V_E max)	It represents the maximum ability to ventilate (V_E max) during exercise in relation to the theoretical value (maximum ventilatory volume or MVV)
3	Relation between tidal volume and inspiratory capacity (V_T/CI) dimensionless	Represents the capacity of the respiratory system to move air at rest (V_T) in relation to the maximum capacity of introducing air into the alveoli during inspiration
4	Relationship between the volume of dead space and tidal volume (V_D/ V_T) dimensionless	Approximate measure of ventilation / perfusion ratio, given that as exercise progresses, alveolar ventilation (V_A) approaches that of cardiac output (Q)
5	Difference between the partial pressure of oxygen at the alveolar and arterial level (ΔP Aa O_2) mmHg or kPa	Approximate and overall measure of the ventilation / perfusion ratio, given that it relates "oxygenation" of arterial blood (arterial pressure of oxygen or P_aO_2) to the "oxygenation" of the alveoli (alveolar pressure of oxygen or P_AO_2)
6	Difference between the partial pressure of carbon dioxide at the arterial level and pressure of this gas at the end of exhalation (Pa-et-CO_2) mm g or kPa	Indirect measurement of ventilation and perfusion ratio that expresses the amount of carbon dioxide at the arterial level (arterial pressure of carbon dioxide or $PaCO_2$) regarding the capacity to its removal during exhalation (end-tidal pressure of carbon dioxide $P_{ET}CO_2$)
7	Respiratory equivalents for oxygen (V_E/ VO_2) and carbon dioxide (V_E/ VCO_2) dimensionless	Approximate measure ventilation / perfusion ratio, given that it relates air moved by the respiratory system in relation to two global parameters (VO_2 and VCO_2)

Table 4. Parameters used in ergospirometric assessment.

However, as previously pointed out, pulse oximetry has certain limitations, especially noticeable when applied to sports, where movement artifacts appear when undergoing a test in motion [20].

Lately, important progress is being made in the technology used in pulse oximetry, achieving reliable reading results in stress tests, minimizing the movement artifacts, even in maximal exercise.

In addition to these approximate parameters of assessment of gas exchange during exercise, other parameters should also be noted, including those that provide information regarding the load (watts or treadmill speed), cardiovascular system function (EKG, blood pressure), the blood transportability (hemoglobin concentration, etc.) and acid-base state (pH, bicarbonate concentration, lactate concentration, etc.). These additional variables yield further complexity in understanding the body's response to incremental exercise.

Since the objective of this work is to provide a basic overview of the practical information provided by ergospirometry in the assessment of lung disease (obstructive and restrictive types), we outline the most useful applications. This does not call for any experienced reader to think that all the important variables are described.

V_D/ V_T. Normally, the V_D is about 1/3 of V_T and during exercise it is reduced to 1/5 or more, reaching the lowest V_D/ V_T ratio when V_A/ Q ratio is even. Under conditions of a poor ventilation/perfusion ratio, when the respiratory system is "ineffective", the result is an increase in V_D (poorly ventilated and/or perfused alveoli) even at rest. Upon increasing the intensity, although VT increases, the number of nonfunctional alveoli also increases, resulting in a possible alteration of V_A/ Q ratio.

In Figure 4 the ratio V_D/ V_T is represented during incremental exercise in a healthy person and in a patient with the obstructive respiratory disease. In the model of Figure 5, having an obstruction, it is consistent that the ratio V_D/ V_T is stable for two reasons: 1) these patients have limited capacity to raise their V_T progressively and 2) they increment their V_E in the expense of their respiratory rate (RR).

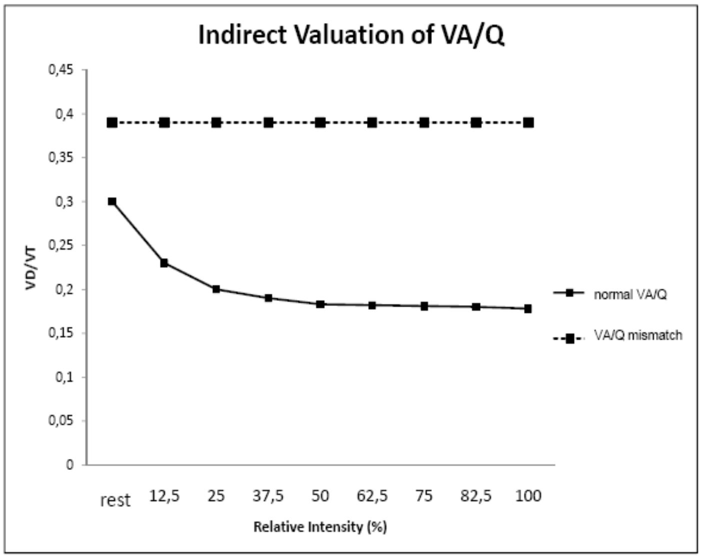


Figure 4. V_D/V_T ratio during incremental exercise in a healthy person and in a patient with obstructive respiratory disease.

P (A-a) O_2. If there is a respiratory disease that determines that some alveoli do not receive sufficient oxygen, the alveolar partial pressure of oxygen (PpAO_2) may maintain if the other alveoli offset malfunction. However, the partial pressure of oxygen (PpO_2) will decrease, and, therefore, the alveolar-arterial (A-a) gradient will increase. This problem is accentuated during exercise, as illustrated in Figure 5. This parameter has the disadvantage of being invasive, as the partial pressure of oxygen must be measured in arterial blood.

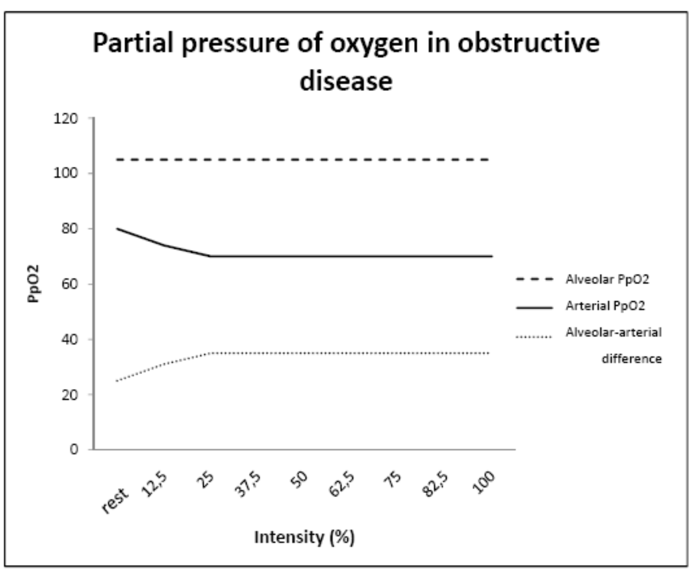


Figure 5

P (a-ET)CO_2. The end-tidal pressure of oxygen (ETP of CO_2) is a parameter that Wasserman proposed to give an idea lung's ability to remove CO_2. The response of this variable may suggest an altered VA / Q ratio, or an increase in alveolar dead space. For example, if the patient suffers from a disease that keeps some alveoli from removing carbon dioxide, ETP of CO_2 will remain below normal values. During exercise, as CO_2 removal demand is increased, ETP of CO_2 will keep stable as it was at rest, instead of decreasing as it happens in healthy people. Generally, Pa CO_2 at rest is about 2 mm Hg greater than the ETP of CO2; however, during exercise, ETP of CO_2 increases in relation to PaCO_2, with a negative difference between both (about - 4 mm Hg). Figure 6 shows the response of this variable in a healthy person (side a) and in a patient with an obstructive disease.

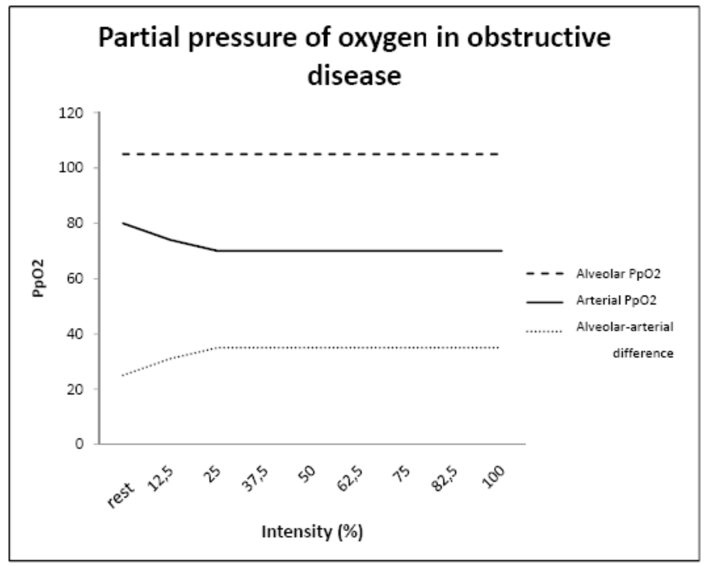


Figure 6

1) at rest, ventilation rate in patients is higher than in healthy people. Considering that VO_2 and VCO_2 values at rest are equal in both groups (about 300 mL/min), patients will have higher ventilatory equivalents numbers.

2) during exercise, the behavior of this parameter is similar in patients and healthy subjects, but patients show higher values.

3) when reaching maximum exercise intensity, patients with the obstructive disease cannot hyperventilate, and since VO_2 remains constant, ventilatory equivalents stay constant.

Other parameters. Within this section, we have included many of the parameters that can help in determining the differential diagnosis. These parameters are tidal volume versus inspiratory capacity ratio (TV/IC), and breathing reserve (BR). Objectively, it is necessary to keep in mind that BR is one of the key variables analyzed included in the ergospirometry software. The first thing to keep in mind when evaluating these parameters is to relate them to parameters obtained in the spirometry test. As illustrated in Figure 6, the response of tidal volume to an incremental exercise is closely related to the maximum minute ventilation.

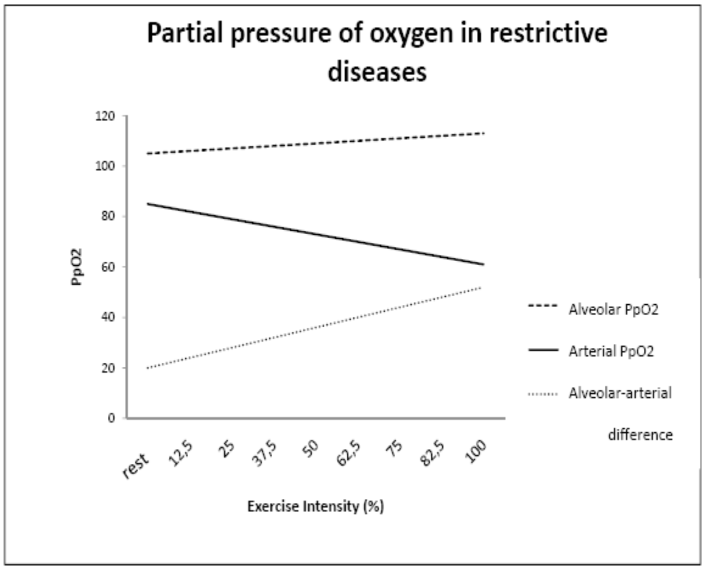


Figure 7

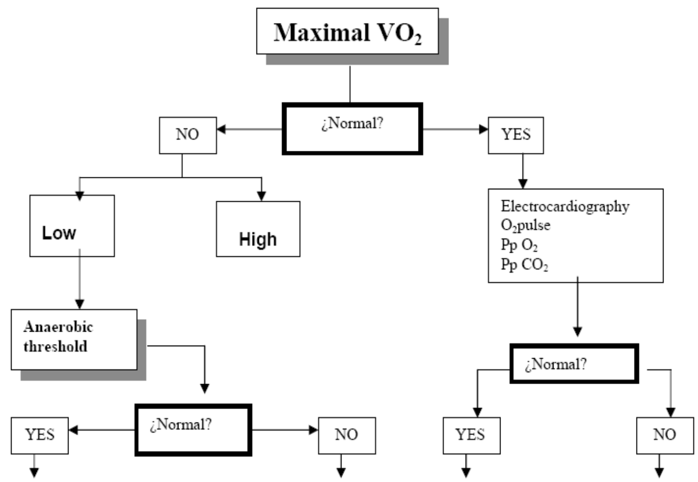
3. Procedure and Interpretation of Results

The procedure for evaluating the test is to follow the logical reasoning, from the general to the specific. Seeing as the VO_2 max is an integrative parameter in many physiological functions, it seems consistent to start by evaluating this parameter and to continue with more specific ones, such as the anaerobic threshold (AT). However, although this system is simple, it is difficult for both parameters (VO_2 max and AT) to be modified independently.

Figure 9 (shows a flow chart (a decision tree) proposed by Calderon for an ergospirometry test [21], which is a simplified version of the flow charts proposed by Wasserman et al [5]. The proposed diagram has the advantage of being very simple, as it consists of eliminating invasive tests results at the expense of losing diagnostic rigor, in order to make these tests more accessible. However, it has the disadvantage of being too simple when there are associated pathologies, something that happens quite often.

Figure 9. Flow chart proposed by Calderon for an ergospirometry test [21], a simplified version of the flow charts proposed by Wasserman et al [5].

Next, a brief explanation of the flow chart procedure is shown, according to both major respiratory diseases, classified as obstructive and restrictive. When assessing both the VO_2max and the AT, the first problem the ergospirometry expert faces is assessing the criteria of normality. To our judgment, the best way to establish the criteria of normality is to have an available database of healthy people, ranging different ages and different fitness levels. As additional information, tables 5 (5) and 6 (6) show the most relevant values from our laboratory, published in a Ph.D. thesis [22].



Pulmonary disease

Coronary disease

Chronic metabolic acidosis

Anaemia

Poor physical condition

Peripheral vascular disease Pulmo-
-nary disease cardiovascular disease

Pulmonary vascular disease

Pulmonary disease
(obstructive, restrictive)

It is widely known that VO_2 max evolves with age [23-28] and training[24,25,29-31] and that there are gender-related differences [32]. Paradoxically, there are few studies where values for ventilatory thresholds (VT_1 and VT_2) in large populations of different age, gender, and physical condition are shown. The lack of data may be due to the complexity of the processes used to determine aerobic-anaerobic transition [10,18,33].

	Meana	S.D.	Min.	Max.	Percentiles								
					10	20	30	40	50	60	70	80	90
Age (years)	23,7	8,2	9,0	58,0	15,0	17,0	19,0	20,0	22,0	24,0	26,0	29,0	35,0
Weight (kg)	69,4	10,0	30,0	103,0	59,0	62,0	65,1	67,8	69,0	71,0	73,0	77,0	82,0
Heigth (cm)	175,4	7,9	136,0	202,0	167,0	170,0	172,0	174,0	176,0	177,0	179,0	181,0	185,0
FVC (L)	5,377	0,877	2,310	8,030	4,308	4,724	5,000	5,260	5,450	5,630	5,850	6,050	6,370
FEV1 (L)	4,558	0,790	1,460	6,880	3,644	4,010	4,230	4,418	4,585	4,750	4,930	5,200	5,540
VO_2 max (mL/min)	4375	837	1410	6450	3310	3749	4017	4230	4413	4614	4832	5106	5375
VO_2 kg (mL/kg/min)	63,46	11,34	25,53	92,56	48,22	53,03	56,41	59,60	63,52	67,01	70,92	74,34	77,99
V_E max (L/min)	162	36	40	268	115	133	145	156	165	173	182	191	206

Table 5. Most relevant values from spirometry and ergospirometry in healthy men.

	Mean	S.D.	Min.	Máx.	Percentiles								
					10	20	30	40	50	60	70	80	90
Age (years)	20,7	7,5	9,0	47,0	12,0	15,0	16,0	17,6	20,0	21,4	23,0	26,0	29,1
Weight (kg)	57,0	9,5	30,0	89,0	46,9	50,8	53,0	55,6	57,0	58,0	61,0	64,0	69,0
Heigth (cm)	163,7	8,4	136,0	184,0	154,0	158,0	160,7	162,0	164,0	167,0	168,0	170,0	174,0
FVC (L)	3,904	0,710	1,610	5,900	2,993	3,426	3,610	3,788	3,910	4,030	4,243	4,482	4,753
FEV1 (L)	3,386	0,672	1,370	5,240	2,460	2,884	3,119	3,310	3,415	3,560	3,699	3,874	4,190
VO_2 max (mL/min)	2704	856	1270	6200	1561	2005	2268	2492	2646	2776	3079	3351	3613
VO_2 kg (mL/kg/min)	47,17	11,17	23,06	86,11	34,19	36,76	39,15	42,72	46,14	49,12	52,51	57,98	62,73
V_E max (L/min)	98	34	39	237	50	68	84	91	96	104	110	122	136

Table 6. Most relevant values from spirometry and ergospirometry in healthy women.

(1^0) VO_2max assessment. It seems logical to think that any patient suffering from either obstructive or restrictive type diseases will have a reduced VO_2max compared to a healthy sedentary individual of the same age range and gender population. Considering Equation 2, any reduction in ventilation values will determine a decrease in VO_2max, even while the oxygen difference is maintained between inhaled and exhaled air.

The maximum ventilation during exercise happens to be reduced in patients with various respiratory diseases regardless of the disease type (obstructive versus restrictive) [34-41].

Both $P(A\text{-}a)O_2$ and $P(a\text{-}et)CO_2$ are indirect parameters for ventilation/perfusion ratio and/or increased alveolar dead space. Differential diagnosis can intuitively be made by observing the

VE peak value and comparing it with the same subject´s reference values at rest, i.e, maximum voluntary ventilation (MVV). Only respiratory patients have a low value of the difference between MVV and the maximum VE. These respiratory problems could be inferred by noting the changes in all parameters affecting the first member of the equation VEx (F_IO_2 - F_EO_2). The relationship between static spirometry values (maximum voluntary ventilation, breathing reserve) and maximum V_E value will be altered, and so will estimative ergospirometry parameters related to ventilation/perfusion rate be.

2) Anaerobic threshold Assessment. The difficulty here is precisely based on which one of both ventilatory thresholds (VT1 or VT2) should be used. Initially, from a common sense point of view, it seems coherent to use VT1, for it is the parameter that denotes the aerobic-anaerobic transition, and is commonly used in untrained people.

However, as noted by Wasserman et al [5] an isolated decrease of AT does not occur, but rather, if the VO_2 is low, then the AT will also be low. Therefore, respiratory patients will have low AT values. The analysis of a respiratory patient with low VO_2max and AT levels is difficult to analyze, since, first, there are multiple causes that can that can lead to these alterations in ergospirometry (heart disease, peripheral vascular disease, anaemia, chronic metabolic acidosis, etc.), and, second, in these circumstances, there are often many related diseases that make it hard to discern what is the most significant illness that explains the symptoms. Due to this complexity, this is probably the least applicable case for ergospirometry as a diagnostic tool. Either way, it is essential to analyze every parameter previously pointed out in Section 2.

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