Pulmonology approach in the investigation of chronic unexplained dyspnea

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ABSTRACT
Chronic unexplained dyspnea and exercise intolerance represent common, distressing symptoms in outpatients. Clinical history taking and physical examination are the mainstays for diagnostic evaluation. However, the cause of dyspnea may remain elusive even after comprehensive diagnostic evaluation—basic laboratory analyses; chest imaging; pulmonary function testing, and cardiac testing. At that point (and frequently before), patients are usually referred to a pulmonologist, who is expected to be the main physician to solve this conundrum. In this context, cardiopulmonary exercise testing (CPET), to assess physiological and sensory responses from rest to peak exercise, provides a unique opportunity to unmask the mechanisms of the underlying dyspnea and their interactions with a broad spectrum of disorders. However, CPET is underused in clinical practice, possibly due to operational issues (equipment costs, limited availability, and poor remuneration) and limited medical education regarding the method. To counter the latter shortcoming, we aspire to provide a pragmatic strategy for interpreting CPET results. Clustering findings of exercise response allows the characterization of patterns that permit the clinician to narrow the list of possible diagnoses rather than pinpointing a specific etiology. We present a proposal for a diagnostic workup and some illustrative cases assessed by CPET. Given that airway hyperresponsiveness and pulmonary vascular disorders, which are within the purview of pulmonology, are common causes of chronic unexplained dyspnea, we also aim to describe the role of bronchial challenge tests and the diagnostic reasoning for investigating the pulmonary circulation in this context.

Keywords: Dyspnea; Exercise test; Bronchial provocation tests; Vascular diseases.

INTRODUCTION
Dyspnea is a common and distressing symptom. Population-based studies have shown that the prevalence of mild-to-moderate dyspnea is 9-37% among community-dwelling adults.(1) Higher dyspnea scores were associated with decrements in health status and physical activity in subjects with COPD,(2) and the magnitude of dyspnea can be more discriminating than the functional staging of disease severity (based on FEV1) concerning survival(3) and health-related quality of life.(4) Dyspnea has been shown to be a better predictor of mortality than has angina in patients referred for cardiac stress testing(5) and was associated with a higher risk of mortality when compared with asymptomatic population-based subjects.(6)

There is no definitive classification of dyspnea according to its duration. Dyspnea is usually considered acute when it lasts over hours to days and is considered chronic when it lasts for more than 4 to 8 weeks.(7,8) Multiple conditions can cause chronic dyspnea. Although clinical history taking and physical examination are often insufficient to unequivocally identify the etiology(ies), they remain the mainstays of the diagnostic evaluation, providing guidance to narrow the possibilities and to select appropriate tests. Together with initial examinations, the potential underlying cause(s) can usually be identified in a significant proportion of cases. In two previous seminal studies by Pratter et al.(8,9) investigating chronic dyspnea in clinical practice, approximately half of the participants were considered as having their diagnosis defined based on clinical history taking, physical examination, chest X-ray, and spirometry. Respiratory and cardiac disorders made up the most common etiologies. Dyspnea that remains unexplained after this initial testing sequence represents a major diagnostic challenge. In fact, the cause of dyspnea may remain elusive even after aggressive evaluation.(10,11) Such cases are frequently referred to various different specialists who may conduct the investigation of dyspnea with different—and sometimes contrasting—approaches, and quite often there is no effective communication and collaboration among them. This situation generally results in repeated medical appointments and diagnostic testing, treatments being delayed while the cause of...
dyspnea is being investigated, and, in the end, it frequently remains “unexplained”. (12) There is no consensus definition, but unexplained dyspnea or dyspnea of unknown origin could be characterized as persistent dyspnea (for at least 3 months) that is clinically and significantly severe (modified Medical Research Council scale score ≥ 2) and remains unexplained after thorough clinical assessment, basic biochemical testing, complete blood count, thyroid function testing, pulmonary function testing, and chest imaging (Figure 1; initial evaluation). (13) Again, although the definition is questionable, the concept of disproportionate or out-of-proportion dyspnea emerges, that is, when a patient has mild abnormalities relative to resting cardiac and pulmonary function testing or imaging findings that do not convincingly explain the severity of dyspnea, at least as expected based on clinical experience and the literature available. (13) Given the epidemiological importance of cardiopulmonary diseases in this context (8,14) and the widespread availability of “advanced” lung function testing, cardiovascular testing, and CT of the chest, it is our impression, based on clinical practice and the literature available, (10-14) that chronic dyspnea is only assumed to be unexplained if the results of those tests are inconclusive (Figure 1; advanced evaluation). In this context, we suggest that HRCT of the chest should be performed using inspiratory/expiratory maneuvers (to detect expiratory dynamic airway collapse, and regional air trapping). Specific studies in this setting are scarce, probably due to the complexity to gather such cases and provide an unequivocal final diagnosis. Those cases account for about 15% of all chronic dyspnea cases and are usually reported in the literature as being treated in multidisciplinary specialized centers, (7,15,16)

Our intention is not to describe the diagnostic criteria to confirm all potential etiologies of chronic dyspnea. Instead, the overarching objective of the current review is to present the clinical utility of cardiopulmonary exercise testing (CPET) in the evaluation of chronic dyspnea by describing the syndromic patterns related to exercise responses and by indicating a set of different etiological possibilities. Furthermore, given the low specificity and sensitivity of clinical evaluation to detect airway hyperresponsiveness (AHR) (17,18) and pulmonary vascular diseases, (14) the frequency of these conditions causing chronic unexplained dyspnea being high (Table 1), as well as the frequent inconclusive results from spirometry, lung volume measurements, DLCO, and CT of the chest in this context, specific tests to diagnose these conditions should be considered (Figure 1; specific evaluation). Therefore, we also aim to describe the role of bronchial challenge tests (BCTs) and the reasoning for the evaluation of pulmonary circulation in the diagnostic

| Stages of evaluation | History & physical examination + pulse oximetry |
|----------------------|-----------------------------------------------|
| Initial              | Blood testing: blood cell count, TSH (also consider arterial gas analysis, natriuretic peptides, electrolytes, and renal and hepatic function) |
| Advanced             | Lung function: spirometry                    |
|                      | Chest X-ray                                  |
| Lung                 | Lung function: static lung volumes, DLCO, maximal respiratory pressures |
| Heart                | HRCT of the chest                            |
| CPET                 | Echocardiography                             |
| Specific             | Cardiac stress testing (ECG or scintigraphy) |
|                      | “traditional”:                                |
|                      | central hemodynamic measurements (“invasive”) |
|                      | laryngoscopy (searching for inducible laryngeal obstruction) |

Figure 1. Suggested workup for the investigation of chronic dyspnea. The stages are based on the complexity of the tests and the epidemiology of the most common underlying diseases. Note that the sequence can be modified on the basis of the clinical impression and local resource availability. ECG: electrocardiogram; and CPET: cardiopulmonary exercise testing.
workup to unveil the cause(s) of chronic unexplained or disproportionate dyspnea.

**CPET**

Multiple causes, such as exercise-induced disorders not manifested at rest, exaggerated dyspnea from common conditions (obesity, adverse events of medications), skeletal muscle disease, psychogenic dyspnea (unexplained by organic dysfunction), and rare miscellaneous conditions, should be considered in the face of chronic unexplained dyspnea. In other words, chronic unexplained dyspnea might be caused by conditions presenting with greater complexity, unusual presentations of common diseases, or rare disorders, or might even have a psychogenic origin. CPET is a safe procedure that can identify specific physiological abnormalities of the integrated cardiopulmonary, neuromuscular, and sensory systems that contribute to persistent perceived respiratory discomfort. Also of utmost importance is the objective assessment of aerobic capacity and exercise tolerance, as well as of physiological and sensory dynamic responses to exercise. Given the possible dissociation between the perception of dyspnea during activities of daily living and that perception objectively measured during an exercise test, as well as of the complex neurophysiology of breathlessness and the influence of psychological and cultural factors, CPET frequently uncovers a preserved exercise capacity and normal responses to exercise, reassuring the patient and the medical team that a relevant organic abnormality is not present. Caution should be considered regarding incipient pathological conditions that lead to a decrement in exercise capacity without reducing peak measurements below the lower limit of normality or that cause abnormal submaximal responses. This can be suspected if a subject whose physical fitness was previously good/excellent complains about exercise intolerance with no evident reason (e.g., reduction or interruption of the physical activity) and is controlled by repeating the CPET (one or more times) during follow-up.

Based on the most common causes of chronic unexplained dyspnea (Table 1), we consider that when the etiology of dyspnea remains elusive after the initial evaluation (Figure 1), and the patient’s medical history and physical examination point out to no specific direction, CPET is uniquely poised to unveil the main physiological system(s) that could be related to the perception of dyspnea and to measure exercise tolerance objectively, as well as the perception of dyspnea for a given workload or ventilation, or, in the best scenario, to indicate the absence of physiological impairment. In various circumstances, CPET is not diagnostic per se, but it can uncover patterns of physiological dysfunction, guide further investigation(s), or reassure that no significant cardiopulmonary or other underlying disease is explicit at that moment. Therefore, CPET might guide the investigation and could avoid unnecessary tests and costs. Because there are multiple and combined causes of dyspnea and no cogent scientific evidence to dictate the sequence of evaluation, it seems that good practice follows the clinical impression based on medical history taking, physical examination, and availability of local resources and expertise (Figure 1). After the “supposed” cause(s) of dyspnea is/are

| Table 1. Major etiologies identified in studies on chronic unexplained dyspnea. Cardiopulmonary diseases comprise two-thirds of the underlying causes. |
|-------------------------------------------------|
| **Etiology** | **Prevalence, %** |
|-------------------------------------------------|
| **Respiratory** | |
| “Unspecified” airway disease | 25-37 |
| Asthma | 16-29 |
| Airway hyperresponsiveness | 25 |
| Pulmonary vascular disease | 5-17 |
| COPD | 9-14 |
| Interstitial lung disease | 7-14 |
| Other | 2-9 |
| **Cardiocirculatory** | |
| Chronic (systolic or diastolic) heart failure | 6-17 |
| Ischemic heart disease | 5 |
| Other | 8 |
| **Noncardiopulmonary diseases (less common)** | |
| Obesity | 16 |
| Dysfunctional breathing | 5-32 |
| Deconditioning | 3-28 |
| Myopathies | 1-24 |
| Dysautonomia | 21 |
| Miscellaneous | 2-7 |
| Information extracted from references. | |

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identified, it is crucial to consider the response to the treatment(s) employed (e.g., weight loss, exercise training, use of inhaled corticosteroids, etc.), which, if subjectively and objectively effective, reinforces the diagnosis(es) being considered.

CPET is usually performed using a cycle ergometer or a treadmill, although cycling is more frequently used in the setting of chronic respiratory diseases and investigation of dyspnea. The most commonly used protocol includes a resting steady-state period of a few minutes, followed by 2–3 min of unloaded pedaling and, thereafter, a rapidly incremental continuous "ramp" or 1–2-min stepwise increases in the work rate (WR) until exhaustion. Breath-by-breath responses should be recorded and presented in both numerical (tabular report) and graphical formats at average time intervals of 10–20 s. Modern equipment allows routine serial inspiratory capacity (IC) measurements during exercise to track operating lung volumes.

Due to overlapping responses during exercise across disease states, CPET may provide pathognomonic information in rare circumstances; however, it is more realistic to recognize that CPET shortens the list of differential diagnoses. Based on clustering findings, we can derive a syndromic approach indicative of: a) "normal" physiological responses; b) oxygen delivery/utilization mismatch; c) mechanical ventilatory impairment; d) impaired pulmonary gas exchange/altered ventilatory control; e) obesity; and f) dysfunctional breathing/hyperventilation disorder (Table 2). These patterns of exercise responses must be integrated with the clinical impression based on medical history taking and previous investigations, allowing a specific diagnosis or guiding the next diagnostic steps. Eventually, "conventional" CPET might indicate exercise-related abnormalities; however, it might still be insufficiently discriminative to point out a specific disorder. If metabolic myopathies, exercise-induced pulmonary hypertension (PH), or heart failure with preserved ejection fraction are suspected, invasive CPET (including central hemodynamic assessment via a pulmonary artery catheter and arterial blood gas

| Pattern | Finding | Differential diagnosis |
|---------|---------|------------------------|
| O₂ delivery/utilization mismatch | $\downarrow$ peak $\dot{V}O_2$ | Chronic (systolic or diastolic) heart failure |
| | $\downarrow$ lactate threshold | |
| | $\Delta$O₂/ΔWR | Pulmonary vascular disease |
| | $\Delta$HR/ΔO₂ | Ischemic coronary disease |
| | $\dot{V}O_2$/HR | Heart valve disease |
| | Flat or decreasing $\dot{V}O_2$/HR trajectory | Severe sedentariness |
| | | Peripheral muscle dysfunction |
| | | Endocrine/metabolic disorder |
| | | Anemia |
| Mechanical ventilatory impairment | $\uparrow$ peak $\dot{V}O_2$ | COPD |
| | $\uparrow$ peak $\dot{V}_i$/MVV | Interstitial lung disease |
| | $\uparrow$ peak $\dot{V}_i$/IC | Other persistent airflow obstructive disorders: asthma with airway remodeling, cystic fibrosis, bronchiectasis |
| | $\uparrow$ peak EIVL/TLC | Chest wall disease |
| | Constraint to $\dot{V}_e$ expansion | Respiratory muscle dysfunction |
| | $\uparrow$ peak f and $f/\dot{V}_e$ | |
| | Decrement in IC as $\dot{V}_e$ increases | |
| | $\downarrow$ dyspnea-WR and $\downarrow$ dyspnea-$\dot{V}_e$ relationships | |
| Impaired gas exchange/altered ventilatory control | $\downarrow$ peak $\dot{V}O_2$ | Chronic (systolic or diastolic) heart failure |
| | $\downarrow$ $\dot{V}_i$/VCO₂ metrics | Pulmonary vascular disease |
| | Significant $\text{SpO}_2$ decrement | Lung V/Q mismatch disorders: COPD, interstitial lung disease |
| | $\downarrow$ dyspnea-WR but unaltered dyspnea-$\dot{V}_e$ relationship | |
| Obesity | Preserved peak $\dot{V}O_2$ (% of predicted) | |
| | $\uparrow$ peak WR | |
| | $\downarrow$ $\dot{V}O_2$ and $\dot{V}_e$ for a given WR | |
| | $\downarrow$ symptoms for a given WR | |
| Dysfunctional breathing | $\downarrow$ peak $\dot{V}O_2$ | |
| | $\downarrow$ $\dot{V}_i$/VCO₂ | |
| | Significant fluctuations in $\dot{V}_i$/VCO₂ | |
| | $\downarrow$ $\dot{V}_i$/VCO₂ slope | |
| | $\downarrow$ RER (usually at rest) | |

Peak: at peak exercise; $\dot{V}O_2$: oxygen uptake; WR: work rate; $\dot{V}_i$: minute ventilation; MVV: maximum voluntary ventilation; IC: inspiratory capacity; EIVL: end-inspiratory lung volume; f: breathing frequency; VCO₂: carbon dioxide output; V/Q: ventilation/perfusion; and RER: respiratory exchange ratio.

Table 2. Key cardiopulmonary exercise test findings in relation to different patterns of abnormality and potential etiologies.
analysis via a radial catheter) might be indicated.\textsuperscript{(24)} Another less common cause of unexplained chronic dyspnea that can be investigated with an “adapted” CPET is exercise-induced laryngeal obstruction.\textsuperscript{(25)} Exercise protocols vary, but what is crucial is the ability to promote sustained high-intensity efforts for as long as necessary to induce the symptoms. Continuous laryngoscopy during exercise uses a flexible laryngoscope fixed to a head apparatus, which allows real-time visualization of the larynx throughout the study.\textsuperscript{(25)}

**Physiological responses to exercise**

The normal response is characterized by ventilatory, circulatory, and metabolic trajectories throughout and at peak exercise within thresholds derived from sedentary healthy populations adjusted for sex and age (Table 3).\textsuperscript{(18)} Table 3 should also be used in order to check abnormalities regarding each parameter, which will allow the characterization of abnormal exercise response patterns described below.

A submaximal test is suspected when no main physiological domain reaches critical values at the end of exercise to constrain exercise continuity\textsuperscript{(26)}:

a) metabolic domain: carbon dioxide output (\(\dot{V}_{\text{CO}_2}\))/oxygen uptake (\(\dot{V}_{\text{O}_2}\)), i.e. respiratory exchange ratio > 1.05; and/or b) cardiovascular domain: HR > 85% of the predicted value; and/or c) ventilatory domain: minute ventilation (\(V_{\text{E}}\))/maximum voluntary ventilation (MVV) > 0.80—MVV usually being estimated as FEV\(_1\) × 35-40—; \(V_{\text{E}}/\text{IC} > 0.70\); and/or end-inspiratory lung volume (EILV)/TLC > 0.9.\textsuperscript{(27)}

CPET is considered “nonphysiologically” limited when none of the above thresholds are reached. In that case, reasons for exercise interruption should be pursued, and CPET should be repeated if the limitation can be relieved: e.g., better hydration for dry throat, analgesics for orthopedic pain, improvement of the seat comfort, familiarization with the cycling equipment, etc.

**Oxygen delivery/utilization mismatch**

This pattern involves an imbalance between \(O_2\) delivery and the energetic needs of the working muscles. Although this pattern implies compromised vascular transport of \(O_2\) (reduced cardiac output or convective peripheral \(O_2\) delivery in the arterial system) in the majority of the clinical situations, low arterial \(O_2\) content and metabolic dysfunction of skeletal muscles (severe sedentariness or myopathies) might produce a similar pattern of responses making it impractical to differentiate between such conditions based on CPET alone. The cluster of findings indicative of this pattern includes:

a) low \(\dot{V}_{\text{O}_2}\) at peak exercise (Figure 2A) and at lactate threshold (Figure 2B)—the latter figure demonstrates the noninvasive estimation of the lactate threshold by the V-slope method\textsuperscript{(29)}:

| Parameter | Age, years | Male | Female | Male | Female | Male | Female | Male | Female |
|-----------|------------|------|--------|------|--------|------|--------|------|--------|
| **Metabolic** |           | 20   |        | 40   |        | 60   |        | 80   |        |
| Peak \(\dot{V}_{\text{O}_2}\) (% predicted) | > 83 | > 83 | > 83 | > 83 | > 83 | > 83 | > 83 | > 83 | > 83 |
| \(\Delta \dot{V}_{\text{O}_2}/\Delta \text{WR} (\text{mL/min/W})\) | > 9.0 | > 8.5 | > 9.0 | > 8.5 | > 9.0 | > 8.5 | > 9.0 | > 8.5 | > 8.5 |
| \(\dot{V}_{\text{O}_2}\) at LT (peak \(\dot{V}_{\text{O}_2}\) % predicted) | > 35 | > 40 | > 40 | > 45 | > 50 | > 55 | > 60 |        |        |
| **Cardiovascular** |           |      |        |      |        |      |        |      |        |
| Peak HR (bpm) | >175 | >170 | >160 | >155 | >150 | >145 | >130 | >125 |        |
| \(\dot{O}_2\) pulse (mL/min/beat) | > 12 | > 10 | > 10 | > 8  | > 9  | > 7  | > 7  | > 6  |        |
| \(\Delta \text{HR}/\Delta \dot{V}_{\text{O}_2}\) (beat/L/min) | < 60 | < 85 | < 70 | < 90 | < 80 | < 100 | < 90 | < 105 |        |
| **Ventilatory/gas exchange** |           |      |        |      |        |      |        |      |        |
| Peak \(V_{\text{E}}\)/MVV | < 0.80 | < 0.75 | < 0.75 | < 0.75 | < 0.75 | < 0.75 | < 0.80 | < 0.75 |        |
| Peak \(V_{\text{E}}\)/MVV at LT | < 0.35 | < 0.40 | < 0.40 | < 0.40 | < 0.45 | < 0.45 | < 0.50 | < 0.50 |        |
| \(\Delta V_{\text{E}}/\Delta \text{VCO}_2\) | < 26 | < 28 | < 28 | < 30 | < 30 | < 32 | < 32 | < 32 |        |
| \(\dot{V}_{\text{E}}/\text{VCO}_2\) nadir | < 30 | < 32 | < 32 | < 32 | < 34 | < 34 | < 34 | < 34 |        |
| Peak \(f\) (breaths/min) | < 50 | < 50 | < 50 | < 45 | < 45 | < 45 | < 60 |        |        |
| Peak \(f\)/\(V_{\text{E}}\) | < 28 | < 30 | < 28 | < 30 | < 30 | < 35 | < 40 |        |        |
| Peak \(V_{\text{E}}/\text{IC}\) | < 0.70 | < 0.75 | < 0.70 | < 0.75 | < 0.70 | < 0.75 | < 0.70 | < 0.75 |        |
| \(P_{\text{ETCO}_2}\) at LT (mmHg) | > 43 | > 41 | > 41 | > 40 | > 39 | > 39 | > 37 | > 37 |        |
| Peak \(\text{SpO}_2\) (%) | > 93 | > 93 | > 93 | > 93 | > 93 | > 93 | > 93 | > 93 |        |
| \(\text{SpO}_2\) rest-peak (%) | < 5 | < 5 | < 5 | < 5 | < 5 | < 5 | < 5 | < 5 |        |

Reproduced with permission of the European Respiratory Society.\textsuperscript{(22)} Peak: at peak exercise; \(\dot{V}_{\text{O}_2}\): oxygen uptake; \(\text{WR}\): work rate; LT: lactate threshold; \(V_{\text{E}}\): minute ventilation; MVV: maximum voluntary ventilation; \(\text{VCO}_2\): carbon dioxide output; \(f\): breathing frequency; IC: inspiratory capacity; and \(P_{\text{ETCO}_2}\): end-tidal carbon dioxide pressure.
the inflection in the \( \dot{V}CO_2 \) rate of increment as a function of \( \dot{VO}_2 \) corresponds to the point where there is a progressive accumulation of lactate as the workload intensifies;

b) a slower increment of \( \dot{VO}_2 \) by incremental WR (\( \Delta \dot{V}O_2/\Delta WR \); Figure 2A);

c) low reserve to increase cardiac output at the expense of stroke volume, resulting in an exaggerated increase in HR to increments in \( \dot{VO}_2 \) (\( \Delta HR/\Delta \dot{V}O_2 \)) and, consequently, low \( \dot{VO}_2 \) for a given HR during submaximal and peak exercise (\( \dot{VO}_2/HR = \dot{O}_2 \) pulse; Figure 2C)—a flattened or decreasing \( \dot{O}_2 \) pulse trajectory during incremental CPET was more commonly found in conditions associated with impaired stroke volume, that is, cardiocirculatory dysfunction. (30,31)

**Mechanical ventilatory impairment**

Conceptually, this pattern occurs when mechanical abnormalities of the interface between the lung and the thorax compromise the adequate ventilation required to a given metabolic demand. The classical approach is to assess how close ventilation is to its ceiling, i.e., measured peak \( \dot{V}_e \) in relation to the estimated maximum ventilatory capacity. A rough guide to this maximum is provided by MVV: peak \( \dot{V}_e/MVV \) above a certain threshold (Table 2) has been used to indicate "ventilatory limitation" (Figure 3A). (32) However, this ratio correlates poorly with exertional dyspnea in individual subjects with both obstructive and restrictive ventilatory defects. (33) Several dyspneic patients with COPD, mainly those with mild-to-moderate FEV\(_1\) reduction, (34) stop exercising and show a preserved \( \dot{V}_e/MVV \) ratio, but there is unequivocal evidence of constrained ventilatory mechanics according to parameters of operating lung volumes during exercise. (35) Conversely, a peak \( \dot{V}_e \) close to MVV may occur in an otherwise fit subject who can exercise up to high workloads. (36) Therefore, a \( \dot{V}_e/MVV \) ratio above the upper limit of normal should be valued to indicate low ventilatory reserve in the context of reduced exercise capacity; however, a high ratio in fit subjects or a low value in subjects with impaired peak \( \dot{V}_O_2 \) should not be considered as proof of the presence or absence of mechanical ventilatory abnormalities, respectively. There is convincing evidence that dyspnea increases when the mechanical output of respiratory muscles becomes uncoupled from increases in neural respiratory drive. (33,37) Accordingly, indexes of neuromuscular uncoupling have revealed the contribution of impaired ventilation to exertional dyspnea and exercise tolerance better than has peak \( \dot{V}_e/MVV \). (27,28)

In practice, neuromechanical coupling is searched by means of serial measurements of VT and IC across the CPET. The difference between EILV and IC results in a line of the form: O\(_2\) pulse = \( b + m \cdot HR \), where \( b \) is the y-intercept and \( m \) is the slope. The fit of the line is expressed as the correlation coefficient \( r \).

**Figure 2.** Selected panels from incremental cardiopulmonary exercise test to evaluate metabolic and cardiocirculatory responses. In A–C, a 52-year-old woman with a normal BMI and chronic heart failure due to reduced ejection fraction shows a typical pattern of \( O_2 \) delivery/utilization mismatch. See text for further details. In D–F, sex- and age-matched physiological responses in a healthy subject. \( \dot{V}O_2 \): oxygen uptake; \( \dot{V}CO_2 \): carbon dioxide output; peak: at peak exercise; WR: work rate; and GET: gas exchange threshold.
TLC dictates the position of Vt on the sigmoid-shaped pressure-volume relationship of the respiratory system. Independently of exercise-induced reduction in IC,[33,38] when the Vt/IC ratio reaches approximately (≈70%) of the inspiratory capacity (IC) during cycling exercise close to TLC—inspiratory reserve volume (IRV) < 0.5-1.0 L—VT expansion is constrained, and any increment in Vt mainly occurs at the expense of a faster breathing frequency (f). VCO2: carbon dioxide output.

**Impaired gas exchange/altered ventilatory control**

From a practical perspective, these two pathophysiological mechanisms are intrinsically connected, resulting in characteristic responses to exercise. An insufficient decrease in the fraction of breath that is wasted—dead space (Vd)—calculated as Vd/Vt > 0.15-0.20—due to reduced perfusion in relation to alveolar ventilation—ventilation/perfusion (V/Q) mismatch—and/or a low PaCO2 set point at the central control of ventilation results in an increased Vd/VCO2 ratio, which can be assessed by different metrics (Figure 4).[42] Therefore, the so-called “ventilatory inefficiency” (Vd/VCO2) more commonly reflects poor intrapulmonary gas-exchange efficiency.[43] Examples of high Vd/VCO2 include aging, increased pulmonary artery resistance, pulmonary vascular disorders, congestive heart failure, wasted ventilation in lung diseases—COPD or interstitial lung disease (ILD)—and extraneous sources that activate ventilation (muscle ergoreceptor overactivity, pulmonary C-fiber receptors, or mechanoreceptors), which can exist in the context of all of the abovementioned conditions.[43] Of note, the Vd/VCO2 slope (i.e., Vd plotted as a function of VCO2) increases only if the ventilatory pump is free from mechanical constraints and may even decrease if an obstructive airway disease worsens.[44] Accordingly, caution should be taken not to discard impaired gas exchange in patients with advanced obstructive lung disease and a preserved Vd/VCO2 slope. In this context, evaluating the intercept of the Vd/VCO2 slope might represent an alternative for estimating the presence of ventilatory inefficiency.[45]

Other findings in patients with significantly impaired gas exchange include exercise-induced hypoxemia (altered PaCO2 in some circumstances) and an enlarged alveolar-arterial O2 tension gradient (> 20 mmHg). Although mild-to-moderate decrements in PaO2 might be missed when oxyhemoglobin saturation is measured by pulse oximetry (SpO2), this is the parameter usually available in practice (Figure 4A). Exertional oxygen desaturation is not a formal feature in healthy subjects unless they are extremely well trained or are exercising at low inspired O2 tension (high altitude). Therefore, SpO2 remains greater than 93% and does not decrease during exercise by more than 4% (Table 3). Low SpO2 (< 88%) stimulates peripheral chemoreceptors and increases inspiratory neural drive and dyspnea. Exercise-related O2 desaturation usually implies disorders with a preponderance of alveoli...
Pulmonology approach in the investigation of chronic unexplained dyspnea presenting with low V/Q ratios, which are commonly associated with low mixed venous $O_2$ saturation. Other less common causes are right-to-left shunt and alveolar hypoventilation.\(^{(13)}\)

Surprisingly, the major complaint that brings such unexplained cases to medical attention (i.e., dyspnea) is virtually neglected in most international guidelines and clinical laboratories nowadays. Given that CPET measures a multitude of physiological responses that are important for the genesis of dyspnea, it seems natural that special attention should be given to the measurement and interpretation of this symptom. In the absence of mechanical ventilatory constraints, an increased reflex chemostimulation\(^{(42)}\) translates into excessive ventilatory response that is proportional to the metabolic demand.\(^{(35)}\) Therefore, when an increased drive to breathe can be coupled with the act of ventilating, patients tend to report higher dyspnea for a given workload due to a higher need to ventilate but similar (or slightly increased) dyspnea for the level of ventilation when compared with normal subjects.\(^{(46)}\) Conversely, dynamic mechanical ventilatory constraints lead to higher perception of dyspnea as a function of both WR and ventilation (Figure 5).\(^{(13,41)}\) Thus, evaluating the intensity of dyspnea as a function of WR and ventilatory demand and compare it with a reference frame obtained from healthy subjects\(^{(47)}\) might be useful to discriminate between an increased drive to breathe and mechanical ventilatory impairment as the main pathogenesis of dyspnea.

**Figure 4.** In A, a 50-year-old male with pulmonary arterial hypertension demonstrates gas exchange impairment (significant $O_2$ desaturation) and altered ventilatory control (excessive exercise ventilation). Ventilatory equivalents for $O_2$ uptake ($\dot{V}_E/\dot{V}_O2$) and carbon dioxide output ($\dot{V}_E/\dot{V}_CO2$), and arterial oxygen saturation by pulse oximetry ($SpO2$) plotted against $O2$ uptake during incremental cycle exercise are used to assess gas exchange and ventilatory control. In B, higher ventilation for the metabolic demand can also be observed as steep ventilation ($\dot{V}_E$) versus $\dot{V}_CO2$ increment. In C and D, physiological responses in a sex- and age-matched healthy subject.
In summary, the presence of impaired gas exchange and altered ventilatory control will infrequently occur in isolation (except during an incipient disorder) from at least one of the other two abnormal patterns—O₂ delivery/utilization mismatch and/or mechanical ventilatory impairment. The clinician receiving the CPET results can restrict the list of possible diseases according to the presence of one or more abnormal patterns in conjunction with the whole medical history of the patient available up to that point \(^{(13,22)}\):

(a) Isolated O₂ delivery/utilization mismatch: chronic (systolic or diastolic) heart failure; other cardiovascular abnormalities (ischemic coronary or valve disease); extreme sedentariness; skeletal myopathy; endocrine/metabolic disorders, and anemia

(b) O₂ delivery/utilization mismatch plus impaired gas exchange/altered ventilatory control: chronic (systolic or diastolic) heart failure; other cardiovascular abnormalities; and pulmonary vascular disease (especially if associated with O₂ desaturation)

(c) Mechanical ventilatory impairment with or without impaired gas exchange/altered ventilatory control: COPD; other persistent obstructive airway diseases (remodeled asthma, cystic fibrosis, bronchiectasis, or bronchiolitis); exercise-induced obstructive airway disease (asthma), ILD (usually associated with O₂ desaturation); chest wall disease; and isolated respiratory muscle dysfunction

It must be recognized that not all features typical of a given pattern will necessarily be present in every subject and that the final diagnosis of each disease continues being based on defined criteria provided in specific guidelines for each condition.

**Obesity**

Obesity represents a unique challenge to ventilatory control during exercise due to the increased metabolic demand to displace a large mass against gravity, the increased work of breathing due to thick chest wall, and altered breathing mechanics.\(^{(48)}\) Although such a challenge can go unnoticed in several adapted obese subjects, some can report distressing dyspnea. Despite the fact that the diagnosis of obesity is obvious from resting measurements (height and weight), CPET may be useful to measure exercise capacity and symptoms objectively and to demonstrate the typical exercise response of obese subjects: preserved or even increased aerobic capacity (expressed as % of predicted) despite poor exercise tolerance (low peak WR); exaggerated symptoms; and absence of the abovementioned abnormal exercise response patterns.

The increased metabolic demand (\(\Delta VO_2\) and \(\Delta VCO_2\)) to a given WR is accompanied by proportionally higher cardiovascular and ventilatory responses. The rate of increase in \(\Delta VO_2\) as a function of WR (\(\Delta VO_2/\Delta WR\)), however, remains normal, indicating preserved aerobic efficiency. Starting from a high resting \(VO_2\), there is an upward and parallel shift of \(VO_2\) as work increases, with peak \(VO_2\) reaching normal or near-normal values despite a low peak WR. Due to the increased metabolic demand, obese subjects also tend to report higher leg discomfort and dyspnea for the level of external WR than do nonobese subjects.\(^{(22)}\) Finally, the negative effect of reduced chest compliance seems to be counterbalanced by a lower end-expiratory lung volume due to increased intra-abdominal pressure, resulting in a greater volume available for tidal expansion (i.e., IC). Consequently, there is a downward shift in the operating lung volumes and relatively large inspiratory reserve volumes at exercise cessation, which is in contrast to what is observed in the mechanical-ventilatory impairment pattern.\(^{(49)}\)

Caution should be taken regarding the obesity hypoventilation syndrome in morbidly obese (BMI > 40 kg/m²)\(^{(50)}\) subjects, who may present with exaggerated abnormalities in ventilatory control and mechanical ventilatory response, respectively.

**Figure 5.** Perception of dyspnea (Borg scale score) as a function of work rate (in A) and minute ventilation (\(VE\); in B) during incremental cardiopulmonary exercise test in subjects with COPD, subjects with chronic heart failure (CHF), and sex- and age-matched controls. The arrows indicate the upward inflections in the dyspnea score found in the COPD group that can be characteristically observed both against work rate and ventilation increment. Reproduced with permission of the European Respiratory Society.\(^{(41)}\) ‘COPD vs. controls (p < 0.05). ‘CHF vs. controls (p < 0.05). ‘CHF vs. controls at standardized submaximal or at peak exercise (p < 0.05).
Dysfunctional breathing/hyperventilation disorder

Last, but not least, up to one third of the subjects referred for CPET for the investigation of unexplained dyspnea may present with a dysfunctional breathing pattern and/or signals of hyperventilation.\(^{(8,10)}\) Albeit not new,\(^{(52)}\) given the lack of a formal definition and a gold standard diagnostic method,\(^{(53)}\) this condition remains poorly understood and is usually underdiagnosed.\(^{(54)}\)

Dysfunctional breathing is a wide term describing a group of breathing disorders in subjects with chronic changes in their breathing pattern, resulting in dyspnea and other nonrespiratory symptoms in the absence of, or in excess of, a respiratory disease. Various other terms have been used interchangeably in the literature, including functional breathing disorder, breathing pattern disorder, and behavioral or psychogenic breathlessness. Even though hyperventilation syndrome is often used synonymously with dysfunctional breathing, the former is just one type of the latter, and hyperventilation (i.e., reduced PaCO\(_2\)) is not necessarily seen in dysfunctional breathing.\(^{(53)}\) Before establishing a diagnosis of dysfunctional breathing, organic diseases must be excluded. When common investigations for chronic dyspnea have normal or inconclusive results, CPET seems to be uniquely poised to determine whether breathlessness can be explained (or not) by the presence of any of the aforementioned abnormal exercise response patterns that are indicative of an organic disease. If not, further investigations are required to confirm the presence of dysfunctional breathing (see a detailed description of those methods in this reference).\(^{(53)}\) Nevertheless, the exercise responses during CPET can indicate the presence of dysfunctional breathing\(^{(22)}:\)

- a) chaotic breathing, consisting in surges of low and high \(V\)\(_e\) in a background of fast \(f\)
- b) clear dissociation between ventilation and metabolic demand represented by large variations in \(V\)\(_e\)/\(V\)\(_CO2\), associated with noncyclic fluctuations of end-tidal O\(_2\) and CO\(_2\) pressures
- c) high respiratory exchange ratio at rest (frequently but not always) and a steep \(E/CO2\) slope
- d) high perception of dyspnea for a given WR (a frame of reference for assessing the magnitude of exertional dyspnea during incremental cycle ergometry has been recently published),\(^{(47)}\) possibly associated with classical symptoms of hyperventilation (tingling, perioral numbness, and dizziness)

Dysfunctional breathing may occur in the context of a coexistent respiratory disease. There is a close link with asthma, but this is less evident regarding COPD and ILD. Therefore, it is important to identify objective evidence of these conditions and optimize treatment as soon as possible before attributing symptoms mainly (or uniquely) to dysfunctional breathing.\(^{(53)}\) In addition, close follow-up is recommended in order to investigate the development of commonly associated conditions (especially asthma\(^{(55)}\) or other causes of AHR) or some infrequent and difficult-to-diagnose alternative abnormalities (e.g., neuromuscular disease, respiratory muscle weakness,\(^{(56,57)}\) and inducible laryngeal obstruction).\(^{(23)}\)

BCTs or bronchial provocation tests

AHR is a common diagnosis in the context of unexplained dyspnea\(^{(9,10,14)}\) and is defined as an increased sensitivity and exaggerated response to non-allergic stimuli that cause airway narrowing. Although most commonly associated with asthma, AHR is also seen in other obstructive or inflammatory airway diseases, it is common in athletes, and it sometimes occurs in patients with heart failure.\(^{(17,58)}\) The magnitude of AHR might increase during exacerbations of underlying diseases, decrease with the use of anti-inflammatory medication, or be absent during asymptomatic periods.\(^{(17)}\) BCTs are most often indicated to exclude or confirm the diagnosis of asthma, which can be easily achieved by the clinical history taking, presence of wheezing, and appropriate response to therapy. In this context, reversible airflow obstruction on spirometry is confirmatory. However, spirometry is not always performed when the symptoms are present and may be inconclusive, especially in patients with normal or near-normal lung function. Therefore, BCTs emerge as important tools to unveil AHR as a potential cause of chronic unexplained dyspnea.

In clinical practice, the most common BCTs involve the direct stimulus of the muscarinic receptors on airway smooth muscle using methacholine or the indirect hyperosmolar stimulus due to water loss caused by airflow drying and cooling through exercise.\(^{(17)}\) In the setting of ongoing clinical symptoms, a negative result of a methacholine BCT, which has higher sensitivity than the indirect method, can be most helpful in making AHR improbable. Exercise BCTs are best indicated when the history of the patient suggests that this type of stimulus triggers clinical complaints. In contrast to the methacholine BCT, exercise BCTs stimulate inflammatory mediators and mechanisms involved in clinical asthma. Therefore, exercise BCTs have higher specificity, but they are less sensitive for the diagnosis of asthma and are preferable when the intention is to confirm asthma, rather than exclude it. Although the recommended exercise protocol to detect AHR is a high-intensity, constant-load test (90% of predicted maximum HR or 60% of MVV for the last 4 min of an overall 6-8 min exercise test),\(^{(59)}\) spirometric measurements obtained at 5, 10, 15, and 20 min after a rapid incremental WR protocol (duration: 8-12 min) showed to be as useful in diagnosing AHR in susceptible subjects (>90% of positive and negative predictive values).\(^{(60)}\)

Pulmonary circulation assessment

In previous studies, pulmonary vascular diseases are causes of unexplained dyspnea in 5-17% of the patients, mostly being secondary to PH or
thromboembolic disease (Table 1).\textsuperscript{[14,61]} Those patients often have an unremarkable physical examination. Abnormalities on chest X-rays and on electrocardiograms generally occur only in advanced disease. It is important to highlight that an isolated reduction in DLCO (and normal spirometry) can be a clue for early pulmonary vascular disease when other signs are missing.\textsuperscript{[62]}

The symptoms of PH are nonspecific and mainly related to progressive right ventricular dysfunction. Initial symptoms are typically induced by exercise and include shortness of breath, fatigue, weakness, angina, and syncope, which might be modified by other diseases that cause or are associated with PH as well as by other concurrent diseases.\textsuperscript{[63]} At presentation, almost all patients with PH report dyspnea, which is most often severe and long lasting. In the French National Registry, the majority of the patients with PH had severe symptoms in the initial assessment, almost all patients with PH report dyspnea, which is intermediate or high, patients should undergo right heart catheterization, if the echocardiographic probability of PH is highly suggestive of PH. In the appropriate clinical context, if the echocardiographic probability of PH is low but clinical suspicion is high, CPET is indicated. In the context of high pre-test probability, O\textsubscript{2} delivery/utilization mismatch plus impaired gas exchange is highly suggestive of PH. In the appropriate clinical context, if the echocardiographic probability of PH is intermediate or high, patients should undergo right heart catheterization. Occasionally, some patients may have normal right heart catheterization results at rest, and PH is detected only during invasive CPET, being defined as mean pulmonary arterial pressure ≥ 30 mmHg, cardiac output < 10 L/min, and total pulmonary resistance ≥ 3 Wood units at peak exercise.\textsuperscript{[66]}

In prospective studies, the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after symptoms of acute pulmonary embolism is reported to range from 0.4% to 6.2%.\textsuperscript{[67]} An important prerequisite to confirm this diagnosis is adequate anticoagulation for at least 3 months. About 75% of the patients with CTEPH have previously confirmed venous thromboembolic event(s). V/Q lung scintigraphy remains the screening test for CTEPH because its accuracy is higher than that of CT angiography. In the future, modern dual-energy CT angiography can become the major test, because it allows the evaluation of anatomical and functional perfusion aspects simultaneously. Different from acute pulmonary embolism with low clinical suspicion when a low D-dimer level has a high negative predictive value, D-dimer alone cannot be used to rule out CTEPH in patients with PH.\textsuperscript{[68]}

Chronic thromboembolic disease (CTED) is characterized by presenting with similar symptoms and perfusion defects similar as to those of CTEPH, but no PH at rest. Exercise intolerance in patients with CTED has been attributed either to exercise-induced PH, showing an increased slope of the pulmonary arterial pressure-flow relationship, or to high dead space ventilation (increased V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}}).\textsuperscript{[69]} New/worsened dyspnea and persistent perfusion defects are often encountered after acute pulmonary embolism in 30% and 30-50% of the patients, respectively, hindering the diagnosis of CTED.\textsuperscript{[70]} CPET and echocardiography are recommended to recognize patients in whom symptoms are secondary to (nonvascular) lung disease, left heart disease, obesity, or physical deconditioning. Selected symptomatic patients with CTED may benefit from pulmonary endarterectomy.\textsuperscript{[71]}

Pulmonary arteriovenous malformations are structurally abnormal vessels that provide direct capillary-free communication between pulmonary and systemic circulations (hence, an anatomic right-to-left shunt). Those malformations may be related to hereditary hemorrhagic telangiectasia. Patients complain of dyspnea in 14-51% of the cases.\textsuperscript{[72]} Saline contrast echocardiography is the recommended initial screening test when pulmonary arteriovenous malformations are suspected. The circulatory transit of microbubbles generated by intravenously injected agitated saline contrast is detected by the image of bubbles arriving in the left heart or in the systemic circulation. Positive screening can be confirmed with unenhanced thin-slice (1-2 mm) multidetector CT of the chest and CT pulmonary angiography, being considered the gold standard to confirm the diagnosis. Hepatopulmonary syndrome is another type of intrapulmonary shunt that causes dyspnea, as well as occasional findings of platypnea-orthodeoxia.

Chronic dyspnea is an unusual presentation of pulmonary vasculitis. The clinical picture is more acute and has other clinical and laboratory signs of extrapulmonary manifestations. The diagnosis is made by autoantibody findings and histopathological analysis.\textsuperscript{[73]} Neoplasms of pulmonary vasculature are extremely rare, and the diagnosis can be suspected during the investigation of CTEPH or lung masses.\textsuperscript{[74]}

**FINAL CONSIDERATIONS**

We showed that CPET can identify physiological abnormalities involving cardiopulmonary, neuromuscular, and sensory systems that can be clustered into patterns of exercise response that are useful for a pragmatic interpretation during the investigation of chronic unexplained or out-of-proportion dyspnea. These clusters of findings should be analyzed in conjunction with the patient’s medical history and the results of other complementary tests (i.e., pre-test likelihood of a disease) in order to restrict the list of possible diagnoses, indicate the next step(s), or, hopefully, reach a final diagnosis. In addition, practical issues of BCTs and pulmonary circulation...
assessment, as well as the spectrum of suspected lung vascular diseases, should be closely acknowledged by pulmonologists dealing with unresolved cases of chronic dyspnea. In selected cases, patients should be evaluated in specialized centers that use advanced/ specific methods of investigation.

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