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Dyspnoea, hyperventilation and functional cough: a guide to which tests help sort them out

Physiology masterclass

Dyspnoea is a multifactorial symptom, defined by the American Thoracic Society as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [1]. Dyspnoea is caused by a wide range of conditions, ranging from asthma to pulmonary embolism, and including such nonrespiratory factors such as diabetic ketoacidosis. A patient with asthma who is aware of an increase in the muscular work of breathing during an attack, another patient with a pneumothorax experiencing increased efferent nerve stimulation from pulmonary stretch receptors and a third patient with type 1 respiratory failure would all describe themselves as "breathless", but for very different physiological reasons. Identifying the exact source of the patient's symptoms can be a lengthy process.

Cough and breathlessness are two of the most commonly reported respiratory symptoms with many possible causes that may require significant investigation before the cause is identified. After potential organic diseases such as asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease and pulmonary vascular disease have been investigated and eliminated, a potential functional diagnosis can be considered.

Much of the published literature surrounding the investigation of either acute or chronic hyperventilation has centred on patients with anxiety, depression and panic disorder but patients with a pre-existing respiratory condition may also experience periods of acute or chronic hyperventilation. Although most published data refer to asthma [2], other conditions such as COPD and pulmonary fibrosis can also be associated with hyperventilation.

This article will briefly describe methods that can be used to investigate dyspnoea in a newly referred patient. Methods of assessing functional breathlessness and cough when other investigations have been found to be normal, or where the degree of symptoms reported by the patient is out of proportion to any abnormalities found, will also be discussed. No mention will be made of the treatment of either functional cough or breathlessness.

It is assumed that readers will have access to a clinical respiratory physiology laboratory

that is equipped to perform spirometry, make measurements of transfer factor and lung volumes, and carry out exercise tests, preferably a cardiopulmonary exercise test.

Investigation of dyspnoea

Before a diagnosis of functional breathlessness can be considered, other potential causes of dyspnoea must be investigated and either excluded or quantified. Spirometry can identify patients with obstructive or restrictive disorders and assessing a patient's response to a short-acting β_2-agonist, such as terbutaline or salbutamol, can help to identify patients with asthma. Flow–volume loops can also help to identify the location of airflow obstruction (intrathoracic or extrathoracic).

Although airflow obstruction can be identified with confidence from spirometry, a restrictive defect is best identified from measurement of lung volumes, either by inert gas dilution or body plethysmography. Measurement of lung volumes can also identify significant air trapping, which may be found in patients with more severe degrees of airflow obstruction. Measurements of carbon monoxide transfer factor are an effective (and noninvasive) method of assessing the efficiency of the pulmonary circulation, although an abnormally low result does not help to identify the possible cause of the impairment.

When a patient complains of dyspnoea on exercise, some form of field exercise test should be carried out to investigate. In many patients, a walking test such as a 6-min distance test or a shuttle walking test is the most appropriate test to use. Where a more intense workload is required to replicate the conditions when the patient becomes symptomatic, a bicycle exercise test may be more appropriate.

In all field exercise tests, the main factors to be investigated are oxygen desaturation and heart rate response. Any patient showing clinically significant desaturation (traditionally defined as a fall in oxygen saturation measured by pulse oximetry >3%) requires further investigation to identify the reason for the desaturation.

Additional information can be obtained if patients are asked to rate their breathlessness at rest and at the end of exercise, using either a Borg score or visual analogue scale. Information on the patient's perception of breathlessness can be especially useful in serial exercise tests, where a patient reports an increase in symptoms but with no reduction in exercise capacity or increase in desaturation.

When a patient complains of cough and dyspnoea, one potential cause could be asthma. Tests of bronchial hyperreactivity, using challenge agents such as histamine, methacholine or mannitol, can identify patients with an enhanced bronchoconstrictor response, which is one of the hallmarks of asthma. If the patient only experiences symptoms during or immediately after exercise, then tests to investigate exercise-induced asthma should be considered. The patient should have spirometry performed before exercise and then at regular intervals (usually every 5 min) for 20–30 min after the completion of exercise, with the first post-exercise measurements made as soon as possible after completion.

Any readers requiring further information on the use of laboratory tests in the investigation of dyspnoea are referred to the publications by Hughes [3] and Gibson [4] who explore this topic in more detail.

Investigation of functional cough

Functional cough is one of the most problematic symptoms to investigate in a general respiratory clinic. The American College of Chest Physicians produced guidelines in 2006 based on a literature review of the diagnosis and management of functional cough [5]. This guideline was updated in 2015 [6] but both papers highlighted the lack of research in this area regarding the diagnosis and management of functional cough.

The European Respiratory Society produced an excellent guideline outlining the detailed assessment of cough *via* specific cough challenges [7]. A cough challenge can identify patients with an exceptionally sensitive cough reflex, which should be absent in a patient with a purely functional cough.

As not all centres may have the facilities to carry out specific cough challenges (using citric acid or hypertonic saline, for example) a suitable alternative may be a bronchial challenge test, as mentioned above. All three challenge agents are known to provoke cough as well as bronchoconstriction in patients and repeated bronchial challenges could be performed in a patient to assess the effectiveness of therapeutic interventions on a patient's cough. This type of investigation should be considered inferior to a formal cough challenge.

Ambulatory cough monitors have become more common in clinical practice and they can provide information on the frequency of cough, but are less valuable in assessing the intensity of the cough [8]. Cough monitoring may be useful to identify if there is a periodicity to the cough or any environmental triggers. Questionnaires investigating the impact of cough on quality of life have been developed and can provide insight into a patient's perception of their cough but they are not intended to specifically identify patients with functional cough [9].

Investigation of hyperventilation

An average adult at rest has a respiratory rate of 8–14 breaths per minute and a mean tidal volume

of 500 mL per breath. This maintains the arterial carbon dioxide tension (P_{aCO_2}) between 4.6 and 6.0 kPa. Hyperventilation is traditionally defined as breathing more than the metabolic requirements of the body [10] and could be further defined as an increase in alveolar ventilation that is more than the level required to maintain blood gas homeostasis, resulting in a fall in P_{aCO_2} and the development of respiratory alkalosis. Hyperventilation is not synonymous with tachypnoea, as patients may have an increased respiratory rate but a low tidal volume, thus maintaining a normal P_{aCO_2}.

The mechanisms behind hyperventilation are controversial, often considered to either be the result of anxiety or hypochondria [10], or due to a resetting of the carbon dioxide sensitivity in patients with chronic idiopathic hyperventilation [11]. Hyperventilation may also be present in patients with chronic respiratory or cardiac disease that is either well controlled or only of mild severity.

Hyperventilation commonly occurs in three distinct forms:

- acute hyperventilation, which is episodic in nature and is often described as the classic "panic attack";
- chronic hyperventilation, where the P_{aCO_2} is always below the normal range but the patient may experience few symptoms; and
- hyperventilation during (or on recovery from) acute periods of exercise.

Patients may present with a mixture of all three forms of the condition.

The Nijmegen questionnaire

The Nijmegen questionnaire was designed as a screening tool to help to identify patients who may be suffering from dysfunctional breathing who would benefit from breathing retraining [12]. It is quick to administer, containing only 16 questions, which relate to specific symptoms that may be associated with hyperventilation and asks about the frequency with which these symptoms are noted by the patient. A score >23 is considered positive. The authors have never claimed that the Nijmegen questionnaire was developed as a standalone diagnostic test and feel that it should only be part of the assessment process, along with assessment of end-tidal carbon dioxide (ETCO$_2$) [13].

Many patients who have a confirmed diagnosis of asthma can score highly on the Nijmegen questionnaire [2, 14], which may relate to poor asthma control. While this reduces the utility of the questionnaire, it is still a very useful way of finding out about the frequency of symptoms the patient experiences, but this must only be part of the investigation process rather than the whole content.

The hyperventilation provocation test

Investigation of hyperventilation requires some method of recording respiratory rate and ETCO$_2$. In a patient with normal lung function, ETCO$_2$ should be very close to P_{aCO_2}, which means that measurements of ETCO$_2$ should be a suitable noninvasive alternative to arterial blood gas analysis. In patients with airflow obstruction, ETCO$_2$ measured either at the mouth or nose may be a slight underestimate of P_{aCO_2} and this should be borne in mind when interpreting the results of any assessments from patients with documented obstructive disease. Measurements of spirometry should be made prior to the hyperventilation provocation test (HPT).

An HPT can be performed using simple equipment such as a capnograph, which will provide real-time information on respiratory rate and ETCO$_2$. Data on tidal volume will not be available. Using a capnograph is preferable to transcutaneous measurements as there tends to be a delay in response in transcutaneous measurements, which makes this technique less suitable for a dynamic test such as the HPT [15]. It is important that a good-quality capnograph waveform trace is obtained before the HPT begins. It is necessary to ensure that a good plateau is seen on the carbon dioxide trace so that the true ETCO$_2$ is measured (figure 1).

Several different protocols exist for assessing hyperventilation, ranging from asking the patient to take 20 deep breaths to try to elicit symptoms [16] all the way through to a full cardiopulmonary exercise test [11]. The author has used a 9-min protocol for a number of years, which seems to identify patients with either chronic or acute hyperventilation (investigation of hyperventilation on exercise will be discussed separately). The 9-min protocol is split into 3-min periods of resting breathing, voluntary hyperventilation and recovery (figure 2). The aim of
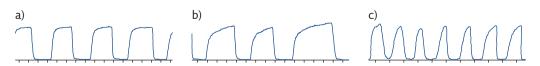

Figure 1 *Capnography traces. a) A good-quality trace showing a clear plateau that will ensure an accurate measurement of ETCO$_2$. b) A trace from a patient with airflow obstruction (forced expiratory volume in 1 s 40% predicted). c) A trace from a patient with chronic hyperventilation. This trace is less than technically ideal, as there is no clear plateau, meaning that ETCO$_2$ may be underestimated.*
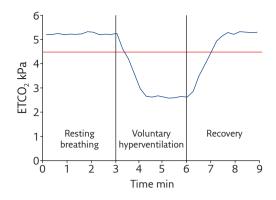
Figure 2 *HPT in a normal patient. 3 min resting breathing is followed by 3 min voluntary hyperventilation (to a target ETCO$_2$ of 2.6 kPa) and 3 min of recovery. The red line indicates the lower limit of ETCO$_2$.*

Figure 4 *HPT in a patient with chronic hyperventilation. ETCO$_2$ is below the lower limit (red line) during resting breathing.*

the voluntary hyperventilation period is to reduce the patient's ETCO$_2$ to as close to 2.65 kPa as the patient can achieve, as this level of ETCO$_2$ is usually low enough to induce symptoms [17]. The patient should be closely observed during voluntary hyperventilation to ensure that they do not become excessively dizzy or experience significant chest pain. Operators should be prepared to terminate the voluntary hyperventilation phase if the patient begins to exhibit signs of distress. Not all patients can manage to maintain voluntary hyperventilation for the full 3-min period, either due to fatigue or the severity of symptoms induced. Operators should endeavour to maintain the voluntary hyperventilation period for a minimum of 90 s. Some patients will require significant encouragement to maintain the necessary effort.

An alternative strategy may be rather than trying to achieve a single target ETCO$_2$ in all patients during voluntary hyperventilation that there should be an aim to reduce the patients' resting ETCO$_2$ by 50%.

The result of the HPT should be considered negative if the patient has a resting ETCO$_2$ within the normal range and this returns to (or close to) the resting value during recovery (figure 2). In patients suffering from acute hyperventilation, the ETCO$_2$ will
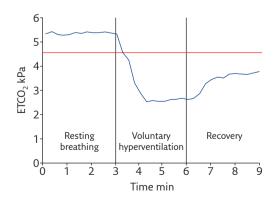
remain below the normal range during the recovery period (figure 3).

If a patient has a resting ETCO$_2$ <4.0 kPa they can be considered to have chronic hyperventilation (figure 4). Care should be taken to ensure that a patient is not assessed to have chronic hyperventilation when they exhibit anxiety and apprehension regarding the assessment they are about to undertake, which would make the results more in keeping with acute hyperventilation. Patients can modify their breathing pattern (either consciously or subconsciously), which can result in false positive or false negative results [18, 19].

The HPT has been criticised for a lack of specificity [20]. An alternative approach is to carry out a cardiopulmonary exercise test, which will provide detailed information over and above that available during an HPT. Oxygen uptake, carbon dioxide production, ECG and ventilatory pattern can all be recorded on a breath-by-breath basis which makes this an excellent method of identifying patients with hyperventilation. The potential disadvantage of this technique is that it is not suitable for all patients, especially those with mobility issues. Many patients with chronic hyperventilation are also deconditioned, which may result in a submaximal (and inconclusive) test.

Alternatives to the HPT

Very few viable alternatives to the HPT exist. One option that could be considered is ambulatory capnography [21, 22], which has been used as part of a biofeedback protocol to help asthmatics maintain control. Using a portable capnograph with a data storage facility along with a symptoms diary would allow clinicians to review data at the time the patient experiences their symptoms. Transcutaneous measurements of PaCO$_2$ could also be made, but this technique may be of limited use as the sensor site needs to be changed every 4 h.
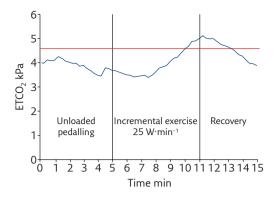

Figure 3 *HPT in a patient with acute hyperventilation. Resting ETCO$_2$ is within the normal range but recovery from voluntary hyperventilation is slow. The red line indicates the lower limit of ETCO$_2$.*

Figure 5 *Patient with chronic hyperventilation undergoing an exercise test. $ETCO_2$ is low at rest, normalises as exercise progresses before falling below the normal range during recovery. The red line indicates the lower limit of $ETCO_2$.*

Figure 6 *Patient with acute hyperventilation undergoing an exercise test. $ETCO_2$ is normal at rest and during exercise before falling below the normal range during recovery. The red line indicates the lower limit of $ETCO_2$.*

Investigation of hyperventilation on exercise

The most appropriate method to investigate hyperventilation on exercise is to perform a cardiopulmonary exercise test as this should provide the necessary information required to identify the source of a patient's dyspnoea on exertion. If cardiopulmonary testing is not available or is not appropriate for a patient, then a capnograph can be used to record $ETCO_2$ during exercise. Care should be taken to ensure that motion artefact is minimised during exercise, as this can lead to either partial or complete occlusion of the capnograph sampling tube, which will invalidate the measurements.

Hyperventilation during exercise can manifest itself in two main ways: a patient with chronic hyperventilation will have a low resting $ETCO_2$ that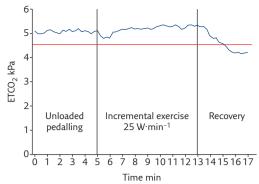 will gradually normalise as exercise progresses before falling again during recovery (figure 5). A patient with acute hyperventilation tends to have a normal $ETCO_2$ at rest and during exercise but $ETCO_2$ falls during the recovery phase (figure 6). In the author's experience, this pattern may be encountered more often in younger, fitter patients with good lung function.

Conclusion

A potential diagnosis of either functional cough or dyspnoea should only be considered after other potential causes of the patients' symptoms have been investigated and either eliminated or quantified. Investigation of functional breathlessness is much easier to investigate in a routine clinical physiology laboratory than functional cough.

Conflict of interest

None declared.

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