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Saturday May 31, 2003 Euroanaesthesia 2003 - Glasgow

INTRODUCTION

Dyspnoea is a clinical term used to represent the symptom of breathlessness, or shortness of breath, reported by patients with cardiopulmonary disease or by those suffering from anxiety and panic disorder. Healthy subjects will also experience shortness of breath, for example during exertion, breath holding or suffocation. It can be an unpleasant and frightening experience and, for patients, it is a debilitating symptom that can markedly restrict daily activity and reduce their quality of life. The symptom of dyspnoea should be considered an important and normal component of respiratory (blood gas) homeostasis; it indicates that some inadequacy of ventilation exists that should be righted. As such, dyspnoea should be accompanied by some 'motor response'. This may be a change in ventilation, but alternatively the motor response may be a change in behaviour: for example, the degree of physical exertion may be reduced to prevent cardio-pulmonary collapse or a period of breath hold diving may be ended. Clearly, in disease states, the presence of dyspnoea represents an underlying pathophysiological deficit in ventilation that cannot be fully compensated. Dyspnoea should therefore be considered one component of the sensory limb of breathing, itself a complex sensory-motor behaviour.

In many conditions, such as heart disease, terminal cancer or pneumothorax, dyspnoea may co-exist with pain. Dyspnoea is frequently present in the late stages of terminal disease. It is perhaps when managing pain that anaesthesiologists are most likely to encounter dyspnoea in their clinical practice. Although pain and dyspnoea share many common features, remedies for dyspnoea are far less numerous or effective than those for pain and it remains a poorly managed symptom. The aim of the present review is to consider some fundamental aspects of the pathophysiology of dyspnoea; particular emphasis will be placed on recent advances in our understanding of the regulation of breathing and of the representation of dyspnoea in the central nervous system. For a fuller consideration of the clinical assessment and treatment of the dyspnoeic patient, the reader is directed to an excellent text elsewhere (1).

THE SYMPTOM OF DYSPNOEA

Dyspnoea is derived from Greek: dys, meaning painful or difficult and pneuma meaning breath. The symptom subsumes several sensations such as sense of respiratory work and effort, the tightness of asthma, and an uncomfortable urge to breathe (or "air hunger") and patients may use a wide range of terms to describe it (2). In disease, increased work, effort, or chest tightness are commonly present with air hunger; it appears that air hunger, in particular, is important in producing the unpleasant nature of dyspnoea. Clinically, dyspnoea can be associated with inappropriately low levels of exertion, or may even be present at rest. A consensus statement from the American Thoracic Society (3)proposed the following definition:

> *"Dyspnoea is a term used to characterise the a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioural responses."*

Dyspnoea is distinct from observable clinical signs such as tachypnoea, 'pursed lip' breathing, hyperinflation or cyanosis.

CONTROL OF BREATHING IN HUMANS

A wealth of evidence from animal studies indicates that specialized structures within the brain stem are essential for the generation of the rhythmic motor activity (4). These structures are, however, inadequate to explain respiratory control in humans, for human respiratory behaviour includes acts such as speech, laughter and the playing of wind instruments. As was indicated above, dyspnoea is a component of the control of breathing, evident only in humans. Before considering the physiological basis for this symptom, it is useful to summarise some recent advances in our understanding of the control of breathing in humans. Studies using

neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), indicate that the voluntary control of breathing is mediated in a similar way to other voluntary motor tasks. Voluntary breathing is associated with activity in the primary motor cortex as well as in other motor related structures, including the supplementary motor cortex, pre motor cortex, thalamus, basal ganglia and cerebellum (5). Although voluntary breathing may be perceived as an atypical motor act, these same networks are implicated in the normal ventilatory response to exercise and in the control of breathing for speech. Further, in humans, the ventilatory responses to CO_2 stimulated breathing (6) and to loaded breathing (7) are associated with activity in widespread supra-brainstem structures.

Mechanisms of dyspnoea

Dyspnoea is increased by afferent inputs demanding more ventilation and is decreased by afferent inputs reporting the prevailing ventilation. For example, stimulation of respiratory chemoreceptors by CO_2 or hypoxia increases dyspnoea, while mechanoreceptor traffic reporting tidal inflation of the lungs relieves dyspnoea. Increases in ventilation produced by mechanical support or by voluntary hyperventilation induce little or no dyspnoea, suggesting that the level of ventilation, *per se*, is not important in the genesis of dyspnoea. Banzett et al. demonstrated that hypercapnia itself can directly induce breathlessness, independent of any changes in ventilation or respiratory muscle activity (8). These experimenters induced breathlessness, in totally curarised, unsedated subjects who were mechanically ventilated, by inducing changes only in inspired CO_2. Further evidence that intact brainstem respiratory control is necessary for the genesis of breathlessness comes from observations in patients with congenital central hypoventilation syndrome. Such patients, as well as lacking ventilatory sensitivity to CO_2 or to hypoxia, lack any sensation of dyspnoea arising from these symptoms (9).

Dyspnoea presumably arises from the integration of many disparate inputs within the CNS. Until very recently, the cerebral representation of dyspnoea was entirely unknown, mainly due to an absence of useful animal models or relevant clinical lesion studies. Functional neuroimaging (PET and fMRI) has been widely used to study pain in humans; these studies show prominent cerebral representation in limbic areas (reviewed by (10)). A PET study of respiratory motor activation during CO_2-stimulated breathing initial suggested that limbic areas might be involved in dyspnoea perception (6). Subsequently, we have used fMRI to identify specifically the neural correlates of experimentally induced dyspnoea (air-hunger) (11). We detected activation within limbic and para-limbic structures including the anterior insula, anterior cingulate, operculum cerebellum, amygdala, thalamus and basal ganglia. In addition, elements of frontoparietal attentional networks were also identified. Other studies of cerebral activation using PET in humans, during laboratory-induced dyspnoea, have also indicated strong activation of the anterior insular cortex. The consistency of anterior insular activation across published studies suggests that the insula is essential to dyspnoea perception, although it appears that, for perception of this symptom, it must act in concert with a wider neural network. An important extension of these present studies will be to determine the similarities, or differences, between the neural correlates of experimentally induced dyspnoea and of dyspnoea due to disease.

Dyspnoea and perceptions of other bodily states

Air hunger, similar to hunger for food, thirst, and the need to escape from pain, is a powerful and primal sensation alerting the organism to a threat to survival. The limbic/paralimbic system, which includes the insula, cingulate gyrus and amygdala, is thought to aid survival by integrating behaviour with the perception of physiological needs (12). Human neuroimaging studies have shown activation of the cerebellum, limbic, and paralimbic structures in response to essential survival stimuli including pain, hunger, thirst, and dyspnoea. However it is not clear to what extent these limbic/paralimbic activations are a response to general discomfort. As one example, the anterior insula may serve only as a nonspecific “alarm centre” for physiological threat, or it may be that there are specific insular neurons activated by each of these stimuli. It will require higher resolution techniques to determine whether air hunger activations in the insula are identical, or different but closely adjacent to, pain or thirst activations. Furthermore, differences between the afferent pathways for air hunger and for other visceral sensations remain to be clarified (13).

Conclusion

Dyspnoea is a debilitating and widespread symptom associated with cardiopulmonary disease. The symptom subsumes several sensations, each related to different components of respiratory perception; however the affective component of the symptom appears most strongly related to the sensation of ‘air-hunger’. Recent advances in functional neuroimaging indicate many similarities between the central nervous system representations of air hunger, pain and other visceral sensations. The pathology underlying dyspnoea is frequently intractable and, at present, palliative treatments of the symptom are usually inadequate.

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Saturday May 31, 2003 Euroanaesthesia 2003 - Glasgow

For many years, pre-operative assessment considered the risk of bleeding rather than the risk of thrombosis, assuming that a range of tests of coagulation would indicate the haemostatic stateof the patient and avoid intra-operative bleeding. (1-4). Only a limited group of specialized physicians were interested in possible post-operative arterial thrombosis. Venous thrombo-embolism was systematically prevented by low-dose heparin or low molecular weight heparin but any intrinsic biological hypercoagulability of the patient was ignored. Information on peri-operative hypercoagulability was not available and most of the thrombotic congenital disorders had not been discovered. Publications stressed the value of good preoperative questioning rather than empirical and unhelpful coagulation screening(2-4) but they concentrated on haemorrhagic aspects. Times have changed: the poor predictive value of preoperative biological tests and a better knowledge of haemostasis have led to considering the patient in general and avoiding tests other than in a limited number of situations. In addition, thrombosis after surgery is now considered a major event, which can be life-threatening. The sequelae of thombosis (e.g. pulmonary embolism, TIA, stroke, peripheral ischaemia) are generally more severe than the consequences of haemorrhage (such as haematomas, or the need for transfusion). For example, stopping antiplatelet agents before surgery could lead to myocardial infarction(5).

PREOPERATIVE SCREENING

"When the whole blood clotting time and the Duke bleeding time were the tests used to screen hemostatic function preoperatively, the question : "preoperative hemostatic evaluation, which tests, if any" was easy to answer :"do not bother with these insensitive tests, rely on the patient's history" Samuel I Rapaport, 1983 (2)

Indeed, if everybody agrees with this opinion, then routine tests such as the Ivy bleeding time, activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen concentration would be more sensitive and specific than older tests. Unfortunately, it is now clear that only the patient's personal history is reliable, for both haemorrhage and thrombotic risks, and can increase the sensitivity and the specificity of several tests of haemostasis. For thrombotic risks, no tests give useful information about hypercoagulable states. The prevalence of haemostatic defects in the Caucasian population is low (6). History, physical examination, platelet count, bleeding time, PT, APTT and fibrinogen level were obtained systematically in 4141 patients. Only one prolonged PT and 19 prolonged APTT results (0.48%) were found, and only 8 patients judged to be at risk from bleeding: patients with factor XI deficiency (3), antibody to factor VII (1), and von Willebrand disease (4).. Only 3 histories were positive in these 8 patients, showing that the value of systematic screening was very low (5/4141 i.e 0.12%). In addition, the number of potential thrombotic abnormalities was also very low (7/4141 i.e 0.17%).

A detailed questionnaire should be given to the patient (table 1) to improve the quality of the preoperative assessment. This questionnaire should be designed to detect adverse events in the patient history. It should ideally be completed by the patient before the first meeting with the anaesthesiologist. However, in addition to the history, some tests may be necessary in some circumstances :

- patients may not be detected if the doctor fails to take an adequate history
- some patients may give an unreliable history i.e mild bleeding disorders, and
- some abnormalities may cause bleeding only after surgery or dental extractions (factor XI deficiency, Willebrand)
- acquired haemostatic defects related to the onset of severe disease (thrombocytopenia in AIDS patients for instance) may be discovered.
- a family or personal history of thrombophilia with either venous or arterial events indicates the need for extensive biological preoperative screening (antithrombin, protein C and S, factor V Leiden, hyperhomocysteinemia, 20210G/A prothrombin gene mutation, etc…),depending on the indication for surgery and the operation to be performed.

Obviously some surgical procedures can cause intra or post-operative bleeding complications and other ones will favour thrombotic events.