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Drive respiratório anormal na doença vibroacústica

Abnormal respiratory drive in vibroacoustic disease

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Resumo

Enquadramento: As alterações do sistema nervoso central em trabalhadores expostos a ruído de baixa frequência (RBF, <500 Hz, incluindo infra-sons) foram observadas pela primeira vez há 25 anos, em técnicos de aeronaves. Ao mesmo tempo, foi também identificada patologia respiratória nos mesmos trabalhadores, mais tarde reproduzida em modelos animais sob exposição a RBF. Actualmente, a doença vibroacústica (VAD) define-se como patologia sistémica causada por exposição excessiva a RBF. O aparelho respiratório continua sob estudo intensivo, quer em modelos humanos quer animais, expostos a excessivo RBF, e tem sido confirmado como um alvo preferencial do RBF. Uma vez que ambos os sistemas, respiratório e nervoso central, estão comprometidos nestes trabalhadores, torna-se pertinente a investigação do estado do controlo neurológico da respiração em doen-

Abstract

Introduction: Central nervous system disorders in workers exposed to low frequency noise (LFN, <500 Hz, including infrasound) were first observed 25 years ago among aircraft technicians. Concurrently, respiratory pathology was identified in these workers, and later reproduced in LFN-exposed animal models. Today vibroacoustic disease (VAD) is defined as the systemic pathology caused by excessive exposure to LFN. The respiratory tract continues to be under heavy scrutiny in both LFN-exposed humans and animal models and has been confirmed as a major target for LFN-induced damage. Given that both the respiratory and central nervous systems were compromised in these workers, it became pertinent to investigate the status of the neurological control of breathing in VAD patients. **Methods:** The $P_{-0.1}$ value, a measure of the suction pressure developed at the mouth 0.1

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tes com a VAD. O propósito deste estudo é a exploração das implicações destes resultados. **Métodos:** Avaliaram-se as pressões respiratórias máximas, incluindo a pressão aos 0,100 seg de uma inspiração profunda, com início na capacidade residual funcional ($P_{0.1}$), em respiração com ar ambiente, e também após estabilização respiratória face à inalação de uma mistura de ar com 5,9% de CO_2 (Masterscreen versão 4.3, Viasys, Wurzburg, Alemanha), por válvula em Y com oclusão – $P_{0.1}CO_2$. Foram observados 22 indivíduos de sexo masculino, de 50,5 anos (± 8,5, entre 36-66 anos), expostos a nível ocupacional a ambientes ricos em RBF. Também se avaliou um grupo de controlo, de 7 indivíduos, exposto a menores níveis acumulados de RBF, idade média 42,4 ±14, entre 25 e 61 anos. **Resultados:** Os exames funcionais respiratórios foram normais, quer em doentes com VAD quer em controlos. O índice de $P_{0.1}(CO_2)$ (% do valor de referência) ficou muito abaixo em doentes com VAD (média: 22,9%) relativamente ao grupo de controlo (>60%). **Conclusões:** Na resposta reflexa ao acréscimo de PCO_2, os quimio-receptores centrais são responsáveis por 70% do estímulo ventilatório. Um estímulo ventilatório diminuído pode traduzir certa disfunção do tronco cerebral. Em doentes com VAD, esta disfunção é corroborada por anomalias dos potenciais evocados auditivos do tronco cerebral, bem como por alterações detectáveis em ressonância magnética. O índice $P_{0.1}CO_2$ pode revelar-se um indicador clínico útil para o diagnóstico e seguimento da VAD. Em resumo, o controlo neurológico da respiração está comprometido em doentes com VAD.

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Palavras-chave: Ruído de baixa frequência, infra-sons, controlo da respiração, $P_{0.1}CO_2$, pressões respiratórias máximas.

seconds after the start of inspiration, depends on the respiratory centres and the autonomic nervous system pathway of the neural control of respiratory function. By rebreathing CO_2, (6% in air) normal individuals present an average seven-fold increase in $P_{0.1}(CO_2)$ as compared to basal $P_{0.1}$. Twenty-two male VAD patients (ave. age 50.5±8.5 years, range: 36-66 years) underwent the $P_{0.1}(CO_2)$ index respiratory drive tests, as well as standard pulmonary function tests. Seven individuals (ave. age 42.4 ±14 years, range: 25-61 years) with reduced LFN exposure served as controls. **Results:** Pulmonary function tests were normal in both VAD patients and controls. The $P_{0.1}(CO_2)$ index was below average value in VAD patients (average: 22.9%) while it presented normal values in the control group (average >60%). **Discussion:** In the involuntary response to increased PCO_2 levels, central chemoreceptors are responsible for 70% of the ventilatory stimulus. In VAD patients, this dysfunction may originate in the brainstem. This is corroborated by the fact that VAD patients register abnormal values for auditory brainstem evoked potentials, and disclose lesions with magnetic resonance imaging. The neurological control of breathing is compromised in VAD patients. The $P_{0.1}(CO_2)$ index may be a useful clinical indicator for VAD diagnosis and follow-up.

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Key-words: Low frequency noise, infrasound, respiratory control, $P_{0.1}CO_2$, peak respiratory pressure.

Introduction

Low frequency noise (LFN, <500 Hz, including infrasound) is an agent of disease that can cause vibroacoustic disease (VAD), a systemic pathology characterized by the abnormal growth of extra-cellular matrices, namely collagen and elastin[1]. In the early 1980s, auditory brainstem evoked potentials (BAEP) were studied in VAD patients where statistically significant delays in nerve conduction were identified[2,3]. Concurrently, respiratory pathology emerged as an important feature in these patients[4], and many aspects have already been reproduced in LFN-exposed animal models[5].

The involuntary control of ventilation is mediated by the medullary inspiratory neurons, modulated by inputs from two different types of chemoreptors. The peripheral chemoreceptors, located in the carotid and aortic bodies, provide input to the medullary inspiratory neurons by detecting changes in the partial pressure of arterial carbon dioxide (PCO_2). The central chemoreceptors, located in the medulla, are stimulated by the changes in hydrogen-ion concentration [H^+], also as a consequence of changes in the arterial PCO_2 [6].

Central chemoreceptors are responsible for 70%-80% of the ventilatory stimulus, induced by the reflex response to elevated PCO_2. This is because CO_2 is a lipid-soluble molecule that can rapidly diffuse across the extra-cellular fluid that surrounds the chemoreceptor. Medullary chemoreceptors respond to an increased [H^+], hence, an increased arterial PCO_2 regulates ventilation by changing the [H^+] (or pH)[7].

There are two methods of clinically assessing the output of the medullary respiratory center[8]. With the rebreathing technique, a small bag is filled with a low concentration of CO_2 (6-7% in air), and the patient rebreathes into the bag over a period of several minutes. PCO_2 increases at a rate of 4-6 mm Hg and thus changes in ventilation can be easily determined[9].

Measurements of the inspiratory pressure (or suction) developed at the mouth 0.1 seconds after the start of inspiration is achieved by occlusion of the airway during expiration, so that the first 0.1 second of the next inspiration is still against an occluded airway (maintained for 0.5 seconds). The pressure generated within the first 0.1 seconds is considered to be a measure of the total neural discharge of the respiratory centre[8]. The re-breathing technique does not make a distinction between abnormalities in chest mechanics and inadequacies of the neuronal control, while the $P_{0.1}$ technique is largely unaffected by the mechanical properties, although it can be influenced by lung volume.

Suspicion of respiratory damage in LFN-exposed workers began with four unusual cases of pleural effusion which did not respond to therapy, had very prolonged recovery periods, and whose aetiology was never identified[10]. This prompted, in 1992, the first studies of LFN-exposed animal models, where the respiratory tract epithelia were examined with scanning and transmission electron microscopy. Fibrosis of the pleura, lung and trachea was identified, along with destruction of ciliary populations and fusion of brush cell microvilli[5]. Subsequent high-resolution CT scan of the lung of LFN-exposed workers, with and without respiratory symptoms, disclosed focal fibrosis and air-trapping[4], among other findings.

Taking together the damage induced by LFN exposure on the nervous and respiratory systems, it became pertinent to investigate the condition of the involuntary respiratory reflex, or respiratory drive, in LFN-exposed individuals diagnosed with VAD.

Methods

Respiratory drive

Respiratory drive was calculated through CO_2 sensitivity of the $P_{0,1}$ index, in resting conditions, using a spirometer. The $P\text{-}_{0.1}$ index is a measure of the pressure generated spontaneously in the early inspiratory effort, at the end of a forced expiration (see above). This initial respiratory drive originates in the autonomic (or involuntary) pathway of the neural control of respiratory muscles. By rebreathing CO_2, normal individuals would present a minimum six-fold increase in the $P_{0.1}(CO_2)$ value when compared to basal (standard air) $P\text{-}_{0.1}$ (Masterscreen 4.3, Viasys, Jaeger, Wurzburg, Germany).

$P_{0.1}$ measurements were obtained during breathing of standard air, and during breathing of air containing 5.9% CO_2, via a Y-valve with shutter – $P_{0.1}CO_2$. The ratio between both measurements is an indicator of respiratory drive. The best values between five trials were chosen.

$P_{0.1}$ measurements were always performed first during air breathing. The patient approached the mouthpiece and was instructed to breath normally while the $P_{0.1}$ curve was registered. Then, connected to the CO_2 bag circuit, the patient inspires from the 5.9% CO_2 gas mixture. Patients with normal ventilatory drive show a clearly increased tidal volume, breathing frequency and ventilation, and after about 1-3 minutes a steady state (stable) is reached. No such ventilatory stability, hyperventilation state, or unstable breathing level is obtained if the patient has a disorder of respiratory drive. The $P_{0.1}$ measurement with the 5.9% CO_2 gas mixture was then initiated, and the $P_{0.1}CO_2$ value was registered after a minimum 3-minute period of CO_2 breathing. The shutter was activated endexpiratorily, and the trial ended after about 10-15 occlusions of the shutter.

All subjects also underwent standard pulmonary function tests.

Study population

This study encompasses to 22 male individuals, average age 50.5 years (± 8.5, range: 36-66 years). All were occupationally exposed to LFN-rich environments, and all had been diagnosed with VAD. All patients were informed volunteers. Some were part of the initial VAD study group of aircraft technicians[11], while others have approached our group with complaints of LFN-induced pathology and have been diagnosed with VAD[12,13].

Within the context of VAD studies, controls are individuals who are not excessively exposed to LFN, and who are not diagnosed with VAD. Since pericardial thickening in the absence of an inflammatory process and with no diastolic dysfunction is the hallmark of VAD[14], echocardiography is necessary to ascertain whether an individual is an adequate control group element. Age-matched control populations have been fairly difficult to obtain. To date, there is an insufficient number of controls to constitute a statistically robust comparison population (N=7, ave. age 42.4 ±14 years, range: 25-61). Hence, the values for

the $P_{0.1}(CO_2)$ values obtained for the study group will be compared to the normal value provided by the manufacturer (Jaeger, Germany), accepted as >60% of reference, corresponding to ± 2 standard deviations. Although the authors are in the process of obtaining the studies on which these values are based directly from the manufacturer, the comparison with manufacturer values, as described, is not considered to be very reliable, because no details are known regarding noise-exposure histories of manufacturer control populations.

Results

Standard pulmonary function tests were normal in all 22 VAD patients. However, the $P_{0.1}(CO_2)$ values were significantly below normal (60%): average: 25.6 % of reference (± 10.8%, range: 63%-6.3%).

Although insufficient in number (N=7), the few elements already identified as controls subjects have been disclosing $P_{0.1}(CO_2)$ values similar to those quoted by the manufacturer as normal values, all reaching >60%.

Discussion

The $P_{0.1}(CO_2)$ values reflect the neural output of the medullary respiratory center. While this parameter could be altered due to lung mechanical and functional impairments, as standard lung function tests were normal, this hypothesis is eliminated. These results accordingly confirm that some pathway(s) of the involuntary control of ventilation in VAD patients is severely damaged. In these individuals, no hyperventilation occurs in the presence of airborne CO_2. The $P_{0.1}(CO_2)$ value does not take into consideration individual variances of lung volume. However, given the extremely low indices obtained for the respiratory drive, it is supposed that individual variations alone cannot account for these pathological values.

Once again, the insidious nature of LFN-induced pathology is evidenced. Loss of hyperventilatory function in the presence of an increased amount of CO_2 may bring long-term consequences. In apnea divers, this response is often impaired due to excessive exposure to increased levels of PCO_2. Apnea divers often have an increased tolerance of the medullary center to electrolyte and local pH variations induced by hypercapnia. Hypercapnia is usually well tolerated in divers until the limit of toxicity after which, symptoms become evident. In VAD patients, the PCO_2 re-breathing test is often uncomfortable. Some VAD patients cannot tolerate the 5.6% CO_2 mixture for the minimum required 2 minute measurement. Studies are underway to investigate this feature in VAD patients.

The medullary centers, or central CO_2-sensitive areas (rostral, intermediate and caudal), are located in the ventrolateral medulla, between the origins of the 7th (facial) and 10th (vagus) cranial nerves, and account for 70% to 80% of the CO_2 induced increases in ventilation. Brainstem damage has already been identified in VAD through BAEP[2,3] and MRI[11]. Thus it would not be surprising if the impairment of the PCO_2 response in VAD patients was related to brainstem lesions. Within the scope of VAD, this simple and inexpensive test could serve as an indication of brainstem damage, and could justify the prescription of more sophisticated tests to ascertain the extent of brainstem damage.

In accordance with data gathered to date, it seems that the respiratory reflex is not elicited during normal daily activities. In the more common situation, an increase in CO_2 is normally associated with a decrease of O_2, and/or an increase in CO. Thus, the consequences of not possessing a functional neurological control of breathing are not clearly understood. However, this cannot be equated with the situation of respiratory acidosis, common in severe COPD patients or hypoventilation-obesity syndromes (obstructive apnea-hypopnea).

The authors invite fellow scientists and physicians to perform this non-invasive and inexpensive test on LFN-exposed individuals they may have under their care.

Conclusions

The involuntary respiratory reflex, controlled by brainstem respiratory centres, is impaired in VAD patients. This simple, non-invasive and inexpensive diagnostic test could become a mandatory test for confirming a VAD diagnosis but the lack of a viable control population impedes further conclusions on the usefulness of this medical examination.

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