To the extent that resistive breathing is a potent stimulus for upregulation of cytokines involved in the process of angiogenesis, a review dealing with the immune response to resistive breathing may present the angiogenetic response as well.

Exercise training induces a series of adaptive responses in the cardiovascular and skeletal muscular system, including myofibrillar protein changes, increased activity of oxidative and glycolytic enzymes, and an increased number of capillaries. Such changes in the capillary bed of skeletal muscles in athletes have been detected since the mid 1970s [2, 3]. Since then, angiogenesis has been studied extensively and found to be an extremely complex process involving, among others, the dissolution of the extra cellular matrix underlying endothelium, cell migration and endothelial cell proliferation [4, 5]. Specific growth factors and predominantly vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and transforming growth factor (TGF)-b1 were found to regulate the angiogenic response to a variety of stimuli [4]. A single bout of exercise increases the mRNA levels for the previously mentioned factors [6]. Recent data have shown that acute exercise upregulates the mRNA expression, while there is a graded response in the expression of mRNA of this angiogenic factor with the metabolic stress. Furthermore, it is demonstrated that mRNA for VEGF and bFGF in the diaphragm of rats rises significantly as a result of active increased ventilation due to hypoxia and/or hypercapnia, while no changes in mRNA levels were observed in paralysed, mechanically ventilated animals at similar arterial blood gases and ventilation levels [7, 8]. However, there is evidence that resistive breathing upregulates mRNA for VEGF, but not for bFGF and TGF-b1 [9].

Therefore, angiogenesis, as a result of loading of the respiratory system, is an important part of the integrated immune response to resistive breathing.

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DOI: 10.1183/09031936.05.00018105

From the authors:

We would like to thank N.M. Siafakas and I. Mitrouska for their insightful comments about our recent article published in the *European Respiratory Journal* [1]. They suggest that resistive breathing may be a potent stimulus for upregulation of angiogenesis-promoting factors within the diaphragm.

Preliminary data (which have appeared only in abstract form) suggest that resistive breathing might lead to an upregulation of vascular endothelial growth factor (VEGF), but not basic fibroblast growth factor (bFGF) and transforming growth factor-b1 [2]. Other forms of increased diaphragmatic activation, such as hyperventilation induced by hypercapnia and/or hypoxia, lead to increased expression of the mRNA levels of both VEGF and bFGF [3]. This angiogenetic response was not solely caused by the deranged blood gases or by the hyperventilation-induced passive stretching and shortening of the diaphragm, since mechanical ventilation leading to similar blood gases levels did not result in a diaphragmatic angiogenetic response.

The stimuli for the expression of angiogenesis-promoting factors within skeletal muscles (in general) and respiratory muscles (in particular) remain elusive. Interestingly, in an *in vitro* cell culture system of skeletal myocytes fused into myotubes, reactive oxygen species stimulated the expression of VEGF [4] in a similar fashion to their effect of inducing interleukin-6 production [5]. This raises the interesting possibility that oxidative stress generated intramuscularly, secondary to increased muscular activation/contraction [6], might be the stimulus for both upregulation of cytokines and expression of an angiogenesis programme. Despite being sound, such a hypothesis has never been experimentally tested.

Angiogenesis is a prerequisite for the development of hypertrophy and hyperplasia, secondary to chronic exercise training in skeletal muscles. This might be important for the increased ventilation requirements of some elite athletes during athletic performance, although the benefit from additional specific respiratory muscle training is uncertain [7]. However, angiogenesis is even more important for the beneficial effects of rehabilitation programmes involving training of the respiratory muscles [8].

Our review focused on the response of the ''classical'' cytokines (those usually produced by blood mononuclear cells) to resistive breathing. This is why it did not cover other

important aspects, such as the response of chemokines or adhesion molecules, as well as angiogenesis-related factors to resistive breathing. More research is needed to study not only the factors driving the expression of an angiogenetic programme within the respiratory muscles, but also the actual process of angiogenesis, as well as its clinical relevance.

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DOI: 10.1183/09031936.05.00029505

Technical practices are important to consider when assessing noninvasive ventilation failure

To the Editors:

In their recent publication in the *European Respiratory Journal*, CONFALONIERI *et al*. [1] nicely describe relevant clinical predictive factors of noninvasive ventilation (NIV) failure in chronic obstructive pulmonary disease patients hospitalised for acute hypercapnic respiratory failure. The authors provide an interesting tool that could help to quantify this risk better and, thus, shorten the delay of a possible intubation.

NIV failures are linked to the clinical severity at admission and to the location where it was performed, as confirmed by the authors, who focused their work on clinical determinants of immediate NIV failure. However, technical factors, which are more difficult to assess, may modify the results of such prognostic studies, even if they are performed by experienced personnel. Recommendations and experts' opinions concerning NIV in the acute setting [2–4] mention the fact that a proportion of patients fail NIV because of technical problems related to humidification, interfaces, ventilatory modes and patient–ventilator interactions [4].

Humidification of inspired air is a critical factor, since heat and moisture exchangers increase the work of breathing and may lead to NIV failure [5, 6]. NIV failure may also be linked to a poor adaptation to nasal/facial masks, leading to asynchrony and/or unintentional leaks. In real world studies, most teams change the interface during the ventilatory course, using facial masks to reduce leaks and, as soon as possible, nasal masks to improve tolerance [7]. Finally, it would be interesting to know if the pressure support mode was modified or shifted during NIV courses in this study. A shift from pressure support to assist–control ventilation is mentioned by some authors in the literature [8], and this could help to resolve some situations, avoiding endotracheal intubation.

In addition to clinical parameters at admission, technical practices obviously need to be taken into account when assessing noninvasive ventilation success or failure during an acute hypercapnic respiratory failure episode. It is, of course, extremely difficult to design clinical studies that would control all technical factors, and we do not know to what extent such control would have modified the final message from CONFALONIERI *et al*. [1]. However, since a non-negligible percentage of patients with chronic obstructive pulmonary disease and acute hypercapnic respiratory failure still fail to be successfully treated by noninvasive ventilation, the important results from CONFALONIERI *et al*. [1] would need to be extended in a prospective study assessing the role of technical factors in the outcome of acute hypercapnic respiratory failure.

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