Passive stretch of the diaphragm following unilateral phrenic nerve stimulation

To the Editor:

MASMOUDI *et al.* [1] reported an exciting pilot study on the beneficial effects of unilateral phrenic nerve stimulation on diaphragm muscle trophicity and structure in mechanically ventilated sheep. They observed that, during 72 h of mechanical ventilation, stimulation sessions of 30 min at 4-h intervals attenuated the development of muscle fibre atrophy in the stimulated hemidiaphragm. Fibres from the unstimulated contralateral hemidiaphragm served as controls.

We postulate that, due to the design of the study, the results of MASMOUDI *et al.* [1] may provide an underestimation of the beneficial effects of diaphragm pacing on diaphragm structure. This is based on the following. During unilateral diaphragm pacing, only the stimulated hemidiaphragm contracts. Shortening of the fibres from the stimulated hemidiaphragm ''pulls'', *via* the central tendon, on the passive fibres of the contralateral unstimulated hemidiaphragm. Consequently, in the sheep studied by MASMOUDI *et al.* [1], the unstimulated ''control'' diaphragm fibres were actually exposed to 30-min bouts of cyclic stretch.

Why would cyclic stretch of the control diaphragm fibres affect the study outcome and lead to an underestimation of the beneficial effects of unilateral phrenic nerve pacing? Cyclic passive stretch is a strong stimulus for muscle protein synthesis and hypertrophy. This effect of passive stretch on diaphragm trophicity is evident from studies that investigated the effects of unilateral diaphragm denervation, by laceration of one phrenic nerve, on diaphragm fibre structure in spontaneously breathing rats and mice [2–4]. These studies showed that within days after phrenic nerve laceration, the denervated hemidiaphragm undergoes marked hypertrophy. In line with these findings, we recently observed in patients that fibres from unilaterally denervated hemidiaphragms only very slowly develop atrophy [5]. These diaphragm muscle fibres preserved size and strength up to 8 weeks after denervation, indicating that the cyclic stretch-induced hypertrophic response was so strong that it outweighed the atrophic response caused by contractile inactivity.

Thus, the study design employed by MASMOUDI *et al.* [1] probably induced an undesired hypertrophic stimulus in the unstimulated control hemidiaphragm. The observation that the fibres of the stimulated hemidiaphragm nevertheless had larger cross-sectional areas strengthens the idea that phrenic nerve pacing is a powerful approach to attenuate mechanical ventilation-induced diaphragm atrophy.

We underscore the notion postulated in the correspondence by GAYAN-RAMIREZ [6] that it is ''time for contr(action)''. Future studies should extend the exciting pilot results from MASMOUDI *et al.* [1] and consider employing bilateral, rather than unilateral, pacing to fully grasp the potential of phrenic nerve stimulation.

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Future studies should consider employing bilateral pacing to fully grasp the potential of phrenic nerve stimulation http://ow.ly/qQRQI

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References

1 Masmoudi H, Coirault C, Demoule A, *et al.* Can phrenic stimulation protect the diaphragm from mechanical ventilation-induced damage? *Eur Respir J* 2013; 42: 280–283.
2 Gutmann E, Schiaffino S, Hanzlikova V. Mechanism of compensatory hypertrophy in skeletal muscle of the rat. *Exp Neurol* 1971; 31: 451–464.
3 Norrby M, Tagerud S. Mitogen-activated protein kinase-activated protein kinase 2 (MK2) in skeletal muscle atrophy and hypertrophy. *J Cell Physiol* 2010; 223: 194–201.

4 Gosselin LE, Brice G, Carlson B, *et al.* Changes in satellite cell mitotic activity during acute period of unilateral diaphragm denervation. *J Appl Physiol* 1994; 77: 1128–1134.
5 Welvaart WN, Paul MA, van Hees HW, *et al.* Diaphragm muscle fiber function and structure in humans with hemidiaphragm paralysis. *Am J Physiol Lung Cell Mol Physiol* 2011; 301: L228–L235.
6 Gayan-Ramirez G. Ventilator-induced diaphragm dysfunction: time for (contr)action! *Eur Respir J* 2013; 42: 12–15.

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Asthma and risk of pulmonary thromboembolism

To the Editor:

We read with interest the article by CHUNG *et al.* [1] about the risk of pulmonary thromboembolism in asthmatic patients. This nationwide population cohort study suggests that the risk of developing pulmonary thromboembolism significantly is increased in asthmatic patients compared to those of the general population, with a multivariable-adjusted hazard ratio of 3.24 (95% CI 1.74–6.01). The authors considered that as concentrations of thrombin were elevated in the sputum and bronchoalveolar lavage of asthmatic patients, and as local coagulation activation existed in asthma, it is possible that the results of this study may, in part, be explained through this mechanism. However, there are other plausible mechanisms that might explain the risk.

In asthmatic patients, plasma oxidant–antioxidant status was abnormal, with increased plasma malondialdehyde and decreased plasma ascorbic acid, which support the emerging concept of free-radical injury in asthma [2]. The pathogenesis of venous thromboembolism is also linked to oxidative stress [3]. Therefore, the involvement of oxidative stress may potentiate the increased risk of pulmonary thromboembolism in asthmatic patients.

Moreover, as the study by MAJOOR *et al.* [4] suggested, on one hand, that inactivity of severe asthmatic patients might be a potential trigger for venous thromboembolic events, but on the other hand, asthmatic patients, especially severe cases, continuously use high doses of glucocorticoids, receive bursts of systemic glucocorticoid during exacerbations and often need chronic oral glucocorticoid treatment for control of their asthma. Recent studies suggested that use of glucocorticoids may be at an increased risk of venous thromboembolism [5] and pulmonary embolism [6]. Just as CHUNG *et al.* [1] recognised when discussing the limitations of their study, glucocorticoid use information was lacking in the multivariable Cox proportional-hazards regression analysis.

Notably, MAJOOR *et al.* [4] found that the risk of pulmonary embolism was increased in severe asthma only, not in mild-to-moderate asthma.

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Asthma and risk of pulmonary thromboembolism: more epidemiological studies are required
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References

1 Chung WS, Lin CL, Ho FM, *et al.* Asthma increases pulmonary thromboembolism risk: a nationwide population cohort study. *Eur Respir J* 2014; 43: 801–807.
2 Ruprai RK. Plasma oxidant–antioxidants status in asthma and its correlation with pulmonary function tests. *Indian J Physiol Pharmacol* 2011; 55: 281–287.
3 Martinez M, Cuker A, Mills A, *et al.* Nitrated fibrinogen is a biomarker of oxidative stress in venous thromboembolism. *Free Radic Biol Med* 2012; 53: 230–236.