Can phrenic stimulation protect the diaphragm from mechanical ventilation-induced damage?

To the Editor:

Mechanical ventilation is a prominent lifesaving treatment. It is, however, associated with an array of adverse effects, which include ventilator-associated pneumonias, volume-induced lung injury and, more recently identified, ventilator-induced diaphragm dysfunction (VIDD) [1–3]. VIDD combines diaphragm weakness with muscle fibre atrophy, remodelling and injury. Its mechanisms involve decreased protein synthesis, increased proteolysis, increased oxidative stress and mitochondrial dysfunction [2, 4]. Controlled mechanical ventilation appears to be the main, if not the sole, risk factor for VIDD, which in animal models is attenuated by the maintenance of respiratory efforts (assisted ventilatory modes) [2]. Although the corresponding human evidence is still lacking, this underlies the current notion that "clinicians should encourage persistent diaphragmatic activity" in patients receiving mechanical ventilation [2]. Diaphragm pacing has been proposed as a surrogate for spontaneous respiratory activity when the latter is not compatible with the condition of the patient [2, 5], but this approach has, seemingly, not yet been tested experimentally.

Here we report a preliminary description of putative beneficial effects of diaphragm pacing in three mechanically ventilated sheep. Three female adult sheep (41, 32 and 34 kg), were anaesthetised (premedication: acepromazine 1.3 mg·kg^{-1} *i.m.*, 30 min before induction; induction: propofol 6 mg·kg^{-1} *i.v.*; maintenance: continuous propofol 1–2 mg·kg^{-1}·h^{-1}, midazolam 0.3–2 mg·kg^{-1}·h^{-1} and morphine 0.2–0.3 mg·kg^{-1}·h^{-1}; no paralysing agents), tracheotomised and mechanically ventilated with a minute ventilation ensuring normocapnia (Aisys, GE Healthcare, Datex Ohmeda, Madison, WI, USA). Additional oxygen was given to maintain transcutaneous-pulsed oxygen saturation >92%. Adequate fluid and nutritional support was provided and glycaemia controlled. Body temperature, heart rate and arterial pressure were monitored. Intradiaphragmatic phrenic nerve stimulation electrodes were inserted bilaterally in the hemidiaphragms using the cervical incision thoraco-endoscopic approach (CITES) [6]. Diaphragm pacing (NeurRxDP4 stimulator, Synapse Biomedical Inc., Oberlin, OH, USA) was instituted within 2 h following the initiation of mechanical ventilation. Only one hemidiaphragm was stimulated throughout the experiments (right in two cases, left in one case), allowing comparison between mechanically ventilated hemidiaphragms (nonstimulated side) and mechanically ventilated with diaphragm pacing (MV+stim) ones (stimulated side). 30 min stimulation sessions were superimposed upon mechanical ventilation at 4 h intervals (18 breaths per minute, stimulation intensity 15 mA, stimulation frequency 20 Hz, inspiratory time 1.1 s and pulse width 150 μs, mechanical and electrical inspirations were synchronous). One animal suddenly died after 48 h of mechanical ventilation (#3) and the two others (#1 and #2) were sacrificed after 72 h of mechanical ventilation. Costal diaphragm strips measuring 10 × 8 cm were taken through an abdominal incision, immediately *post mortem* in animal #3 and immediately before sacrifice in animals #1 and #2. Diaphragm samples were mounted on a small mound of 10% Gum Tragacanth placed on a cork disc and frozen in isopentane cooled with liquid nitrogen. Transverse serial cryosections (8 μm thick) of the costal diaphragm were stained with haematoxylin and eosin, and analysed qualitatively for structural abnormalities. Other sections were stained for adenosine triphosphatase (ATPase pH 9.4) and fibre types were identified, according to their histochemical reactions, as slow twitch type I or fast-twitch type II fibres using ImageJ software (US National Institutes of Health, Bethesda, MD, USA). For each fibre type, an average cross-sectional area was determined from at least 150 fibres taken from six different fields in each hemidiaphragm, using NIS software (Nikon Instruments Europe B.V., Amsterdam, The Netherlands). Graphpad Prism (Graphpad Software, San Diego, CA) was used to calculate and plot the means and standard errors of the mean of measured quantities. Differences between the mechanically ventilated and MV+stim conditions were assessed using paired t-tests and were considered significant at p<0.05.

In the three animals studied, mechanically ventilated hemidiaphragms showed signs of severe damage consisting of hypercontracted fibres with apparent lipid droplet accumulation and intense oedematous infiltrate of the interstitium leading to fibre disorganisation (fig. 1a). These structural abnormalities were not observed in the MV+stim hemidiaphragms, even after 72 h of mechanical ventilation (fig. 1a). The

relative proportion of fibre types was not different between the mechanically ventilated and the MV+stim hemidiaphragms. Signs of diaphragm fibre atrophy were present in both the mechanically ventilated and MV+stim hemidiaphragms (fig. 1b) after 72 h (note the smaller type 1 fibre area in the animals mechanically ventilated for 72 h compared to the 48 h one, fig. 1c, middle), but these signs were markedly less pronounced in all the MV+stim hemidiaphragms. The surface area of type 2 fibres, the main fibre type in the sheep diaphragm [7], was significantly greater at 72 h in the MV+stim hemidiaphragms (fig. 1c, bottom) than in the mechanically ventilated hemidiaphragms. The area of type 2 fibres was smaller in the animals mechanically ventilated for 72 h than in the 48 h one on the mechanically ventilated side, but not on the MV+stim side.

This is a preliminary study, involving very few animals and a limited analysis of diaphragm structure, biology and function. In particular, we did not measure diaphragm contractility. Its preservation would have been expected in the paced hemidiaphragms, but this will have to be specifically demonstrated because
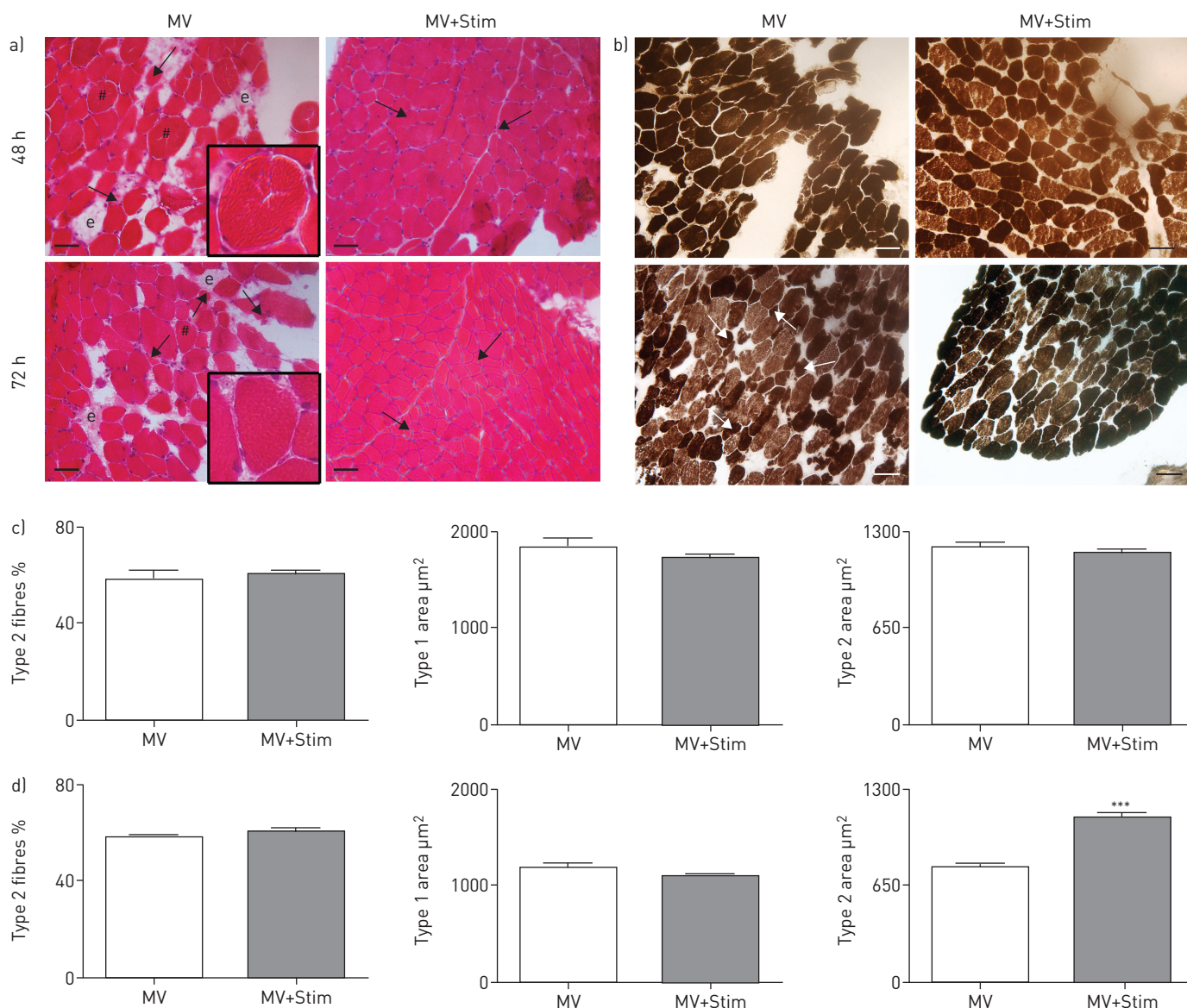

FIGURE 1 Morphological comparison between the hemidiaphragms on the mechanical ventilation only side (MV) and the hemidiaphragms on the mechanical ventilation plus diaphragm pacing side (MV+stim). a) Haematoxylin and eosin staining reveals hypercontracted fibres (#) and interstitial oedema (e) in the MV diaphragms, both in the animal ventilated for 48 h and in the animals ventilated for 72 h; arrows indicate atrophic fibres. Insert: close up view showing lipid droplets accumulation within hypercontracted fibres. Scale bar=50 μm. b) ATPase staining at pH 9.4, fibres were identified as type 1 or type 2 (darker) according to their histochemical reactions; arrows indicate atrophic fibres. Scale bar=50 μm. Proportion of type 2 fibres as a percentage of the total fibres (left), type 1 fibre area in μm^2 (middle) and type 2 fibre area in μm^2 (right) in c) the animal ventilated for 48 h and d) the two animals ventilated for 72 h. ***: $p < 0.001$ versus non-paced diaphragm.

the preservation of muscle structure is not necessarily associated with the preservation of muscle strength. Therefore, our results do not go beyond a proof of concept and cannot be considered conclusive in any manner. Importantly, our data pertain to healthy animals, as do all the currently available data about experimental VIDD. This calls for caution regarding extrapolation to acutely ill humans. Our observations are, however, worth reporting at this very early stage because they seem to provide the first experimental arguments supporting a putative utility of diaphragm pacing to prevent VIDD. Indeed, in our animals, the paced hemidiaphragms exhibited strikingly less damage (fig. 1a) and less type 2 fibre atrophy (fig. 1b–d) than the nonpaced ones. The design of the protocol (a large animal study conducted in intensive care unit (ICU)-like conditions; comparison of paced hemidiaphragms with non-paced ones in the same animals) lends strength to our observations. Muscle damage, as depicted in figure 1a, has not specifically been described as a feature of VIDD before, but these observations are consistent with those made in human VIDD using electron microscopy [8]. The presence of lipid droplets within the hypercontracted muscle fibres is also in line with the metabolic muscle dysfunction that has been described in human VIDD [4]. Finally, type 2 fibre atrophy is also concordant with the available VIDD data, in both animals and humans [2]. None of these features were present in the MV+stim hemidiaphragms in our animals. Diaphragm pacing could be protective against VIDD by opposing several of its mechanisms. It could counteract a "disuse atrophy" component and preserve muscle mass, in a manner similar to what has been described with electrostimulation of limb muscles in mechanically ventilated patients [9]. It could exert an anti-inflammatory effect, as described for other types of electrical muscle stimulation [10]. It could also prevent eccentric or strain injuries provoked by the ventilation-induced stretching of a tonic diaphragm. All of the above hypotheses will have to be tested. Minimally invasive techniques for temporary diaphragm pacing in humans are being developed, including transcutaneous repetitive magnetic stimulation [11] and transvenous electrical stimulation [12, 13]. Therapeutic phrenic nerve stimulation in critically ill patients is, therefore, within the realm of possibility in the near future, for the prevention or treatment of VIDD or other ICU-related diaphragm disorders. We submit that our data, as rudimentary as they may be, provide a basis for future studies of this approach. Our observations will have to be corroborated and consolidated in much larger animal groups, with a detailed description of the biological and physiological effects of diaphragm pacing during mechanical ventilation. Many questions will have to be answered: to identify optimal stimulation protocols; to describe the long-term effects, keeping in mind that low-frequency diaphragm stimulation tends to promote the development of type 1 fibres [14]; to identify deleterious effects due to electrical stimulation itself [15] or to clinical contexts such as sepsis where muscle stimulation could be counterproductive; to determine the best target population (will diaphragm pacing be restricted to patients in controlled ventilatory modes because of coma or any other reason? How does it compare with the maintenance of some spontaneous breathing activity when possible?); and, finally, to establish a risk–benefit balance.

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In animals, implanted phrenic stimulation attenuates diaphragm type 2 fibre atrophy after 72 h of mechanical ventilation http://ow.ly/kTzHT

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Menasche, head of the Laboratoire de recherches Biochirurgicales Fondation Alain Carpentier (Centre de Recherche Cardiovasculaire, Assistance Publique Hôpitaux de Paris; unité INSERM U633, Paris, France) for welcoming the experiments in his experimental facilities.

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Quality of life after lung resection is not associated with functional objective measures

To the Editor:

Patient and physician perspectives about surgical risk may differ. Physicians are mostly focused on objective end-points (*i.e.* mortality and survival), whereas most patients are worried about permanent physical and emotional disability resulting from the operation [1]. Can objective clinical information be used to predict patient-reported health status?

In the attempt to respond to this question, we studied 221 consecutive patients submitted to major anatomic pulmonary resections (204 lobectomy and 17 pneumonectomy) during a 36-month period. All patients had a pre-operative measurement of maximum oxygen uptake ($V'O_{2max}$), as a part of their routine pre-operative functional work-up, and a complete assessment of their pre-operative and post-operative (3 months after surgery) quality of life. All patients gave their consent for inclusion of their clinical data in our institutional database for clinical and scientific purposes and the Institutional Review Board of our hospital approved the study. No formal pre-admission or post-discharge physiotherapy or psychological support programmes were administered in this series. Neurological or psychotropic personal medications, if present, were generally resumed the day after surgery.