Editorial

Ultrasound: a novel translational tool to study diaphragmatic dysfunction in critical illness

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The diaphragm has an essential role in spontaneous breathing in humans and animals. Extensive data obtained in animal models show a time-dependent atrophy and decreased force-generating capacity of the diaphragm during ventilation and sedation, both *in vitro* and *in vivo* (1). Underlying pathophysiological mechanisms, as studied mostly in ventilated rodents, comprise microvascular, electrical, biochemical, structural and metabolic alterations, interacting in a complex way and culminating in not only loss of muscle strength and diaphragm myofibril contractility but even muscle atrophy (2).

A substantial number of patients hospitalized in the intensive care unit (ICU) are prone to develop weakness of striated muscles including the diaphragm. Limb muscle weakness is a gradual process (3), whereas diaphragm dysfunction seems to occur more rapidly. Many factors contribute to this problem, but mechanical ventilation (MV) seems to independently affect the diaphragm. These effects of MV and respiratory muscle unloading on the diaphragm were originally described by Vassilakopoulos and Petrof as 'ventilator-induced diaphragmatic dysfunction' (VIDD) (4). In ventilated patients, it contributes to poor outcome and even increased mortality.

Significant progress has been made in identifying the molecular mechanisms responsible for VIDD in animal models, but it took a long time to unable researchers and ICU physicians to translate these animal data into humans. In humans, the impact of prolonged MV on myofibril active and passive human diaphragm myofibrillar force generating a contractility of the diaphragm remained largely unknown as the diaphragm is not directly accessible in living patients. Innovative research to explore the underlying pathophysiology of VIDD in humans included the study of atrophy of the diaphragm in brain-dead patients who had undergone MV for 18 to 69 h (5). A reliable tool to measure the respiratory muscle force of the diaphragm was essential to guide further research concerning causes and consequences of respiratory muscle weakness and potential therapies aimed at preserving respiratory muscle force in critically ill patients. A measurement of maximal diaphragmatic force generating capacity is the gold standard to assess diaphragm muscle dysfunction (6). Using this technique of transdiaphragmatic pressure measurements after magnetic stimulation, it has recently been demonstrated that the duration of MV is associated with a logarithmic decline in diaphragmatic force, compatible with the concept of VIDD (6). However, his technique measures force only, not morphology, and is not routinely available.

Obviously, there was and is a need for non-invasive tools to monitor intensive care unit or ventilation-acquired diaphragmatic weakness in the critically ill (ventilated) patient, not only just for clinical practice but also in order to streamline future therapeutic, prospective randomized trials. In a recent review in *Intensive Care Medicine*, Zambon and colleagues (7) nicely illustrate how bedside ultrasound, as a non-invasive technique, is able to measure both

diaphragmatic inspiratory excursion and force, as thickness and thickening fraction of this muscle in the critically ill (ventilated) patient (7). Furthermore, these authors describe how sequentially performed (daily) B-mode end-expiratory thickness measurements of the diaphragm can demonstrate a change in muscle mass. While we know that VIDD is more than just disuse atrophy, diaphragmatic muscle thinning remains an essential part of VIDD.

Why did it take ICU physicians a long time to use ultrasound for this translational approach? Long after the discovery of the basis of ultrasound physics in 1794, ultrasound only became widely available in the second part of the last century to study the morphology and function of e.g., the heart, abdominal organs and vessels. It took until 1983 before Daniel Lichtenstein pioneered general ultrasound in the ICU calling it '*the real stethoscope*' (8). Although an old idea, ultrasound was not routinely used in the ICU and certainly neglected for studying the lung and respiratory muscles including the diaphragm. Many ICU physicians even thought that lung and diaphragmatic ultrasound was unfeasible (9). Now, many start to believe that ultrasonography is valuable as the only non-invasive, non-ionizing imaging technique widely available to directly assess diaphragmatic function (10). Two different sonographic approaches permit the assessment of the diaphragm: muscle thickening in the zone of apposition and excursion of the dome of the diaphragm in a more anterior approach (10). Thanks to the new hand-held ultrasound instruments, both the morphology and function of the diaphragm can be assessed in different settings, including the hospital department but certainly the ICU, and under different conditions (10). Thanks to recent improvements in ultrasound technology we now have the possibility to accurately measure diaphragm thickness to the tenth of a millimeter (11). Ultrasound is now the promising tool to be routinely performed at patients' bedsides to provide real-time and accurate information on the status of the diaphragm (7). The use of diaphragmatic ultrasound semiology alongside typical examinations may therefore allow for the monitoring, and evaluation of the respiratory function and maybe guide us towards a more 'muscle-protective' way of ventilation in patients (12).

The possibility of exploring the diaphragm using ultrasound, at the bedside and noninvasively, is gaining popularity among clinical researchers. Lung ultrasound would be of minor interest if the usual tools (bedside radiography, CT) did not have drawbacks (e.g., ionizing radiation, low information content for plain radiography and often the need to transport the patient). Ultrasound in the ICU specifically helps the ICU physician to deal with findings and problems of immediate clinical relevance throughout the body. For example, on a regular basis, the intensivist encounters patients who are difficult to wean from mechanical ventilator support (13). The causes for failure to wean are often multifactorial and involve a complex interplay between cardiac and pulmonary dysfunction, but almost always are driven by a weakened diaphragm (14). A potential application of point of care ultrasonography thus also relates to its utility in the process of weaning the patient from mechanical ventilatory support (8). Reviews like this by Zambon *et al*. (7) bring forward the possible applications of ultrasound in assessing the diaphragm, but also refresh reader's knowledge on the importance and pathology of the diaphragm as the main inspiratory respiratory muscle in the critically ill.

Translational research occurs where laboratory science and clinical medicine meet to develop novel therapies to prevent diagnose and treat disease in humans. It is also, although far less frequent, bidirectional, which means that findings in humans can be checked again in animals. Functional analysis of rodent respiratory skeletal muscles, particularly the diaphragm, is commonly performed using invasive surgical procedures by isolating muscle strips directly from the euthanized animal (15). Although this is an effective method of assessing *in vitro* diaphragm activity, it involves non-survival surgery. Diagnostic ultrasound imaging techniques are frequently applied to larger animals or human subjects but seldom in the smaller animals, certainly not in those rodent species in which VIDD has been studied. There exist only a limited number of studies using ultrasound for studying the diaphragm in a rodent model (16-18), which is likely due to the challenges of performing ultrasound on small-scale subjects. Likely triggered by the increasing use in ventilated human subjects, diagnostic ultrasound imaging techniques have been applied in rodents to accurately evaluate *in vivo* longitudinal assessments of diaphragm mobility in mice (16). Furthermore, long-term treatments focused on enhancing diaphragm contractility may be accurately assessed via ultrasound in rodent models without sacrificing animals for experimentation; it is also suitable for monitoring disease progression in live animals (17,18).

The history and evolution of diagnostic ultrasonography has been founded on the combined efforts of engineers and physicians, as well as large commercial companies and individual entrepreneurs. Ultrasound imaging has

a multitude of advantages, as it is noninvasive, sensitive, safe, portable, and allows for real time measurements at a relatively low cost in humans. This way, diagnostic ultrasound imaging may serve as an easily accessible and reproducible screening method for real-time monitoring. It now also enables rapid analysis of diaphragm function in rodents, which helps the understanding of diaphragm function *in vivo*, avoids invasive methods to animals, and aids in the development of therapeutic treatments for diaphragmatic dysfunction. Twenty studies in humans have thus far shown that ultrasound can diagnose diaphragmatic dysfunction, predict weaning outcome, and assess muscular workload and diaphragm atrophy [as reviewed in (7)]. Its reproducibility with a short learning curve and allowing to longitudinally (i.e., usually daily) follow-up the course of diaphragm thickness in ventilated patients (11,19) are its key features. The versatility of lung ultrasound heralds a kind of visual medicine (20), a priority in intensive care as well as many other disciplines and settings. Ultrasound has thus found its steady place in the ICU environment, being easily applicable to diagnose a multitude of abnormalities (21). The next major challenge in the field will be to move these findings from the bench to the bedside in daily practice in our modern ICUs. Reviews like this by Zambon and co-authors will hopefully stimulate the clinician to help us achieve this goal.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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