Lack of Association between Diaphragm Thickening Fraction and Transdiaphragmatic Pressure Swing in COVID-19 Pneumonia during Helmet Continuous Positive Airway Pressure: Research Letter

To the Editor:

Recently, evaluation of the diaphragm by means of ultrasound has become popular.[1] The increase in diaphragm thickness during inspiration (thickening fraction) has been proposed as a noninvasive bedside measure of diaphragm function,[2,3] although previous studies have reported wide variability between thickening, inspiratory effort, and transdiaphragmatic pressure.[4–6] We hypothesized that the force-length and force-generating relationship in the diaphragm is altered by different positive end-expiratory pressure (PEEP) levels in patients with SARS-CoV-2.[7]

We investigated the relationship between diaphragm thickening fraction and transdiaphragmatic pressure swing during noninvasive helmet continuous positive airway pressure. From March to December 2021, a total of 26 consecutive patients with laboratory-confirmed SARS-CoV-2 infection admitted to the intensive care unit of Santa Chiara Hospital (Trento, Italy) were prospectively enrolled. The study was approved by the ethics committee (Rep. Int. 282/2022), and written informed consent was obtained. At intensive care unit admission, according to the local protocol, noninvasive respiratory assistance with helmet continuous positive airway pressure was started, and a nasogastric tube provided with two balloons for registering the esophageal and gastric pressures was inserted.[8] Intragastric positioning of the tube was checked with standard methods; both balloons were inflated with manufacturer-recommended volume. Intragastric position of the lower balloon was confirmed by positive pressure deflections during gentle abdominal compressions; the mid-lower third esophageal position of the proximal balloon was confirmed by inspiratory negative deflections and the presence of cardiac artifacts. *In vivo* calibration of the filling volume was performed. Patients underwent a trial with three increasing levels of PEEP, lasting 30 min each. The first level was set at 0 cm H_2O. PEEP was then increased to 5 and 10 cm H_2O; fractional expired oxygen tension was left unchanged. An average of three measurements was made, with careful attention to select the same breaths for the diaphragm ultrasound and for esophageal/gastric pressure measurements. During the last 5 min of each step, esophageal and transdiaphragmatic pressure swing and diaphragmatic ultrasound were recorded. The right hemidiaphragm was identified in the zone of apposition as a three-layered structure by B-mode ultrasonography, with the probe at the mid-axillary line at the 10th intercostal space.[1] Thickness was measured from frozen M-mode images as the distance from the pleural to the peritoneal line. All the examinations were performed by the same expert physician and recorded for a subsequent offline analysis.

The study population had a median age of 67.5 [62.3–72.5 interquartile range] yr, 16 (61.5%) were male, body mass index was 27 [24–33 interquartile range] kg/m^2, and Pao_2/fractional expired oxygen tension ratio and $Paco_2$ at admission were 122 [103–139 interquartile range] and 39 [37–44 interquartile range] mmHg, respectively. No association was found between diaphragm thickening fraction and transdiaphragmatic pressure swings or esophageal pressure swings, at 0 cm H_2O, 5 cm H_2O, and 10 cm H_2O (fig. 1).

In a previous investigation, Steinberg *et al.*[9] found that neither thickening fraction nor diaphragmatic excursion was able to estimate esophageal pressure swings in patients with SARS-CoV-2. We sought to extend these findings by investigating the relationship between diaphragm ultrasound and the transdiaphragmatic pressure swing, which should be more representative of the contribution of the diaphragm to the total inspiratory effort. Similar to other authors,[4] we confirm the lack of association between diaphragm thickening and the transdiaphragmatic pressure. Despite that it may lie on the nonlinear pressure–volume relationship of the diaphragm, during a single breath, the diaphragm inspiratory thickening and the transdiaphragmatic pressure generated depend on the specific pattern of thoracoabdominal motion (*i.e.*, a descent of the diaphragm rather than expansion of the rib cage). The application of PEEP also causes changes in the diaphragm geometry also modifying the force generated by the diaphragm that may not be uniform across the muscle.

The different position of the diaphragm muscle over its force or length relationship is likely explained by changes in end-expiratory lung volume during the PEEP trial. Although not directly measured, diaphragm dysfunction can also be a contributing factor; COVID-19 is associated with a viral myositis,[10] which might have affected diaphragm force-generating capacity.

However, the impact of the small sample size on any statistical inference must be considered, and the lack of Gilbert index and pressure-time product of diaphragmatic pressure calculation reduces the interpretation of our results.

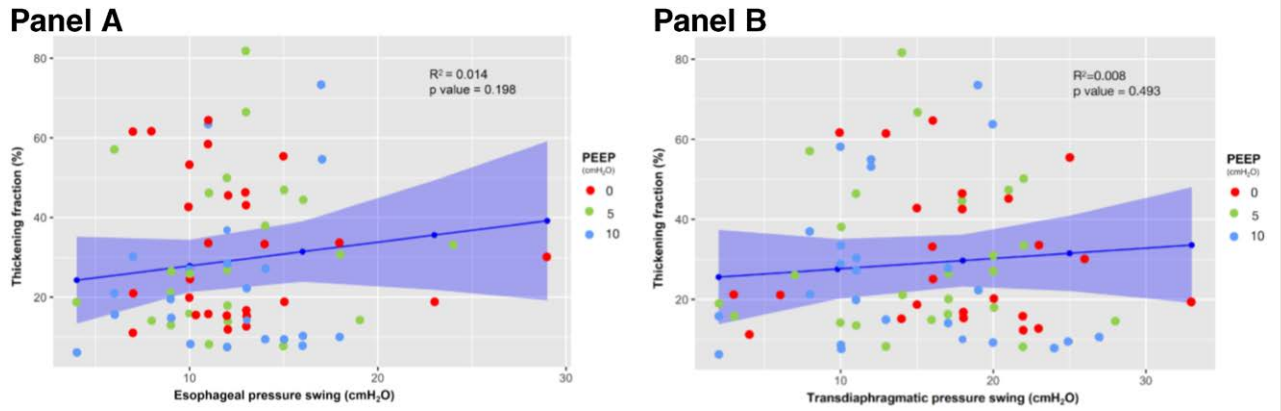

Fig. 1. Relationships between diaphragm thickening fraction, transdiaphragmatic pressures swings, and esophageal pressure swings. (*A*) Association between diaphragm thickening fraction and esophageal pressure swings at positive end-expiratory pressure (PEEP) 0 cm H_2O, 5 cm H_2O, and 10 cm H_2O (respectively, *red*, *green*, and *blue* circles, $P = 0.198$, marginal $R^2 = 0.014$ [95% CI, 0.001–0.03]). (*B*) Association between the diaphragm thickening fraction and the transdiaphragmatic pressure swings at PEEP 0 cm H_2O, 5 cm H_2O, and 10 cm H_2O (respectively, *red*, *green*, and *blue circles*, $P = 0.493$, marginal $R^2 = 0.008$ [95% CI, 0.001–0.092]). R Core Team 2022 (R Foundation for Statistical Computing, Austria, https://R-project.org/) was used for statistical analysis. The association between diaphragmatic thickening fraction and the study variables was analyzed with by a linear mixed model for repeated measures to deal with the longitudinal structure of our data set: the subject is the random factor, and the esophageal (or transdiaphragmatic) pressure swing and PEEP (within-subject) are fixed factors. The model included the interaction effect of PEEP on the esophageal (or transdiaphragmatic) pressure swing. The association between variables was expressed as the coefficient of determination for the mixed model, the marginal R^2 (95% CI, *i.e.*, the attributable variance due to the fixed effect portion of the model). The *blue line* represents the fit line from the mixed effects model, with the 95% CI as a *purple area*.

In summary, despite being promising for its feasibility and noninvasive characteristics, the assessment of diaphragm thickening should not be used as a surrogate for inspiratory effort. In SARS-CoV-2 patients during helmet continuous positive airway pressure in the acute setting, an increase in inspiratory effort, as measured by transdiaphragmatic pressure swings, is not related to diaphragm thickening fraction. We suggest caution against using this tool to inform clinical choices about respiratory support, at least until more robust data will be available.

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Competing Interests

The authors declare no competing interests.

Sergio Lassola, M.D., Sara Miori, M.D., Andrea Sanna, M.D., Michele Umbrello, M.D., Silvia De Rosa, M.D., F.C.C.N., Giacomo Bellani, M.D., Ph.D.
Santa Chiara Hospital, Trento, Italy (S.L.).
sergio.lassola@apss.tn.it

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Cryoneurolysis: Interest and Caution: Comment

To the Editor:

Anesthesiology recently published an editorial titled "Cryoneurolysis: Interest and Caution" which addressed an accompanying study investigating the treatment of postmastectomy pain with ultrasound-guided percutaneous cryoneurolysis.[1] The editorial raised multiple important and valid limitations of the study, as well as noting that caution is warranted because "neuropathic pain is produced so reliably after cryoneurolysis that it has been used as a model of chronic pain development in rodents since the 1990s."[2] Although we agree that an abundance of caution is indeed warranted before widespread implementation of this analgesic modality, the authors of this letter have potentially important *un*published information that will help put the cited laboratory evidence in perspective for future clinical and laboratory research.

The editorial-cited study involved the treatment of Sprague-Dawley rats with cryoneurolysis, coauthored by this letter's senior author nearly 3 decades ago (R.W.).[3] As described in the Methods, "A 3-cm incision was made… and the common sciatic nerve was exposed by blunt dissection… [and] the nerve was frozen with a cryoprobe as illustrated in Fig. 1."[3] Left unspecified in the text was that each nerve was completely exposed and elevated with forceps at least 4 mm, as can be seen in figure 1 of that article. All animals subsequently exhibited bilateral mechanical allodynia, suggesting central sensitization.[3] The investigators were intentionally inducing chronic pain to be used as an animal model for the subsequent study of various analgesics. The critical step of lifting the nerve out of the body was specified in subsequent articles describing this pain model: "…the sciatic nerve was gently freed from surrounding tissue and elevated. Elevation of the nerve involved *moderate stretching* [emphasis added]."[4,5]

What was never reported was that elevating the nerve was *required* to induce chronic pain in this animal model. In other words, neuropathic pain could not be elicited if the nerve was left *in situ* for cryoneurolysis treatment. Because the investigators were specifically describing a pain model and not studying the clinical risks of cryoneurolysis, they did not publish this information.

However, these unreported laboratory findings have significant implications when comparing percutaneous and "open" cryoneurolysis and may explain the widely varying incidence of cryoanalgesia-related postthoracotomy neuropathic pain in human-subject investigations. As noted in the editorial,[2] two randomized, sham-controlled clinical trials identified an increased incidence of neuropathic pain 3 to 6 months after open thoracotomy with cryoneurolysis applied *via* the incision.[6,7] In contrast, the majority of randomized, controlled studies failed to report a similar increase in chronic pain.[8] Notably, there were considerable differences in intraoperative cryoneurolysis technique, with some surgeons treating nerves *in situ* while others reported significant nerve manipulation that included elevation of the target nerve.[9] For example, one study with a high neuralgia incidence (20%) reported that each intercostal nerve was "*exposed* paravertebrally, *lifted* with a nerve hook, and frozen at *two close sites* [emphasis added]…," suggesting both manipulation and double-crush.[10]

Unfortunately, it is impossible to correlate technique and outcome because the majority of publications do not adequately describe the precise technique or degree of nerve manipulation. However, considering the previously unreported laboratory finding that nerve elevation was required to induce chronic pain—and treatment of the nerve *in situ* never resulted in chronic pain—it is perhaps unsurprising that the incidence of neuralgias after open surgical cryoneurolysis varies so dramatically from 0% (one series of greater than 1,500 patients)[11] to 38%.[12]