Expiratory muscle function in critically ill ventilated patients

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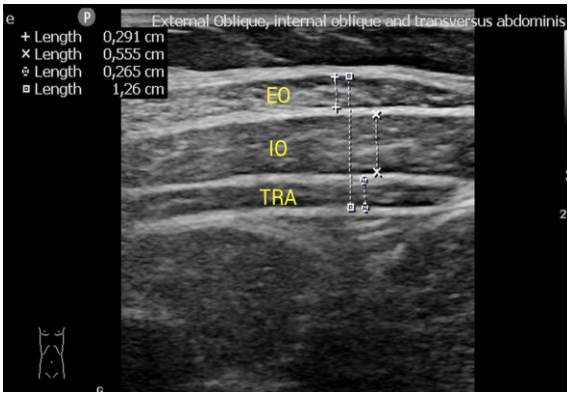
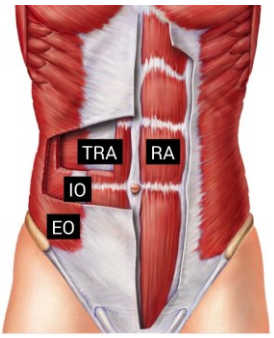
Rationale	Inspiratory muscle weakness develops rapidly in ventilated critically ill patients[1-4] and is associated with adverse outcome, including prolonged duration of mechanical ventilation and mortality.[5-7] Surprisingly, the effects of critical illness on expiratory muscle function have not been studied. The main expiratory muscles are the abdominal wall muscles, including the external oblique (EO), internal oblique (IO) and transversus abdominis muscles (TRA).[8,9] These muscles are activated when respiratory drive or load increases, which can be during e.g. exercise,[10-12] diaphragm fatigue,[13] increased airway resistance, or positive airway pressure ventilation.[14] The abdominal wall muscles are also critical for protective reflexes, such as coughing.[15] Reduced abdominal muscles strength may lead to decreased cough function [16,17] and thus inadequate airway clearance.[18] This will lead to secretion pooling in the lower airways, atelectasis, and ventilator associated pneumonia (VAP).[19,20] Studies have shown that decreased cough function is a risk for weaning failure and (re)hospitalization for respiratory complications.[21] Further, high mortality was found in patients with low peak expiratory flow.[22] Considering the importance of a proper expiratory muscle function in critically ill patients, it is surprising that the prevalence, causes, and functional impact of changes in expiratory abdominal muscles thickness during mechanical ventilation (MV) for critically ill patients are still unknown.

	Ultrasound is increasingly used in the ICU for the visualization of respiratory muscles. In a recent pilot study we confirmed the feasibility and reliability of using of ultrasound to evaluate both diaphragm and expiratory abdominal muscle thickness in ventilated critically ill patients (manuscript in preparation). An example of such measurement can be found in figure 1. Accordingly, the primary aim of the present study is to evaluate the evolution of abdominal expiratory muscle thickness during MV in adult critically ill patients, using ultrasound data.   Figure 1. Left: ultrasound of the abdominal expiratory muscles (EO, IO, TRA). Right: anatomical overview of the abdominal muscles. RA = rectus abdominis, less involved in respiration
Objective	<u>Primary objective:</u> to establish the effects of critical illness and mechanical ventilation on thickness of the abdominal expiratory muscles. <u>Secondary objectives:</u> - to establish the effect of changes in abdominal expiratory muscle thickness on the expiratory muscle function.

	- to establish the correlation between changes in thickness of the abdominal expiratory and inspiratory muscles. - to study whether changes in the thickness of the abdominal expiratory muscles also affects weaning outcome, and ICU readmission due to respiratory complications.
Study design	Prospective cohort study.
Study population	Patients who have been mechanically ventilated at the intensive care unit (ICU)
Inclusive criteria	- Age > 18 years - Invasive mechanical ventilation < 48 hours - Expected duration of mechanical ventilation > 72 hours
Exclusive criteria	- Past medical history of neuromuscular disorders - Mechanical ventilation > 48 hours within the current hospital admission - BMI > 35 kg/m2 - Pregnant women - Open abdominal wounds at proposed location of the ultrasound probe, due to recent abdominal surgery
Sample size	100 subjects
Recruiting subjects	Because mechanical ventilation is a requirement for eligibility, the participants frequently will be incapable of consent at the time of inclusion. Therefore, we will ask delayed informed consent from the patient as soon as he/she is capable of providing consent. If patients are not able to give consent during their hospital stay, we will send an opt-out letter to the patient.

Intervention	Data from ultrasound measurements and from the electronic patient record will be obtained / analyzed. One additional blood sample will be obtained within 24 hours after inclusion, during planned blood collection (from arterial line or venous puncture).
Study eindpoint	- Thickness of the abdominal expiratory muscles (external oblique, internal oblique, transverse abdominis muscle), during the inspiratory and expiratory phases of breathing.
Study parameters	- Thickness of the diaphragm muscle - Inflammatory markers (TNF-alpha, IL-6, IL-10) at inclusion (measured from blood sample using ELISA technique). - Respiratory function parameters: maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), cough peak flow (CPF), diaphragm pressure and diaphragm electrical activity (in selected patients with these measurements available in clinical practice). - Mechanical ventilation parameters. - Weaning outcome - Ventilator associated pneumonia (VAP) - Follow-up of 6 weeks: readmission to ICU / hospital, reason for readmission, pneumonia acquired after discharge when subject is hospitalized. - Critical illness parameters (e.g. medication, APACHE II score) - Patient characteristics (e.g. gender, age, neurological and cardiopulmonary co-morbidities, BMI) This data will be retrieved from the electronic patient record and anonymously filed in a database. Data on muscle thickness (thickness of diaphragm muscle and expiratory muscles) will be collected directly

	from ultrasound measurements on the ultrasound device.
Statistical Analysis Plan	SPSS statistical software package version 22.0 or R software for statistical computing version 3.2.0 will be used. **Primary endpoint:** *change of thickness of expiratory abdominal muscles during MV.* Change in thickness will be presented as ratio change compared to baseline, to account for inter-subject variation in baseline thickness. The Wilcoxon signed-rank test will be used to compare changes in baseline and nadir values. Association of categorical independent variables (such as sex, use of corticosteroids during ICU stay, sepsis on admission, etc.) with nadir change in expiratory muscle thickness will be assessed using a Mann-Whitney U test. Association of continuous independent variables (such as duration of mechanical ventilation, days taken to wean, inflammation at inclusion, etc.) with nadir change in expiratory muscle thickness will be assessed using a linear regression model, with change in expiratory muscle thickness as dependent variable. Correlation between change in thickness during the acute stage of MV (5 days) with the total time spent on the ventilator will be examined using a linear regression model. **Correlation between diaphragm and expiratory muscles** Correlation between change in expiratory muscle thickness and change in diaphragm thickness will be assessed with Pearson's correlation test to compare population means. The difference between change in

	expiratory muscle thickness and change in diaphragm thickness will be assessed with a Student's t-test that is paired per subject. This will be done by using the change in thickness between baseline and the last data point obtained. Second, this will be evaluated by using the slope of the thickness curves assessed with a goodness of fit model. We will use a goodness of fit model to first describe the course of both diaphragm and expiratory muscle thickness for each subject. The type of model will be determined after data is obtained. **Subgroup analysis** Based on the outcomes of these analyses, a subgroup analysis may be performed to compare the subjects with high change in expiratory muscle thickness, to a group with low change in expiratory muscle thickness. A cutoff value to divide these groups will be determined based on how data will emerge. Variables as respiratory function measurements can be compared between groups with a Student's t-test, using group average values. Further, a Kaplan-Meier survival analysis will be carried out to quantify differences in time to wean between groups.
Referenties	1. Heunks LM, Doorduin J, van der Hoeven JG. Monitoring and preventing diaphragm injury. Curr Opin Crit Care. 2015;21(1):34-41. 2. Hooijman PE, Beishuizen A, Witt CC, et al. Diaphragm muscle fiber weakness and ubiquitin-proteasome activation in critically ill patients. Am J Respir Crit Care Med. 2015;191(10):1126-38. 3. Watson AC, Hughes PD, Louise HM, et al. Measurement of twitch transdiaphragmatic, esophageal,

and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. Crit Care Med 2001; 29:1325–31.
4. Chang AT, Boots RJ, Brown MG, et al. Reduced inspiratory muscle endurance following successful weaning from prolonged mechanical ventilation. Chest 2005; 128:553–9.
5. De Jonghe B, Bastuji-Garin S, Durand MC, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Critical care medicine, 2007; 35(9).
6. Adler D, Dupuis-Lozeron E, Richard JC, et al. Does inspiratory muscle dysfunction predict readmission after intensive care unit discharge?. American journal of respiratory and critical care medicine, 2014;190(3): 347-50.
7. Medrinal C, Prieur G, Frenoy É, et al. Respiratory weakness after mechanical ventilation is associated with one-year mortality-a prospective study. Critical Care,2016;20(1): 231.
8. DeTroyer A, Estenne M, Ninane V, et al. Transversus abdominis muscle function in humans. J Appl Physiol 1990;68:1010–6.
9. Misuri G, Colagrande S, Gorini M. et al. In vivo ultrasound assessment of respiratory function of abdominal muscles in normal subjects.Eur Respir J 1997;10:2861–7
10. Aliverti A, Cala SJ, Duranti R, et al. Human respiratory muscle actions and control during exercise. Journal of Applied Physiology, 1997;83(4):1256-69.

	11. Aliverti A, Iandelli I, Duranti R, et al. Respiratory muscle dynamics and control during exercise with externally imposed expiratory flow limitation. Journal of Applied Physiology, 2002;92(5); 1953-63. 12. Macklem PT. Act of breathing: the ventilatory pump. In: Hamid O, Shannon J, Martin J, eds. Physiologic basis of respiratory disease. Hamilton: BC Decker Inc; 2005:61-6. 13. Goldman MD, Mead JE. Mechanical interaction between the diaphragm and rib cage. Journal of Applied Physiology. 1973;35(2):197-204. 14. Bishop B. Reflex control of abdominal muscles during positive-pressure breathing. J Appl Physiol 1964;19:224-32 15. Iscoe S. Control of abdominal muscles. Progress in neurobiology. 1998 Nov 30;56(4):433-506. 16. Klefbeck B, Nedjad J. Effect of inspiratory muscle training in patients with multiple sclerosis. Arch Phys Med Rehabil 2003; 84: 994-99. 17. Chiara T, Martin D, Davenport PW, Bolser DC. Expiratory muscle strength training in persons with multiple sclerosis having mild to moderate disability: effect on maximal expiratory pressure, pulmonary function, and maximal voluntary cough. Arch Phys Med Rehabil 2006; 87: 468-73. 18. Epstein SK. Decision to extubate. Intensive Care Med 2002;28:535-46. 19. Lahrmann H, Wild M, Zdrahal F, Grisold W. Expiratory muscle weakness and assisted cough in ALS. Amyotroph Lateral Scler Other Motor Neuron Disord. 2003 Apr;4(1):49-51.

	20. Lin VW, Hsiao IN, Zhu E, Perkash I. Functional magnetic stimulation for conditioning of expiratory muscles in patients with spinal cord injury. Arch Phys Med Rehabil 2001; 82: 162–6. 21. Huang CT, Yu CJ. Conventional weaning parameters do not predict extubation outcome in intubated patients requiring prolonged mechanical ventilation. Respiratory care. 2013 Jan 9:respcare-01773. 22. Smina M, Salam A, Khamiees M, et al. Cough peak flows and extubation outcomes. CHEST Journal. 2003 Jul 1;124(1):262-8.