ULTRASOUND ASSESSMENT OF DIAPHRAGM AS A PREDICTOR TOOL OF SUCCESSFUL EXTUBATION IN MECHANICALLY VENTILATED PATIENTS

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I am thankful to God, whose guidance had led me to choose anaesthesia as my career and I am always grateful for that.

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My heartfelt gratitude to my parents Mr Kuang Meng Hue and Madam Lim Gok Lan for their endless love and support. Their endurance and patience has become my inner strength and motivation.

Last but not least, to all my colleagues, friends and supporting staffs who have helped me in various ways, I express my deepest gratitude.

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LIST OF ABBREVIATIONS

ABG	Arterial blood gas
BP	Blood pressure
CXR	Chest X-ray
GBS	Gullain-Barre Syndrome
GCS	Glasgow Coma Scale
HDW	High Dependency Ward
ICU	Intensive Care Unit
JEPeM	Human Research Ethics Committee Universiti Sains Malaysia
MOH	Ministry of Health, Malaysia
MREC	Medical Research & Ethics Committee
NMRR	National Medical Research Register
PEEP	Positive End Expiratory Pressure
POCUS	Point of Care Ultrasound
PR	Pulse rate
PS	Pressure Support
RSBI	Rapid Shallow Breathing Index
SD	Standard Deviation
IQR	Interquartile Range
SBT	Spontaneous Breathing Trial
SOFA	Sequential Organ Failure Assessment
SPSS	Statistical Product and Service Solutions
VAP	Ventilator associated pneumonia

ABSTRAK

Latar belakang

Hampir 20% pesakit yang memerlukan bantuan pernafasan mekanikal mengalami kegagalan untuk extubasi atau ulangan intubasi dalam tempoh 48 jam. Terjejasnya fungsi diafragma telah dikenalpastikan sebagai salah satu faktor yang boleh menyebabkan kegagalan dalam extubasi. Kajian ini bertujuan untuk menilai fungsi diafragma melalui pemeriksaan ultrasound sebagai cara untuk menjangka kejayaan extubasi dalam pesakit yang memerlukan bantuan mekanikal pernafasan.

Kaedah

Kajian ini telah dijalankan di Hospital Queen Elizabeth, Sabah dan Hospital Universiti Sains Malaysia, Kelantan. Tujuh puluh lima pesakit dengan bantuan mekanikal pernafasan yang dirancang untuk extubasi dan memenuhi kelayakan penyertaan telah menyertai kajian ini. Keizinan secara bertulis didapatkan daripada penjaga. Ultrasound diafragma telah dilakukan sebelum extubasi oleh penyelidik. Keputusan ultrasound diafragma tidak didedahkan kepada doktor yang memberi rawatan. Keputusan untuk extubasi adalah bergantung kepada doktor yang memberi rawatan dan keputusan ultrasound diafragma tidak mempengaruhi rawatan yang pesakit terima. Pesakit telah ditindaklanjuti selama 48 jam (2 hari) selepas extubasi.

Keputusan

Didapati perbezaan yang ketara secara statistik dalam purata pecahan ketebalan diafragma dan purata pergerakan diafragma di antara kumpulan pesakit yang berjaya

diextubasikan dan kumpulan pesakit yang gagal diextubasikan. Setiap pertambahan purata pecahan ketebalan diafragma sebanyak 1% meningkat peluang kejayaan extubasi sebanyak 1.29 kali.

Kesimpulan

Penilaian pecahan ketebalan diafragma dengan ultrasound boleh digunakan untuk menjangka kejayaan extubasi dalam pesakit yang memerlukan bantuan mekanikal pernafasan

Kata Kunci

Ultrasound, pecahan ketebalan diafragma, pergerakan diafragma, extubasi.

ABSTRACT

Background

Weaning failure is defined as failure to pass a spontaneous breathing trial or the need for re-intubation within 48 hours following extubation. An estimated 20% of all mechanically ventilated patients will encounter a failed extubation scenario. The pathophysiology of weaning failure is multifactorial but a recent factor of interest described in current literature is that of diaphragm dysfunction. The purpose of this study is to determine the role of ultrasound assessment of diaphragm as a predictor tool of successful extubation in mechanically ventilated patients

Methods

This study was carried out in Hospital Queen Elizabeth, Sabah and Hospital Universiti Sains Malaysia, Kelantan. Seventy-five mechanically ventilated patients who were planned for extubation and met the inclusion criteria were enrolled into the study. Written consent was obtained from the next of kin. Bedside diaphragmatic ultrasound was carried out prior to extubation to assess diaphragm excursion and diaphragm thickness fraction. The diaphragm ultrasound was performed by the clinician who had no role in the management of the patients. Extubation was based on intensivist's or anaesthetist's decision who were blinded of the ultrasound results. The patients were followed up for 48 hours post extubation.

Results

There was a statistically significant difference in both the mean diaphragm excursion and the mean diaphragm thickness fraction between the successful extubation group and

the failed extubation group. When the diaphragm thickness fraction increased by 1 %, the chance of successful extubation increased by 1.29 times.

Conclusion

Ultrasound assessment of diaphragm thickening fraction can be used as a predictor tool of successful extubation in mechanically ventilated patients.

Keywords

Ultrasonography, diaphragm thickening fraction, diaphragm excursion, successful extubation.

CHAPTER 1

INTRODUCTION

Weaning failure is defined as the failure to pass a spontaneous breathing trial (SBT) or the need for re-intubation within 48 hours following extubation. An estimated 20% of all mechanically ventilated patients will encounter a failed extubation scenario [1]. The pathophysiology of weaning failure is multifactorial but a recent factor of interest described in current literature is that of diaphragm dysfunction [2].

The diaphragm is the main inspiratory muscle. It constitutes of a non-contractile central tendon and peripheral contractile muscle fibers. The diaphragmatic muscle fibers radiate centrifugally and insert peripherally onto the inner surface of the lower six ribs laterally, the costal cartilages and sternum anteriorly, and the arcuate ligaments that extend form the upper lumbar vertebrae to the 12^{th} ribs posteriorly. Neurological inputs to the diaphragm originate from the phrenic nerve, which stem from the third, fourth and fifth cervical nerves bilaterally.

Diaphragmatic dysfunction can be the result of spinal cord disease, nerve damage, neuromuscular junction disease, primary muscle pathology or problems with the muscle's interaction with the chest wall. It can involve either the whole diaphragm (bilateral) or either hemidiaphragm.

Sepsis impairs the function of respiratory muscle and is a common cause of diaphragm dysfunction. The impairment can be rapid in onset and observed soon after the disease process and may persist after several weeks depending on the infectious aggression. Mechanical ventilation in itself is also associated with decreased muscle weight and alteration in contractile properties of the diaphragm. [2]

Unilateral diaphragm dysfunction can be identified on a chest radiograph by the presence of an elevated hemidiaphragm and basal subsegmental atelectasis. This chest radiograph finding has a high sensitivity (90%), but has an unacceptably low positive predictive value of 33% [3]. It is also a poor predictor of normal diaphragmatic motion. Other imaging modalities available include fluoroscopy to assess the excursion of diaphragm and computed tomography to assess diaphragm structure. Non-imaging diagnostic tests include pulmonary function test to help diagnose diaphragm weakness, but their accuracy and reproducibility are limited.

A recent emerging modality that has been making its rounds in recent literature is the use of point of care ultrasound (POCUS) to assess the diaphragm. Besides being relatively portable (especially useful in the setting in critical care), it offers the front liner the ability to perform a structural and functional assessment of the diaphragm at the bedside. It has been shown to be relatively comparable in terms of accuracy to preexisting modalities in the assessment of diaphragm function [3].

LITERATURE REVIEW

Weaning is a process of gradual reduction in ventilator support that the patient receives from the mechanical ventilator in order for the patient to assume a greater proportion of his or her own ventilator effort [4]. The purpose is to assess the probability that mechanical ventilation can be subsequently weaned off successfully.

Delayed weaning is deleterious as it leads to an increased risk of complications such as ventilator associated pneumonia (VAP), ventilator-induced diaphragmatic atrophy and ventilator associated lung injury. On the other hand, premature weaning is not risk free as it can lead to complications such as loss of airway, aspiration and defective gas exchange.

General preconditions for commencement of weaning include [4]:

Reversal of primary pathology causing need for mechanical ventilation

Patient is awake and responsive

Good cough effort

Minimal/No inotropic support

Normalizing metabolic status

Adequate haemoglobin concentration

Traditional methods of weaning include spontaneous breathing trial (SBT), which is the progressive decrease in the level of pressure support during pressure support ventilation. SBT can be done either through a T-piece or with minimal ventilator support. An initial SBT of 30 minutes duration is generally sufficient to determine whether mechanical ventilation can be subsequently discontinued.

There are several clinical parameters that have been used to predict the outcome of weaning, including:

Minute ventilation <10 liters per min

Respiratory rate <35 breaths per min

Rapid shallow breathing index < 105 per liter

Maximum inspiratory pressure < -25cmH2O

Many of the above mentioned indices have high sensitivity but low specificity. Although Rapid Shallow Breathing Index (RSBI) is a helpful index for weaning, the application of RSBI alone cannot accurately predict the successful spontaneous breathing trial (SBT) outcome in mechanically ventilated patients [5]

Recently, diaphragmatic ultrasound has been studied as a means to predict outcome of weaning from mechanical ventilation [6,7]. Clinicians are attracted by the ability of point of care ultrasound (POCUS) to directly visualize the diaphragm and assess its function in real time. The diaphragm is typically identified sonographically by its curved geometry, muscular echotexture and deep location. The diaphragm can be seen as 2 echogenic layers of peritoneum and pleura sandwiching a more hypoechoic line of muscle itself. It thickens during inspiration, unless it is severely atrophic. Thickness and echogenicity of the diaphragm can be assessed using B mode ultrasound [8].

Diaphragm movement can be visualized via the anterior subcostal view. It requires a lower frequency (e.g. curvilinear or phased-array) probe placed in the anterior subcostal region between the midclavicular and anterior axillary lines. B mode is used to visualize the diaphragm moving towards or away from the transducer. Imaging is then changed to M mode with the line of sight positioned in order to obtain maximum excursion. Amplitude of excursion can be measured on M mode.

Ultrasonographic assessment of either diaphragm excursion or diaphragmatic thickness fraction can be used to predict extubation outcome [9]. DiNino et al [10] first described in 2013 the use of B mode ultrasound to directly visualize the diaphragm thickening during inspiration, reflecting diaphragm shortening and is analogous to the ejection fraction of the heart. Their study of 63 patients revealed that measures of diaphragm thickening as superior to other standard measures of extubation outcome. Based on their study, a diaphragm thickness fraction of more than 30% is associated with successful extubation outcomes. With regards to diaphragm excursion, Farghaly et al [9] studied 54 mechanically ventilated patients that has passed SBT and discovered a diaphragm excusion cutoff of 1.05cm is associated with successful extubation. Dres et al [11] used both diaphragm thickness fraction and diaphragm excursion as a means to assess the degree of diaphragm dysfunction in the effort to prove that intensive care associated diaphragm dysfunction is associated with prolonged mechanical ventilation.

The advantage of diaphragm ultrasound in comparison with other modalities to assess diaphragm (e.g. chest x-ray, fluoroscopy, computed tomography) include its nonionizing radiation, noninvasive technique, ease of use, reproducibility, low cost and speed of testing. However, there are some limitations of diaphragm ultrasound. It is difficult to visualize in patients with elevated BMI and diaphragm motion sometimes is affected by the abdominal contents and pressure that limit diaphragm displacement. [12]

In conclusion, they are many factors that have impact on the extubation outcome. Weaning and extubation must be guided by multiple parameters. Diaphragm dysfunction is one of the common causes that can lead to failure to wean in mechanically ventilated patients. It can occur as a result of mechanical ventilation, sepsis, critical illness neuromyopathy, malnutrition or electrolyte abnormalities (e.g.

hypomagnesaemia, hypokalaemia) in ventilated patients. Diaphragm ultrasound can be used as an attractive new parameter for the prediction of weaning outcome.

CHAPTER 2

OBJECTIVES

General objective

To evaluate the use of ultrasound assessment of diaphragm as a predictor tool of extubation outcome in mechanically ventilated patients.

Specific objectives

1. To compare the mean diaphragm thickness fraction in mechanically ventilated patients between the successful extubation group and the failed extubation group.
2. To compare the mean diaphragm excursion in mechanically ventilated patients between the successful group and the failed extubation group.
3. To assess the relationship between diaphragm thickness fraction with extubation outcome.

Null hypotheses

1. There is no difference in the mean diaphragm thickness fraction between the successful group and the failed extubation group.
2. There is no difference in the mean diaphragm excursion between the successful extubation group and the failed extubation group.
3. There is no relationship between diaphragm thickness fraction with successful extubation outcome.

CHAPTER 3

STUDY PROTOCOL

Research title

Ultrasound assessment of diaphragm as a predictor tool of successful extubation in mechanically ventilated patients.

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Hospital Universiti Sains Malaysia

JEPeM Code

USM/JEPeM/19010007

MREC Study ID

NMRR-18-2884-44719

Study Sites

1. Intensive Care Unit/ High Dependency Ward, Hospital Queen Elizabeth, Sabah

2. Intensive Care Unit, Hospital Universiti Sains Malaysia, Kelantan

INTRODUCTION

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The diaphragm is the main inspiratory muscle. It constitutes of a non-contractile central tendon and peripheral contractile muscle fibers. The diaphragmatic muscle fibers radiate centrifugally and insert peripherally onto the inner surface of the lower six ribs laterally, the costal cartilages and sternum anteriorly, and the arcuate ligaments that extend form the upper lumbar vertebrae to the 12^{th} ribs posteriorly. Neurological inputs to the diaphragm originate from the phrenic nerve, which stem from the third, fourth and fifth cervical nerves bilaterally.

Diaphragmatic dysfunction can be the result of spinal cord disease, nerve damage, neuromuscular junction disease, primary muscle pathology or problems with the muscle's interaction with the chest wall. It can involve either the whole diaphragm (bilateral) or either hemidiaphragm.

Sepsis impairs the function of respiratory muscle and is a common cause of diaphragm dysfunction. The impairment can be rapid in onset and observed soon after the disease process and may persist after several weeks depending on the infectious aggression. Mechanical ventilation in itself is also associated with decreased muscle weight and alteration in contractile properties of the diaphragm [2].

Unilateral diaphragm dysfunction can be identified on a chest radiograph by the presence of an elevated hemidiaphragm and basal subsegmental atelectasis. This chest radiograph finding has a high sensitivity (90%), but has an unacceptably low positive predictive value of 33% [3]. It is also a poor predictor of normal diaphragmatic motion. Other imaging modalities available include fluoroscopy to assess the excursion of diaphragm and computed tomography to assess diaphragm structure. Non-imaging diagnostic tests include pulmonary function test to help diagnose diaphragm weakness, but their accuracy and reproducibility are limited.

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to visualize the diaphragm moving towards or away from the transducer. Imaging is then changed to M mode with the line of sight positioned in order to obtain maximum excursion. Amplitude of excursion can be measured on M mode.

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The advantage of diaphragm ultrasound in comparison with other modalities to assess diaphragm (e.g. chest x-ray, fluoroscopy, computed tomography) include its nonionizing radiation, noninvasive technique, ease of use, reproducibility, low cost and speed of testing. However, there are some limitations of diaphragm ultrasound. It is difficult to visualize in patients with elevated BMI and diaphragm motion sometimes is affected by the abdominal contents and pressure that limit diaphragm displacement. [13]

In conclusion, they are many factors that have impact on the extubation outcome. Weaning and extubation must be guided by multiple parameters. Diaphragm dysfunction is one of the common causes that can lead to failure to wean in mechanically ventilated patients. It can occur as a result of mechanical ventilation, sepsis, critical illness neuromyopathy, malnutrition or electrolyte abnormalities (e.g. hypomagnesaemia, hypokalemia) in ventilated patients. Diaphragm ultrasound can be used as an attractive new parameter for the prediction of weaning outcome.

OBJECTIVES

General objective

To evaluate the use of ultrasound assessment of diaphragm as a predictor tool of extubation outcome in mechanically ventilated patients.

Specific objectives

1. To compare the mean diaphragm thickness fraction in mechanically ventilated patients between the successful extubation group and the failed extubation group.
2. To compare the mean diaphragm excursion in mechanically ventilated patients between the successful group and the failed extubation group.
3. To assess the relationship between diaphragm thickness fraction with extubation outcome.

Null hypotheses

1. There is no difference in the mean diaphragm thickness fraction between the successful group and the failed extubation group.
2. There is no difference in the mean diaphragm excursion between the successful extubation group and the failed extubation group.
3. There is no relationship between diaphragm thickness fraction with successful extubation outcome.

RESEARCH METHODOLOGY

Study Design: Prospective cohort study

Study Period: 2 years (1st January 2019 – 31st December 2020)

Study Population:

Mechanically ventilated patients in Hospital Queen Elizabeth, Sabah

Mechanically ventilated patients in Hospital USM, Kubang Kerian

Study setting:

Intensive Care Unit/ High Dependency Ward Hospital Queen Elizabeth, Sabah

Intensive Care Unit, Hospital USM, Kubang Kerian

Inclusion Criteria:

- Age above 18 years old, below 65 years old

    * Aging is associated with muscular atrophy; patients with extreme of ages will be excluded in this study

- Haemodynamically stable with no inotropic support

- Mechanically ventilated patients who passed spontaneous breathing trial (SBT) with leak test positive

    *Please refer to appendix 1 for more information on SBT

Exclusion Criteria:

- Patients with any form of neuromuscular disorders that results in diaphragmatic paralysis (e.g. Guillain-Barre Syndrome (GBS), Myasthenia Gravis)
- Patients with pneumothorax
- Patients with pleural effusion
- Patients with lung fibrosis
- Patients with previous cardiothoracic surgery

- Patients presented with upper airway obstruction (e.g. stridor), or leak test negative
- Pregnant patients
- Patients whom sonographic access to diaphragmatic area are difficult (e.g. dressing over right lower rib cage, chest tube in situ)

Methodology Flowchart

**Please refer to appendix 1 for methodology flowchart*

Sampling design:

Subjects are selected using convenience sampling. In order to reduce bias, the target population is properly defined and that the sample frame matches it as much as possible. Ensure that the excluded populations do not differ from the overall one in terms of the statistics to be measured.

Sample size determination:

Sample size is calculated based on previous study

For objective 1 to compare the means of diaphragm thickening fraction between the successful extubation group and the failed extubation group, we need at least 9 subjects in the failed extubation group and 18 subjects in the successful extubation group, given SD = 13.3765 [11] in both groups, to detect a difference of 16% [11] with 80% power at 5% level of significance. The ratio of group 1 to group 2 is set at 1:2.

For objective 2 to compare the means of diaphragm excursion between the successful extubation group and the failed extubation group, we need at least 23 subjects in the failed extubation group and 46 subjects in the successful extubation group, given SD = 0.4175 [11] in both groups, to detect a difference of 0.3 cm [11] with 80% power at 5% level of significance. The ratio of group 1 to group 2 is set at 1:2.

For objective 3, a logistic model with one predictor i.e., diaphragm thickening fraction will be fitted. According to Peduzzi et al [14], at least 10(r+1) events of the least

frequent outcome should be observed where r is the number of regression parameters to be estimated (excluding the intercept). For our model, r = 1 and the least frequent outcome is failed extubation. Therefore, we need to observe at least 20 failed extubations.

Based on the 3 objectives samples size calculation, the highest number of sample size based on objective 2 is selected, which is at least 46 subjects in the successful extubation group and at least 23 subjects in the failed extubation group need to be observed.

In conclusion, at least 70 mechanically ventilated patients who planned for extubation and meet the inclusion criteria will be enrolled into the study.

Planned Data Analysis:

All analyses will be undertaken using SPSS Version 25. Continuous variables are expressed as mean (SD) or median (interquartile range) and categorical variables are expressed as absolute and relative frequency. t-test will be used to compare the mean diaphragm thickening fraction and mean diaphragm excursion between the successful extubation group and the failed extubation group. For all final comparisons, a p value less than or equal to 0.05 is considered statistically significant. General logistic regression will be used to assess the relationship between diaphragm thickness fraction with extubation outcome.

Research tools and material:

1. Ultrasound operator- This is a single operator study. The primary investigator will be the operator conducting the diaphragm ultrasound.

2. Ultrasound machine with phased-array and curvilinear probe. (ClearVue 350, PHILIPS Healthcare, Amsterdam, Netherlands/LOGIQ S8, GE Healthcare, Waukesha, Wisconsin, USA)

Diaphragm thickening fraction will be examined with a linear probe (5-12MHz) or curvilinear probe (2-5MHz) depending on patient's body habitus using B-mode.

Diaphragmatic excursion will be measured with a phased-array probe (2.5-5MHz) or curvilinear US probe (2-5MHz) using M-mode.

3. Data Collection Form

LIMITATIONS

1. Failure in extubation can be multifactorial.

2. This is a study done only in 2 different hospitals in Malaysia. There will be a need for multicentre, multinational studies in the future.

3. Different ultrasound machine used in the study can be a potential source of confounding factor as the resolution and other specifications might differ.

ASESSMENT OF RISK

Ultrasound assessment of diaphragm is non-invasive and painless. There is no evidence that ultrasound scans are harmful. Information obtained from this study will help improve the management of other patients with the same disease or condition.

ETHICAL CONSIDERATION

This study will be registered in the National Medical Research Register (NMRR). It will only be initiated upon attaining approval from the Medical Research & Ethics Committee (MREC) of the Ministry of Health (MOH), Malaysia. Participation in the study is voluntary and will require prior written consent (bilingual Participant Information Sheet and Informed Consent Form constructed). The participants are allowed to refuse participation in the study at any time.

All collected data and responses obtained from the interview will be kept strictly confidential and no unique identifier(s) will be required in the final data analysis.

Results and data presented in the report will not identify individual participant. Participants will not be given any forms of reward for participating in the study.

MANAGEMENT OF DATA

All data collection forms in paper forms will be kept as confidential item and only the investigators or regulatory bodies will have access to them. After all the primary data have been transcribed into statistical packages, the study data will be anonymized and password protected when saved into the primary investigator's computer. All the study data (paper forms and anonymized digital data) will be kept for a duration of 3 years and will be destroyed thereafter via paper shredding and complete wipe out from the computer.

PUBLICATION POLICY

All the information obtained from this study will be kept confidential and only summarised data will be presented in reports or publications.

INVOLVEMENT OF VULNERABLE SUBJECTS

The participation in this study is entirely voluntary. Patients are allowed to refuse participation in the study at any time, without any penalty or loss of benefits to which the patient otherwise entitled.

To reduce/eliminate bias, the supervisors who are involved in the clinical management of the participants will not act as the principal investigator study (in order to be blinded to the ultrasonographic findings).

CRITERIA FOR SUSPENDING OR TERMINATING THE STUDY

The study will be terminated once the target sample size has been achieved and/or ends on 31st December 2020.

SUBJECT WITHDRAWAL CRITERIA

- Patient's request for withdrawal

- Poor ultrasonographic view of the diaphragm due to patient's body habitus.

SUBJECT'S ACCESSIBILITY TO THE PERSONAL INFORMATION AND STUDY DATA

Subjects will be given access to their own personal information and study data if requested.