

Continuous Negative Abdominal Pressure in Acute Respiratory Distress Syndrome
(CNAP in ARDS)

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BACKGROUND AND RATIONALE

Adult respiratory distress syndrome (ARDS) is a serious pulmonary disease affecting adults and children. It has a high mortality and there is no specific therapy. The mortality is high (approx. 40% in severe cases) and this has not changed in the last 20 years (Bellani, 2016). Mechanical ventilation is the mainstay of management, and this assists the patient by increasing oxygenation and removal of carbon dioxide. Despite optimizing tidal volume, driving pressure and positive end-expiratory pressure (PEEP), patients with ARDS develop large areas of atelectasis (collapse) and poor oxygenation (Slutsky, 2013). There are few additional ventilator approaches that have proven to be effective in preventing this type of injury.

A major aim of ventilator support is recruitment of atelectatic (i.e. de-aerated) lung, but while this is supported by excellent rationale and laboratory data, the recent large clinical trial has revealed that recruitment with positive pressure worsened patient outcome (Costa Leme, 2017). Most atelectasis in ARDS occurs in the dorsal (dependant, lower-most) lung regions, and these are near the diaphragm.

The main ways to recruit lung are to increase the airway distending pressure (but this overexpands and damages the already-aerated lung regions); or, to turn the patient into the prone position (but clinicians are reluctant to utilize this approach – despite evidence that it may increase survival (Bellani, 2016). Continuous Negative Abdominal Pressure (CNAP) aims to selectively recruit basal atelectatic areas of lung, while enabling the patient to remain in the supine (usual) position (Chierichetti, 2012; Yoshida, 2017).

PREVIOUS RELATED WORK

We have extensive data from rodent and large animal experiments in our laboratory that demonstrate the effectiveness of a novel approach: we applied negative pressure to the abdomen in order to selectively recruit lung that lies against the diaphragm.

We have demonstrated, in rodents (Chierichetti, 2012), and in a large animal [i.e. anesthetized pig with lung injury] model (Yoshida, 2017) that CNAP augments oxygenation and improves compliance, and importantly, it reduces the degree of subsequent lung injury. In the rodent application, the animals developed hypotension, but not in the large animal model. We have recently completed a Phase 1 study on healthy volunteers (HSC REB#1000057680). This demonstrated that the CNAP is well tolerated in awake healthy subjects and caused no adverse effects. Others have used a variation of this approach in anesthetized pigs (Valenza, 2005) and in humans with ARDS (Valenza, 2003), but they did not use recruitment maneuvers; and, the devices used did not encircle the abdomen or achieve effective transmission of negative pressure across the abdominal wall.

In these applications, the approach did not augment ventilation but, neither did they cause any adverse impact.

Finally, the technique has been used (although for a different indication) to reduce elevated intra-abdominal pressure in critically ill patients (Bloomfield, 1999 #247).

Device: A patent (US) application has been filed for the device (owned by SickKids)

RESEARCH OBJECTIVES AND HYPOTHESIS

We wish to perform a safety, 'Phase 2' study in patients that have been diagnosed with Acute Respiratory Distress Syndrome (ARDS) to determine primary safety and efficacy of using CNAP.

Safety (Stop rules)

- ↓ mean arterial pressure <60 mmHg or ↓15%
(despite 500 mL fluid or increase norepinephrine)
- ↓ SpO₂ (drop >5%)
- ↓ PaO₂/FiO₂ >20% .

Efficacy ↑ PaO₂/FiO₂ >20%

RECRUITMENT PROCESS

Patients will be recruited from the Intensive Care Unit, following completion of informed consent from the patient or legally authorized substitute decision maker (SDM) (see Consent Form). Please see "Inclusion and Exclusion criteria"

POPULATION TO BE STUDIED

Patients with ARDS. Weight range 40-100 kg. Ventilated with positive pressure ventilation and a P/F ratio ≤ 200 mmHg with PEEP ≥ 5 cmH₂O

Inclusion Criteria:

- 1) Patients ≥ 18 years old
- 2) Patients with moderate to severe ARDS as per the Berlin definition (PaO₂/FiO₂ ≤ 200 mmHg) (Ranieri, 2012)
- 3) Patients with absence of any significant cardiopulmonary disease

Exclusion Criteria:

- 1) Contraindication to CNAP
 - a. open abdominal wounds or drainage tubes
 - b. Acute brain Injury with intracranial pressure >30 mm Hg or cerebral perfusion pressure <60 mmHg
 - c. Decompensated heart insufficiency or acute coronary syndrome
 - d. Major hemodynamic instability: Mean arterial pressure lower than 60 mm Hg despite adequate fluid resuscitation and two vasopressors or increase of vasopressor dose by 30% in the next 6 hours.
 - f. Unstable spine, femur, or pelvic fractures
 - g. Pregnancy
 - h. Pneumothorax
- 2) Contraindication to EIT electrode placement
Burns, chest wall bandaging limiting electrode placement
- 3) Severe liver insufficiency (Child-Pugh score > 7) or fulminant hepatic failure
- 4) Major respiratory acidosis or PaCO₂ > 60 mmHg
- 5) Severe COPD (according to the GOLD criteria defined as severe = FEV₁: 30-50% or very severe = FEV₁ < 30%)
- 6) Clinical judgement of the attending physician

INTERVENTIONS AND RESEARCH PROCESS

Pre-Human Testing: The device has been extensively tested (the first prototype was successfully tested on a pig with good success (Yoshida, 2017).

The current device has undergone a closed loop stress test for 24 hours (-10 cmH₂O) and showed no signs of failure. This device was made in the laboratory of Thomas Looi in the department of Biomedical Engineering.

The device has also been tested on a Mannequin (please see photograph in the appendix), with no leakage.

Protocol (summarized in Flow Chart):

- 1) Eligible patients will be identified with research coordinators by daily screening in the intensive care unit
- 2) Consent for participation will be obtained from the patient's substitute decision maker
- 3) Prior to starting the application of CNAP, patients will be sedated deeply with sedatives and/or opioids, and will be paralyzed with a continuous infusion of rocuronium, if not started (7 µg/kg/min).
- 4) Also we will install the EIT to visualize the ventilation pattern.
- 5) Baseline measurement (see Appendix, ARDS Registry Form)

- a) Lung Mechanics
- b) Pressure-Volume Curve,
- c) determination of Recruitability, and
- d) Fluid Responsiveness.

6) Stage 1

the CNAP device is attached to the abdomen (but no suction), and a complete set of vital signs recorded.

7) Stage 2

a suction is applied to the CNAP device until chamber pressure will reach -5cmH₂O, and vital signs carefully monitored. If no impact, go to stage 3.

8) Stage 3

the suction level will be increased until esophageal pressure will decrease by -3cmH₂O, as per the primary team, and vital signs recorded. If no impact, go to next stage after discuss with the clinical team and attending physician responsible for the patient's care

9) Stage 4 & 5

First, lung recruitment with CPAP 40cmH₂O for 10sec. Then the suction will be applied until esophageal pressure will decrease by -3cmH₂O, as per the primary team, and vital signs recorded.

10) Stage 6

when the study is finished, and the device removed, monitoring will continue –along with primary team- as per usual ICU care.

At each stage, if any concern (Safety-Stop rules, see above), the primary care team will immediately stop the CNAP. If effective (Efficacy, see above), CNAP will continue for 2 hours.

If the device appears to have helped, it can (at the request of the care team) be left in place for a total of 24h.

A SCHEMATIC of the study protocol is appended (Flow chart).

The following parameters will be recorded (see Flowchart & Case report form):

Hemodynamic (S/M/DAP, HR, CVP)

Respiratory Mechanics (RR, VT, mPaw, PIP, Pplat, PEEP, end-exp. Pes, EIT)

Gas Exchange (FiO₂, SpO₂, PaO₂, PaCO₂)

Abdominal Pressure (Pbladder)

ANTICIPATED OUTCOME

We anticipate no significant impact on cardiovascular physiology; we expect some improvement of the P/F ratio, lung compliance and ventilation distribution.

SAMPLE SIZE AND JUSTIFICATION

A convenience sample size of 20 patients will be invited to participate. We anticipate that patient oxygenation will increase with CNAP application in conjunction with positive pressure ventilation vs positive pressure ventilation alone.

Because we will use sensitive markers of any impact on respiratory or circulator parameters (including patient reported dyspnea, and key parameters (see Data Sheet), this will facilitate detection of any potentially adverse effects.

RESEARCH PROCEDURES

Analysis will consist of inspection of the data associating transition to and withdrawal from CNAP.

We estimate that the total time in the CNAP device might be around 6 hours, but it could take less time or more time. Throughout this period, close monitoring will ensure comfort and safety.

SAFETY PROCEDURES

The testing will be performed beside in the Intensive Care Unit at St Michael's Hospital. A staff physician will be present, and dedicated to monitoring the subject and ensuring safety. No medications will be administered. All data will be digitized and securely stored.

DEFINITION AND MEASUREMENTS

Demographic Data: Demographic data will be obtained from the patient's medical file: Age, gender, height and weight, Admission diagnosis, Cause of acute respiratory failure, Significant comorbidities (COPD, CHF, other chronic organ insufficiency), Days on ICU and days on MV (days), APACHE II severity score and SOFA score on the day of the test, etc (See case report form).

Electric Impedance Tomography: EIT data will be recorded using the PulmoVista®500 (Dräger, Lübeck, Germany) with 16-electrode silicon belt, placed on the perimeter defining a cross sectional plane of the thorax at the level of the 5th intercostal space (parasternal line). In all patients, EIT data will be recorded at each stage, and analyzed with the dedicated analysis tool (Dräger EIT analysis Tool 6.1). EIT images will be divided into two (and four) zones, each covering 50% (and 25%) of the ventro-dorsal direction, for the analysis of ventilation pattern.

Airway Pressure, Esophageal Pressure and Flow: The esophageal balloon (Copper Surgical, Trumbull, CT, USA) will be inflated by 1.0 ml of air volume. If applicable, we will record the data as follows (if not applicable, we will record the data from the ventilator monitor and portable monitor). The proximal end of the catheter is connected to a pressure transducer and recording equipment (MP150; Biopac systems, Goleta, CA,

USA). Airway flow and pressure sensors will be connected to the respiratory circuit, proximal to the Y-piece. The flow will be measured through a pneumotachograph (Fleish No. 2; Metabo; Epalinges, Switzerland) adequately calibrated using a 1 L syringe to obtain integration of 1 L equals to 1 Volt. Proximal airway pressure will be measured using a differential pressure transducer (TSD160series: Biopac systems, Goleta, CA, USA) previously calibrated at 10 and 0 cmH₂O using a water column. Signals will be acquired with an analogue-digital converter (MP150; Biopac systems, Goleta, CA, USA), sampled at 200 Hz and stored in a laptop computer for subsequent off-line analysis (Acqknowledge 4.3, Biopac Systems).

1) Transpulmonary pressure (PL): Maximal values of PL = [airway pressure – esophageal pressure] will be recorded as peak PL. We also will calculate Δ PL as the difference between the airway driving pressure and Δ esophageal pressure (i.e. airway pressure – PEEP – Δ esophageal pressure) corresponding to the same time phase and we will pick up the maximal value as peak Δ PL. Plateau PL will be calculated as [airway pressure - esophageal pressure] after making an inspiratory hold (i.e. zero flow phase). Expiratory PL will be calculated as [airway pressure - esophageal pressure] after making an expiratory hold.

2) Airway pressure and flow: Plateau pressure, peak airway pressure and PEEP will be measured, as previously described (Henderson, 2017). Tidal volume will be calculated as integral of flow. Considering the total stretching pressure across respiratory system (lung + chest wall) with spontaneous breathing during mechanical ventilation, driving pressure will be calculated as the sum of [plateau pressure – PEEP] and the changes in esophageal pressure corresponding to plateau phase when compared with passive conditions (Yoshida, 2013). During muscle paralysis, driving pressure was calculated as [plateau pressure – PEEP]. The dynamic compliance of the respiratory system was defined as: [VT/ driving pressure].

Hemodynamics: Arterial blood pressure and heart rate will be continuously monitored on the ICU bedside monitor.

Arterial Blood Gas: pH, PaCO₂, PaO₂ will be measured by standard clinical technique using the ICU blood gas analyzer.

STATISTICAL ANALYSIS

Statistical analysis will be performed using standard software SPSS13.0 for Windows (SPSS, Chicago, IL, USA). The results are expressed as mean \pm standard deviation. 1-way analysis of variance for repeated measures will be used to evaluate the impact of time. In the post hoc analysis to separate differences between the means, a Tukey's pair-wise multiple comparison test will be used. All tests were two-tailed, and differences were considered significant when $p < 0.05$

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