Ultrasound evaluation of the respiratory changes of the inferior vena cava and axillary vein diameter at rest and during positive pressure ventilation in healthy volunteers

Protocol proposal for research report

for

Master of Medicine (Emergency Medicine)

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INTRODUCTION

The expansion of ultrasound use as a tool in patient care in the Emergency Department (ED) has proven to be an invaluable asset to the Emergency Physician (EP). Ultrasound in the ED made its mark approximately 25 years ago and EPs have welcomed its pragmatic and non-invasive benefits to patient care[1].

Bedside ultrasound has proven itself useful for monitoring the intravascular volume status of the critically ill and injured patient[2]. It allows the physician to not only clinically assess deranged patient haemodynamics but to also diagnose aetiology and hence rapidly institute life-saving treatment[2]. This speaks to the core function of the EP.

Correlation between Inferior vena cava and central venous pressure[3]

Inferior vena cava size (cm)	Respiratory Change	Central Venous Pressure (cmH_2O)
< 1.5	Total Collapse	0-5
1.5-2.5	> 50% Collapse	6-10
1.5-2.5	< 50% Collapse	11-15
>2.5	< 50% Collapse	16-20
>2.5	No Change	>20

ESTIMATING VOLUME STATUS USING RESPIRATORY VARIATION AND CENTRAL VENOUS PRESSURE

The above table depicts the non-invasive alternative to estimating central venous pressure (CVP) or right atrial pressure (RAP) using inferior vena cava diameter (IVC)

and respiratory variation. The IVC is a thin-walled compliant vessel that changes with total body blood volume, respiration, downward pressure from the right atrium as well as intra-abdominal pressure. During spontaneous ventilation the negative pleural pressure created during inspiration results in in-drawing of blood from the lower half of the body to the thoracic cavity thus resulting in a collapsed IVC diameter. The opposite occurs during expiration. The collapsibility or respiratory variation of the IVC can then be used to estimate volume status. Despite the stratification of the parameters in the above table, good correlation between the caval index and CVP is only proven if collapsibility is greater then fifty percent (CVP less then 8-10mmHg) or less than fifty percent (CVP greater than 10mmg)[4] . The caval index (see equation below) is accentuated in patients with volume loss and hence has been suggested as a guide to fluid management.

Caval index={(IVC expiratory diameter- IVC inspiratory diameter)/ IVC expiratory diameter} X100

ASSESSING VOLUME RESPONSIVENESS:

THE FULLY MECHANICALLY VENTILATED PATIENT- NO SPONTANEOUS BREATHING

Fluid balance is particularly important in the critically ill patient as hypervolaemia or hypovolaemia may result in increased morbidity and/or mortality[5,6]. Determining which patients should receive a fluid challenge was traditionally based on haemodynamic parameters solicited from devices such as the pulmonary artery catheter (PAC) and/or the central venous line[6]. These devices were for a long time regarded as the gold standard for preload and cardiac output monitoring of the critically ill patient. The credibility of these static preload indices has been called into question[6]. The most important concern being that these devices have, to date, no

evidence to support their indicated use[6,7]. In fact, patient outcomes studied thus far show that the use of the PAC may increase patient mortality[6,7]. The reasons for the increased mortality are debatable. Complications secondary to PAC insertion and/or an aggressive clinician treatment approach based on PAC parameters are a few of the speculated potential factors. Whilst the future of PAC hangs in the balance, a means to guide fluid therapy in the critically ill patient is still needed.

Based on the Frank-Starling volume-pressure curve (appendix 1 figure 1), it is known that an increase in preload results in an increase in stroke volume which translates into increased cardiac output (cardiac output= stroke volume x heart rate)[5,8]. The slope of the Frank-Starling curve graphically represents the definition of volume responsiveness which is the potential to increase cardiac output significantly secondary to a fluid challenge[5,8].An increase in cardiac output however will only be seen if the healthy heart is on the steep slope of the curve. In the clinical setting however, only 50% of critically ill patients follow the Frank-Starling curve and respond positively to a fluid challenge[9].This is seen on the curve as it reaches a plateau indicating that fluid challenges increase cardiac output only to a point.

The passive leg raise (PLR) allows the clinician to determine which patient may benefit from a fluid challenge without actually administrating the fluid intravenously[5,6,10].The manoeuvre is a non-invasive and reversible method of assessing volume responsiveness. This manoeuvre will provide the clinician with reliable results in the spontaneously breathing patient with or without cardiac arrhythmias[5,6,10].The manoeuvre requires the patient to be moved from a seated 45˚ semi-recumbent position to a supine position with the patient's legs elevated at a 45˚

angle, hence redistributing the patient's own blood volume from the legs to the central chest and increasing the preload (giving the patient an autotransfusion)[5]. A 15% increase in stroke volume after performing the PLR means the patient is volume responsive and will benefit from a fluid challenge[5,9].In the trauma setting, however, the clinician may not always be able to elevate a patient's legs e.g. lower limb fractures or head injury, and would have to find alternate means of assessing volume responsiveness.

Barbier et al,[10] Feissel et al[11] and Vieillard-Baron et al[12] all conducted studies which show that respiratory cyclic changes in the inferior vena cava (IVC)[10,11] and superior vena cava (SVC)[12] can be utilised to determine volume responsiveness. Patients from all three studies were all sedated and invasively mechanically ventilated. These authors studied the heart-lung respiratory cyclical changes to the right and left sides of the heart which occurred during controlled mechanical ventilation. They were able to parallel the physiology engaged in the ventilated patient to that of the Frank-Starling curve in a normal functioning heart (appendix 1 figure 2).

Several limitations exist, however, when using dynamic indices in mechanically ventilated patients. Respiratory cyclical changes induced by intra-thoracic pressure during spontaneous ventilation does not guarantee the exact same tidal volume with each breath. The patient's ventilation therefore needs to be strictly controlled in order to produce reliable results. In order to tightly control ventilator parameters, patients have to be deeply sedated, paralysed with predetermined tidal volumes and respiratory rates[10]. Currently, most intensive care units (ICU) limit such tight ventilation control to specific patients. Other limitations for dynamic indices which

look at stroke volume and stroke volume surrogates e.g. Pulse Pressure Variation (PPV) or Stroke Volume Variation (SVV) prove unreliable in spontaneously breathing patients with cardiac arrhythmias[10].These limitations in dynamic preload indices leave gaps in medical literature and thus clinical practise for further studies to be undertaken to investigate rapid, non-invasive reliable determinants of intravascular volume status and volume responsiveness.

Application of Positive End Expiratory Pressure (PEEP) increases airway pressure which is transmitted to the mediastinum and to the right side of the heart. Increasing intra-thoracic pressure will decrease venous return and increase right ventricular afterload. This will subsequently result in decreased left ventricular output i.e. cardiac output[14] (appendix 1 figure 1). PEEP can be administered via invasive or non-invasive ventilation (NIV). NIV provides positive pressure ventilation via a face mask or nasal prongs.

Lambert et al[14] studied the effect of increasing levels of PEEP on stroke volume in healthy pigs. Lambert et al studied various haemodynamic parameters but of note is that at a PEEP of 10cmH_20 in hypovolaemic and normovolaemic pigs the stroke volume, cardiac output, mean arterial pressure and distensibility index (see below) all significantly decreased. Concomitantly the stroke volume variation and heart rate increased. Even with its limitations this study was able to infer that increasing PEEP levels could be used with the distensibility index to assess volume responsiveness. In this study the pigs were anaesthetized, intubated and all measurements were taken during muscle paralysis and volume controlled ventilation.

Distensibility index={(IVC maximum inspiratory diameter- IVC minimum expiratory diameter)/ IVC minimum expiratory diameter} x100

MERGING THE TWO: CAN THE CAVAL INDEX BE USED TO PREDICT VOLUME RESPONSIVENESS IN THE SPONTANEOUSLY BREATHING PATIENT?

The current general consensus is that dynamic monitoring indices cannot be used in spontaneously breathing patients. The whole premise of controlled mechanical ventilation allows for minimal variation in patient breathing patterns and therefore control of the respiratory variation. Despite this, Muller et al[15] attempted to assess volume responsiveness using the caval index in spontaneously breathing patients.

The outcome was what was known. Volume responsiveness cannot be reliably determined in spontaneously breathing patients but their figures suggest, using a caval index of 40% one cannot exclude volume responsiveness (sensitivity 70% and specificity 80%). Muller et al[15] recommends further studies to take their hypothesis further with some adjustments, the most significant being taking the IVC diameter measurements closer to the right atrium as there is less respiratory variability.

Viellard-Baron et al[12] and Lorsomradee et al[15] were the only studies to evaluate the diameter changes of a central vein other than the IVC for volume responsiveness. SVC unlike IVC resides wholly in the chest cavity and is not exposed to intra-abdominal pressures which may influence IVC diameter[15].The most accurate way to visualise SVC is via transoesophageal echocardiography (TOE)[16].TOE is an invasive procedure and is generally not used in the ED. Therefore if one was to use transthoracic ultrasound (TTE), a substitute vein for SVC would have to be found.

Access to the central venous system for catheter placement is usually via the subclavian vein, internal jugular vein, femoral vein or the axillary vein (Axv)[16].The veins most proximal to the SVC are the subclavian, internal jugular and the axillary

vein. The Axv becomes the subclavian after it crosses the lateral border of the first rib[17].

Using ultrasound to visualise the exact location of veins before placement of a central venous catheter is now recommended best practise[18]. Without the use of the TOE to directly image the SVC, TTE can be used to image one of its immediate tributaries as a potential surrogate. The internal jugular vein and the subclavian vein unite to form the short brachiocephalic vein which drains into the SVC. Understanding the anatomy of these veins allows the hypothesis that the Axv can be a SVC surrogate and used as the comparative vessel for evaluating preload status and volume responsiveness against the IVC.

The aim of this study therefore is to evaluate and compare respiratory changes in the IVC compared to the Axv diameters as markers for volume status assessment as well as to evaluate the effects of increasing levels of PEEP delivered via NIV on these vessels. These vessels will be visualised using realtime ultrasound. The participants will be breathing spontaneously throughout the duration of the study.

STUDY AIM AND OBJECTIVES

Study aim:

The aim of this study is to evaluate the respiratory variation in IVC and Axv diameters using ultrasound, at rest and during positive pressure ventilation with increasing PEEP levels, as markers of volume assessment and responsiveness.

Study objectives:

1. To measure the IVC and Axv diameter in the spontaneously breathing participant at baseline (negative pressure ventilation) and calculate the caval index
2. To measure IVC and Axv diameter variation during a respiratory cycle in response to the same participant receiving NIV with increasing levels of PEEP
3. To determine the IVC and Axv distensibility index (IVCi and Axvi) at each level of PEEP and to evaluate the trend in the change in IVCi and Axvi from baseline to the highest level of PEEP (see appendix 3)
4. To compare the measurements from the IVC against similar measurements recorded from the Axv

METHODS

Design

Prospective cross-sectional study

Site of study

Helen Joseph Hospital Emergency Department

Study population

Participants will be staff members working in the Helen Joseph Hospital who volunteer to participate in the study.

Inclusion criteria:

Participants included in the study will be 18 years or older.

Exclusion criteria:

1. Failure to obtain consent;
2. Persons with known tricuspid valve disease;

3. Persons with known chronic obstructive lung disease;
4. Pregnant women;
5. Failure to obtain adequate imaging on ultrasound
6. Persons who are known or disclose a history of anxiety disorder or suffer from claustrophobia

SAMPLE SIZE

This study will enrol 30 adult participants. This number of participants is large enough to allow paired data analysis as each participant is their own control. The sample population is also sufficient to perform logistic regression with 15 people per group.

EQUIPMENT

The ultrasound machine used will be one of the resident machines in the Helen Joseph ED. The ventilator, tubing, NIV masks and monitoring equipment used will be provided by the department. Equipment will be cleaned in-between participants as per specified manufacturer instructions.

EXPERIMENTAL METHODOLOGY

- Participants will have to complete a health questionnaire and meet inclusion criteria
- Participants will read information sheet and voluntarily sign a consent form
- The entire data collection process will be conducted in a carefully selected cubicle in the ED so as to afford participants their privacy
- Participants will be placed supine on a stretcher.

- Monitors will be placed on the participant at rest and the first set of vitals taken (appendix 3)
- The participant's right shoulder and abdomen will be exposed (females will need to wear a strappy or strap-less top or the equivalent to allow access to the right delto-pectoral groove located-see appendix)
- The first set of sonographic measurements will be done with the participants breathing spontaneously at rest (negative pressure ventilation).
- A curvilinear probe will be placed on the participant's subxiphoid region for three measurements of the IVC diameter.

  - Measurements of the IVC will be taken with the vessel in the longitudinal axis in B-mode (2D).

  -Measurements of the IVC will be taken 2cm distal to the cardiac/IVC junction

  -Measurements will be captured during one respiratory cycle.

  -The final measurement recorded will comprise the average of three repeats.

  -Participants will then be connected to a ventilator via a well-fitting NIV mask.

  -The level of PEEP will be set to 5cmH_2O then to 10cmH_2O and the above described measurements at baseline (including vital sign measurements) will be repeated at each pressure level.

  -Repeat vital signs will be taken after each participant has acclimatized to the new PEEP setting (approximately five minutes) (appendix 3)

- Measurements (at baseline and PEEP levels mentioned above) of the Axv will require ultra-sound probe change to a linear probe. The linear probe will be placed over the right delto-pectorial groove to visualize the Axv.

-Measurements will be captured during one respiratory cycle during spontaneous breathing.

-The final measurement recorded will comprise the average of three repeats

-Similar measurements taken for the IVC (above) will be taken for the Axv with the participant at rest and during PEEP levels of 5cmH_2O and 10cmH_2O

- The caval and distensibility indices will be calculated from the measured data.
- All ultrasound imaging will be conducted by a level 1 trained ultrasound accredited investigator- myself
- Data collection will be performed in the ED without hindrance to the normal functioning of the department.

DATA ANALYSIS

The data collected will be recorded in an Excel spreadsheet.

Univariate descriptive statistics will be calculated for each outcome variable (IVC diameter at maximum and minimum sizes, IVCi, Axv diameter at maximum and minimum sizes, Axvi) as well as for key covariates (age, sex, blood pressure, weight, height and heart rate). Continuous variables will be characterized by the mean, median, standard deviation, measures of skewness and kurtosis as well as their frequency distribution.

Categorical variables will be described by means of frequency distributions for each outcome variable (as listed above). The differences between airway pressures (baseline, 5cmH_2O/ 10cmH_2O) will be analysed by a mixed model for repeated measures. The repeated measures model allows for the correlation of the measurements within and between subjects and allows for covariates to be used as control variables.

TIMING OF RESEARCH

	April-June 2013	July 2013	April 2014	May 2014	June 2014	July 2014	August 2014	September 2014	November 2014	December 2014
Literature Review	x									
Preparing Protocol	x									
Protocol Assessment		x								
Protocol resubmission post corrections			x							
Ethics application				x						
U/S accreditation				x						
Collecting data					x	x				
Data analysis							x			
Write up- Mmed								x	x	
Submission Mmed										x

LIMITATIONS

Selection bias may be encountered in participants whose blood vessels cannot be adequately visualized e.g. obese participants or increased bowel gas in abdominal cavity.

The study population will be limited to healthy volunteers.

ETHICS

Written informed consent will be obtained from the participant prior to enrolment in the study (see appendix 2 for consent form).

The consent form highlights the following points:

1. There is no obligation to participate in the study.

2. There may be minor discomfort when the NIV mask is initially applied and with increasing ventilation pressures.
3. There are no risks or any financial benefits to individual participants for their enrolment in the study.
4. The collected data will be kept behind lock and key and in a password protected computer.

Permission to conduct the study will also be obtained from the Human Research Ethics Committee (HREC) of the University of the Witwatersrand. Once permission has been granted by the ethics committee then permission will be sought from the superintendant of the Helen Joseph Hospital. Permission has already been granted by head of department of the Helen Joseph Emergency Department.

FUNDING

All the equipment used will be provided by the Helen Joseph Emergency Department. Other incidental expenses will be borne by the investigator.

PROBLEMS

Technical difficulties may be encountered in obese participants (difficulty in locating vessels to be studied). Additional participants may be needed more than the indicated sample size.

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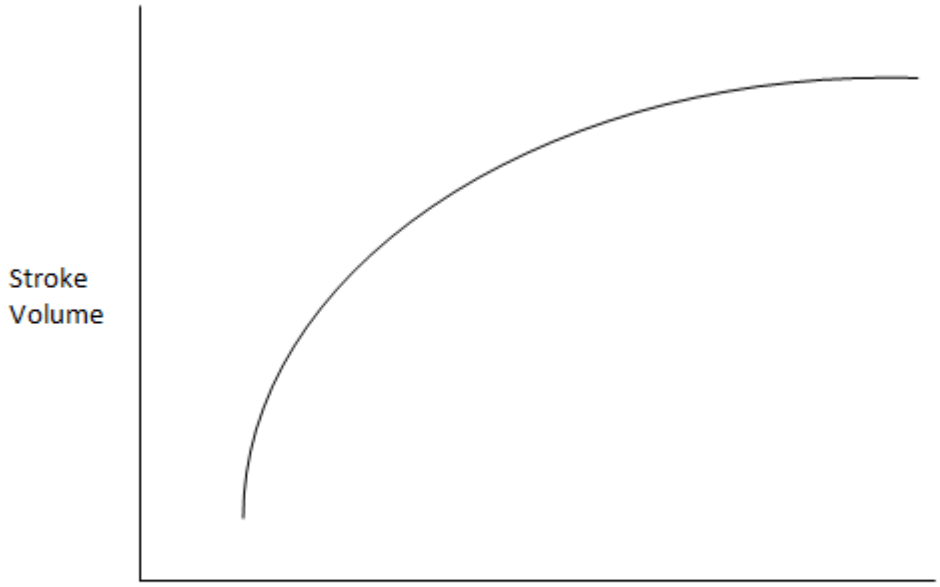
Available http://www.acep.org/workarea/downloadasset.aspx

APPENDIX 1
Figure 1



Frank-Starling Curve

APPENDIX 1
Figure 2

Marik *et al. Annals of Intensive Care* 2011, **1**:1
http://www.annalsofintensivecare.com/content/1/1/1

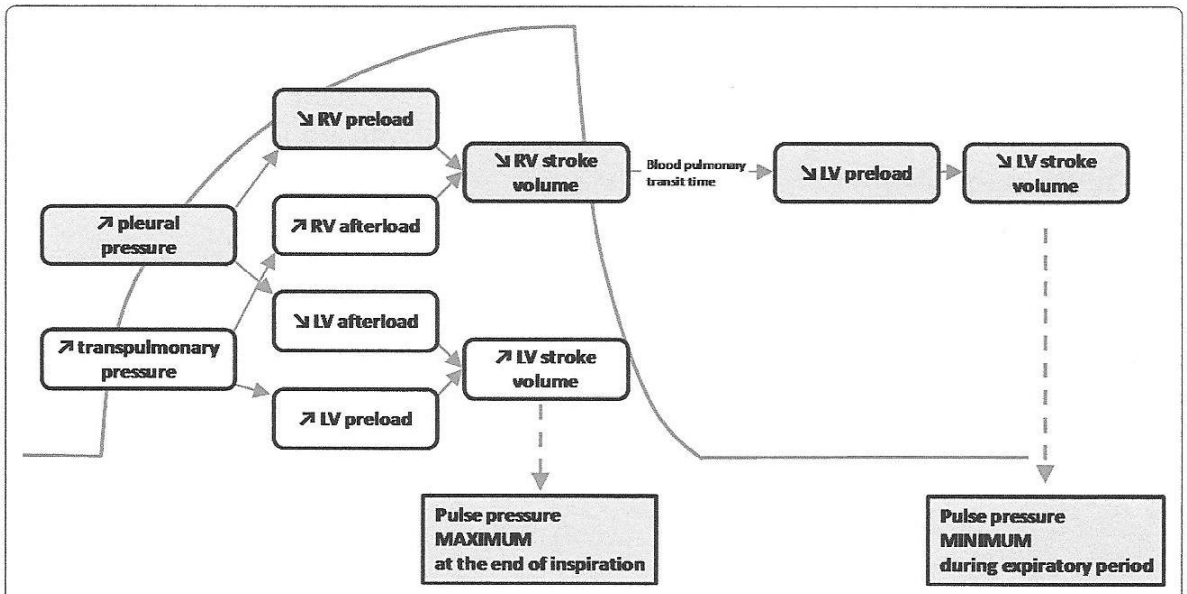


Figure 2 Heart-lung interactions. Hemodynamic effects of mechanical ventilation. The cyclic changes in left ventricular (LV) stroke volume are mainly related to the expiratory decrease in LV preload due to the inspiratory decrease in right ventricular (RV) filling. Reproduced with permission from Critical Care/Current Science Ltd [24].

APPENDIX 2

HEALTH QUESTIONNAIRE

1) How would you describe your overall health?

    - In good physical health (no significant illnesses or disabilities)

    - Mild physical impairment (minor illness which would benefit from medical treatment or lifestyle change or minor illness for which you are already on treatment)

2) Are you taking any chronic medication for any physical or mental illness?

    - Yes

    - No

   If “Yes” which medication are you taking?

3) Do you/did you smoke cigarettes?

    - Yes

    - No

   If “Yes” how many per day and for how many years?

4) Do have any heart valve abnormalities that you are aware of?

    - Yes

    - No

   If “Yes” do you know which valve is abnormal?

5) If you are female, is there any chance that you are currently pregnant?

    - Yes

    - No

APPENDIX 3

PATIENT INFORMATION SHEET

Hi

My name is Dr Kamo Molokoane and I am an emergency medicine registrar. As part of my specialist training I am required to conduct research for my Masters of Medicine.

DESCRIPTION**:** You are invited to participate in my research which is looking at how best emergency physicians (emergency doctors) can determine at what point a critically ill patient (a very sick trauma patient or medical patient) will benefit from fluid given via a drip.

PROCEDURES: For this research to be successful, I need 30 healthy people to take part in my study.

What will be expected of you during the study: You will be requested to lie on a stretcher and expose your abdomen and right shoulder (females will need to wear a strappy or strap-less top or equivalent). Once you are on the stretcher I will then use a sonar machine to look at blood vessels (inferior vena cava and axillary vein) inside your body. Following which, I will request that you put on a mask over your nose and mouth and receive positive pressure ventilation (high pressure oxygen) for a short period of time whilst I relook at the blood vessels to see the temporary effect of the positive pressure ventilation on these blood vessels. Please note you may need a few minutes to acclimatize to the face mask and the positive pressure ventilation. The use of the sonar machine or high pressure mask will not cause you any pain.

This procedure will be conducted in a private cubicle in the Helen Joseph Hospital Emergency Department. I will require approximately 30 minutes of your time. I will conduct this research with the aid of an assistant who will be seated just outside the cubicle capturing all the relevant findings.

RISKS AND BENEFITS: There are no risks associated with this study. You will not receive any direct benefit from participating in this study. If you suffer from anxiety disorders or from claustrophobia, you run the risk of mild discomfort when receiving the positive pressure ventilation. (I can assure you however that most people acclimatize to the mask and the ventilation).

I also need you to let me know if you suffer from any other medical illnesses such as heart valve problems, lung problems or if you are pregnant as these factors may affect my study measurements (we will refer to a health survey questionnaire together).

PAYMENTS: You will not be paid to participate in this study.

PARTICIPANT'S RIGHTS: Once you have read this information sheet (and completed the health survey) and decide to participate in this research, it is important to note that your participation is completely voluntary and you have the right to withdraw your consent/permission and discontinue your participation at any time without penalty.

The results of this research study may be presented at scientific or professional meetings or published in scientific journals. Your identity will, however not be disclosed. The outcomes of this research may improve the way doctors administer intravenous fluids (drips) to the critically ill patient and ultimately benefit all patients who present to our hospitals.

I have obtained approval for my study from the Human Research Ethics Committee of the University of the Witswatersrand. They can be contacted via Anisa Keshav, Wits Research Office, New Phillips Tobias Building, Princess of Wales Terrace, level 3 Room 304

Telephone 011-717-1234 Fax 011-717-1265 Email anisa.keshav@wits.ac.za.

Please remember your participation is voluntary and you may withdraw at anytime during the study without providing any explanation. If you have any questions please feel free to contact me on 079 873 3925

Or email me molokoane_kamo@yahoo.co.uk

Thank you for your time

APPENDIX 4

CONSENT FORM

I,....., being 18years or older hereby give consent to participate in the following study: “Ultrasound evaluation of the respiratory changes of the inferior vena cava and axillary vein diameter at rest and during positive pressure ventilation in healthy volunteers”.

The procedure has been explained to me by the investigator (Dr Kamo Molokoane) and I understand the purpose of the research, risks involved (no risks), and the extent of my involvement. I have read and understood the attached participant information sheet.

I understand that the procedures form part of a research project, and may not provide any direct benefit to me.

I understand that all experimental procedures have to be approved by the Human Research Ethics Committee of the University of the Witwatersrand.

I understand that my participation is voluntary, and that I am free to withdraw from the study at any time without giving reasons for my exit from the study. I also understand that there are exclusion criteria to participation in the study and even if I volunteer I may not be a suitable candidate. This does not penalize me in any way.

..... Participant’s name
..... Participant’s signature
..... Date consent form signed
..... Investigator’s signature
..... Date of Investigator’s signature

Contact details Investigator: Kamo Molokoane 0798733925
molokoane_kamo@yahoo.co.uk

APPENDIX 5

DATA COLLECTION SHEET

	M/F	Age(yrs):	Weight(kg):	Height(m):
RR(bpm): HR(bpm):		V_t (ml): BP(mmHg):		Sats (%):

Baseline		Baseline	
$IVCmax_1$:	$IVCmin_1$:	$Axvmax_1$:	$Axvmin_1$:
$IVCmax_2$:	$IVCmin_2$:	$Axvmax_2$:	$Axvmin_2$:
$IVCmax_3$:	$IVCmin_3$:	$Axvmax_3$:	$Axvmin_3$:
Comments: Estimated Tidal Volume			

PEEP 5cmH_20		PEEP 10cmH_20	
RR : HR: Vt: BP: Sats:		RR: HR: Vt: BP: Sats:	
$IVCmax_1$:	$IVCmin_1$:	$Axvmax_1$:	$Axvmin_1$:
$IVCmax_2$:	$IVCmin_2$:	$Axvmax_2$:	$Axvmin_2$:
$IVCmax_3$:	$IVCmin_3$:	$Axvmax_3$:	$Axvmin_3$:
Comments:			

RR= Respiratory Rate
HR= Heart Rate
Vt= Tidal volume
BP= Blood Pressure
Sats= Pulse oximetry saturation