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Invasive mechanical ventilation practices in adult patients in three academic intensive care units

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Invasive mechanical ventilation practices in adult patients in three academic intensive care units

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology.

March, 2023

Declaration

I, Gerhard Jacobus Coetzee, declare that this research report is my own unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



28 March 2023

Abstract

Background

Patients with, or at risk of developing, acute respiratory distress syndrome (ARDS) should be identified early, and lung-protective ventilation (LPV) instituted. This study aimed to describe invasive mechanical ventilation practices in adult patients at three academic intensive care units (ICUs) in Johannesburg from November 2021 to January 2022.

Methods

A point-prevalence, cross-sectional study using consecutive sampling.

Results

A total of 127 patients were included with a mean age of 40 (±15) years and 66.1% were male. Trauma-related causes (n=51, 40.2%) were the main indications for ventilation. Overall, 107 (84.3%) had risk factors for developing ARDS and 78 (61.4%) had PaO_2:FiO_2 $\leq$300. The most commonly used ventilatory mode was pressure support ventilation (n=62, 48.8%). Within the spontaneous ventilation group (n=62), 11 (17.7%) were ventilated with Vt $\leq$6 ml/kg IBW, 100% with PIP <30 cmH20, 98.3% with FiO_2 <0.6 and 29% had SpO_2 of 88 – 96%. In the controlled ventilation group (n=55), 7 (12.7%) of patients were ventilated with Vt $\leq$6 ml/kg IBW, 92.7% had PIP <30 cmH_20, 76.4% FiO_2 <0.6 and 27.3% had SpO_2 88 – 96%. Those with PaO_2:FiO_2 $\leq$300 had a mean PEEP of 8.6 cmH_2O and set FiO_2 of 0.45. In patients with PaO_2:FiO_2 >300, the mean PEEP was 8 cmH_2O with a set FiO_2 of 0.3. The mean Vt/kg IBW of 5.5 ml/kg IBW in patients who received $\leq$6 ml/kg IBW was significantly lower than 8.3 ml/kg IBW in those who were ventilated at >6 ml/kg IBW (p=0.0001).

Conclusion

In this study, a large proportion of patients suffered from acute hypoxaemic respiratory failure, with the vast majority at risk of developing ARDS. Given this profile of patients, compliance with the use of recommended LPV strategies was surprisingly low.

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Abbreviations

ARDS	Acute respiratory distress syndrome
CPAP	Continuous positive airway pressure
IBW	Ideal body weight
ICU	Intensive care unit
LPV	Lung protective ventilation
NMB	Neuromuscular blockade
PaO_2:FiO_2	Arterial oxygen partial pressure: fraction of inspired oxygen
PEEP	Positive end-expiratory pressure
SpO_2	Peripheral oxygen saturation
VILI	Ventilator/ventilation-induced lung injury
Vt	Tidal volume

Statement

The Research Report consists of a literature review, draft article, study proposal and appendices. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the author guidelines of the Southern African Journal of Critical Care, the journal to which it is intended to be submitted, in order to comply with the university's style guide.

Section 1: Review of the literature

1.1 Introduction

Invasive mechanical ventilation forms a cornerstone of modern critical care management. This review will briefly look at the history of ventilation, the evolution of the diagnosis and risk factors for developing acute respiratory distress syndrome (ARDS). This is followed by exploring ventilation practices, looking at various ventilation parameters including: indications for ventilation, ventilatory practices and various ventilator settings, ventilating the patient with ARDS and ventilatory adjuncts.

1.2 Background

The origins of modern mechanical ventilatory support can be traced back to the fifteenth century when Vesalius referred to the act of opening the trachea and placing some form of conduit through which air can be blown to expand the lungs (1). The development of ventilators, which function primarily based on the physiological principles accepted today, occurred in the late nineteenth century with the development of negative pressure ventilation (1,2). Positive pressure ventilation gained much attention and made drastic advances with the resurgence of polio in the 1950s. The benefits of positive-pressure mechanical ventilation quickly became apparent during the polio crisis. During this epidemic, the logistical challenges of providing so many patients with positive hand-driven mechanical ventilation in one location led to the development of the first intensive care units (ICUs) as they are known today (1).

Mechanical ventilation, intended to be a supportive and therapeutic intervention, can also lead to harmful effects. It is known that positive pressure ventilation can lead to potentially damaging stretch and strain of the lungs, leading to ventilator-associated lung injury and acute respiratory distress syndrome (ARDS) (3–5). In 2017 Pham and Rubinfeld (6), in a 50-year ARDS review, concluded that risk factors for the development of ARDS are multivariate. A consistent pattern of clinical risk factors in ARDS development is seen in patients with pneumonia (35-50%), sepsis not involving the pulmonary system (30%), aspiration (10%) and

trauma (10%). Thoracic surgery, septic shock and transfusion-related lung injury are also included (6). Non-clinical risk factors include older age, non-white race and some genetic variants. Chronic alcohol abuse and smoking, as modifiable risk factors, are also associated with the development of ARDS (6,7).

The concept of ARDS was formally described in 1967 by Ashbaugh et al. (8), and it remains an important focus in critical care (6). In 1994 during the American-European Consensus Conference, a formal definition was created (9). From this, the diagnostic criteria for ARDS stated: “the acute onset of hypoxaemia (PaO_2:FiO_2 $\leq$200), radiological evidence of bilateral opacifications on chest radiograph, with no clinical evidence of left atrial hypertension (evidence based on a pulmonary artery wedge pressure of $\leq$18 mmHg)” (9). A new concept, “acute lung injury” also emerged from this consensus conference indicating a less severe form of hypoxaemia (PaO_2:FiO_2 $\leq$300) than in ARDS. There were limitations with these diagnostic criteria that questioned their reliability and validity in diagnosing ARDS accurately. In 2012 the ARDS Definition Task Force (10) developed a new definition for ARDS, the Berlin definition, to create a more feasible and reliable definition that could increase the validity and objective evaluation of ARDS. The timeframe for acute onset was clarified to within one week of a known clinical insult, or respiratory symptoms that are new or worsening. Radiological investigation of bilateral chest infiltrates on chest radiograph was amended to include chest computed tomography findings. Effusions, atelectasis or nodules should not explain these findings. These bilateral opacifications caused by oedema could not be secondary to congestive cardiac failure or fluid overload. The acute lung injury entity was removed, and the severity of hypoxaemia in ARDS was subdivided into three classes:

- Mild PaO_2:FiO_2* >200 – $\leq$300, PEEP** or CPAP*** of 5 cmH_2O
- Moderate PaO_2:FiO_2 >100 – $\leq$200, with a PEEP of 5 cmH_2O
- Severe PaO_2:FiO_2 $\leq$100 with a PEEP of 5 cmH_2O (10).

*PaO_2:FiO_2 – arterial oxygen partial pressure: fraction of inspired oxygen,
**PEEP – positive end-expiratory pressure,
***CPAP – continuous positive airway pressure

The Berlin definition for ARDS has been used to date. Although its application has been questioned in various clinical scenarios, it is still globally used to diagnose and grade ARDS (11).

1.3 Indications for ventilation

Many indications necessitate the use of mechanical ventilation. These include airway compromise, acute respiratory failure, a significant change in mental status, cardiac arrest or neuromuscular disease affecting breathing mechanics (12,13). The altered mental status could be secondary to either traumatic brain injury with a significant reduction in mentation, a drug or chemical overdose, and non-traumatic brain injuries caused by hypoperfusion and hypoxic injury (7,14). The main goals of ventilatory support are to reduce the work of breathing, treat significant hypoxaemia (12,15) and assist with the clearance of excessive carbon dioxide (15).

1.4 Ventilation in ICU

Guidance regarding ventilation practices stem almost exclusively from studies undertaken in patients with ARDS. Ventilation practices, ARDS ventilation and ventilatory adjuncts will briefly be discussed.

1.4.1 Ventilation practices

Gattinoni et al. (16) stated, “Ventilator/ventilation-induced lung injuries (VILI) result from the interaction between what the ventilator delivers to the lung parenchyma and how the lung parenchyma accepts it”. Ventilator parameters are adjusted to mitigate the potentially harmful effects of mechanical ventilation (5,17). The following parameters will briefly be reviewed: ventilatory modes, tidal volume, respiratory rate, PEEP and fraction of inspired oxygen/arterial oxygen saturation (FiO_2/SaO_2).

Ventilatory modes

Selecting the ventilation mode is user-dependent and often open to debate (17). It is unclear whether a pressure-controlled ventilation-based mode is superior to volume-controlled ventilation (17). A meta-analysis of three randomised controlled

trials (18) and a narrative and systematic review (19) showed no significant difference in ICU and hospital mortality between pressure-controlled and volume-controlled ventilation. Airway pressure release ventilation mode potentially recruits alveoli by increasing airway pressures and allows for spontaneous breathing (20). High-frequency oscillatory ventilation aims to deliver tiny tidal volume breaths in a rapidly oscillatory manner at a constant mean airway pressure (20). These modes theoretically provide benefits; however, clinical evidence on improved ARDS patients' outcomes is controversial and remains unproven (5,17,20).

Spontaneous breathing modes (for example, pressure support ventilation, synchronised intermittent mandatory ventilation and adjustable pressure release ventilation modes) provide the potential benefits of a decrease in sedation and neuromuscular blockade use, shorter duration of mechanical ventilation and an improvement in cardiac function (17,21). However, spontaneous ventilatory efforts, in addition to mechanical ventilation, may lead to harmful effects and a form of patient self-induced lung injury (21,22)

Tidal volumes

Lung-protective ventilation strategies using low tidal volumes, $\leq$6 ml/kg ideal body weight (IBW), have improved outcomes in patients with ARDS (3,23), but it is unclear if the same strategy is beneficial in patients without ARDS. A meta-analysis found that reducing the tidal volume led to fewer pulmonary complications (4). There is potential harm if low-volume strategies are mandated, as there can be a higher need for sedation and even neuromuscular blockade use. The use of these medications can lead to higher incidences of ICU-acquired delirium, diaphragm dysfunction and prolonged ventilation (24,25). The 2016 PRoVENT (26) trial looked at epidemiological characteristics, ventilatory practices and clinical outcomes of patients at risk of ARDS. The Lung Injury Prediction Score was used as the primary outcome to assess which patients were at risk of ARDS (scored >4). The secondary outcomes looked at ventilatory management strategies, the incidence of ARDS development according to the Berlin definition (10) and the development of other pulmonary complications. Of the 935 patients enrolled, 282 (30.2 %) were at risk of developing ARDS. Median tidal volumes of 500 ml were used in both groups. There was no significant statistical difference in tidal volume

per kg IBW used among those at risk of developing ARDS and those not at risk (7.6 ml/kg versus 7.9 ml/kg IBW, respectively). However, approximately half of the patients received tidal volumes of >8 ml/kg IBW. Plateau pressures remained <30 cmH_2O in both groups. Between the patients at risk of developing ARDS and those not, higher respiratory rates, FiO_2 use, driving pressures and plateau pressures were used, which were all statistically significant. The most frequently used ventilatory modes were synchronised intermittent mandatory ventilation (26%) and pressure-control ventilation (23%). The number of patients who developed pulmonary complications, ARDS and pneumonia was significantly higher in those at risk of developing ARDS than those who were not. Patients at risk of developing ARDS had a longer duration of stay in both ICU and the hospital, and their 90-day mortality rates were significantly higher (26).

The 2018 PreVENT (27) trial assessed whether a low-tidal volume ventilation strategy had better outcomes versus an intermediate-tidal volume strategy. The low-tidal volume strategy aimed to ventilate with 4 – 6 ml/kg IBW using volume-controlled or pressure-support ventilation. In the intermediate tidal volume strategy, 10 ml/kg IBW was the starting point, and the tidal volume was weaned at 1 ml/kg per hour to maintain plateau pressures at less than 25 cmH_2O. At 28 days, there was no significant difference in ventilator-free days or hospital stay. Mortality rates at 28- and 90-days were also not significantly different between the two groups. There was no difference between the two groups when evaluating the development of pulmonary complications (27).

Respiratory rate

The role of respiratory rate in developing ARDS and ventilator-associated injuries has not been independently researched. It is known that repetitive stretch and collapse of the lungs can lead to lung injury. However, the degree of damage is thought to result from how much pressure is applied rather than the respiratory rate (28). A higher frequency of respiratory breaths can have beneficial effects by decreasing the expiratory time, leading to intrinsic PEEP, which can decrease the incidence of alveolar derecruitment (17).

PEEP

The 2000 ARDS Network (3) study provided the only evidence-based protocol for setting PEEP to date. The protocol tabulates PEEP and FiO_2 combinations that allow some atelectasis providing a given combination results in acceptable arterial oxygenation of 55 – 80 mmHg. A 2010 meta-analysis by Briel et al. (29) found evidence suggesting that higher PEEP levels than those described in the 2000 ARDSnet protocol (3) could improve both aeration of lung tissue and clinical outcome. The LUNGSAFE (14) trial in 2016 showed that higher airway pressures, lower PEEP and a higher respiratory rate, active neoplasms, chronic hepatic disease and older age were associated with higher mortality rates in patients with ARDS. Pettenuzzo et al. (30) in a 2021 meta-analysis of randomised controlled trials (RCTs), assessed the outcomes of 1 007 patients receiving higher (IQR 8 – 10 cmH_2O) versus 991 patients receiving lower PEEP (IQR 0 – 5 cmH_2O) levels in patients with ARDS. There was no significant difference in ICU or hospital mortality. The incidence of barotrauma, hypotension, ventilation duration and length of stay between the two groups were similar. However, among secondary outcomes, higher PEEP levels were associated with improved oxygenation, improved respiratory system compliance, decreased risk of hypoxaemia and lower risk of ARDS occurrence (30).

FiO_2/SaO_2

Hypoxaemia in critically ill patients is associated with multi-organ dysfunction and higher mortality rates (31,32). Oxygen therapy remains the mainstay of treating hypoxaemia in the hospital setting, especially in critically ill patients. However, hyperoxaemia can lead to numerous harmful effects, including atelectasis, interstitial fibrosis, inflammation of the tracheobronchial tree (33), decreased heart rate and cardiac output, increased systemic vascular resistance and a decrease in cerebral and coronary blood flow (34). There is a delicate balance between too little and too much oxygen administration. A 2019 systematic review and meta-analysis by Hirase et al. (35) comparing conservative (peripheral oxygen saturation 88-94% target) and conventional (minimum peripheral oxygen saturation 96-97%) oxygenation found significantly lower rates of ICU, 28-day and in-hospital mortality, as well as a significant decrease in new-onset non-respiratory

organ failure (35) in the conservative group. In 2022 a review by Young et al. (34) advised against the routine use of PaO_2 targets greater than 110 mmHg and less than 60 mmHg in adult ICU patients.

1.4.2 Ventilation in ARDS

Due to not all ARDS being the same, it remains unclear precisely what ventilation strategy is best for managing these patients (36). In 2019 Constantin et al. (36) attempted to tailor mechanical ventilation strategies to the patient's lung morphology and ARDS phenotype. The investigators personalised ventilation in moderate to severe ARDS patients. There was no significant change in mortality in this group versus the control group who received low tidal volume-based ventilation of $\leq$6 ml/kg IBW, PEEP/FiO_2, according to the ALVEOLI (37) study. The results of this trial were potentially influenced by the fact that the investigators misclassified lung morphology in 21% of the 400 patients in both control and study groups and therefore applied incorrect ventilation strategies for those patients. There was a significant increase in mortality in these misclassified patients, and in the correctly classified patients, there was a significant reduction in mortality (36).

1.4.3 Ventilatory adjuncts

Four of the most used ventilatory adjuncts, recruitment manoeuvres, prone positioning, neuromuscular blockade (NMB) and sedation, will be briefly discussed.

Recruitment manoeuvres

Alveolar recruitment improves hypoxaemia in patients and has been used in ARDS patients since the 1970s (38). Alveolar recruitment is achieved by either applying PEEP or lung recruitment manoeuvres, or both (17). As well as improving oxygenation, alveolar recruitment aims to decrease the risk of atelectrauma and ventilator-induced lung injury (37,39,40). In 2014, in a systematic review, Suzumura et al. (39) found a 6% improvement in mortality in moderate to severe ARDS patients who received alveolar recruitment manoeuvres. Lung recruitment manoeuvres are often incorporated to treat refractory hypoxaemia in critically ill patients (17). According to Bein et al. (17) the “simplest, tough smart open-lung

approach" is the lung recruitment manoeuvres described in the Express (40) study, whereby PEEP is increased in a stepwise manner to an end-expiratory plateau pressure of 30 – 32 cmH_2O while ventilating with low tidal volumes of 4 – 6 ml/kg IBW. De Matos et al. (41) proposed a very aggressive "open-lung" approach whereby PEEP is increased in a stepwise approach to 45 cmH_2O while ventilating the patient with tidal volumes of 10 – 15 cmH_2O. The assumption is that the open lung approach may lead to dramatic increases in oxygenation and decrease the incidence of ventilation-induced lung injuries (17).

Prone positioning

Clinical improvement in patients ventilated in the prone position can be explained by the physiological changes that occur in this position. (42). However, it remains unclear if patients with acute hypoxaemic respiratory failure benefit significantly from being ventilated in the prone position. In 2010, a review by Sud et al. (42) reported improvement in oxygenation in patients with acute hypoxaemic respiratory failure when proned versus when in the supine position. A significant improvement in oxygenation and mortality was found, but only in patients with severe hypoxaemia (PaO_2:FiO_2 <100). Furthermore, it was found that prone positioning decreased the development of ventilator-induced lung injury (42).

The 2013 PROSEVA (43) trial, a prospective, multicentre randomised controlled trial, explored whether the early application of prone positioning in patients who had developed ARDS (criteria of PaO_2:FiO_2 <150 and PEEP of 5 cmH_2O) improved survival. The authors showed a significant reduction in mortality at day 28 between proned (16%) and supine (32.8%) patients. A significant decrease in mortality at day 90 was also found. There was also a significant difference between successful extubation rates in the proned (80%) versus the supine (65%) patients (43). In the LUNGSAFE (14) trial, only 7.8% of the 2377 patients with ARDS were proned, of which almost two-thirds had severe ARDS (14). In the PreVENT (27) trial, 4.8% of the 961 patients were proned.

Neuromuscular blockade use

Early NMB infusions could have potential benefits in ARDS patients. In the 2010 ACURASYS (44) trial of 340 patients with severe ARDS, 178 patients (NMB

group) received early NMB after 48 hours of continuous infusion were compared to the 162 patients who received a placebo infusion. At 90 days, mortality was significantly decreased in those who received the early NMB infusion. Furthermore, the NMB group had more ventilator-free days and fewer incidences of pneumothorax. There was no significant difference in ICU-acquired weakness between the two groups.

In 2019 the PETAL Clinical Trials Network (45) designed a study similar to the 2010 ACURYSAS (44) trial. This study enrolled 1 006 patients after moderate to severe ARDS onset, with 501 of these patients receiving a continuous NMB infusion. There was no significant difference in mortality at 90 days versus the control group (505 patients) who received a placebo infusion. There was also no significant difference in ventilator-free days, days to hospital discharge or pneumothorax incidence between the two groups. In the LUNGSAFE (14) trial, NMB was only used in 516 out of the 2 377 patients, and of these patients, 53% had severe ARDS. In the PreVENT (27) trial, 113 patients out of 961 received a NMB infusion of longer than an hour.

Sedation in ICU

Mechanically ventilated patients are often agitated, restless and experience some form of discomfort. Sedation is used to try and decrease these symptoms (21). Undersedation and oversedation can both be problematic in these patients and lead to complications. These include prolonged ICU stay, increased need for mechanical ventilation, episodes of delirium and potentially increased mortality (21,46). A 2015 meta-analysis by Minhas et al. (21) compared protocolised sedation with non-protocolised usual sedation administration strategies. It was found that a protocol-based sedation strategy significantly reduced mortality, ICU length of stay, and the need for a tracheostomy. There was no significant difference in the duration of mechanical ventilation, reintubation or self-extubation rates and no difference in the incidence of delirium (21).

Olsen et al. (46) in 2020 compared light sedation to no sedation strategies in mechanically ventilated patients. Using the Richmond Agitation and Sedation Scale (47) to define light sedation as a score of -2 – -3, the authors found no

significant difference in 90-day mortality incidence. ICU and ventilator-free days did not differ significantly between the two groups. There was also no significant difference in the number of days free from coma or delirium between the two groups (46).

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Section 2: Author's guidelines

Southern African Journal of Critical Care

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must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org).

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  Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' – www.icmje.org.

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  Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'. Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and <) should be placed immediately preceding the relevant number, i.e. 'women >40 years of age'. The same applies to ± and °, i.e. '35±6' and '19°C'.

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Section 3: Draft article

Invasive mechanical ventilation practices in adult patients in three academic intensive care units

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Abstract

Background

Patients with, or at risk of developing, acute respiratory distress syndrome (ARDS) should be identified early, and lung-protective ventilation (LPV) instituted. This study aimed to describe invasive mechanical ventilation practices in adult patients at three academic intensive care units (ICUs) in Johannesburg from November 2021 to January 2022.

Methods

A point-prevalence, cross-sectional study using consecutive sampling.

Results

A total of 127 patients were included with a mean age of 40 (±15) years and 66.1% were male. Trauma-related causes (n=51, 40.2%) were the main indications for ventilation. Overall, 107 (84.3%) had risk factors for developing ARDS and 78 (61.4%) had PaO_2:FiO_2 $\leq$300. The most commonly used ventilatory mode was pressure support ventilation (n=62, 48.8%). Within the spontaneous ventilation group (n=62), 11 (17.7%) were ventilated with Vt $\leq$6 ml/kg IBW, 100% with PIP <30 cmH20, 98.3% with FiO_2 <0.6 and 29% had SpO_2 of 88 – 96%. In the controlled ventilation group (n=55), 7 (12.7%) of patients were ventilated with Vt $\leq$6 ml/kg IBW, 92.7% had PIP <30 cmH_20, 76.4% FiO_2 <0.6 and 27.3% had SpO_2 88 – 96%. Those with PaO_2:FiO_2 $\leq$300 had a mean PEEP of 8.6 cmH_2O and set FiO_2 of 0.45. In patients with PaO_2:FiO_2 >300, the mean PEEP was 8 cmH_2O with a set FiO_2 of 0.3. The mean Vt/kg IBW of 5.5 ml/kg IBW in patients who received $\leq$6 ml/kg IBW was significantly lower than 8.3 ml/kg IBW in those who were ventilated at >6 ml/kg IBW (p=0.0001).

Conclusion

In this study, a large proportion of patients suffered from acute hypoxaemic respiratory failure, with the vast majority at risk of developing ARDS. Given this profile of patients, compliance with the use of recommended LPV strategies was surprisingly low.

Introduction

The management of the critically ill patient involves a myriad of treatment modalities, all to support the patient's various organ systems and assist the body in optimising outcomes. One of the most common reasons patients are admitted to an intensive care unit (ICU) is for mechanical ventilatory support (1). There are many indications that necessitate the use of mechanical ventilation. These include acute respiratory failure, a significant change in mental status, cardiac arrest and neuromuscular disease affecting breathing mechanics (1,2). The main goals of ventilatory support are to reduce the work of breathing, treat significant hypoxaemia (1,3) and assist with the clearance of excessive carbon dioxide (3). Mechanical ventilation initially targeted the normalisation of arterial blood gas parameters (2,3), often using tidal volumes (Vt) as high as 10 – 15 ml/kg of body weight to achieve this (4). However, an enhanced appreciation of ventilator-induced lung injury has more recently seen a shift in focus toward minimising iatrogenic ventilator-induced lung injury with consequent alteration to acceptable targets of gas exchange (2,3,5,6). Patients receiving invasive mechanical ventilation are at risk of developing various pulmonary complications, such as ventilator-associated pneumonia, barotrauma, pulmonary oedema, pulmonary embolic events, alveolar collapse and acute respiratory distress syndrome (ARDS) (7).

The concept of ARDS was formally described in 1967 by Ashbaugh et al. (8) and remains an important focus in critical care (6). In 1994 a formal definition of ARDS was created by an American-European consensus team (9). In 2012 this definition was updated and referred to as the Berlin definition of ARDS (10). A small (n=53) 1998 randomised control trial by Amato et al. (5) was the first to successfully demonstrate a reduction in mortality of ARDS patients ventilated with a lung-protective strategy which consisted of: positive end-expiratory pressure (PEEP) titrated to the lower inflection point of the static pressure-volume curve, the use of Vt $\leq$6 ml/kg ideal body weight (IBW), driving pressure <20 cmH_2O, acceptance of permissive hypercapnia and preferential use of pressure limited ventilatory modes. This was followed in 2000 by the landmark multicentre ARDSnet ARMA (4) trial, which showed a 22% reduction in mortality using low Vt ventilation in isolation.

This has led to low Vt ventilation forming the cornerstone of lung-protective ventilation strategies. Additionally, the limitation of plateau pressures to <30 cmH_2O and fraction of inspired oxygen (FiO_2) concentrations, together with the application of a higher PEEP, have been proposed as vital components of lung-protective ventilation (3,4,5).

Inappropriate mechanical ventilation strategies are not only detrimental to already injured lungs (11), but can also lead to lung injury in healthy lungs in as little as 30 minutes of ventilation (2,11,12). From the 2016 global LUNGSAFE (13) study, it is clear that patients with ARDS are not all being ventilated in a way that is in keeping with lung-protective ventilation strategies. Mean tidal volumes used were in excess of 6 ml/kg IBW (7.6 ml/kg IBW, n=2 377), and PEEP levels were low for the high levels of FiO_2 used (13).

It is paramount that healthcare workers who ventilate patients do so for the right reasons and in the safest and most appropriate way for the patients' disease profiles. No published data regarding critically ill patient ventilation practices in South Africa could be identified. The aim of this study was to describe the invasive mechanical ventilation practices in adult patients in three academic ICUs in Johannesburg over three months.

Methods

A point prevalence cross-sectional study design was followed and included patients from 1 November 2021 to 31 January 2022. The University of the Witwatersrand Human Research Ethics Committee (Medical) approved the study (M200268).

The study population consisted of adult patients (18 years and older) receiving invasive mechanical ventilation for more than four hours, admitted to three selected academic multidisciplinary closed ICUs in Johannesburg. ICU A (18 bed) and C (10 bed) were medical, surgical and trauma units and ICU B was a 12 bed medical and surgical unit. As this was a point prevalence study, the sample size was realised by the number of mechanically ventilated patients during the study period. A consecutive convenience sampling method was used. Patients were

excluded if they had been ventilated for more than 72 hours before data collection or if consent was declined.

Data were collected by one author (GC). GC telephonically contacted all three ICUs daily. If eligible patients were admitted, data were then collected in person. Patients were only enrolled once. Consent was obtained from the patient (post-extubation in the ICU) or from the next of kin. This was done in person if a family member was present during data collection or telephonically due to Covid protocols that made family visiting hours challenging. Where a patient was not identifiable and no next of kin or identification information was available, consent was acquired from the head of that ICU.

Data were collected using a standardised data collection sheet based on the study objectives. In this study, a formal diagnosis of ARDS could not be made as all the data needed to do this were unavailable for each patient at the time of data collection. Missing data included radiology (chest X-Ray or computerised tomography scan of chest) not done or available for review at the time of data collection, and the timing of lung pathology (onset or worsening from baseline) was not documented to compare with. In this study, if patients were diagnosed with ARDS by the treating physician, this was captured. In patients with acute hypoxaemic respiratory failure where a diagnosis of ARDS was not documented in the patient's records, the Berlin definition (10) of ARDS severity stratification using the PaO_2:FiO_2 was used to classify the severity of acute hypoxaemic respiratory failure. Ventilation adjuncts included recruitment manoeuvres, proning of a patient and early neuromuscular blocker usage. Using the Richmond Agitation-Sedation Scale (RASS), sedation use and adequacy thereof were documented. IBW of the patient was determined using a tape measure to measure from the highest point on the head to the heel of the patient in the supine position and calculated as follows:

- men as 50 + (0.91 × [height in centimetres − 152.4]) and in
- women as 45.5 + (0.91 × [height in centimetres − 152.4]) (4).

For the purpose of this study, lung-protective ventilation was regarded as ventilation with a tidal volume of <6 ml/kg of IBW (4) aiming for a PIP of <30 cmH2O and making use of a conservative FiO2 strategy of <0.6 aiming for

peripheral oxygen saturation (SpO2) 88 – 96% (14,15). PIP was used as a surrogate for the conventional plateau pressure given that the non-interventional nature of the study precluded the necessary administration of sedatives and neuromuscular blocking agents prior to the performance of an inspiratory pause hold to determine the true plateau pressure. The author proposes that a PIP of <30 cmH20, in the absence of marked tachypnoea and obstructive lung disease, is likely to be associated with a plateau pressure of <30 cmH2O (16). Risk factors for developing ARDS were separated into direct and indirect. Direct risk factors included pneumonia, aspiration of gastric content, pulmonary contusion and drowning. Indirect risk factors included non-pulmonary sepsis, major trauma, pancreatitis, non-cardiogenic shock, drug overdose and transfusion-related lung injuries. Patients with an established diagnosis of ARDS were classified as mild, moderate or severe using the Berlin definition (10). Patients with acute hypoxaemic respiratory failure were classified using the PaO_2:FiO_2 as mild (>200 – $\leq$300), moderate (>100 – $\leq$200), or severe ($\leq$100) using criteria in keeping with the Berlin definition (10). Pressure support ventilation (PSV) was regarded as the only spontaneous ventilatory mode, and only pressure-assist control ventilation (PACV) and volume-assist control ventilation (VACV) were regarded as purely control ventilatory modes. During data collection, no changes were made if a concern with a specific patient's ventilation strategy was identified; however, the treating physician was informed.

Data were analysed using STATA version 15.0 (StataCorp, USA). Categorical variables were described using frequencies and percentages, and continuous variables using means and standard deviations or medians and interquartile ranges depending on the data distribution. Comparisons between groups were made using t-tests or Mann-Whitney tests. A p-value of <0.05 was considered statistically significant.

Results

Of the 138 patients screened for eligibility, 127 patients were included as 7 were extubated, 3 demised prior to data collection, and 1 patient declined consent.

The patient characteristics are shown in Table 1. Of the patients, 55 (43.3%) had documented co-morbidities, including 23 (18.1%) with hypertension and 13 (10.2%) with diabetes mellitus. Some patients had more than one reason for needing ventilation. The majority of patients were intubated and ventilated prior to ICU admission, with the mean time elapsed from ventilation initiation to data collection being 37.3 hours.

Table I: Patient characteristics

Characteristics	Mean	SD	Range
Age	40	15	18 – 86
Height measured (cm)			
Male	177.3	6.6	157.0 – 190.0
Female	164.3	6.1	147.0 – 176.0
Bodyweight (kg)			
Measured (n=22)	74.6	20.1	42.7 – 127.0
Estimated (n=105)	77.7	14.5	50.0 – 120.0
IBW (kg)	67.2	9.7	
Male	72.7	6.0	54.2 – 84.2
Female	56.3	5.6	40.6 – 67
	n	**%**	
Sex			
Male	84	66.1	
Female	43	33.9	
Indication for ventilation			
Altered mental state/airway protection	**57**	**44.9**	
Traumatic brain injury	18	31.6	
Neck trauma/surgery	9	15.8	
Drug/chemical overdose	18	31.6	
Non-traumatic brain injury	12	21.1	
Cardiac arrest	**7**	**5.5**	
Acute respiratory failure	**87**	**68.5**	
Pulmonary cause	17	19.5	
Non-pulmonary sepsis	23	26.4	
Trauma	44	50.6	
Neuromuscular	1	1.1	
Cardiac failure	2	2.3	
Post-operative ventilation	**1**	**0.8**	

Risk factors for developing ARDS are shown in Table 2. One hundred and seven (84.3%) patients had risk factors for developing ARDS. Of the 91 (71.7%) patients

who had indirect risk factors, 53 (58.2%) had 1 risk factor, 33 (36.3%) had 2 risk factors, and 5 (5.5%) had 3 risk factors.

Table 2: Risk factors for developing ARDS

Risk factors	n	%
Direct (39 risk factors)		
Pneumonia	12	30.8
Aspiration of gastric content	4	10.3
Pulmonary contusion	22	56.4
Drowning	1	2.6
Indirect (134 risk factors)		
Non-pulmonary sepsis	22	16.4
Major trauma	35	26.1
Pancreatitis	2	1.5
Non-cardiogenic shock	38	28.4
Drug overdose	17	12.7
TRALI*/multiple transfusions	20	14.9

*Transfusion-related lung injury

Arterial blood gas and oxygenation parameters are shown in Table 3.

Table 3: Arterial blood gas and oxygenation parameters

Parameters	Mean/Median	SD/IQR	Range
Arterial blood gas			
SpO_2 (%)	98	96 – 99	85 – 100
PaO_2 (mmHg)	97.3	23.5	54.8 – 194
$PaCO_2$ (mmHg)	41.2	12.2	16 – 121
pH	7.38	0.1	6.95 – 7.59
Base excess (mmol/L)	-1.1	6.1	-20.5 – 14.2
HCO_3 (mmol/L)	23.8	5.0	8.6 – 37.7
Oxygenation			
FiO_2	0.35	0.30 – 0.45	0.21 – 1.00
PaO_2:FiO_2	265	92	63 – 485

Using the PaO_2:FiO_2, 78 (61.4%) patients had acute hypoxaemic respiratory failure. Of these, 46 (59.0%) were mild, 26 (33.3%) were moderate and 6 (7.7%) were severe. Only 3 (2.4%) patients had ARDS as a diagnosis documented on their ICU charts.

The treating physicians used only 5 ventilatory modes. Across the whole cohort, mean tidal volume was 520 ml (± 123), mean Vt per kg IBW 7.9 ml/kg (± 2.1), mean FiO_2 0.4 (± 0.15), mean PaO_2:FiO_2 265 (± 62), mean PEEP 8 cmH_2O (± 2), mean PIP 20 cmH_2O (± 5), mean MAP 12 cmH_2O (± 3) and mean respiratory rate 19 breaths per minute (± 5). Ventilation parameters stratified by ventilator mode are presented in Table 4. There were only two patients ventilated with adjustable pressure release ventilation mode. Their tidal volumes were 390 ml and 780 ml, Vt per kg IBW 9.6 and 16 ml/kg, FiO_2 1.0 and 0.4, PaO_2:FiO_2 63 and 328, pressure low 2.2 and 0 cmH_2O, pressure high 33 and 27 cmH_2O, MAP 25 and 20 cmH_2O, respiratory rates 55 and 20 breaths/min, respectively. Only 5 (3.9%) patients met all the criteria of lung-protective ventilation. With regards to Vt/IBW-based ventilation, 21 (16.5%) patients received ≤6 ml/kg, 90 (70.9%) were ventilated with 6 – 10 ml/kg, 13 (10.2%) with 10 – 12 ml/kg and 3 (2.4%) with ≥12 ml/kg IBW. Those with PaO_2:FiO_2 ≤300 had a mean PEEP of 8.6 cmH_2O and set FiO_2 of 0.45. In patients with PaO_2:FiO_2 >300, mean PEEP was 8 cmH_2O with set FiO_2 of 0.3. The 4 patients ventilated with VACV all had plateau pressures less than 30 cmH_2O charted.

Table 4: Ventilator parameters by ventilator mode

Mode	Vt (ml)	Vt/IBW (ml/kg)	FiO2	PaO2:FiO2	PEEP (cmH2O)	PIP (cmH2O)	MAP (cmH2O)	Respiratory rate (breaths/min)
	Mean (SD) [Range]							
PACV (n=51, 40.2%)	505 (103) [320 – 84]	7.7 (1.5) [14 – 32]	0.4 (0.2) [0.24 – 1]	252.3 (87.7) [90 – 485]	8.9 (1.8) [6 – 14]	20.9 (4.2) [14 – 32]	13 (2.8) [8 – 23]	17 (4) [7 – 29]
VACV (n=4, 3.1%)	385 (39) [340 – 430]	6.1 (1.3) [4.6 – 7.4]	0.6 (0.1) [0.5 – 0.7]	129.1 (30.5) [97.1 – 157.1]	6.3 (2.9) [3 – 10]	26.5 (9.5) [16 – 35]	10.9 (3.3) [8 – 15]	18 (7) [8 – 23]
†SIMV-VC (n=8, 6.3%)	479 (77) [340 – 560]	7.5 (1.8) [5.9 – 11.1]	0.4 (0.2) [0.3 – 1]	278 (103.5) [83 – 435]	9 (1.5) [8 – 12]	24.9 (4.4) [18 – 32]	13.3 (2.7) [10 – 18]	20 (8) [10 – 36]
PSV (n= 62, 48.8%)	544 (136) [330 – 1100]	8 (2.3) [4.6 – 18.2]	0.4 (0.1) [0.2 – 0.6]	285.5 (86) [99.6 – 463.3]	8 (1.7) [4 – 12]	17.5 (4) (9 – 27)	10.7 (2.3) [5 – 15]	19 (5) [8 – 29]

†Synchronised intermittent mandatory ventilation with volume control

Table 5: Lung protective ventilation strategies

Lung protective ventilation strategies	n	%
Vt/kg IBW ≤6ml/kg	21	16.5
PIP <30 cmH_20	122	96.1
FiO_2 <0.60	112	88.2
SpO_2 88 – 96%	36	28.3
Spontaneous mode	62	48.8
Vt/kg IBW ≤6ml/kg	11	17.7
PIP <30 cmH_20	62	100
FiO_2 <0.60	61	98.4
SpO_2 88 – 96%	18	29.0
Control modes (PACV, VACV)	55	43.3
Vt/kg IBW ≤6ml/kg	7	12.7
PIP <30 cmH_20	51	92.7
FiO_2 <0.60	42	76.4
SpO_2 88 – 96%	15	27.3

The mean (SD, 95% CI) PIP for the spontaneous ventilation mode was 17.5 (4, 16.5 – 18.5), which was significantly lower than the control ventilation modes, 21.8 (4.9, 20.5 – 23) (p=0.0001). The mean (SD, 95% CI) Vt/kg IBW in spontaneous ventilation, 8 (2.3, 7.4 – 8.5), was not significantly higher than in control modes, 7.6 (1.5, 7.2 – 8) (p=0.32). The mean Vt/kg IBW in the group who received ≤6 ml/kg IBW, 5.5 (0.5, 5.3 – 5.8), was lower than in those who were ventilated at >6 ml/kg IBW, 8.3 (1.9, 7.9 – 8.7) (p=0.0001).

There was no documented use of neuromuscular blockade infusions post-intubation or recruitment manoeuvres done by clinicians, and none were proned. Sedative agents used in ICU were mainly midazolam 36 (28,3%), propofol 12 (9,4%), ketafol 7 (5,5%) and ketamine 3 (2,4%). Neither dexmedetomidine nor clonidine was used. The median (IQR) RASS was -3 (-4 – -2).

Discussion

In this study the mean age of patients was 40 years. This is lower than the 61.5, 68 and 65 years reported in the LUNGSAFE (13), PreVENT (17) and PROVENT (18) trials, respectively. The sex distribution favoured males (66.1%) and was similar to the other studies (13,17,18), as was the IBW of 67.2 kg (17,18). The

major indication for intubation and ventilation in this study was trauma-related (40.2%), which was higher than the 0.7% reported in the PreVENT (17) trial. Cardiac arrest (23.9%) and elective surgery (33.5%) were the main indications for intubation and ventilation in the PreVENT (17) and PROVENT (18) trials, respectively. The younger male population admitted to the ICUs in this study, with a high incidence of trauma-related need for intubation and ventilation, is indicative of the known trauma burden among younger males in South Africa (19,20).

The choice of ventilation mode varies internationally and appears to depend on the unit culture, the treating physician's preference and available technology. In this study, PSV was the most commonly used mode of ventilation (48.8%), followed by PACV (40.2%) and SIMV-VC (6.3%). The PreVENT (17) trial used mainly pressure-controlled (49.4%), volume-controlled ventilation (30.9%) and PSV (20%). The PROVENT (18) trial mainly used SIMV (26%), pressure-controlled ventilation (23%), and volume-controlled ventilation (14%) and only 9% used PSV. In this study, non-conventional modes were infrequently utilised.

As expected, the mean PIP in spontaneous ventilation modes was significantly lower (17.5 cmH_2O) than in control ventilation (21.8 cmH_2O) modes in this study. The mean PIP in this study was 20 cmH_2O. The PROVENT (18) and LUNGSAFE (13) trials reported a mean PIP of 20 cmH_2O and 27 cmH_2O, respectively. It is important to note that the LUNGSAFE trial included only patients with ARDS. Of the four patients ventilated in this study where plateau pressure could be measured, all four had a plateau pressure of less than 30 cmH_2O. Due to the non-interventional nature of this study, no inspiratory hold manoeuvres were done to assess plateau pressures in the other patients. However, due to the low occurrence of obstructive respiratory illnesses and mean respiratory rates of 19 breaths/min, a PIP of <30 cmH_20 was assumed to be associated with plateau pressures of <30 cmH_2O.

In this study, the mean Vt/kg IBW in ml/kg IBW was 8.0 in spontaneous ventilatory mode and 7.6 in control mode groups. This is similar to the PreVENT (17) trial, which reported approximately 7.2 ml/kg and the PROVENT (18) trial, which reported 7.7 ml/kg in control modes and 8 ml/kg in spontaneous modes. In the LUNGSAFE (13) trial, 7.5 and 7.9 ml/kg IBW were used in control and

spontaneous modes, respectively (13). This study's mean Vt/kg of IBW was not significantly higher in spontaneous modes than in control modes, similar to some international studies (13,17,18). Two patients being ventilated with Vt/kg IBW higher than 12 ml/kg (13.1 and 18.2 ml/kg IBW) were receiving spontaneous ventilation and were at increased risk of developing lung injury (4). Of the patients ventilated with Vt/kg IBW above 10 ml/kg, 12 patients were ventilated with spontaneous ventilation, and 3 patients with control modes. Of this group, eight patients had acute hypoxaemic respiratory failure, and all 15 had risk factors for developing ARDS. These patients, already at risk of having or developing lung injury, were exposed to potentially injurious ventilation strategies. Neither transpulmonary nor driving pressures could be measured in this study. Patients receiving spontaneous ventilation, on average, received Vt of 544 ml, with those receiving controlled ventilation receiving 496 ml. In spontaneous mode ventilation, the cumulative transpulmonary pressure across the alveoli is a combination of set pressures and patients' pleural pressures. At high Vt ventilation, more strain is placed on the lungs, with transmural pressure elevated in patients taking large spontaneous breaths while being mechanically ventilated. (21)

Due to the limitations of diagnosing ARDS in this study, PEEP and FiO_2 were analysed in patients with acute hypoxaemic respiratory failure (PaO_2:FiO_2 $\leq$300) and those with a PaO_2:FiO_2 >300. Those with PaO_2:FiO_2 $\leq$300 had a mean PEEP of 8.6 cmH_2O with an associated set FiO_2 of 0.45. The LUNGSAFE (13) trial reported a mean PEEP of 8.4 cmH_2O and FiO_2 of 0.65. The set PEEP and FiO_2 in this study were in keeping with the ARDSnet ALVEOLI (22) protocol recommendations, namely a PEEP of 8 cmH_2O with a FiO_2 0.4 – 0.5 and a PEEP of 10 cmH_2O with a FiO_2 0.5 – 0.7 combination. In patients with PaO_2:FiO_2 >300, the mean PEEP was 8 cmH_2O with FiO_2 of 0.3. This is in contrast to the set PEEP and FiO_2 in the PreVENT (17) trial (7 cmH_2O and 0.50), PROVENT (18) trial (5 cmH_2O and 0.50) and the 2020 RELAx (23) trial. In the RELAx trial, lower (mean 5 cmH_2O) was compared with higher (mean 7 cmH_2O) PEEP strategies with a mean FiO_2 of 0.5 for both groups. The use of higher PEEP (8 – 10 cmH_2O) is associated with better oxygenation, decreased incidence of hypoxaemia and a lower risk of ARDS development (24).

In this study, a higher PEEP with a lower associated mean FiO_2 was used, which is in keeping with the aims of LPV. However, the median SpO_2 in this study was 98%. Only 28.3% of patients had a SpO_2 of <96%, suggesting room for further reductions in ventilatory support either in the magnitude of applied PEEP, the FiO_2, or both. Therefore, even lower FiO_2 could have been used for patients in this study, which would have resulted in the more conservative SpO_2 goal of LPV. Within the spontaneous mode ventilation group (n=62), 17.7% were ventilated with Vt $\leq$6 ml/kg IBW, 100% with PIP <30 cmH20, 98.4% with FiO_2 <0.6 and 29% had SpO_2 of 88 – 96%. In the control mode ventilation group (n=55), 12.7% of patients were ventilated with Vt $\leq$6 ml/kg IBW, 92.7% had PIP <30 cmH_20, 76.4% FiO_2 <0.6 and 27.3% had SpO_2 88 – 96%. LPV in the control mode ventilation group is where treating physicians have more control in choosing and adjusting ventilator settings. It is of note that such a low portion of patients received $\leq$6 ml/kg IBW, especially since the mean PaO_2:FiO_2 in the control mode ventilation group was 243, indicative of a high likelihood that these patients were candidates for low Vt/kg IBW ventilation.

Using PaO_2:FiO_2 ratios in keeping with the Berlin definition (10), 61.4% of patients in this study had acute hypoxaemic respiratory failure and 84.3% had risk factors for developing ARDS. Despite the very low rate of ARDS diagnoses within the cohort, it is plausible that many patients may have had ARDS at enrolment, which is concerning, particularly given the low rate of low Vt ventilation observed. If the actual rate of ARDS was higher than the diagnosed rate, it is crucial to investigate possible reasons for the low diagnostic rates, given the potential impact on patient outcomes.

This study gave insight into ventilation practices in these three ICUs and it cannot be generalised to other units. ARDS could not be formally diagnosed; therefore, the incidence of potentially having ARDS was estimated and assumed based on PaO2:FiO2 only, which could have resulted in an overestimation. Another limitation is that PIP was used as a surrogate for the conventional plateau pressure, which is not traditionally utilised to ensure lung protective ventilation. This study represents a snapshot of practice, which may not necessarily

encompass the full spectrum of ventilatory practice applied to each individual patient and collectively.

It is recommended that an evidence-based ventilatory strategy education programme be implemented in the study ICUs, with regular follow-up audits in these units to monitor adherence. Furthermore, it is recommended that other units in South Africa evaluate their ventilatory practices.

Conclusion

In this study, a large proportion of patients suffered from acute hypoxaemic respiratory failure, with the vast majority at risk of developing ARDS. Given this profile of patients, compliance with the use of recommended LPV strategies was surprisingly low.

Conflict of interest

The authors declare that we have no financial or personal relationships, which may have inappropriately influenced us in writing this paper.

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Section 4: Proposal

Invasive mechanical ventilation practices in adult patients in three academic intensive care units

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4.1 Introduction and problem statement

The management of the critically ill patient involves a myriad of treatment modalities, all with the aim to support the patient's various organ systems and assist the body in optimising outcomes. One of the most common reasons patients are admitted to an intensive care unit (ICU) is for mechanical ventilatory support (1). There are many indications that necessitate the use of mechanical ventilation. These include acute respiratory failure, a significant change in mental status, cardiac arrest and neuromuscular disease affecting breathing mechanics (1,2). The main goals of ventilatory support are to reduce the work of breathing, treat significant hypoxaemia (1,3) and assist with the clearance of excessive carbon dioxide (3). Mechanical ventilation initially targeted the normalisation of arterial blood gas parameters (2,3), often using tidal volumes (Vt) as high as 10 – 15 ml/kg of body weight to achieve this (4). However, an enhanced appreciation of ventilator-induced lung injury has more recently seen a shift in focus toward minimising iatrogenic ventilator-induced lung injury with consequent alteration to acceptable targets of gas exchange (2,3,5,6). Patients receiving invasive mechanical ventilation are at risk of developing various pulmonary complications, such as ventilator-associated pneumonia, barotrauma, pulmonary oedema, pulmonary embolic events, alveolar collapse and acute respiratory distress syndrome (ARDS) (7).

The concept of ARDS was formally described in 1967 by Ashbaugh et al. (8) and remains an important focus in critical care (6). In 1994 a formal definition of ARDS was created by an American-European consensus team (9). In 2012 this definition was updated and was referred to as the Berlin definition of ARDS (10). A small (n=53) 1998 randomised control trial by Amato et al. (5) was the first to successfully demonstrate a reduction in mortality of ARDS patients ventilated with a lung-protective bundle strategy which consisted of: positive end-expiratory pressure (PEEP) titrated to the lower inflection point of the static pressure-volume curve, the use of Vt $\leq$6 ml/kg ideal body weight (IBW), driving pressure <20 cmH_2O, acceptance of permissive hypercapnia and preferential use of pressure limited ventilatory modes. This was shortly followed by the landmark multicentre ARDSnet ARMA trial (4), which showed a 22% reduction in mortality using low Vt

ventilation in isolation. This has led to low Vt ventilation forming the cornerstone of lung-protective ventilation strategies. Additionally, the limitation of plateau pressures to <30 cmH_2O and fraction of inspired oxygen concentrations (FiO_2) together with the application of PEEP have been proposed as vital components of lung-protective ventilation (3,4,5)).

Inappropriate mechanical ventilation strategies are not only detrimental to already injured lungs (11), but can also lead to lung injury in healthy lungs in as little as 30 minutes of ventilation (2,11,12). From the 2016 global LUNGSAFE study (13), it is clear that patients with ARDS are not all being ventilated in a way that is in keeping with lung-protective ventilation strategies. Mean tidal volumes used were in excess of 6 ml/kg IBW (7.6 ml/kg IBW, n=2 377), and PEEP levels were low for the high levels of FiO_2 used (13).

It is paramount that health care workers who ventilate patients do so for the right reasons and in the safest and most appropriate way for the patients' disease profiles. No published data regarding critically ill patient ventilation practices in South Africa could be identified. The aim of this study was to describe the invasive mechanical ventilation practices in adult patients at three academic ICUs in Johannesburg over three months. The primary objectives of this study were to determine the: indication for ventilation, patient and ventilation parameters, risk factors for developing ARDS and likely presence of ARDS, use of ventilation adjuncts and if IBW based ventilation was used. The secondary objective was to compare the Vt per kg IBW between patients receiving lung-protective ventilation and those not and peak inspiratory pressure (PIP) and PEEP between those receiving controlled mechanical ventilation and those receiving spontaneous ventilation modes.

4.2 Aim and objectives

4.2.1 Aim

The aim of this study is to describe the invasive mechanical ventilation practices in adult patients at three academic ICUs in Johannesburg over three months.

4.2.2 Objectives

The primary objectives of this study are to determine the:

- indication for ventilation
- causes of acute hypoxaemic respiratory failure
- patient parameters
- mode of ventilation
- ventilation parameters
- presence of ARDS and risk factors
- use of ventilation adjuncts
- use of IBW based ventilation.

The secondary objective of this study is to compare:

- tidal volume per kg IBW between patients receiving lung-protective ventilation and those not
- peak inspiratory pressure (PIP) and PEEP between those receiving controlled mechanical ventilation and those receiving spontaneous ventilation modes

4.3 Research assumptions

The following definitions will be used in this study.

Adult: is a person 18-years and older.

ARDS diagnostic criteria: in this study are radiological evidence of bilateral pulmonary infiltrates, respiratory failure not completely explained by fluid overload or cardiac failure, and a PaO_2:FiO_2 <300 with a PEEP $\geq$5 cmH_2O (14).

Ventilation adjuncts: in this study, these will include recruitment manoeuvres, proning of a patient, early neuromuscular blocker usage, sedation use and adequacy thereof using the Richmond Agitation-Sedation Scale (RASS).

IBW: in this study ideal body weight is calculated as follows:

- men as 50 + (0.91 × [height in centimetres − 152.4]) and in

- women as 45.5 + (0.91 × [height in centimetres − 152.4]) (4).

Lung protective ventilation: in this study is ventilation with a tidal volume of ≤6 ml/kg of IBW aiming for a peak inspiratory pressure of <30 cmH_2O (4) and making use of a conservative FiO_2 strategy of <0.6 aiming for SpO_2 88 – 96% (15,16).

4.4 Demarcation of study field

The study will be conducted in ICUs of three academic hospitals affiliated with the University of the Witwatersrand.

- Chris Hani Baragwanath Academic Hospital (CHBAH) is a 2 888-bed central hospital. The general ICU is a multidisciplinary unit with 18 beds for adults and 9 beds for paediatric patients.
- Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is a 1 200-bed central hospital. The general ICU is a multidisciplinary unit with 12 beds for adults.
- Helen Joseph Hospital (HJH) is a 500-bed tertiary hospital. The ICU is a multidisciplinary unit with 10 beds for adults.

4.5 Ethical considerations

Approval to conduct this study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand. Further approval will be obtained from the Medical Advisory Committee of CHBAH, the CEO of CMJAH and the HJH Research Committee (Appendix 1). Approval has been obtained from the Heads of ICU at CHBAH, CMJAH and HJH (Appendix 2).

The researcher will approach patients who qualify for the study, and if they can provide consent, the details of the study will be explained, and they will be given an information letter (Appendix 3A). Informed consent will be obtained from those patients who agree to participate (Appendix 4A). If the patient is unable to provide consent, the surrogate decision-maker will be approached and asked if their family member can be included in the study. If they agree, the study will be explained, and they will be given an information letter (Appendix 3B). Informed consent will

be obtained from the surrogate decision-maker (Appendix 4B). The National Health Act defines a surrogate decision-maker in this order: a spouse or partner, parent, grandparent, an adult child or sibling (17). When the patient can give consent, the patient will be approached, and it will be explained to them that consent was given on their behalf. The details of the study will be explained, and they will be given an information letter (Appendix 3C). Deferred consent will then be obtained from the patient if they agree to their inclusion in the study (Appendix 4C). If the patient is not willing to participate in the study, their decision will not influence the standard of medical care, and their information will not be used. Where a patient is not identifiable, and no next of kin or identification information is available, consent will be acquired from the head of that ICU.

Anonymity will be ensured by collecting data without any identifying information. Each patient will receive a study number. A list with the patient's name, hospital number and study number will be generated and filed separately. Confidentiality will be ensured as only the researcher and supervisors will have access to the raw data.

If it is identified that a patient is being ventilated inappropriately, the doctor in charge of the patient will be informed at that time.

Data will be documented and saved in a password-protected electronic database and will be stored for a minimum of six years after the completion of this study. The study will be conducted according to the principles of the Declaration of Helsinki (18) and the South African Guidelines for Good Clinical Practice (19).

4.6 Research methodology

4.6.1 Research design

This will be a cross-sectional study design – a type of observational study that samples and compares data from different population groups at a point in time (20,21). In this study, the ventilator practices of adult patients in three academic ICUs will be observed and described at one point in time.

4.6.2 Study population

The study population will consist of adult patients receiving invasive mechanical ventilation admitted to the three selected ICUs in CHBAH, CMJAH and HJH at a point in time.

4.6.3 Sample size

This is a point prevalence study. Therefore, the sample size will be realised by the number of mechanically ventilated patients during the study period.

4.6.4 Sampling method

In this study, a consecutive convenience sampling method will be used. Consecutive convenience sampling is used as every available patient receiving invasive mechanical ventilation will be included (22). This will be done by the researcher contacting all three ICUs daily to find out whether any eligible patients have been admitted. If so, the ICUs will be visited daily, if need be, to perform the data collection with necessary consent in place.

4.6.5 Inclusion and exclusion criteria

The inclusion criteria for this study are:

- adult patients 18 years and older
- receiving invasive mechanical ventilation
- for more than four hours.

The exclusion criteria in this study are:

- patients ventilated for more than 72 hours at the time of data collection
- consent declined
- patients previously enrolled in the study.

4.6.6 Data collection

Once the appropriate approvals are in place, data collection will start. Data will be collected by the researcher only. All three ICUs will be contacted daily. If eligible

patients are admitted, the researcher will visit those ICUs daily, if need be, in order to collect the data. Patients will only be enrolled once in the study, regardless of the length of ICU stay. Consent will be obtained, as described in section 1.5. The researcher will use a research assistant in each of the ICUs to assist with obtaining consent.

The following data will be collected using a standardised data collection sheet. (Appendix 5)

- demographics
- indication for ventilation
- causes of acute hypoxaemic respiratory failure
- patient parameters
- mode of ventilation
- ventilation parameters
- presence of ARDS and risk factors
- ventilation adjuncts
- use of IBW based ventilation
- use of lung-protective ventilation.

In order to determine the IBW of the patient, the patient's height will be measured in the supine position using a tape measure, from the highest point on the head to the heel.

During data collection, if it is identified that a patient is being ventilated inappropriately, no changes will be made by the researcher, and the doctor in charge of the patient will be informed at that time.

4.6.7 Data analysis

Data will be entered onto a Microsoft Excel spreadsheet and analysed in consultation with a biostatistician using the statistical program STATA version 15.0 (StataCorp, USA). Categorical variables will be described using frequencies and percentages, and continuous variables using means and standard deviations or medians and interquartile ranges depending on the distribution of the data.

Comparisons between groups will be made using t-tests or Mann-Whitney tests. A p-value of <0.05 will be considered statistically significant.

4.7 Significance of the study

From the 2016 global LUNGSAFE (13) trial, it is evident that appropriate ventilation practices are not always used, even in patients with significant lung pathology. The ARDSnet ARMA (4) trial of 2000 showed significant improvement in patient outcomes by using lung-protective ventilation strategies. Therefore, it is essential to know how patients are being ventilated.

The results of this study will give insight into the appropriateness of the invasive mechanical ventilation practices in the three ICUs. If the practices are not appropriate, the results of the study may be used to motivate for initiatives such as education and training to ensure safe mechanical ventilation practices.

4.8 Validity and reliability of the study

Validity is the extent to which the research design and method truly represent the phenomenon being studied. Reliability refers to the consistency and repeatability of the measurements obtained (20).

The validity and reliability of this study will be ensured by:

- using an appropriate research design
- one researcher collecting data using a standardised data collection sheet
- analysing data in consultation with a biostatistician.

4.9 Potential limitations

The study will be done contextually in three academic ICUs in Johannesburg and may not be generalisable to invasive mechanical ventilation practices in other settings.

Data will be collected at one point in time only for each patient and may not reflect the longer-term ventilation practice of the patient.

Accurate plateau pressure is unlikely to be documented due to the non-interventional nature of this study.

4.10 Project outline

4.10.1 Time frame

Activity	Jan - March 2020	Apr - June 2020	Jul - Sept 2020	Oct - Dec 2020	Jan - March 2021	Apr - Oct 2021	Nov - Jan 2021-22	Feb – June 2022
Proposal preparation								
Literature review								
Proposal submission								
Postgraduate approval								
Ethics approval								
Data collection								
Data analysis								
Draft article								
Submission								

4.10.2 Budget

Item	Price/page	No of pages	Copies	Total
Proposal	R1	15	6	R90
Cover letter	R1	1	6	R6
Postgraduate form	R1	2	6	R 12
Complete report	R1	80	4	R320
Consent forms	R1	1	300	R300
Information letter	R1	1	300	R300
Data capture sheet	R1	3	150	R450
Phoning of patients/family				R600
Grand total				**R 2 078**

The Department of Anaesthesiology will incur the costs of paper and printing of the postgraduate application forms, consent, and information letters.

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4.12 Appendices

Appendix 1A: Study information letter (Patient)

Invasive mechanical ventilation practices in adult patients in the ICUs of three academic hospitals.

Dear Patient

Hello, my name is Gerhard Coetzee. I am studying at the University of the Witwatersrand in Johannesburg to become an anaesthesiologist. An anaesthesiologist is a doctor that puts patients to sleep for an operation and ensures that the patient is pain-free, comfortable, and safe at all times during the operation. Part of my studies requires that I do a research project. We do research so that we can improve on how we care for patients.

My research project will be looking at how we assist very ill patients when they need a machine to help them breathe so that we can help their bodies rest. I want to know if you would be willing to take part in my study so that we can understand better, and over time ensure that we are doing the best we can to help you.

I will need you, if you agree to this, to sign a consent form granting me permission to record the necessary information I need. Your information will be kept confidential at all times, and I will provide you with a unique study number, the details of which will only be known to me.

In no way will I potentially bring harm to you during this process. By granting me permission to collect this data, you will be helping me with my research so that we can find out if we are doing the best that we can to help you and further improve in order to provide better care to our patients.

If you do not agree to this, your care will not be affected in any way. You can withdraw the permission you gave me to record the information at any time, and you will not be harmed in any way. There will be no payment given for being involved in this study.

This study has been approved by the Human Research Ethics Committee (medical) and the Graduate Studies Committee of the University of the Witwatersrand. If you have any questions about this study, you may contact me on 011 488 4344. If you have any concerns over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za.

By signing your name on the consent form, it means that you agree that I use your information in the study.

Thank you for your time and for reading this study information sheet.

Kind regards

Dr Gerhard Coetzee

Appendix 1B: Study information letter (Family member)

Invasive mechanical ventilation practices in adult patients in the ICUs of three academic hospitals.

Hello, my name is Gerhard Coetzee. I am studying at the University of the Witwatersrand in Johannesburg to become an anaesthesiologist. An anaesthesiologist is a doctor that puts patients to sleep for an operation and ensures that the patient is pain free, comfortable, and safe at all times during the operation. Part of my studies requires that I do a research project. We do research so that we can improve on how we care for patients.

My research project will be looking at how we assist very ill patients when they need a machine to help them breathe so that we can help their bodies rest. I want to know if you would be willing to allow your family member to be part of this study, so that we can understand better, and over time ensure that we are doing the best we can to help your family member.

I will need you, if you agree to this, to sign a consent form granting me permission to record the necessary information I need. Your family member's information will be kept confidential at all times, and I will provide your family member with a unique study number, the details of which will only be known to me.

In no way will I potentially bring harm to your family member during this process. By granting me permission to collect this data, you will be helping me with my research so that we can find out if we are doing the best that we can to help your family member and further improve in order to provide better care to our patients.

If you do not agree to this, your family member's care will not be affected in any way. You can withdraw the permission you gave me to record the information at any time, and again, your family member will not be harmed in any way. There will be no payment given for being involved in this study.

This study has been approved by the Human Research Ethics Committee (medical) and the Graduate Studies Committee of the University of the

Witwatersrand. If you have any questions about this study, you may contact me on 011 488 4344. If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za.

By signing your name on the consent form, you agree that I use your family member's information in the study.

Thank you for your time and reading this study information letter.

Kind regards

Dr Gerhard Coetzee

Appendix 1C: Study information letter (Deferred consent)

Invasive mechanical ventilation practices in adult patients in the ICUs of three academic hospitals.

Hello, my name is Gerhard Coetzee. I am studying at the University of the Witwatersrand in Johannesburg to become an anaesthesiologist. An anaesthesiologist is a doctor that puts patients to sleep for an operation and ensures that the patient is pain free, comfortable, and safe at all times during the operation. Part of my studies requires that I do a research project. We do research so that we can improve on how we care for patients.

My research project will be looking at how we assist very ill patients when they need a machine to help them breathe so that we can help their bodies rest.

While you were asleep and very ill, one of your family members granted me permission to collect your information to include in my study. I want to know if you are willing to allow me to use your information, so that we can understand better and over time ensure that we are doing the best we can to help you.

I will need you, if you agree to this, to sign a consent form granting me permission to keep your information and include it in this study. Your information will be kept confidential at all times, and I will provide you with a unique study number of which the details will only be known by me.

In no way did I bring harm to you during this process. By granting me permission to collect this data, you will be helping me with my research so that we can find out if we are doing the best that we can to help you and further improve in order to provide better care to our patients.

If you do not agree to this, the rest of your care will not be affected in any way. You can withdraw the permission you gave me to record the information at any time and no harm will come to you. There will be no payment given for being involved in this study.

This study has been approved by the Human Research Ethics Committee (medical) and the Graduate Studies Committee of the University of the

Witwatersrand. If you have any questions about this study, you may contact me on 011 488 4344. If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za.

By signing your name on the consent form, it means that you agree that I use your information in the study.

Thank you for your time and for reading this study information sheet.

Kind regards

Dr Gerhard Coetzee

Study No:

Date:

Appendix 2: Patient Data Collection Sheet

Demographics		
Age (years)		
Sex (M/F)		
Height (cm)		
Body weight (kg) [Measured (M) or Estimated (E)]	**M:**	**E:**
IBW (kg)		
Time since ventilation initiation (hours)		
Co-morbidities	Yes	No
If yes, Specify:		

	Indication for ventilation	Tick
A	**Airway compromise**	
B	**Altered mental status**	
	1. Traumatic brain injury	
	2. Drug/chemical overdose	
	3. Non-traumatic brain injury	
C	**Cardiac arrest**	
D	**Acute respiratory failure**	
	1. Pulmonary cause	
	2. Non-pulmonary sepsis	
	3. Trauma	
	4. Neuromuscular	
	5. Cardiac failure	
E	Other	

Acute hypoxaemic respiratory failure causes	Tick
Pneumonia	
Cardiac failure	
Asthma	
ARDS	
COPD	
Unknown	
Other	

ARDS Risk Factor			
Direct		**Indirect**	
Pneumonia		Non-pulmonary sepsis	
Aspiration of gastric content		Major trauma	
Inhalational injury		Pancreatitis	
Pulmonary contusion		Severe burns	
Pulmonary vasculitis		Non-cardiogenic shock	
Drowning		Drug overdose	
		TRALI/multiple transfusions	
Other			

Patient Parameters	
SaO_2	
PaO_2	
$PaCO_2$	
pH	
Base excess	
HCO_3	

Ventilation Parameters		
Ventilation mode		
Respiratory rate set		
Respiratory rate (total)		
Tidal volume (V_T) (ml)		
V_T/kg IBW		
PIP (cmH_2O)		
Plateau pressure (cmH_2O)		
MAP (cmH_2O)		
Inspiratory pause (Y/N)		
Flow time curve (PIP vs P_{Plat})	**=**	**>**
PEEP (cmH_2O)		
FiO_2		
I:E		
T_{insp} (s)		

Adjuncts	Yes	No
Recruitment manoeuvre		
Neuromuscular blockade		
Proning		
Sedation used		
Sedation agent used and dose interval		
RASS		

Lung Protective Ventilation	Yes	No
V_T/kg IBW $\leq$6 ml/kg		
Plateau Pressure <30 cmH2O		

IBW based ventilation	Yes	No

Section 5: Annexures

5.1 Ethics approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr G Coetzee

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200268

NAME: (Principal Investigator)	Dr G Coetzee
DEPARTMENT:	School of Clinical Medicine Department of Anaesthesiology Medical School University
PROJECT TITLE:	*Invasive mechanical ventilation practices in adult patients in three academic ICUs*
DATE CONSIDERED:	2020/02/28
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Ms H Perrie, Prof J Scribante & Dr K Naidoo
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/02/25

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **«Missing mail merge field»** and therefore reports and re-certification will be due in the month of **«Missing mail merge field»** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

07/03/2021
Date

5.2 Graduate studies approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

28 June 2020
Person No: 2246132
PAG

Dr GJ Coetzee
Unit 27
Parkview Manor
7 Lower Park Drive
Parktown
2193
South Africa

Dear Dr Gerhard Coetzee

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Invasive mechanical ventilation practices in adult patients in three academic intensive care units* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

5.3 Turnitin report

31052022 GJ Coetzee MMED Turnitin Sections-1.docx

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