

SCHOOL OF MEDICINE



Airway Pressure Release Ventilation Mode in Lung Injury

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Abstract

Airway pressure release ventilation (APRV) is a promising, unconventional mode of ventilation for the treatment of various respiratory diseases, including acute respiratory distress syndrome (ARDS). However, despite increasing global use and reported advantages of APRV over other modes, definitive conclusions cannot be drawn due to several concerns. First, the major confusion between APRV and other, similar modes, such as bi-phasic positive airway pressure (BIPAP). Second, clinical and methodological heterogeneity among published studies of APRV are understandably extensive, which contributes to outcome variability. Third, the absence of consensus on a standard protocol with clear rationale for the settings.

This thesis provides an overview of the spectrum of ventilator settings that may be designated as APRV, summarises the research and clinical use status of APRV, exemplifies the need to clarify the characteristics that comprise the mode, and to assure reports of APRV use, from case reports through RCTs, including adequate data for a proper assessment. It encourages continued publication of observational as well as experimental clinical trial data, and discusses the feasibility of analysis strategies that may expand the information available from small patient samples. It also presents an unpublished, comprehensive, multifaceted clinical practice protocol (Al-ahmad protocol) for the use of APRV.

Using the Al-ahmad protocol, four studies were conducted on non-spontaneously breathing patients who had ARDS (arising from a variety of

pathologies). One study used a validated physiological simulator called integrated cardiopulmonary models (ICPMs) while the other three, were prospective cohort observational studies on real patients. The first study evaluated patients' responses to changes in inspiratory pressure during conventional ventilation (CV) and APRV modes, using ICPMs vs. a real patient. The second study compared partial pressure of carbon dioxide (PaCO_2) at any given ventilatory minute ventilation (M_v) during CV and APRV. The third study aimed to identify proper configurations to optimise PaCO_2 on patients with diverse pulmonary pathologies including restrictive (e.g. ARDS) and obstructive (e.g. chronic obstructive pulmonary disease) when using APRV. The fourth study compared oxygenation and haemodynamic status during CV and APRV.

Results from ICPMs appeared to be analogous for both modes except for the significant difference in M_v and tidal volume observed in the simulated vs. real APRV patients. We found in our clinical studies that compared to conventional modes, APRV was associated with significantly lower PaCO_2 at significantly lower levels of M_v , better oxygenation, and haemodynamic status.

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Contents

ACKNOWLEDGEMENT	III
CONTENTS	II
LIST OF TABLES	III
LIST OF FIGURES.....	IV
LIST OF ABBREVIATIONS.....	V
	1
1.1 INTRODUCTION	1
1.2 LITERATURE REVIEW	13
1.3 HAS THE DURATION OF MV EVER BEEN INVESTIGATED IN PROSPECTIVE CLINICAL TRIALS?	32
1.4 WHAT IS THE SITUATION OF APRV IN CLINICAL PRACTICE?	52
1.5 ONGOING STUDIES	54
1.6 CONCLUSION	59
1.7 QUESTION.....	62
1.8 PRIMARY OUTCOMES	62
1.9 SECONDARY OUTCOMES	62
1.10 INTRODUCTION	62
1.11 METHOD	63
1.12 RESULTS	68
1.13 DISCUSSION	78
1.14 CONCLUSION	81
1.15 HYPOTHESIS:	84
1.16 RESEARCH QUESTION IS:.....	84
1.17 INTRODUCTION	84
1.18 METHODS	86
1.19 STATISTICAL ANALYSIS:	90
1.20 RESULTS	91
1.21 DISCUSSION	92
1.22 CONCLUSION	96
1.23 BACKGROUND	98
1.24 AIM	100
1.25 PATIENTS AND METHOD	100
1.26 STATISTICAL ANALYSIS	103
1.27 RESULTS	104
1.28 DISCUSSION:	119
1.29 CONCLUSION	120
1.30 HYPOTHESIS:	123
1.31 RESEARCH QUESTION	123
1.32 PRIMARY OUTCOMES	123
1.33 SECONDARY OUTCOMES	123
1.34 INTRODUCTION	123
1.35 METHODS	125
1.36 RESULTS	130
1.37 DISCUSSION	136
1.38 CONCLUSION	144
1.39 <i>PREVALENCE OF APRV USE IN REAL WORLD PATIENTS</i>	154
1.40 ANALYSIS STRATEGIES TO ENHANCE CONTRIBUTION OF SMALL AND OBSERVATIONAL STUDIES.....	159

1.41	PROPENSITY SCORE ANALYSIS.....	159
1.42	INDIVIDUAL PATIENT DATA META-ANALYSIS	160
1.43	NETWORK META-ANALYSIS.....	161
1.44	THESIS CONTRIBUTION TO THE EXISTING KNOWLEDGE.....	162
1.45	POTENTIAL AREAS FOR FUTURE RESEARCH PROJECTS.....	164
1.46	CONCLUSION	166
REFERENCES		170

List of Tables

Table 1 Comparison of ventilatory modes and outcomes.....	22
Table 2 Comparison of duration of mechanical ventilation and ICU, length of stay (LOS) ...	33
Table 3 Mode of MV and persistence of spontaneous breaths in the studies that were compared.....	35
Table 4 Some indicators of the severity of illness	38
Table 5 ISS and APACHE II in the three studies	38
Table 6 Comparison of the studies conducted by Varpula, Putensen, and Maxwell.....	46
Table 7 Comments on the studies conducted by Varpula, Putensen, and Maxwell	49
Table 8 Some commonalities in APRV application that have been suggested to be associated with positive outcomes	51
Table 9 Ongoing APRV Trials	56
Table 10 Physiological and initial mechanical ventilator sittings on the conventional mode for the virtual patient used in this investigation	66
Table 11 Model configurations for V/Q mismatch in both modes	66
Table 12 variables to be adjusted on APRV and conventional modes during examination	66
Table 13 Physiological and initial mechanical ventilator sittings upon switching the mode to APRV for the virtual patient used in this investigation	67
Table 14 Physiological and initial mechanical ventilator sittings in conventional mode for the real patient.....	67
Table 15 Physiological and initial mechanical ventilator sittings upon switching the mode to APRV for the real patient	67
Table 16 summary of results for the outcome measures between the two modes.....	70
Table 17 Summary of results for the CV_{Sim}	71
Table 18 Summary of results for the simulated APRV _{Sim} mode	71
Table 19 comparison between CV_{Real} and APRV _{Real}	72
Table 20 values of $P_{aw/Peak}$ and $P_{aw/Mean}$ during CV_{Real} and CV_{Sim} (corrected)	72
Table 21 values of $P_{aw/Peak}$ and $P_{aw/Mean}$ during APRV _{Real} and APRV _{Sim} (corrected)	72
Table 22 Configurations of APRV _{Real} and APRV _{Sim} for final comparison (after alignment).....	78
Table 23 Baseline characteristics for patients enrolled in the study (severe, moderate, mild ARDS are classified based on the Berlin criteria).....	91
Table 24 Statistical analysis for outcome measures M_v and RR	92
Table 25 Demographic data and clinical characteristics.....	105
Table 26 CO_2 retainers who did not receive $NaHCO_3$	106
Table 27 Non- CO_2 retainers who did not receive $NaHCO_3$	107
Table 28 Non- CO_2 retainers who received $NaHCO_3$	107
Table 29 Response profile	111
Table 30 Analysis of Maximum Likelihood Estimates	111
Table 31 Odds Ratio Estimates.....	111
Table 32 Overall statistical analysis for T_{High} , T_{Low} , P_{High} , and P_{Low} for the entire cohort....	117
Table 33 statistical analysis for T_{High} , T_{Low} , P_{High} , and P_{Low} for each group (CO_2 retainers and non- CO_2 retainers).....	117
Table 34 statistical analysis for PaO_2/FiO_2 ratio (mmHg) for the entire cohort and for each group (CO_2 retainers and non- CO_2 retainers).....	118
Table 35 American-European Consensus Conference Criteria for ARDS	127
Table 36 Baseline characteristics for patients enrolled in the study	134
Table 37 Statistical analysis of PaO_2 , Sys , Dia , HR , MAP , $PEEP_M$, P_{Mean} , RR , VT , MAP , and PaO_2/FiO_2	135

List of Figures

Figure 1 Measured change in PaCO ₂ between CVsim (PC) and APRVsim.....	73
Figure 2 Measured changes in exhaled Mv between CVsim (PC) and APRVsim.....	73
Figure 3 Measured change in the exhaled V _T between CV _{Sim} (PC) and APRV _{Sim}	74
Figure 4 Measured change mean V/Q between CV _{Sim} (PC) and APRV _{Sim}	74
Figure 5 Measured change in Alv/ _{Peak} between CV _{Sim} (PC) and APRV _{Sim}	75
Figure 6 Measured change in C _{Alv} between CV _{Sim} (PC) and APRV _{Sim}	75
Figure 7 Measured change in P _{aw/Mean} between CV _{Sim} (PC) and APRV _{Sim}	76
Figure 8 Summary of Variables on APRV _{Sim} vs APRV _{Real} Data of the APRV _{Sim} were corrected to match all configurations on the APRV _{Real}	77
Figure 9 Flowchart of patient-selection for the study	88
Figure 10 Flowchart of patients enrolled in the study	102
Figure 11 PaCO ₂ levels of the entire cohort	109
Figure 12 PaCO ₂ vs. V _T (ml/kg) values of the entire cohort	109
Figure 13 PaCO ₂ vs. T _{High} (seconds) values of the entire cohort.....	110
Figure 14 PaCO ₂ vs. V _T levels for CO ₂ retainers	112
Figure 15 PaCO ₂ vs. V _T levels for non-CO ₂ retainers	112
Figure 16 PaCO ₂ vs. T _{High} levels for CO ₂ retainers.....	113
Figure 17 PaCO ₂ vs. T _{High} levels for non-CO ₂ retainers	113
Figure 18 PaCO ₂ and pH values for CO ₂ retainers who did not receive NaHCO ₃	114
Figure 19 PaCO ₂ levels for patients who received NaHCO ₃	115
Figure 20 Arterial pH values for patients who received NaHCO ₃	116
Figure 21 T _{High} and V _T settings for patients who received NaHCO ₃	116
Figure 22 PaO ₂ /FiO ₂ , HR, Sys, Dia, and MAP for CV vs. APRV (1 st and 2 nd intervals).....	132
Figure 23 PaO ₂ , FiO ₂ , PEEP, and P _{Mean} for CV vs. APRV (1 st and 2 nd intervals).....	133
Figure 24 PaCO ₂ , PIP, RR, V _T and M _V for CV vs. APRV (1st and 2nd intervals)	133
Figure 25 initial settings of APRV.....	183
Figure 26 managing Oxygenation on APRV mode	184
Figure 27 managing ventilation (CO ₂) on APRV mode	185
Figure 28 weaning.....	186

List of Abbreviations

ABG	Arterial blood gases
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
APRV	Airway pressure release ventilation
CV	Conventional ventilation
BE	Extracellular base excess
BTPS	body temperature and pressure saturated
C(a-v)O ₂	Arterial-mixed venous oxygen content difference
CaO ₂	Arterial oxygen content
CCM	Critical care medicine
CcO ₂	Pulmonary capillary oxygen content
CCU	Critical care unit
CMV	Controlled mandatory ventilation
CO ₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CvO ₂	Mixed venous oxygen content
FIO ₂	Fraction of inspired oxygen
Hb	Haemoglobin
HCO ₃ ⁻	Bicarbonate
I:E ratio	Inspiratory to expiratory time
ICU	Intensive care unit
M _v	Minute ventilation
NPS	Nottingham physiology simulator
ICPMs	Integrated cardiopulmonary models
O ₂	Oxygen
P (A-a)O ₂	Difference between alveolar partial pressure of oxygen and arterial
PaCO ₂	Arterial partial pressure of carbon dioxide
PACO ₂	Alveolar partial pressure of carbon dioxide
PaO ₂	Arterial partial pressure of oxygen
PB	Barometric pressure
PCV	Pressure control ventilation
PEEP	Positive end expiratory pressure
PH ₂ O	The saturated vapour pressure of water
PIP	Peak inspiratory pressure
PSV	Pressure support ventilation
PvO ₂	Partial pressure of venous oxygen tension
Q _{sp} /Q _t	Intrapulmonary shunt
CRS	Respiratory system compliance
RR	Respiratory rate
SaO ₂	Arterial oxygen saturation
SBT	Spontaneous breathing trial
SD	Standard deviation
SIMV	Synchronised intermittent mandatory ventilation
SIMV/PS	Synchronised intermittent mandatory ventilation plus pressure support

SIMV-PC/PS	synchronised intermittent mandatory ventilation/pressure control combined with pressure support
SpO ₂	Arterial oxygen saturation
SvO ₂	Mixed venous oxygen saturation
$\dot{V}/\dot{Q}$	Ventilation to perfusion
VCO ₂	Carbon dioxide production
V _E	Minute ventilation
VO ₂	Oxygen consumption
V _T	Tidal volume
PaO ₂	Arterial oxygen tension
Paw	Peak airway pressure
PaO ₂ /FiO ₂	Arterial oxygen tension/inspiratory oxygen fraction;
CI	Cardiac index
C.O.	Cardiac output
P _{Mean}	Mean airway pressure
P _{Plat}	plateau pressure
PEFR	Peak expiratory flow rate
DO ₂	Oxygen delivery
PVO ₂	Mixed venous oxygen tension
CVP	Central venous pressure
V _D /V _T	Dead space
ISS	Injury Severity Score
APACHE II	Acute physiology and chronic health evaluation
AaDO ₂ /FIO ₂	Alveolio-arterial O ₂ tension difference (AaDO ₂)/fraction of inspired oxygen (FIO ₂)

Chapter 1

Introduction and literature review

1.1 Introduction

Patients hospitalised for surgery, trauma, respiratory and other conditions who experience apnoea, acute or impending ventilatory failure, or severe oxygenation deficit often require what may be life-saving respiratory support with mechanical ventilation (MV) (1-3). More than two-thirds (71.2%) of acute respiratory failure diagnoses in U.S. adults in 2009 were associated with medical rather than surgical conditions, and approximately half (49.7%) of the patients with ARF received ventilatory support (4). The use of invasive MV in U.S. adults was reported to increase from 178.9 per 100,000 inpatient cases in 1993 to 310.9 per 100,000 in 2009 (5). Acute respiratory distress syndrome (ARDS) can develop in patients with previously healthy lungs, following direct and indirect insults to the lung (6). The period prevalence of ARDS was 10.4% of intensive care unit (ICU) admissions in the 2014 LUNG SAFE cohort study in 50 countries (7). In the PROVENT study of the epidemiology, ventilation practices, and outcomes in patients at risk of ARDS in ICUs in 16 countries, 30% of patients receiving MV were at risk of developing ARDS, and the prevalence of ARDS was greater in patients at risk compared with those not at risk (7% vs. 3%; $p = .004$) (8).

Mechanical ventilation can be a double-edged sword. While it is crucial to safely support life and maintain gas exchange, it also can cause a lung injury or aggravate a pre-existing lung injury, producing ventilator-induced lung injury (VILI) (9-13). Acute lung injury (ALI) and its more

severe form, ARDS, are associated with a high mortality rate in intensive care units (ICUs). Overlapping interactions contributing to the complex pathophysiology of VILI include high tidal volume (V_T) causing over distension; cyclic closing and opening of peripheral airways during tidal breath, causing lung strain; increased transpulmonary pressure causing lung stress; low lung volume associated with recruitment and derecruitment of unstable lung units producing atelectrauma; increased surface tension related to inactivation of surfactant; and local and systemic release of lung-based inflammatory mediators (11). Protective ventilator strategies in previously non-injured lungs based on V_T 6 mL/kg, positive-end expiratory pressure (PEEP) 6-12 cmH₂O, and recruitment manoeuvres can decrease the development of ARDS, but have not been shown to have an effect on mortality (11). In the PROVENT study, V_T was similar in patients at risk and not at risk of ARDS (median 7.6 vs. 7.9 mL/kg), while PEEP was higher in patients at risk compared with those not at risk (median 6.0 vs. 5.0 cmH₂O) (8).

In the PROVENT study, in hospital mortality was significantly higher in patients at risk compared with those not at risk of ARDS (32% vs. 16%; $p < .0001$), as was ICU mortality (29% vs. 12%; $p < .0001$) and 90-day mortality (31% vs. 17%; $p < .0001$) (8). Once ARDS develops, it imposes a high mortality burden, with hospital mortality associated with mild, moderate, and severe ARDS reported at 34.9%, 40.3%, and 46.1% in the LUNG SAFE study (7). A recent review reported that mortality benefits are not common in randomised controlled trials (RCTs) in ARDS

patients (14). The study examined 159 published RCTS, of which 44 included mortality as a primary outcome. Only 7 interventions reported a statistically significant survival benefit, and 2 trials reported an adverse survival effect. Among these studies and 29 meta-analyses that were also reviewed, MV using low tidal volumes and prone positioning provided the most consistent, yet sporadic, evidence for a mortality benefit in patients with severe ARDS.

Therefore, finding appropriate interventions to avert, or at least limit, the progression of such a lethal syndrome is extremely essential to reduce mortality, morbidity, and costs. The current goals of MV emphasise recruiting de-recruited alveolar units, limiting lung damage (by preventing over-distention of lung units), limiting cyclical collapse (by maintaining an appropriate level of mean airway pressure [P_{Mean}]), and maximising oxygen delivery. These goals were meant to ensure appropriate gas exchange while avoiding possible risks associated with either the modes or the applications of MV. An MV mode that consistently achieves all of these goals has not yet been established, necessitating compromises between supporting gas exchange and minimising risks that may be associated with the applied pressures and volumes that endeavour to do so (15). However, it may not be possible to achieve these goals simultaneously by using a single mode without having a negative effect on other goals.

Airway pressure release ventilation (APRV) is an MV mode that was first described almost 30 years ago by Stock and Downs (16), and

became commercially available in the mid-1990s (17). With the existing evidence, when compared with conventional ventilation (CV) modes, the APRV mode generally has been associated with superior success in achieving the MV goals, and this may qualify it as the mode of choice for such an important and difficult task. However, there are relevant questions concerning the adequacy of published data on the APRV mode that must be answered to reach a definitive conclusion concerning its clinical significance in managing patients with all forms of lung injury, but mainly ARDS.

1.1.1 What is APRV?

APRV is a pressure-limited, time-cycled, time-triggered mode that applies two levels of continuous positive airway pressure (CPAP) with very short release phases from the higher to the lower CPAP levels (18). Unlike conventional modes, APRV applies an extreme inverse inspiratory to expiratory ratio (I:E) in which the larger inspiratory pressure level (P_{High}) lasts significantly longer than the lower expiratory pressure level (P_{Low}).

In the APRV mode, the respiratory cycle is comprised of two periods: T_{High} is the longer duration of P_{High} and occupies 80-95% of the cycle (18), while T_{Low} is the shorter duration of P_{Low} . These two phases produce a $T_{\text{High}}:T_{\text{Low}}$ ratio that corresponds to the I:E ratio in the CV modes in the absence of spontaneous breathing. However, if spontaneous breathing exists during APRV, each spontaneous breath (mainly during T_{High}) has its own inspiratory/expiratory time. In contrast to I:E ratios in CV, the time

parameters are adjusted independently in APRV (18). The comparatively longer T_{High} creates a higher mean airway pressure (P_{Mean}) compared with CV modes, without a corresponding increase in peak airway pressure (PIP), and a perceived positive effect on alveolar recruitment (12, 19). Another advantage of APRV is that its open expiratory valve allows patients to breathe spontaneously at any time during the ventilatory cycle. These spontaneous breaths could be supported by activating either pressure support (PS) or automatic tube compensation (ATC) in accordance with the machine that is being utilised.

Although adding PS to APRV was suggested to possibly reduce the benefits of spontaneous breathing (18), a small cohort of patients ($N=22$) with severe ARDS secondary to sepsis experienced significant improvement in oxygenation after being switched from the ARDS net protocol to APRV with low level PS (5 cmH₂O) (20). The authors had previously noted a dramatic decrease in minute ventilation (M_V) with a concomitant acute rise in carbon dioxide (CO_2) when patients were switched to APRV without low level PS. Patients also became tachypnoeic and agitated without PS, which was suggested to result from increased work of breathing (WOB). These contradicting results may have been caused by the utterly different clinical protocols indicated in both studies. For instance, Habashi (18, 20) recommended setting the P_{High} to match the same level of plateau pressure (P_{plat}) on CV while Marik (18, 20) used a P_{High} of 25 cmH₂O (or 75% of P_{plat} on CV), and the levels of P_{Low} were also different (0 vs. 5) cmH₂O, respectively (18, 20). This may have caused a significant difference in the

driving airway pressure that could have affected recruitment, altered gas exchange, and led to tachypnoea and increased WOB. Notably, Habashi recommended setting the ATC at 100% (17) which may eliminate the need for PS. Several studies have reported that ATC has been shown to be as effective as PS in reducing the WOB necessary to overcome the endotracheal tube (ETT) resistance (21, 22).

APRV has been increasing in popularity over time as a result of the positive results that have been reported in some trials, and it has been described as a safe alternative mode for ventilating the lungs of patients who have ARDS and ALI (18). Several studies have indicated that APRV may be superior to CV modes in many aspects. For example, APRV has been associated with better oxygenation, cardiac performance, renal perfusion, and recruitment of de-recruited lung units, as well as reduced peak airway pressure, neuromuscular blockade and sedation use. However, with the exception of two retrospective studies, no significant mortality differences have been reported in published studies.

1.1.2 Why APRV?

The American-European Consensus Conference (AECC) on ARDS, Part 2, was organised in an attempt to: 1) re-evaluate the existing treatments for ALI/ARDS; 2) analyse recovery features for ALI by defining and quantifying the pathological and clinical aspects that need resolution; and 3) analyse the pathophysiological mechanisms of lung injury as they relate to different

strategies of (23). Accordingly, they published the following goals of ventilator management (23):

- 1- Ensure appropriate O₂ delivery to vital organs along with sufficient CO₂ removal to maintain homeostasis.
- 2- Minimise O₂ toxicity.
- 3- Recruit alveoli.
- 4- Prevent atelectasis.
- 5- Minimise high airway pressures.
- 6- Use sedation and paralysis judiciously.

However, it might not be possible to achieve all of these goals simultaneously with one modality; vis-a-vis their statement: "It may be naive to assume that any single therapy will be a 'magic' bullet to treat all aspects of ARDS" (23). For example, in order to achieve goals 2, 3, and 4, it was recommended (23) that the P_{Mean} be increased. Such a high P_{Mean} can improve arterial oxygenation by recruiting collapsed alveoli, preventing further lung collapse, and improving ventilation-perfusion (V/Q) matching, which in turn allows reduction in the fraction of inspired oxygen (FIO₂) and therefore minimises the risk of oxygen toxicity (23).

An efficient modality that provides a higher P_{Mean} is the high frequency oscillatory ventilation (HFOV), yet this will certainly preclude goal 6 and promote the development of other adverse effects. In a recent multi-centre, randomised, controlled trial (RCT) involving 39 ICUs, comparing HFOV with conventional, low tidal volume strategy (LOVT) for patients with moderate-to-severe ARDS, HFOV was associated with a significantly higher mortality

rate (47% vs. 35%; $p = 0.005$), more use of sedation (199 mg/day vs. 141 mg/day of midazolam; $p < 0.001$), increased use of neuromuscular blockers (83% vs. 68%; $p < 0.001$), and more vasoactive agents (91% vs. 84%; $p = 0.01$) (24). Similarly, when the gold-standard, low tidal-volume approach used in the ARDS Network trial (ARDSnet) is used to achieve goal 5, other goals may be sacrificed; however, the levels of sacrifice may depend on the severity of the illness.

Severely injured lungs with low compliance may require higher airway pressure to correct life-threatening hypoxia; however, using LOVT may lead to repetitive shear forces, low volume lung injury, de-recruitment (18, 25), increased use of sedation, and more dys-synchrony (26, 27). Alternatively, a recruitment manoeuvre also can be used during conventional modes as an adjunct intervention to improve oxygenation and to achieve goals 2, 3, and 4. However, a systematic review of 636 patients indicated that, despite improved oxygenation caused by recruitment manoeuvres, there was a rapid decline in oxygenation shortly after the manoeuvres, some of which occurred within 15-20 minutes (26).

Hence, an intervention that provides solutions for these goals is needed, for instance, by providing a higher P_{Mean} without causing the adverse effects associated with HFOV, LOVT, and recruitment manoeuvres. Although APRV may be viewed as a virtually continuous recruitment manoeuvre (18), none of the above adverse events have been reported during the use of APRV. As an open-lung approach, APRV is designed to provide a higher P_{Mean} than

other conventional modes, which, in turn, may help achieve goals 2, 3, and 4. In addition to the higher P_{Mean} , APRV allows spontaneous breathing throughout the respiratory cycle, which may significantly enhance the achievement of goals 1, 3, and 6. It has been reported that spontaneous breathing during APRV may preferentially recruit dependent lung units without requiring any additional increase in applied airway pressure, supporting goal 5 (18). However, when conventional modes are used to achieve goal 1 for patients with ARDS, it is credible that any additional pressure, such as the positive end-expiratory pressure (PEEP), will lead to a disproportionate distribution of lung volume due to different levels of compliance among lung units (10). Although such increase in the level of PEEP can reduce intrapulmonary shunt in areas with low compliance, it may simultaneously hyper-inflates compliant lung units and converts well-ventilated areas into non-perfused dead space (28). This might not be the case with the APRV mode, e.g. Yoshida and colleagues stated, "Our results demonstrate that spontaneous ventilation during APRV improves lung aeration by decreasing atelectasis in a short time, which contributes to improved pulmonary oxygenation" (29).

Many studies have shown the proficiency of the APRV mode over other modes, which may qualify APRV as an appropriate tool to achieve most, if not all, of these goals (Table 1).

1.1.3 Why ALI and ARDS?

ALI/ARDS represent a major challenge in ICUs (30) because of the clinical consequences and high mortality rates associated with these conditions. Their management may require MV over a prolonged duration, extending the length of stay (LOS) in the ICU. This can put the patient at increased risk for serious complications, such as ventilator-associated pneumonia (VAP) (31), multi-organ failure, and even death, while significantly increasing costs (32). Although the implementation of the LOVT strategy in accordance with the ARDSnet recommendation was associated with a reduction in the mortality rate of almost 9%, the overall mortality rate remained high, i.e. 31% (33).

In contrast, a systematic review of 89 studies (36 RCTs and 53 observational studies) reported that the overall mortality rate for ARDS was 44.3% (34). The authors concluded that the mortality rate did not decrease from when the first consensus definition was published in 1994 until 2006, meaning that it remained at a high level. For that reason, they emphasised the need for effective therapeutic interventions for such a highly-lethal syndrome (34). Hence, such a need might be one of the driving forces to investigate this relatively new mode as an alternative intervention that may lead to better outcomes, including reduced duration of MV as well as mortality.

1.1.4 Objectives

To review the use of APRV in the treatment of various diseases, mainly ALI/ARDS, and to clarify any ambiguities in published studies concerning the use of APRV and similar modes, such as BIPAP. Such clarification of ambiguities may represent a basis for future studies and subsequent work.

The focus will be on:

- 1- Clarifying the description of the APRV mode.
- 2- Identifying potential factors associated with the inconsistent results from clinical trials, including differences in clinical applications.

In addition, since none of the published RCTs investigated mortality, the duration of MV has many clinical implications related to patient complications and administrative associations with resource use and patient-associated costs. Therefore, more focus was placed on RCTs that studied the duration of MV to exemplify the need for including this important variable along with other significant outcomes in future APRV trials. For this reason, RCTs that investigated the duration of MV and their comparative designs and outcomes were diligently studied.

1.1.5 Method

To achieve the objectives of this review, the following questions were formulated and answered according to available evidence:

1. Is there confusion about APRV in the literature?
2. What RCT outcomes were reported?

3. What are the main contributing factors to the different outcomes in APRV studies?
4. Is there a consensus about APRV application i.e. clinical protocol or clinical practice guidelines (CPGs)?
5. Are there any aspects of heterogeneity that can be shown to have associations with study outcomes?
6. Has the duration of MV been investigated in prospective clinical trials?
7. Are there ongoing studies?
8. What is the situation of APRV in clinical practice?

1.2 Literature Review

1.2.1 Is there confusion about APRV in the literature?

The frequent consideration of APRV and BIPAP as the same modes, with little attention paid to the ventilation settings that characterise the modes, is a common source of confusion that can interfere with making an accurate assessment of APRV (8, 35, 36). For example, in the PRoVENT study, which showed no difference among use of ventilation modes for patients at risk and not at risk of ARDS ($P = .111$), BiPAP/APRV were reported as a single mode (8). Also, some reviews have merged the two modes into one abbreviation, referring to them as a single modality, i.e. BIPAP/APRV (37). Daoud (38) Frawley (39) and Habashi (18) acknowledged the existence of confusion about APRV by stating, "Somewhat confusing to the understanding of APRV have been the subsequent descriptions of modes of ventilation that appear very similar to it" (39). However, the usage may reflect geographical variations in that APRV is commonly used in North America, whereas BIPAP is perceived as a very similar mode in Europe (40). Although some authors have indicated (40, 41) that BIPAP differs from APRV only in the ratio of T_{High} and T_{Low} , T_{High} is usually shorter than T_{Low} in BIPAP. However, even for its minimum ratio, APRV must never reach a level at which T_{High} is shorter than T_{Low} . In fact, it is recommended that a minimum acceptable T_{High} on APRV is four seconds (39), which is much greater than any reported time on BIPAP mode. Therefore, it is

questionable whether the two modes of ventilation can be described accurately as a single mode.

Rose (42) and Hawkins (42) attempted to resolve the existing confusion by identifying definitive criteria for the APRV and BIPAP modes. Their comprehensive review included 50 studies that met their inclusion criteria of having sufficient data about inspiratory and expiratory times. Their analysis included percent utilisation of each mode, differences in I:E ratios, and patient characteristics; the latter is beyond the scope of this review. They found that APRV was described in 78% of the studies, whereas BIPAP was described in 22%. They categorised the I:E ratios used into four categories: 1) extreme inverse ratio ($> 2:1$); 2) non-inverse ratio; 3) 1:1 ratio; and 4) mild inverse ratio ($> 1:1$ to $\leq 2:1$). They found that an extreme inverse ratio of $> 2:1$ was utilised in 46% of the studies on APRV, while none of the BIPAP trials used such a ratio ($p = 0.004$) (42). This means that 100% of BIPAP studies used a ratio of less than 2.1:1, of which 91% used a ratio of 1:1 or less, which is not compatible with APRV. In addition, even for those studies that were described as having used APRV, 55% of them used a ratio of $> 1:1$ to $\leq 2:1$, of which 31 used an I:E ratio of 1:1, while 21% of the APRV trials used a mild ratio of $> 1:1$ to $\leq 2:1$ (42).

This may raise the crucial question concerning whether the mode used in these studies should really be referred to as APRV, especially when one considers the recommended ratios for this mode. It has been reported that

initial APRV settings producing an I:E ratio of 5 to 19 demonstrate the considerable variation in this parameter in clinical and preclinical studies, including lung simulation models (12, 39, 43). Similarly, a well-known guideline by Habashi recommends that T_{High} generally should be set to occupy 80 to 95% of the total respiratory cycle when using the APRV mode to maintain optimum alveolar recruitment (18). This major consideration alone may elucidate that all BIPAP studies conducted alongside many studies that claimed to be assessing the APRV mode should not be assumed to be studies that used a factual APRV mode, because they are not one mode.

Furthermore, Henzler, in his commentary on two recent studies, described the difficulty of comparing these modes with the existing confusion and confounding factors and stated, "The calamity of ventilation research is revealed in a way such that inhomogeneous groups of full or partial ventilatory support modalities cannot be compared well" (44). As such, he wondered if the different application of the APRV mode in North America was, indeed, the cause of the more favourable outcomes than those in Europe. He also emphasised that the lack of such explicit definitions precludes drawing meaningful conclusions, and he highlighted the critical need for precise, standardised definitions that could differentiate the clearly distinct modes that appear alike in clinical research (44).

From the above, one could inquire about the clinical relevance of such a core difference ($T_{\text{High}}:T_{\text{Low}}$ ratio) between the two modes and whether it deserves special attention.

1.2.1.1 Is the $T_{\text{High}}:T_{\text{Low}}$ ratio clinically relevant?

Stewart and colleagues indicated in their review that it is the extreme inverse $T_{\text{High}}:T_{\text{Low}}$ ratio of 8:1 to 10:1 that distinguishes APRV from other modes that seem similar to it (45). Similarly, Rose and Hawkins stated, "There is the potential that expected improvements in gas exchange might not occur without the use of an extreme inverse ratio" (42). This may explain why using a prolonged T_{High} has been gaining in popularity since Downs, in 1987, introduced the use of a 1.3:1 ratio in normal lungs and a 1.4:1 ratio in injured lungs (46). Since then, T_{High} has been prolonged progressively to much longer durations, which can reach up to 95% of the total respiratory cycle (18).

In a porcine model with ALI, Markstaller (47) reported that different zones of the lungs exhibited considerable variations in their inspiratory and expiratory time constants. Some lung zones may require inspiratory times of up to 10 seconds to recruit them, while only 0.8 second might suffice to de-recruit them during the release phase (46). However, in addition to the physiological and clinical relevance of T_{High} , T_{Low} may have even more clinical significance since a long T_{Low} may lead to serious consequences, such as reducing the P_{Mean} (37) as well as causing regional collapse that can occur in lung units that have short time constants. Such collapse may occur in less than a second if airway pressure (P_{aw}) drops below a critical point (47). Therefore, some researchers have advocated that determining

the correct multiple of time constants to calculate T_{Low} should be an objective of future research (39).

Despite the fact that T_{Low} is perhaps the most closely studied of the four ventilation parameters, i.e. T_{High} , T_{Low} , P_{High} and P_{Low} , there is no definite consensus about its ideal application. In earlier studies, a T_{Low} of 1.5 seconds was recommended to allow the lungs to be fully emptied (16, 48), yet this duration may not be consistent with APRV; rather, it is more reflective of BIPAP or even a conventional setting. Downs reported that a longer T_{Low} (3.0–4.0 seconds) was associated with the accumulation of haemorrhagic fluid in the ETT and lower arterial oxygenation (46). Daoud and colleagues reported that de-recruitment and alveolar atelectasis can occur in ARDS, even with a T_{Low} of 0.8 second because the time constant typically is very short (38). Rose and Hawkins reported that the mean expiratory time was almost three times longer in BIPAP studies than in APRV studies (3.4 ± 1.6 s and 1.3 ± 0.4 s, respectively; $p = .01$) (42). This could be another distinction that may imply that these modes are, in fact, different.

In summary, although some modes, e.g. BIPAP, bi-level, bi-phasic positive airway pressure, and APRV, have been described as being the same modes, the extreme inverse ratio of APRV contributes to its being a distinct mode. Daoud summarised the I:E ratio characteristics of different modalities as conventional ventilation: 1:4–1:1; inverse ratio ventilation: $> 1:1$; BIPAP: 1:4 – 1:1; and APRV: $> 2:1$ (38). Yet, some researchers unintentionally may have mixed these characteristics. For example, Richard (49) published

a review in which he addressed the inconsistent application of the APRV mode, which may represent an aspect of clinical heterogeneity. He reported that some published clinical studies (50-53) allowed mechanical frequencies of ≥ 20 cycles per minute, which overlap with the frequencies of conventional mechanical ventilation (49). The above disparities in application may have contributed to the different outcomes.

1.2.2 What are the outcomes of APRV in the literature?

Many studies have compared APRV to other conventional modes and have reported several positive outcomes, including better gas exchange (mainly oxygenation), lower peak pressure, higher P_{Mean} , and similar or better CO_2 elimination at lower levels of minute ventilation (M_V). In addition, other positive outcomes have been reported, including better haemodynamics, reduced incidents of ventilator-associated pneumonia (VAP), less use of sedation and muscle paralyzing agents were reported. (as shown in Table 1).

1.2.2.1 Gas exchange

Several clinical trials on APRV reported improved V/Q matching, better oxygenation, and decreased pulmonary dead space (V_D/V_T) compared with conventional ventilation (16, 20, 29, 51-57).

1.2.2.2 Peak pressure

Other studies have reported that the use of APRV resulted in significantly lower peak pressures than conventional ventilation (50-52, 58, 59).

1.2.2.3 Mean airway pressure (P_{Mean})

One of the substantial advantages of the APRV mode is that it is associated with a significantly higher P_{Mean} compared to conventional modes (20, 52, 53, 59, 60)

1.2.2.4 Ventilator-Associated Pneumonia (VAP)

In 64 patients with pulmonary contusions, Walkey and colleagues (61) reported that APRV was associated with a significant reduction in the VAP rate ($p = .01$) and significantly better arterial oxygen tension (PaO_2)/ FiO_2 ($\text{PaO}_2/\text{FiO}_2$) ratio ($p < .001$) than conventional ventilation (mostly A/C volume mode).

1.2.2.5 Cardiac performance and sedation

Other studies have reported that APRV provides better oxygen delivery, cardiac performance, and reduced use of vasopressors, sedatives and paralyzing agents (54, 55) including a recent RCT (62).

1.2.2.6 Recruitment

Animal studies on ALI have shown that spontaneous breathing during APRV promotes recruitment of de-recruited, dependent lung units and improves aeration (63, 64). These results are in agreement with human studies in which Yoshida and colleagues (29) investigated the effect of APRV compared to pressure support ventilation (PSV) mode on lung aeration. They included 18 patients with early ALI/ARDS for whom thoracic helical computed tomography (CT) scans were performed twice within three days (baseline and follow-up). Lung regions were labelled into four categories according to their densities: normally aerated; poorly aerated; non-aerated; and hyper-inflated. They reported that APRV was superior to PSV in that the normally aerated areas increased significantly from 29 to 43% ($p < 0.008$), compared with a non-significant increase from 39 to 44% on PSV ($p < 0.445$). Similarly, APRV reduced atelectatic areas from 41 to 19% ($p < 0.008$), whereas PSV reduced these areas from 39 to 29% ($p < 0.379$) (29). They also reported significant improvement in the $\text{PaO}_2/\text{FiO}_2$ ratio and in the alveolar-arteriolar oxygen gradient (PA-aO_2).

1.2.2.7 Atypical outcome

Contrary to popular belief, lower $\dot{V}_E$ may not necessarily result in higher PaCO_2 . It has been speculated that the reduced $\dot{V}_E$ after switching the mode from CV to APRV could result in an acute rise in PaCO_2 level and marked increase in WOB, inspiratory drive, and respiratory muscle power output (65). However, some studies of APRV have identified some remarkable concepts that may be of clinical value for many clinicians and for future researchers. Stock and colleagues (16) found that APRV patients had lower

PaCO₂ values ($p < 0.004$) than patients in a conventional mode even though they had similar M_v values. Similarly, Maxwell and colleagues (60) reported that patients in the LOVT group had significantly higher PaCO₂ values ($p < 0.039$) at significantly higher M_v values ($p = 0.004$) than those treated with APRV.

1.2.2.8 Mortality

Despite the reported beneficial effects of APRV, none of the prospective trials has reported significant reduction in mortality. However, a retrospective study of 58 patients compared APRV to synchronised intermittent mandatory ventilation (SIMV) and reported a trend toward decreased mortality (31% vs. 59%, respectively, $p = 0.05$) (66). This is in agreement with another retrospective study of 129 patients conducted in our tertiary-care hospital that had similar findings (67). The latter reported that APRV was associated with significantly lower ICU mortality than the CV mode following the ARDSnet protocol, 29% vs. 51%, $p = 0.022$.

Table 1 Comparison of ventilatory modes and outcomes

Author	n	Modes compared & design	Outcome (APRV group)
Stock ⁽¹⁶⁾ 1987	10 (dogs)	IPPV + PEEP vs. APRV; Randomised	↑ PaO ₂ , ↓ PaCO ₂ , ↑ P _{aw}
Yoshida ⁽²⁹⁾ 2009	18	PSV vs. APRV; Retrospective	↓ Atelectasis, ↑ Lung recruitment, ↑ mean arterial pressure
Rasanen ⁽⁵¹⁾ 1991	50	Conventional volume-controlled ventilation vs. APRV prospective, multicenter, non-randomised, crossover trial	↓ P _{aw}
Sydow ⁽⁵²⁾ 1994	18	VC IRV vs. APRV; Randomised	↓ P _{aw} , ↑ P _{Mean} , ↑ AaDO ₂ /FIO ₂ , ↑ venous admixture
Dart ⁽⁵³⁾ 2005	46	Variable conventional mode (SIMV, CPAP+PSV) vs. APRV	↓ P _{aw} , ↑ PaO ₂ /FiO ₂ , ↑ P _{Mean} , ↑ V _T
Davis ⁽⁵⁹⁾ 1993	15	IMV vs. APRV	Similar gas exchange, ↓ P _{aw} & PEEP, ↑ P _{Mean}
Kaplan ⁽⁵⁴⁾ 2001	12	PCV-IRV Pilot study	↑ Urine output, CI and DO ₂ ↓ Use of neuromuscular blockade & sedatives, CVP, lactate and P _{aw}
Putensen ⁽⁵⁷⁾ 1999	24	APRV with/out spontaneous breathing vs. PSV; RCT	↑ PaO ₂ , CO, DO ₂ , ↑ PVO ₂ and pulmonary blood flow distribution, ↓ PVR and O ₂ extraction

Putensen ⁽⁵⁶⁾ 1994	10 (dogs)	APRV with/without spontaneous breathing vs. PSV; RCT	↑PaO ₂ , ↑CO, ↑DO ₂
Cane ⁽⁵⁰⁾ 1991	18	APRV vs. CPPV; Prospective study non-randomised	↓ Paw, ↓V _T
Garner ⁽⁵⁸⁾ 1988	14	APRV vs. PPV	↓ Paw (periodically), no change in blood gases or haemodynamics
Liu ⁽⁶⁶⁾ 2009	58	APRV vs. SIMV; Retrospective	↑PaO ₂ /FIO ₂ , ↓Vasopressors , ↓mortality
Paul ⁽²⁰⁾ 2009	22	APRV vs. (A/C ARDSnet protocol)	↑ PaO ₂ /FIO ₂ , ↓ V _D /V _T , ↓V _{min} , ↑P _{Mean}
Li ⁽⁶³⁾ 2016	52	APRV vs. SIMV; RCT	↑ Lung function and haemodynamics ↑ days without sedatives (p = 0.036) ↑ days off MV (p = 0.046), and ↓ ICU days (p = 0.035).
Lim ⁽⁵⁸⁾ 2016	50	APRV vs. SIMV; Retrospective	↑ PaO ₂ /FIO ₂ (p < 0.005) (early and sustained) ↓ incidence of clinically significant barotrauma and progression to ECMO

PaO₂= arterial oxygen tension; P_{aw}= Peak airway pressure; AaDO₂/FIO₂= alveolio-arterial O₂ tension difference (AaDO₂)/fraction of inspired oxygen (FIO₂); PaO₂/FiO₂ = arterial oxygen tension/inspiratory oxygen fraction; PaCO₂ = arterial carbon dioxide tension; CI = cardiac index; C.O. = Cardiac output; P_{Mean} = mean airway pressure; DO₂= oxygen delivery; PVO₂ = Mixed venous oxygen tension; CVP = central venous pressure; V_D/V_T = Dead space; ECMO= exploring extracorporeal membrane oxygenation

1.2.2.9 Other patient groups

Case reports have reported positive effects associated with the use of APRV in specific patient groups. Hirani and colleagues (68) studied two pregnant women whose conditions were complicated further by severe, life-threatening ARDS and pneumonia. Both patients had refractory hypoxaemia on conventional mode, despite high FiO_2 of 90% and 100%, V_T of 8 and 7.5 mL/kg Ideal body weight (IBW), and PEEP of 10 and 14 cmH₂O, respectively. Upon initiation of APRV, the $\text{PaO}_2/\text{FiO}_2$ ratio was extremely low for both cases (87 and 47, respectively) with haemodynamic instability (the latter case); however, they responded well to treatment and experienced rapidly improved gas exchange in terms of oxygenation and ventilation, followed by timely weaning, extubation, and discharge from the hospital. Based on their preliminary experience, the authors recommended that pregnant women with severe ARDS should be considered for APRV mode (68). However, it was reported that pregnant women with ARDS are even more vulnerable to barotrauma than non-pregnant population when using higher V_T , (69, 70) and this may indicate that APRV may be a safe intervention even for such fragile group of patients; however, since it is a case series, it should be used with diligent monitoring.

1.2.3 What are the possible causes of different outcomes in the published studies?

Possible causes of different outcomes in the published studies warrant discussion. This includes substantial factors such as clinical practice guidelines used in published studies along with clinical and methodological heterogeneity. (Each of these factors is discussed separately.)

1.2.3.1 Is there a consensus about the use of APRV, i.e. standard guidelines in published trials?

Despite the conceptual simplicity of APRV settings, there is no consensus on a standard protocol for its use (71). In the absence of robust data to resolve important questions concerning the $T_{\text{High}}:T_{\text{Low}}$ ratio, PEEP, and weaning strategy, (71) various procedures have evolved by combining limited guidelines and recommendations from consensus conferences with clinicians' understanding of MV, pulmonary physiology, and pathophysiology (39). Daoud reported in his 2007 review that APRV is a simple ventilator mode to apply; (72) however, five years later, he published another review in which he indicated that there are two different schools of thoughts on this issue, and he stated, "We will not make any recommendations on how to set the parameters as there are no solid data to support them" (38). The latter is in agreement with what has been reported recently, i.e. that the application of APRV entails much more knowledge and clinical skills than the descriptions in the literature indicate, (73) and this may indicate the need for a consensus concerning the use of APRV.

For example, the main parameters, such as T_{High} and T_{Low} , have been inconsistent among the various studies. Some researchers have suggested that T_{Low} should be set to a level at which some intentional auto-PEEP is achieved to prevent de-recruitment, (12, 37) whereas others (72) have suggested that T_{Low} should be set to a level at which gas flow will reach zero, thereby allowing no intrinsic PEEP and assuring complete emptying of air. It also has been recommended that T_{Low} be increased as a step to enhance the elimination of CO_2 and correct hypercapnia (72). However, since initially there is no intrinsic PEEP (as recommended in the initial settings) (72), such an increase in T_{Low} easily could cause de-recruitment of unstable lung units.

Unlike conventional modes of ventilation, APRV may be more complicated to maintain when hypoxaemia and/or hypercapnia occur. For example, in conventional modes, increasing either FiO_2 or PEEP commonly is used to correct hypoxaemia. In contrast, the clinician has more options to improve oxygenation in the APRV mode, including increasing FiO_2 , P_{High} , P_{Low} , or T_{High} or decreasing T_{Low} . The studies that are available in the literature have not clearly defined how to progress through or choose one of these options.

A recent review (12) suggested that APRV should be started with the following setting: a P_{High} that is equal to the plateau pressure (P_{plat}) in the volume-control mode (maximum of 30 cmH₂O); P_{Low} of 0 cmH₂O; T_{High} of 4 s; T_{Low} of 0.6 –0.8 s to produce a peak expiratory flow rate (PEFR) of 40%; and that sedation should be titrated so that spontaneous breathing is at

least 10% of total M_v . Also, several adjustments were recommended to correct hypoxaemia and hypercapnia. To counter hypoxaemia, increasing T_{High} by 0.5–1.0 s or increasing P_{High} by 2–5 cmH₂O was recommended. If there is no response, an alternative ventilation mode should be started. The authors recommended tolerating “permissive hypercapnia” with a pH ≥ 7.15 ; however, the response to severe hypercapnia should be to reduce T_{High} by 0.5–1.0 s to increase the respiratory rate (RR) or the addition of pressure support (12). Several aspects of these recommended procedures warrant discussion. In these recommendations, T_{Low} , which is an extremely critical variable, is not adjusted as part of correcting either hypoxaemia or hypercapnia. This is significant because patients may be deprived of the potential benefits of this mode if T_{Low} is fixed at 40% of PFER throughout the course of APRV. In addition, different PEFr levels may be warranted for different lung pathologies because of their different time constants. Following these recommendations, patients with COPD and those with very low compliance, as in severe ARDS, would be managed in the same manner without considering the different time constants and intrinsic PEEP associated with these types of diseased lungs.

The review also recommended setting the P_{High} at a maximum of 30 cmH₂O, as an initial setting, but its maximum level throughout the course of the APRV was not addressed, although it was recommended that P_{High} be increased by 2–5 cmH₂O to correct hypoxaemia. Nonetheless, as with many

other protocols, although it has been recommended that P_{High} be increased repeatedly, e.g. by 2-5 cmH₂O in the case of hypoxaemia, the acceptable level of V_T displaced by such frequent increases in P_{High} seems to have been overlooked. Therefore, it is quite intuitive to question what the resulting V_T after such frequent and repetitive increase in P_{High} will be and what the maximum P_{plat} should be since it is at least equal to P_{High} when using APRV. If we take the above guidelines as an example, we may start with a P_{plat} of 30 cmH₂O initially; however, to encounter hypoxaemia, one could increase the P_{High} to 32-35 cmH₂O, and this could be repeated to improve oxygenation or alternative modes could be considered, such as HFOV, in the event there is no response. One could ask, "Is this the P_{plat} that ARDSnet recommends?" Also, what about the spontaneous breathing that occurs above this P_{plat} (P_{High})? Even so, despite the possible high V_T and P_{plat} , the mortality rates for patients in all reported studies of APRV groups did not exceed those of CV; thus, determining whether the APRV mode, despite its higher V_T and P_{plat} , produces a safer modality than CV should be an area for future investigation. Richard (65) indicated that, out of APRV studies that have measured V_T , mean values for the release volumes were between 550 to 840 ml and 9 ml/kg (measured body weight), which possibly translates into 11 ml/kg IBW. These differences may explain why some researchers indicated that the APRV mode might be a source of confusion and may also have prevented many centres from using APRV. In the absence of consensus on a standard protocol with clear rationale for the settings, these inconsistencies preclude defining an optimal method (74), and reports do

not always clarify the APRV protocol or settings that were used. However, the Habashi protocol continues to be the most detailed guide to APRV initiation and management, providing details on settings for patients newly intubated and for those transitioning from conventional or HFOV, as well as responses to specific circumstances (18). Explanations are provided to assist selection when ranges of ventilator settings are allowed; for example, for restrictive recruitable lung disease, T_{Low} should be set to ensure T_{PERF} is >50 and $\leq 75\%$ to limit derecruitment. When reports note initial ventilator settings and cite that the Habashi protocol was followed, readers may infer that subsequent ventilator settings were based on individual patient circumstances. However, such inference might not be always correct, and more data regarding protocols, their adherence, and deviations implemented to individualise treatment are needed. Failure to standardise and document APRV protocols has contributed to the lack of robust evidence regarding its potential benefit and role.

Since the publication of the Habashi protocol in 2005 until the time of this review (i.e. 2016), many reviews addressed this issue of inconsistent application of APRV. For instance, in 2012, Guldner stated, "A large prospective, randomised clinical trial combining APRV with spontaneous breathing is justified." Thus, he suggested that, before such a trial can commence, the optimal setup and guidelines pertaining to time and pressure settings, along with the amount of spontaneous breathing, must be defined clearly in advance (37). Also, a recent review in 2016 indicated

that adjustments responding to patient characteristics during APRV should follow a defined protocol (75).

Although clinical heterogeneity could have contributed to the variation in results described in the previous trials, it might not be the only source of heterogeneity; there might be other types, including methodological heterogeneity, caused by the use of different study designs and control groups.

1.2.3.2 Heterogeneity

Study design features that contribute to the heterogeneity among APRV studies include: a) the control group, in terms of modes of MV; b) intervention factors, such as inverse ratio ventilation (IRV); and c) subject characteristics (patient group), including diagnosis, the type of illness, and its severity. These three features will now be discussed separately.

a) Control Group

In addition to inconsistent procedures comprising APRV in the intervention group, the studies also used a variety of modes as controls. Comparator modes used in the control group varied widely among published studies. It is important to remember that the most commonly-used modes of MV are assist-control ventilation (ACV), synchronised intermittent mandatory ventilation (SIMV), and PSV. Each of these modes describes whether breaths are volume constant or pressure constant, which breaths are mandatory or spontaneous, or both. Note that almost all modes of MV were used as controls in APRV studies, including volume control ventilation (VCV)

(35, 50), intermittent mandatory ventilation (IMV) (51, 59), synchronised intermittent mandatory ventilation/pressure control combined with pressure support (SIMV-PC/PS) (76), pressure-controlled ventilation (PCV) (55), and PSV (29, 57).

b) Intervention factor

Some studies used the above modes with an alternative strategy, i.e. inverse ratio ventilation (IRV). IRV has been used with both pressure-controlled ventilation (IR-PCV) (54) and with volume control ventilation (IR-VCV) (52). Although disparities in either the control or the intervention group might be enough to cause heterogeneity, these variations may occur in both groups.

c) Patient group

Any study of an intervention that can be applied to several patient populations is plagued by constraints to enrolling subjects with consistent baseline disease characteristics. ALI (52), early ALI/ARDS (29, 55), late ALI/ARDS (54, 76), trauma (60), post-cardiac surgeries, such as coronary revascularisation (58), and acute respiratory failure (ARF) (50, 51) are all associated with indications for MV for which practitioners logically aspire to manage more effectively. This may demonstrate the different types and illness severity APRV studies comprised which adds to the heterogeneity. Since this review was focused on randomised studies that investigated the duration of MV as a significant outcome, the above features are addressed later in the discussion of studies that investigated the duration of MV. In

addition, the discussion includes other features, such as reliability, consistency of outcome measures, and adjunct interventions (e.g. prone positioning) (76), and randomisation methods (60).

1.3 Has the duration of MV ever been investigated in prospective clinical trials?

The RCTs of Putensen (55), Varpula (76), Maxwell (60), and colleagues matched one of the focuses of this review, so their studies are discussed in more detail. Although all of these researchers measured the duration of MV, their results varied. Putensen (55) randomised 30 patients to either APRV or pressure control ventilation (PCV) and reported a statistically significant reduction in the length of ventilatory support (APRV Group: 15 ± 2 d; PCV Group: 21 ± 2 d) ($p < 0.032$), intubation ($p < 0.011$), and ICU stay (APRV Group: 23 ± 2 d; PCV Group: 30 ± 2 d) ($p < 0.032$). Whereas, Varpula (76) reported comparable ventilator-free days in both the APRV and SIMV groups; 13.4 ± 1.7 d) vs. 12.2 ± 1.5 d, respectively; likewise, he reported the number of ICU-free days out of 28 days, which was 11.9 ± 1.7 d in APRV group vs. 10.7 ± 1.4 d in SIMV, which revealed only a slight 9% difference (1.2 days) in ventilator-free days in favour of APRV. However, their trial was terminated due to the slow recruitment of participants, the need to change several principles of care, and the interim analysis, which showed that APRV would not make a significant difference for two-thirds of the estimated 80 patients in the study. Likewise, Maxwell (60) reported no statistical differences between APRV and LOVT for

ventilator days (10.49 ± 7.23 d vs. 8.00 ± 4.01 d) and/or ICU LOS (16.47 ± 12.83 d vs. 14.18 ± 13.26 d). Table 2 shows the differences in the durations of MV among the three studies.

Table 2 Comparison of duration of mechanical ventilation and ICU, length of stay (LOS)

Author	Putensen (55)		Maxwell (60)		Varpula (76) *(Calculated from VFDs)	
Duration of Mv (days)	15 $\pm$ 2	21 $\pm$ 2	10.49 $\pm$ 7.23	8.00 $\pm$ 4.01	VFDs = 13.4 ($\pm$ 1.7) * 14.6 (12.9 - 16.3)	VFDs = 12.2 ($\pm$ 1.5) * 15.8 (14.3– 17.3)
LOS in ICU (days)	23 $\pm$ 2	30 $\pm$ 2	16.47 $\pm$ 12.83	14.18 $\pm$ 13.26	VFDs = 11.9 ($\pm$ 1.7) * 16.1 (14.4 - 17.8)	VFDs = 10.7 ($\pm$ 1.4) * 17.3 (15.9 – 18.7)

Varpula reported these durations in a form of ventilator-free days (VFD), therefore, it is * calculated.
MV=Mechanical ventilation; LOS = Length of stay

Unlike most APRV studies that reported better oxygenation, both Maxwell (60) and Varpula (76) reported similar oxygenation. However, in Maxwell's (60) study, the majority of patients in both the APRV and LOVT groups did not have lung injuries, and ARDS represented only 8/31 (25.8%) and 9/32 (28.1%), respectively, whereas ALI comprised 6/31 (19.3%) and 2/32 (6.25%), respectively. Although Varpula (76) reported significant improvement in oxygenation during the first 24 hours (hr), it started to mitigate until it converged with the oxygenation level of the control group at day 4. On the contrary, Putensen (55) found a significantly better ($p < 0.05$) PaO₂ and oxygen delivery (DO₂). He also reported other positive aspects, such as better respiratory system compliance (CRS) ($p < 0.05$), better cardiac index (CI) with significantly reduced venous admixture

(VA/T) ($p < 0.05$), and better oxygen extraction and peak airway pressure (Paw) (54). These positive outcomes were in agreement with those of other studies that used analogous guidelines and reported significantly better haemodynamics (29, 54) and oxygenation (20, 53).

The disparities in outcomes between the Varpula's (76), Putensen's (55), and Maxwell's (60) studies might be related to 1) the mode used in the control and intervention groups; 2) the timing of the intervention; 3) patient characteristics; 4) the equipment used; 5) differences in the applications or the protocols used; and 6) other adjunct factors. A summary of differences is presented in Tables 3, 4, and 5.

1.3.1 Modes of ventilation used in the control groups

Putensen (55) used a PCV mode, which is an A/C mode, whereas Varpula (76) used an SIMV-PC/PS mode. It is widely known among critical care practitioners that these two modes are quite dissimilar. Maxwell (60) used a synchronised intermittent mandatory ventilation/volume control combined with pressure support (SIMV-VC/PS), which was quite similar to that of Varpula (76). Principally, during SIMV, the ventilator is programmed to deliver a set number of breaths at either a pre-determined tidal volume (SIMV-VC) or pressure control (SIMV-PC), and Maxwell (60) used the former, while Varpula (76) used the latter. SIMV allows patients to breathe spontaneously between these set mandatory breaths, but each spontaneous breath depends on the patient's own ventilatory drive, respiratory muscle, and the level of PS.

During the application of either the volume or the pressure SIMV mode with PS, Varpula (76) and Maxwell (60) ensured that their patients were breathing spontaneously with the pressure support throughout the study periods, whereas Putensen's (55) mode allowed only assisted (not spontaneous) breaths, which were suppressed intentionally by deep sedation and neuromuscular blockade. (Table 3 depicts these differences.) The persisting spontaneous breathing that Varpula (76) and Maxwell (60) maintained in the control group might have influenced the outcome, because spontaneous breathing has been considered to improve both gas exchange and the distribution of ventilation to dependent lung units, most probably by the diaphragmatic contraction that opposes alveolar compression (57, 77).

Table 3 Mode of MV and persistence of spontaneous breaths in the studies that were compared

	Mode in control group	Persistent spontaneous breathing
Varpula	SIMV-PC/PS	Yes
Putensen	PCV	No
Maxwell	SIMV-VC/PS	Yes

1.3.2 Timing of the intervention

Since APRV is considered as a recruitment manoeuvre, the time of its institution could be clinically relevant. It has been reported that recruitment manoeuvres are efficient in improving gas exchange only when implemented in early ARDS, i.e. within 24–48 hr of the onset of the lung injury (78). Varpula (76) started randomisation quite late, wherein the median length of time on mechanical ventilation prior to randomisation was

39 ± 2.3 hr, which was significantly longer than the time in the other two studies. Putensen (55) started APRV much earlier, i.e. within 6 hr, as a primary ventilatory modality, and Maxwell (60) enrolled patients immediately after the development of ARF. It can be expected that the delayed intervention of recruitment measures, such as the APRV mode, may reduce their efficacy. This might be the case in Varpula's trial, in which the patients may have reached the late stages of ARDS. Their description of the stabilisation phase, i.e. "This practice confirmed that patients really had severe failure of gas exchange." indicates that this may be the case (76).

Besides the initial, severe lung injury, Varpula indicated that 62.1% of patients in the APRV group and 53.6% in the SIMV group had fibroproliferative ARDS, for which high doses of methylprednisolone were required (76).

1.3.3 Patient characteristics

Varpula (76) included patients who suffered from severe ARDS, whereas Putensen (55) studied a mixed population of patients who had severe, multiple traumata with ARDS or who were at risk of ARDS. In contrast, the majority of patients in Maxwell's study did not have lung injuries, so it is not compared extensively with the other two studies in this discussion, since it is quite logical to expect insignificant differences between two

groups that generally had almost normal baseline $\text{PaO}_2/\text{FiO}_2$ ratio. During the first day, the vast majority of Maxwell's patients had fairly normal $\text{PaO}_2/\text{FiO}_2$ ratios of (320 vs. 375) in both study arms.

The baseline $\text{PaO}_2/\text{FiO}_2$ ratio varied extensively among these studies; Varpula reported the worst $\text{PaO}_2/\text{FiO}_2$ in both the APRV and SIMV groups, i.e. 150 ± 10.5 and 164 ± 10.5 , compared to a $\text{PaO}_2/\text{FiO}_2$ of 250 in Putensen's study for both groups. Furthermore, the types of lung injury in Varpula's study indeed were different, in that the majority of the patients (77%) had direct/primary lung injuries in both groups, whereas the patients in the other two studies had indirect/secondary lung injuries. (Table 4 illustrates these differences.).

Table 4 Some indicators of the severity of illness

	ALI (%)		ARDS (%)		P/F at baseline		Type of lung injury
	APRV	Control Group	APRV	Control Group	APRV	Control Group	
Varpula	100	100	100	100	150	164	Majority are direct
Putensen	40	33	14	21	250	250	
Maxwell	19.3	25.6	25.8	28.1	320	375	

In addition to the above indicators that may be used to assess lung injuries, other available severity-of-disease classification systems are illustrated in Table 5, i.e. Acute Physiology and Chronic Health Evaluation (APACHE II) and Injury Severity Score (ISS).

Table 5 ISS and APACHE II in the three studies

Indicator of lung injury	ISS		APACHE II	
	APRV	Control Group	APRV	Control Group
Putensen	50 ± 2	49 ± 2	NA	NA
Varpula	NA	NA	15 (12.5-18.0)	14 (11.25-17.0)
Maxwell	30.3 ± 9.8	28.6 ± 6.4	20.5 ± 5.3	16.9 ± 7.2

1.3.4 Equipment used

Varpula used a Servo 300 SV ventilator that did not have APRV among its installed modes; however, as a substitute, they attached a special module (Bivent, Siemens-Elema) to the ventilator (76, 79). Such a module lacks some important features, and this could have negatively affected the functionality of the mode. The methodological limitations in that module deterred the researcher's ability to obtain accurate measurements; for example, the P_{Mean} (76), which constitutes one of the distinguishing factors between APRV and other conventional modes, was not measured. Furthermore, their assessment of the amount of spontaneous breathing was questionable, because they observed its presence only through the waveform on the ventilator display (76), which could have been affected by artefacts, such as the presence of water or secretions in the circuit. This may have affected the mode's application and the quality of the results that were obtained. Having such severe forms of respiratory failure with high pulmonary resistance without any pressure support might have imposed an additional burden on the APRV group, unlike patients in the control group whose spontaneous respiration was completely supported (PS). In contrast, Putensen (55) and Maxwell (60) used Evita ventilators from Drager, which were equipped with a factual APRV mode from which accurate measurements could be obtained directly.

1.3.5 Applied ventilatory protocol

The applied ventilatory protocol might have had a substantial association with the outcomes that were observed. In addition to the technical deficiencies in Varpula's (76) machines, the three researchers applied the mode quite differently for both the control and intervention groups, as discussed below.

1.3.6 Control group

Varpula (76) and Maxwell (60) allowed patients to breath spontaneously with a PS of (10 cmH₂O) on the SIMV mode; Putensen (55) used the A/C mode and allowed no spontaneous breaths.

Varpula (76) used a V_T of (9–10 ml/kg) which was significantly greater than that of Putensen, who used a V_T of less than 7 ml/kg (55). Although Maxwell (60) used the lowest V_T (6.4 ± 1.2 ml/kg) among the three trials, and it is debatable whether it should qualify for comparison with the other two studies for the following reasons, i.e. 1) the majority of Maxwell's patients had no lung injuries and 2) at 72 hr, all of the patients in the SIMV group, except two, were switched to CPAP+PS mode, which is a completely different mode. These disparities in the control group and the other differences that existed in the APRV group might be enough to produce different outcomes.

1.3.7 APRV group

Keeping in mind that, for the reasons stated above, Maxwell's (60) study may not be discussed extensively and used in the comparison, the disparities in the intervention group of Varpula's (76) and Putensen's studies (55) are described in more detail below, including T_{High} , T_{Low} , P_{High} , P_{Low} , and adjunct interventions.

1.3.8 T_{High}

Maxwell (60) initiated the T_{High} at (4.0, 4.5, or 5.0 s), depending on patients' spontaneous breathing at the onset and allowed its titrations between 4–8 s to correct oxygenation and ventilation, i.e. the minimum possible T_{High} was 4.0 s. Although Varpula (76) initiated the T_{High} at 4.0 s, their protocol stated that correcting the ventilation (CO_2) could be achieved by either reducing the sedation level (in order to enhance more spontaneous breathing) or by reducing the T_{High} (to increase the minute ventilation) (76); yet, one could simply question the extent to which the T_{High} should be reduced. This was not specified in the protocol, though it may consequently lead to a completely conventional mode that's overlaid with the APRV mode. Such reductions in the T_{High} could have also reduced the P_{Mean} and therefore affected lung recruitment as well as the entire oxygenation. It is likely that any reduction in T_{High} would cause a proportional reduction in the P_{Mean} , which in turn may affect recruitment and therefore decrease oxygenation (18).

This may illuminate the gradual, yet dramatic, decline in $\text{PaO}_2/\text{FiO}_2$ ratio in Varpula's trial, which correlated well with the reduced T_{High} that started

after the first 24 hr. Such a hypothesis could be confirmed by Varpula's statement that "moderate hypercapnia developed during the first study day and PaCO_2 was returned towards normal after 4 days" (76). This probably means that, when the T_{High} was set initially at its highest level (4 s), a certain P_{Mean} was produced that could have caused statistically significant improvement in the $\text{PaO}_2/\text{FiO}_2$ ratio that was observed at the outset. However, despite such improvement in oxygenation, the PaCO_2 was high, and this may have necessitated a reduction in the T_{High} to correct it. Consequently, this reduction could have reduced the P_{Mean} , causing de-recruitment and worsening the $\text{PaO}_2/\text{FiO}_2$ ratio, and changed the ratio to more of a BIPAP mode or even a conventional mode as opposed to the APRV mode. By looking at the M_V measurements, it was apparent that it started to increase continuously after day 1, going from 8.5 to 10 L/min by day 5 and subsequently maintained at 10 L/min, which may explain the corrected PaCO_2 as a result of reducing the T_{High} . Still, the question is, "Can one explicitly describe the mode that was utilised without knowing the actual values of T_{High} ?"

It is noteworthy that Varpula (76) allowed T_{High} to be reduced to compensate for hypercapnia, whereas Putensen (55) did exactly the opposite, i.e. he increased T_{High} and reduced the RR simultaneously in a constant and speedy rhythm. The respiratory cycle started from 4 s and was gradually increased up to 10 s over the course of 10 days (an increase in the respiratory cycle of almost 0.6 s/day) (55). It seems that RR and T_{High} , which solely affected P_{Mean} and M_V in both trials, were adjusted in

totally opposite directions, which may explain the different outcomes. Therefore, the reduction in the RR from 16 to 6 breaths per minute (b/min) in Putensen's trial was associated with a simultaneous improvement in oxygenation due to the increased P_{Mean} (55), which couldn't be measured in Varpula's study (76) due to the methodological limitations.

1.3.9 T_{Low}

Some protocols may unintentionally permit latent de-recruitment, either during initial settings or throughout the application process, which may offset the main principle of such a recruitment mode. This could occur effortlessly through the prolonged release time (T_{Low}), especially during the initial settings, in which recruitment is exceptionally crucial. Although Varpula's (76) patients had severe ARDS with de-recruited lungs, the initial T_{Low} was 1.0 s and allowed the expiratory flow to decay to zero, which to our knowledge is longer than that recommended by any recent guidelines and even exceeds the recommended upper limit, which is 0.2 - 0.8 s (18). Habashi recommended that T_{Low} should be set to achieve a PEFR of 50 to 75% to minimise de-recruitment for restrictive lung disease. However, Varpula (76) allowed the PEFR to reach zero, yet they used a PEEP of about 11 cmH₂O. Such settings of T_{Low} and PEEP might not have been enough to prevent de-recruitment or to recruit the collapsed lung units of their ARDS patients. It was reported that these lung regions could be extremely resistant to measures to recruit them (80), especially in dependent regions after the development of consolidation or collapse. Moreover, an expiratory

time of ≤ 0.6 s or a PEEP of > 20 cmH₂O was required to prevent cyclic alveolar collapse in oleic acid-induced ARDS (81).

1.3.10 P_{High} and P_{Low}

The initial P_{High} in Maxwell's (60) trial was adjusted to equal the P_{plat} from the original SIMV settings, while the P_{Low} was set at zero. Varpula (76) adjusted the P_{High} to deliver a V_T between 8-10 ml/kg, but P_{High} never exceeded the upper inflection point (UIP) if ever detected from the pressure-volume curve (PV-curve). When setting the P_{Low}, Varpula (76) used inconsistent PEEP settings, because he changed the method of constructing the PV curve after the twelfth patient. He stated, "PEEP was titrated above the lower inflection point (LIP) of the PV curve. If the LIP was not detectable, PEEP was set to 10 cmH₂O" (76). The overall PEEP was 11 ± 0.3 cmH₂O during the first week (76). Conversely, Putensen (55) used constant, clearly-defined LIP and UIP values on the static P-V curve for all patients, on which they based the level of PEEP around 12 ± 1 cmH₂O. Although both Varpula and Putensen used almost the same PEEP levels, these levels may have been suboptimal for the patients in Varpula's study since their conditions were much more serious than those in Putensen's study.

1.3.11 Adjunct intervention

Prone positioning was part of the protocol for both groups in Varpula's study, and the patients were assessed twice a day and placed in the prone

position for a six-hour period (76). This intervention easily could have disconnected the ETT from the ventilator circuit and caused immediate derecruitment, given that a disconnection of just 0.8 s is enough to cause such deterioration in critically-ill patients. Neumann and colleagues used dynamic CT scanning in a porcine ALI model and reported that a PEEP level of at least 20 cmH₂O or an expiratory phase of 0.6 s, at most, was required to avoid cyclic alveolar collapse (81). Table 6 compares several aspects of the three studies.

Table 6 Comparison of the studies conducted by Varpula, Putensen, and Maxwell

Author Year	Varpula 2004	Putensen 2001	Maxwell 2010
Design	RCT	RCT	RCT
Diagnosis	Confirmed ARDS	Multiple Trauma	Trauma
N	58	30	63
Patient population	ARDS	ALI/ARDS	Respiratory failure
Intervention group	APRV	APRV	APRV
Duration of MV	Primary outcome	Secondary outcome	One of the uncategorised outcomes
Outcomes (APRV group)	Significant improvement in PaO ₂ /FiO ₂ ratio within the first 24 hr ↓ inspiratory pressures (p = 0.007)	↓ duration of mechanical Ventilation (p = 0.032) ↓ ICU stay (p = 0.032) ↑ CRS, PaO ₂ , P _{aw} and DO ₂ (p = 0.05) ↓ CI, SVR, PVR, venous admixture and O ₂ extraction (p = 0.05)	↑ Mv p = 0.004, and ↑ PaCO ₂ in LOVT group. ↑ P _{Mean} (p = 0.001)
Timing of the intervention	Median = 39.1 (± 2.3 hr)	APRV was used as a primary mode	Immediately after developing respiratory failure

1.3.12 Further concerns

Further concerns on these three studies are discussed separately below:

1.3.12.1 Varpula's trial (76):

Although Varpula's patients fulfilled the criteria of ARDS, he did not follow the gold-standard, low-tidal volume approach used by the ARDSnet trial; He explained this by stating "We planned this study before the ARDS network study was published." Therefore, one may have the following concerns:

1. SIMV mode was used instead of the A/C mode that was used in the ARDSnet trial.

2. The large V_T plus the persistent spontaneous breathing in the control group may draw clinician's attention, and these questions may be asked:

- a) Will this large V_T be used in conventional modes to treat ARDS patients?
- b) Is SIMV recommended to ventilate such critically-ill patients?
- c) Was the mode in the interventions group representative of the real APRV mode?

1.3.12.2 Maxwell's trial (60):

Although Maxwell and colleagues used a low V_T of (6.4 ± 1.2 ml/kg), which indicates a reasonable compliance with the ARDSnet criteria, they utilised an SIMV+PS that allowed spontaneous breathing, unlike the mode used in the ARDSnet trial. Moreover, most of the patients, especially those in the control group, had no lung injury.

1.3.12.3 Putensen (55):

Putensen administered muscle paralysis and heavy sedation to all patients in the control group. He used APRV mode also for the control group 72 hr after randomisation.

It seems clear that none of the three trials used the ARDSnet gold standard, lung-protective strategy for their control groups, making meaningful comparisons difficult due to significant clinical and methodological heterogeneity. However, in the last 5 years, a single RCT that included the duration of MV among its outcome measures was recently published (62).

The study seems to have avoided most of the limitations of the above three RCTs. It enrolled 52 patients with moderate-to-severe ARDS at a Chinese hospital over a 2-year period, randomised between APRV and SIMV with LOVT using an AVEA ventilator. APRV settings were described: P_{High} 30 cmH₂O, T_{High} 4-8 sec, P_{Low} 0 cmH₂O, T_{Low} 0.4-0.8 sec, and PEEP $P_{\text{flex}} + 2$ cmH₂O. Lung function and haemodynamics were significantly improved in the APRV compared with SIMV patients, and the APRV group had more days without sedatives (22 vs. 17; $p = .036$), more days off MV (20 vs. 15; $p = .046$), and fewer ICU days (7 vs. 10; $p = .035$). However, mortality at 28 days was similar between APRV and SIMV groups (28.5% vs. 34.6%; $P > .05$). These positive findings may have been resulted due to several reasons; 1) better selection of patients (e.g. comparable baseline data); 2) consistent method (e.g. using proper equipment); 3) and an application of a real APRV (e.g. settings indicated above). However, two concerns can be noted in this study, the small sample and the use of SIMV rather than VC (according to the ARDSNet guidelines) although they used small V_T lung protective ventilation.

Table 7 shows some comments that should be considered when comparing these studies. As discussed earlier, many confounding factors could have caused the inconsistent outcomes in the published studies

Table 7 Comments on the studies conducted by Varpula, Putensen, and Maxwell

Author	Comments
Varpula ⁽⁷⁶⁾	• The study was terminated for futility. • They changed several general principles of care. • The ventilator that was used was not originally equipped with an APRV mode. • Very late intervention. • T_{High} was adjusted in opposite direction. • Minimum T_{High} and maximum T_{Low} were not addressed, • Inconsistent P-V curve measurements and PEEP adjustment. • Lack of accurate measurements of clinically-relevant data, such as the P_{Mean}.
Putensen ⁽⁵⁵⁾	• Assisted breaths were completely suppressed with neuromuscular blockade in control group (PCV) for 72 hr.
Maxwell ⁽⁶⁰⁾	• All but two SIMV patients were switched to PSV mode within 72 hr. • Baseline APACHE II was significantly worse for APRV than LOVT patients, (p = 0.027). • No named primary outcome

However, studies that revealed positive outcomes, such as oxygenation, ventilation, recruitment, and haemodynamic status, seemed to have some commonalities (some examples are indicated in Table 8), i.e. 1) early institution with APRV, 2) using a long T_{High} of almost 4 s that was either maintained or increased throughout the course of APRV, and 3) using a short T_{Low} of (0.2-0.8 s) to keep the PEFr in the range of 50-75%; however, if T_{Low} was allowed to reach 1.0 s for any reason, the potential loss of intrinsic PEEP must be compensated for by maintaining an appropriate level of PEEP (through P_{Low}) to prevent de-recruitment. Misty and colleagues reported that a T_{Low} of 0.4 - 0.7 s was required to achieve PEFr of 50% in a low compliance lung model (82).

Table 8 Some commonalities in APRV application that have been suggested to be associated with positive outcomes

Author	Initial T _{High} (seconds)	T _{Low} (seconds)	PEFR (%)	P _{Low} (cmH ₂ O)	Outcomes (On APRV compared to CV)
Kaplan((54) 2001	4.5	0.8	NI	0	↑ Urine output, CI, and DO ₂ ↓ CVP, lactate, Paw use of neuromuscular blockade and sedatives (p = 0.01)
Yoshida(29) 2009	4	NI	50-75	0	↑ MAP (p = 0.018) ↑ P/F (p = 0.018) ↓ PA-aO ₂ (p = 0.015)
Dart(53) 2005	3-4 **	NI	40-50	0	↑ PaO ₂ /FIO ₂ (p = 0.017) Authors were not able to assess haemodynamic and sedation requirement
Paul(20) 2009	4	0.7-1.0	NI	5	↑ PaO ₂ /FIO ₂ (p = 0.03) ↓ V _D /V _T (p = 0.01)
Li (62) 2016	4-8	0.4-0.8	NI	0	↑ Lung function and haemodynamics ↑ days without sedatives (p = 0.036) ↑ days off MV (p = 0.046), and ↓ ICU days (p = 0.035).
Lim (58) 2016	4-6	0.2-0.8	50-75%	0	↑ PaO ₂ /FIO ₂ (p < 0.005) (early and sustained) ↓ incidence of clinically significant barotrauma and progression to ECMO

MAP= mean arterial blood pressure (cmH₂O); PA-aO₂ = alveolar-arteriolar oxygen gradient, NI= not indicated in the study, ECMO= exploring extracorporeal membrane oxygenation

** These settings only in case of absent spontaneous breathing; otherwise the T_{High} was longer

1.4 What is the Situation of APRV in Clinical Practice?

1.4.1 ARDS Guidelines

Guidelines for the ventilatory management of ARDS are emerging, and are under development by the American Thoracic Society and UK Intensive Care Society (83). The Scandinavian guideline on MV in adults with ARDS includes a weak recommendation that “partial modes” of ventilatory support such as APRV may be used if clinically feasible, based on “very low quality” evidence, noting that their Putensen et al (55) and Varpula et al (76) resources had inadequate control groups and the studies were underpowered to assess mortality (84).

The 2013 Brazilian recommendations for MV suggest using APRV when maintenance of spontaneous ventilation and alveolar recruitment is necessary, noting that APRV may improve gas exchange and reduce dead space and asynchrony (85). The guideline differentiates between APRV and BIPAP as reversed lengths of P_{High} and P_{Low} , without referencing a protocol.

1.4.2 Prevalence of APRV Use in Real World Patients?

One review article was followed by a panel discussion where a contributor noted that APRV was “all but outlawed” at his hospital, which is affiliated with a major U.S. university (86). Despite this observation, several reports indicate that APRV, or the nebulous BiPAP/APRV, is in widespread use. In the prospective PROVENT study of ICU admissions during a specified week

in 2014 in 16 countries, BiPAP/APRV was the third most common ventilation mode, reported for 22% of 935 patients (8).

In the Gonzalez study, 11.3% of 4,968 patients in 23 countries, comprising $\leq 2\%$ ARDS patients, were ventilated for at least 1-day with BiPAP/APRV (35). Although the conventionally ventilated patients were distributed among Europe (30%), Latin America (40%), and USA/Canada (27%), most (98%) of the BiPAP/APRV cohort was from Europe, of which 84% were from Germany.

A survey that received responses from 70 ICUs in Ontario Canada reported that 70% had protocols for MV in place (87). However, the initial mode was not specified in 80% of protocols. APRV was the most commonly used option for treating refractory hypoxaemia, reported by 61% of respondents.

An exploratory survey that received responses from 46 burn centres in North America revealed approximately 15% used APRV for cases without inhalation injury, which increased to approximately 25% when inhalation injury was present (88). For mild ARDS, 11% changed MV to APRV, which increased to 28% for severe ARDS.

A survey of extracorporeal membrane oxygenation (ECMO) use in managing severe ARDS among academic medical centres in the U.S. received 381 responses (89). APRV was reported as being available and used by 64% of respondents. The survey acquired the rank preference order for rescue treatment when conventional MV failed, and APRV was the

first choice over inhaled nitric oxide (iNO), prone positioning (PP), HFOV, and ECMO.

Finally, an international survey to describe ventilation practices in centers registered with the Extracorporeal Life Support Organisation received 141 responses (90). For adult patients, 11% (4/38) reported using APRV as the primary initial ventilator mode during ECMO, and APRV was the protocol-defined mode for that use in 1 of 38 submitted MV protocols.

Despite all concerns, the use of APRV has been increasing globally over time; RCTs are being conducted to investigate more about APRV.

1.5 Ongoing Studies

Ongoing Trials

A few ongoing APRV trials are registered (

	1	2	3	4
NIH NCT No.	01339533	01901354	02866513	00793013
Location	U.S. (UT)	U.S. (WI)	France (Marseille)	U.S. (TN)
Design	Parallel group RCT	Randomised crossover	Single group	Parallel group RCT
Patients	Hypoxemic respiratory failure	ALI for <7 d MV <14 days	On APRV per clinician discretion	Hypoxia and pulmonary distress, with ≤ 6 h CV
Experimental Group(s)	Habashi protocol ($P_{Low}=0$) Low stretch (titrate P_{Low} to release volume 4-8 cc/kg)	APRV	N/A	APRV
Comparator Group	AC/VC Conventional	ARDS Net	N/A	ARDS Net

	Ventilation (ARDS Net protocol)			
Primary Outcome	P/F ratio Day 3	IL-6 at 6 and 12 hours	24-h transpulmonary pressure	All cause mortality (28-day or in hospital)
Secondary Outcomes	Sedative/vasoactive medication use Feasibility of and compliance with 2 APRV protocols	Other lung injury biomarkers, metabolic and respiratory variables	Tidal volume	Other respiratory and metabolic outcomes
Estimated N	246	100	20	368
Start Date	2011	2013	2016	2011
Estimated Completion	2016	2017	2017	2015
Comments	Closed. Data analysis and report preparation underway (Hirshberg, personal communication)			Closed due to lack of financial support after enrolling 50 patients (Tumlin, personal communication)

Table 9). NCT01339533 is a 3-arm parallel group RCT comparing APRV following either the Habashi protocol or a “low stretch” APRV protocol with CV (163). The primary outcome is P/F ratio on day 3 of MV. In addition to evaluating the feasibility of the 2 APRV protocols, the study is assessing compliance with each protocol. The study is now closed, and data analysis is ongoing. (163) (Personal communication). When published, this important protocol-focused study is expected to be the largest APRV RCT to date (N=246); however, mortality is not among the primary or secondary endpoints.

Two other shorter term trials include the ALIVE study in the United States, which is investigating IL-6 and other lung injury biomarkers in a crossover study comparing APRV with low-tidal-volume ventilation in an estimated enrolment of 100 patients (164). A 24 hr transpulmonary pressure study is

underway in a single group of patients in France who are on APRV at the discretion of their physician (N=20) (165). Completion of both studies is expected in 2017.

The BIRDS and EOLIA studies in France have large enrolment targets, with mortality as primary outcomes (162). The BIRDS study is a parallel group RCT comparing APRV with the ARDSnet protocol in an expected enrolment of 700 patients, with in hospital mortality as the primary outcome (162). The study has enrolled over 550 patients, and is on target for the projected 2018 completion (personal communication).

EOLIA is exploring extracorporeal membrane oxygenation (ECMO) compared with CV in an estimated 331 patients with ARDS (162). The ECMO group therapy will be combined with either VAC or APRV using PEEP ≥ 10 cmH₂O and P_{High} ≤ 20 cmH₂O (91). EOLIA also has an estimated completion during 2018.

Table 9 Ongoing APRV Trials

	1	2	3	4
NIH NCT No.	01339533	01901354	02866513	00793013
Location	U.S. (UT)	U.S. (WI)	France (Marseille)	U.S. (TN)
Design	Parallel group RCT	Randomised crossover	Single group	Parallel group RCT
Patients	Hypoxemic respiratory failure	ALI for <7 d MV <14 days	On APRV per clinician discretion	Hypoxia and pulmonary distress, with ≤ 6 h CV
Experimental Group(s)	Habashi protocol ($P_{Low}=0$) Low stretch (titrate P_{Low} to release volume 4-8 cc/kg)	APRV	N/A	APRV
Comparator Group	AC/VC Conventional Ventilation (ARDS Net protocol)	ARDS Net	N/A	ARDS Net
Primary Outcome	P/F ratio Day 3	IL-6 at 6 and 12 hours	24-h transpulmonary pressure	All cause mortality (28-day or in hospital)
Secondary Outcomes	Sedative/vasoactive medication use Feasibility of and compliance with 2 APRV protocols	Other lung injury biomarkers, metabolic and respiratory variables	Tidal volume	Other respiratory and metabolic outcomes
Estimated N	246	100	20	368
Start Date	2011	2013	2016	2011
Estimated Completion	2016	2017	2017	2015
Comments	Closed. Data analysis and report preparation underway (Hirshberg, personal communication)			Closed due to lack of financial support after enrolling 50 patients (Tumlin, personal communication)

	5	6	7 BiRDS	8 EOLIA
NIH NCT No.	02639364	02071277	01862016	01470703
Location	China (Sichuan)	Canada (Toronto)	France (Angers)	France (Paris)
Design	Parallel Group RCT	Random crossover	Parallel group RCT	Parallel group RCT
Patients	ARDS, ≤ 48 h MV	MV with assist controlled mode (volume or pressure)	ARDS	ARDS MV ≤ 6 days
Experimental Group(s)	APRV Nellcor Puritan Bennett 840	APRV	APRV	ECMO with VAC or APRV
Comparator Group	ARDS Net	1. BIPAP 2. BIPAPassist	ARDS Net	CV
Primary Outcome	MV free days	TV at 20 min	In hospital mortality	Mortality day 60
Secondary Outcomes	Hospital mortality, ICU / hospital stay, respiratory and treatment variables	Transpulmonary pressure WOB Breath type frequencies	28 day mortality, other clinical outcomes	Other mortality endpoints
Estimated N	200	15	700	331
Start Date	2015	2014	2013	2011
Estimated Completion	2016	2017	2018	2018

An RCT in the United States (NCT00793013) was launched in 2001 with a target enrolment of over 350 patients to compare APRV with the ARDSnet protocol (166). The primary endpoint was 28-day or in hospital all-cause mortality. After enrolling 50 patients, this study was closed due to lack of financial support (personal communication).

These trials are expected to produce valuable data; however, acquiring additional supporting evidence is also necessary. The unfortunate termination of NCT00793013 is accompanied by anecdotal evidence that suggests numerous APRV studies were planned but never initiated. RCT funding is a major constraint, and equipoise may be an issue when study team members have a foregone conclusion regarding the role of APRV. Therefore, other strategies for assessing the potential benefits of APRV should be considered.

These reports, surveys, and on-going trials indicate that APRV is in use globally, despite continuing concerns over the lack of evidence for a benefit. With this notable use of a controversial MV, centres using APRV should be encouraged to adopt discrete protocols for its use and establish registries that can provide data to help clarify the role of APRV.

1.6 Conclusion

APRV is a promising mode for the treatment of various respiratory diseases using an open-lung approach. When compared with CV and HFOV, APRV generally has been associated with better success in achieving the goals of ventilator management set by the AECC on ARDS, Part 2 which include: minimise O₂ toxicity, recruit alveoli, prevent atelectasis, minimise high airway pressures, and use sedation and paralysis judiciously. However, despite the reported advantages of APRV, decisive conclusions cannot be drawn due to the major confusion between APRV and other, similar modes, such as BIPAP. Heterogeneity among studies of APRV is understandably extensive, which contributes to outcome variability among published studies. Even in the RCTs that investigated the duration of MV, they were generally plagued by various aspects of heterogeneity. This could be due to the diverse clinical practice among centres as well as the confusing nomenclature. APRV is in use globally, despite continuing concerns over the lack of evidence for a benefit.

It is clear from the evidence that some remarkable aspects may represent attractive areas for future research to investigate clinically relevant outcomes such as mortality. Therefore, there is a need for well-designed, human, randomised clinical trials comparing APRV to the ARDSnet gold-standard, lung-protective strategy before drawing definitive conclusions. RCTs remain the benchmark of evidence-based medicine. Accordingly, the call for robust RCT data to confirm a possible role for APRV is appropriate. However, the performance of APRV RCTs has not expanded sufficiently to

resolve the controversies surrounding its role, particularly in ARDS. Carefully designed and documented observational studies can provide important real world data, particularly with the increasing presence of registries and healthcare databases. However, clear clinical practice guidelines for optimum use of APRV must be developed to standardise the application for further research.

Chapter 2

Evaluating patients' responses to changes in inspiratory pressure on APRV mode compared with conventional ventilation in patients with moderate ARDS: An investigation using physiological modelling vs. a real patient

1.7 Question

What is the effect of varying P_{High} , on gas exchange, airway and alveolar pressures in a moderately diseased modelled patient?

1.8 Primary outcomes

Arterial pH (p_{Ha}), PaO_2 , PaCO_2 , $\text{PaO}_2/\text{FiO}_2$ ratio, airway and alveolar pressures.

1.9 Secondary outcomes

Inhaled/exhaled $\dot{M}_V$ and V_T , partial pressure of oxygen in the venous blood (PvO_2), partial pressure of carbon dioxide in the venous blood (PvCO_2), shunt fraction (Q_s/Q_t), and mean ventilation/perfusion ratio (V/Q).

1.10 Introduction

The use of CV modes of pulmonary ventilation has been extensively addressed in the literature; however, there is no consensus on a standard guidelines for the use of APRV (71). It has been reported that the application of APRV entails much more knowledge and clinical skills than the descriptions in the literature indicate (73). Unlike CV, APRV may provide more choices when correcting hypoxaemia and/or hypercapnia. For example, in conventional modes, increasing either FiO_2 or PEEP commonly is used to correct hypoxaemia. In contrast, the clinician has more options to improve oxygenation in the APRV mode, including increasing P_{High} , P_{Low} , or T_{High} , or decreasing T_{Low} . Therefore, the aim of this study was to evaluate the responses of the integrated cardiopulmonary models (ICPMs) to

changes in blood gases, airway and alveolar pressures, and measured ventilator variables after alterations were made to patient's mode and ventilator configurations including P_{High} , P_{Low} , T_{High} , and T_{Low} , where possible. ICPMs represent the upgraded version of the Nottingham Physiology Simulator (NPS) that has been extensively tested and validated in several studies (92, 93).

1.11 Method

Using ICPMs (169), we simulated a 70 kg moderately diseased, adult male patient that is mechanically ventilated initially with Conventional ventilation (CV_{Sim}) using pressure control (PC) mode; Table 10 shows the physiological and the initial respiratory parameters. The patient's $\text{PaO}_2/\text{FiO}_2$ ratio was 19.1 kPa which indicates moderate ARDS severity, according to the Berlin Definition (94). The model was configured to produce a certain level of V/Q mismatch; the defect was created by varying the compartmental bronchiolar and pulmonary capillary resistances in addition to a true (absolute) shunt fraction, as shown in

Table 11. Outcome measures including, pHa , PaO_2 , PaCO_2 , PvO_2 , PvCO_2 , airway and alveolar pressures, measured inhaled/exhaled M_V and V_T , measured positive end-expiratory pressure (PEEP_M), Q_s/Q_t , and V/Q were recorded on the initial settings. For alveolar pressures, we used alveolar peak pressure (Alv/Peak) as a surrogate for P_{Plat} while alveolar minimum pressure ($P_{\text{Alv/Min}}$) as a surrogate for PEEP_M . Then, we increased the level of

inspiratory pressure control (PC) up to 45 cmH₂O in a step of 5 cmH₂O as shown in

Table 12, outcome measures were recorded at each PC. Subsequently, the ventilator mode was switched to simulated airway pressure release ventilation (APRV_{Sim}) with initial respiratory parameters, as shown in

Table 13. We chose to vary P_{High} only while keeping other parameters (i.e. P_{Low}, T_{High}, and T_{Low}) constant; with the aim of varying other configurations in the future in the same manner if the results of this study were credible. In this study, we used the term inspiratory pressure for the set peak airway pressure; P_{High} is used during APRV while PC is used for CV. During APRV, the protocol of increasing the inspiratory pressure and data recording of CV_{Sim} was repeated at each P_{High}, as shown in

Table 12. Subsequently, we reviewed data of 87 patients receiving intensive therapy with APRV mode in all adult intensive care units (69 beds) at King Fahad Medical City (KFMC) including surgical, general, and cardiac ICUs.

We took any dataset that met the following inclusion criteria:

1. Receiving MV via APRV mode
2. Having no spontaneous breathing
3. Matching the configurations (T_{High} , T_{Low} , and P_{High}) that we used in our simulated patient
4. Having all pertinent results of arterial blood gases
5. Being ventilated with a CV prior to the institution of APRV
6. Having an analogous $\text{PaO}_2/\text{FiO}_2$ to that of simulated subject

Only one real patient met our inclusion criteria,

Table 14 and

Table 15 show the physiological and initial mechanical ventilator settings on conventional (CV_{Real}) and APRV ($\text{APRV}_{\text{Real}}$) modes, respectively. The trend of relevant outcome measures of this real patient was consequently compared with that of simulated (CV_{Sim} & APRV_{Sim}) subjects to identify any associations.

Finally, the data of the real patient was aligned and the simulation was re-run, i.e. we readjusted the configurations of the simulated subject to match that of the chosen real patient. In that we adjusted the P_{High} to 36 cmH₂O, P_{Low} to 8 cmH₂O, FiO_2 to 0.55, and V_T at 565 ml. Next, we compared all

variables between these two aligned patients (simulated and real) to identify areas of agreement; variables were analysed and discrepancies were discussed for further investigations in future work.

It is noteworthy that automatic tube compensation (ATC) was not used in this study as it has been developed to overcome the imposed work of breathing due to artificial airways during spontaneous breathing which is not the case with our patients who had only mandatory mechanical breaths.

Table 10 Physiological and initial mechanical ventilator settings on the conventional mode for the virtual patient used in this investigation

Weight	70 kg
Height	1.70 meter
Ideal Body Weight	65.8 kg
Gender	Male
Body surface area	1.83 m ²
body mass index	24.2 kg/m ²
Inspired gas	Warmed and humidified to 37C
Pressure control	25 cmH ₂ O
PEEP	10 cmH ₂ O
Inspiratory time (T_I)	1.3 sec
Expiratory time (T_E)	2.5 sec
Respiratory rate (RR)	16 b/min
Tidal volume (V_T)	525 ml
Inspiratory to expiratory ratio (I:E ratio)	1:2.03
Automatic tube compensation (ATC)	OFF
Base excess	0 mmol litre ⁻¹
Endotracheal tube information	Length/internal diameter 24 cm/ 8.0 mm
Air way resistance	0.732 Pa/L/min
Atmospheric pressure	101 kPa

Table 11 Model configurations for V/Q mismatch in both modes

Bronchial resistance	400.0-1	1.0-20	28.1-50	1.0-80	1.0-100
Vascular resistance	1.0-1	1.0-20	1.0-50	1.0-80	506.3-100
Anatomical shunt %	27				

Table 12 variables to be adjusted on APRV and conventional modes during examination

	Baseline	Examined range	Increment
P_{High} (cmH₂O)	25	25-45	5
Pressure control (cmH₂O)	25	25-45	5

Table 13 Physiological and initial mechanical ventilator sittings upon switching the mode to APRV for the virtual patient used in this investigation

P_{High}	25
P_{Low}	0 cmH ₂ O
T_{High}	4.5 sec
T_{Low}	0.5 sec
Respiratory rate	12 b/min
V_T	525 ml
PEEP_M	0 cmH ₂ O
Inspiratory to expiratory ratio	9:1
ATC	OFF
Base excess	0 mmol litre ⁻¹
Endotracheal tube information Length/ internal diameter	24 cm/ 8.0 mm
Air way resistance	0.732 Pa/L/min
Atmospheric pressure	101 kPa
Inspired gas	Warmed and humidified to 37C

Table 14 Physiological and initial mechanical ventilator sittings in conventional mode for the real patient

Height	1.58 meter
Ideal Body Weight	54.5 kg
Gender	Male
Pressure control	28 cmH ₂ O
PEEP	14 cmH ₂ O
T_I	1.3 sec
T_E	2.45 sec
Respiratory rate	16 b/min
V_T	320 ml
PEEP_M	14 cmH ₂ O
Inspiratory to expiratory ratio	1:1.8
Base excess	1.5 mmol litre ⁻¹

Table 15 Physiological and initial mechanical ventilator sittings upon switching the mode to APRV for the real patient

P_{High}	36 cmH ₂ O
P_{Low}	8 cmH ₂ O
T_{High}	4.5 sec
T_{Low}	0.5 sec
Respiratory rate	12 b/min
V_T	565 ml
PEEP_M	8 cmH ₂ O
Inspiratory to expiratory ratio	9:1
ATC	OFF
Base excess	0.55 mmol litre ⁻¹

1.12 Results

1.12.1 Simulated patient

Both datasets (conventional and APRV) included adjustments of inspiratory pressure ($P_{aw/Peak}/P_{High}$) from 25 to 45 in increments of 5 cmH₂O. Agreement between the expected and measured magnitude of changes in PaO_2 , PaO_2/FiO_2 , and $P_{aw/Mean}$ were good. However, the magnitude of changes in pH_a and $PaCO_2$ after changes in ventilator mode and settings were significantly large. The mean absolute changes with standard deviation (SD) and 95% confidence interval (CI) in the simulated subject following intervention in both modes are shown in

Table 16. Detailed results of these outcome measures are shown in

Table 17 and Alv/P_{Peak} (cmH₂O); $PaCO_2$, PF, and PaO_2 (kPa); M_V/Exh L/min; V_T/Exh (ml/Kg); and C_{Alv} (ml/cmH₂O)

Table 18 for conventional and APRV modes, respectively. The mean absolute change in the mean airway pressure ($P_{aw/Mean}$) was 13.2 cmH₂O higher during APRV which is in agreement with many published studies.

Figure 1 illustrates the differences in $PaCO_2$ levels between the two modes (CV_{Sim} and $APRV_{Sim}$) at different levels of inspiratory pressures. Figure 2 depicts the significant changes in the M_V following the mode change from CV_{Sim} to $APRV_{Sim}$. Figure 3, Figure 4, Figure 5, Figure 6, and Figure 7 show differences in $V_{T/Ext}$, mean V/Q , Alv/P_{Peak} , C_{Alv} , and $P_{aw/Mean}$ between CV_{Sim} and $APRV_{Sim}$ modes, respectively.

1.12.2 Real patient and relevant comparison with simulated subject

Of the 87 patients, only one dataset of a real patient met our inclusion criteria with the exception of FiO_2 and P_{Low} . FiO_2 was set at 0.7 and 0.55 while P_{Low} was 0 and 8 cmH₂O for APRV_{Sim} and $\text{APRV}_{\text{Real}}$, respectively. However, these differences were readjusted through proper alignment of identical values of simulated subject to match the real ones for precise comparison (discussed later in this chapter). This patient was 73 years old male who was diagnosed with Left Maxilla basal cell carcinoma and severe ARDS according to the Berlin definition (94) with $\text{PaO}_2/\text{FiO}_2$ of 10.1 kPa.

Table 19 depicts summary comparison of exhaled M_V , PaCO_2 , $P_{\text{aw/Mean}}$, and oxygenation ($\text{PaO}_2/\text{FiO}_2$ and PaO_2) between CV_{Real} and $\text{APRV}_{\text{Real}}$.

1.12.3 M_V and ventilation (PaCO_2)

APRV was associated with significantly lower M_V values compared to CV in both real and simulated subjects; however, the PaCO_2 values in the $\text{APRV}_{\text{Real}}$ mode were significantly lower than those of APRV_{Sim} .

1.12.4 $P_{\text{aw/Mean}}$

A better agreement was observed in the $P_{aw/Mean}$ in real and simulated subjects during both modes; conventional modes always revealed lower $P_{aw/Mean}$ compared to APRV. However, for precise comparison, $P_{aw/Mean}$ for the $APRV_{Real}$ was calculated based on the standard equation: $((P_{High} \times T_{High}) + (P_{Low} \times T_{Low})) / (T_{High} + T_{Low})$ because this patient had identical data except for the P_{High} which was fitted into the equation as follow: $((28 \times 4.5) + (8 \times 0.5)) / (4.5 + 0.5) = 26 \text{ cmH}_2\text{O}$. All configurations were readjusted to ensure that simulated and real subjects are identical for proper comparison; this is what we referred to as “corrected”. After correcting all configurations, we re-ran the simulator and obtained relevant measurements. The absolute $P_{aw/Peak}$ and $P_{aw/Mean}$ were good in real and simulated subjects during all modes, as shown in Table 20 and Table 21.

Table 21.

1.12.5 Oxygenation

Significant improvement in PaO_2 was observed after changing the mode from CV_{Real} to $APRV_{Real}$; in that PaO_2 increased from 7 to 10.2 kPa. This was associated with a significantly better PaO_2/FiO_2 which increased from 10.1 to 18.7 kPa. However, compared with CV_{Real} , $APRV_{Real}$ had significantly higher PaO_2 and PaO_2/FiO_2 despite lower PEEP (14 vs. 8) cmH_2O and M_v (8610 vs 7200) L/min, respectively.

1.12.6 Single patient alignment

Figure 8 depicts summary of variables obtained from APRV_{Real} (that met our inclusion criteria) compared to APRV_{Sim} on identical configurations, as shown in

Table 22. Results appeared to be reasonably comparable except for the significant difference in M_V and V_T which may have led to the significant change in $PaCO_2$ (increased) and pHa (decreased).

Table 16 summary of results for the outcome measures between the two modes

	mean Difference (SD)	95% Confidence interval	
		Lower	Upper
$Alv/_{Peak}$ (cmH ₂ O)	12.84 (1.5)	0.65	11.04
$PaCO_2$ (kPa)	7.052 (1.1)	0.50	5.66
pHa	0.11 (0.04)	0.02	0.06
PF ratio (kPa)	8.56 (3.7)	1.66	3.95
PaO_2 (kPa)	6.71 (3.1)	1.36	2.92
$Mv/_{Exh}$ (L/min)	1158.2 (569.5)	254.71	451.02
VQ	22.766 (12.2)	5.44	7.67
$VT/_{Exh}$ (ml/Kg)	27.2 (20.5)	9.17	1.75
C_{alv} (ml/cmH ₂ O)	10.8 (17.8)	7.97	-11.33

Table 17 Summary of results for the CV_{Sim}

PC	$Alv/_{Peak}$	$PaCO_2$	pHa	PF	PaO_2	$Mv/_{Exh}$	mean VQ	$V_T/_{Exh}$	C_{Alv}	$P_{aw}/_{Mean}$
45	28.7	9.8	7.248	17.7	13.15	4677	110.2	289	18	21.6
40	24.6	11.7	7.199	18.0	13.44	4016	94.86	248	18	19.9
35	20.3	14.6	7.134	18.6	13.94	3341	79.06	207	20	18.3
30	15.8	19.45	7.05	19.3	14.44	2666	63.25	165	26	16.6
25	11.4	29.9	6.92	19.7	14.74	1990	47.44	123	56	15
$Alv/_{Peak}$ (cmH₂O); $PaCO_2$, PF, and PaO_2 (kPa); $Mv/_{Exh}$ L/min; $V_T/_{Exh}$ (ml/Kg); and C_{alv} (ml/cmH₂O)										

Table 18 Summary of results for the simulated APRV_{Sim} mode

P_{aw}/Peak	Alv/Peak	PaCO₂	pHa	PF	PaO₂	Mv/Exh	mean VQ	V_T/Exh	C_{Alv}	P_{aw}/Mean
45	42.2	16.8	7.094	19.3	14.4	2804	72.2	234	18	40.5
40	37.4	19.2	7.056	19.6	14.6	2492	64.2	208	18	36
35	35.2	22.5	7.008	19.9	14.9	2180	56.2	182	17	31.5
30	27.6	27.2	6.948	20.1	15.1	1868	48.2	156	17	27
25	22.6	35.1	6.871	20.1	15.1	1555	40.2	130	17	22.5

Alv/Peak (cmH₂O); PaCO₂, PF, and PaO₂ (kPa); Mv/Exh L/min; V_T/Exh (ml/Kg); and C_{Alv} (ml/cmH₂O)

Table 19 comparison between CV_{Real} and APRV_{Real}

	CV_{Real}	APRV_{Real}
Exhaled M_v (L/min)	8610	7200
PaCO₂ (kPa)	5.45	5.18
PEEP (cmH₂O)	14	8
P_{Mean} (cmH₂O)	21	26
PaO₂/FiO₂ (kPa)	10.1	18.7
PaO₂ (kPa)	7	10.2

Table 20 values of P_{aw}/Peak and P_{aw}/Mean during CV_{Real} and CV_{Sim} (corrected)

	Conventional	
	P_{aw}/Peak (cmH₂O)	P_{aw}/Mean (cmH₂O)
Simulated (corrected) *	28	19
Real	28	21

* The corrected values indicate measurements taken after adjustments of all configurations to match those of the real patient

Table 21 values of P_{aw}/Peak and P_{aw}/Mean during APRV_{Real} and APRV_{Sim} (corrected)

	APRV	
	P_{aw}/Peak (cmH₂O)	P_{aw}/Mean (cmH₂O)
Simulated (corrected) *	28	26.6
Real	28	26.6

* The corrected values indicate measurements taken after adjustments of all configurations to match those of the real patient

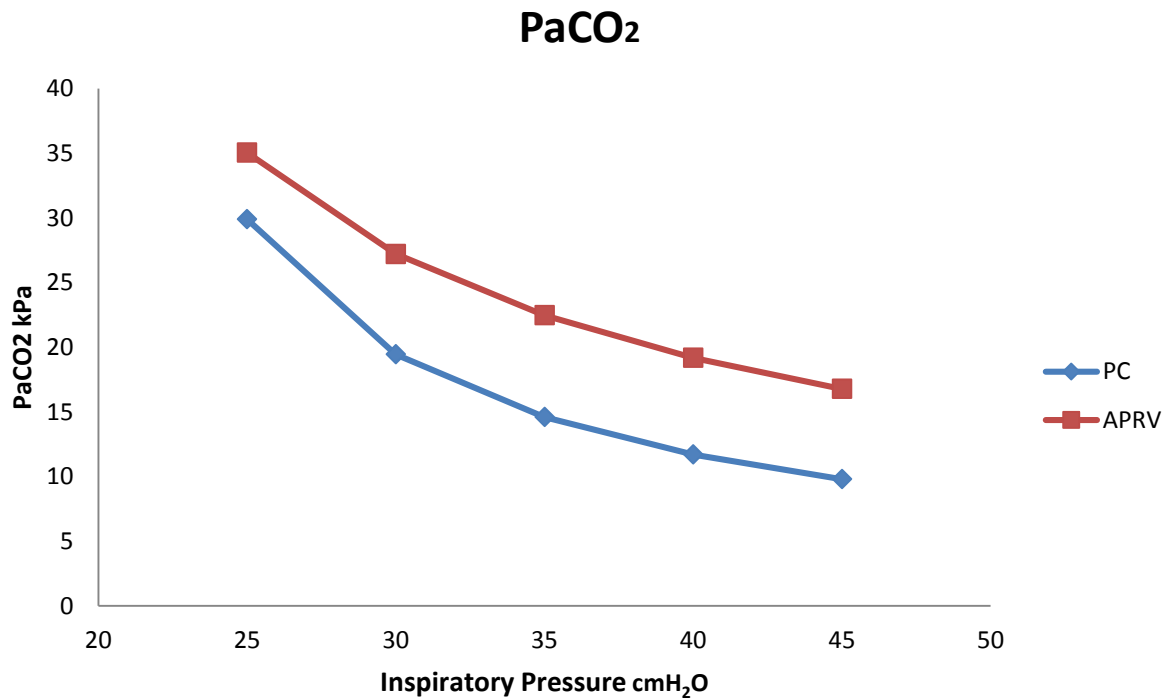


Figure 1 Measured change in PaCO₂ between CVsim (PC) and APRVsim

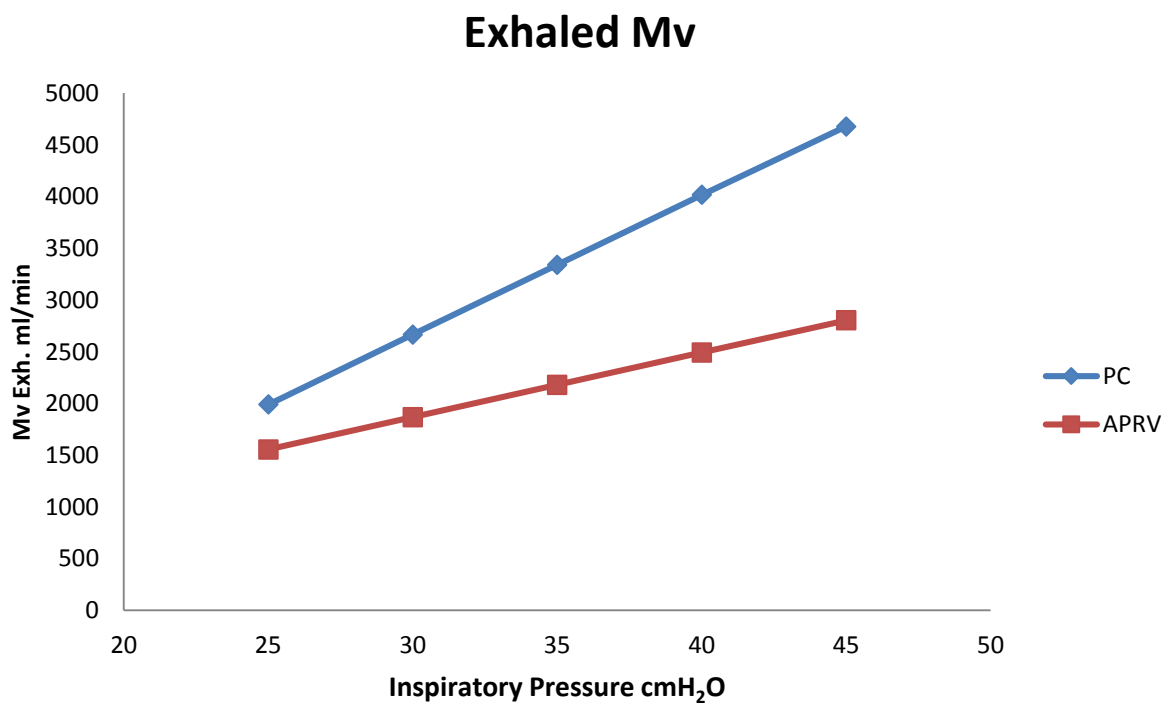


Figure 2 Measured changes in exhaled Mv between CVsim (PC) and APRVsim

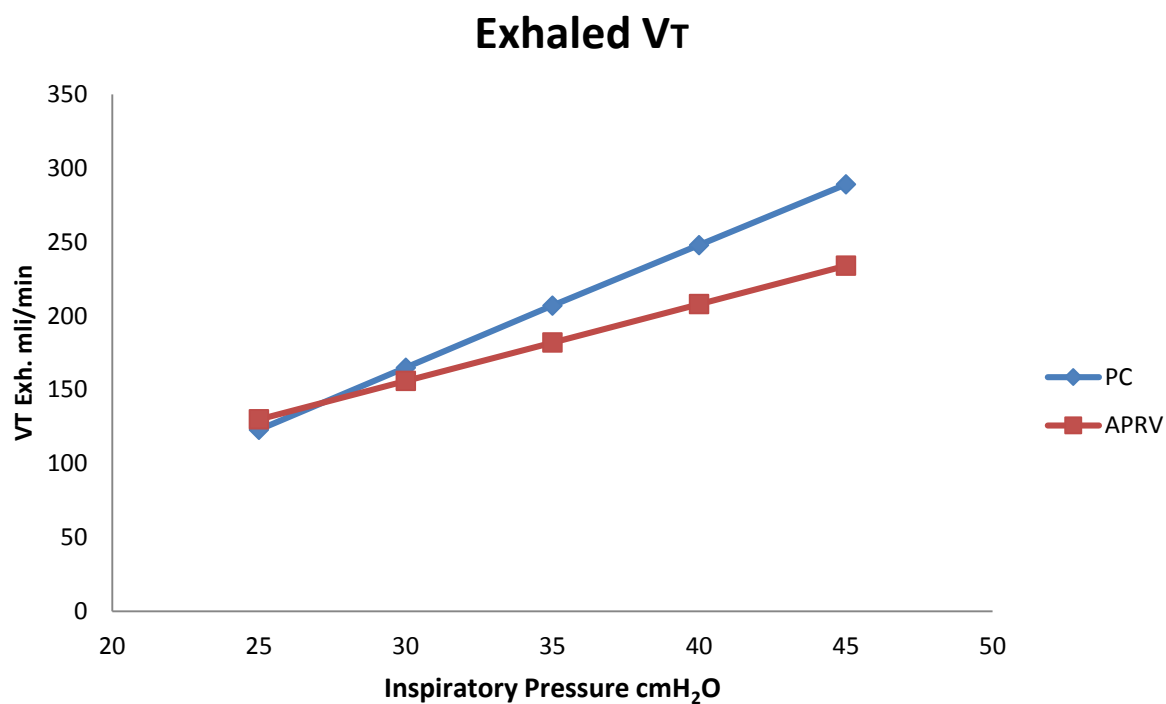


Figure 3 Measured change in the exhaled V_T between CV_{Sim} (PC) and $APRV_{Sim}$

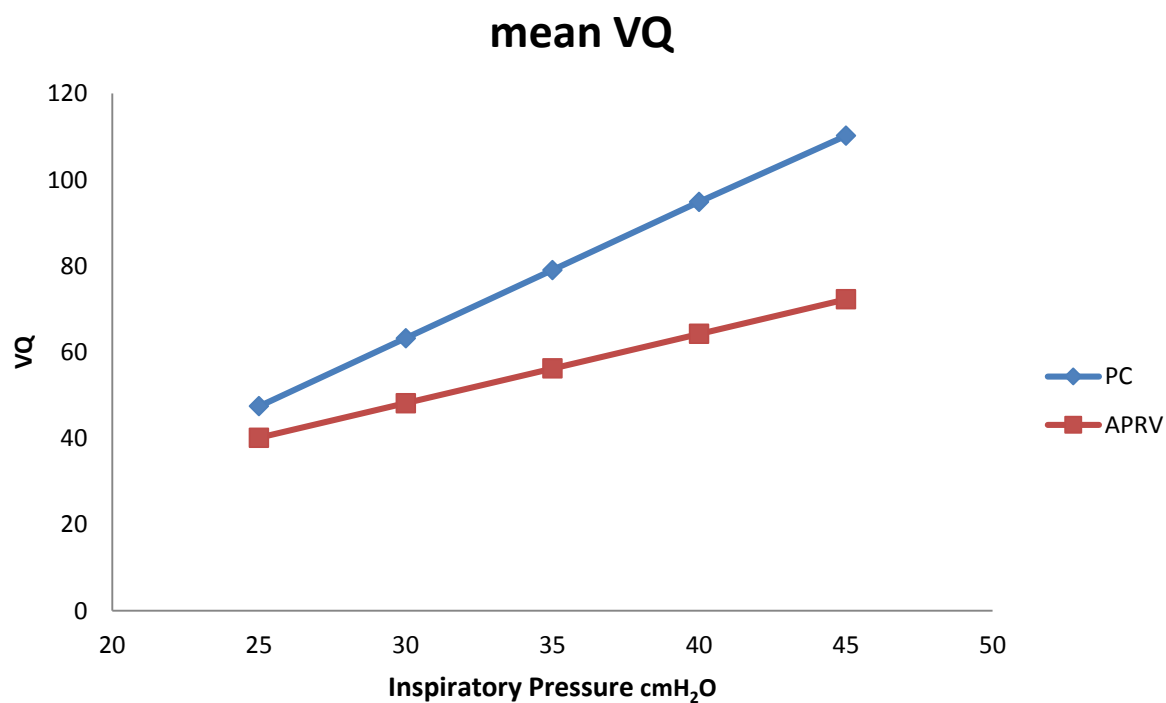


Figure 4 Measured change mean V/Q between CV_{Sim} (PC) and $APRV_{Sim}$

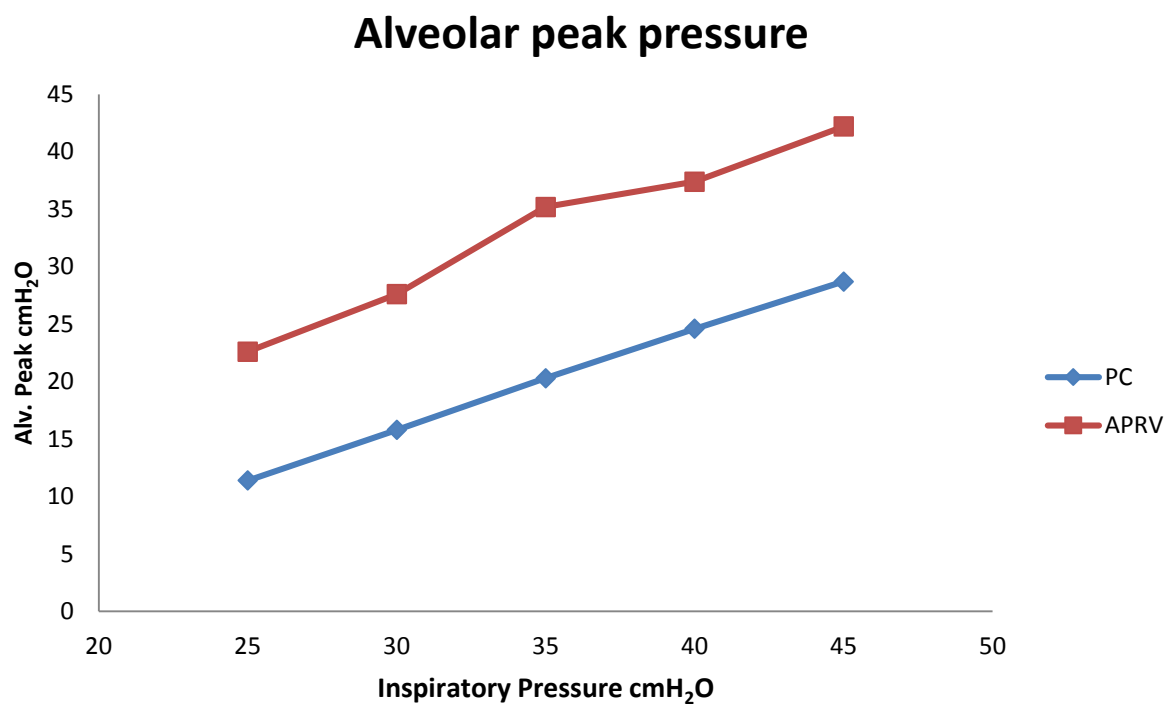


Figure 5 Measured change in Alv/P_{peak} between CV_{Sim} (PC) and $APRV_{Sim}$

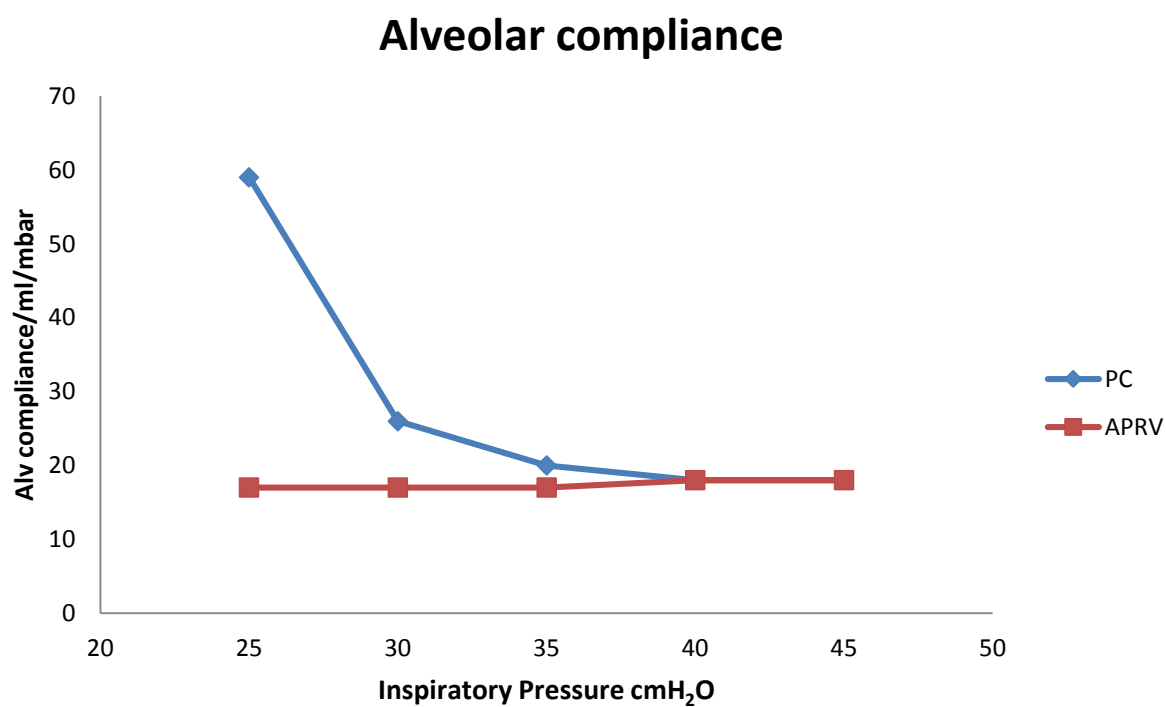


Figure 6 Measured change in C_{Alv} between CV_{Sim} (PC) and $APRV_{Sim}$

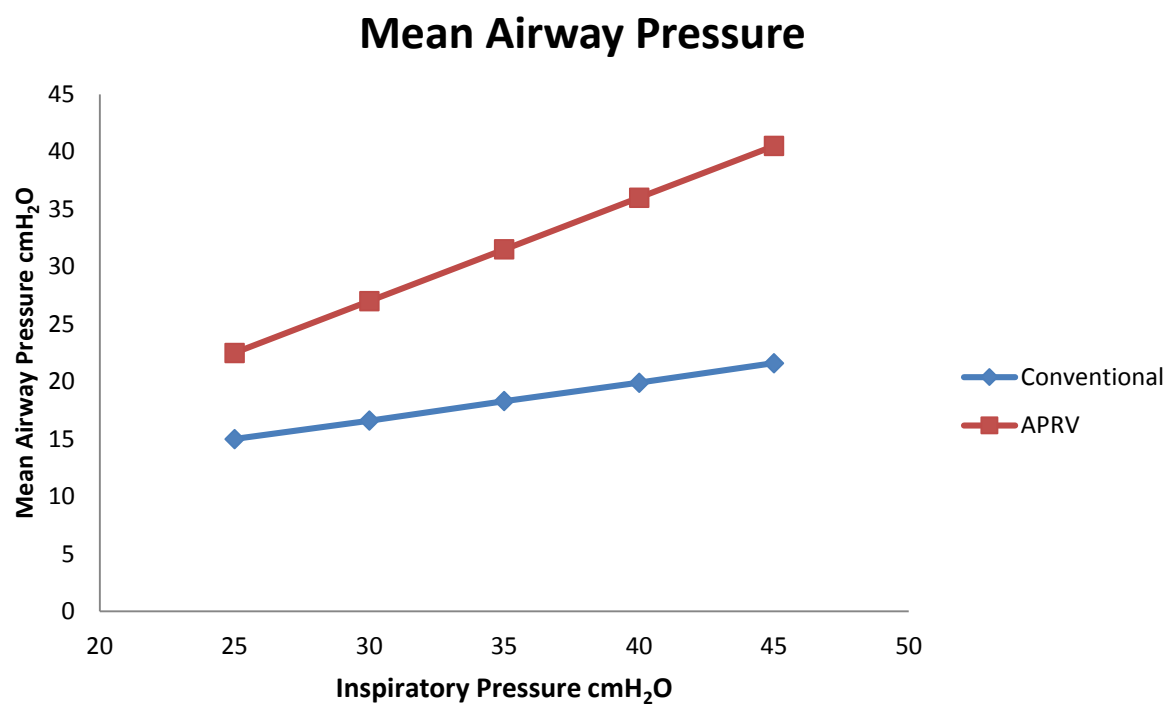


Figure 7 Measured change in $P_{aw/mean}$ between CV_{Sim} (PC) and $APRV_{Sim}$

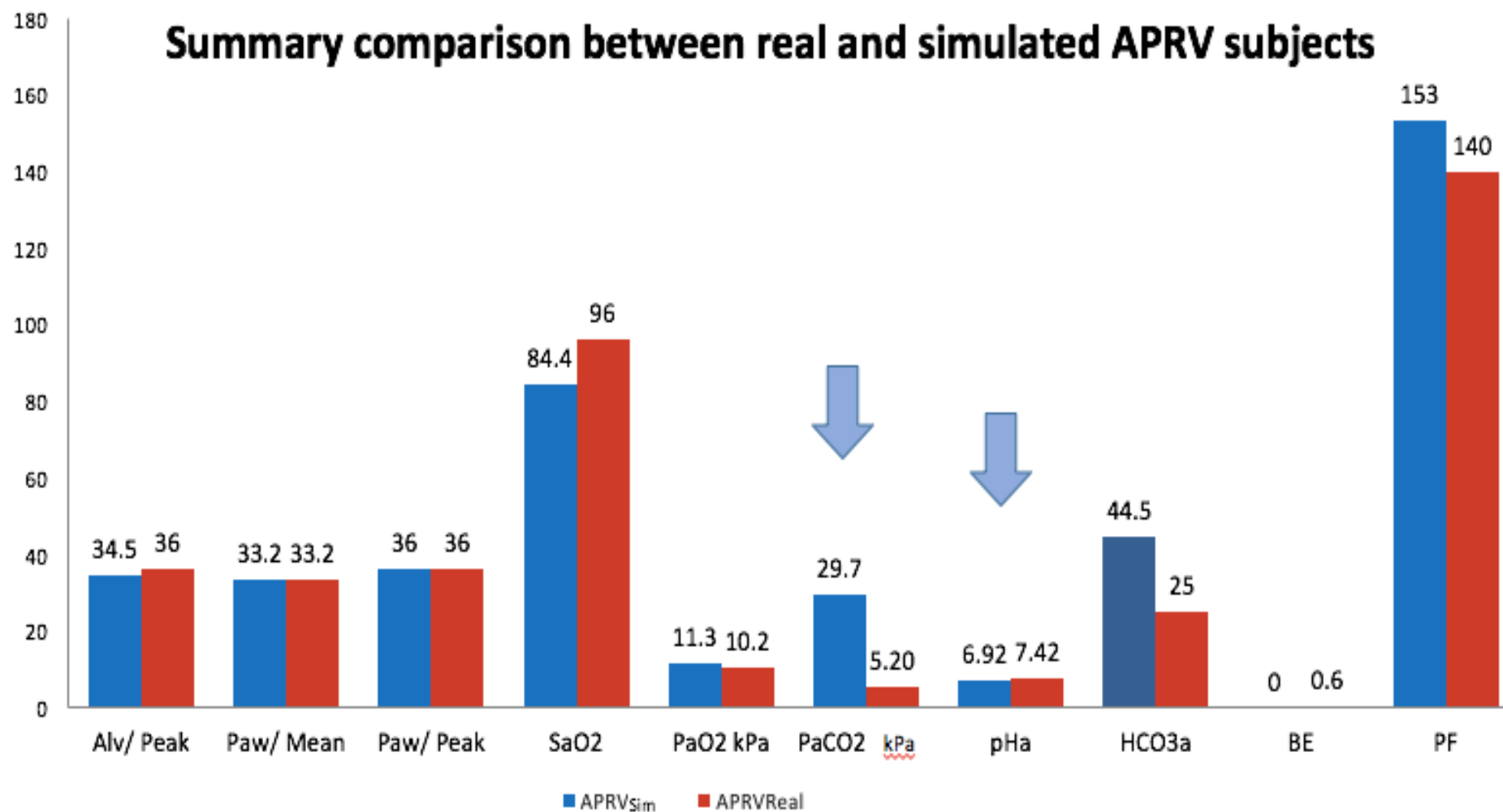


Figure 8 Summary of Variables on APRV_{Sim} vs APRV_{Real} Data of the APRV_{Sim} were corrected to match all configurations on the APRV_{Real}

Table 22 Configurations of APRV_{Real} and APRV_{Sim} for final comparison (after alignment)

P_{High}	36 cmH ₂ O
P_{Low}	8 cmH ₂ O
T_{High}	4.5 sec
T_{Low}	0.5 sec
Respiratory rate	12 b/min
V_T	565 ml
PEEP_M	8 cmH ₂ O
Inspiratory to expiratory ratio	9:1

1.13 Discussion

Our study used highly sophisticated ICPMs that have been extensively tested and validated in several studies. However, ICPMs do not include APRV mode among the incorporated modes of ventilation, but rather conventional ones. To our knowledge, APRV has not been used in the ICPMs. Therefore, we tried to mimic the settings of APRV by modifying the I:E ratio to the maximum permissible level in the ICPMs which was 9:1; this ratio agrees with published recommendations. Well-known guidelines by Habashi recommend that T_{High} generally should be set to occupy 80 to 95% of the total respiratory cycle when using the APRV mode to maintain optimum alveolar recruitment (7). However, this ratio was associated with a significant drop in the mean M_V compared to that of the CV_{Sim}. Such significant drop in the M_V could have contributed to the corresponding significant increase in the mean PaCO₂ that was revealed from the ICPMs. Contrary to popular belief, lower M_V on APRV may not necessarily result in higher PaCO₂, though this could be true when it comes to conventional modes. Studies of APRV have identified some remarkable concepts that may be of clinical value for many clinicians and for future researchers. Stock

and colleagues (16) found that APRV patients had lower PaCO_2 values ($p < 0.004$) than patients in the CV even though they had similar $\dot{V}_V$ values. Similarly, in the largest RCT comparing APRV with LOVT, Maxwell and colleagues (60) reported that patients in the LOVT group had significantly higher PaCO_2 values ($p < 0.039$) at significantly higher $\dot{V}_V$ values ($p = 0.004$) than those treated with APRV. In line with these studies, the results of our real patient showed that despite lower V_T and $\dot{V}_V$ values, $\text{APRV}_{\text{Real}}$ had a lower PaCO_2 value compared to that of CV_{Real} .

Of note, there was a significant reduction of the mean V/Q ($p = .0138$) during APRV_{Sim} , nonetheless, instead of improving ventilation (i.e. reducing PaCO_2), the PaCO_2 was still significantly higher compared to conventional modes. This may require deeper analysis to identify proper intervention to adapt the current ICPMs to precisely mimic APRV mode. Such improvement in the V/Q matching may explain the results observed in clinical settings (real patients ventilated with APRV) which refute the measurements that are revealed from the current ICPMs.

The improved ventilation (PaCO_2) seen in real patients during APRV may have been caused by the improved V/Q matching as a result of the potential recruiting nature of APRV rather than the actual numerical value of $\dot{V}_V$. Therefore, it is credible that the results revealed from the simulated APRV mode do not agree with the published clinical data. We postulate that the significant variation observed in PaCO_2 in simulated patient was due to the concept of CV adapted in the ICPMs, i.e. the lower the $\dot{V}_V$ the higher the PaCO_2 . Furthermore, like in real patients in clinical settings, we expected

to see some level of auto-PEEP (or so-called $PEEP_M$) in the $APRV_{Sim}$ as a result of the short set expiratory time which was 0.5 sec (represented as T_{Low}). However, this could not be obtained by the current version of ICPM which may need special implementation of the APRV mode to better match the real one.

One of the substantial advantages of the APRV mode is that it is associated with a significantly higher mean airway pressure compared to conventional modes (20, 60, 95), and (96) which is in agreement with what we found in this study. Nonetheless, it is credible that such increase in the $P_{aw/mean}$ may not necessarily associate with haemodynamic compromise as shown in several studies (this needs further research beyond the scope of this chapter).

It seems that the main difference between $APRV_{Sim}$ and $APRV_{Real}$ was the V_T which has a direct effect on M_v and may therefore have caused such significant disparities in $PaCO_2$ and pHa .

APRV in KFMC is mostly used with spontaneous breathing, so it was not very easy to find much data that exactly match the simulated subject, therefore, we selected data that match best the simulated configurations such as RR, I:E ratio, T_{High} , T_{Low} , P_{Low} and P_{High} . The results of this single patient are mostly in line with many published studies in terms of better $P_{aw/mean}$, PaO_2 , and $PaCO_2$, though was not enough to draw a decisive conclusion. It is noteworthy that we have not used ATC as it has been designed for spontaneously breathing patients, thus, has no role in our study.

Although we have data for 87 patients, we could not align their data into the ICPMs due several limitations such as, lack of controlling major parameters (e.g. T_{High} and T_{Low}), imprecise measurements for some variables (e.g. $PEEP_M$), and lacking spontaneous breathing.

1.13.1 Limitations

Unlike factual APRV mode that allows clinician to set T_{High} and T_{Low} autonomously, i.e. each parameter can be set independently; ICPMs do not have such a feature which may preclude expansion of the study to different scenarios through more diverse configurations (i.e. P_{Low} , T_{High} , and T_{Low}). Therefore, our aim of varying other configurations in the future in the same manner might not be appropriate with the current ICPMs as some results (namely, V_T and M_V) were not credible.

V_T values were much lower on $APRV_{Sim}$ (corrected) than that of CV_{Sim} which doesn't seem to represent factual APRV. This may be due to the fact that the pressure mode we selected during our study was quite different in its function from real APRV; $APRV_{Sim}$ might be a non-PEEP compensated. Such extremely low V_T was associated with extravagantly high $PaCO_2$ which in turn reduced pH_a to lethal levels.

1.14 Conclusion

We found that results obtained from ICPMs and the real patient appeared to be reasonably comparable. $APRV_{Sim}$ and $APRV_{Real}$ were found to reveal almost analogous results except for the significant difference in V_T that

could have affected the M_V , and led to the significant change in PaCO_2 (increased) and pHa (decreased). The highly sophisticated ICPMs have been validated and used with conventional modes. However, the models may need further modification to integrate APRV mode, especially V_T , M_V , and PEEP_M to be used efficiently in future studies. Prospective studies on real patients with proper alignment with the ICPMs may provide robust validation and be of clinical values for future studies.

Chapter 3

Minute ventilation and carbon dioxide elimination in APRV vs. conventional ventilation modes in patients with ARDS: A prospective study from a tertiary care centre in Saudi Arabia

1.15 Hypothesis:

We hypothesise that APRV mode is more efficient than CV modes in removing CO₂ at any given ventilatory M_V.

1.16 Research question is:

Is APRV more efficient than CV at CO₂ elimination at any given ventilatory M_V?

1.17 Introduction

The ability to provide safe and adequate ventilation of the lungs of patients with ARDS can be challenging when applying LOVT according to the ARDSnet recommendations (97). LOVT may lead to repetitive shear forces, and low volume lung injury (25, 98) which may cause hypoxaemia (99, 100) and hypercapnia (101, 102). Such impairment in gas exchange could be caused by reduced lung volumes due to atelectasis and oedema (103, 104); therefore, an intervention that can safely provide alveolar recruitment is needed. Although APRV may be viewed as a virtually continuous recruitment manoeuvre (98), it has been described as a lung-protective mode (12, 72, 98). Compared to PSV, APRV with spontaneous breathing has shown significant improvement in lung aeration by decreasing atelectasis in a short time, which contributes to improved pulmonary oxygenation in patients with ALI/ARDS (105).

It is credible that upon transition from CV modes to APRV, M_V can drop significantly due to the extremely long T_{High} which could, theoretically,

cause a significant increase in PaCO_2 . However, it has been reported that compared with CV, APRV was associated with significantly lower PaCO_2 levels at similar (16), or, even lower $\dot{V}_V$ values (106), yet all subjects in these studies (animals and patients, respectively) had spontaneous breathing. No study has compared the efficiency of APRV (without spontaneous breathing) and CV in CO_2 elimination in patients with ARDS. In previous work on a moderately diseased, simulated patient ventilated with conventional (CV_{Sim}) and APRV (APRV_{Sim}) modes, we presented data showing that when using ICPMs, APRV_{Sim} showed significantly higher levels of PaCO_2 compared to CV_{Sim} . This dramatic increase in PaCO_2 could have been caused by the significant drop in the $\dot{V}_V$ that was evident upon switching the mode from CV_{Sim} to APRV_{Sim} . We also presented data for a single real patient whose lungs were ventilated with CV and APRV modes. When compared to the simulated patient, the real patient had had relatively similar outcomes (e.g. oxygenation, and peak and mean airway pressures) except for PaCO_2 and pH which were significantly better than those of the APRV_{Sim} despite the lower $\dot{V}_V$. In this paper we will extend the previous work in terms of a much larger sample of real patients with different severity lung injuries, in that we will evaluate CO_2 elimination during APRV without spontaneous breathing, as compared with CV modes.

1.18 Methods

This study was approved by the institutional review board (IRB) at the KFMC with a waiver of the requirement for informed consent because this was an observational study with no change to standard care. We enrolled a prospective cohort study on 54 consecutive mechanically ventilated patients with ARDS refractory to CV and being transitioned to APRV (as shown in Figure 9) in all adult ICUs at KFMC. Patients were recruited from 69 adult ICU beds that are distributed in surgical, general, and cardiac ICUs. As shown in Table 35 ARDS was diagnosed according to the American-European Consensus Conference criteria (31). Although the decision to change the mode from CV to APRV was solely left to the discretion of the treating team (led by the attending intensivist), failure of CV was generally defined as failing to maintain acceptable gas exchange, especially oxygenation ($\text{PaO}_2/\text{FiO}_2 > 26.7 \text{ kPa}$) despite high FiO_2 , persistently elevated peak inspiratory pressure (PIP) of $\geq 35 \text{ cmH}_2\text{O}$ and/or PEEP of $\geq 10 \text{ cmH}_2\text{O}$ with signs of bilateral lungs infiltrate and derecruitment (as judged radiographically by the treating team). Patients had a variety of pathologies with moderate and severe lung injury, and were not excluded on the basis of diagnosis. Through the following inclusion and exclusion criteria, we compared PaCO_2 , M_V , RR, and V_T during CV and APRV, i.e. each patient had these variables measured during both CV and APRV. Each dataset included all pertinent data of ABGs and ventilator parameters (mode of MV, M_V , RR, V_T , T_{High} , and T_{Low}). Each patient had two datasets measured at two time-points; 1) the last dataset on CV just before

transition to APRV, and: 2) the dataset that comprised the longest T_{High} within the first 96 hours of APRV. AGBs analysis was performed within one hour of each ventilator configuration, providing no spontaneous breathing occurred during this window.

1.18.1 Conventional

The initial mode of ventilation at KFMC ICUs is mainly the volume control-continuous mandatory ventilation (VC-CMV); however, in rare cases, PCV is used to control peak pressures. Yet, for either CV modes, we use LOVT (6-8 ml/kg, IBW) and P_{plat} (< 33 cmH₂O) according to the ARDSnet protocol.

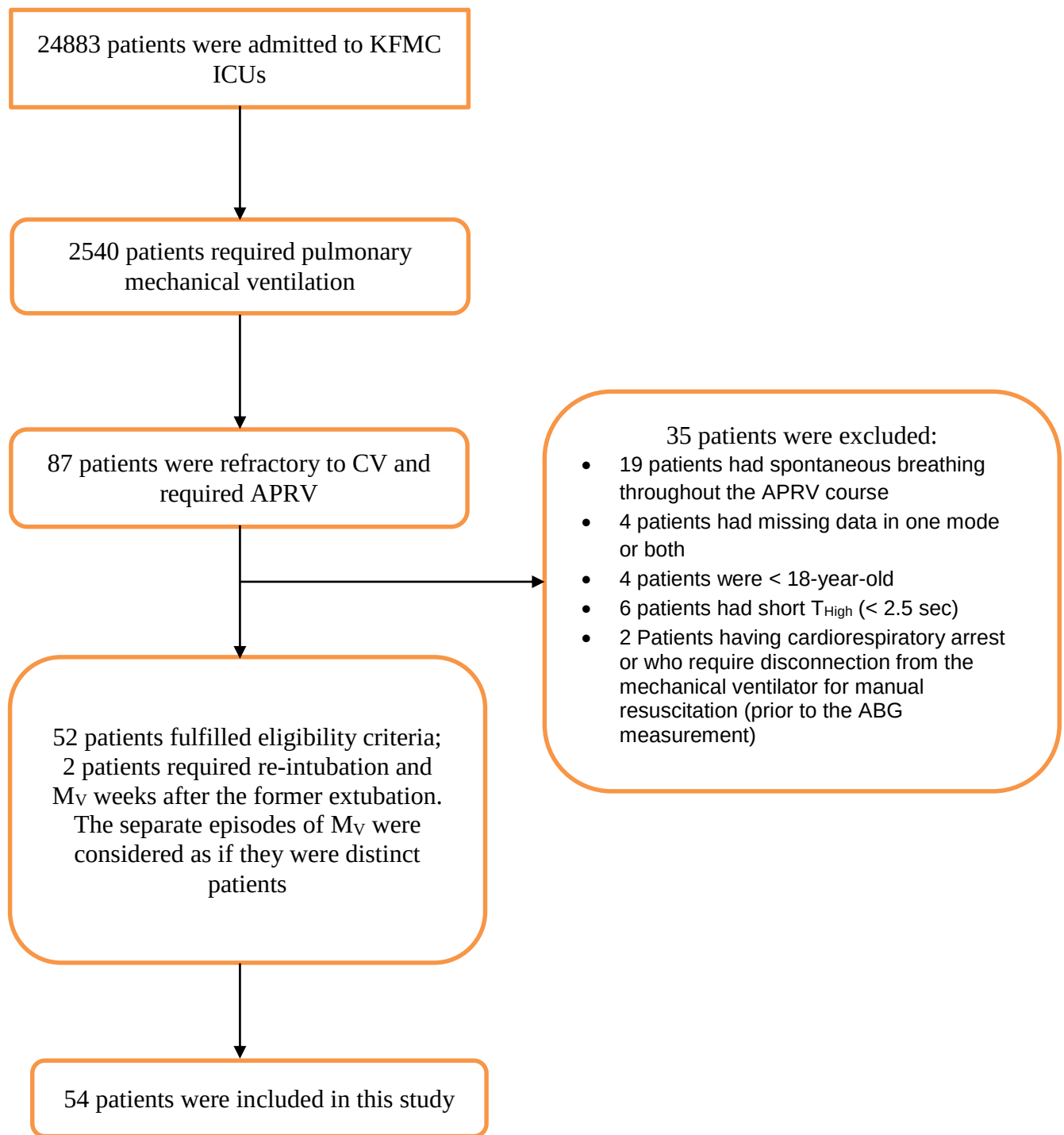


Figure 9 Flowchart of patient-selection for the study

1.18.2 APRV settings

We followed the approved hospital clinical practice protocol at KFMC (Al-ahmad protocol) that provides a detailed description regarding initiation, management, maintenance, transportation, and weaning of patients during APRV (as shown in figures **Error! Reference source not found.**Figure **26**Figure **27** in the appendix). However, initial settings are as follow:

- P_{High} was set to achieve V_T of 8 ml/kg (IBW); then was adjusted accordingly
- T_{High} was set to 4–6 sec, depends on the adequacy of spontaneous breathing (i.e. the more adequate spontaneous breathing, the longer the T_{High} settings)
- P_{Low} was 0 cmH₂O; then, was adjusted as needed to achieve desired $PEEP_M$ by either T_{Low} (initially) or by direct adjustments of P_{Low}
- T_{Low} was set to 0.2–0.8 sec; then, was adjusted as needed to achieve desired levels of oxygenation and/or ventilation ($PaCO_2$) according to the adequacy of $PEEP_M$ and V_T . For example, patients with an obstructive disease (COPD) may achieve a certain $PEEP_M$ at 0.8 sec, however, this exact $PEEP_M$ can be achieved for patients with a restrictive disease (e.g. ARDS) at much lower levels of T_{Low} (e.g. 0.2 sec) due to physiological and anatomical differences that could lead to different time constants.

1.18.3 Inclusion criteria:

- Receiving mechanical ventilation refractory to conventional modes and being transitioned to APRV

- Having no spontaneous breathing
- Having ARDS (defined as: $\text{PaO}_2/\text{FiO}_2 < 26.7 \text{ kPa}$) signs of bilateral lungs infiltrates and derecruitment (as judged radiographically by the treating team)

1.18.4 Exclusion criteria:

- Less than 18-years-old
- $T_{\text{High}} < 2.5 \text{ sec}$
- The Interval between APRV dataset and CV dataset $> 96 \text{ hr}$
- Having cardiorespiratory arrest or who require disconnection from the mechanical ventilator for manual resuscitation (prior to the ABG measurement)

Each dataset comprising the following variables:

1. M_V , RR, V_T , T_{High} , and T_{Low} which were measured by the internal mechanisms of the Drager EvitaXL (Drager, Lubeck, Germany) and SERVOI (Maquet Critical Care, Sweden) ventilators. Each of these ventilators was calibrated before use in each patient.
2. PaCO_2 (measured using Siemens Rapidlab 1265 blood gas machine).

1.19 Statistical analysis:

Continuous data were presented as means (SD) or medians with Interquartile Range (IQR) as appropriate, and categorical data as frequencies and percentages. To assess the difference in PaCO_2 between modes, the mean value of PaCO_2 during APRV was subtracted from the mean value of PaCO_2 during CV for each pair and the distribution of these variables were summarised using mean (SD), minimum, maximum, and

95% CI. To assess the significance of differences in PaCO₂ between study groups, paired *t*-test was performed as the distribution was roughly normal. However, for M_V, RR, and V_T a non-parametric test (Wilcoxon's signed rank test) was performed and variables were summarised using minimum, IQR 25%, median, IQR 75%, and maximum. A *p*-value of less than 5% was considered to be statistically significant. Statistical analysis was performed using SPSS (version: IBM SPSS Statistics 22, Inc, Chicago, Illinois, USA).

1.20 Results

As shown in Figure 9, 54 patients fulfilled eligibility criteria and were included in this study. Table 23 summarises the baseline demographics and an estimate of the severity of lung injury ARDS according to the Berlin definition (of the PaO₂/FiO₂, kPa) (94). The mean (SD) reduction in PaCO₂ after switching the mode from CV to APRV was 0.92 (1.68) kPa (0.5 – 1.43 kPa; 95% CI; *p* < 0.001) while the median (IQR) reduction in M_V was 2.6 (1.2 – 4.1 L/min); *p* < 0.001). The absolute mean (SD) PaCO₂ was significantly lower during APRV than during CV 5.65 (1.37) kPa vs. 6.56 (1.95) kPa, respectively.

Table 24 shows minimum, IQR 25%, median, IQR 75%, maximum, and *p*-value for both M_V and RR. The mean (SD) T_{High} and T_{Low} during APRV was 4.42 (1.0) sec (4.1–4.7 s; 95% CI) and 0.5 (0.1) sec (0.47–0.54 s; 95% CI), respectively.

Table 23 Baseline characteristics for patients enrolled in the study (severe, moderate, mild ARDS are classified based on the Berlin criteria)

Age, median (IQR), years	52 (30.5-66.5)
Male/Female (number)	28 / 23
PaO₂/FiO₂ (kPa), median (IQR)	9.1 (7.3-13.1)
Severe ARDS, number (%)	41 (75.9%)
Moderate ARDS, number (%)	12 (22%)
Mild ARDS, number (%)	1 (1.86%)

Table 24 Statistical analysis for outcome measures M_V and RR

Variable	n	Mode	Min	IQR 25%	Median	IQR 75%	Max	p value
M_V (L/min)	54	CV	3.8	6.9	8.3	11.1	22	< 0.001
		APRV	3.7	4.8	5.5	7.3	11.6	
RR (b/min)	54	CV	14	20	23	30	42	< 0.001
		APRV	8.0	11.8	13	15	36.0	

The median (IQR) V_T values for CV and APRV were 7.1 (6.6–8.1) ml/kg vs. 8.6 (8.0–9.5) ml/kg (p = 0.075), respectively. The duration from the time of changing the mode of ventilation (from CV to APRV) until the time of obtaining measured data (PaCO₂, M_V, RR, V_T, T_{High}, and T_{Low}) was median 19:54 (IQR 07:03–39:05 hr:min).

1.21 Discussion

LOVT may be associated with repetitive shear forces, low volume lung injury, de-recruitment (25, 98) which in turn, may worsen gas exchange as a whole, i.e. hypoxaemia and hypercapnia. Therefore, severely injured lungs such as those of the patients enrolled in this chapter may require higher airway pressure to correct life-threatening hypoxia. Although APRV has been shown to be an effective modality in improving oxygenation

through lung recruitment, there is a misconception that an acceptable level CO_2 cannot be achieved without the compensation of spontaneous breathing. Theoretically, PaCO_2 may increase dramatically during APRV due to the significant reduction in the $\dot{V}_V$ that is caused by the extremely long T_{High} , especially in the absence of spontaneous breathing. However, studies of APRV have identified some remarkable concepts that may be of clinical value for many clinicians. Stock and colleagues (16) found that dogs ventilated with APRV had significantly lower PaCO_2 values than those in the conventional mode even though they had similar $\dot{V}_V$ values. Similarly, but in human with respiratory failure, Maxwell and colleagues (106) reported in the largest RCT on APRV that patients in the LOVT group had significantly higher PaCO_2 values at significantly higher $\dot{V}_V$ values than those treated with APRV. Nonetheless, one could argue that all subjects (animals and human) in these studies had spontaneous breathing. This may raise the crucial question concerning whether the findings of these studies could really be extrapolated to APRV without spontaneous breathing.

In this chapter, we found that in patients with moderate to severe ARDS, PaCO_2 , $\dot{V}_V$, and RR were significantly lower during APRV compared with CV. However, although V_T was higher in the APRV group compared to the CV group, the difference did not reach statistical significance. It has been reported that, out of APRV studies that have measured V_T , mean values for the release volumes were between 550 to 840 ml and 9 ml/kg (measured body weight), which possibly translates into 11 ml/kg IBW (65).

However, one can argue that such a higher V_T can cause more harm than benefit when using APRV compared to CV. Yet, extrapolating the negative

effect of higher V_T during CV to a totally different mode (i.e. APRV), without solid evidence, might not be plausible due to several reasons. For example, the continuous escalation of ventilatory parameters in the control group in the ARDSnet trial (33) may indicate a worsening lung injury which could have led to higher mortality rate. It was found that after the significantly higher PaO_2/FiO_2 ratio in the control group on days 1 and 3, PEEP and FiO_2 levels were significantly higher on day 7 (33). In contrast, as discussed earlier in this thesis, many studies (58, 63) on APRV have reported consistent improvement in PaO_2/FiO_2 ratio over time that was associated with a concomitant reduction in FiO_2 and airway pressures; this may indicate improving lung function throughout the course of APRV. Moreover, unlike traditional ventilation treatment in the ARDSnet study, which might have exacerbated lung injuries (33), APRV has been described as a lung-protective mode (12, 18, 72). Despite the reported higher V_T , the mortality rates for patients in all reported studies of APRV groups did not exceed those of conventional ventilation. In contrast, a recent review stated: "APRV is a novel mechanical ventilation strategy for delivering a protective breath that has been shown to block progressive acute lung injury (ALI) and prevent ALI from progressing to ARDS" (75). Thus, determining whether the APRV mode, despite its higher V_T , produces a safer modality than CV should be an area for future investigation. A recent review by Jain and colleagues provides detailed summaries of animal and human APRV studies, and concludes that no studies showed a worse outcome with APRV, and some showed significant benefits in cardiopulmonary variables (107).

Our results may support the hypothesis that, compared to CV, for any given mechanical M_V APRV will produce lower $PaCO_2$ than CV. The reason why we took the readings with the longest T_{High} for any particular patient was because it would provide the lowest M_V ; this should have challenged APRV more as it could have led to higher $PaCO_2$.

As published in some clinical protocols (12), the protocol of Varpula (RCT) stated that correcting the hypercapnia could be achieved by reducing the T_{High} (108); however, this could unintentionally change the mode from being an APRV mode to a CV mode (though still labelled as APRV), i.e. the ventilator screen is still showing APRV mode while the actual function represents CV rather than a factual APRV. It has been reported that some published clinical studies (95, 109) allowed mechanical frequencies of ≥ 20 cycles per minute, which overlap with the frequencies of conventional mechanical ventilation (49). However, our study in this chapter has shown significantly lower RR compared to CV.

In contrast, $PaCO_2$ may decrease despite the increase of inspiratory to expiratory ($T_{High}:T_{Low}$) ratio; this could be seen on APRV (as in this chapter) wherein the T_{High} is much longer than the inspiratory time on CV. This concept has been shown in previous studies (110, 111). It has been reported that during breath-holding with patent airways, delivery of CO_2 continues as cardiac output transfers CO_2 that in turn diffuses into the alveolar space; the diffusing capacity increases as lung volume increases and is not a consequence of the changing distribution of inspired air (112). CO_2 clearance is assisted by recruitment of the patient's lung at close to total lung capacity; elastic recoil creates large volume gas flow during T_{Low}

(113). Some modalities may improve one aspect of gas exchange (e.g. oxygenation) while other aspects such as ventilation (CO_2 removal) may be sacrificed; however, the levels of sacrifice may depend on the severity of the illness.

Despite very low baseline $\text{PaO}_2/\text{FiO}_2$, that indicates severe ARDS according the Berlin definition, we found that APRV was associated with improvement in $\text{PaO}_2/\text{FiO}_2$ that was achieved in relatively short time. Such improvement in oxygenation might be due to the higher MAP—this will be discussed in detail in Chapter Five.

We believe that this is the first study to compare the effect of APRV (without spontaneous breathing) on CO_2 elimination with that of CV modes in patients with ARDS.

1.22 Conclusion

In this chapter APRV was associated with significantly lower PaCO_2 at significantly lower M_v and RR than observed during CV modes in patients with moderate and severe ARDS. Prospective RCTs may be needed to investigate clinically relevant outcomes such as mortality and duration of MV. However, proper settings to manage patients during APRV should be defined and clarified to clinicians around the globe.

Chapter 4

The impact of different ventilatory configurations on carbon dioxide and pH during APRV in the absence of spontaneous breathing: A prospective study in a tertiary hospital

1.23 Background

For mechanically-ventilated patients with ALI/ARDS, the management of hypercapnia during CV and the HFOV has been extensively described in the literature; however, standard management guidance for patients on APRV is not well defined. In addition, reviews have acknowledged the existence of confusion about APRV by stating, "Somewhat confusing to the understanding of APRV have been the subsequent descriptions of modes of ventilation that appear very similar to it" (39). APRV and BIPAP have been frequently described as if they were one mode. In fact, some researchers have merged the two modes into one abbreviation, referring to them as a single modality, i.e. BIPAP/APRV (37). Although some authors have indicated (40, 41) that BIPAP differs from APRV only in the ratio of T_{High} and T_{Low} . T_{High} is usually shorter than T_{Low} in BIPAP. However, even for its minimum ratio, APRV must never reach a level at which T_{High} is shorter than T_{Low} .

Rose and Hawkins (42) attempted to resolve the existing confusion by identifying definitive criteria for the APRV and BIPAP modes. Their comprehensive review included 50 studies. They found that APRV was described in 78% of the studies, whereas BIPAP was described in 22%. They categorised the inspiratory to expiratory (I:E) ratios used into four categories: 1) extreme inverse ratio ($> 2:1$); 2) non-inverse ratio; 3) 1:1 ratio; and 4) mild inverse ratio ($> 1:1$ to $\leq 2:1$). I:E ratio. These two phases produce a ratio that corresponds to the inspiratory to expiratory $T_{\text{High}}:T_{\text{Low}}$

ratio in the conventional modes. They found that an extreme inverse ratio of $> 2:1$ was utilised in 46% of the studies on APRV, while none of the BIPAP trials used such a ratio ($p = 0.004$) (42). This means that 100% of BIPAP studies used a ratio of less than 2.1:1, of which 91% used a ratio of 1:1 or less; both ratios are not compatible with APRV. In addition, even for those studies that were described as having used APRV, 54% of them utilised a ratio of $> 1:1$ to $\leq 2:1$, of which 31% utilised an I:E ratio of 1:1, while 21% of the APRV trials used a mild ratio of $> 1:1$ to $\leq 2:1$ (42).

Stewart and colleagues indicated in their review that it is the extreme inverse $T_{\text{High}}:T_{\text{Low}}$ ratio of 8:1 to 10:1 that distinguishes APRV from other modes that seem similar to it (45). However, it is credible that the extreme inverse $T_{\text{High}}:T_{\text{Low}}$ ratio during the APRV mode is associated with a significantly lower M_v that could hypothetically result in an increase in PaCO_2 unless it is compensated by adequate spontaneous breathing (65). Furthermore, in response to inadequate or absent spontaneous breathing during APRV, patients with CO_2 retention may have a greater increase in PaCO_2 than patients without pre-existing CO_2 retention (chronic hypercapnia), such as COPD. Auto positive end expiratory pressure (auto-PEEP), dynamic hyperinflation, and respiratory acidosis (CO_2 retention) are common features in patients with COPD (114), which may impose further constraints on achieving normal CO_2 levels. Moreover, proper setting of V_T during APRV is not well defined in the literature. Like many published protocols, a recent review recommended setting the P_{High} at a level that is equal to the plateau pressure (P_{Plat}) in the volume-control mode (maximum

of 30 cmH₂O) as an initial setting which can be increased repeatedly, e.g. by 2-5 cmH₂O in the case of hypoxaemia (12). However, the acceptable level of V_T displaced by such frequent increases in P_{High} seems to have been overlooked.

Both the lack of definite consensus about the ideal application of APRV alongside the existed confusion could have prevented many centres from using it.

Therefore, identifying proper APRV configurations to normalise the PaCO₂ in non-spontaneously breathing patients may be of clinical value and may result in better outcomes. In this chapter, we focused on normalising ventilation (CO₂ elimination) more than oxygenation, and the latter was assessed using PaO₂/FiO₂ ratio.

1.24 Aim

To identify proper configurations to optimise PaCO₂ on non-breathing patients with diverse pulmonary pathologies including restrictive (e.g. ARDS) and obstructive (e.g. COPD) when using APRV.

1.25 Patients and method

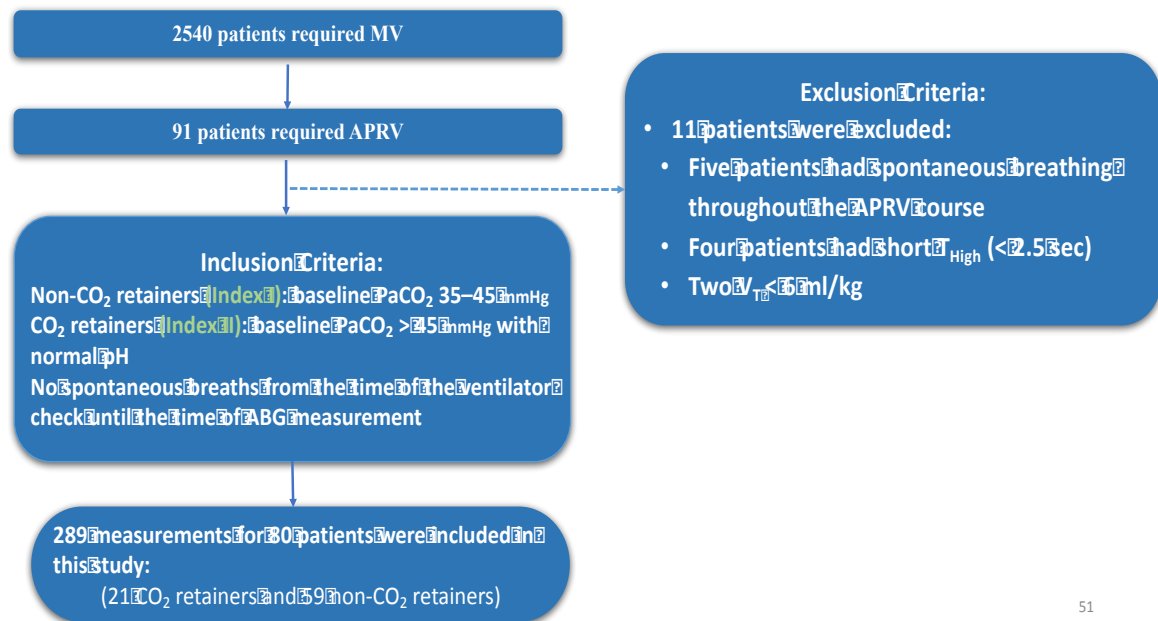
The IRB at KFMC approved this study. In our tertiary-care ICUs at KFMC, we explored the effect of APRV settings on CO₂ elimination in a heterogeneous patient group. We conducted a prospective cohort study in 91 patients, who were mechanically ventilated with APRV in our ICUs over three years, to identify all cases that met the below criteria. We observed that some APRV configurations appeared to result in improved CO₂

elimination in non-breathing patients. We tested this by categorising patients by the adequacy of their CO₂ elimination and then analysing the APRV configurations used. We further hypothesised that COPD patients might have a greater requirement for M_V due to physiological and anatomical differences to non-COPD patients. To test this hypothesis, we analysed this sub-group and tested the hypothesis that optimising arterial pH (rather than PaCO₂) would require a configuration as in non-COPD patients.

Furthermore, we hypothesised that patients who received sodium bicarbonate (NaHCO₃) for the severe metabolic acidosis may have a higher CO₂ production than those who did not receive NaHCO₃. This subgroup may require shorter T_{High} and/or larger V_T than those in the other groups. This study included 80 patients (Figure 10 shows the flowchart of patients enrolled in this study) who met our eligibility criteria (21 CO₂ retainers and 59 non-CO₂ retainers), which were:

1.25.1 Inclusion Criteria

1. On APRV mode
2. Non-CO₂ retainers (Index I): baseline PaCO₂ < 45 mmHg
3. CO₂ retainers (Index II): baseline PaCO₂ > 45 mmHg with normal pH
4. No spontaneous breaths from the time of the ventilator check until the time of ABG measurement



51

Figure 10 Flowchart of patients enrolled in the study

1.25.2 Exclusion Criteria

1. Patients with a cardiorespiratory arrest or who require disconnection from the mechanical ventilator for manual resuscitation (prior to the ABG measurement)
2. $T_{\text{High}} < 2.5 \text{ s}$
3. $V_T < 6 \text{ ml/kg}$

1.25.3 Ventilator used

In this study, we used two ventilators that are capable of providing APRV; (1) 71 patients (88.75%) were ventilated with the APRV mode in the Dräger EvitaXL ventilator (Dräger, Lubeck, Germany), and (2) 9 patients (11.25%)

were ventilated with the Bi-Vent mode by Servo-I ventilator (Maquet Critical Care, Sweden).

1.25.4 Measurements and variable

Demographic data (age and gender), $\text{PaO}_2/\text{FiO}_2$ ratio prior to conversion to APRV were recorded; for patients whose primary mode was APRV and who had no ABG prior to tracheal intubation, pulse oximetric saturation/ FiO_2 ($\text{SpO}_2/\text{FiO}_2$) ratio was considered. It has been reported that for SpO_2 (values < 97%); the $\text{SpO}_2/\text{FiO}_2$ ratios of 235 and 315 are appropriate and reliable surrogates for the $\text{PaO}_2/\text{FiO}_2$ ratios of 200 and 300 (115). PaCO_2 , pH, PaO_2 were measured using (Siemens Rapidlab 1265) blood gas machine. V_T , T_{High} , T_{Low} , P_{High} , P_{Low} , FiO_2 , and $\text{PaO}_2/\text{FiO}_2$ ratio were measured by the internal mechanisms of the Dräger EvitaXL ventilator (Dräger, Lubeck, Germany) and SERVOI (Maquet Critical Care, Sweden) ventilators. Each of these ventilators was calibrated before use in each patient. CO_2 retention status (CO_2 retainers or non- CO_2 retainers) was also recorded. In addition, we identified those who received NaHCO_3 (infusion or stat doses) within 2 hours of the ABG sampling.

1.26 Statistical analysis

Continuous data were presented as means (SD) or medians (IQR) as appropriate, and categorical data as frequencies and percentages. To assess the significance of differences in T_{High} , T_{Low} , P_{High} , P_{Low} and $\text{PaO}_2/\text{FiO}_2$ between study groups (CO_2 retainers or non- CO_2 retainers), paired *t*-test was performed as the distribution was roughly normal. A *p*-value of less

than 5% was considered to be statistically significant. Statistical analysis was performed using SPSS (version: IBM SPSS Statistics 22, Inc, Chicago, Illinois, USA).

1.27 Results

289 measurements for 80 patients with ALI/ARDS were analysed. 77 (96.25) patients had either $\text{PaO}_2/\text{FiO}_2$ (67 patients) or $\text{SpO}_2/\text{FiO}_2$ (10 patients) ratio obtained prior to the APRV mode, while only 3 (3.75 %) patients had neither $\text{PaO}_2/\text{FiO}_2$ nor $\text{SpO}_2/\text{FiO}_2$ ratios. Of the 67 patients who had a $\text{PaO}_2/\text{FiO}_2$ ratio measured prior to APRV, 55 patients (82 %) had $\text{PaO}_2/\text{FiO}_2$ ratio < 26.7 kPa, of whom 48 patients (71.6 %) had $\text{PaO}_2/\text{FiO}_2$ ratio < 13.3 kPa, indicating moderate and severe ARDS, respectively (according to the Berlin definition) (94). Though, 10 patients (12.5 %) had $\text{SpO}_2/\text{FiO}_2$ (rather than $\text{PaO}_2/\text{FiO}_2$) ratio calculated at baseline, nine of whom had $\text{SpO}_2/\text{FiO}_2$ ratios < 235 ratio that correlates to a $\text{PaO}_2/\text{FiO}_2$ ratio of < 26.7 kPa. Table 25 summarises the baseline demographics and an estimate of the severity of lung injury (according to the $\text{PaO}_2/\text{FiO}_2$ and $\text{SpO}_2/\text{FiO}_2$ ratios).

Table 25 Demographic data and clinical characteristics

	No. of patients	80
Gender	Male	40
	Female	40
Age (years)	mean	50 (13 - 91)
PaO₂/FiO₂ Ratio (kPa)	< 100, n (%)	48 (71.6)
	100–200, n (%)	17 (25.4)
	201–300, n (%)	2 (2.99)
	Total, n (%)	67 (100)
SpO₂/FiO₂ Ratio	< 235, n (%)	9 (90)
	236 – 315, n (%)	1 (10)
	Total, n (%)	10 (100)
Mode	Bi-Vent (Servo-I), n (%)	9 (11.25)
	APRV (EvitaXL), n (%)	71 (88.75)
	Total, n (%)	80 (100)

SpO₂/FiO₂ = pulse oximetric saturation/ fraction of inspired oxygen ratio

Tables 26, 27, and 28 present summary statistics of APRV configurations (T_{High} and V_T) and their outcomes (PaCO_2 and pH) for both study groups; the tables also specify patients who received NaHCO_3 . The indicator for optimal outcome in the non- CO_2 retainers was PaCO_2 , whereas the indicator for optimal outcome in the CO_2 retainers group was arterial pH. In addition, these tables depict the optimal and non-optimal outcomes, minimum (min), maximum (max), and 95% CI for T_{High} and V_T . Of the 62

measurements for the CO₂ retainers group who did not receive NaHCO₃, 16 (23.3%) measurements showed non-optimal pH levels (7.27 – 7.31; 95% CI) when the following configurations were used: V_T (7.6 – 9.1 ml/kg; 95% CI), and T_{High} (2.96 - 3.85 s; 95% CI). Whereas 46 (76.7 %) measurements revealed optimal pH levels (7.41 – 7.44; 95% CI) when using the following configurations: V_T (8.46 – 9.10 ml/kg; 95% CI) and T_{High} (3.79 – 4.39 s; 95% CI). (Table 26.).

Table 26 CO₂ retainers who did not receive NaHCO₃

CO ₂ Status	N	Variables	Min	95% CI	Max
Non-Optimal	16	V _T (ml/Kg)	6.30	7.60 - 9.13	10.40
		T _{High} (sec)	2.50	2.96 - 3.85	5.50
		PaCO ₂ (mmHg)	38.00	43.72 - 58.97	80.00
		pH	7.21	7.27 - 7.31	7.34
Optimal	46	V _T (ml/Kg)	6.50	8.46 - 9.10	11.00
		T _{High} (sec)	2.50	3.79 - 4.39	6.00
		PaCO ₂ (mmHg)	35.00	51.43 - 57.11	73.00
		pH	7.35	7.41 - 7.44	7.57

Table 27 shows that, of the 185 measurements for the non-CO₂ retainers group who did not receive NaHCO₃, 30 (16.22%) measurements showed non-optimal PaCO₂ levels (48.2 – 51.7 mmHg; 95% CI) when the following configurations were used: V_T (7.4 – 8.3 ml/kg; 95% CI), and T_{High} (3.8 - 4.5 s; 95% CI). Whereas 155 (83.8 %) measurements revealed optimal PaCO₂

levels (35.9 – 37.4 mmHg; 95% CI) when using the following configurations: V_T (8.5 – 8.8 ml/kg; 95% CI) and T_{High} (4.1 – 4.3 s; 95% CI).

Table 27 Non-CO₂retainers who did not receive NaHCO₃

CO ₂ Status	N	Variables	Min	95% CI	Max
Non Optimal	30	V_T (ml/Kg)	6.10	7.39 - 8.33	10.40
		T_{High} (sec)	3.00	3.77 - 4.53	7.00
		PaCO ₂ (mmHg)	45.10	48.15 - 51.65	62.00
		pH	7.07	7.29- 7.38	7.53
Optimal	155	V_T (ml/Kg)	6.20	8.50 - 8.81	10.90
		T_{High} (sec)	2.50	4.08 - 4.33	6.50
		PaCO ₂ (mmHg)	25.00	35.92 - 37.42	45.00
		pH	6.92	7.37 - 7.40	7.58

However, of the 43 measurements for the non-CO₂ retainers group who received NaHCO₃, 6 (13.95%) measurements showed non-optimal PaCO₂ levels (45.9 – 69.4 mmHg; 95% CI) when the following configurations were used: V_T (6.7 – 9.1 ml/kg; 95% CI), and T_{High} (2.3 - 4.2 s; 95% CI). Whereas 37 (86%) measurements revealed optimal PaCO₂ levels (32.7 – 36.2 mmHg; 95% CI) when using the following configurations: V_T (9.2 – 9.8 ml/kg; 95% CI), and T_{High} (3.3 – 3.6 s; 95% CI), as shown in Table 28.

Table 28 Non-CO₂retainers who received NaHCO₃

CO ₂ Status	N	Variables	Min	95% CI	Max
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Non-optimal	6	V_T (ml/Kg)	6.50	6.71 - 9.05	8.90
		T_{High} (sec)	2.50	2.33 - 4.17	5.00
		PaCO₂ (mmHg)	46.00	45.93 - 69.37	74.00
		pH	7.04	7.04 - 7.33	7.38
Optimal	37	V_T (ml/Kg)	7.90	9.23 - 9.81	11.00
		T_{High} (sec)	2.50	3.25 - 3.61	4.00
		PaCO₂ (mmHg)	25.40	32.73 - 36.16	45.00
		pH	6.90	7.20 - 7.28	7.55

The CO₂ retainers group who received NaHCO₃ was not discussed as it contains only one measurement. Figure 11 shows the PaCO₂ levels for the entire cohort, Figure 12 shows the PaCO₂ vs. V_T values, and Figure 13 shows the PaCO₂ vs. T_{High} of the entire cohort (CO₂retainers, non-CO₂retainers, and those who received NaHCO₃)

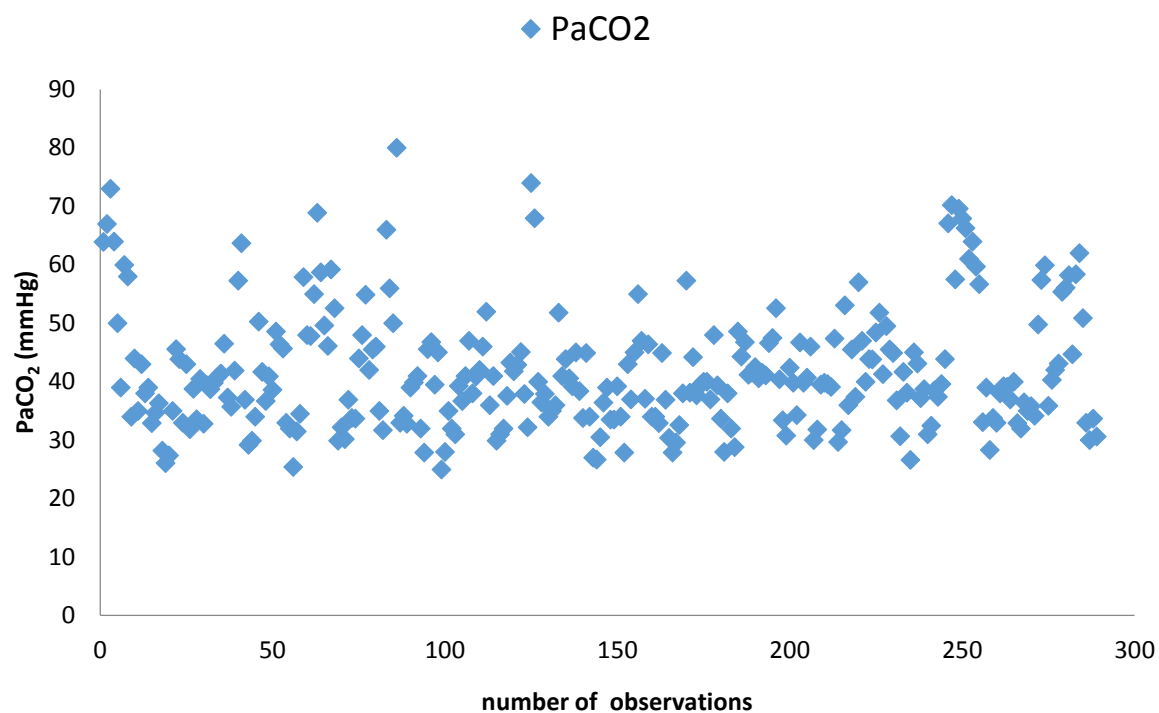


Figure 11 PaCO₂ levels of the entire cohort

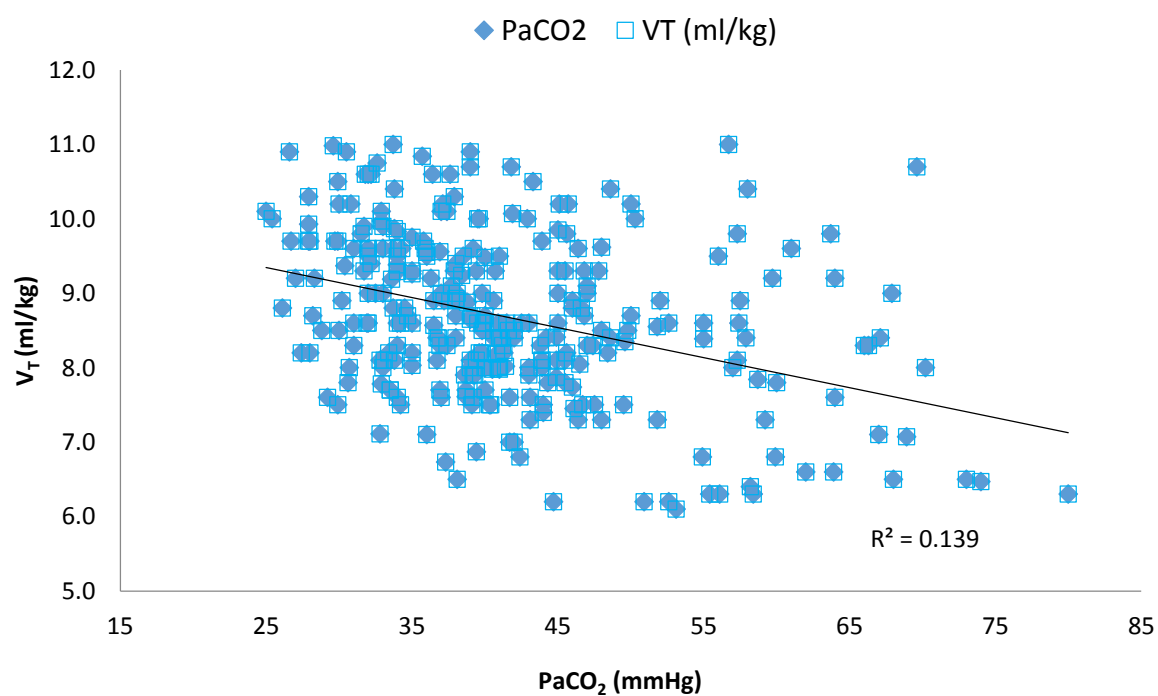


Figure 12 PaCO₂ vs. V_T (ml/kg) values of the entire cohort

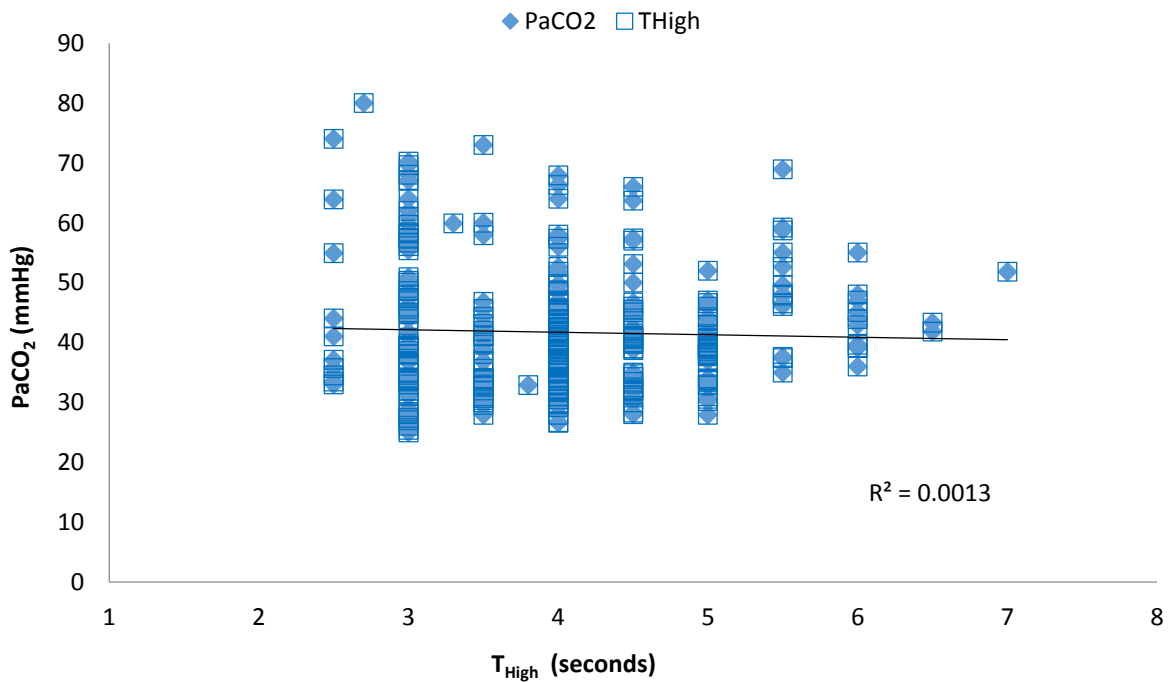


Figure 13 PaCO_2 vs. T_{High} (seconds) values of the entire cohort

Figure 14 shows the PaCO_2 vs. V_T levels for CO_2 retainers, Figure 15 shows PaCO_2 vs. V_T levels for non- CO_2 retainers. Figure 16 shows the PaCO_2 vs. T_{High} levels for CO_2 retainers, Figure 17 shows the PaCO_2 vs. T_{High} levels for non- CO_2 retainers. Figure 18 shows PaCO_2 and pH values for CO_2 retainers who did not receive any NaHCO_3 . However, 21.3% received NaHCO_3 ; Figure 19 and Figure 20 show the values of PaCO_2 and pH, respectively, whereas Figure 21 shows the configurations of T_{High} and V_T settings for patients who received NaHCO_3 .

The correlations between the (V_T and PaCO_2) and between the (T_{High} and PaCO_2) were assessed. Of the 289 measurements, 238 (82.4 %) had optimal outcomes, whereas 51 (17.6 %) had non-optimal outcomes

(Table 29); Tables 30 and 31 show statistically significant correlation between the V_T and PaCO_2 ; $p < .0001$. A patient with one unit higher of V_T (ml/kg) has 1.95 folds increase in the odds (likelihood) of achieving optimal CO_2/pH . However, T_{High} by itself does not significantly affect CO_2/pH ($p\text{-value} > 0.50$).

Table 29 Response profile

Ordered Value	$\text{CO}_2\text{-Ph}$	Total Frequency
1	Non-optimal	51
2	Optimal: Non- CO_2 retainers, $\text{PaCO}_2 \leq 45$, CO_2 retainers: $\text{pH} \geq 7.35$	238

Table 30 Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-5.6706	1.5414	13.5347	0.0002
V_T (ml/Kg)	1	0.6679	0.1613	17.1481	<.0001
T_{High} (sec)	1	0.1300	0.1952	0.4432	0.5056
CO_2 retainers	1	0.6090	0.3680	2.7382	0.0980

Table 31 Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
V_T (ml/Kg)	1.950	1.422	2.675
T_{High} (sec)	1.139	0.777	1.670
CO_2 retainers	1.839	0.894	3.782

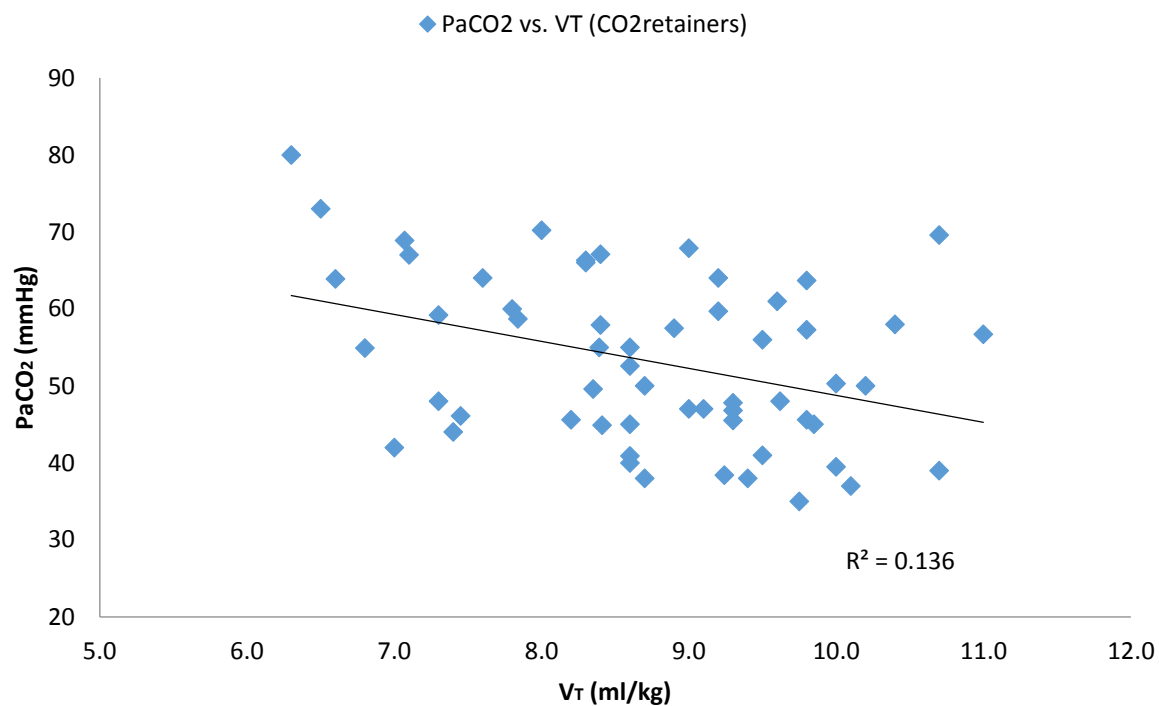


Figure 14 PaCO₂ vs. V_T levels for CO₂ retainers

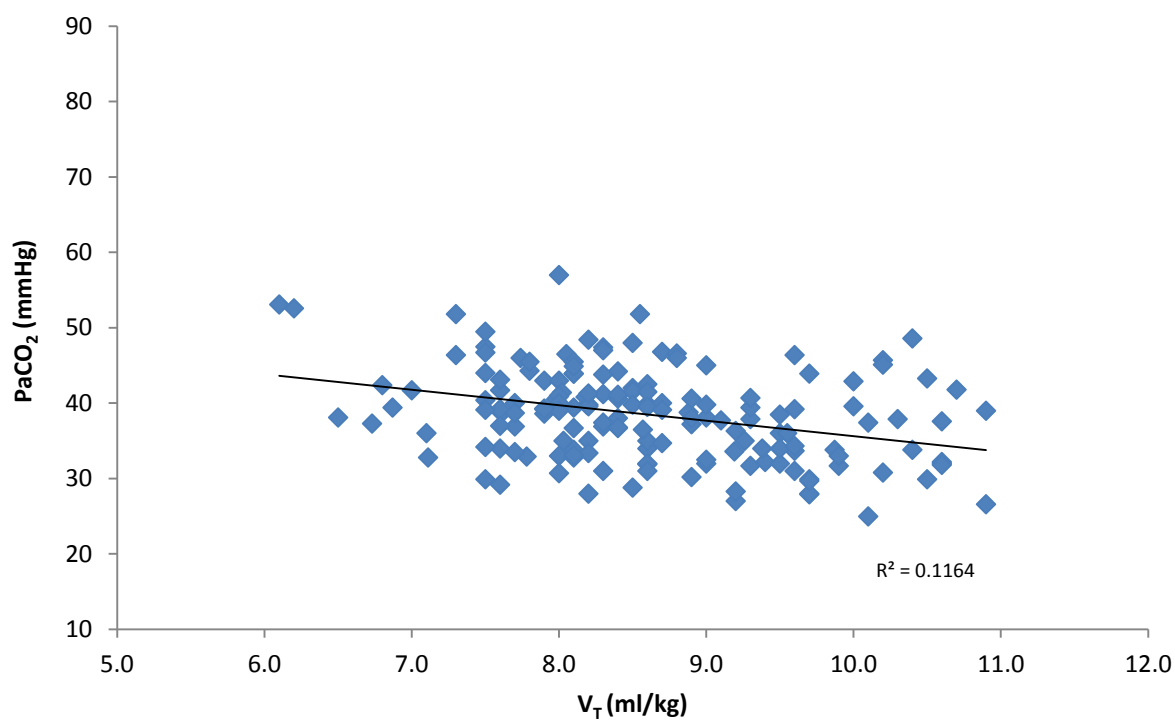


Figure 15 PaCO₂ vs. V_T levels for non-CO₂ retainers

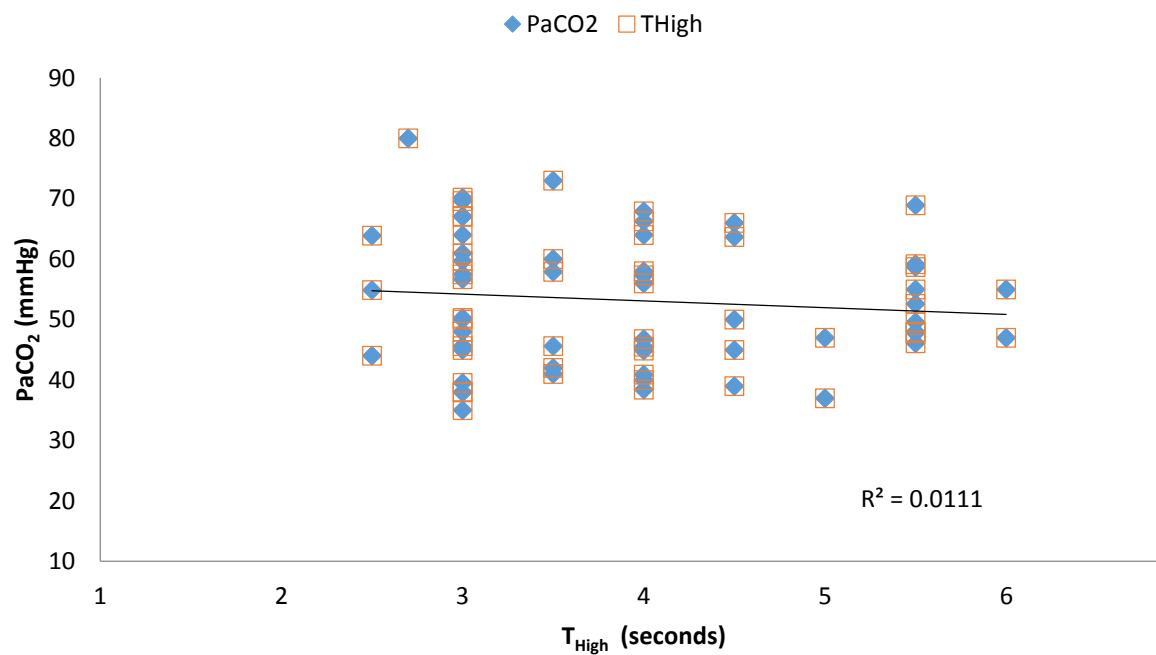


Figure 16 PaCO₂ vs. T_{High} levels for CO₂ retainers

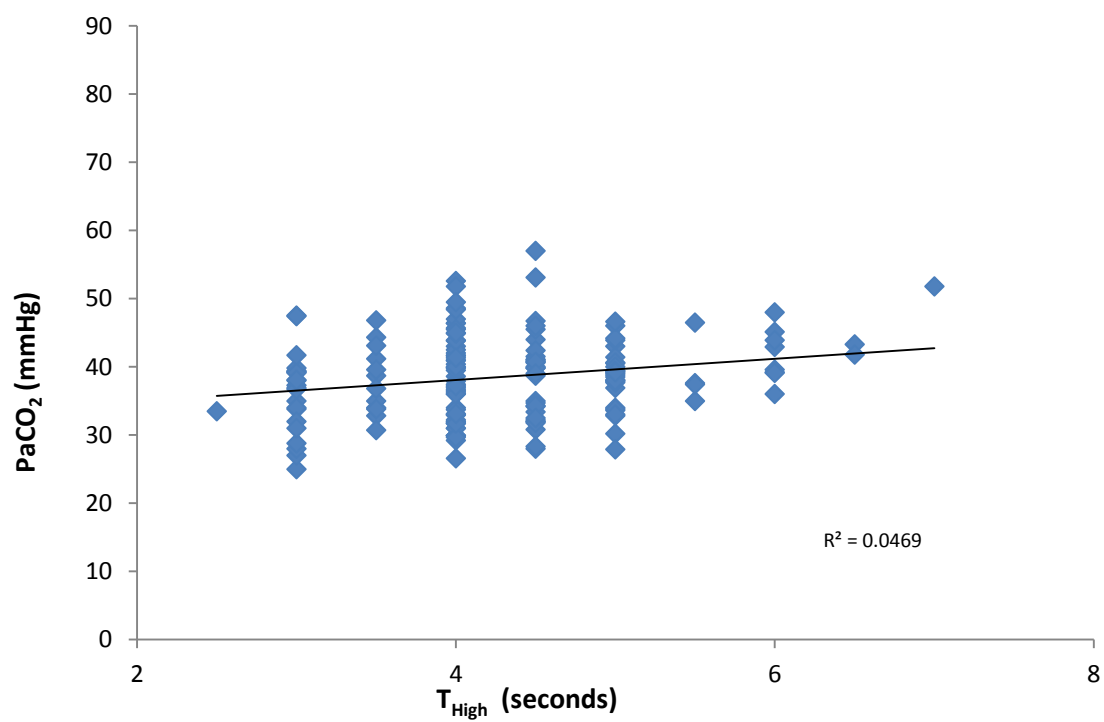


Figure 17 PaCO₂ vs. T_{High} levels for non-CO₂ retainers

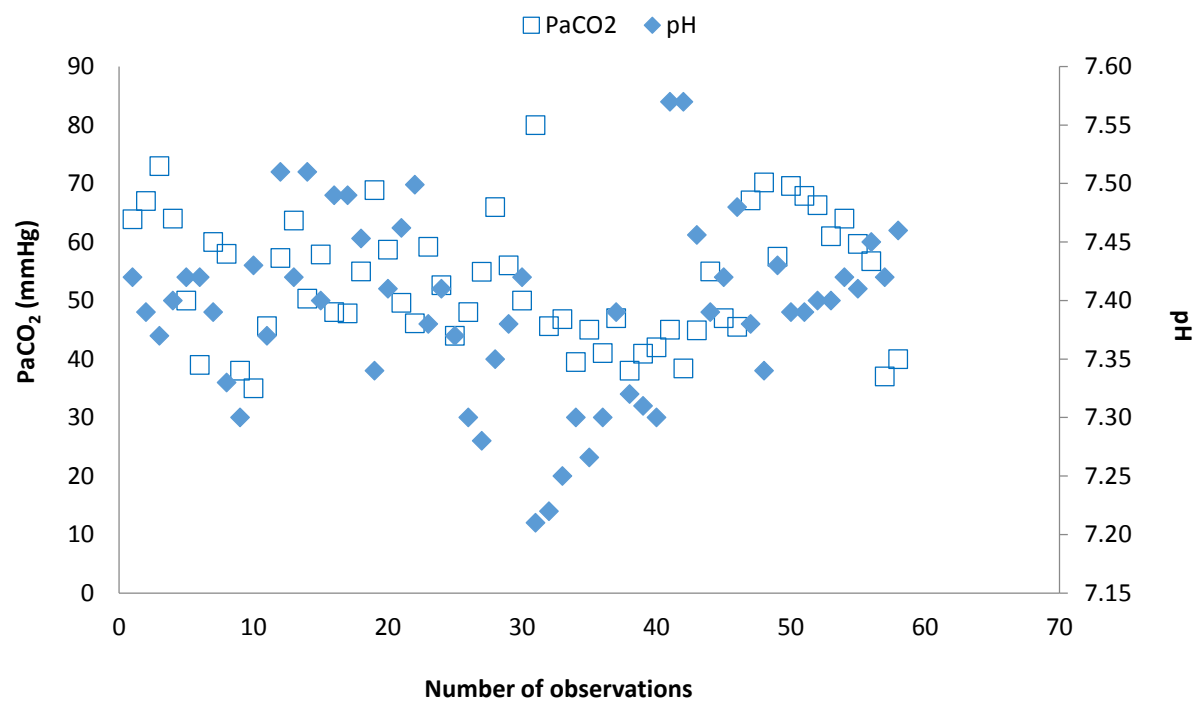


Figure 18 PaCO₂ and pH values for CO₂ retainers who did not receive NaHCO₃

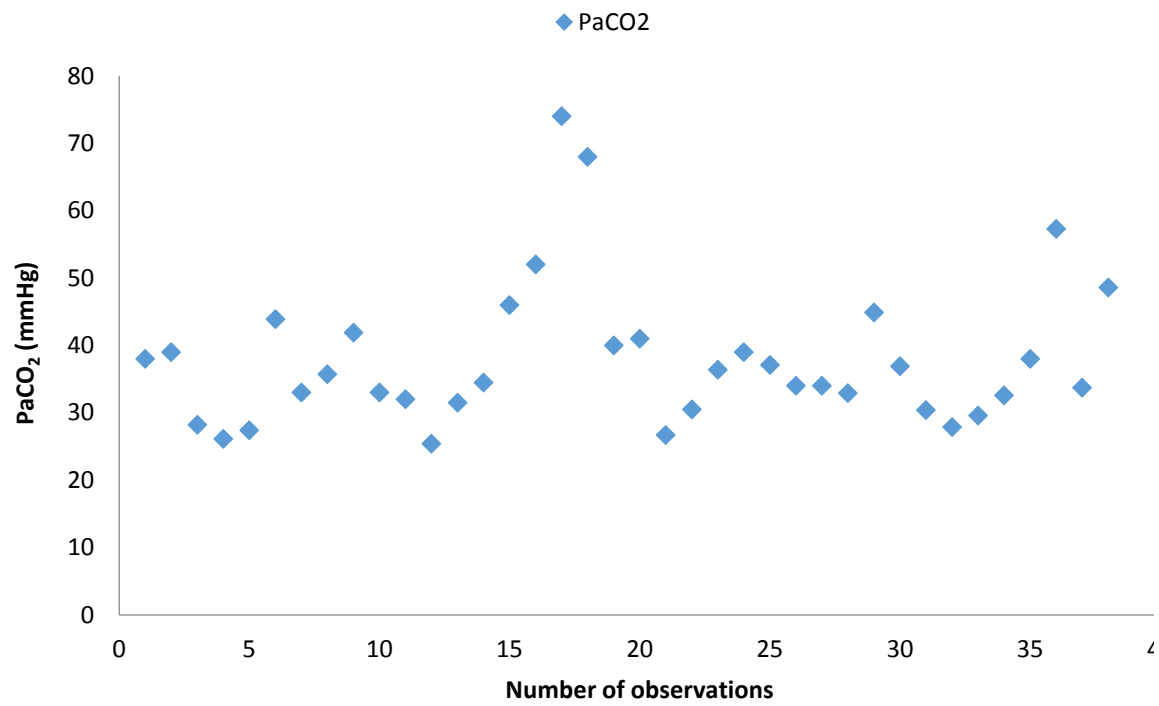


Figure 19 PaCO₂ levels for patients who received NaHCO₃

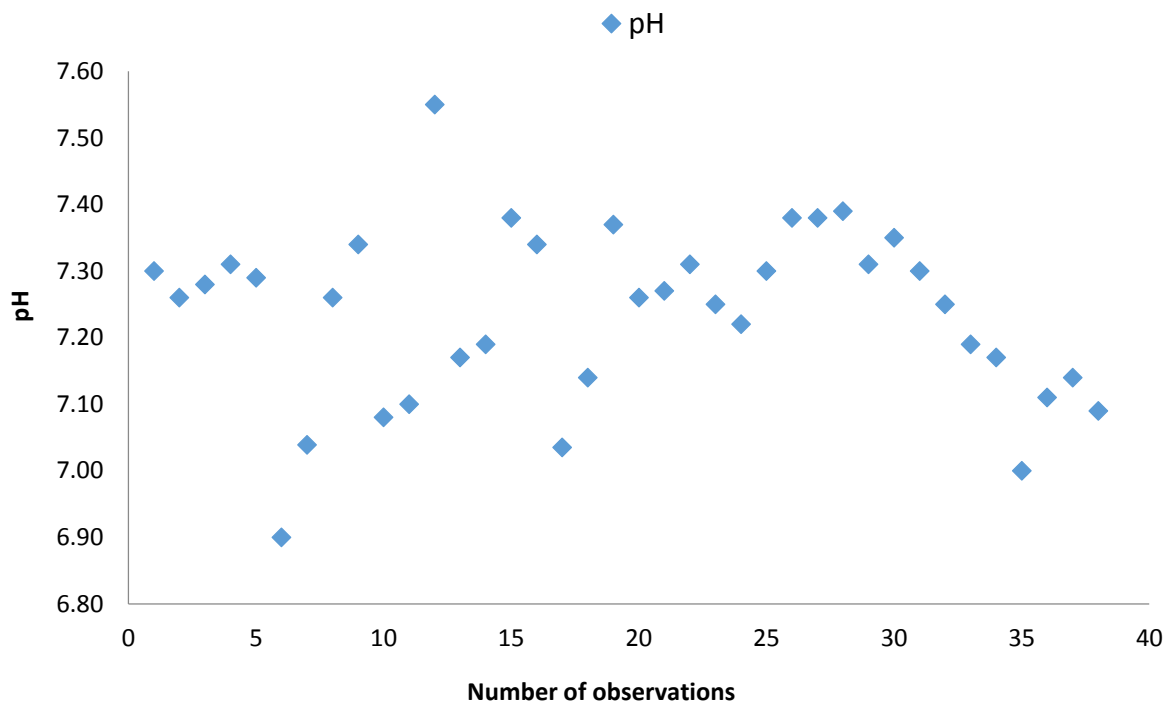


Figure 20 Arterial pH values for patients who received NaHCO_3

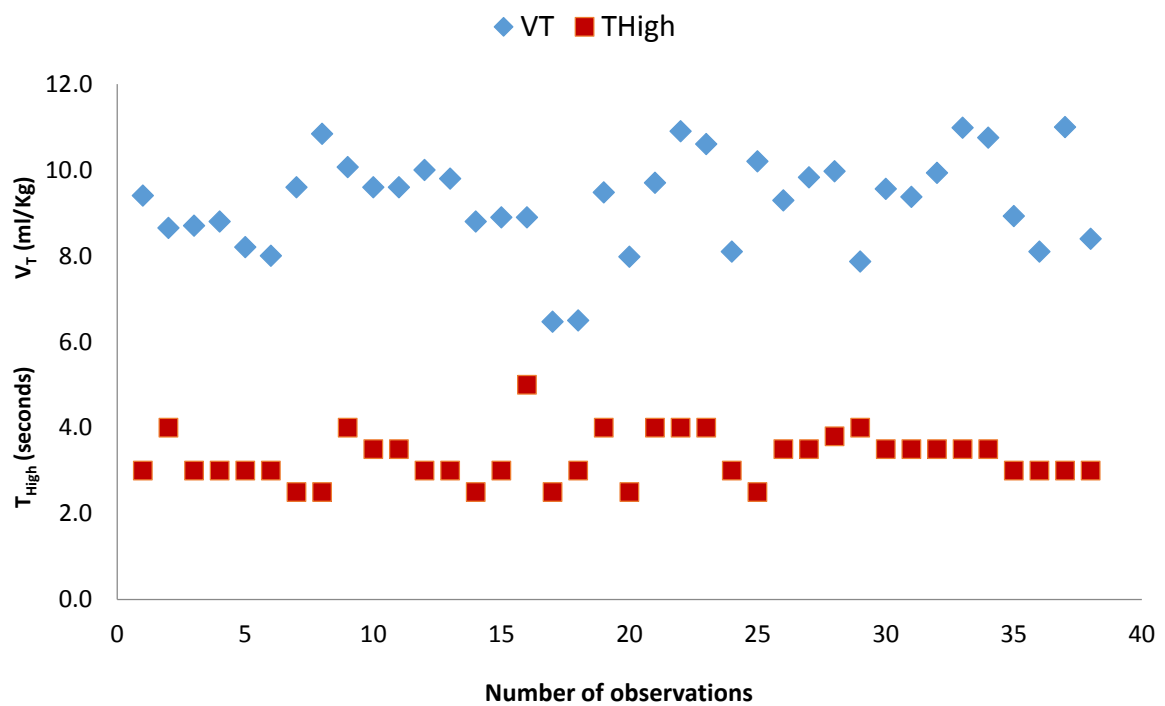


Figure 21 T_{High} and V_T settings for patients who received NaHCO_3

Table 32 shows the overall min, mean (SD), max, and 95% CI for T_{High} , T_{Low} , P_{High} , P_{Low} for the entire cohort. However, Table 33 shows the same statistics measure for each group (CO₂ retainers or non-CO₂ retainers) individually. Although T_{High} was indicated previously in Table 26, it is repeated in these tables to give an overall view of the all set configurations for each group.

Table 32 Overall statistical analysis for T_{High} , T_{Low} , P_{High} , and P_{Low} for the entire cohort

Variables	N	Min	Mean (SD)	95% CI	Max
T_{High} (sec)	286	2.5	4.02 (0.88)	3.92 – 4.13	7.0
T_{Low} (sec)		.20	0.51 (0.136)	0.497 – 0.529	0.9
P_{High} (cmH ₂ O)		22	32	31.6 – 32.6	45
P_{Low} (cmH ₂ O)		0	6 (4.3)	5.48 – 6.47	14

Table 33 statistical analysis for T_{High} , T_{Low} , P_{High} , and P_{Low} for each group (CO₂ retainers and non-CO₂ retainers)

Status	N	Variables	Min	Mean (SD)	95% CI	Max
CO ₂ retainers	61	T_{High} (sec)	2.5	3.92 (0.99)	3.66 – 4.17	6.0
		T_{Low} (sec)	0.30	0.525 (0.11)	0.50 – 0.55	.85
		P_{High} (cmH ₂ O)	22	33.9 (4.8)	32.8 – 35	45
		P_{Low} (cmH ₂ O)	0	8.2 (3.1)	7.4 – 9.0	12
Non-CO ₂ retainers	225	T_{High} (sec)	2.5	4.1 (0.85)	3.9 – 4.2	7
		T_{Low} (sec)	0.20	0.51 (0.14)	0.49 – 0.53	0.9
		P_{High} (cmH ₂ O)	22	31.6 (4.1)	31 – 32	42
		P_{Low} (cmH ₂ O)	0	5.4 (4.3)	4.8 – 6.0	14

However,

Table 34 shows min, IQR 25%, median, IQR 75% and max for PaO₂/FiO₂ ratio (mmHg) for the entire cohort and for each group (CO₂ retainers or non-CO₂ retainers); the latter were presented with a p value.

Table 34 statistical analysis for PaO₂/FiO₂ ratio (mmHg) for the entire cohort and for each group (CO₂ retainers and non-CO₂ retainers)

Mode	n	Min	IQR 25%	Median	IQR 75%	Max	p value
Entire cohort	289	44	111	173	240	488	----
CO₂retainers	61	44	96.5	136.8	205	342	< 0.002
Non- CO₂retainers	228	48.8	116.6	179	251	488	

1.28 Discussion:

The lack of consensus on a standard protocol for APRV use (71) has led to inconsistent applications among hospitals. This may have limited its use and could have contributed to the existed disparities among published studies that claimed to be using APRV. Also, significant aspects in the management of patients receiving MV via APRV seem to have been overlooked. Varpula and colleagues recommended in their randomised controlled trial that lower PaCO₂ could be achieved by either reducing the sedation level (in order to enhance more spontaneous breathing) or by reducing the T_{High} (to increase the M_V) (76); yet, one could simply question the extent to which the T_{High} should be reduced. This was not specified in their reports, though it may consequently lead to a completely conventional mode that's overlaid with the APRV mode. However, a well-known guideline by Habashi recommends that T_{High} generally should be set to occupy 80 to 95% of the total respiratory cycle when using the APRV mode to maintain optimum alveolar recruitment (18). Likewise, in some reviews (12), T_{Low}, which is an extremely critical variable, is not adjusted as part of correcting either hypoxaemia or hypercapnia.

At KFMC, we started using APRV following the available less-than-perfect guidelines at that time. After that, we developed our own guidelines aiming to improve some concerns that were existed in published ones. These concerns include safety, ease of use, thoroughness and comprehensiveness. Detailed description of our multifaceted ventilation

guidelines is beyond the scope of this chapter; this chapter focused only on normalising PaCO₂ on non- breathing patients.

It is notable that the PaCO₂ levels were less in the non-CO₂retainers group compared to the CO₂retainers group in spite of the longer T_{High} settings; though, the ventilatory management was almost the same.

However, despite higher PaCO₂ levels in the CO₂ retainers group, most pH levels were within an acceptable range, and patients with a pH level < 7.35 (due to metabolic acidosis) had normal PaCO₂ readings (≤ 45 mm Hg). It is credible that the administration of NaHCO₃ increases PaCO₂ (116). We noticed that this subgroup of patients who received NaHCO₃ did require shorter T_{High} settings than those in the other groups. In our study the mean T_{High} in the entire cohort occupied 87% of the total respiratory cycle which is in compliance with published recommendation. One can notice that our results of both PaCO₂ (for Non-CO₂retainers) and PH (for CO₂retainers) were 35.92-37.42 mmHg and 7.41-7.44, respectively. This gives clinicians more options for escalation of treatment and/or more space for weaning of parameters (e.g. reducing V_T or increasing T_{High}), if needed. This may also indicate that lower V_T and/higher T_{High} than the settings we used in this study could still have led to normal PaCO₂ and PH for both non-CO₂retainers and CO₂retainers, respectively.

1.29 Conclusion

The results of this chapter suggest that CO₂ elimination can be optimised in this heterogeneous group in the absence of spontaneous breathing

through particular ventilator configurations. However, given the novel, preliminary nature of this study, further investigation on APRV with larger samples may be warranted to identify optimal configurations in the absence of spontaneous breath.

Chapter 5

Oxygenation and Haemodynamic status in APRV vs. CV modes in patients with ARDS: a prospective study in a tertiary hospital

1.30 Hypothesis:

We hypothesise that APRV mode (without spontaneous breathing) is associated with better oxygenation and haemodynamic status than CV modes incorporating LOVT strategy for patients with ARDS.

1.31 Research question

Is APRV (without spontaneous breathing) associated with better oxygenation and haemodynamic preservation than CV using low-tidal-volume ventilation strategy for patients with ARDS?

1.32 Primary outcomes

PaO₂/FiO₂ ratio, mean arterial pressure (MAP), heart rate (HR), P_{Mean}.

1.33 Secondary outcomes

PEEP_M, PaO₂, PIP, systolic and diastolic blood pressure, PaCO₂, and “measured M_V”.

1.34 Introduction

The ability to provide safe and adequate ventilation of the lungs of patients with ARDS can be challenging when applying a LOVT according to the ARDSNet recommendations (97). LOVT may lead to repetitive shear forces, and low volume lung injury (25, 98) which may cause hypoxaemia (99, 100) and hypercapnia (101, 102). Such impairment in gas exchange could be caused by reduced lung volumes due to atelectasis and oedema (103, 104); therefore, an intervention that can safely maintain alveolar recruitment may be needed. Although APRV may be viewed as a virtually

continuous recruitment manoeuvre (98), it has been described as a lung-protective mode (12, 72, 98). Compared to pressure support ventilation, APRV with spontaneous breathing has shown significant improvement in lung aeration by decreasing atelectasis in a short time, which contributes to improved pulmonary oxygenation in patients with ALI and ARDS (105). It is credible that, upon transition from CV to APRV, some considerations need to be observed as the patient may experience some physiological changes due to the change in the manner of pulmonary ventilation. These changes may include altered intrathoracic pressure because of the increased P_{Mean} during APRV compared to CV. Although such an increased P_{Mean} may improve oxygenation (e.g. $\text{PaO}_2/\text{FiO}_2$), it may, potentially, affect the haemodynamic status by reducing venous return to the heart and therefore may reduce cardiac output. However, evidence shows that the haemodynamic effects of pulmonary ventilation are complex. Pulmonary ventilation can intensely alter haemodynamic status via complex, often conflicting, processes which include the possible interaction between many factors. These factors include intrathoracic pressure, lung volume, endocrine responses, autonomic tone, blood flow distribution, circulating blood volume, left and right ventricular pump function, myocardial reserve, and the pressures that surround the remaining parts of circulation (117). Discussing such complex processes is beyond the scope of this paper as it focuses on the possible effects of APRV on some indicators that may reflect haemodynamic status, namely blood pressure and HR.

In a previous work (chapter Three), we initially compared CO₂ elimination during APRV (without spontaneous breathing) and CV modes before analysing the data for oxygenation and haemodynamic status. We found that APRV was associated with improved CO₂ elimination (i.e. lower PaCO₂ at lower M_V) compared with CV modes in patients with ARDS. In this chapter, we presented the data for oxygenation (as shown in PaO₂/FiO₂) and haemodynamic status during APRV without spontaneous breathing, as compared with CV modes for the same patients. The main reason we chose the same patients was mainly to assess whether the improved ventilation (as shown in chapter Three) was accompanied by improvement in oxygenation and haemodynamic status (the outcome measures of the study in this chapter). However, there is a slight difference in this chapter compared to chapter Three; in chapter Three, only one dataset that comprised the longest T_{High} during APRV was compared with the dataset of CV. However, in this study we took the same datasets as in that study plus the first dataset that met our eligibility criteria on APRV (i.e. one dataset on CV vs. two datasets on APRV). We also discussed the potential causes for the observed results.

1.35 Methods

This study was approved by the IRB at the KFMC with a waiver of the requirement for informed consent because this was an observational study with no change to standard care. We enrolled into a prospective cohort study 54 consecutive mechanically ventilated patients with ARDS refractory

to CV and being transitioned to APRV (as shown in Figure **9**) in all adult ICUs at KFMC. Patients were recruited from 69 adult ICU beds that are distributed in surgical, general, and cardiac ICUs. As shown in Table 35, ARDS was diagnosed according to the American-European Consensus Conference criteria (31). Although the decision to change the mode from CV to APRV was solely left to the discretion of the treating team (led by the attending intensivist), failure of CV was generally defined as failing to maintain acceptable gas exchange, especially oxygenation ($\text{PaO}_2/\text{FiO}_2 > 26.7 \text{ kPa}$) despite high FiO_2 , persistently elevated PIP of $\geq 35 \text{ cmH}_2\text{O}$ and/or PEEP of $\geq 10 \text{ cmH}_2\text{O}$ with signs of bilateral lungs infiltrate and derecruitment (as judged radiographically by the treating team). Our patients had a variety of pathologies and were not excluded on the basis of diagnosis. Through the following inclusion and exclusion criteria, we compared oxygenation ($\text{PaO}_2/\text{FiO}_2$) and haemodynamic indicators, including MAP, systolic (Sys) and diastolic (Dia) blood pressures, and HR during CV and APRV, i.e. each patient had these indicators measured during both CV and APRV.

Table 35 American-European Consensus Conference Criteria for ARDS

American-European Consensus Conference criteria for ARDS:

- Timing: acute onset
- Oxygenation: $\text{PaO}_2/\text{FiO}_2 < 26.7 \text{ kPa}$
- Frontal chest radiography findings: bilateral infiltrates
- No clinical evidence of left atrial hypertension of pulmonary artery wedge pressure $\leq 18 \text{ mm Hg}$

1.35.1 Inclusion criteria:

- Receiving MV refractory to conventional modes and being transitioned to APRV
- Having no spontaneous breathing
- Having ARDS (defined as: $\text{PaO}_2/\text{FiO}_2 < 26.7 \text{ kPa}$) signs of bilateral lungs infiltrate and derecruitment (as judged radiographically by the treating team)

1.35.2 Exclusion criteria:

- Less than 18-year-old
- $T_{\text{High}} < 2.5 \text{ s}$
- The Interval between APRV dataset and CV dataset $> 96 \text{ hr}$
- Having cardiorespiratory arrest or who require disconnection from the mechanical ventilator for manual resuscitation (prior to the ABG measurement)

Each dataset comprised all pertinent ventilator parameters (mode of MV, FiO_2 , P_{High} , P_{Low} , T_{High} , T_{Low} , PEEP_M , P_{Mean} , RR, PaO_2 , V_T , M_V , PIP, and ABG analysis. During CV, one dataset was taken immediately before transition from CV to APRV (CV dataset). During APRV, two datasets were taken at two time-points (where possible): 1) at the first dataset that met eligibility criteria during APRV ($\text{APRV}^{1\text{st}}$); 2) and the dataset that met our eligibility criteria which comprised the longest T_{High} within the first 96 hours of APRV ($\text{APRV}^{2\text{nd}}$). However, some patients had only one dataset that met our eligibility criteria during APRV; this single dataset was then considered as $\text{APRV}^{2\text{nd}}$ to be compared with that of CV. The time at which the mode was switched to APRV (T_1) until the time of $\text{APRV}^{1\text{st}}$ (T_2) was labelled as first interval (1^{st} interval) whilst the second interval (2^{nd} Interval) represents the time between T_1 and the dataset for the ventilator settings that comprised the longest T_{High} for that patient (T_3). ABGs were performed within one hour of each ventilator settings, providing no spontaneous breathing occurred during this window.

As shown in Figure 9, 87 patients with ARDS were refractory to CV and being transitioned to APRV was screened for eligibility to this study. Of these patients, 19 patients did not have periods of absent spontaneous breathing and four patients had some missing data on one mode or both, such as those whose tracheas were intubated and immediately switched to APRV (due to their severely critical illness) before obtaining ABGs during CV. Of the remaining 64 patients, four were less than 18-year-old and six patients had short T_{High} (< 2.5 sec) which might not be compatible with APRV and two patients had cardiorespiratory arrest around the time of obtained data. However, 52 patients did meet our inclusion criteria. Two of these patients required re-intubation and MV weeks or months after the former extubation (i.e. they required MV on two separate occasions); the separate episodes of ventilation were considered as if they were distinct patients. Each dataset comprising the following variables:

- FiO_2 , P_{High} , P_{Low} , T_{High} , T_{Low} , PEEP_{Set} , PEEP_M , P_{Mean} , RR, V_T , and PIP which were measured by the internal mechanisms of the Dräger Evita_{XL} ventilator (Dräger, Lubeck, Germany) and SERVO_I (Maquet Critical Care, Sweden) ventilators. Each of these ventilators was calibrated before use in each patient.
- PaCO_2 , PaO_2 and $\text{PaO}_2/\text{FiO}_2$ (measured using Siemens Rapidlab 1265 blood gas machine).

- MAP, systolic and diastolic blood pressures, and HR
(measured using GE Medical Systems, Model NO. USE1903A, Freiburg, Germany).

1.35.3 Statistical analysis

Normally distributed, continuous variables were compared using paired t-test and reported as mean with standard deviation (SD), while non-normally distributed variables were compared using Wilcoxon rank-sum tests and reported as median (interquartile range). Categorical data are presented as frequencies and percentages. To assess the difference between modes, the values of $\text{PaO}_2/\text{FiO}_2$, HR, MAP, P_{Mean} , Sys, Dia, PaO_2 , FiO_2 , PEEP_M, PaCO_2 , PIP, RR, V_T , and M_V , during APRV were subtracted from the values of the same variables during CV for each pair and the distribution of these variables were summarised using minimum, IQR 25%, median, IQR 75%, and maximum. To assess the significance of differences for these variables between study groups, we performed the analysis using a non-parametric test (Wilcoxon's signed rank test). However, to assess the significance of differences in PaCO_2 between study groups, paired t-test was performed because of its normal distribution. A p-value of less than 5% was considered to be statistically significant. Statistical analysis was performed using SPSS (version: IBM SPSS Statistics 22, Inc, Chicago, Illinois, USA).

1.36 Results

Of the 54 patients enrolled in this study, 134 datasets met our eligibility criteria; 26 patients (48.1%) of patients had three datasets (i.e. during CV,

APRV^{1st}, and APRV^{2nd}) for each patient (78 datasets). Whilst all patients had the two main datasets (CV and APRV^{2nd}) for each patient. Table 36 summarises the baseline demographics and an estimate of the severity of lung injury ARDS according to the Berlin definition (94). The median (IQR) values for PaO₂/FiO₂ during CV were 9.2 (IQR 7.3–13.2) kPa vs. APRV during the 1st and 2nd intervals which were 17.2 (IQR 12.8–26.9) kPa and 22.2 (IQR 14.0–34.7) kPa, respectively (both had $p < 0.001$). The median values for MAP were 72.8 (IQR 63.8–84.3) mmHg during CV vs. 78.5 (IQR 69.0–89.1; $p = 0.09$) and 81.7 (IQR 71–88.7; $p = 0.004$) mmHg during APRV for 1st and 2nd interval, respectively. The median values for HR during CV were 106.5 (IQR 89.5–118.3) beats/min vs. 105.5 (IQR 86.8–118.3; $p = 0.16$) beats/min and 101.0 (IQR 80.0–120.0; $p = 0.11$) beats/min on APRV during 1st and 2nd intervals, respectively. The aforementioned substantial improvement in oxygenation (higher PaO₂/FiO₂) was observed in both intervals (1st and 2nd intervals) with median times of 04:47 (IQR 01:14–09:24) hr:min and 19:54 (IQR 07:03–39:05) hr:min, respectively. However, despite the constant improvement in haemodynamic status, statistically significant improvement was shown during the 2nd interval, i.e. in time of median 19:54 (IQR 07:03–39:05) hr:min. The median values of P_{Mean} during CV were 17.0 (IQR 14.8–19.3) cmH₂O vs. 30 (IQR 28–31.3) cmH₂O and 30 (IQR 26.0–32.0) cmH₂O during APRV in the 1st interval and 2nd intervals, respectively (both had $p < 0.001$). **Error! Reference source not found.** shows PaO₂/FiO₂, HR, Sys, Dia, and MAP for CV vs. APRV (1st and 2nd intervals. Figure 23 shows PaO₂, FiO₂, PEEP, and P_{Mean} for CV vs.

APRV (1st and 2nd intervals). Figure **24** shows PaCO₂, PIP, RR, V_T and M_V for CV vs. APRV (1st and 2nd intervals).

The mean (SD) T_{High} and T_{Low} during APRV was 4.42 (1.0) sec (4.1–4.7 sec; 95% CI) and 0.5 (0.1) sec (0.47–0.54 sec; 95% CI), respectively.

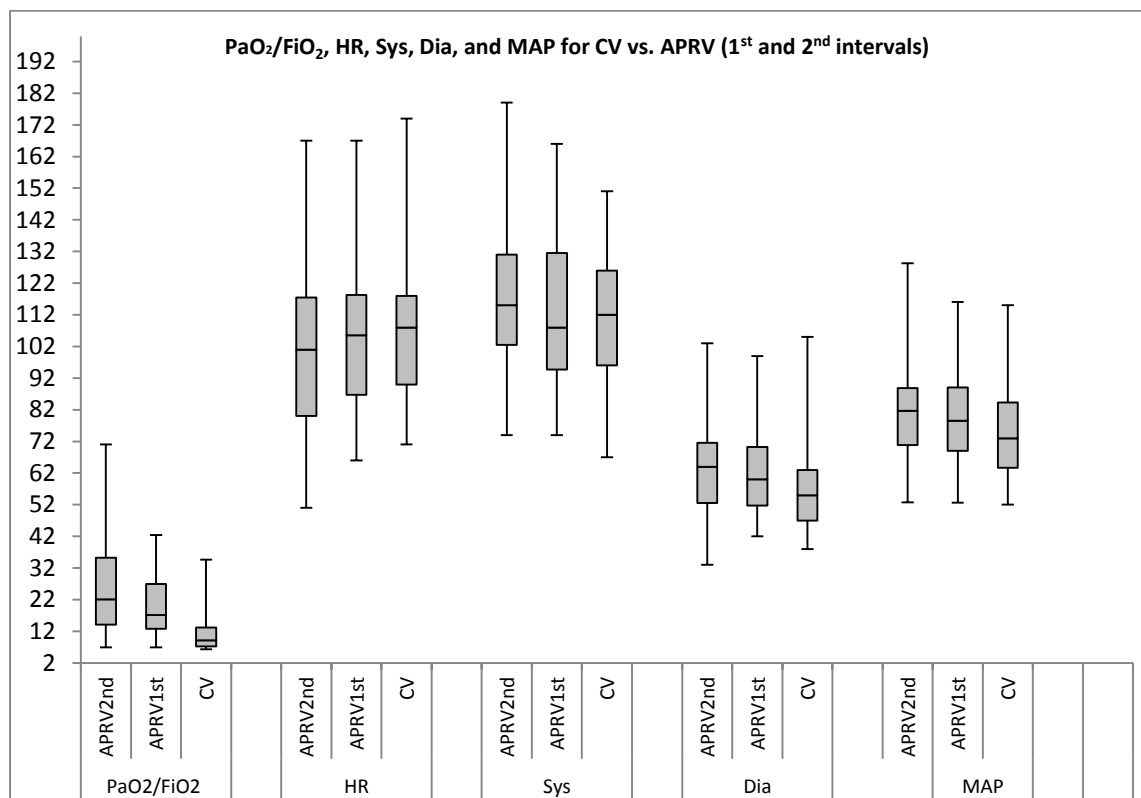


Figure 22 PaO₂/FiO₂, HR, Sys, Dia, and MAP for CV vs. APRV (1st and 2nd intervals)

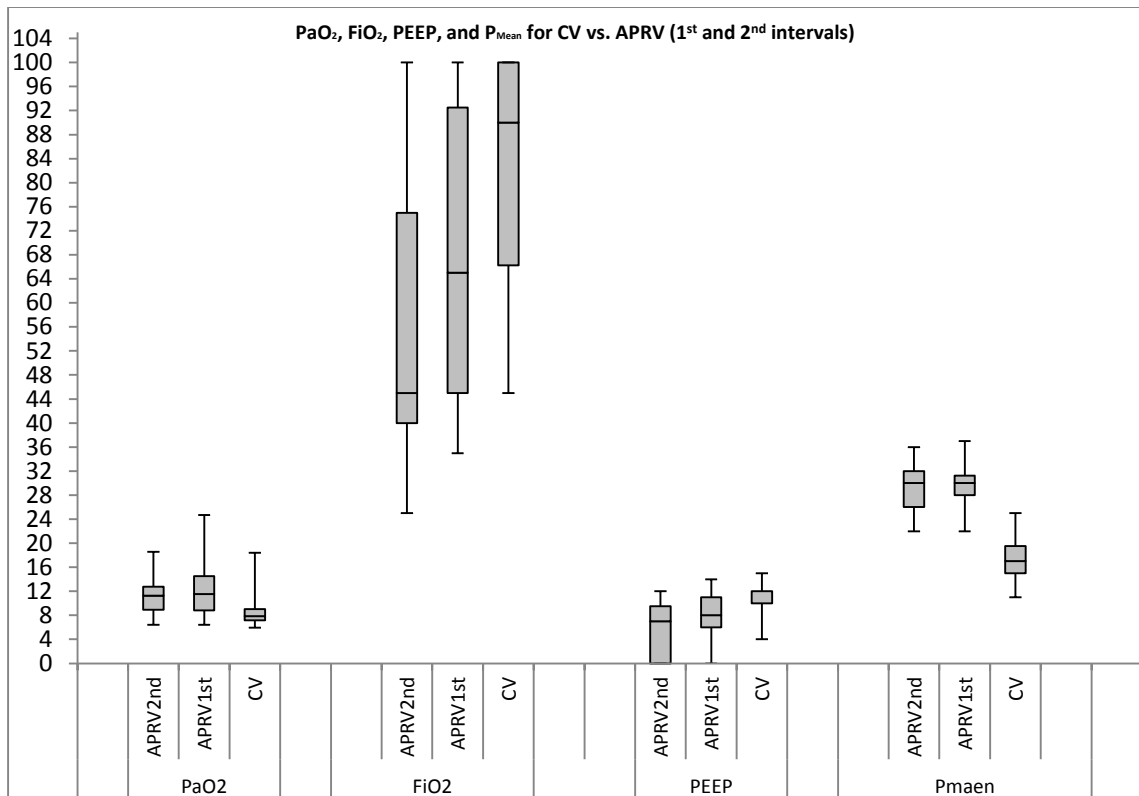


Figure 23 PaO₂, FiO₂, PEEP, and P_{Mean} for CV vs. APRV (1st and 2nd intervals)

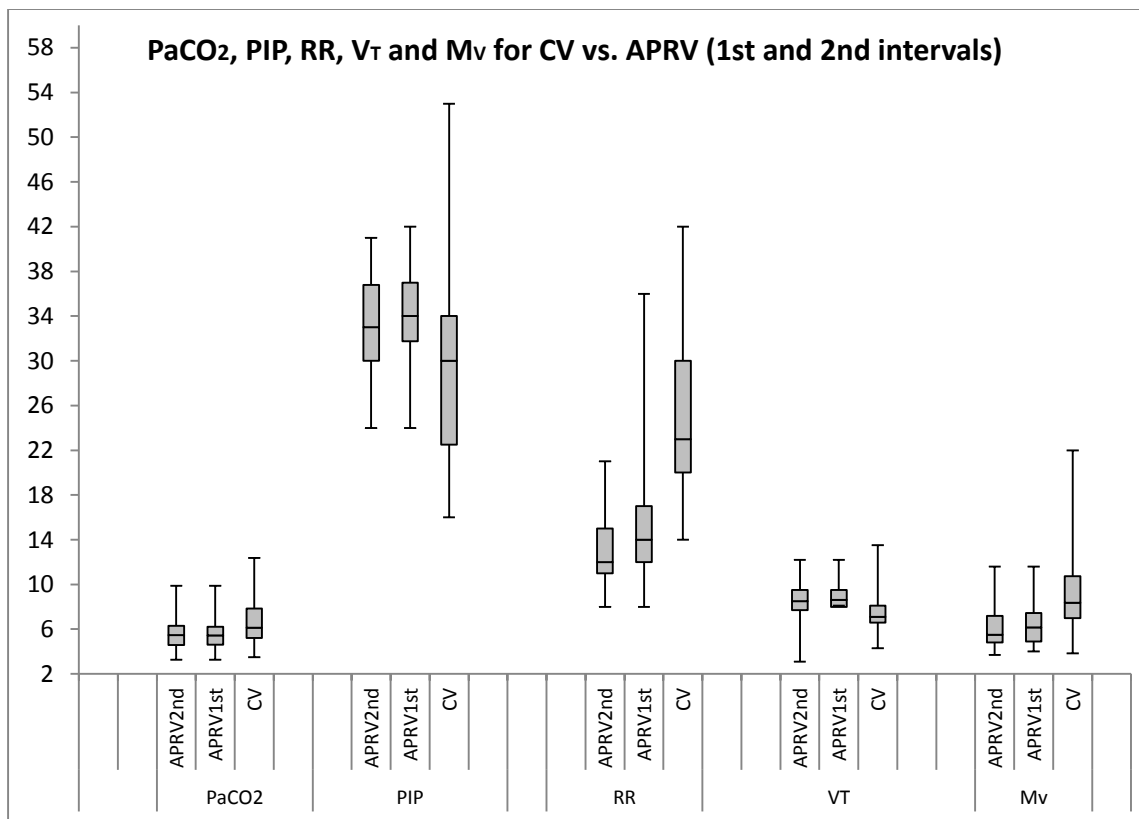


Figure 24 PaCO₂, PIP, RR, V_T and M_V for CV vs. APRV (1st and 2nd intervals)

Table 36 Baseline characteristics for patients enrolled in the study

Age, median (IQR), years	53 (30.5-66.5)
Male/Female (n)	28 / 23
PaO ₂ /FiO ₂ , median (IQR), kPa	9.1 (7.3-13.1)
Severe ARDS, n (%)	41 (75.9%)
Moderate ARDS, n (%)	12 (22%)
Mild ARDS, n (%)	1 (1.86%)

Table 37 shows statistical analysis of PaO₂, Sys, Dia, HR, MAP, PEEP_M, P_{Mean}, RR, V_T, MAP, and PaO₂/FiO₂.

There was a significant reduction in both PEEP_M during APRV compared to the required PEEP in the CV mode; the median was 7 cmH₂O (IQR 6–10) vs. 10 cmH₂O (IQR 10–12); $p < 0.001$, respectively. The absolute mean (SD) PaCO₂ was significantly lower during APRV (1st and 2nd intervals) 5.64 (1.4) kPa and 5.65 (1.37) kPa, respectively, compared to CV which was 6.56 (1.95) kPa; (both had $p < 0.001$).

Table 37 Statistical analysis of PaO₂, Sys, Dia, HR, MAP, PEEP_M, P_{Mean}, RR, VT, MAP, and PaO₂/FiO₂

Variable	N	Mode	Min	Median	IQR 75%	Max	p value
PaO₂ (kPa)	53	CV	3.7	5.5	7.3	11.6	< 0.001
		APRV	3.8	8.3	11.1	22	
Sys	43	CV	67	112	120.50	151	=0.059
		APRV	74	115	131	179	
Dia	43	CV	38	55	63	80	=0.002
		APRV	33	64	71.50	103	
HR	45	CV	71	108	118	174	=0.125
		APRV	51	101	117.50	167	
PEEP	51	CV	4.0	10	12	15	< 0.001
		APRV	1	7	10	13	
P_{Mean}	51	CV	11	17.00	19.25	25	< 0.001
		APRV	22	30	32	37	
RR	49	CV	14	24	30	42	< 0.001
		APRV	8	12	15	21	
MAP	43	CV	52	72.7	82.5	98	=0.003
		APRV	52.7	81.7	88.84	128.3	
PaO₂/FiO₂ (kPa)	53	CV	6.3	9.1	13.1	34.7	< 0.001
		APRV	6.9	21.7	32.4	71	

1.37 Discussion

Moderately and severely injured lungs such as those of the patients enrolled in this study may require higher airway pressure to correct life-threatening hypoxaemia. Several studies showed that APRV was associated with better oxygenation, improved V/Q matching, and decreased pulmonary dead space (V_D/V_T) compared with CV (12, 16, 20, 51-57, 98). Similarly, our study in this chapter showed that despite a very low baseline PaO_2/FiO_2 which indicated severe ARDS according the Berlin definition (94), we found that APRV was associated with significant improvement in PaO_2/FiO_2 during both intervals (1st and 2nd intervals), which was achieved in relatively short time. Although the Berlin definition (94) of ARDS was published almost a year after the commencement of this study; our patients met the criteria stated in that definition including: (1) onset within one week of a known clinical insult or new or worsening respiratory symptoms; (2) PaO_2 / FiO_2 ratio ≤ 300 mmHg with PEEP or CPAP ≥ 5 cmH₂O; (3) bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules; and (4) respiratory failure not fully explained by cardiac failure or fluid overload and needs objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor is present. Of all patients enrolled in this study, only one patient had a mild ARDS according to the Berlin definition; however, this patient required an extravagantly high peak inspiratory pressure (53 cmH₂O) to deliver desired V_T which mandated switching the mode to APRV.

Such a significant improvement in oxygenation seen in patients included in this study might have been caused by better lung recruitment due to the significantly higher P_{Mean} during APRV compared to CV; this could be presumed by both subjective (e.g. better lung aeration in chest radiographs) as well as objective (e.g. the consistent improvement in $\text{PaO}_2/\text{FiO}_2$ at lower airway pressures) measures. However, although APRV has been shown to be an effective modality in improving oxygenation through lung recruitment, it has been speculated that venous return and cardiac output may decline in the absence of spontaneous breathing (98). It is credible that the application of positive pressure, namely PEEP or P_{Mean} during MV, may negatively impact haemodynamic status (118). Fougères reported that increasing PEEP level with limited V_T and P_{Plat} in patients with ARDS was associated with a reduced cardiac output due to an increased right ventricular afterload (119). In KFMC we followed the low tidal volume strategy in accordance with the ARDSNet guidelines (120), thereby, our patients in the CV mode group met the conditions stated in the study of Fougères in terms of the settings of PEEP and V_T . A number of studies reported that compared to CV, APRV was associated with significantly higher P_{Mean} (52); this is in agreement with the findings of our study in both time intervals. Therefore, one could argue whether such a significantly higher P_{Mean} during APRV has a negative impact on haemodynamics. Rasanen and colleagues compared the haemodynamics in dogs that had ventilatory failure with and without parenchymal lung injury ventilated with APRV and conventional positive pressure ventilation (CPPV). Although the

modes were applied in opposite orders (i.e. APRV then CPPV), they reported that CPPV resulted in a significant depression in stroke volume, cardiac output, and blood pressure, including systemic oxygen delivery (121). Likewise, some studies in human reported that APRV was associated with better oxygen delivery, cardiac performance, and reduced use of vasopressors when compared to CV; however, these positive observations were ascribed to the spontaneous breathing during APRV (54, 55). Other studies reported similar haemodynamic status (59, 122); however, both studies reported no differences in gas exchange between APRV and CV. Another study showed better oxygenation but no difference haemodynamic status (52); yet, it compared APRV to inverse-ratio ventilation (IRV) rather than CV. Two RCTs compared APRV (with spontaneous breathing) to CV; the trial of Varpula and colleagues (76) who compared APRV group (30 patients) with SIMV-PC/PS group (28 patients) and the trial of Maxwell and associates (60) who compared APRV (31 patients) to SIMV-VC/PS while assuring LOVT (32 patients). Extensive critical appraisal about these two studies was detailed in Chapter One of this thesis; however, we would be comparing the primary outcomes of our studies with that of these two studies. Keeping in mind all the disparities discussed in Chapter One, Varpula found no differences in $\text{PaO}_2/\text{FiO}_2$ ratio, MAP, PaCO_2 , M_v between study groups. However, Maxwell did show lower PaCO_2 and M_v , in favour of APRV but similar $\text{PaO}_2/\text{FiO}_2$; haemodynamics were not measured among their outcomes. In contrast, our current study compared APRV with LOVT assist-control mode which is in reasonable compliance with the ARDSNet

guidelines; we found significantly better $\text{PaO}_2/\text{FiO}_2$ ratio, lower PaCO_2 at lower $\dot{V}_E$ in favour of APRV during both time intervals (1st and 2nd intervals) despite the absence of spontaneous breathing. This multifaceted improvement in gas exchange could have contributed to the improved MAP seen in our study as will be discussed later.

This study is the first study that aimed to shed light on the haemodynamic effects of APRV in patients with moderate-to-severe ARDS in the absence of spontaneous breathing compared to CV. We chose specific indicators (i.e. MAP and HR) for the assessment of haemodynamic status because they were continuously monitored via an arterial cannula. Moreover, we selected the MAP as a primary outcome rather than systolic/diastolic blood pressures because it has been reported to be the most consistent metric for monitoring blood pressure in the ICU (123). In spite of the rapid improvement in MAP observed during 1st interval, it did not reach statistical significance, however, it did during the 2nd interval and was significantly higher than that of CV. The improvement in MAP observed in our study in spite of higher P_{Mean} during APRV could have been caused by several reasons. Firstly, the positive end expiratory pressure (P_{Low} and/or PEEP_M) during the 1st and 2nd intervals of APRV was significantly lower than the required PEEP during CV; yet, it was even lower in the 2nd interval than it was in the 1st interval. This may have produced a lower intrathoracic pressure during the pressure release phase (T_{Low}), thereby, augmenting the venous return which contributed to an increased cardiac output. We found that the improvement in MAP was inversely related to the PEEP (P_{Low} and/or

PEEP_M); therefore, when PEEP reached the lowest levels (i.e. in the 2nd interval), the MAP reached the highest. Secondly, lung inflation mainly affects cardiac output and cardiac function by changing right ventricular afterload and LV preload (124, 125); however, the mechanism by which pulmonary MV alters pulmonary vascular resistance (PVR) is complex (117). It is credible that when regional alveolar PO₂ drops below 60 mmHg (8.0 kPa), local blood flow reduces due to an increased vasomotor tone (126); this process is referred to as hypoxic pulmonary vasoconstriction (HPV). Our patients in the CV group had significantly lower oxygenation indices including PaO₂ compared to APRV during both intervals (1st and 2nd intervals), median 7.9 (IQR 7.1–9.0) kPa vs. 11.53 (IQR 8.79–14.53) kPa and 11.4 (IQR 8.9–12.8) kPa, respectively (both: $p < 0.001$), we speculate that the HPV could have been different too, though it was not objectively measured. Such significant improvement in oxygenation indices such as PaO₂/FiO₂ and PaO₂ could have a positive impact on reducing PVR. Thirdly, it has been reported that restoration of lung volume to normal values by recruitment manoeuvres and PEEP usually decreases PVR by reversing HPV (127). We found that V_T was greater in the APRV than CV group despite comparable inspiratory pressures. It has been suggested that if an increase in PEEP produces a large improvement in PaO₂, a reduction in PaCO₂, and better compliance, it suggests significant recruitment (128). It has been reported that both hypoxaemia and hypercapnia augment RV afterload (44, 45). Our patients showed significant improvement in PaO₂ and PaCO₂ after being switched to APRV during both time intervals; however, compliance

was not measured. It is noteworthy that the median (IQR) P_{High} on APRV (1st and 2nd intervals) were 34 (IQR 31.8–37.0) mmHg and 32 (IQR 29–35) cmH₂O, respectively; P_{High} may give a clue about the P_{Plat} in the absence of spontaneous breathing like the case of our patients. The median (IQR) P_{Plat} in the CV group was 29 (26–33) cmH₂O; yet, it was measured for 7 patients only as most of them were ventilated with pressure control rather than volume control mode. We found significant improvement in V_T during the 1st and 2nd intervals compared to CV despite lower inspiratory pressures namely P_{High} ; this may have been due to better lung recruitment and compliance. Fourthly, it has been reported that variations in venous return must ultimately produce directionally similar variations in the left ventricular preload after two or three heart beats, as seen in Valsalva manoeuvre (129). However, this phase delay from right ventricular to left ventricular output may accentuate with large tidal volumes which is a major components of M_v (130). In our study, APRV was associated with significantly lower M_v than observed during CV due to significantly lower RR. Moreover, knowing that cardiac output is a function of HR and stroke volume, one can speculate that our patients could have had an increase in stroke volume rather than HR, because compared to CV, the HR was lower during the 1st interval of APRV and was even lower in the 2nd interval compared to the 1st interval. It is credible that a larger end-diastolic volume will stretch the heart. Stretching the muscles of the heart optimises the length-strength relationship of the cardiac muscle fibres, resulting in

stronger contractility and greater stroke volume; this in turn could increase cardiac output and MAP.

The results of this study show that besides the significant improvement in PaCO_2 and M_v , oxygenation and haemodynamic status were significantly better during APRV compared with CV. Also, we found a significant drop in the FiO_2 during APRV compared to CV. This can be of great value for clinicians in critical care settings as it may help reducing potential risk of oxygen toxicity and providing options for escalation of treatment, if needed. It has been reported that $\text{FiO}_2 \geq 50\%$ for ≥ 48 successive hr is considered to be potentially harmful (131, 132). Also, erythema and oedema of large airways could be observed bronchoscopically in the majority of patients receiving an FiO_2 of 90% for six hr and are thought to reflect hyperoxic bronchitis (133). A small retrospective study of 16 formerly healthy, non-smoking survivors of ARDS reported that treatment with an $\text{FiO}_2 > 60\%$ for > 24 hr was both sensitive and specific predictor of a reduced diffusing capacity at one year (134). Despite potential biases in this study based on severity of illness (patients with more biologically severe ARDS probably received higher O_2 concentration), the only variable that predicted the degree of such diffusing abnormality was the duration of FiO_2 of more than 60%.

Our study has several limitations such as a small sample size and lack of continuous monitoring. However, compared with published studies, our data exceeds the number of the largest randomised control trials to date. Each of the studies of Varpula and Maxwell had less than 33 patients in

each group; yet, datasets that met out criteria were 54 patients in each group, making such a small sample size reasonably fair, especially with such lack of evidence in the literature. Also, we had to take the same data we used in the previous study (Chapter Four) because our aim was to prove (or disprove) the hypothesis that the use of APRV (According to the Al-ahmad protocol) could improve both oxygenation and haemodynamics besides the observed lower PaCO₂ and M_V. If we had not narrowed our inclusion criteria, we could have included a much larger sample and had more observations (datasets) in each group. Moreover, finding non-spontaneously breathing patients during APRV was not an easy task, especially with such an extremely inverse ratio. The reason why we mainly took the dataset that comprised the longest T_{High} was because it would provide the lowest M_V (T_{High}:T_{Low} was 9:1); this should have challenged APRV more as it could have led to higher PaCO₂. Some modalities may improve one aspect of gas exchange (e.g. oxygenation) while other aspects such as ventilation (CO₂ removal) may be sacrificed; however, the levels of sacrifice may depend on the severity of the illness. Another limitation was that the timing of ABGs was not consistent; although the vast majority of ABGs were taken within 25–60 min while a few ABGs were taken within 61–90 min; this delay was due to uncontrolled circumstances (e.g. occlusion of the radial artery or cleaning the patient). Also, as this study was observational we cannot prove causation between the improved outcomes and the absence of spontaneous breathing because most patients enrolled in our study had periods of spontaneous breathing during APRV course.

We did not measure the use of vasopressors, sedatives nor paralysing agents, however, a group of researchers in our hospital using our protocol compared this outcome retrospectively and found statistically significant improvement in the use of sedation in favour of APRV. They also found the use of APRV in septic patients restores haemodynamic stability earlier than CV. There was a significant improvement in ICU survival in favour of APRV; they found that the early institution of APRV was associated with lower ICU mortality ($p = 0.022$) (67).

Finally, prospective RCTs using our protocol (Alahmad protocol) or similar protocol that assures appropriate application of APRV including extreme $T_{\text{High}}:T_{\text{Low}}$ ratio and appropriate recruitment pressures may be needed to prove the findings of this study and other clinically relevant outcomes such as mortality.

1.38 Conclusion

In this study, APRV without spontaneous breathing was associated with significantly better oxygenation and haemodynamic status than observed during conventional modes in patients with moderate and severe ARDS. Prospective RCTs may be needed to confirm the results of this study and to investigate clinically relevant outcomes such as mortality and duration of mechanical ventilation.

Chapter Six:

General Discussion and Conclusion

ALI and its more severe form, ARDS, are associated with several negative consequences such as high mortality rate, morbidity, and costs in ICUs. Although the implementation of the LOVT strategy (the gold standard intervention) in accordance with the ARDSnet recommendation was associated with a reduction in the mortality rate of almost 9%, the overall mortality rate remained high, i.e. 31% (33). In contrast, a systematic review of 89 studies (36 RCTs and 53 observational studies) reported that the overall mortality rate for ARDS was 44.3% (34). The authors concluded that the mortality rate did not decrease from when the first consensus definition was published in 1994 until 2006, meaning that it remained at a high level. For that reason, they emphasised the need for effective therapeutic interventions for such a highly-lethal syndrome (34). Moreover, it has been reported that such gold standard may lead to several negative consequences such as repetitive shear forces, low volume lung injury, de-recruitment (18, 25), increased use of sedation, and more dys-synchrony (26, 27). Patients enrolled in our study at KFMC had moderate-to-severe ARDS (according to Berlin definition) and were treated with LOVT during CV, i.e. before being switched to APRV. Although each chapter of this thesis has its own discussion section where every research question was independently answered and compared with published knowledge, this general discussion tends to collectively answer the questions posed in the introduction. Answers will discuss the findings of our studies in relation to the goals of MV set by the AECC on ARDS, Part 2 (23). These goals generally emphasise recruiting de-recruited alveolar units, limiting lung damage (by

preventing over-distention of lung units), limiting cyclical collapse (by maintaining an appropriate level of P_{Mean}), and maximising oxygen delivery. However, it might not be possible to achieve all of these goals simultaneously with one modality; vis-a-vis their statement: "It may be naive to assume that any single therapy will be a 'magic' bullet to treat all aspects of ARDS" (23). Although HFOV might, hypothetically, achieve these goals, when compared with LOVT, HFOV was associated with a significantly higher mortality rate, more use of sedation, increased use of neuromuscular blockers, and more vasoactive agents (24). Therefore, finding appropriate interventions that outperform the current gold-standard to avert, or at least limit, the progression of such lethal syndromes is extremely essential to reduce their negative consequences. Some recent studies and reviews have reported that since ARDS is a progressive disease that is associated with high mortality rate, the key to treatment lies on preventing it from ever occurring (i.e. while it remains sub-clinical). Therefore, they concluded that early protective institution of APRV appears to offer substantial benefit in this regard and might be the prophylactic modality of choice for preventing ARDS (75) (135).

As discussed in Chapter One, although studies on the APRV mode were plagued with both clinical and methodological heterogeneity, in general, they showed superiority of APRV over CV in achieving these goals. Likewise, our studies at KFMC showed that APRV outperformed CV in achieving most of the outlined goals. In this discussion, each goal as stated by the AECC on ARDS, Part 2 will be discussed separately. The first goal states:

“ensuring appropriate O₂ delivery along with sufficient CO₂ removal to maintain homeostasis”. Our studies (Chapters Three and Five) showed significant improvement in both oxygenation and ventilation (CO₂ removal) after switching the mode from CV to APRV; this was achieved in a relatively short time. As discussed earlier in this thesis, many studies have shown similar improvement in oxygenation during APRV compared to other modes. Although it is credible that the lower the M_v the higher the CO₂, our study showed that the CO₂ during APRV was significantly lower than that of CV at significantly lower M_v. Although this is considered to be an unusual finding, it is in agreement with the largest RCT on APRV which also showed significantly lower CO₂ at significantly lower M_v (60). However, they did not find significant difference in oxygenation status which might be due the type of patients enrolled in that study who had almost normal PaO₂/FiO₂ (as discussed earlier in chapter One) (60) In contrast, our patients had significantly lower PaO₂/FiO₂ during CV which indicates moderate-to-severe ARDS according to Berlin definition (94).

The second goal states: “minimise O₂ toxicity”, our study at KFMC showed a consistent, yet significant reduction in FiO₂ that was associated with a significant improvement in PaO₂/FiO₂ shortly after switching the mode from CV to APRV. This may represent a protective benefit of APRV in reducing the risk of many debilitating conditions associated with high FiO₂. It has been reported that high FiO₂ has been associated with several pulmonary consequences such as absorptive atelectasis that can eventually lead to an increased intrapulmonary right-to-left shunt fraction and diminished lung

volumes; accentuation of hypercapnia; and damage to airways and pulmonary parenchyma (9, 10, 16-18, 23, 24). The term "oxygen toxicity" is usually reserved for the last of these consequences, namely tracheobronchial and pulmonary parenchymal damage (25-28). Therefore, reducing such detrimental consequences might be of clinical value that might be in favour of APRV. As discussed in Chapters One and Five, many studies are in agreement with our findings concerning better oxygenation which ultimately allowed reduction in FiO_2 during APRV compared with CV. The third goal states: "Recruit alveoli", this might be the most noteworthy advantage of APRV over CV. Although APRV may be viewed as a virtually continuous recruitment manoeuvre (98), it has been described as a lung-protective mode (12, 72, 98). Compared to PSV, APRV with spontaneous breathing has shown significant improvement in lung aeration by decreasing atelectasis in a short time, which contributes to improved pulmonary oxygenation in patients with ALI/ARDS (105). It has been suggested that if an increase in PEEP produces a large improvement in PaO_2 , a reduction in PaCO_2 , and better compliance, it suggests significant recruitment (128). Our patients showed significant improvement in PaO_2 and PaCO_2 after being transitioned to APRV; yet, compliance was not measured in our studies. However, several studies reported that when compared to CV, APRV was associated with better RSC compliance and dynamic compliance (54) (63); also, static compliance was found to be significantly higher after transition from CV to APRV (75). There was a notable improvement in our patients' chest radiographs as perceived by the

treating team; yet, as it was not quantified (i.e. objectively), it was not included in the outcome measures due to the subjectivity of the interpretation.

The fourth goal indicates: "Prevent atelectasis", this might be another momentous benefit APRV may possess over other recruitment manoeuvres. A systematic review of 636 patients indicated that, despite improved oxygenation caused by recruitment manoeuvres during CV modes, there was a rapid decline in oxygenation shortly after the manoeuvres, some of which occurred within 15–20 minutes (25). Hence, an intervention that provides a better solution for this goal is needed, for instance, by providing a higher P_{Mean} without causing the adverse effects associated with HFOV, LOVT, and recruitment manoeuvres. APRV may be viewed as a virtually continuous recruitment manoeuvre (18); however, none of the above adverse events have been reported during the use of APRV. From the significant, yet consistent improvement in gas exchange, better V_T , and improved chest radiographs, despite lower inspiratory pressures (continued to be weaned constantly since the time of transition to APRV) seen in our patients, one may infer that this goal (prevent atelectasis) might have been achieved. The significant improvement in oxygenation seen in our patients was not observed only between CV and APRV, but even between APRV^{1st} and APRV^{2nd} wherein P/F was 17.2 (IQR 12.8–27.0) kPa vs. 21.9 (IQR 14.2–33.7) kPa, respectively ($p < 0.001$) which indicates a continuous improvement over time. As stated previously in this thesis that several studies have reported positive effects of APRV concerning this goal.

The fifth goal indicates: “minimise high airway pressures”, several studies have reported that the use of APRV resulted in significantly lower peak pressures than CV (50-52, 58, 59). However, these studies did not find any differences in gas exchange except the study of Sydow which reported significant improvement in $AaDO_2/FiO_2$ and QS/QT (32). In contrast, our study showed higher P_{aw} during APRV compared to CV. Nevertheless, the median (IQR) P_{aw} during APRV in our study was 32 (29–35) cmH₂O which is similar to that of the LOVT group in the ARDSnet study. The mean (SD) P_{aw} values for the LOVT group were between 32 ± 8 to 33 ± 9 cmH₂O throughout their study (97).

The sixth goal states: “Use sedation and paralysis judiciously”, a recent RCT included 52 patients with moderate-to-severe ARDS compared APRV to LOVT reported that APRV group had more days without sedatives (22 vs. 17; $p = .036$) (62). Also, few small studies have compared the use of sedation and analgesia between APRV and CV. A small pilot study of 12 ARDS patients reported a significant reduction in the use sedatives and paralyzing agents after switching the mode from IRV(PCV) to APRV (54, 55). Another prospective observational study of three teaching hospitals reported significantly lower doses of analgesics and sedatives during APRV compared to CV. However, beside the fact that the data of this study was only analysed on day 1 after ALI diagnosis, the sample size for patients receiving APRV was very small compared to CV, 17 vs. 165 patients, respectively (29). Conversely, a prospective randomised study of 33 ALI patients being ventilated in the prone position showed no significant

difference in the dose of narcotic and sedative agents used between APRV and SIMV-PC/SIMV (76, 79); however, the limitations of this particular study were discussed extensively in Chapter One. In our studies, we did not include the use of sedative and paralysing agents amongst the outcome measures. However, a retrospective study compared this outcome using our protocol and found statistically significant improvement in the use of sedation in favour of APRV. It was found that the use of APRV in septic patients restores haemodynamic stability earlier than CV. There was a significant improvement in ICU survival in favour of APRV; they found that the early institution of APRV was associated with lower ICU mortality ($p = 0.022$)(67).

Based on the discussion of the abovementioned goals, APRV seems to have provided a promising alternative to achieve these goals and in the overall management of ARDS (e.g. haemodynamics). However, one could argue that with such positive effects, what may have limited the use of APRV in a larger scale. The answer to this question may shed a light on the reasons behind the limited number of RCTs in the literature. First and foremost, might be the lack of consensus on a standard protocol with clear rationale for the settings for APRV use (71) which has led to inconsistent applications among hospitals. This precluded defining an optimal method, (74) and reports do not always clarify the APRV protocol or settings that were used. It has been reported that adjustments responding to patient characteristics during APRV should follow a defined protocol (75). Failure to standardise and document APRV protocols has contributed to the lack of robust

evidence regarding its potential benefit and role. Daoud provides a discrete summary of both animal and human data associated with several potential benefits of APRV, noting inconsistencies when applicable, and that increased adoption of APRV will necessitate overcoming several obstacles, including lack of standardisation and inadequate research evidence (136).

Secondly, as discussed in Chapter One that the frequent consideration of APRV and other modes (e.g. BIPAP) as the same modes, with little attention paid to the ventilation settings that characterise the modes, is a common source of confusion that can interfere with making an accurate assessment of APRV (8, 35, 36). Although APRV has been the focus of numerous reviews (19, 136, 137) and is addressed in many general MV review articles (12, 36, 138-142), the inability to assess the true risks and benefits of APRV is noted. This might be due to the incomplete, inconsistent mode definition and terminology, and accompanying uncertainties; however, the “fuzzy” version of APRV continues to be propagated. For example, the U.S. Centres for Disease Control and Prevention (CDC) includes a ventilator associated event (VAE) surveillance program as part of the National Healthcare Safety Network (143). BiLevel, BiVent, PiPhasic, PCV+, and DuoPAP are included under the umbrella of APRV, in keeping with the naming among mechanical ventilators. The CDC explains that participants are required to record the number of patients on APRV in their ICUs for each day of VAE surveillance to determine frequency of APRV use, allowing determination of the incidence of VAE on APRV. The categorisation of these different modes as APRV precludes obtaining accurate data on the incidence

of VAEs on APRV. Consequently, this may have limited its use, thereby, limited conducting homogeneous studies that can be compared to draw decisive and meaningful conclusions.

Unlike CV, APRV may require more knowledge and skills (like many new interventions) to manage and maintain when hypoxaemia and/or hypercapnia occur. For example, in conventional modes, increasing either FiO_2 or PEEP is commonly used to correct hypoxaemia. In contrast, clinicians have more options to improve oxygenation in the APRV mode, including increasing FiO_2 , P_{High} , P_{Low} , or T_{High} or decreasing T_{Low} . Published studies and their guidelines/protocols have not clearly and sufficiently defined how to progress through or choose one of these options (e.g. which parameter shall clinicians start with and when?). Beside the inconsistent applications, significant aspects in the management of patients during APRV seem to have been overlooked in the existent guidelines or clinical protocols. With such significant confusion, uncertainties, and concerns over the lack of evidence for a benefit, one can inquire about the prevalence of APRV use in real world.

1.39 Prevalence of APRV Use in Real World Patients

One review article was followed by a panel discussion where a contributor noted that APRV was “all but outlawed” at his hospital, which is affiliated with a major U.S. university (86). Despite this observation, several reports indicate that APRV, or the nebulous BiPAP/APRV, is in widespread use. In the prospective PROVENT study of ICU admissions during a specified week

in 2014 in 16 countries, BiPAP/APRV was the third most common ventilation mode, reported for 22% of 935 patients (8).

In the Gonzalez study, 11.3% of 4,968 patients in 23 countries, comprising $\leq 2\%$ ARDS patients, were ventilated for at least 1-day with BiPAP/APRV (35). Although the conventionally ventilated patients were distributed among Europe (30%), Latin America (40%), and USA/Canada (27%), most (98%) of the BiPAP/APRV cohort was from Europe, of which 84% were from Germany.

A survey that received responses from 70 ICUs in Ontario Canada reported that 70% had protocols for MV in place (87). However, the initial mode was not specified in 80% of protocols. APRV was the most commonly used option for treating refractory hypoxaemia, reported by 61% of respondents. An exploratory survey that received responses from 46 burn centres in North America revealed approximately 15% used APRV for cases without inhalation injury, which increased to approximately 25% when inhalation injury was present (88). For mild ARDS, 11% changed MV to APRV, which increased to 28% for severe ARDS.

A survey of ECMO use in managing severe ARDS among academic medical centres in the United States received 381 responses (89). APRV was reported as being available and used by 64% of respondents. The survey acquired the rank preference order for rescue treatment when CV failed, and APRV was the first choice over inhaled NO, PP, HFOV, and ECMO.

Finally, an international survey to describe ventilation practices in centres registered with the Extracorporeal Life Support Organisation received 141

responses (90). For adult patients, 11% (4/38) reported using APRV as the primary initial ventilator mode during ECMO, and APRV was the protocol-defined mode for that use in 1 of 38 submitted MV protocols.

These reports indicate that APRV is in use globally, despite continuing concerns over the lack of evidence for a benefit. With this notable use of a controversial MV, centres using APRV should be encouraged to adopt discrete protocols for its use and establish registries that can provide data to help clarify the role of APRV.

The Habashi protocol continues to be the most detailed guide to APRV initiation and management, providing details on settings for patients newly intubated and for those transitioning from CV or HFOV, as well as responses to specific circumstances (18). However, Habashi protocol has some concerns that will be discussed later in this chapter.

APRV was introduced at KFMC in 2009; however, it was used on a very limited scale as a rescue modality only when CV failed. At the beginning, we used to follow the published less-than-perfect guidelines including the Habashi guidelines, yet, we had several queries and concerns regarding safety, ease of use, thoroughness, and comprehensiveness. After that, we developed our own guidelines aiming for improving these concerns. For example, it is common in published guidelines to set the P_{High} at specific level, as an initial setting, but its maximum level throughout the course of the APRV might not be addressed, although it was recommended in some guidelines that P_{High} be increased by 2-5 cmH₂O, for example, to correct hypoxaemia. Nonetheless, the maximum level of V_T displaced by such

frequent increases in P_{High} seems to have been overlooked. Therefore, it is quite intuitive to question what the resulting V_T after such frequent and repetitive increase in P_{High} will be and what the maximum P_{plat} should be since it is at least equal to P_{High} when using APRV. These questions are applicable in the absence of spontaneous breathing; however, V_T might be even higher in the presence of spontaneous breathing during P_{High} . Similarly, when changing other parameters such as T_{Low} which may significantly alter V_T .

In our protocol at KFMC (Al-ahmad protocol), we clearly defined the acceptable range of V_T , i.e. the minimum and maximum levels. We have implemented a new concept called “the third eye”; this concept helps clinicians to boost their critical thinking process and to be fully aware of any possible consequences when changing any parameter. For instance, when changing the T_{Low} , one eye should be looking at the $PEEP_M$, the second is looking at the V_T , and the third is looking at the ICU monitor which display vital signs mainly MAP, HR, and SPO_2 . Ensuring acceptable V_T while changing any parameter that may affect V_T such as (P_{High} , P_{Low} , and, T_{Low}) is rigorously emphasised on in our protocol. This may represent one of the central safety features of the Al-ahmad protocol over other many published protocols.

Moreover, despite the fact that the application of APRV entails much more knowledge and clinical skills than the descriptions in the literature indicate (73), we claim that our protocol may provide a clear and appropriate guide to initiate, manage, maintain, transport and wean patients on ventilated

with APRV through detailed guidelines (as shown in **Error! Reference source not found.**Figure 26Figure 27 in the appendix). Our protocol has been made in an objective manner through which human errors are minimised and patient's safety is maximised by clear indications of minimum and maximum levels of other parameters (not only V_T). With proper education and adherence to Al-ahmad protocol, parameters can be set and managed relatively easy and be monitored continuously, e.g. instead of using PEFR (e.g. 50-75%) to set T_{Low} , we use $PEEP_M$. This may provide a more precise measure that can be quantified objectively (a direct number), monitored promptly (a quick glance at the ventilator screen) and continuously (always appears on screen). It also provides guides on when and how to transport patients ventilated with APRV should they require emergency transportation (e.g. emergency CT) and how to encounter any changes in patient's condition. Detailed description of our protocol can be found in the appendix.

Studies that revealed positive outcomes, such as oxygenation, ventilation, recruitment, and haemodynamic status, seemed to have some commonalities (some examples are indicated in Table 8 in chapter one), i.e. 1) early institution with APRV, 2) using a long T_{High} of almost 4 s that was either maintained or increased throughout the course of APRV, and 3) using a short T_{Low} of (0.2-0.8 s) to keep the PEFR in the range of 50-75%; however, if T_{Low} was allowed to reach 1.0 s for any reason, the potential loss of intrinsic PEEP must be compensated for by maintaining an appropriate level of PEEP (through P_{Low}) to prevent de-recruitment. Misty

and colleagues reported that a T_{Low} of 0.4 - 0.7 s was required to achieve PEFR of 50% in a low compliance lung model (82). Al-ahmad protocol fulfils all these common features at once while providing easy-to-set and continuously monitored, objective measures. In our studies included in this thesis, the mean (SD) T_{High} and T_{Low} during APRV was 4.42 (1.0) sec (4.1 – 4.7 sec; 95% CI) and 0.5 (0.1) sec (0.47 – 0.54 sec; 95% CI), respectively. In a step to achieve better evidence concerning APRV, this thesis encourages continued publication of observational as well as experimental clinical trial data, and discusses the feasibility of analysis strategies that may expand the information available from small patient samples.

1.40 Analysis Strategies to Enhance Contribution of Small and Observational Studies

Data from registries and other real world databases can provide valuable information if appropriate design, data collection, and analytical procedures are followed. Sophisticated methodologies including propensity score analysis (PSA) and individual patient data network meta-analyses may be appropriate if adequate high quality data are available.

1.41 Propensity Score Analysis

Properly constructed PSA has the potential to reduce bias by sampling from a large reservoir of potential control comparators (144, 145). The analysis is performed using controls that have covariates similar to the distribution in the investigational treatment sample.

Gonzalez and colleagues performed an important study that should motivate practitioners who use APRV to keep adequate records describing ventilator models and settings, and patient characteristics, responses, and outcomes throughout the MV experience (35). The group performed a PSA on data from a cohort of 234 patients ventilated with APRV/BIPAP in routine clinical practice compared with 234 propensity score matched patients who received ACV in the same settings. Less than 2% of patients in the cohort had ARDS. Improved outcomes were not observed for patients on APRV/BIPAP in the multivariate PSA. BIPAP was described according to Rose et al (42) and Putensen and colleagues (146) as being similar to APRV by allowing spontaneous breathing, but dissimilar by not having restrictions on the time of P_{Low} . This allowed a P_{Low} that was not always shorter than P_{High} . Despite this difference, the 2 distinct modes were combined as a single group, precluding an assessment of the APRV mode used according to its basic principles.

In unmatched comparisons, mortality was significantly less in the APRV/BIPAP group compared with the CV group (35). However, mortality was similar in matched-case analysis, exemplifying the contribution of propensity score matching to the comparison.

1.42 Individual Patient Data Meta-analysis

Meta-analyses have a long history of providing increased power when analysing small numbers of events in studies with limited sample sizes. An individual patient meta-analysis (IPMA) is a relatively new strategy that has

emerged in recent years, which may provide increased power, reduced bias, and allow subgroup and interaction analyses of data that are not achieved with traditional meta-analyses (147, 148). An IPMA combines patient data from multiple studies into a single dataset for analysis, which can be subjected to a range of univariate and multivariate analyses.

1.43 Network Meta-analysis

A network meta-analysis (NMA) indirectly compares 2 or more interventions by combining evidence from multiple studies. For example, an NMA constructs a network that allows estimating the effect size for A versus C based on studies that compare A with B and B with C. Individual patient data can also be used in network meta-analyses. Although this strategy is primarily used for RCT data, non-randomised studies can also be included; in fact, they may be necessary to allow completion of the network (149). Propensity scores can be incorporated into existing covariate-adjusted NMA models; however, it is reported to be a difficult process.

A systematic review and network meta-analysis compared lung ventilation strategies for ARDS based on 36 RCTs of 26 ventilation strategies, including 3 small APRV trials that provided the lowest number of patients (n=10) for the Bayesian network meta-analysis (150). Although the confidence intervals of all APRV mortality comparisons included 1, this innovative study set a precedent for using this analysis strategy to compare ventilation modes. Its feasibility was further exemplified in a network meta-analysis of

6 ventilation strategies in 17 RCTs of ICU patients without ALI or ARDS (151).

1.44 Thesis contribution to the existing knowledge

This thesis may provide some substantial aspects concerning the use of APRV; however, each chapter may present one aspect of contribution.

1.44.1 Chapter One

This chapter provided an overview of the spectrum of ventilator settings that may be designated as APRV, summarised the research and clinical use status of APRV, exemplified the need to clarify the characteristics that comprise the mode, and to assure reports of APRV use, from case reports through RCTs, include adequate data for a proper assessment. More importantly, it emphasised the real demand of developing clear clinical practice guidelines for optimum use to standardise the application of APRV. This chapter should be considered as an “wake-up call” to all APRV users around the globe to join forces to have a consensus on a standard application. This might be the first step to overcome heterogeneity which may lead to better quality researches.

1.44.2 Chapter Two

The results of this chapter may provide a golden opportunity for clinicians in the ICUs. In that, proper integration of a genuinely installed APRV mode into such sophisticated ICPMs may be a potentially powerful aid in

understanding the best application of APRV and the impact of different configurations on cardiopulmonary systems.

1.44.3 Chapter Three

This chapter provided a novel result about the potential capability of APRV to eliminate CO₂ more efficiently than CV at significantly lower values of M_v. The novelty here might be associated with the efficiency of CO₂ elimination during APRV despite the absence of spontaneous breathing, with such extreme T_{High}: T_{Low} ratio; the mean T_{High} in the entire cohort occupied 87% of the total respiratory cycle.

1.44.4 Chapter Four

This chapter provided an insight on specific ventilatory settings and considerations that clinicians should pay attention to, when managing patients on APRV. CO₂ elimination can be optimised in inhomogeneous group (e.g. COPD and ARDS) in the absence of spontaneous breathing.

1.44.5 Chapter Five

The results of this chapter showed that despite the absence of spontaneous breathing, APRV was associated with significantly better oxygenation and haemodynamic status than observed during CV modes using LOVT. The novelty here might be that this might be the only study that compared these outcomes in such patient group.

1.44.6 Chapter Six

This chapter presented an unpublished, comprehensive, multifaceted clinical practice protocol (Al-ahmad protocol) for the use of APRV. This may provide better alternative protocol to the current ones in terms of safety, ease of use, thoroughness, and comprehensiveness.

1.45 Potential areas for future research projects

Since APRV has shown superiority over CV modes in some aspects, irrespective to the fact that most studies have been plagued with major heterogeneity, future research should focus on the common physiological aspects that have been associated with significant outcomes such as mortality. Two prospective studies (152, 153) included 56 and 41 patients with ARDS, respectively; both studies used lung-protective ventilation strategy. The patients who had minimal improvement in their $\text{PaO}_2/\text{FiO}_2$ ratio after the first 30 minutes (153) or during the first 24 hours (152) had a significantly higher mortality rate (52.9% vs. 12.5%; $p = 0.01$) (153) and (68% vs. 22.6%; $p = 0.0016$) (152) than patients who had rapid improvement in $\text{PaO}_2/\text{FiO}_2$ ratio and disease severity within the same periods of time.

Many studies have reported rapid, yet significant, improvement in oxygenation due to lung recruitment in APRV groups compared to CV modes. Sydow and colleagues (52) reported a significant improvement in alveolar-arterial O_2 tension difference/ FiO_2 ($\text{AaDO}_2/\text{FI0}_2$) ($p < 0.001$) as well as QS/QT ($p < 0.005$) within a short period (8–16 hr) after onset. However, for the ARDSnet trial (33), one could argue that despite the

significantly higher $\text{PaO}_2/\text{FiO}_2$ ratio on days 1 and 3 in the control group, PEEP and FiO_2 levels were significantly higher on day 7; not only that, but more importantly, the mortality rate was higher in the control group. Nevertheless, this argument might not be applicable when compared with APRV, simply because of the significant, yet, consistent improvement in $\text{PaO}_2/\text{FiO}_2$ ratio that was concomitant with a continuous reduction in FiO_2 and airway pressures. As discussed earlier in this thesis, many studies (58, 63) including our studies at KFMC, have shown that when compared to CV, APRV showed significant, yet, consistent improvement in $\text{PaO}_2/\text{FiO}_2$ throughout the course of APRV. Moreover, unlike traditional ventilation treatment group in the ARDSnet study, which might have exacerbated lung injuries, APRV has been described as a lung-protective mode (12, 18, 72). A recent study of a clinically applicable lung injury model indicated that, when compared to CV, early institution of APRV 1) prevented the development of ARDS by $\text{PaO}_2/\text{FiO}_2$ ratio ($p < 0.001$), 2) prevented injuries to lung tissue, as shown by the quantitative histological scoring ($p < 0.001$), 3) lowered the water content of lungs ($p < 0.001$), and 4) lowered total protein and interleukin 6 ($p < 0.005$) while preserving surfactant proteins A and B. The study also indicated that ARDS, like gastric stress ulceration and venous thromboembolism, can be preventable (135).

In addition, several studies have reported significant association between V_D/V_T and important outcomes, such as mortality and duration of MV. In a prospective cohort study of 42 patients, Cepkova and associates reported that in early ALI, an elevated V_D/V_T in non-survivors (0.61 ± 0.09 vs.

0.53±0.10, $p = 0.02$) was associated with higher mortality. They also found a significant association with V_D/V_T and the duration of MV, patients with elevated V_D/V_T (0.61 ± 0.08) had <7 ventilator-free days compared with > 7 ventilator-free days for those with lower V_D/V_T (0.52±0.11; $p = 0.008$) (154). Furthermore, in a prospective study of 80 patients with early ARDS and 49 patients with an intermediate phase of ARDS reported that patients who died had a significantly higher V_D/V_T than those who survived in both groups (0.64±0.09 vs. 0.53±0.11; $p < 0.001$, and 0.62±0.09 vs. 0.50±0.10; $p = .001$, respectively) (155).

Similarly, in 126 ALI patients enrolled into a prospective, multi-centre study, Richard H and colleagues reported that a V_D/V_T of ≥ 0.60 in early ARDS is associated with increased mortality (156). As discussed above, a significant reduction in the V_D/V_T has been reported in APRV studies that included this measurement in their results. Therefore, the rapid improvement in oxygenation during APRV (which is considered as a lung protective strategy) as well as the reduced V_D/V_T ; and their association with mortality can be potential areas for future research.

1.46 Conclusion

Despite advancements that were made possible by the introduction of the ARDSnet lung-protective MV protocol, patient management remains challenging and the need for personalising MV has been emphasised (157, 158). Regardless of the ventilation mode used, acquiring the capability to

individualise patient management requires following detailed MV protocols, which define proper clinical respiratory data monitoring.

APRV appears to be a promising, unconventional mode of ventilation for the treatment of various respiratory diseases including ALI/ARDS. When compared with modes and the HFOV, APRV generally has been associated with better success in achieving the goals of ventilator management (minimise O₂ toxicity, recruit alveoli, prevent atelectasis, minimise high airway pressures, and use sedation and paralysis judiciously) that have been indicated by the American-European Consensus Conference on ARDS, Part 2. Several studies have shown that APRV may be superior to CV modes in many respects, such as more days off MV, fewer ICU days, better lung function, haemodynamics, oxygenation, recruitment of de-recruited lung units, cardiac performance, renal perfusion, reduced peak airway pressure, and neuromuscular blockade, and the use of sedation; yet, only two retrospective studies have reported significantly lower mortality.

However, despite increasing global use and reported advantages of APRV over other modes, decisive conclusions cannot be drawn due to several concerns. First, the major confusion between APRV and other, similar modes, such as BIPAP. Secondly, clinical and methodological heterogeneity among published studies of APRV are understandably extensive, which contributes to outcome variability. Thirdly, the absence of consensus on a standard protocol with clear rationale for the settings. For these reasons, the 30-year history of APRV has not produced

conclusive data supporting benefits of its use. In keeping with the requisites of personalised medicine, clear descriptions of APRV treatment protocols are necessary, both in clinical practice and research studies. This thesis provided a new, unpublished, clinical practice protocol (Al-ahmad protocol) that has been used in KFMC. We found that compared to CV modes, APRV (following Al-ahmad protocol) was associated with significantly lower PaCO₂ at significantly lower levels of M_v, better oxygenation, and haemodynamic status for patients with moderate and severe ARDS.

Clinicians in centres that use APRV should be encouraged to differentiate APRV from other modes that were erroneously believed to be similar (e.g. BiPAP) and to establish databases documenting relevant treatment parameters (e.g. type of mechanical ventilator, clinical protocol, and configurations) and patient characteristics and outcomes. Performing observational studies and reporting unique cases and case series should be encouraged, following standard data management practices. Analysis strategies that expand the dataset should be pursued. RCTs should continue, despite the constraints. Adhering to documentation and data standards should increase the availability of real world data from high-quality observational studies. The output of these combined efforts may lead to a clear definition of the mode and an accurate assessment of its role in mechanically ventilated patients, especially those with or at risk of ARDS.

Finally, APRV may offer potential clinical advantages for ventilator management of ALI/ARDS. Whether APRV prevents the development of ARDS or reduces mortality rate compared with CV modes using LOVT will require future RCTs.

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Appendix: Al-ahmad protocol

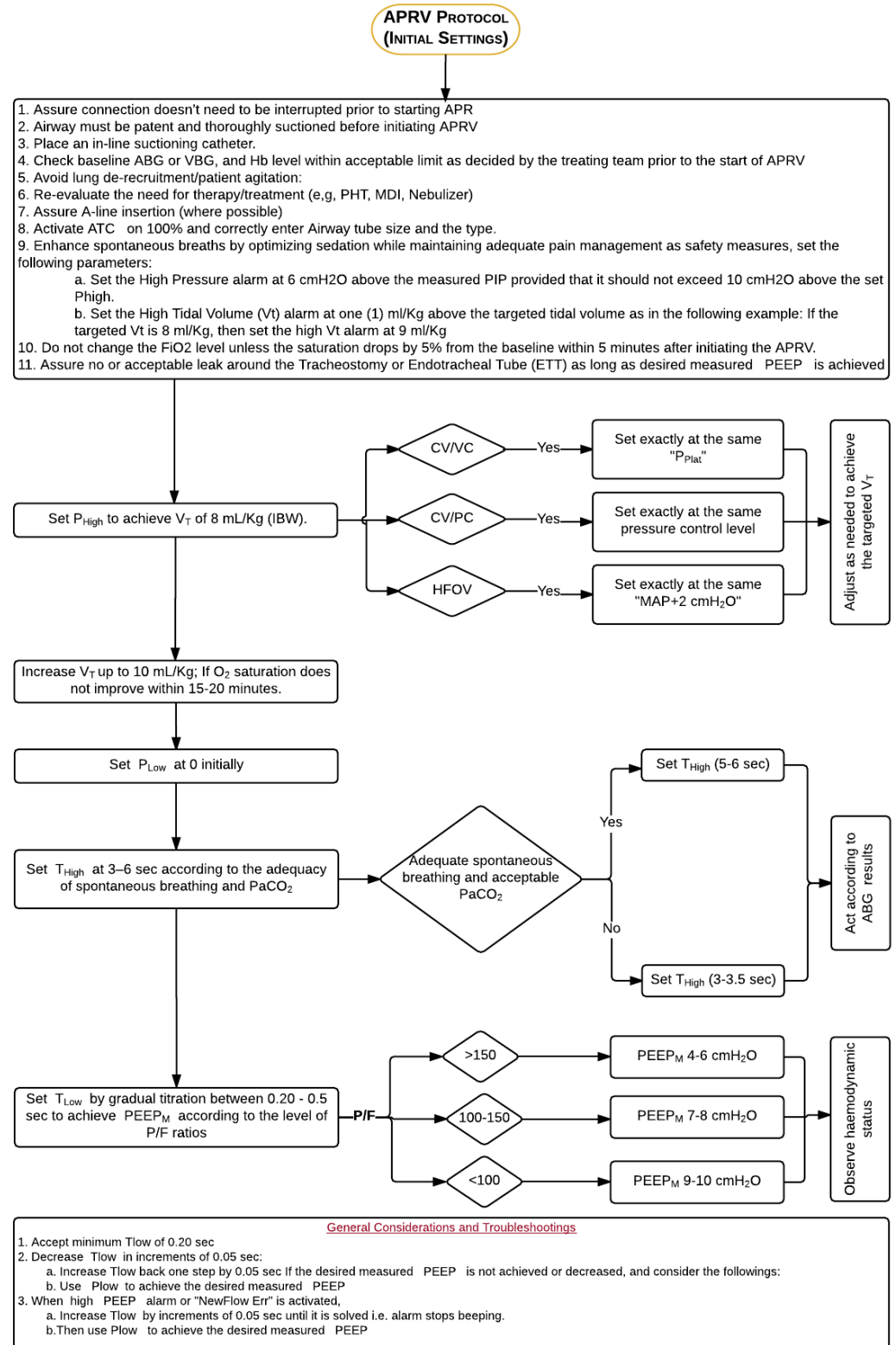


Figure 25 initial settings of APRV

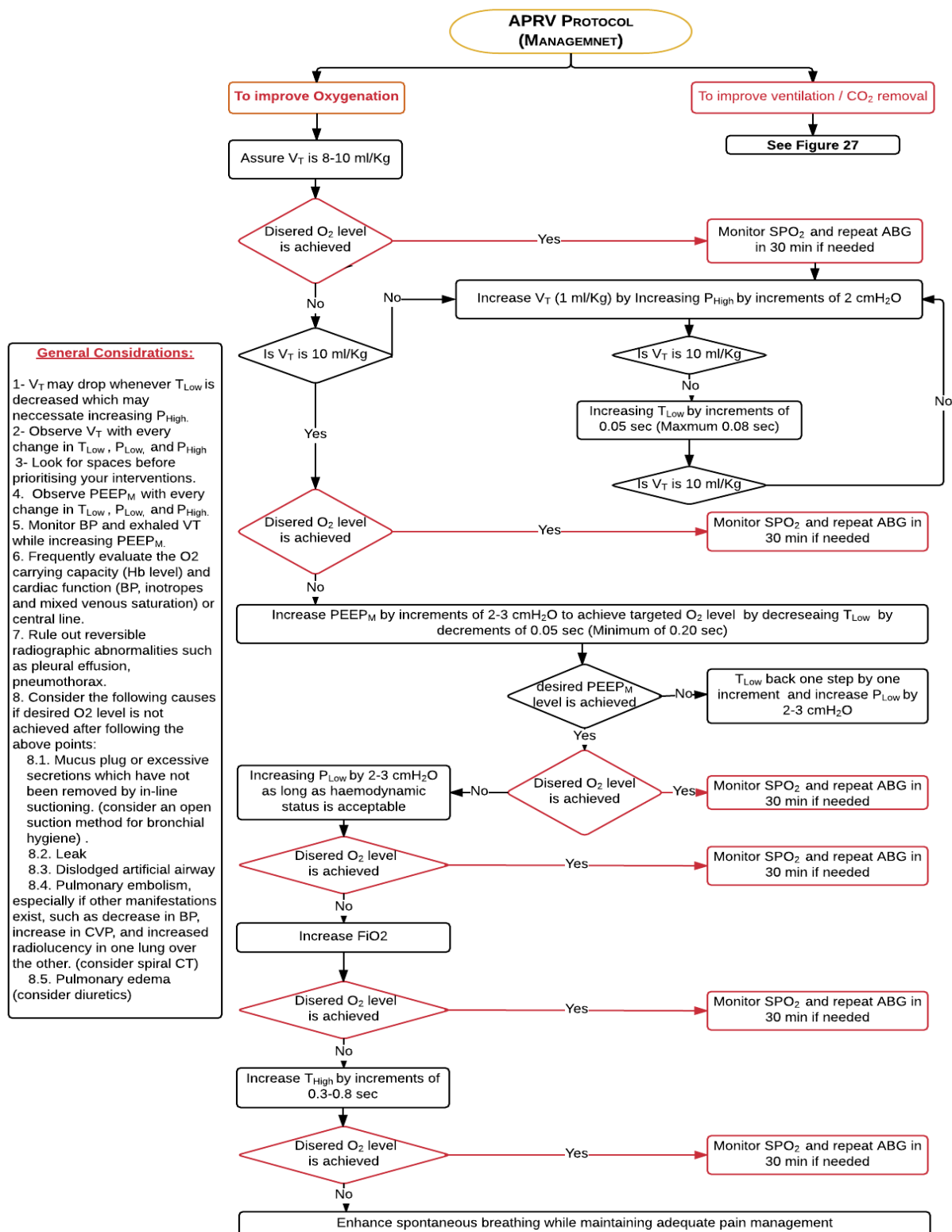


Figure 26 managing Oxygenation on APRV mode

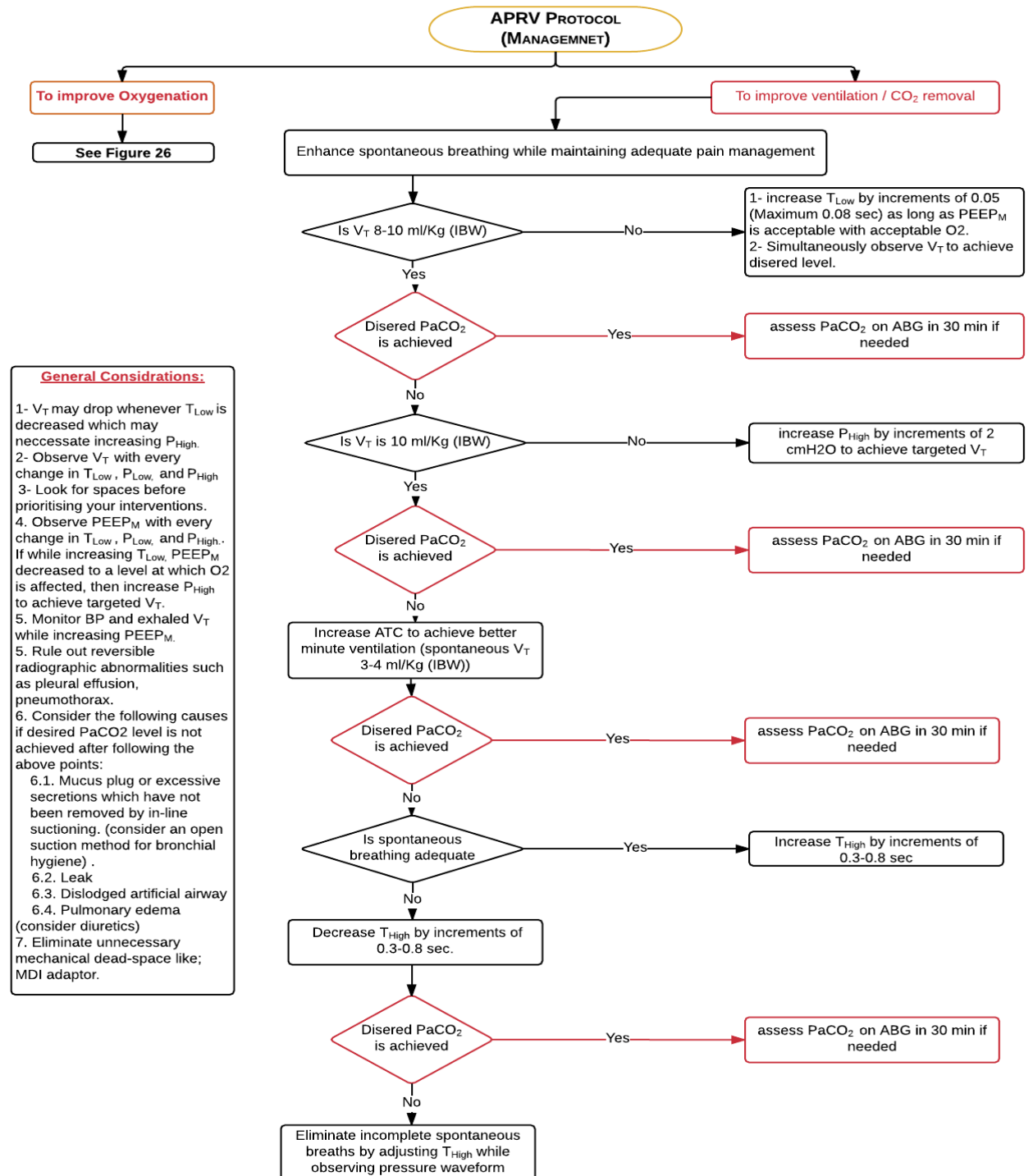


Figure 27 managing ventilation (CO₂) on APRV mode

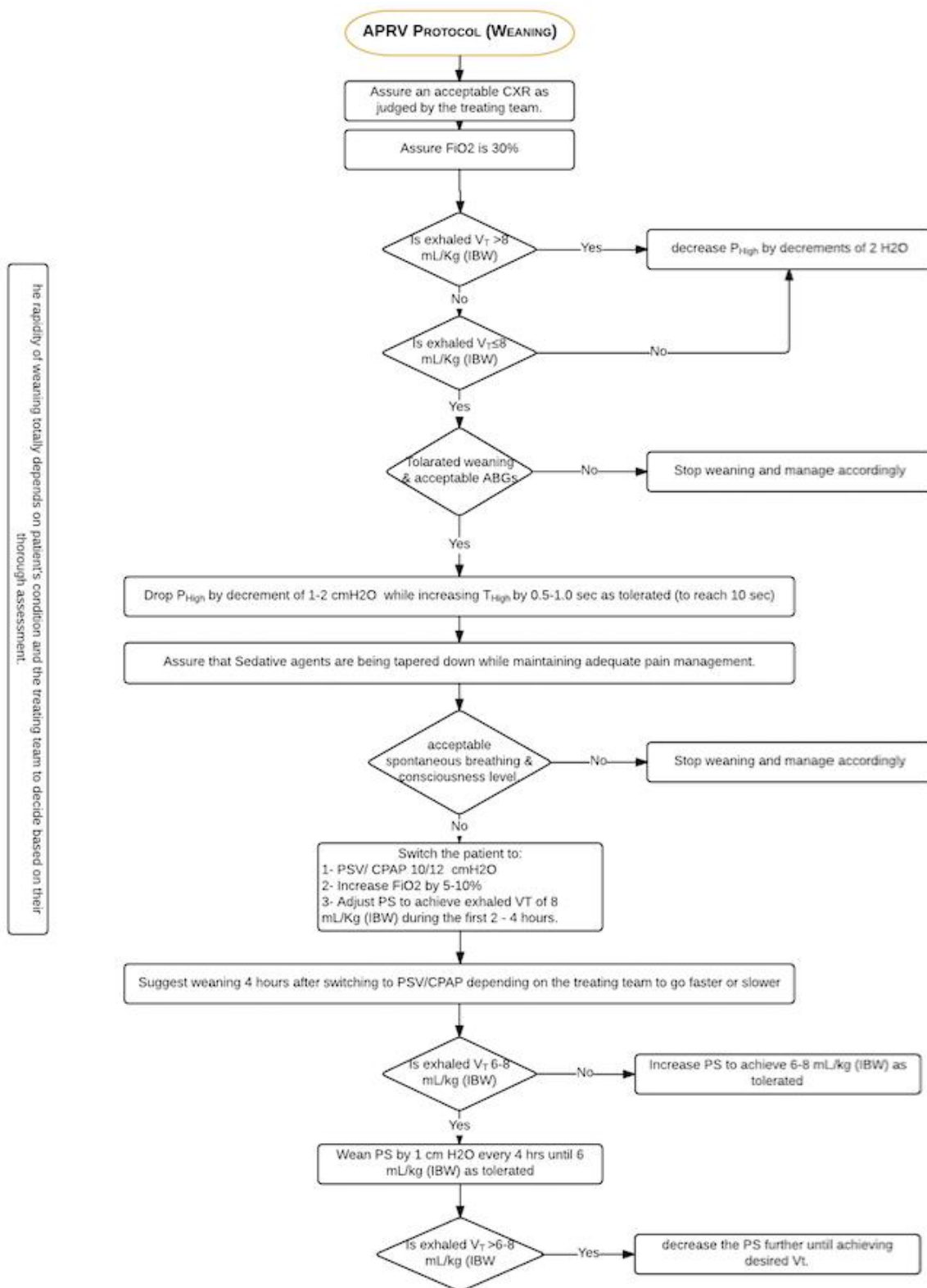


Figure 28 weaning