Common complications of mechanical ventilation and multimodal prevention strategies

Markle, Andrew Gordon

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

Andrew Markle

Common Complications of Mechanical Ventilation and Multimodal Prevention Strategies

GRADUATE THESIS

Zagreb, 2014

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

Andrew Markle

Common Complications of Mechanical Ventilation and Multimodal Prevention Strategies

GRADUATE THESIS

Zagreb, 2014

This graduation paper was made at the department of Anaesthesia and Intensive Care at Sveti Duh hospital under supervision of Prof. dr. sc. Dinko Tonković and it was submitted for evaluation in the academic year 2014.

Graduation paper was made at the department of Anaesthesia and Intensive Care, University of Zagreb School of Medicine.

Mentor: Prof. dr. sc. Dinko Tonković

Table of Contents

INTRODUCTION 2

ABSTRACT 2
KEY WORDS 2
LIST OF ABBREVIATIONS 3

RESPIRATORY PHYSIOLOGY 4

NORMAL RESPIRATORY FUNCTION 4
NORMAL RESPIRATORY IMMUNE RESPONSE 8

POSITIVE PRESSURE VENTILATION 11

HISTORY AND MECHANISMS OF POSITIVE PRESSURE VENTILATION 11
ADVANTAGE AND REASONS FOR POSITIVE PRESSURE VENTILATION 13
CARDIOVASCULAR RESPONSES TO VENTILATION 14
COMMON COMPLICATIONS OF MECHANICAL VENTILATION 16
DIFFICULTY WEANING 16
VENTILATOR-ASSOCIATED PNEUMONIA 18
VENTILATOR-ASSOCIATED/INDUCED LUNG INJURY (VALI/VILI) 20
COMPLICATIONS AND EFFECTS OF GENERAL ANAESTHESIA 24

STRATEGIES FOR THE PREVENTION OF VENTILATOR-ASSOCIATED COMPLICATIONS 26

PERIOPERATIVE PREVENTION STRATEGIES 26
SMOKING CESSATION 27
ANALGESIA 29
POST-OPERATIVE RESPIRATORY FAILURE (PRF) 30
INSPIRATORY MUSCLE TRAINING 31
SEDATIVE REDUCTION AND SEDATIVE SELECTION 32
EARLY IMMUNOMODULARY NUTRITION 34
LUNG-PROTECTIVE STRATEGIES DURING GENERAL ANAESTHESIA AND MECHANICAL VENTILATION 36
LOW-VOLUME VENTILATION 36
POSITIVE END EXPIRATORY PRESSURE (PEEP) 39
RECRUITMENT MANOEUVRES 42
VENTILATOR-ASSOCIATED PNEUMONIA BUNDLES 44

CONCLUSION 46

BIBLIOGRAPHY 49

Introduction

Abstract

Mechanical ventilation has undergone tremendous change in its fifty years of mainstream usage. In that time it has made the treatment of previously fatal diseases possible. Importantly, research has shown that it also has the potential to cause or exacerbate disease. This paper seeks to explore some of the more common complications of mechanical ventilation, and methods in which they may be prevented or ameliorated.

Key Words

Mechanical ventilation, weaning, ventilator-associated pneumonia, ventilator - associated lung injury, positive end expiratory pressure, recruitment, post-operative respiratory failure.

List of Abbreviations

Abbreviation	Meaning
ALI	acute lung injury
APACHE	acute physiology and chronic health evaluation II
ARDS	acute respiratory distress syndrome
BAL	broncho-alveolar lavage
CDC	centres for disease prevention and control
$ETCO_2$	end-tidal carbon dioxide
FiO_2	fraction of inspired oxygen
ICU	intensive care unit
LA	left atrium
LV	left ventricle
PaO2	partial pressure of arterial oxygen
PBW	predicted body weight
PEEP	positive end expiratory pressure
POPC	post-operative pulmonary complications
PRF	post-operative respiratory failure
RA	right atrium
RASS	Richmond agitation and sedation scale
RV	right ventricle
TIVA	total intravenous anaesthesia
TNF	tumour necrosis factor
V:Q	ventilation to perfusion ratio
VALI	ventilator-associated lung injury
VAP	ventilator-associated pneumonia
VILI	ventilator-induced lung injury
Vt	tidal volume
WOB	work of breathing

Respiratory Physiology

Normal Respiratory Function

Breathing in humans is typically facilitated through two groups of muscles (1). The diaphragm lengthens the thorax during inspiration and shortens via elastic recoil during expiration. The diaphragm is usually the only respiratory muscle playing a significant role during normal, quiet breathing.

The second group of muscles are those that cause changes in thoracic dimensions. The major muscles of thoracic excursion are the external intercostals, the sternocleidomastoid, the anterior serati, and the scaleni (2). During heavy, exertional breathing, the ribs are pulled caudally, expanding the thorax some twenty per cent. Muscles that contract the thorax are the abdominus recti and the interior intercostals. These muscles are active during times of heavy breathing. Pathologies causing either an increase in abdominal pressure or dysfunction of abdominal musculature may interfere with breathing (3).

The tracheobronchial tree consists of 23 generations (trachea = 0, alveoli = 23), which are counted using the Weibel classification system (2, 3). The number of passages roughly doubles with each generation so the number of passages can be mathematically expressed as $number\ of\ passages = (generation\ number)^2$. The mean diameter of the trachea is 1.8cm and is supported by U-shaped cartilaginous rings. Posteriorly, the trachea joins the oesophagus via bands of smooth muscle. This is of import because, despite the solid nature of the cartilaginous rings, it is possible to occlude the trachea if the intrathoracic pressure exceeds 50 – 70 cmH_20.

Small bronchi begin at approximately generation number 7 and have a diameter ranging from 3.5mm – 1mm. Because smaller bronchi do not attach directly to the pulmonary parenchyma, they rely on a discontinuous network of cartilage to maintain patency, and on transmural pressure for airflow. By the eleventh generation, the cartilage disappears from the airway wall (now ≤1mm in diameter) and the pulmonary parenchyma and the elastic recoil of the lung

instead hold the passages open (3). The bronchioles also have a layer of helical smooth muscle under three types of control. The sympathetic nervous system causes dilation of the bronchioles via ß adrenergic stimulation by nor/adrenaline. Conversely, the parasympathetic nervous system via acetylcholine and the vagus nerve promote constriction. Additionally, histamine exerts local control and leads to constriction as well.

The average adult lung contains 130.000 primary lobules, with each lobule containing approximately 2000 alveoli in a diameter of 3.5mm. From a functional standpoint, each primary lobule can be viewed as a large alveolus (3). Ranging from 200 – 600 million, the average, healthy adult lung contains around 300 million alveoli. The size of the alveoli is directly proportional to lung volume, except at the point of maximal inflation. This size differential is exhibited in a vertical, gravity-dependant gradient, with the larger alveoli found at the apex of the lung. At functional residual capacity, the mean alveolar diameter is 0.2mm (3).

Gravity-dependence is seen to a greater degree in the pulmonary vasculature. The pulmonary vasculature carries the same flow as its systemic counterpart, however is does so at about 1/6 the pressure. These lower pressure vessels are significantly thinner than their systemic counterparts, with the media being approximately half as thick (2, 3). Pulmonary arterioles are mostly elastic and lack significant muscle. At rest, approximately 75% of the pulmonary vascular bed is filled, creating a gravity-dependant V/Q ratios. Inflation of the alveoli at higher (or lower) pressures will cause a change in vascular resistance, leading to redistribution of blood within the pulmonary system.

The walls of the alveoli consist of a basement membrane sandwiched between 2 layers of pulmonary epithelium. Within the walls are the pulmonary capillaries, elastin, collagen, and various immunologically active cells such as neutrophils and macrophages (4). Intra-alveolar septa are fenestrated by pores of Kohn, allowing for movement of air and immunologic cells. In the area of gas exchange, the capillary and alveolar epithelia are closely opposed, sitting 0.4µm apart.

Pressure drives air movement in the respiratory system, and as such, a brief review of pressures and volumes is warranted.

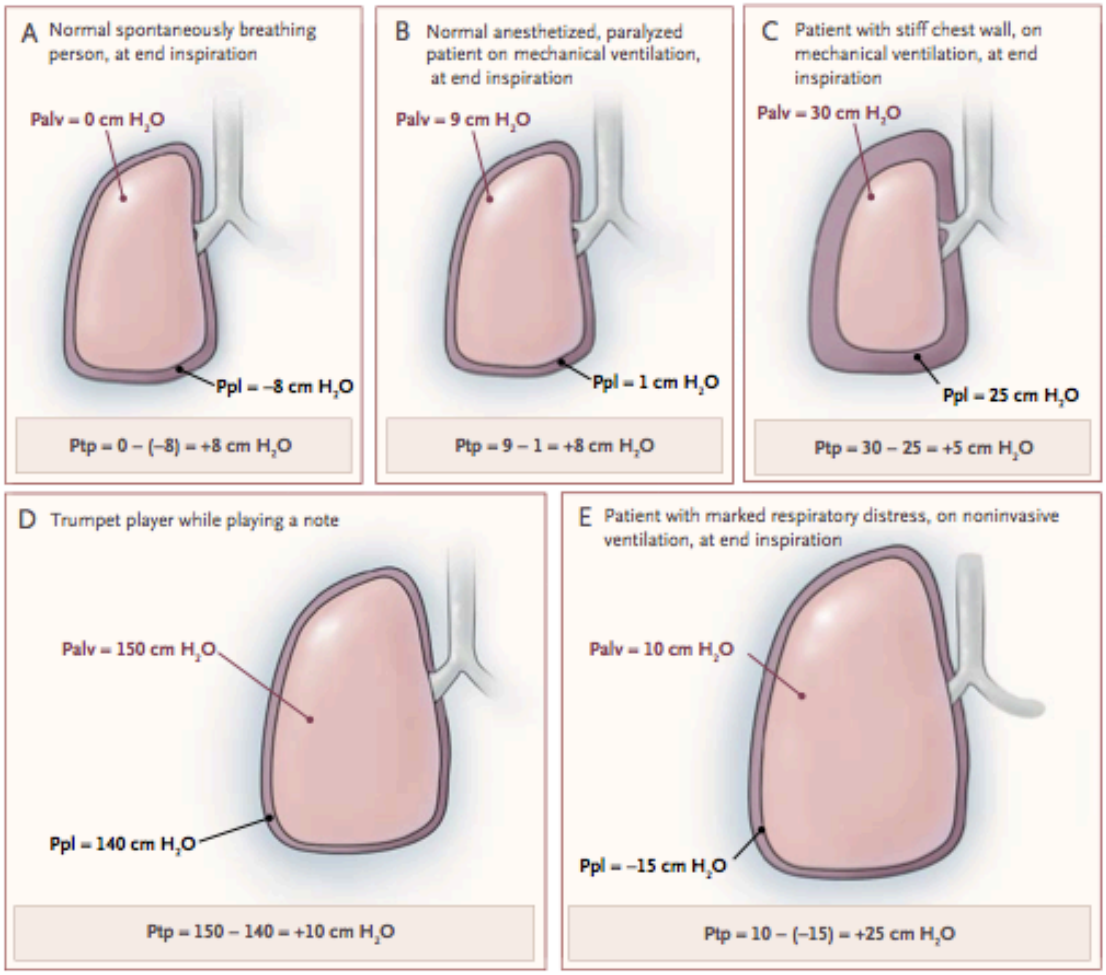
The alveolar pressure at rest, with unimpeded airways and an open glottis, is 0cmH_2O (or equal to atmospheric pressure).

Plural pressure holds the alveoli open and in a normal, healthy lung sits at about -5cmH_2O at the beginning of inspiration. During inspiration, the plural pressure drops to -7.5cmH_2O.

Transpulmonary pressure is the difference between the alveolar and plural pressures. It is also referred to as the recoil pressure.

Compliance is used as a measure by which certain changes in ventilation are monitored, and is defined as the extent to which the lungs will expand per unit of increase in transpulmonary pressure. There are two characteristics of compliance. The first is the tissue-elastic forces tending towards the collapse of the air-filled lung. The tissue-elastic forces account for approximately 1/3 of the total lung elasticity. Alveolar fluid:air surface tension accounts for the remaining 2/3. Importantly, if one were to measure the compliance of the entire lung-thorax system, it would be approximately half of the lungs alone. This means that the thorax contributes the same tendency to collapse the air-filled lungs as do the lungs and pleura themselves (3, 4).

Figure 1



Reproduced with permission from the New England Journal of Medicine.
Intrathoracic Pressures and Lung Stretching. Panel A shows end inspiration in a patient with normal lung function who is breathing spontaneously (with an open glottis); the alveolar pressure (Palv) is 0, and the pleural pressure (Ppl) is negative (−8 cm of water), creating a transpulmonary pressure (Ptp) of +8 cm of water (Palv minus Ppl). Panel B shows the same lung while the patient undergoes general anesthesia and positive-pressure ventilation with the use of the same tidal volume as in Panel A. The lung would be similarly stretched, with an alveolar pressure of 9 cm of water and a pleural pressure of 1 cm of water for a transpulmonary pressure of +8 cm of water. Panel C shows end inspiration in a patient with severe obesity, massive ascites, or pleural effusions, who may have a very stiff chest wall. In such patients, much of the pressure that is applied by the ventilator will be used to distend the chest wall rather than the lung. As such, the plateau pressure may be high, but so will the pleural pressure, and hence there may not be an increase in transpulmonary pressure with accompanying lung overdistention. Panel D shows a musician playing a trumpet, which can result in airway pressures of as much as 150 cm of water. However, because of the positive pleural pressure developed by the respiratory muscles, the pressure across the lung will not exceed normal values. Panel E shows a patient with marked dyspnea who is undergoing a type of mechanical ventilation that requires the active contraction of the respiratory muscles to initiate the assisted breath (e.g., noninvasive ventilation or pressure-support ventilation). In such cases, there may be large negative swings in pleural pressure, leading to a very high transpulmonary pressure, even though the airway pressure is only 10 cm of water.

Of particular note in this paper is the clinical ability to measure the various airway pressures. Alveolar pressure is relatively simple to measure in a sedate patient who is breathing passively and is termed “plateau pressure”. It

represents the pressure required to distend the chest wall and lung together. Likewise, mean airway and peak inspiratory pressures are both easily obtained. Unfortunately, if we are to calculate transpulmonary pressure, then measurement of pleural pressure is also required. Currently, no method exists to directly measure this pressure in the clinical environment. The only readily available surrogate is oesophageal pressure, which provides only a rough estimate as it is affected by the cardiac movement, the lungs, and by the oesophagus itself. (5)

Normal Respiratory Immune Response

Protection of the respiratory system actually begins at the nose where the air is warmed, humidified, and filtered via turbulent airflow and gravitational precipitation (2-4).

In its entirety the respiratory system is coated in mucous (to varying degrees) secreted by goblet cells and sub-mucosal glands. This mucous serves several purposes. It keeps the surfactant moist, allowing for a continued decrease in surface tension. Respiratory mucous also traps small particles before they reach the terminal airways.

The particles trapped in the mucous are the removed to the pharynx by ciliated epithelium which beats approximately 10 – 20 times per second (3). The cilial beat has two phases, fast and slow. The fast beats are always directed caudally and are responsible for moving particulate matter out of the airways. Normally a particle within the mucous layer will be moved a few millimetres every minute (2). Upon reaching the pharynx, the particle-containing mucous is either coughed or swallowed.

Though comprising only 8% of pulmonary cells, the type I pneumocyte (epithelium) covers 95% of the alveolar surface area. Importantly, these cells are able to take in particulate matter and then either facilitate movement of the particle away from the alveoli or undergo oxidative apoptosis. Type I pneumocytes are not mitotically active.

Type II pneumocytes are best known for supplying surfactant to the alveoli via the release of osmophilic granules. Surfactant reduces the alveolar surface tension and prevents collapse at lower pressures. Type II cells are mitotically active and are able to replace damaged epithelium, eventually transforming into type I cells as required (2, 3).

There are 3 types of macrophage commonly found within the respiratory system: airway, interstitial, and alveolar. The three types share many commonalities and move between the three areas to varying degrees. As a group they are derived from bone marrow, though – in the presence of bone marrow dysfunction, and in times of stress – they are able to undergo functional division for several generations (3). All contain primary and secondary lysosomes. All have surface receptors for IgG, IgM, C3, and various other opsonins. All function as antigen-presenting cells for T cells. Finally, pulmonary macrophages produce mediators such as fibronectin, prostaglandins, leukotrienes, interferons,
and α1 anti-trypsin.

Figure 2

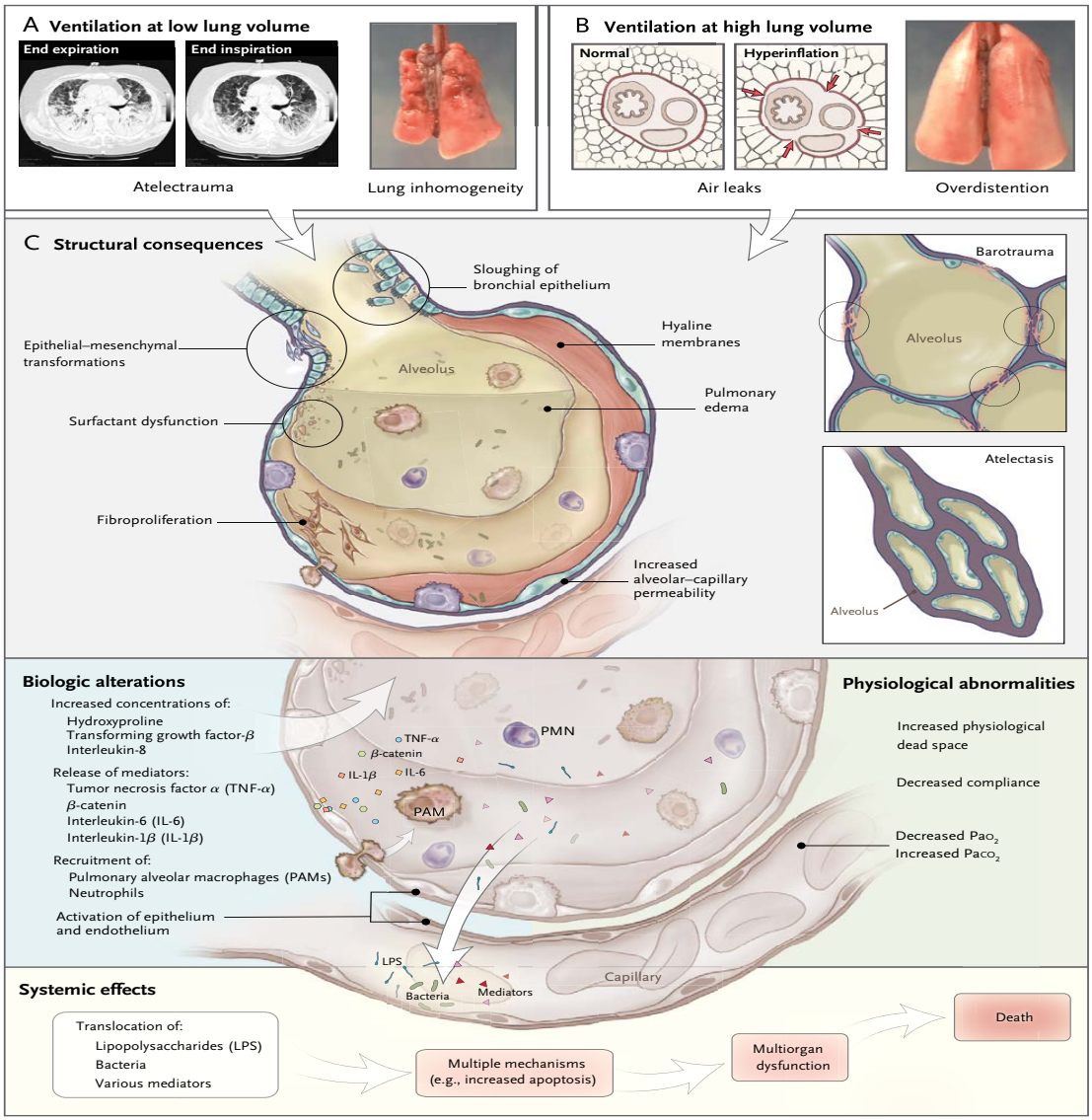


Figure 2, previous page.
Reproduced with permission from the New England Journal of Medicine.
Lung Injury Caused by Forces Generated by Ventilation at Low and High Lung Volumes.
When ventilation occurs at low lung volumes, lung in- jury can be caused by the opening and closing of lung units (atelectrauma) as well as by other mechanisms. This injury is magnified when there is increased lung inhomogeneity, as shown on computed tomography (Panel A), especially in patients with the acute respiratory distress syndrome (ARDS) who have surfactant dysfunction, pulmonary edema, and atelectasis.[11] In addition, ventilation may be very inhomogeneous, a status that may be partially or fully reversed by the use of positive end-expiratory pressure (PEEP), as shown in a ventilated ex vivo rat lung (see video in Slutsky and Hudson[12]). At high lung volumes, overdistention can lead to gross barotrauma (air leaks)[13] (Panel B). Overdistention can also lead to increased alveolar–capillary permeability and gross pulmonary edema. Ventilation at both high and low lung volumes has structural, physiological, biologic, and systemic effects (Panel C). Mediators that are released into the lung can cause further lung injury, recruit neutrophils to the lung, or set the stage for the development of pulmonary fibro- sis. In addition, the increased alveolar–capillary permeability associated with ventilator-induced lung injury can lead to translocation of mediators, lipopolysaccharides, and bacteria into the systemic circulation, potentially leading to multiple-organ dysfunction and death. $PaCO_2$ denotes partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, and PMN

The pulmonary lymphatic system has a capacity of approximately 500ml with the vessels lying mostly within potential spaces surrounding the vasculature and the various air passages. Lymphatic flow from the left lung is to the thoracic duct, while the right lung drains to the lymphatic duct (2).

Positive Pressure Ventilation

History and Mechanisms of Positive Pressure Ventilation

The idea of artificial ventilation is credited to Paracelsus, who used fire bellows connected to a tube inserted into the patient's mouth. In 1744 John Fathergill reported the first effective use of mouth-to-mouth resuscitation. In 1775 John Hunter devised a double-bellows system, a kind of a push-pull system designed to both introduce and draw out air. In 1911 Dräger Medical produced what was probably the first commercially available, purpose built artificial respirator, called the Dräger Pulmoter; it was designed to be used by first responders. The late 1800s and early 1900s also saw the development of negative pressure pulmonary ventilators, largely in response to polio. Two main types reached common usage. The first and most dramatic was the iron lung. The patient was inserted, bodily, into a metal tube or box with his or her head left protruding. The pressure in the device was reduced cyclically thereby drawing air in through the patient's nose and or mouth. The second type was known as the chest cuirass. It was designed to enclose only the thorax and work on a similar principle to the iron lung. It had the advantage of being significantly small and simpler, allowing many patients to remain at home. (6)

Mechanical ventilation entered mainstream medicine as a result of its extensive use in the 1952 polio epidemic in Copenhagen, Denmark. Throughout the course of the epidemic, many principles were developed which have today become standard. These include the use of cuffed endotracheal tubes, periodic sighs, and weaning. It was also in this time period that the first mechanical positive-pressure ventilators were designed for long-term use. During this time, the use of mechanical ventilation to support

patients with paralytic polio reduced the mortality rate from approximately 80% to 40%. (7, 8)

The 1960s gave rise to the era of respiratory intensive care with the production of the first proper volume-controlled and pressure-controlled ventilators. While they are positively archaic by today's standards, it is interesting to note the designers attempted to mimic normal breathing with sinusoidal waveforms, periodic sighs, and even PEEP to mimic pursed-lip breathing. During the late 1960s and early 1970s, the first reports and conferences concerning what would later be termed ARDS began to appear. (6)

The mid 1970s though the 1980s harkened the development of low-pressure endotracheal tubes to combat tracheal necrosis, permissive hypercapnoea, gas mixtures, high-frequency oscillatory ventilation, and high-frequency jet ventilation. Various modes of ventilation, some still in use today, were also developed during this time. These include pressure-support, pressure-control, and interestingly inverse ratio ventilation. (6) The period covering the 1980s until now has brought about not only derivative modes of ventilation, often focused on synchronisation, but more importantly an incredible amount of research. Some, such as the ARDSnet studies, have forever changed the way we treat patients. While others, such as the disappointing transition of high-frequency oscillatory ventilation to the adult population, have severed as a scientific head-scratch. What has become clear is that mechanical ventilation can represent a potentially life-saving intervention, but that it also requires careful use and on-going, patient-specific tailoring. (6)

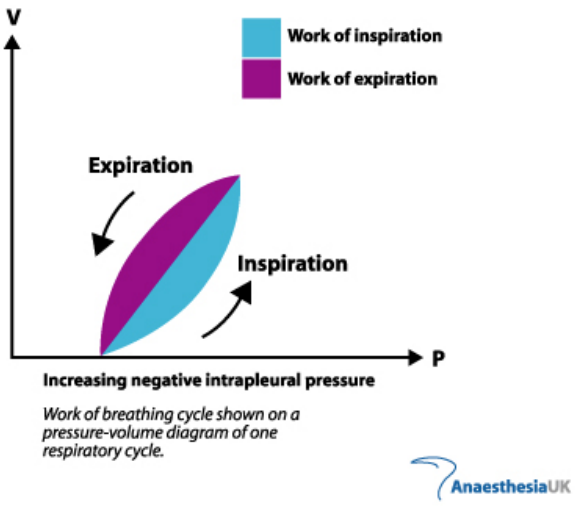
Between forty and 60 per cent of ICU patients will require some sort mechanical ventilatory support. This makes it only less common than the use of intravenous therapy, antibiotics, and – presumably – a bed. From a different point-of-view, this represents about 3% to 4% of the hospitalised population. (9, 10) Unfortunately, there is no good European data available calculating the cost of mechanical ventilation. However, in the US in 2005, mechanical ventilation represented approximately 12% of hospital costs at

around twenty-seven billion US dollars per year. (10) Whilst one must acknowledge that US healthcare costs are the highest in the world and that the increase in cost is likely not analogous to Europe, there is – regardless of location – an increase in labour intensity and complications regardless of location. For the most part the increase in labour intensity occurs at the beginning of each patient's mechanical ventilation.

Advantage and reasons for Positive Pressure Ventilation

Mechanical ventilation has essentially two main advantages. Firstly, in the spontaneously breathing patient ,it allows us to reduce the work of breathing. Whilst this may sound trivial to some, work of breathing in a patient suffering from respiratory distress can represent up to forty per cent of the body's energy and oxygen consumption. Work of breathing is normally expressed in joules and is quite complex, (3) but in healthy individuals ranges from 0.3 – 0.5 joules/L. (11) Normal determinants of work of breathing are essentially a sum of the inspiratory and expiratory forces to be overcome by the patient.

Figure 3

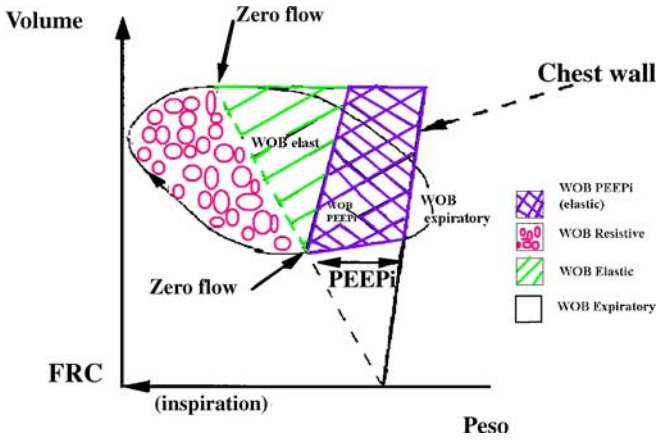


Reproduced with permission from AnaestheisaUK

These include the chest wall elastance, lung elastance, transpulmonary pressure, resistive forces, and intrinsic PEEP. This is best described using Campbell's diagram in figure 2 below. Obviously, when lung function is deranged, work of breathing increases significantly, mechanical ventilation

can reduce this work and allow the patient's body to rest and redirect the oxygen and energy sources elsewhere. (3) Work of breathing is measurable in the clinical environment and research is underway to assess the utility of this in the prediction of success of weaning. Unfortunately, due to the complexity of the research at these early stages, it is beyond the scope of this paper.

Figure 4



Reproduced with permission from Wiley Interscience.
Campbell's diagram. Work of breathing measured by the esophageal pressure: resistive WOB (W_{resist}), elastic WOB (W_{elast}), WOB related to active expiration (*WOB expiratory*) and WOB related to intrinsic PEEP (W_{PEEPi}). *Chest wall*: this *thick line* (the chest wall compliance) represents the pleural (esophageal) pressure obtained when muscles are totally relaxed and lung volume increases above functional residual capacity, measured in static conditions

The second major advantage of mechanical ventilation is the ability to control pressure, volume, and gas mixtures in patients unable to do so themselves. (3) This includes patients in total respiratory failure, trauma patients, and patients undergoing surgery to name but a few.

Cardiovascular Responses to Ventilation

When considering the effects of mechanical ventilation on cardiac function, one must remember that mechanical ventilation functions in almost exactly the opposite manner as spontaneous respiration. During positive pressure inspiration, air is forced into the lung at higher than atmospheric pressure, increasing the thoracic pressure. The increase in thoracic pressure increases pressure in the right atrium (RA) and venous return as a whole, impeding

filling. Increases in thoracic pressure are inversely proportional to right ventricular (RV) preload. (1, 12, 13). In fact, one of the most common early complications of mechanical ventilation is the so-called “post-intubation cardiovascular collapse”. Likely this is an unmasking of the patient’s fluid status as a result of decreased venous return, possible in combination with increased pulmonary vascular resistance and impaired RV function. This can be largely offset by fluid challenge or appropriately, careful monitoring and fluid maintenance.

RV function is also affected by lung volume. At hyper-inflated lung volumes, lung volume may raise pressure on the pulmonary vessels enough to produce an increase in pulmonary vascular resistance. Likewise, a decrease in lung volume can result in an increase in pulmonary vascular resistance through two mechanisms. First, in ateletic areas of the lung, the pulmonary vasculature becomes tortuous and tends towards collapse. Secondly, in both ateletic and poorly ventilated areas hypoxic vasoconstriction appears. Any of these mechanisms either alone or, more likely in combination, have the potential to significantly increase pulmonary vascular resistance, consequently increasing RV afterload and inhibiting RV function. (1, 12, 13) Outside of these two extremes, the pulmonary vascular resistance tends to remain within physiologic norms. There is, however, a small but significant rise in pulmonary arterial pressure.

Interestingly, the left ventricle (LV) is differently affected than the right. Because the aorta lies within the pleura it is subject to plural pressures. For this reason, the pressure increase during mechanical ventilation decreases LV afterload, actually increasing cardiac output in certain populations of patients. Likewise the application of PEEP may be of cardiovascular benefit in patients suffering the effects of ventricular interdependence, such as those with a fluid overloaded RV or weak LV. (1, 12, 13) More often, however, the increase in RV afterload leads to a decrease in LV preload, leading to decrease LV output.

The use of PEEP, while beneficial from a pulmonary standpoint, prevents the thoracic pressure from ever returning to atmospheric. This creates a situation in which, outside of the normal tidal pressure changes, intra-thoracic pressure remains elevated. This leads to a sustained decrease in venous return, and impaired RV filling. (1, 12, 13) Further, the increase in intra-thoracic pressure stimulates baroreceptors and has the potential to blunt adrenergic reflexes that may be able, to some extent, to counter these effects. This is compounded by the sedatives and analgesics that are often employed in mechanical ventilation.

Though difficult to quantify, one can reasonably suspect that all of these effects are present to varying degrees in the majority of patients under-going mechanical ventilation. With this in mind, it is incumbent upon the user to anticipate and ameliorate them. At present, it is possible to measure, or at least estimate, all of the relevant pressures in the clinical environment. Oesophageal pressure in this setting is an acceptable substitute for intra-thoracic pressure, because the numeric value in this case is less important than the trend. The pressures of all four cardiac chambers are attainable via echocardiography, and via these one is able to estimate pulmonary pressures. Of course, if estimation is not sufficient, pulmonary catheterisation is available. (3) Realistically, this may trumpet the era of specifically tailored ventilator settings in response to cardiovascular function. While this is has been suggested, it has yet to undergo significant clinical research.

Common Complications of Mechanical Ventilation

Difficulty Weaning

Weaning from mechanical ventilation is the process by which ventilatory support is gradually removed. Typically this occurs after resolution of the pathology requiring mechanical ventilation. Success is defined by the absence of ventilatory support forty-eight hours after extubation. (1) Weaning is dependant on respiratory drive, physical and functional nerve integrity, motor end plate integrity, intact respiratory structures, sufficient muscle

strength, and the load against which they work. Failure of any component can lead to weaning failure. (14) Most commonly, failure is a result of inadequate or incomplete resolution of the original problem, but may also be a problem of new onset related or unrelated to mechanical ventilation. In the second category, the most common problems are ventilator-associated pneumonia and ventilator-associated lung injury. (14) Weaning generally comprises about half of the patient's time on mechanical ventilation and is without complication between 70% and 80% of the time. (15)Regardless of the reason for failure, the result is an increase in morbidity and mortality, lengthened ICU stay, poorer general prognosis, and an increase in cost. (16) Data show that prolonged periods of mechanical ventilation are associated with a mortality increase of between twenty and forty per cent. Further, in those that do survive, many require assistance with activities of daily living. (17)

Immobility, prolonged mechanical ventilation, systemic infection and inflammation are all associated with skeletal muscle dysfunction in critically ill patients. (18) Ventilator-associated diaphragmatic dysfunction was first described in 2004 (19) and is a function of altered gene expression, deranged protein synthesis, oxidative stress, and proteolysis producing rapid atrophy of the diaphragm. To a lesser degree, the ancillary respiratory muscles are also accepted. Human studies have shown the onset of ventilator-induced diaphragmatic dysfunction can occur in a little as 2 – 6 hours, however some degree of dysfunction almost universally presents after forty-eight hours. (20) One study measured a decrease in diaphragmatic mass of 6% per day. (21) This is in agreement with animal studies. Additionally, a 2002 study (22) found that the incidence of ICU-associated paralysis was ≥ 25%.

Risk factors for failure to wean include recent infection, cardiovascular dysfunction, electrolyte imbalance, psychological dysfunction, endocrine disorders, neuromuscular weakness, open tracheostomy and previous failure to wean. (14) Additionally, female sex, higher acuity, pre-existing diabetes, and hepatorenal impairment were also associated with poorer outcomes. (22)

Patients undergoing weaning are categorised as simple, difficult, or prolonged, based on the number of spontaneous breathing trials, the number of weaning failures, and the total "weaning time". (14) Of interest, but not yet in clinical use, is diaphragmatic assessment prior to or during weaning. One study found that diaphragmatic dysfunction as demonstrated by excursion of ≤10mm visualised by M-mode ultrasound during SBT was associated difficulty weaning. (23)

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring in a patient undergoing invasive mechanical ventilation. (3) The normal definition suggests 48 – 72 hours of mechanical ventilation are required prior to diagnosis however some data suggests ventilator-association is possible earlier than this. (24, 25) VAP represents approximately 80% of hospital acquired infection (3) and is the most common device-associated infection. (26) Predictably VAP is also the most common nosocomial infection in ventilated patients, and, in fact, the ICU. (27) The incidence of VAP is variable but is thought to sit between 1 - 4 cases per 1000 ventilator-case days in medical patients, and up to 10 cases per 1000 ventilator-case days in surgical patients. (28, 29) In general, this equates to between 8% and 28% of ICU patients.

Despite the relatively clear incidence of VAP the mortality of the disease remains somewhat elusive, with estimates ranging from 0% - 60%. (30) It has been suggested that estimation of mortality in VAP is hampered by numerous confounding variables in a heterogeneous patient population. Whilst multistate and competing risk models account for temporal variances, they are unable to overcome multiple confounding factors. A recent meta-analysis (31) assessed data from 58 randomised prevention studies and concluded that the overall attributable mortality for VAP was 9%. Though this may be accurate, it fails to take into account the complexity of the patient populations that contract VAP. The same authors then conducted a second review in which they grouped patients by severity. (30) In this study they concluded that the overall mortality for VAP was 13%. More interestingly, they noted that VAP

had no statistically significant impact in either trauma or medical patients with low (APACHE score <20 or SAPS <35) or high (APACHE >30 or SAPS >58) severity scores. Patients with medium severity of illness scores were most affect by VAP, with medical patients faring better than surgical. The authors feel that the increased risk of death in VAP could then actually be attributed to risks associated with longer ICU stays, rather than to VAP itself. This conclusion seems reasonable, especially when one considers that the finding are consistent with Schumacher et al. (32) and Nguile-Makao et al. (33) VAP does clearly increase the length of ICU stay, the duration of ventilation, and cost of care. (27, 28)

As with all bacterial pneumonia, VAP occurs when bacteria enter the normally sterile lower respiratory tract and subsequently overcome the host-defence system, (28, 34) a system that is often weekend in ICU patients. The Centres for Disease Control and Prevention (CDC) proposes three mechanisms by which colonisation occurs: aspiration of secretions, colonisation of the aero-digestive tract, and contaminated equipment. (35) Aspiration, probably more commonly microaspiration, from the oropharynx is thought to be the dominant route of entry. (36) Colonisation is often found in the first week of hospital admission in critically ill patients. (3) On top of the complications often seen with pneumonia, VAP has the added complications that it is difficult to diagnose and often exhibits multiple drug-resistance. The most commonly isolated causative pathogens in VAP are *acinetobacter* spp., *P. aeruginosa*, and *S. aureus*, though there is no statistically significant difference in clinical outcomes when the organism is considered.

Some factors associated with VAP (other than intubation itself) are nasogastric tubes, re-intubation, aspiration, supine positioning, pooling of sub-glottic secretions, coma, and enteral nutrition. (37, 38)

Considering the difficulties that VAP presents, the most logical solution is prevention rather than treatment. The primary method of prevention is to minimise intubation frequency and duration of ventilation. (3) To this end the CDC released the recommendations found in table 1 for the prevention of

VAP. (39) Though the exact impact of VAP on patients remains somewhat unclear, it has been shown to negatively affect mortality and morbidity, prolong ICU stays, increase the duration of mechanical ventilation, and increase associated costs.

Table 1 - CDC VAP prevention guidleines

i.	Conduct VAP surveillance
ii.	Adhere to hand-hygiene procedures
iii.	Minimise invasive mechanical ventilation
iv.	Minimise the duration of ventilation
v.	Conduct daily assessments for readiness to wean
vi.	Conduct VAP education
vii.	Maintain head-of-bed (HOB) angle between 30° - 45° whenever possible
viii.	Avoid gastric overdistension
ix.	Avoid unplanned extubation and re-intubation
x.	Use a cuffed ETT with in-line or subglottic suction
xi.	Maintain a cuff pressure of at least 25cm H_2O
xii.	Employ orotracheal intubation (vs. nosotracheal) whenever possible
xiii.	Avoid the use of H2 receptor-blockers and PPIs when possible
xiv.	Perform regular oral care
xv.	Remove condensate from the breathing circuit whilst it remains closed
xvi.	Change or replace the breathing circuit only when it is malfunctioning or visibly contaminated

Ventilator-Associated/Induced Lung Injury (VALI/VILI)

The concept of lung injury as a result of mechanical ventilation is not a new one. The term “ventilator lung” first appeared in 1967 and described the post-mortem findings of diffuse alveolar infiltrates and hyaline membrane formation in patients who had been mechanically ventilated. (5) Deaths often occurred despite normalisation of arterial blood gasses, and have been attributed to barotrauma, oxygen toxicity, and haemodynamic comprise induced by mechanical ventilation. (40) Today ventilator-induced lung injury and the clinical counterpart, ventilator-associated lung injury, are understood to involve inflammatory cell infiltrates, hyaline membranes, increased vascular permeability, and pulmonary oedema. (5) It is largely acknowledged that VILI is as complex and can be as damaging as the diseases supported by ventilation. In fact, the pathology exhibited in VILI is almost identical to that

seen in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). So much so that there is supporting the hypothesis that VILI may actually be capable of inducing both ALI/ARDS and its extra-pulmonary manifestation multiple organ failure (MOF). (35, 41) VILI is a common complication in critically ill patients, contributing to increased mortality, morbidity, and length of stay. (5) Unfortunately, due to the variable nature of the disease, the exact incidence are unknown. It is thought to affect approximately one-quarter of mechanically ventilated patients, though this number is almost certainly higher in those with pre-existing lung injury. VILI appears to be induced via three major mechanisms: volutrauma, atelectrauma, and biotruama.

Volutrauma

In order to fully understand the concept of volutrauma, it is important to recognise that the lung represents a heterogeneous environment in which multiple pressures and pressure gradients exist at any given time, even in a healthy lung. One must also comprehend that volume and pressure in the lung are part of the same concept. With this is mind, it is easier to picture volutrauma as regional tissue overdistension, rather than a global increase in pressure.

Wakabayashi et al. (42) used animal models to conclude that volutrauma caused a greater level of cytokine release compared to atelectrauma, and at least a comparable level of local tissue damage. Post-experiment analysis showed that both volu- and atelectrauma caused significant increases in elastic resistance and lavage fluid protein levels, indicating capillary damage and pulmonary oedema. It has been previously hypothesised that inflammatory mediators released from the lung in response to ventilator-induced damage may be responsible for distant organ dysfunction. (43, 44) Possibly more important than the greater levels of pulmonary chemokines and tumour necrosis factor (TNF) the Wakabayashi study discovered, were the higher systemic levels. The authors concluded the increased systemic levels of the inflammatory mediators were not explainable through overflow from the pulmonary system into systemic circulation, as has been postulated. Rather,

they believe it is representative of an extra-pulmonary source. Predictably, high levels of lung-marginated leukocytes were also seen and may be responsible for secreting TNF into the circulation propagating further production. This seems possible if one accepts that the lungs have the largest available pool of leukocytes in circulation. Also lending credence to this theory is the finding that monocyte-depleted lungs exposed to similar stimulus did not induce such high levels of inflammatory mediators. The monocyte-depleted lungs also showed less pulmonary oedema. Further supporting the concept of volutrauma, another study showed that induced overdistension in spontaneously breathing animals produced lung injury consistent with high-volume mechanical ventilation. (45)

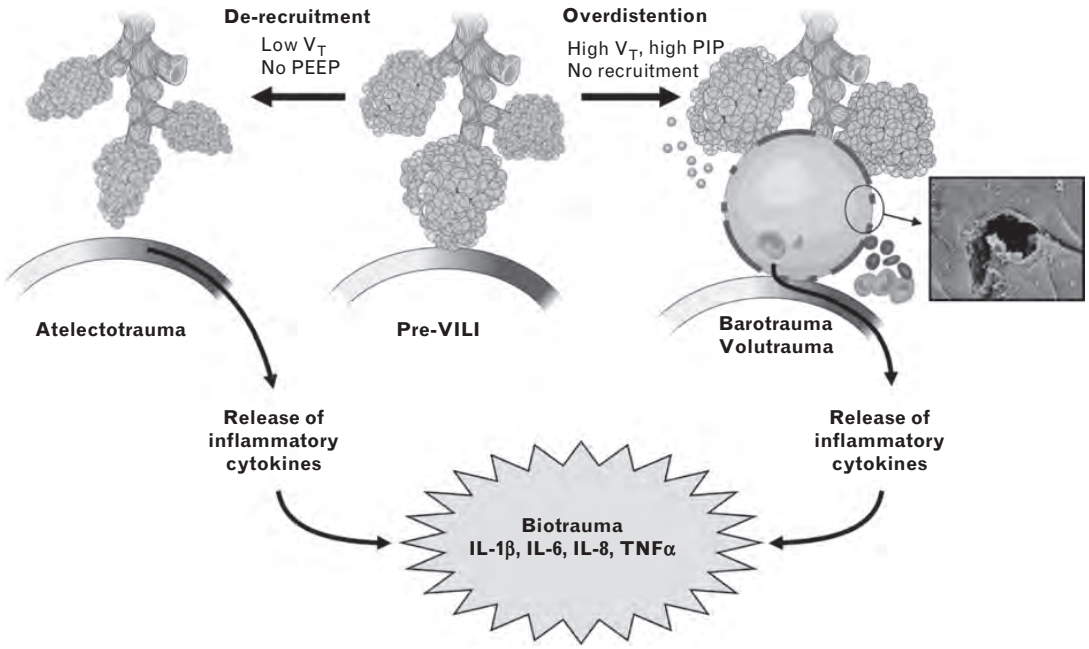
Whilst atelectrauma produced elevated levels of inflammatory mediators it did so only in the alveolar compartment. Both atelectrauma and volutrauma instigated similar levels of pulmonary oedema. This last finding contradicts those of another study showing that high volume ventilation caused a greater level of pulmonary oedema than did high-pressure ventilation. (46)

Atelectrauma

Atelectasis refers to the collapse of the alveoli in response to alteration of regional pressure differences in the lung, surfactant dysfunction, splinting due to injury or other defect, residual effects of neuromuscular blockade or other muscular dysfunction, airway blockage, compression of the pulmonary structures, or high FiO_2. (47) Central to this dysfunction is the alteration in the shape and function of the chest wall, whether caused pharmaceutically, physically, or surgically. Abnormal thoracic wall motion contributes to negative regional V:Q alteration, bringing with it either an increase in dead space or pulmonary shunt. (41) Regardless of the cause, atelectasis is present in up to ninety per cent of intubated patients and is associated with a significant increase in post-operative pulmonary complications (41, 48). As atelectasis is often clinically silent, there is a paucity of data regarding the frequency at which it causes clinically adverse events. Some data exists however demonstrating that up to 36% of patients with radiographically

diagnosed atelectasis proceed to develop pneumonia in the post-operative setting. Atelectasis is also associated with an increase in alveolar bacterial growth. (49, 50)

Figure 5



Reproduced with permission from Wolters Kluwer Health; Lippincott, Williams & Wilkins.
Ventilation of atelectatic areas can result in cyclic opening and closing of lung units (tidal recruitment), leading to release of inflammatory cytokines causing atelectotrauma. High tidal volume and overexpansion of lungs can rupture alveolar- capillary membranes (inset), leading to accumulation of neutrophils and release of inflammatory cytokines. IL, interleukin; TNF, tumor necrosis factor; VILI, ventilator-induced lung injury.

Atelectrauma is thought to be caused by repetitive shear stress and direct inflammation caused by the repeated collapse and inflation of the alveoli in the presence of dysfunctional surfactant or other pathologies. (51) This concept may be thought of as tidal recruitment/derecruitment injury. The healthy lung uses surfactant, alveolar interdependence, collateral ventilation, extracellular matrices, and the thorax to form an incredibly stable structure avoiding both collapse and over-inflation. In general, a healthy lung will show only minimal changes in alveolar size or shape provided the total lung capacity remains between 10% - 80%. (51-53) Loss of any of these mechanisms creates instability and increases the risk of atelectrauma, and subsequently of VILI. A disparate yet plausible theory is that small gas bubbles in non-aerated alveoli create large pressure fronts along the alveolar wall. (54) Such a gradient would cause large local pressure differences

amplifying the interaction of tissues and causing cellular injury. (55) Indirectly, atelectrauma also causes volutrauma via the preferential aeration and over-inflation of the open areas lung as a derivative of the relative decrease in lung size from the loss of the non-aerated areas. (47) Additionally, and perhaps more simply, is the theory that the non-ventilated areas become hypoxic leading to cell death and the release of inflammatory mediators. Given the evidence supporting multiple mechanisms of injury, it seems more likely that no one mechanism is responsible for the damage caused by atelectasis, and that instead multiple small insults accrue until such time as atelectrauma is manifest.

Biotruama

Related to the two above mechanisms, biotruama refers to the "translocation of mediators, bacteria, or lipopolysaccharide from the airspaces into the systemic circulation" (5) in cases of increased alveolar-capillary permeability as seen in ARDS, volutrauma, or epithelial microtears. This translocation may then propagate further pulmonary damage or distant organ dysfunction. All epithelial, endothelial, and of course inflammatory cells in the pulmonary system are capable of participating in inflammatory reactions via various signalling pathways. (5, 42) Specifically IL-6, IL-8, and TNF have been implicated in pulmonary biotruama during clinical trials. (56) Mediator release can occur via two methods. First, tissue trauma my cause cell death (or rupture) provoking the release of mediators. (57) Alternatively, lesser, non-fatal injury to either the cytoskeleton or the extracellular matrix may cause inflammation via discrete intracellular signalling pathways. (58)

Although volu-, bio-, and atelectrauma have been discussed separately, they must be considered, if not as different parts of the same entity, then as 3 extremely interrelated entities.

Complications and Effects of General Anaesthesia

In general, one can predict several changes in patients under general anaesthesia. Volatile agents impair mucous transport from the pulmonary tree, one of the respiratory systems primary protective measures. Data

shows that sevoflurane significantly impairs ciliary beat frequency, thus decreasing bronchial mucous transport velocity (59). The same impairment is not seen in patients undergoing total intravenous anaesthesia. Likewise, almost all anaesthetic agents decrease respiratory drive and blunt respiratory reflexes.

The use of inhaled volatile agents at any point is associated with a significant decrease in CD3+, CD4+ and, CD8+ T lymphocytes, NK cells, and B lymphocytes. Total intravenous anaesthesia is associated with a smaller decrease and more rapid return to normal. (60)

All volatile anaesthetics, and in fact all intravenous anaesthetics save ketamine, cause a decrease in both systemic vascular resistance and mean arterial blood pressure. This change in blood pressure seams almost entirely to occur via a decrease in systemic vascular resistance, as the cardiac index as measured by echocardiography is largely unchanged. (61) Still important but of little impact to this paper: some inhaled anaesthetics demonstrate a propensity towards dysrhythmogenicity and cardiac conduction disturbances, as well as a prolongation of the QT interval.

All volatile anaesthetics increase the respiratory rate whilst decreasing the tidal volume in spontaneously breathing patients. This produces a relatively preserved minute volume in the presence of increased dead-space ventilation. In this setting, oxygenation is typically preserved, though often in the setting of increasing $ETCO_2$. (***Millers) In healthy patients this may be as well tolerated as permissive hypercapnoea in any other ventilated setting. It can however present possible consequences in the comorbid patient. Increased respiratory muscle activity seen during the use of inhaled anaesthetics also alters the chest wall dynamics. (***Millers) Inward displacement of the chest wall and cephalad displacement of the diaphragm produce a simultaneous increase in atelectasis and decrease in functional residual capacity. While all inhaled anaesthetics have the potential to irritate the airways, this occurs almost exclusively during gas induction or at supra-therapeutic concentrations. Of interest, however, is that several inhaled

anaesthetics are capable of bronchodilation. This probably demonstrates a negligible effect in most patients, however it does have significant potential to benefit those with pulmonary comorbidities. (***Millers)

Total intravenous anaesthetic (TIVA) procedures all, to one extent or another, produce a similar decrease in blood pressure, though most often in the presence of a decrease in heart rate. (***Millers) The two can be used in conjunction, termed mixed anaesthesia, in order to blunt the tachycardia seen in gas anaesthesia. Contrary to volatile anaesthetics, TIVA generally inhibits respiratory drive. If not supported, this leads to hypoxia and hypercarbia.

Though not a general anaesthetic, spinal and epidural anaesthesia deserve some mention here. Because the delivery of an anaesthetic to one specific level or dermatome is somewhat imprecise, this procedure sometimes produces hypotension and respiratory distress. (***Millers) The most dangerous potential side effect is termed total spinal anaesthesia. It represents a total derangement of cardiovascular and respiratory control, and requires immediate, careful, and aggressive management.

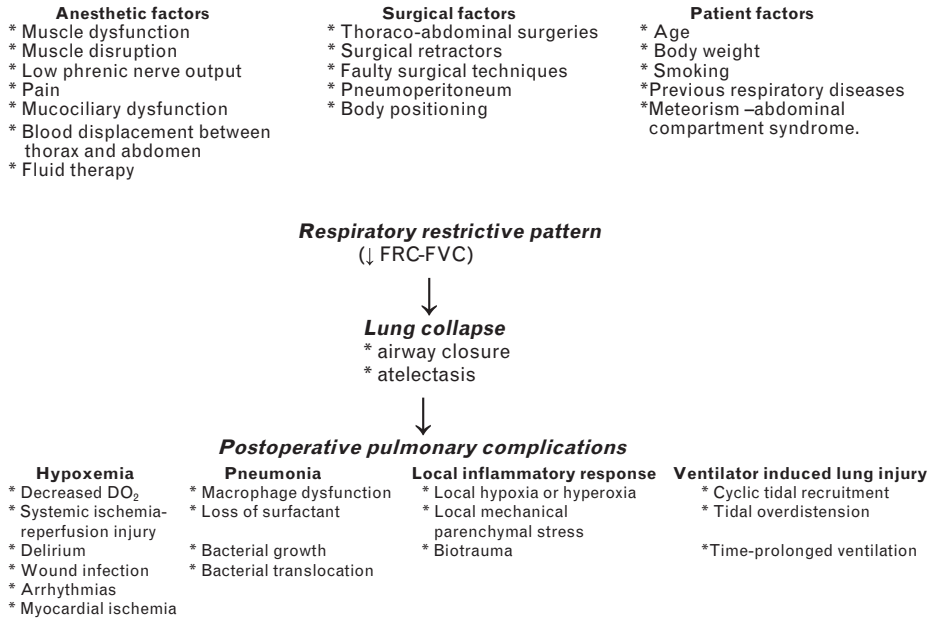
Strategies for the Prevention of Ventilator-Associated Complications

Perioperative Prevention Strategies

Perioperative complications are those conditions related to surgery arising within one month prior and three months after the procedure. Perioperative complications occur in 20% - 67% of elective surgeries, and more often in emergent surgeries. They account for 80% of surgery-related death and reduce median survival by up to 70%. (62-64) Post-operative pulmonary complications (POPC) occur at least as often as post-operative cardiac complications and contribute significantly to increased mortality and ICU admission. (65-68) POPC may be divided into acute, sub-acute, and delayed phases.

Residual neuromuscular blockade is associated with increased incidence of POPC. (66) This is explained via respiratory muscle weakness leading to hypoxia and respiratory failure. Even in the absence of respiratory failure, residual blockade lengthens stays in the post-operative care unit. (47) It is advisable then to use appropriately timed neuromuscular blocking agents and ensure complete reversal through antagonistic agents prior to extubation as this has been shown to decrease POPC. (69)

Figure 6



Reproduced with permission from Wolters Kluwer Health; Lippincott, Williams & Wilkins.
Link between pathophysiological factors, lung collapse and postoperative pulmonary complications.

Failure to wean from the ventilator after surgery may be due to retained anaesthetic or neuromuscular agents, but is more commonly associated with indirect lung injury resulting from the pathology at hand. (66)

Aggressive fluid administration during the perioperative and operative periods is also associated with POPC. (66, 70) Every effort, therefore, should be made to avoid excess fluid whilst continuing to maintain an appropriate fluid balance.

Smoking Cessation

Ample data demonstrates that patients who smoke experience both an increased rate of surgical complications (71-75), and of perioperative death

(73, 75-78). A Cochrane review indicates that pre-operative smoking cessation, especially ≥ 4 weeks prior to surgery may significantly improve outcomes (79). The reduction in perioperative complications ranges from 20% to 34% (80-82). Difficulties in smoking cessation include mainly unwillingness on the part of the patient, increased workload on the staff, and the incurred expenses surrounding support programmes required for patient success (73).

Smoking is a univariate risk factor for respiratory failure, unanticipated intensive care admission, pneumonia, adverse airway events, and unanticipated airway and breathing interventions (83).

Smoking is relevant to anaesthetists for several reasons. First, smoking increases the level of carboxyhaemoglobin, which can reach up to 10% in heavier smokers (83). The increased level of carboxyhaemoglobin not only decreases the total amount of oxygen that is available, but also shifts the oxyhaemoglobin dissociation curve leftwards, impeding the release of oxygen to the tissues (84) This is particularly relevant in patients with cardiovascular disease, or risk, because smoking also causes coronary vasoconstriction (85). This occurs via both direct and indirect sympathetic outflow (86).

In addition to altered gas dynamics smoking also impairs mucociliary clearance (87, 88). This is in addition to the impairment resulting from inhaled volatile agents. Cigarette smoking also impairs the function of both alveolar macrophages and neutrophils (89, 90). One can also expect goblet cell hyperplasia accompanied by increased mucous production, as well as airway hyperreactivity (87, 88).

The above data clearly demonstrates the negative impact of cigarette smoking on perioperative morbidity and mortality, and the benefits of perioperative smoking cessation. It seems therefore worthwhile to promote smoking cessation as part of a structured programme during pre-operative evaluations.

Analgesia

Traditional approaches to post-operative analgesia involve opioids with or without NSAIDS. Whilst this approach may be appropriate for some patients in some cases it has several serious limitations. The larger doses of opioids that are often required to manage post-operative pain following major thoracic, abdominal, or orthopaedic surgery also tend to centrally depress respiratory function. (3) Depression of respiratory function then increases the odds of POPCs. (66)

Alternatively post-operative pain may be managed via neuraxial blockade. A meta-analysis published in 2000 examined 158 trials of neuraxial blockade and found an overall decrease in perioperative mortality of approximately one-third when compared to general anaesthesia and traditional opioid management. (91) Specific to post-operative pulmonary complications the authors identified a decrease in the occurrence of pneumonia as well as a decrease in the rate of respiratory depression. Deaths related to these two reasons dropped in a similar fashion. Interestingly, most studies analysed documented the continued benefit of neuraxial blockade regardless of whether or not it was maintained after the surgery. As far as overall mortality was concerned, there was little difference between neuraxial blockade alone or combined with general anaesthesia. The authors attributed the better outcomes to ease of pain-free breathing, increased blood flow, altered coagulopathy, and a decrease in the “surgical stress response”. Ease of early pain-free movement may also have played a role.

COPD is identified as an independent risk factor for POPC, as these patients can be extremely sensitive to alterations in respiratory drive and function. (47) There is some data supporting the notion that COPD patients may be between 300% - 700% more likely to develop pulmonary complications in the post-operative environment. (92) A study conducted in the Netherlands using this high-risk population documented a decreased risk of pneumonia within 30 post-operative days without evidence of a decrease in pulmonary function as a result of epidural anaesthesia. (93) Neither the pulmonary function nor the

pneumonia rates varied with disease severity. As a secondary end point, they also demonstrated better pain control in the group with epidural anaesthesia versus the traditionally managed group. Despite a clear decrease in the rates of pneumonia, this study failed to demonstrate a statistically significant decrease in the overall mortality rate. This is consistent with a large population-based cohort study that identified a small but statistically significant decrease in 30-day mortality. (94) It is possible that smaller studies will miss this data point as the number-needed-to-treat in that study was 447. More significantly, the study did confirm the safety of epidural anaesthesia in this setting and its efficacy both in preventing POPC and improving pain control.

Though not without risk, neuraxial blockade appears both safe and efficacious when used for the prevention of POPCs and the management of pain. Though the current evidence does not support its routine use to decrease crude mortality, it may be appropriate to employ it in patients at high risk for post-operative pulmonary complications or difficult to manage pain.

Post-Operative Respiratory Failure (PRF)

Post-operative respiratory failure represents the most common post-operative pulmonary complication, at approximately 50%. It shows an incidence of up to 3.4% in general surgical populations and carries a mortality rate of up to 25%. (47, 95) PRF is defined as the impairment of pulmonary gas exchange and hypoxia with or without hypercapnoea, in the absence of cardiac failure and as a result of surgery or anaesthesia. (47) Using PaO2:FiO2 levels, post-operative respiratory failure is classified as mild, moderate, or severe.

Respiratory muscle dysfunction contributes heavily to PRF. (96) Muscular dysfunction arises from residual anaesthetic agents, opiate effects on the central respiratory centre, and splinting from either pain or trauma. (47) Additionally, residual neuromuscular block affects not only the muscles of respiration, but also the airway muscles. This means that, not only are the diaphragm and thoracic muscles potentially unable to completely expand the thorax due to weakness, but also that the muscles of the airways remain dilated. This predisposes to lower pressures and increased risk of airway

collapse and atelectasis. (97) An inability to fully expand the thorax or the predisposition to airway collapse can maintain or perpetuate atelectasis potentially leading to a lengthened post-operative course or further lung injury.

Inspiratory Muscle Training

As inspiratory muscle weakness can be seen within two hours of the initiation of mechanical ventilation and is almost always present to some degree within forty-eight hours, it has been thought that inspiratory muscle conditioning could reverse this process, increasing respiratory muscle strength and endurance, especially that of the diaphragm. Inspiratory training is delivered using a variety of methods that increase the pressure against which patients must draw a breath. Two common methods are increasing the trigger pressure on the ventilator, and the use of an external impedance device. (15) In both methods the resistance is increased incrementally for short intervals over several days until the patient is thought to be capable of weaning.

Whilst this represents a logical intervention, data is contradictory. A 2011 review (15) concluded that although inspiratory muscle training was favoured, it did not statistically improve the duration of weaning in a significant manner. The same conclusion was reached for overall survival. No difference was found when considering re-intubation rates. This is in concordance with a randomised trialconducted more recently that demonstrated no significant shortening of the weaning period. (98) This study however is limited in that patients in both the control and intervention group received non-invasive ventilatory support following extubation. The study also failed to publish re-intubation rates.

Conversely, several studies have successfully demonstrated the benefit of inspiratory muscle training when considering the duration and success of weaning. (99-101) These studies showed small yet significant differences in both duration and outcome.

All studies however reported a significant increase in peak inspiratory pressure, suggesting a significant increase in muscle strength. Peak

inspiratory pressure currently represents the only clinically useful method of measuring respiratory muscle strength. No study found any association between inspiratory muscle training and worsened outcomes. It is possible that the inconsistent outcomes are a reflection of the homogenous nature of ICU patients requiring mechanical ventilation. It would therefore be plausible to consider that there may be a subset of patients who would benefit from inspiratory muscle training. As no danger has been demonstrated, it seems reasonable to consider inspiratory muscle training in patients at risk of failure to wean, such as those with a high Tomin index. Although ultrasound has been shown capable of estimating diaphragmatic mass, no study has combined this with inspiratory training. This may also prove of benefit in the future, assuming a minimum required muscle mass could be determined.

Sedative Reduction and Sedative Selection

Sedation in mechanically ventilated patients is employed to improve patient:ventilator synchrony, reduce patient stress and anxiety, facilitate medical care, and to improve patient comfort. Amelioration of this stress also has the possible effect of reducing endogenous catecholamine release and oxygen consumption. Significant evidence exists, however, demonstrating that excessive and prolonged sedation promotes longer durations of mechanical ventilation, longer ICU stays and worsened outcomes, including long-term cognitive impairment. (102-106)

A recent multi-centre trial showed that deep sedation in the first forty-eight hours is an independent risk factor for delayed extubation and increased mortality. (106) The study concluded that each Richmond Agitation Sedation Scale (RASS) finding in the deep range was associated with a delay in extubation of 12.3 hours, a 10% increase in in-hospital death, and an 8% increase in mortality at six months. Additionally, this study found that the use of midazolam was associated with longer periods of mechanical ventilation. This supports another study associating the use of benzodiazepines with longer periods of ventilation. (107) The fact that this study addressed the first 48 hours is important, as many studies do not. One other study assessed the

outcomes of patients without sedation in the first 48 hours and found significant improvements. (108)

The use of daily sedation interruption, commonly known as a “sedation vacation” offers the theoretical benefit of avoiding the accumulation of the sedative agents and their active or toxic metabolites, providing the opportunity of assessment of the requirement for continued sedation, and allowing the patient to participate in daily spontaneous breathing tests. As prolonged ventilation and deep sedation are known to promote worse outcomes, this potentially leads to a reduction in the duration of ventilatory support, shortened ICU and hospital stay, and an improvement in long-term outcomes. (102, 109)

Currently, the two most common methods for reduction in exposure to sedation are daily sedative interruption, and protocolised targeted light sedation. Hughes et al (104) found that, when used alone, these strategies were equally effective in reducing exposure to sedatives and improving outcomes when compared to deeply sedated patients. The authors further suggested that either the combination of the two, or the combination of daily interruption with an awake spontaneous breathing trial, might be of greater benefit. A finding that supports this is that outcomes are unchanged when the total dose of sedative is not decreased, even in the presence of a sedation vacation or lightened sedation. Girard (110) actually studied the combination of daily sedation vacations in combination with spontaneous breathing tests and found a significant decrease in ventilator time, ICU stay, hospital stay, and overall mortality.

To date only one trial has attempted to combine both targeted light sedation with daily interruption. Paradoxically, the study found that there was no difference in outcome and that the patients in the combined group required higher doses of sedatives. (105) Several potential problems exist within this study. First, the sedation scores published in the article are more consistent with moderate sedation, not light. Also, the compliance with the study protocol was only 72%. Potentially this means that the authors were not

actually studying lightly sedated patients, and that the data rather reflects what is already known about more deeply sedated patients. Interestingly, the authors did identify a sub-set of surgical/trauma patients that benefitted from daily withdrawal of sedation alone.

A recent-meta analysis of five randomised trials covering 699 patients found that daily interruption of sedation alone was not associated with reduced ventilatory duration, nor earlier extubation times. (102) Likewise no decrease in the length of ICU or total hospital stay was found. The analysis did however identify a reduction in the likelihood of requiring tracheostomy. No difference was noted in the re-intubation rates. Importantly, the study found no detrimental effect associated with the use of daily sedation withdrawal.

Good evidence exists to show that over-sedation of patients results in longer ICU and hospital stays, longer ventilation times, and poorer long-term outcomes. It has been shown that total dose reduction of sedatives and that the avoidance of benzodiazepines can improve outcomes. Evidence becomes inconsistent however when examining wither daily withdrawal of sedation or targeted light sedation. Potentially, the introduction of these two practices has simply made clinicians more cognizant of sedation levels and total sedative doses. Alternatively the inconsistent finding of various studies may be the result of an as yet unidentified sub-set of patients that benefit (or suffer) from both or either of these two practices. Regardless of the inconsistencies in the data the adoption of either of these methods of sedation reduction appears safe, and when compared to previous model of sedation is certainly of benefit.

Early Immunomodulary Nutrition

Early perioperative enteral nutrition with substances promoting immunomodulation is controversial and contradictory. Endotoxinaemia is reported in several studies and is thought to occur following abdominal surgery
via direct contamination of more often as a result bacterial translocation. Endotoxinaemia thought to act in a pro-inflammatory manner and is

associated with higher levels of markers of inflammation and poorer outcomes. (111) Theoretically, early enteral nutrition would increase splanchnic circulation and decrease bacterial translocation, preventing an inflammatory cascade. TNF alpha is known to be responsive to endotoxaemia and is probably responsible for the adverse effects, including protein/fat redistribution, cachexia, chemotaxis and inflammatory recruitment, and promoting anaerobic metabolism. (111) Elevated levels of TNFa are associated with worse outcomes. The most common constituents of immunonutrition are omega-3 fatty acids, RNA, glutamine, and arginine. Both animal and in vitro studies have demonstrated their ability to modulate cell-mediated immune function, acute phase proteins, insulin release, and the post-traumatic inflammatory cascade. (112, 113) Unfortunately, despite more than two decades of clinical trials, studies are often equivocal and reliable data is still lacking.

One study examined early perioperative immunomodulatory nutrition compared to a traditional approach and concluded that there was an overall attenuation of the inflammatory response. (114) This conclusion was only reached after the authors discounted the increased cytokine levels found in the interventional group. No overall difference in immunoglobulin levels was reported, nor was a difference in overall mortality.

An industry-funded trial in 2007 reported a statistically significant decrease in the levels of endotoxin, CRP and TNFa. (115) It did not report rates of clinical complications or outcome.

By far the best study is a 2010 meta-analysis reviewing 21 randomised controlled trials including 2730 patients. (116) The study showed that perioperative infections decreased in those receiving specialised early nutrition, as did the total number of days in the hospital. Overall mortality following surgery in the interventional group was unchanged. They further concluded that the cost associated with the programme was probably less than the cost associated with treating the prevented infections.

Current data suggests that early enteral immunonutrition may decrease the rate of postoperative infection, as well as the number of in-hospital days. One possible limitation is that many studies used predominantly cancer patients, a subset of patients known to be immunocompromised and prone to infection. Whether or not these results are transferable to the general surgical population remains to be seen. No study reported statistically significant improvements in outcome or mortality. As no study however reported worse outcomes it seems reasonable that perioperative immunonutrition could be offered to at-risk patients without fear of complication.

Lung-Protective Strategies During General Anaesthesia and Mechanical Ventilation

Low-Volume Ventilation

In 2000 a landmark trial using lower tidal volumes than conventional ventilation protocols in ARDS patients changed the way in which ALI/ARDS patients are ventilated. (117) The trial randomised 861 patients to either a lower Vt group (6ml/kg or predicted body weight) or to a convention ventilation group (10ml/kg – 15 ml/kg predicted body weight). This higher tidal volume time represented the average protocol for a patient with ALI/ARDS at the time, as the goal was often both to ensure not only a viable FiO_2 but also to normalise $PaCO_2$ and pH. So successful was this trial that it was suspended prematurely, as it was no longer possible to ethically enrol patients to the control group. This study went on to form the foundation of the low tidal volume ARDSnet protocol in use around the world today. Overall the reduction in mortality in the ALI/ARDS population requiring mechanical ventilation was reduced 22 per cent. The authors further demonstrated that at all times the peak airway pressure and mean airway pressure remained lower in the interventional group. Moreover, the PaO_2 was not statistically or clinically altered in the interventional group, despite a significant increase in $PaCO_2$. In spite of this permissive hypercapnoea the patients were found to have a lower IL-6 level at every point where the two groups were compared. They also spent fewer days undergoing mechanical ventilation and had more favourable FiO_2:PaO_2 ratios. This data has been confirmed by several studies since and is now the standard of care in ALI/ARDS. (5)

While a complete discussion of ventilation in the ARDS patient is well outside the scope of this paper, it is important to understand the genesis of low tidal volume ventilation. So great was the improvement in mortality stemming from these recommendations, that the concept of low volume ventilation was rapidly transferred to non-ALI/ARDS patients, often without good clinical evidence. (118)

In 2010 a randomised controlled trial compared traditional ventilation (10ml/kg pbw) to low tidal volume ventilation (6ml/kg pbw) in mechanically ventilated patients without acute lung injury. (119) The study was designed with the primary end point of cytokine levels in bronchoalveolar lavage and plasma and a secondary end point of the development of ALI. Similar to the 2000 ARDSnet trial, the 2010 trial was suspended early after the second interim analysis showed significantly higher rate of conversion to ALI in the non-intervention (traditional) group. The authors showed that, even in the absence of diagnosable ALI, the lung injury scores (LIS) were higher in the traditional group. Not only were the LIS lower in the interventional group, they decreased overall from baseline. Baseline plasma and BAL cytokine levels were comparable in both groups. In patients not developing ALI, the plasma IL-6 levels declined more rapidly in the interventional group. Predictably, plasma IL-6 increased in all patients developing ALI regardless of the mode of ventilation. No significant difference was found in oxygenation, PaO_2, or PaO_2:FiO_2 ratio. The authors calculate an odds ratio of 5.1 for developing ALI at a tidal volume of 10ml/kg, and an odds ratio of 1.3 for each ml/kg above 6ml/kg. Statistical analysis of this data showed traditional ventilation to be an independent risk factor for the development or ALI in mechanically ventilated patients. This study may be somewhat underpowered as ARDSnet guidelines had already been adopted at the time of study, requiring a switch to the ARDSnet low tidal volume protocol if ALI was identified.

A 2012 meta-analysis examined 20 studies investigating the use of low Vt in patients without ALI/ARDS. (118) It was found that not only was mortality lowered in the low Vt group, but so was the development of lung injury. Though they were unable to demonstrate a significant difference in either

number of ventilator days or number of ICU days, they did show that low Vt decreased the total number in-hospital days. The analysis also points to significantly lower numbers when considering VAP, atelectasis, and plateau pressure. The authors conclude that higher (previously traditional) tidal volumes promote VILI and that the use of low Vt is associated with better outcomes.

A recently published translational review found that low Vt ventilation in patients with identifiable pulmonary insult resulted in both decreased airway pressures and strain. (120) The study was also able to identify several studied specific types of damage to the lungs associated with mechanical ventilation. It was found that in addition to lowering the incidence of ALI, the overall rates of inflammation, pulmonary oedema, and capillary leakage were all decreased. In contrast to the above meta-analysis from 2012, this study found a shorter duration of ventilation was associated with low Vt. Lower rates of ALI/ARDS, lower mortality, and lower rates of VAP and other pulmonary infections were in concordance with previous studies.

Though the 2012 meta-analysis included studies examining surgical patients, a 2006 study is worth mentioning specifically. This study concluded that the use of more traditional tidal volumes was associated with a significantly higher risk of post-operative pulmonary failure after only a few hours of ventilation. (121) Fifty per cent of the patients developing post-operative respiratory failure met the diagnostic criteria for ALI. The authors calculated an odds ratio of 1.56 per ml/kg above 6ml/kg Vt. The study also associated aggressive fluid management with post-operative respiratory failure.

Low tidal volume ventilation is the current standard of care for ALI/ARDS patients requiring ventilator support. In many institutions, this mode of care is extended to those without ALI/ARDS and the currently available data supports this. No study reviewed during the writing of this paper demonstrated a negative outcome as a result of low Vt ventilation. All studies demonstrated a decrease in the number of ALI cases associated with mechanical ventilation regardless of the clinical setting. Surgical studies included in the meta-

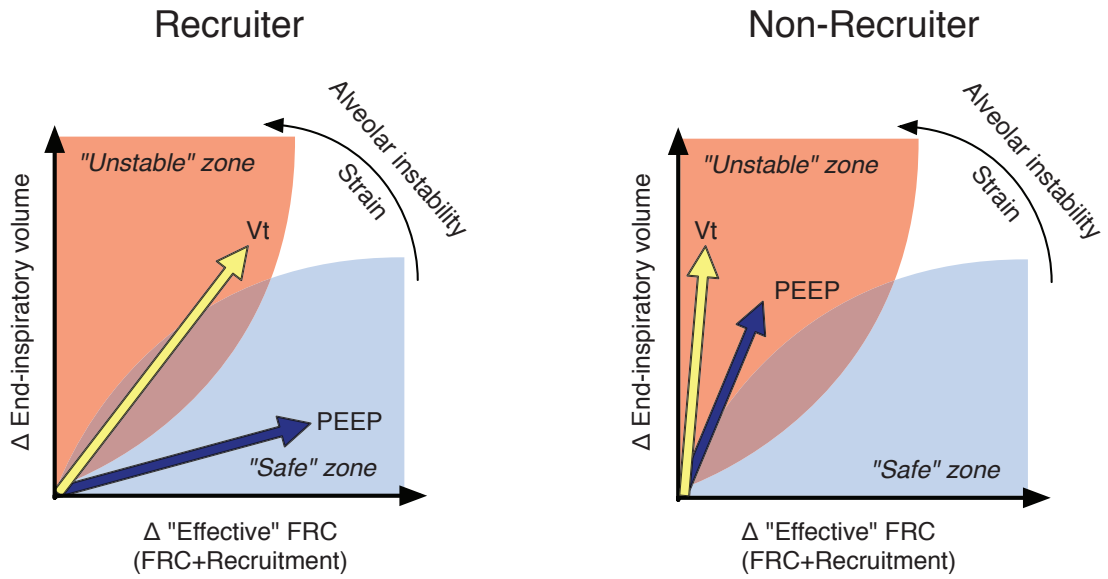
analysis showed a decrease in the rate of post-operative pulmonary failure. In all studies in which it was considered, the PaO_2 was maintained with Low Vt, even in the face of permissive hypercapnoea, which had no statistically significant impact. Considering the available data, it appears that low tidal volume ventilation should now reflect the standard of care in patients requiring mechanical ventilation.

Positive End Expiratory Pressure (PEEP)

As previously discussed, atelectasis occurs in the majority of intubated patients with or without prior lung injury. Atelectrauma occurs through a variety of mechanisms when the alveoli are allowed to repeatedly inflate and collapse resulting in localised inflammation and the release of inflammatory mediators. Such a scenario may subsequently promote systemic inflammation and increases the risk of VILI.

Positive end expiratory pressure prevents the alveolar pressure from reaching zero (atmospheric pressure), and is used as an instrument of stabilisation, preventing recruitment/derecruitment. (1, 122) This is explained by the fact that alveolar derecruitment seems a function of lower plateau pressures rather than low Vt. (123) Halter et al. (122) used diverse ventilation strategies in animal models with alveolar dysfunction and established that higher levels of PEEP effectively prevented alveolar collapse even in the presence of low tidal volumes. During evaluation they found that lower levels of PEEP were associated with an increase in neutrophil infiltration, intra-alveolar oedema, and septal thickening. The same authors also maintain that they were able to maintain a constant number of open alveoli throughout the high PEEP protocol, whilst lower PEEP resulted in progressive atelectasis. This was seen during the experiment as increasing mean airway pressures and was confirmed histologically afterwards. In humans, the use of PEEP with low tidal volumes is associated with a decrease in the frequency of post-operative pulmonary complications. (124, 125)

Figure 7



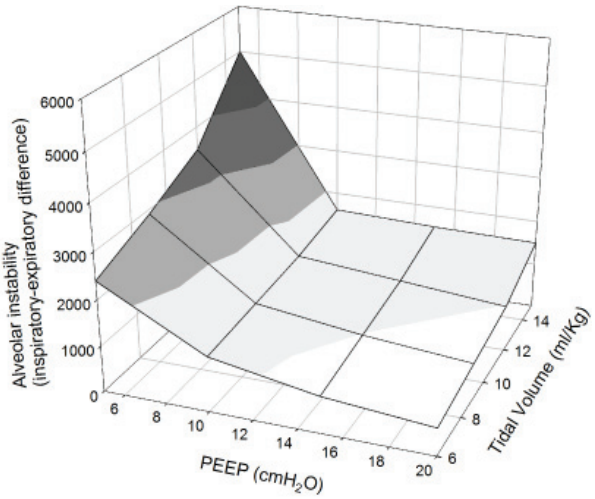
Reproduced with permission from BioMed Central.
Effects of recruitment in alveolar stability.
Alveolar stability can be achieved by the equilibrium between end-inspiratory and end- expiratory volumes. This stability allows definition of a hypothetical safe zone (blue area). Because strain can be viewed as the ratio between these volumes, this zone corresponds to normal or lower strain values. On the contrary, excessive end-inspiratory deformation in lungs with a low resting volume leads to alveolar instability (red area). The arrows represent how the tidal volume (Vt) and positive end-expiratory pressure (PEEP) modify the end-inspiratory/end-expiratory ratio. In recruitable lungs, PEEP induces an increase in end-expiratory lung volume that allows ventilation to stay in the safe zone, and strain decreases. In the absence of recruitment, however, both the Vt and PEEP lead to a predominant increase in end- inspiratory volume, therefore increasing strain. FRC, functional residual capacity.

The use of PEEP, especially higher levels of PEEP in the setting of lung injury, appears to have more impact in the prevention of VILI than the use of low tidal volume ventilation. (122) Predictably it appears that the effect of PEEP on mortality is not uniform. A recent Cochrane review (125) failed to demonstrate a decrease in the overall mortality of patients after the use of PEEP despite an obvious decrease in the rate of post-operative pulmonary complications. In contrast to this, another group of researchers concluded that PEEP brought about a 5% decrease in mortality in patients with poor paO_2:FiO_2 ratios. (126)

Prior to employing PEEP, one must be aware that it does have potential haemodynamic consequences. PEEP can, depending on cardiac function, either increase or decrease cardiac output through elevation of intrathoracic pressures. (41) An increase in intrathoracic pressure typically reduces venous

return and consequently right ventricular preload. A second potential consequence of PEEP is the formation of micro ruptures or blebs, though this is usually only seen at high levels of PEEP. (5) Notwithstanding these two caveats, this author is unaware of any study concluding that appropriate levels of PEEP, even in routine use, contributes to poorer outcomes. Considering the potential benefits of decreased atelectasis, improved V:Q ratios, better oxygenation, and decreased rates of VAPthe routine use of PEEP seems appropriate. More so in the absence of significant contradictory evidence. Outside of routine patient care, there is excellent evidence to support its use in at-risk patients as well as those already presenting difficulties with ventilation.

Figure 8



Reproduced with permission from BioMed Central. Influence of ventilatory settings in alveolar stability. Differences between end-expiratory and end-inspiratory alveolar size increase with tidal volume and decrease with positive end-expiratory pressure (PEEP) (measured in an experimental model of lung injury). Note the synergistic relationship between these two parameters, and that PEEP may decrease the change in size in spite of high tidal volumes.

Considering the potential benefits of decreased atelectasis, improved V:Q ratios, better oxygenation, and decreased rates of VAP in the absence of significant contradictory evidence its routine use of PEEP seems appropriate. Outside of routine patient care there is excellent evidence to support its use in at-risk patients, as well as those already presenting difficulties with ventilation.

Recruitment Manoeuvres

As discussed elsewhere in this paper, lung recruitment manoeuvres form part of the open-lung concept and are used in an attempt to ventilate atelectic areas of the lung so they become available for gas-exchange. Generally, this involves temporary increases in peak inspiratory pressure, an increase in PEEP, inspiratory hold, or a combination of the above, with a subsequent return to open-lung ventilation. (3)

As explained above, PEEP plays a central role in open lung ventilation. Unfortunately, little data exists on exactly how much PEEP should be employed in the clinical setting. Using data available from experimental trials, most authors advocate a starting PEEP of $5cmH_20$. This likely represents either an under- or over-pressure in many patients. Compounding this problem is the fact that few, if any, authors explain what to do after "starting". Recently explored is the concept of individualising PEEP, however this requires more information that is routinely attained at the bedside. Optimal PEEP would be a post-recruitment PEEP level that prevents alveolar collapse while minimising overdistension and promoting maximal arterial oxygen tension and compliance with minimal dead space. (127)

In order to accomplish this, it is necessary that one know that opening and closing pressures of the lungs, or the upper and lower inflection points. Evidence has shown that when the pressure in the lungs stays between these two points the amount of biotruama is reduced. (3) A recent study demonstrated that volumetric capnography and pulse oximetry after titration of $Fi0_2$ are able to serve as accurate real time indicators of opening and closing pressures for the purpose of PEEP individualisation. (128) The authors found a lower prevalence of atelectasis following recruitment in patients whose PEEP had been titrated versus those with standardised PEEP.

In patients undergoing surgery, individualised PEEP was shown to significantly better lung mechanics, oxygenation, and atelectasis. (129) The study demonstrated that alveolar recruitment manoeuvres effectively

increased static compliance, but that this was only maintained using tailored PEEP. This suggests that standardised PEEP may often be set too low to maintain an open lung and prevent recruitment/derecruitment injury. These results are in concordance with Slinger et al who showed that the open lung benefits gained via recruitment were better maintained using titrated PEEP. (130) Likewise, in an animal model, Silva et al demonstrated that the stepwise application of recruitment manoeuvres produced similar results with less biotruama. (131) Alternatively, forced expiratory technique (FOT) has been shown to accurately determine lung tissue elastance. Though requiring significantly more study Zinnan et al demonstrated that FOT could be used to guide ventilator settings in order to minimise recruitment/derecruitment in animals. (132) A direct measure of atelectasis, or derecruitment, is ultrasound. Ultrasound has been successfully used to visualise derecruitment of alveoli during SBTs. (133) These same authors postulate that it could be used to guide ventilator and PEEP settings.

A fairly well documented, but not often used, recruitment method is prone positioning. Prone positioning is thought to be effective through several mechanisms including: an increase in end-expiratory lung volume, better ventilation perfusion matching via removal of lower lobe gravity dependence, lessening the mass-effect of the heart, and improving regional ventilation. (5) These effects combine to improve lung homogeneity. One study showed that 70% of hypoxic patients with ARDS had improved oxygenation once prone. (134) The PROSEVA trial established a sixteen per cent decrease in absolute, and a fifty per cent relative reduction in mortality in ARDS patients when positioned prone as compared to standard. (135) A recent review of two meta-analyses found that prone positioning was associated with improved oxygenation and survival in ALI/ARDS patients. (136) It went on to suggest that prone positioning in hypoxic non-ALI/ARDS patients may be of benefit. It is important to note that prone positioning in the absence of PEEP only improves the ratio of aerated tissue to non-aerated tissue. (137) When combined with PEEP, however, it acts synergistically, significantly improving compliance and gas exchange while decreasing recruitment/derecruitment

injury. This suggests that while prone positioning is an effective recruitment strategy, it requires recruitment maintenance in a manner similar to others.

Good data exists demonstrating the usefulness of prone positioning as a recruitment manoeuvre in both animal models and ALI/ARDS patients. Similar evidence gained from clinical trials harkens improved outcomes when used in combination with PEEP. Little data exists however outside of the ALI/ARDS setting, though a review did suggest that it may be useful. It is important to note that no study demonstrated negative outcomes or complications associated with prone positioning. As such prone positioning may be appropriate in the hypoxic, difficult to ventilate patient with or without ALI/ARDS. Certainly this requires further study.

Ventilator-Associated Pneumonia Bundles

Table 1 shows the CDC recommended guidelines for the prevention of VAP. Several studies have attempted to validate or implement these recommendations – alone or in combination with other strategies – in real-world ICUs with mixed success.

Staff education regarding the pathogenesis, impact, and prevention of VAP is an important first step towards reduction of incidence. Salahuddin et al. (27) established a VAP education programme to reinforce the CDC guidelines and the rational behind them. In doing so they reduced the incidence of VAP in the study ICU by 51%, reaching 6.5 ± 1.5 cases per 1000 ventilator-case days. Jansson et al. (26) conducted a systematic review of 8 previous studies and found that on-going educational programmes directed towards the reinforcement of staff knowledge had a significant impact on VAP rates. Most studies were able to demonstrate a reduction in VAP rates of approximately fifty per cent. There was also an overall decrease in ICU stay and cost. Some, though not all, were further able to express an improvement in clinical outcomes.

As the most probable route of entry for causative pathogens is oropharyngeal microaspiration, the recommendation for regular oral care seems logical. Not all studies have been able to demonstrate a clear benefit however, perhaps because oral care is multifactorial. One conundrum is the decision to use antiseptic or antibiotic agents. Antibiotics may be effective but could also promote increased antibiotic resistance; antiseptics act via multiple receptor sites theoretically reducing the risk of resistance. (138) A systematic review of sixteen trials (139) concluded that both antiseptic and non-iseganan topical antibiotics significantly reduced the risk of VAP. Iseganan-containing antibiotics demonstrated a slight, but not statistically significant increase in VAP rates. Paradoxically, they were unable to demonstrate a significant reduction in all-cause mortality, duration of ventilation, or duration in the ICU even in the presence of reduced VAP numbers. The study did not unfortunately exam the difference in VAP-associated mortality.

Enteral support in critically ill patients plays several roles and is associated with better outcomes in critically ill patients. (140, 141) In this context, however, it can both increase and decrease the incidence of VAP, depending mostly upon the time of implementation. (142) In the critical care environment enteral nutrition typically results in a caloric and nitrogen deficit. This deficit is often overcome using parenteral nutrition, however this does not improve clinical outcomes. (143, 144) One study (142) noted that patients receiving aggressive enteral nutritional support during the first week of ICU admission had higher rates of VAP than those receiving less aggressive enteral nutrition. The authors suggest that one, or a combination of nasogastric tubes, impaired gastric motility, inhibited lower oesophageal sphincter function may contribute to this phenomena. In spite this, and in accordance with the studies examining VAP mortality above, they found no increase in death due to VAP, nor prolongation of ICU stays. They did identify increased rates of septicaemia, VAP and death in patients receiving parenteral nutrition. Finally, no negative outcomes were attributed to lower intake in the patients receiving fewer calories than indicated during the first week of admission. This would seem to suggest that enteral nutrition, even at less than ideal levels required

to prevent the above identified complications, is superior to parenteral nutrition in terms of VAP rates and outcomes in general.

Lastly, a three phase study examines the feasibility and efficacy of the CDC "VAP bundle" alone, combined with regular oral chlorhexadine decontamination, and then in combination with chlorhexadine and continuous aspiration of subglottic secretions (CASS). (145) The authors noted a significant increase in VAP rates when the CDC recommended VAP bundle was implemented alone. Phase 2 added regular oral decontamination with chlorhexadine 0.12% to the VAP bundle and showed a decrease in VAP rates below the starting point. The phase 2 VAP rate ranged from 1.3 – 2.0 case per 1000 ventilator-case days, a statistical rate of almost zero. Not surprisingly then, the addition of CASS in phase three did not significantly affect the VAP rate. CASS has been shown however to positively affect VAP rates in non-"zero VAP" departments (146) and may be beneficial in certain circumstances and institutions.

VAP represents a significant mortality, resource, and cost burden in ICU patients. Prevention is paramount and good evidence exists to supporting strategies to that end. In addition to the CDC VAP bundle data supports ongoing staff education, oral decontamination with or without CASS, and early non-aggressive enteral nutritional support in the ICU.

Conclusion

Though mechanical ventilation only attained wide acceptance in the 1960s, it has rapidly become one of the most widely employed interventions in critical care units the world over. It is now employed in the treatment of almost half of ICU patients. Crucially, since its inception, it has undergone almost constant revision and research. Mechanical ventilation is not in-and-of itself a treatment, rather it allows the patient to be maintained in a state that allows healing and treatment to take place. By far the most common pathologies in which it is employed are sepsis, ALI/ARDS, trauma, and surgical patients. Additionally, it is often employed in specialty settings such as cardiac

intensive care units, and in the out-of-hospital environment. The advent and development of mechanical respiratory support means that these patients can often remain stable enough to undergo treatment of the underlying pathology.

Recently however a growing body of research shows that mechanical ventilation has the ability to cause pathologies as well. In some cases, such as VILI/VALI, the produced disease is as bad, or worse, than the one being treated. Additionally, mechanical ventilation's required adjuvants, such as sedatives, analgesics, positioning, and alternative forms of nutrition all have the potential to contribute in some way to new or worsening disease.

It should be clear that mechanical ventilation has many potential and diverse pitfalls, especially when considered in light of the fact that it is often the sickest and most complex patients who require it. As such, it seems unreasonable to approach all ventilated patients in the same fashion, which until recently is essentially what clinical practice did. Likewise, when one considers the complexity of mechanical ventilation and its complications it should be obvious that anything but multimodal prevention strategies are doomed to failure. It is useless for instance to have a "zero-VAP" ICU, something that is possible, but experience high rates of lung injury because PEEP is not used properly.

Unfortunately it is almost certain that no one multi-modal strategy will be effective, however. What should be universal are risk-stratification and the anticipation of complications. All patients should undergo thorough preoperative assessment, and should have their fluid balance carefully monitored. All ventilated ICU patients should be subject to locally tailored VAP prevention bundles. Low-volume ventilation and PEEP now both have enough evidence behind them that they should be considered standard practice. In order for these to be truly effective, however, they require individual tailoring, something not currently done in most places. Additionally, alternative interventions must be sought for the "difficult to ventilate" patient. This may be simply a repositioning of the patient, or a more in-depth re-evaluation of the current treatment using alternative means.

Mechanical ventilation is a powerful tool, with both negative and positive effects. It is clear that further research is required to clarify how a ventilator programme can be tailored to each individual patient.

Bibliography

1. Cairo JM, Pilbeam SP. Mechanical ventilation : physiological and clinical applications. 5th ed. St. Louis, Mo.: Elsevier; 2012. xvi, 591 p. p.
2. Hall JE, Guyton AC. Guyton and Hall textbook of medical physiology. 12th ed. Philadelphia, Pa.: Saunders/Elsevier; 2011. xix, 1091 p. p.
3. Gabrielli A, Layon AJ, Yu M, Civetta JM, Taylor RW, Kirby RR. Civetta, Taylor, & Kirby's critical care. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. xli, 2765 p. p.
4. Bongard FS, Sue DY, Vintch JRE. Current diagnosis & treatment : critical care. 3rd ed. New York: McGraw-Hill Medical; 2008. xi, 878 p. p.
5. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. The New England journal of medicine. 2013 Nov 28;369(22):2126-36. PubMed PMID: 24283226.
6. Marini JJ. Mechanical ventilation: past lessons and the near future. Critical care. 2013;17 Suppl 1:S1. PubMed PMID: 23514222. Pubmed Central PMCID: 3603465.
7. Lassen HC. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. Lancet. 1953 Jan 3;1(6749):37-41. PubMed PMID: 13011944.
8. Lassen HC. [The poliomyelitis epidemic in Copenhagen in the fall of 1952, with special consideration of the treatment of acute respiratory insufficiency; preliminary report]. Nordisk medicin. 1953 Jan 2;49(1):2-9. PubMed PMID: 13054931. Poliomyelitisepidemien i K|obenhavn efteraret 1952 med saerligt henblik pa behandlingen af acut respirationsinsufficiens; en forel|obig meddelelse.
9. Carson SS, Cox CE, Holmes GM, Howard A, Carey TS. The changing epidemiology of mechanical ventilation: a population-based study. Journal of intensive care medicine. 2006 May-Jun;21(3):173-82. PubMed PMID: 16672639.
10. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. Critical care medicine. 2010 Oct;38(10):1947-53. PubMed PMID: 20639743.
11. Levy MM, Miyasaki A, Langston D. Work of breathing as a weaning parameter in mechanically ventilated patients. Chest. 1995 Oct;108(4):1018-20. PubMed PMID: 7555112.
12. Duke GJ. Cardiovascular effects of mechanical ventilation. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 1999 Dec;1(4):388-99. PubMed PMID: 16599883.
13. Shekerdemian L, Bohn D. Cardiovascular effects of mechanical ventilation. Archives of disease in childhood. 1999 May;80(5):475-80. PubMed PMID: 10208959. Pubmed Central PMCID: 1717913.
14. Yehia K, Emad I, Ahmed S, Mohamed I, Amany ELB. Assessment of risk factors responsible for difficult weaning from mechanical ventilation in adults. Egyptian Journal of Chest Diseases and Tuberculosis. 2012;61.
15. Moodie L, Reeve J, Elkins M. Inspiratory muscle training increases inspiratory muscle strength in patients weaning from mechanical ventilation: a systematic review. Journal of physiotherapy. 2011;57(4):213-21.

16. Vassilakopoulos T, Roussos C, Zakynthinos S. Weaning from mechanical ventilation. Journal of critical care. 1999.
17. Unroe M, Kahn JM, Carson SS, Govert JA, Martinu T, Sathy SJ, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. Annals of internal medicine. 2010 Aug 3;153(3):167-75. PubMed PMID: 20679561. Pubmed Central PMCID: 2941154.
18. Prentice CE, Paratz JD, Bersten AD. Differences in the degree of respiratory and peripheral muscle impairment are evident on clinical, electrophysiological and biopsy testing in critically ill adults: a qualitative systematic review. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2010 Jun;12(2):111-20. PubMed PMID: 20513220.
19. Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. American journal of respiratory and critical care medicine. 2004 Feb 1;169(3):336-41. PubMed PMID: 14739134.
20. Huang TT, Deoghare HV, Smith BK, Beaver TM, Baker HV, Mehinto AC, et al. Gene expression changes in the human diaphragm after cardiothoracic surgery. The Journal of thoracic and cardiovascular surgery. 2011 Nov;142(5):1214-22, 22 e1-20. PubMed PMID: 21463877.
21. Grosu HB, Lee YI, Lee J, Eden E, Eikermann M, Rose KM. Diaphragm muscle thinning in patients who are mechanically ventilated. Chest. 2012 Dec;142(6):1455-60. PubMed PMID: 23364680.
22. De Jonghe B, Sharshar T, Lefaucheur J-P, Authier F-J, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA : the journal of the American Medical Association. 2002;288(22):2859-67.
23. Kim WY, Suh HJ, Hong SB, Koh Y, Lim CM. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. Critical care medicine. 2011 Dec;39(12):2627-30. PubMed PMID: 21705883.
24. Ewig S, Bauer T, Torres A. The pulmonary physician in critical care * 4: Nosocomial pneumonia. Thorax. 2002 Apr;57(4):366-71. PubMed PMID: 11923560. Pubmed Central PMCID: 1746297.
25. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest. 2002 Dec;122(6):2115-21. PubMed PMID: 12475855.
26. Jansson M, Kaariainen M, Kyngas H. Effectiveness of educational programmes in preventing ventilator-associated pneumonia: a systematic review. The Journal of hospital infection. 2013 Jul;84(3):206-14. PubMed PMID: 23769315.
27. Salahuddin N, Zafar A, Sukhyani L, Rahim S, Noor MF, Hussain K, et al. Reducing ventilator-associated pneumonia rates through a staff education programme. The Journal of hospital infection. 2004 Jul;57(3):223-7. PubMed PMID: 15236851.
28. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. American journal of respiratory and critical care medicine. 2005 Feb 15;171(4):388-416. PubMed PMID: 15699079.

29. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in combined medical-surgical intensive care units in the United States. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America. 2000 Aug;21(8):510-5. PubMed PMID: 10968716.
30. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. The Lancet infectious diseases. 2013 Aug;13(8):665-71. PubMed PMID: 23622939.
31. Melsen WG, Rovers MM, Koeman M, Bonten MJ. Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. Critical care medicine. 2011 Dec;39(12):2736-42. PubMed PMID: 21765351.
32. Schumacher M, Wangler M, Wolkewitz M, Beyersmann J. Attributable mortality due to nosocomial infections. A simple and useful application of multistate models. Methods of information in medicine. 2007;46(5):595-600. PubMed PMID: 17938785.
33. Nguile-Makao M, Zahar JR, Francais A, Tabah A, Garrouste-Orgeas M, Allaouchiche B, et al. Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. Intensive care medicine. 2010 May;36(5):781-9. PubMed PMID: 20232046.
34. Chastre J, Fagon JY. Ventilator-associated pneumonia. American journal of respiratory and critical care medicine. 2002 Apr 1;165(7):867-903. PubMed PMID: 11934711.
35. Zubairi AB, Zafar A, Salahuddin N, Haque AS, Waheed S, Khan JA. Atypical pathogens causing community-acquired pneumonia in adults. JPMA The Journal of the Pakistan Medical Association. 2012 Jul;62(7):653-6. PubMed PMID: 23866508.
36. Rello J, Diaz E, Rodriguez A. Advances in the management of pneumonia in the intensive care unit: review of current thinking. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2005 Oct;11 Suppl 5:30-8. PubMed PMID: 16138817.
37. Estes RJ, Meduri GU. The pathogenesis of ventilator-associated pneumonia: I. Mechanisms of bacterial transcolonization and airway inoculation. Intensive care medicine. 1995 Apr;21(4):365-83. PubMed PMID: 7650262.
38. Torres A, el-Ebiary M, Gonzalez J, Ferrer M, Puig de la Bellacasa J, Gene A, et al. Gastric and pharyngeal flora in nosocomial pneumonia acquired during mechanical ventilation. The American review of respiratory disease. 1993 Aug;148(2):352-7. PubMed PMID: 8342898.
39. Coffin SE, Klompas M, Classen D, Arias KM, Podgorny K, Anderson DJ, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America. 2008 Oct;29 Suppl 1:S31-40. PubMed PMID: 18840087.

40. Nash G, Blennerhassett JB, Pontoppidan H. Pulmonary lesions associated with oxygen therapy and artifical ventilation. The New England journal of medicine. 1967 Feb 16;276(7):368-74. PubMed PMID: 6017244.
41. Tusman G, Bohm SH, Warner DO, Sprung J. Atelectasis and perioperative pulmonary complications in high-risk patients. Current opinion in anaesthesiology. 2012 Feb;25(1):1-10. PubMed PMID: 22113182.
42. Wakabayashi K, Wilson MR, Tatham KC, O'Dea KP, Takata M. Volutrauma, but not atelectrauma, induces systemic cytokine production by lung-marginated monocytes. Critical care medicine. 2014 Jan;42(1):e49-57. PubMed PMID: 23963135.
43. Halbertsma FJ, Vaneker M, Scheffer GJ, van der Hoeven JG. Cytokines and biotrauma in ventilator-induced lung injury: a critical review of the literature. The Netherlands journal of medicine. 2005 Nov;63(10):382-92. PubMed PMID: 16301759.
44. Bertok S, Wilson MR, Morley PJ, de Wildt R, Bayliffe A, Takata M. Selective inhibition of intra-alveolar p55 TNF receptor attenuates ventilator-induced lung injury. Thorax. 2012 Mar;67(3):244-51. PubMed PMID: 22156959. Pubmed Central PMCID: 3282043.
45. Mascheroni D, Kolobow T, Fumagalli R, Moretti MP, Chen V, Buckhold D. Acute respiratory failure following pharmacologically induced hyperventilation: an experimental animal study. Intensive care medicine. 1988;15(1):8-14. PubMed PMID: 3230208.
46. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. The American review of respiratory disease. 1988 May;137(5):1159-64. PubMed PMID: 3057957.
47. Canet J, Gallart L. Postoperative respiratory failure: pathogenesis, prediction, and prevention. Current opinion in critical care. 2014 Feb;20(1):56-62. PubMed PMID: 24240985.
48. Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology. 2005 Apr;102(4):838-54. PubMed PMID: 15791115.
49. Matte P, Jacquet L, Van Dyck M, Goenen M. Effects of conventional physiotherapy, continuous positive airway pressure and non-invasive ventilatory support with bilevel positive airway pressure after coronary artery bypass grafting. Acta anaesthesiologica Scandinavica. 2000 Jan;44(1):75-81. PubMed PMID: 10669276.
50. Olper L, Cabrini L, Landoni G, Rossodivita A, Nobile L, Monti G, et al. Non-invasive ventilation after cardiac surgery outside the Intensive Care Unit. Minerva anestesiologica. 2011 Jan;77(1):40-5. PubMed PMID: 21150853.
51. Albaiceta GM, Blanch L. Beyond volutrauma in ARDS: the critical role of lung tissue deformation. Critical care. 2011;15(2):304. PubMed PMID: 21489320. Pubmed Central PMCID: 3219320.
52. Carney DE, Bredenberg CE, Schiller HJ, Picone AL, McCann UG, Gatto LA, et al. The mechanism of lung volume change during mechanical ventilation. American journal of respiratory and critical care medicine. 1999 Nov;160(5 Pt 1):1697-702. PubMed PMID: 10556142.
53. Perlman CE, Bhattacharya J. Alveolar expansion imaged by optical sectioning microscopy. Journal of applied physiology. 2007 Sep;103(3):1037-44. PubMed PMID: 17585045.

54. Bilek AM, Dee KC, Gaver DP, 3rd. Mechanisms of surface-tension-induced epithelial cell damage in a model of pulmonary airway reopening. Journal of applied physiology. 2003 Feb;94(2):770-83. PubMed PMID: 12433851.
55. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol. 1970 May;28(5):596-608. PubMed PMID: 5442255.
56. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA : the journal of the American Medical Association. 1999 Jul 7;282(1):54-61. PubMed PMID: 10404912.
57. Vlahakis NE, Hubmayr RD. Cellular stress failure in ventilator-injured lungs. American journal of respiratory and critical care medicine. 2005 Jun 15;171(12):1328-42. PubMed PMID: 15695492. Pubmed Central PMCID: 2718477.
58. Ridge KM, Linz L, Flitney FW, Kuczmarski ER, Chou YH, Omary MB, et al. Keratin 8 phosphorylation by protein kinase C delta regulates shear stress-mediated disassembly of keratin intermediate filaments in alveolar epithelial cells. The Journal of biological chemistry. 2005 Aug 26;280(34):30400-5. PubMed PMID: 15972820.
59. Ledowski T, Paech MJ, Patel B, Schug SA. Bronchial mucus transport velocity in patients receiving propofol and remifentanil versus sevoflurane and remifentanil anesthesia. Anesthesia and analgesia. 2006 May;102(5):1427-30. PubMed PMID: 16632821.
60. Zhang T, Fan Y, Liu K, Wang Y. Effects of different general anaesthetic techniques on immune responses in patients undergoing surgery for tongue cancer. Anaesthesia and intensive care. 2014 Mar;42(2):220-7. PubMed PMID: 24580388.
61. Cahalan MK, Weiskopf RB, Eger EI, 2nd, Yasuda N, Ionescu P, Rampil IJ, et al. Hemodynamic effects of desflurane/nitrous oxide anesthesia in volunteers. Anesthesia and analgesia. 1991 Aug;73(2):157-64. PubMed PMID: 1854030.
62. Browner WS, Li J, Mangano DT. In-hospital and long-term mortality in male veterans following noncardiac surgery. The Study of Perioperative Ischemia Research Group. JAMA : the journal of the American Medical Association. 1992 Jul 8;268(2):228-32. PubMed PMID: 1608142.
63. Moje C, Jackson TJ, McNair P. Adverse events in Victorian admissions for elective surgery. Australian health review : a publication of the Australian Hospital Association. 2006 Aug;30(3):333-43. PubMed PMID: 16879092.
64. Scott IA, Lodge RS, Russell DM. Evidence-based guide to perioperative medicine. Internal medicine journal. 2007 Jun;37(6):389-401. PubMed PMID: 17535383.
65. Haeck PC, Swanson JA, Iverson RE, Lynch DJ, Committee APS. Evidence-based patient safety advisory: patient assessment and prevention of pulmonary side effects in surgery. Part 2. Patient and procedural risk factors. Plastic and reconstructive surgery. 2009 Oct;124(4 Suppl):57S-67S. PubMed PMID: 20827240.

66. Johnson DC, Kaplan LJ. Perioperative pulmonary complications. Current opinion in critical care. 2011 Aug;17(4):362-9. PubMed PMID: 21734490.
67. Warner DO, Warner MA, Barnes RD, Offord KP, Schroeder DR, Gray DT, et al. Perioperative respiratory complications in patients with asthma. Anesthesiology. 1996 Sep;85(3):460-7. PubMed PMID: 8853074.
68. Garcia-Delgado M, Navarrete-Sanchez I, Colmenero M. Preventing and managing perioperative pulmonary complications following cardiac surgery. Current opinion in anaesthesiology. 2014 Apr;27(2):146-52. PubMed PMID: 24514031.
69. Plaud B, Debaene B, Donati F, Marty J. Residual paralysis after emergence from anesthesia. Anesthesiology. 2010 Apr;112(4):1013-22. PubMed PMID: 20234315.
70. Brandt S, Regueira T, Bracht H, Porta F, Djafarzadeh S, Takala J, et al. Effect of fluid resuscitation on mortality and organ function in experimental sepsis models. Critical care. 2009;13(6):R186. PubMed PMID: 19930656. Pubmed Central PMCID: 2811934.
71. Babayan RK. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. The Journal of urology. 2012 Dec;188(6):2243-4. PubMed PMID: 23141233.
72. Hawn MT, Houston TK, Campagna EJ, Graham LA, Singh J, Bishop M, et al. The attributable risk of smoking on surgical complications. Annals of surgery. 2011 Dec;254(6):914-20. PubMed PMID: 21869677.
73. Lee SM, Landry J, Jones PM, Buhrmann O, Morley-Forster P. The effectiveness of a perioperative smoking cessation program: a randomized clinical trial. Anesthesia and analgesia. 2013 Sep;117(3):605-13. PubMed PMID: 23868890.
74. Sorensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. Annals of surgery. 2012 Jun;255(6):1069-79. PubMed PMID: 22566015.
75. Turan A, Mascha EJ, Roberman D, Turner PL, You J, Kurz A, et al. Smoking and perioperative outcomes. Anesthesiology. 2011 Apr;114(4):837-46. PubMed PMID: 21372682.
76. Myles PS, Iacono GA, Hunt JO, Fletcher H, Morris J, McIlroy D, et al. Risk of respiratory complications and wound infection in patients undergoing ambulatory surgery: smokers versus nonsmokers. Anesthesiology. 2002 Oct;97(4):842-7. PubMed PMID: 12357149.
77. Sorensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. Archives of surgery. 2012 Apr;147(4):373-83. PubMed PMID: 22508785.
78. Sorensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. Annals of surgery. 2003 Jul;238(1):1-5. PubMed PMID: 12832959. Pubmed Central PMCID: 1422652.
79. Thomsen T, Villebro N, Moller AM. Interventions for preoperative smoking cessation. The Cochrane database of systematic reviews. 2010 (7):CD002294. PubMed PMID: 20614429.

80. Sorensen LT, Jorgensen T. Short-term pre-operative smoking cessation intervention does not affect postoperative complications in colorectal surgery: a randomized clinical trial. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2003 Jul;5(4):347-52. PubMed PMID: 12814414.
81. Moller AM, Villebro N, Pedersen T, Tonnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. Lancet. 2002 Jan 12;359(9301):114-7. PubMed PMID: 11809253.
82. Myles PS, Leslie K, Angliss M, Mezzavia P, Lee L. Effectiveness of bupropion as an aid to stopping smoking before elective surgery: a randomised controlled trial. Anaesthesia. 2004 Nov;59(11):1053-8. PubMed PMID: 15479310.
83. Warner DO. Perioperative abstinence from cigarettes: physiologic and clinical consequences. Anesthesiology. 2006 Feb;104(2):356-67. PubMed PMID: 16436857.
84. Rietbrock N, Kunkel S, Worner W, Eyer P. Oxygen-dissociation kinetics in the blood of smokers and non-smokers: interaction between oxygen and carbon monoxide at the hemoglobin molecule. Naunyn-Schmiedeberg's archives of pharmacology. 1992 Jan;345(1):123-8. PubMed PMID: 1538790.
85. Klein LW, Ambrose J, Pichard A, Holt J, Gorlin R, Teichholz LE. Acute coronary hemodynamic response to cigarette smoking in patients with coronary artery disease. Journal of the American College of Cardiology. 1984 Apr;3(4):879-86. PubMed PMID: 6707354.
86. Narkiewicz K, van de Borne PJ, Hausberg M, Cooley RL, Winniford MD, Davison DE, et al. Cigarette smoking increases sympathetic outflow in humans. Circulation. 1998 Aug 11;98(6):528-34. PubMed PMID: 9714109.
87. Saetta M, Turato G, Baraldo S, Zanin A, Braccioni F, Mapp CE, et al. Goblet cell hyperplasia and epithelial inflammation in peripheral airways of smokers with both symptoms of chronic bronchitis and chronic airflow limitation. American journal of respiratory and critical care medicine. 2000 Mar;161(3 Pt 1):1016-21. PubMed PMID: 10712357.
88. Maestrelli P, Saetta M, Mapp CE, Fabbri LM. Remodeling in response to infection and injury. Airway inflammation and hypersecretion of mucus in smoking subjects with chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2001 Nov 15;164(10 Pt 2):S76-80. PubMed PMID: 11734472.
89. Di Stefano A, Capelli A, Lusuardi M, Balbo P, Vecchio C, Maestrelli P, et al. Severity of airflow limitation is associated with severity of airway inflammation in smokers. American journal of respiratory and critical care medicine. 1998 Oct;158(4):1277-85. PubMed PMID: 9769292.
90. Lee LY, Hong JL. Involvement of prostanoids in cigarette smoking-induced pathophysiological effects in the lung. Prostaglandins, leukotrienes, and essential fatty acids. 1999 Sep;61(3):145-55. PubMed PMID: 10582654.
91. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. Bmj. 2000 Dec 16;321(7275):1493. PubMed PMID: 11118174. Pubmed Central PMCID: 27550.

92. von Ungern-Sternberg BS, Regli A, Reber A, Schneider MC. Effect of obesity and thoracic epidural analgesia on perioperative spirometry. British journal of anaesthesia. 2005 Jan;94(1):121-7. PubMed PMID: 15486001.
93. van Lier F, van der Geest PJ, Hoeks SE, van Gestel YR, Hol JW, Sin DD, et al. Epidural analgesia is associated with improved health outcomes of surgical patients with chronic obstructive pulmonary disease. Anesthesiology. 2011 Aug;115(2):315-21. PubMed PMID: 21796055.
94. Wijeysundera DN, Beattie WS, Austin PC, Hux JE, Laupacis A. Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. Lancet. 2008 Aug 16;372(9638):562-9. PubMed PMID: 18692893.
95. Arozullah AM, Khuri SF, Henderson WG, Daley J, Participants in the National Veterans Affairs Surgical Quality Improvement P. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Annals of internal medicine. 2001 Nov 20;135(10):847-57. PubMed PMID: 11712875.
96. Sasaki N, Meyer MJ, Eikermann M. Postoperative respiratory muscle dysfunction: pathophysiology and preventive strategies. Anesthesiology. 2013 Apr;118(4):961-78. PubMed PMID: 23429163.
97. Eikermann M, Vogt FM, Herbstreit F, Vahid-Dastgerdi M, Zenge MO, Ochterbeck C, et al. The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. American journal of respiratory and critical care medicine. 2007 Jan 1;175(1):9-15. PubMed PMID: 17023729.
98. Condessa R, Brauner J, Saul A, Baptista… M. Inspiratory muscle training did not accelerate weaning from mechanical ventilation but did improve tidal volume and maximal respiratory pressures: a randomised trial. Journal of …. 2013.
99. Cader SA, de Souza Vale RG, Zamora VE, Costa CH, Dantas EH. Extubation process in bed-ridden elderly intensive care patients receiving inspiratory muscle training: a randomized clinical trial. Clinical interventions in aging. 2012;7:437-43. PubMed PMID: 23118533. Pubmed Central PMCID: 3484512.
100. Caruso P, Denari SD, Ruiz SA, Bernal KG, Manfrin GM, Friedrich C, et al. Inspiratory muscle training is ineffective in mechanically ventilated critically ill patients. Clinics. 2005 Dec;60(6):479-84. PubMed PMID: 16358138.
101. Fonseca Mde A, Cader SA, Dantas EH, Bacelar SC, Silva EB, Leal SM. [Respiratory muscle training programs: impact on the functional autonomy of the elderly]. Revista da Associacao Medica Brasileira. 2010 Nov-Dec;56(6):642-8. PubMed PMID: 21271128. Programas de treinamento muscular respiratorio: impacto na autonomia funcional de idosos.
102. Augustes R, Ho KM. Meta-analysis of randomised controlled trials on daily sedation interruption for critically ill adult patients. Anaesthesia and intensive care. 2011 May;39(3):401-9. PubMed PMID: 21675059.
103. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Critical care medicine. 2013 Jan;41(1):263-306. PubMed PMID: 23269131.
104. Hughes CG, Girard TD, Pandharipande PP. Daily sedation interruption versus targeted light sedation strategies in ICU patients. Critical care medicine. 2013 Sep;41(9 Suppl 1):S39-45. PubMed PMID: 23989094.

105. Mehta S, Burry L, Martinez-Motta JC, Stewart TE, Hallett D, McDonald E, et al. A randomized trial of daily awakening in critically ill patients managed with a sedation protocol: a pilot trial. Critical care medicine. 2008 Jul;36(7):2092-9. PubMed PMID: 18552687.
106. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. American journal of respiratory and critical care medicine. 2012 Oct 15;186(8):724-31. PubMed PMID: 22859526.
107. Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. Critical care medicine. 2013 Sep;41(9 Suppl 1):S30-8. PubMed PMID: 23989093.
108. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010 Feb 6;375(9713):475-80. PubMed PMID: 20116842.
109. Payen JF, Chanques G, Mantz J, Hercule C, Auriant I, Leguillou JL, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. Anesthesiology. 2007 Apr;106(4):687-95; quiz 891-2. PubMed PMID: 17413906.
110. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008 Jan 12;371(9607):126-34. PubMed PMID: 18191684.
111. Bennett-Guerrero E, Panah MH, Barclay GR, Bodian CA, Winfree WJ, Andres LA, et al. Decreased endotoxin immunity is associated with greater mortality and/or prolonged hospitalization after surgery. Anesthesiology. 2001 Jun;94(6):992-8. PubMed PMID: 11465625.
112. Braga M, Gianotti L, Vignali A, Carlo V. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. Surgery. 2002;132(5):805-14.
113. Zheng Y, Li F, Qi B, Luo B, Sun H, Liu S, et al. Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. Asia Pacific journal of clinical nutrition. 2007;16 Suppl 1:253-7.
114. Gianotti L, Braga M, Fortis C, Soldini L, Vignali A, Colombo S, et al. A prospective, randomized clinical trial on perioperative feeding with an arginine-, omega-3 fatty acid-, and RNA-enriched enteral diet: effect on host response and nutritional status. JPEN Journal of parenteral and enteral nutrition. 1999 Nov-Dec;23(6):314-20. PubMed PMID: 10574478.
115. Giger U, Buchler M, Farhadi J, Berger D, Husler J, Schneider H, et al. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. Annals of surgical oncology. 2007 Oct;14(10):2798-806. PubMed PMID: 17632760.

116. Cerantola Y, Hübner M, Grass F, Demartines N, Schäfer M. Immunonutrition in gastrointestinal surgery. The British journal of surgery. 2011;98(1):37-48.
117. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. New England Journal of Medicine. 2000;342(18):1301-8. PubMed PMID: 10793162.
118. Serpa Neto A, Cardoso S, Manetta J, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: A meta-analysis. JAMA : the journal of the American Medical Association. 2012;308(16):1651-9.
119. Determann RM, Royakkers A, Wolthuis EK, Vlaar AP, Choi G, Paulus F, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Critical care. 2010;14(1):R1. PubMed PMID: 20055989. Pubmed Central PMCID: 2875503.
120. Serpa Neto A, Nagtzaam L, Schultz MJ. Ventilation with lower tidal volumes for critically ill patients without the acute respiratory distress syndrome: a systematic translational review and meta-analysis. Current opinion in critical care. 2014;20(1):25-32 10.1097/MCC.0000000000000044.
121. Fernández-Pérez ER, Keegan MT, Brown DR, Hubmayr RD, Gajic O. Intraoperative Tidal Volume as a Risk Factor for Respiratory Failure after Pneumonectomy. Anesthesiology. 2006;105(1):14-8.
122. Halter JM, Steinberg JM, Gatto LA, DiRocco JD, Pavone LA, Schiller HJ, et al. Effect of positive end-expiratory pressure and tidal volume on lung injury induced by alveolar instability. Critical care. 2007;11(1):R20. PubMed PMID: 17302983. Pubmed Central PMCID: 2151879.
123. Richard JC, Brochard L, Vandelet P, Breton L, Maggiore SM, Jonson B, et al. Respective effects of end-expiratory and end-inspiratory pressures on alveolar recruitment in acute lung injury. Critical care medicine. 2003 Jan;31(1):89-92. PubMed PMID: 12544999.
124. Licker M, Diaper J, Villiger Y, Spiliopoulos A, Licker V, Robert J, et al. Impact of intraoperative lung-protective interventions in patients undergoing lung cancer surgery. Critical care. 2009;13(2):R41. PubMed PMID: 19317902. Pubmed Central PMCID: 2689485.
125. Imberger G, McIlroy D, Pace NL, Wetterslev J, Brok J, Moller AM. Positive end-expiratory pressure (PEEP) during anaesthesia for the prevention of mortality and postoperative pulmonary complications. The Cochrane database of systematic reviews. 2010 (9):CD007922. PubMed PMID: 20824871.
126. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA : the journal of the American Medical Association. 2010 Mar 3;303(9):865-73. PubMed PMID: 20197533.
127. Maisch S, Reissmann H, Fuellekrug B, Weismann D, Rutkowski T, Tusman G, et al. Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized

patients. Anesthesia and analgesia. 2008 Jan;106(1):175-81, table of contents. PubMed PMID: 18165575.
128. Tusman G, Groisman I, Fiolo FE, Scandurra A, Arca JM, Krumrick G, et al. Noninvasive monitoring of lung recruitment maneuvers in morbidly obese patients: the role of pulse oximetry and volumetric capnography. Anesthesia and analgesia. 2014 Jan;118(1):137-44. PubMed PMID: 24356163.
129. Ferrando C, Mugarra A, Gutierrez A, Carbonell JA, Garcia M, Soro M, et al. Setting individualized positive end-expiratory pressure level with a positive end-expiratory pressure decrement trial after a recruitment maneuver improves oxygenation and lung mechanics during one-lung ventilation. Anesthesia and analgesia. 2014 Mar;118(3):657-65. PubMed PMID: 24557111.
130. Slinger PD, Kruger M, McRae K, Winton T. Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung ventilation. Anesthesiology. 2001 Nov;95(5):1096-102. PubMed PMID: 11684977.
131. Silva PL, Moraes L, Santos RS, Samary C, Ramos MB, Santos CL, et al. Recruitment maneuvers modulate epithelial and endothelial cell response according to acute lung injury etiology. Critical care medicine. 2013 Oct;41(10):e256-65. PubMed PMID: 23887231.
132. Zannin E, Dellaca RL, Kostic P, Pompilio PP, Larsson A, Pedotti A, et al. Optimizing positive end-expiratory pressure by oscillatory mechanics minimizes tidal recruitment and distension: an experimental study in a lavage model of lung injury. Critical care. 2012 Nov 7;16(6):R217. PubMed PMID: 23134702. Pubmed Central PMCID: 3672594.
133. Soummer A, Perbet S, Brisson H, Arbelot C, Constantin JM, Lu Q, et al. Ultrasound assessment of lung aeration loss during a successful weaning trial predicts postextubation distress*. Critical care medicine. 2012 Jul;40(7):2064-72. PubMed PMID: 22584759.
134. Piedalue F, Albert RK. Prone positioning in acute respiratory distress syndrome. Respiratory care clinics of North America. 2003 Dec;9(4):495-509. PubMed PMID: 14984068.
135. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. The New England journal of medicine. 2013 Jun 6;368(23):2159-68. PubMed PMID: 23688302.
136. Guerin C. Prone position. Current opinion in critical care. 2014 Feb;20(1):92-7. PubMed PMID: 24366167.
137. Cornejo RA, Diaz JC, Tobar EA, Bruhn AR, Ramos CA, Gonzalez RA, et al. Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. American journal of respiratory and critical care medicine. 2013 Aug 15;188(4):440-8. PubMed PMID: 23348974.
138. Pittet D. Improving compliance with hand hygiene in hospitals. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America. 2000 Jun;21(6):381-6. PubMed PMID: 10879568.
139. Li J, Xie D, Li A, Yue J. Oral topical decontamination for preventing ventilator-associated pneumonia: a systematic review and meta-analysis of

randomized controlled trials. The Journal of hospital infection. 2013 Aug;84(4):283-93. PubMed PMID: 23846238.
140. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition. 2004 Oct;20(10):843-8. PubMed PMID: 15474870.
141. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. The American journal of clinical nutrition. 2001 Oct;74(4):534-42. PubMed PMID: 11566654.
142. Chung CK, Whitney R, Thompson CM, Pham TN, Maier RV, O'Keefe GE. Experience with an enteral-based nutritional support regimen in critically ill trauma patients. Journal of the American College of Surgeons. 2013 Dec;217(6):1108-17. PubMed PMID: 24051065. Pubmed Central PMCID: 3845006.
143. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. The New England journal of medicine. 2011 Aug 11;365(6):506-17. PubMed PMID: 21714640.
144. Sena MJ, Utter GH, Cuschieri J, Maier RV, Tompkins RG, Harbrecht BG, et al. Early supplemental parenteral nutrition is associated with increased infectious complications in critically ill trauma patients. Journal of the American College of Surgeons. 2008 Oct;207(4):459-67. PubMed PMID: 18926446.
145. Caserta RA, Marra AR, Durao MS, Silva CV, Pavao dos Santos OF, Neves HS, et al. A program for sustained improvement in preventing ventilator associated pneumonia in an intensive care setting. BMC infectious diseases. 2012;12:234. PubMed PMID: 23020101. Pubmed Central PMCID: 3521195.
146. Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. Critical care medicine. 2011 Aug;39(8):1985-91. PubMed PMID: 21478738.