The use of positive end-expiratory pressure (PEEP) and alveolar recruitment manoeuvre (ARM) in equine anaesthesia – a review

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Summary: Impairment of gas exchange and arterial oxygenation during general anaesthesia and recumbency of the horse are a common and well-known problem. Often these alterations are poorly responsive to intermittent positive pressure ventilation (IPPV) and increasing levels of supplemental oxygen. Over the last decades the understanding of the underlying pathophysiology developed more and more, recognizing that a decrease in functional residual capacity (FRC), lung collapse and atelectasis, and ultimately ventilation/perfusion mismatch lead to poor oxygenation. Accordingly, new ventilation strategies arose over the course of time including alveolar recruitment manoeuvres (ARMs) and positive end expiratory pressure (PEEP). In 1992 Burkhard Lachmann presented his idea of an 'open lung' concept using high peak inspiratory pressures to reopen atelectatic lung regions followed by sufficiently high PEEP to keep the recruited lung areas open. In equine anaesthesia, early attempts with continuous positive pressure in spontaneously breathing horses yielded rather disappointing results. In combination with IPPV the use of PEEP resulted in unreliable improvements in the partial pressure of oxygen in arterial blood (PaO$_2$). Once the pre-treatment with an ARM prior to PEEP was introduced, improvement in PaO$_2$ could be seen to be more reliable. Despite these promising results, there is a risk of adverse effects with the use of PEEP and ARM in horses due to the high pressures that are necessary to achieve an effect. A reduction in cardiac output proportional to the increase in intrathoracic pressure has been observed and may compromise peripheral blood flow as well as gastrointestinal perfusion once a certain pressure threshold is reached. Similar, an increase in right to left shunt due to forcing blood into already collapsed lung areas can compromise the desired effect. Finally, early signs of ventilator induced lung injury have been detected in horses and it remains to be seen how future ventilation strategies will succeed in finding the optimal balance for each individual horse. This review presents the development and use of ARMs and PEEP in horses and its potential effect and side effects.

Keywords: Equine anaesthesia, ventilation, Positiv End-Expiratory Pressure, Alveolar Recruitment Manoeuvre, ventilator, resistance valve

Introduction

Impairment of gas exchange and in particular arterial oxygenation during general anaesthesia and recumbency of the horse are a common and well-known problem. It soon became clear that neither intermittent positive pressure ventilation (IPPV) nor supplementation of the inspired gases with oxygen was able to reliably and significantly improve oxygenation (*Hall* et al. 1968). It was hypothesized that a marked mismatch between ventilation and perfusion develops, leading to an increased venous admixture and ultimately decreased oxygenation (*Hall* et al. 1968, *Schatzmann* et al. 1982).

The decrease in functional residual capacity (FRC), which e.g. occurs following anaesthesia induction, has been associated relatively early on with impairment of gas exchange in people (*Hickey* et al. 1973). When FRC is reduced below the closing capacity, alveoli tend to collapse, resulting in atelectasis - the degree of which correlates with the degree of gas exchange impairment (*Hedenstierna* 1986).

In combination with a reduced FRC, several mechanisms promoting the development of atelectasis have been described in humans. Compression atelectasis occurs due to relaxation of the diaphragm during general anaesthesia, resulting in trans-

mission of the abdominal pressure into the thoracic cavity, thereby increasing in particular the pleural pressure in dependent lung regions. Atelectasis due to gas absorption was also demonstrated in patients breathing > 40 % oxygen for short periods during anaesthesia (*Agarwal* et al. 2002). Finally, impairment of surfactant function due to general anaesthesia and loss of surfactant during mechanical ventilation can contribute to the development of atelectasis (*Hedenstierna* and *Rothen* 2000).

In equine the occurrence of atelectasis was first demonstrated radiographically in anaesthetized ponies by *McDonnell* and *Hall* (1979) and histologically confirmed by *Stolk* in 1980. *McDonnell* and *Hall*, who were able to demonstrate a pronounced reduction in FCR in anaesthetized horses, proposed that the same factors that favour the development of atelectasis in people might similarly contribute in the equine patient. Nyman et al. demonstrated the development of atelectasis in dependent lung regions with computer tomographic studies in ponies (*Nyman* et al. 1990). The main cause for impaired oxygenation in equines was now defined as a pulmonary ventilation-perfusion mismatch attributable to atelectasis in dependent lung regions, which results in a marked incre-

ase in venous admixture of up to 51% of cardiac output (*Nyman* and *Hedenstierna* 1989). This study group also showed a positive association between the degree of atelectasis and the degree of gas exchange impairment. Several factors favouring its development have been identified in equine such as, positioning (*Schatzmann* et al. 1982) incl. change in body position by hoist (*Braun* et al. 2009), body weight (*Moens* 1989), body shape (*Moens* et al. 1995, *Mansel* et al. 2008) and fraction of inspired oxygen (*Cuvelliez* et al. 1990, *Marntell* et al. 2005).

In humans positive end-expiratory pressure (PEEP) was applied as early as 1948 (*Cournand* et al. 1948) but it was not until the 1970s that it was formally introduced into clinical practice when *Ashbaugh* et al. (1969) showed that the addition of PEEP to mechanical ventilation was able to reverse hypoxemia in patients suffering from acute respiratory distress syndrome (ARDS). Positive end-expiratory pressure has been defined as artificial maintenance of positive pressure at the end of passive exhalation during controlled ventilation (*Wild* and *Alagesan* 2001). The application of PEEP has been shown to stabilize the end-expiratory volume by maintaining the functional residual capacity above the critical closing pressure of the alveoli, thereby preserving or even increasing FRC and thus preventing alveolar collapse. Intrapulmonary shunting is reduced while lung compliance is increased, resulting in improved gas exchange and increased arterial oxygenation.

Since the reduction in FRC and atelectasis formation observed in people also occurred in equines, the use of PEEP was introduced into equine anaesthesia (*Hall* and *Trim 1975*; *Beadle* et al. 1975). These authors investigated the effect of various levels of continuous positive pressure (0 to 20 and 0 to 15 cm H_2O, respectively) in spontaneously breathing horses and found that the partial pressure of oxygen in arterial blood (PaO_2) remained unchanged or even decreased, and that the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) increased with rising expiratory pressure levels. It was concluded that during spontaneous ventilation continuous positive pressure has no place in routine equine anaesthesia (*Hall* and *Trim* 1975) and might in fact be contraindicated (*Beadle* et al. 1975).

More than a decade later the use of PEEP was explored again but this time it was limited to mechanically ventilated horses. Various levels of PEEP (levels of 5 to 30 cm H_2O) were investigated by different authors yielding inconsistent results. *Swanson* and *Muir* (1988) and *Pauritsch* (1997) found no improvements in gas exchange, other studies (*Wilson* and *Soma* 1990, *Wilson* and *McFeely* 1991, *Moens* e t al. 1998, *Ambrosio* et al. 2013) were able to show significant beneficial effects: increased FRC, decreased intrapulmonary shunt fraction; increased PaO_2; improved gas distribution between the lungs.

In the 1990's a new approach for the use of PEEP emerged in human medicine - driven by the high mortality rates in people suffering from acute respiratory distress syndrome (ARDS) and the difficulty to realise and maintain an acceptable oxygenation with conventional IPPV techniques in these patients. During that time, it was realised that mechanical ventilation itself might contribute to respiratory failure (*Lachmann* et al.

1992). Cyclic recruitment followed by de-recruitment of alveoli in certain lung regions during conventional IPPV without PEEP can result in surfactant depletion (*Verbrugge* et al. 1998), cytokine release (*Ranieri* et al. 1999) and barotrauma (*Papadakos* and *Lachmann* 2002) leading to additional formation of atelectasis, pulmonary oedema, pneumonitis, and fibrosis. These problems were addressed by the proposition of a novel ventilation strategy by Burkhardt Lachmann in 1992, the so-called "open lung concept". The aim of this strategy was to "open up the lung and keep the lung open". This was achieved by the use of high peak inspiratory pressures (PIP) to recruit atelectatic lung areas, followed by reduction of the inspiratory pressure and the application of sufficient positive end-expiratory pressure to prevent re-collapse of these recruited lung areas. Today, two different strategies to perform such an alveolar recruitment manoeuvre (ARM) are commonly used:

1. A stepwise incremental and decremental PIP and PEEP titration
2. Sustained hyperinflation of the lung during one or more breaths followed by a pre-determined level of PEEP (Neumann et al. 1999).

Alveolar recruitment manoeuvres have been proposed in people as a possible premeasure to a lung protective ventilation strategy, which relies on ventilating the lungs with low tidal volumes and simultaneous PEEP.

The "open lung concept" and the use of alveolar recruitment manoeuvres are now also explored in equine anaesthesia. The effects of a stepwise PIP and PEEP titration on gas exchange, lung compliance, and cardiovascular performance were for the first time described in experimental ponies by *Wettstein* et al. (2006). They observed similar beneficial effects as described in people using maximum PIP and PEEP levels of 55 and 20 cmH $_2$O respectively, including an increase in PaO_2 and dynamic lung compliance with minimal cardiovascular compromise. *Levionnois* et al. (2006) were able to reverse marked hypoxaemia in a colic horse using a stepwise incremental PEEP from 0 cmH $_2$O to a maximum of 27 cmH $_2$O which resulted in an improvement of PaO_2 from 69 mmHg to 563 mmHg. A similar incremental ARM technique used by *Schürmann* et al. (2008) and *Hopster* et al. (2016a) in adult horses resulted in similar significantly improved PaO_2 values. *Hopster* et al. (2007) altered the technique, calling it the "modified open lung concept", and used hyperinflation of the lungs followed by PEEP, which also resulted in improved oxygenation during inhalation anaesthesia and during total intravenous anaesthesia (*Hopster* et al. 2007, 2011, *Bringewatt* et al. 2010). However, significant increases in PaO_2 using ARM were only achieved in horses positioned in dorsal recumbency, whereas no further improvement could be achieved in horses positioned in lateral recumbency (*Hopster* et al. 2016 b). Recently, using electrical impedance tomography, it was shown that incremental /decremental PIP and PEEP titration directly influenced the regional distribution of ventilation in laterally and dorsally recumbent horses (*Ambrisko* et al. 2015, *Moens* et al. 2014) whereby increasing PEEP levels redirect ventilation towards the dependent lung regions.

Reported maximum PEEP pressures in the aforementioned studies were higher than used for humans and ranged from

$10-30\,cm$ H_2O, with maximum peak inspiratory pressures reaching up to $80\,cm$ H_2O during stepwise recruitment.

It is of importance to note that ARM involving high PIP and the subsequent stabilization with PEEP results in more reliable improvement of oxygenation than the sole use of PEEP during IPPV. This combination results in an improved distribution of ventilation as shown again by the use of electrical impedance tomography by *Ambrisko* et al. (2016). When PEEP is applied solely during IPPV after anaesthetic induction and adoption of recumbency, FRC is already reduced and atelectasis will have developed within 20 minutes of induction. Application of PEEP is not able to re-open collapsed alveoli and instead can cause overdistention of aerated alveoli. Ideally PEEP should be applied before the fall in FRC at anaesthetic induction, but this is difficult to accomplish, in particular in equine anaesthesia.

No matter how and when PEEP is applied, the negative cardiovascular effects due to increased intrathoracic pressure have to be considered, and ideally the PEEP level kept to a necessary minimum. High intra-thoracic pressures during IPPV diminish venous return to the heart and increases pulmonary resistance, resulting in inadequate filling of the left atrium and a subsequent decrease in cardiac output (*Edner* et al 2005). These negative effects of IPPV will be enhanced by the additional use of PEEP. The reduction in cardiac output, which is proportional to the increase in mean intrathoracic pressure, may substantially affect mean arterial blood pressure (MAP) and lead to reduced delivery of oxygen to the tissues (*Bringewatt* et al. 2010). Moreover the raised intrathoracic pressure can force more blood into already collapsed areas causing more right to left shunting resulting in decreased oxygenation. Several authors have recognized these detrimental effects of mechanical ventilation in horses (*Hodgson* et al. 1986, *Steffey* et al 1992, *Mizuno* et al. 1994, *Edner* et al. 2005) while others have found no or minimal detrimental effects on cardiovascular parameters when using IPPV with or without PEEP (*Swanson* and *Muir* 1988, *Wettstein* et al. 2006, *Bringewatt* et al. 2010, *Hopster* et al. 2011, *Ambrosio* et al. 2013). One other study found these cardiovascular effects to be negligible when providing mild hypercapnia (*Kalchofner* et al. 2009). Whether and to which degree the cardiovascular system will be impaired appears to be greatly influenced by pressures used and the time over which high PIP and PEEP pressures are applied.

During an ARM, the high airway pressures may cause even more pronounced cardiovascular side effects; however, none of the authors of ARM studies in horses reported significant decrease in mean arterial pressures. This might be due to the fact that some of these horses received cardiovascular support using positive inotropic agents. It is unclear whether this support was needed due to underlying pathology or the increased airway pressures during mechanical ventilation and recruitment or a combination of both (*Hopster* et al. 2011). In general it appears that high PIP and PEEP over short periods of time, as used for ARMs, have only mild and short-lasting adverse effects on the cardiovascular system (*Wettstein* et al. 2010, *Ambrosio* et al. 2013, *Hopster* et al. 2011), whereas high pressures sustained over a longer period of time result in a more pronounced impact on the cardiovascular system (*Hopster* et al. 2016c).

Despite these positive results, controversies regarding the cardiovascular safety of IPPV, especially in combination with ARM and PEEP, persist both in human and veterinary anaesthesia.

Lately *Hopster* et al. (2016) investigated the effect of PEEP on central and peripheral perfusion and oxygenation during isoflurane anaesthesia. The authors showed that the stepwise increase of PEEP was correlated with a linear decrease in MAP and cardiac index. Interestingly, gastrointestinal blood flow remained constant up to a PIP of $40\,cm$ H_2O and a PEEP of $20\,cm$ H_2O while further increases in pressure led to a sudden drop in blood flow and therefore oxygenation to these organs. The authors concluded that if, during PEEP titration, thresholds in cardiac output or blood pressure are reached, or if venous return falls below a critical minimum, vessels collapse and a sudden impairment of gastro-intestinal perfusion and oxygenation can occur. This may be of particular concern in colic horses who are often hypovolemic and cardiovascular unstable, but may still require mechanical ventilation to counteract the decrease in FRC due to the overdistended gastro-intestinal tract.

It has been shown in an experimental pig study that the negative effect of ARM on MAP is strongly affected by the volume state of the patient. A significant decrease in MAP can be expected in hypo- and even normovolemic patients, while hypervolemia somewhat attenuates these negative effects (*Nielsen* et al. 2006). In humans it is advocated before an ARM either to test the susceptibility of the cardiovascular system by observing arterial pressure with a short sequence of high airway pressure, or to administer fluid boluses before starting an ARM sequence when a suspicion of cardiovascular instability or hypovolemia exists (*Odenstedt* et al. 2005).

Ventilator induced lung injury (VILI), as has been described in humans, was suspected to occur in horses just recently by *Hopster* et al. (2016 c) who reported early signs of possible lung injury in equine patients. This study group was able to demonstrate a higher degree of atelectasis in horses breathing spontaneously and being mechanically ventilated without PEEP, compared to horses receiving IPPV combined with PEEP and ARM. On the contrary a higher degree of alveolar overdistention in horses directed to an ARM was seen. Despite this overdistention cytologically and histopathologically no evidence of lung injury was observed. Elevated levels in interleukins (IL) and matrix metallproteinases (MMP) were detected though in the IPPV and ARM groups which might indicate early signs of VILI. Already in 2003 *Ito* et al. showed increased levels of neutrophils and total protein in bronchoalveolar lavages of laterally recumbent anaesthetised horses undergoing IPPV for 120 minutes that did not return to baseline values until seven days post anaesthesia.

To minimize the adverse effects of PEEP, an individual PEEP titration to define the "optimal PEEP" for each patient has been recommended (*Papadakos* and *Lachmann* 2007). Optimal PEEP is defined as the lowest PEEP at which the maximum beneficial parameters occur with the least cardiovascular side effects and is determined by the individual alveolar closing pressure for each animal.

It is very likely that in horses the alveolar closing pressure, and hence the necessary PEEP, is highly variable and is influenced

by many factors such as body position and the magnitude of intra-abdominal pressure. This is supported by the high variability in PEEP levels and the resulting changes in PaO_2 reported in various equine studies using ARM and PEEP.

The identification of optimal PEEP as proposed by *Tusman* et al. (1999) using an increase of dynamic lung or thoracic compliance (Cdyn) and PaO_2 during incremental PEEP titration indicate recruitment of previously collapsed lung areas whereas a decrease in Cdyn and PaO_2 during decremental steps of PEEP titration indicate alveolar closing, thereby marking the pressure at which re-collapse of lung tissue occurs. This method has been implemented successfully in ponies by *Wettstein* et al. (2006) and *Hopster* et al. (2016 c).

Conclusion

The renewed interest in the use of PEEP in equine anaesthesia with the aim to improve impaired oxygenation seems warranted when it is combined and preceded by a form of ARM. The PIP and PEEP levels used are in general higher than applied in humans. It is also expected that in horses, a high individual variability exists for accompanying cardiovascular side effects as well as for the minimal PEEP level, - which preferably should be identified for each individual. Further research is necessary to fully appreciate the added value of the application of PEEP in equines including new technologies.

Conflict of interest statement

The author's state no conflict of interest.

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Erweiterte Zusammenfassung

Der Einsatz von positivem end-exspiratorischen Druck und alveolären Rekrutierungsmanövern in der Pferdeanästhesie

Die Beeinträchtigung des Gasaustausches und demzufolge der arteriellen Sauerstoffsättigung durch Allgemeinanästhesie und Ablegen des Pferdes ist mittlerweile ein gut bekanntes Problem. Oftmals sprechen diese Veränderungen nur unzureichend auf Interventionen wie intermittierende Druckbeatmung (IPPV nach dem Englischen 'intermittent positive pressure ventilation') und/oder die Erhöhung des inspiratorischen Sauerstoffgehaltes an. Über die letzten Dekaden hinweg hat sich das Wissen um die zugrundeliegende Pathophysiologie mehr und mehr erweitert mit dem heutigen Verständnis, dass eine Verminderung der funktionellen Residualkapazität, Lungenkollaps und Atelektase, sowie schlussendlich Ventilations/Perfusionsstörungen zu Hypoxämie führen. Unterschiedliche ursächliche Faktoren sind als hierzu beitragend bekannt, wie zum Beispiel der Einfluss von erhöhtem Sauerstoffgehalt in der Einatemluft oder die Druckübertragung des abdominalen Druckes auf den Thorax. Insbesondere bei Pferden, auf Grund ihrer Größe und der Anatomie, spielen zusätzliche Faktoren wie z.B. die Positionierung des Tieres, die Körperform und das Gewicht eine Rolle. Demensprechend wurden über die Zeit viele verschiedene Ventilationsstrategien entwickelt, inklusive dem alveolären Rekrutierungsmanöver (ARM) und der Nutzung von positivem endexspiratorischem Druck (PEEP vom Englischen positive end-expiratory pressure).

Bereits in den 1950er Jahren wurde PEEP in der Humanmedizin bei mechanisch ventilierten Patienten eingesetzt. PEEP beschreibt dabei während mechanischer Beatmung einen positiven Druck in der Lunge am Ende der Exspiration, der das end-exspiratorische Volumen stabilisiert und dadurch einen Kollaps der Alveolen bei der Exspiration verhindert. Diese Methode erzielte in der Humanmedizin, vor allem bei Patienten, die am akuten respiratorischen Atemnotssyndrom (ARDS, von dem Englischen `acute respiratory distress syndrome) litten, eine deutliche Verbesserung der Hypoxämie. Da die Symptomatik dieser Patienten der bei anästhesierten Pferden stark ähnelt, wurde der Einsatz von PEEP auch in die Pferdeanästhesie übernommen. Initiale Versuche an jedoch

spontan atmenden Pferden mit kontinuierlichem positivem Druck resultierten tendenziell eher in einer Verschlechterung der respiratorischen Parameter und somit wurde PEEP als nicht sinnvoll und sogar eher kontraindiziert in der Pferdeanästhesie betrachtet. Mehr als 10 Jahre später wurde PEEP in der Pferdeanästhesie neu entdeckt und kam diesmal bei mechanisch ventilierten Pferden zum Einsatz. Unterschiedliche PEEP Stufen wurden ausprobiert, mit sehr unterschiedlichen Resultaten. Während manche Autoren eine deutliche Verbesserung der Hypoxämie erzielten, beobachteten andere Studiengruppen keine Verbesserung.

In der Humanmedizin wurde unterdessen bereits ein neues Ventilationskonzept erprobt; das von Burkhardt Lachman 1992 postulierte „Open lung concept", bei dem kollabierte Lungenareale durch sogenannte alveoläre Rekrutierungen (ARMs) wieder eröffnet werden, und ein Rekollaps der Lunge während der Exspiration durch den Einsatz von einem ausreichend hohen PEEP verhindert wird. Dieses Prinzip kommt seit einigen Jahren nun ebenfalls in der Pferdeanästhesie zum Einsatz und verschiedene Studien und Fallberichte haben eine deutliche Verbesserung der Hypoxämie bei anästhesierten Pferden dokumentieren können, die bis in die Aufwachphase Bestand haben. Allerdings resultieren die bis zu 30 cmH$_2$O hohen PEEP, die nach solch einer Rekrutierung angewandt werden, in zum Teil deutlichen Nebenwirkungen, die vor allem bei hypovolämen oder kardiovaskulär instabilen Pferden problematisch werden können.

Ähnlich wie bei der intermittierenden positiven Druckbeatmung kommt es durch die Erhöhung des intrathorakalen Druckes zu einer Verminderung des venösen Rückstroms, was wiederum zu einer Reduktion des Herzauswurfvolumens und einem konsekutiven Abfall des arteriellen Blutdrucks führen kann. Dies kann sowohl zu einer Minderperfusion der Muskulatur, als auch, wie vor kurzem gezeigt, des Gastrointestinaltraktes führen. In wieweit die Perfusion betroffen ist, hängt vor allem vom Grad und der Dauer der Erhöhung des intrathorakalen Druckes ab, als auch vom Volumenstatus des Pferdes. Ebenso wurden mittlerweile frühe Anzeichen einer Ventilations-induzierten Lungenschädigung dokumentiert, wobei es hier noch recht hohen Forschungsbedarf gibt.

Um negative Effekte zu vermeiden, sollte für jedes Tier die Notwendigkeit, Machbarkeit und der individuelle, optimale PEEP bestimmt werden. Der optimale PEEP ist definiert als der niedrigste PEEP, an dem die maximalen positiven Effekte resultieren, mit den gleichzeitig geringstmöglichen Nebenwirkungen. Dieser kann durch eine schrittweise PEEP Titration ermittelt werden, bei der auf die Zunahme der dynamischen Compliance geachtet wird, die mit Hilfe der Spirometrie gemessen werden kann. Eine Zunahme dieser Compliance wird als Rekrutierung kollabierter Lungenareal gedeutet, während eine Abnahme der dynamischen Compliance auf eine Überblähung bereits ventilierter Lungenareale schließen lässt.

Die vorliegende Übersicht gibt eine Zusammenfassung der geschichtlichen Entwicklung von PEEP und ARMs bei Pferden wieder und beleuchtet die damit assoziierten positiven und negativen Effekte.

Schlüsselwörter: Anaesthesie, Narkose, Ventilation, Positiv End-Expiratory Pressure, Alveolar Recruitment Manoeuvre, Ventilator, Widerstandsventil, Pferd