

Adjustable inspiratory occlusion valve in experimental bronchopleural fistula. A new therapeutic perspective¹

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DOI: <http://dx.doi.org/10.1590/S0102-865020150080000007>

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ABSTRACT

PURPOSE: To assess the efficacy of an adjustable inspiratory occlusion valve in experimental bronchopleural fistula during mechanical ventilation.

METHODS: We studied six mechanically ventilated pigs in a surgically created, reproducible model of bronchopleural fistula managed with mechanical ventilation and water-sealed thoracic drainage. An adjustable inspiratory occlusion valve was placed between the thoracic drain and the endotracheal tube. Hemodynamic data, capnography and blood gases were recorded before and after the creation of the bronchopleural fistula as well as after every adjustment of the inspiratory occlusion valve.

RESULTS: When compared with the standard water-sealed drainage treatment, the use of an adjustable inspiratory occlusion valve improved the alveolar tidal volume and reduced bronchopleural air leak ($p < 0.001$), without hemodynamic compromise when compared with conventional water sealed drainage.

CONCLUSION: The use of an adjustable inspiratory occlusion valve improved the alveolar tidal volume, reduced alveolar leak, in an experimental reproducible model of bronchopleural fistula, without causing any hemodynamic derangements when compared with conventional water sealed drainage.

Key words: Fistula. Respiration, Artificial. Capnography. Models, Animal. Swine.

Introduction

A bronchopleural fistula (BPF) is a condition that has high mortality rate especially when associated with invasive mechanical ventilation (MV). It manifests initially by pneumothorax and, after the installation of adequate chest tube drainage, by air leakage from the airway to the outside¹. The diagnosis of BPF is established when air leak through the chest tube persists for at least 24 hours^{2,3}.

The etiology of BPF is multifactorial and may result from pneumonia, radiotherapy, chemotherapy, tumors, tuberculosis, pulmonary resection surgery, chest trauma, ARDS and, in Intensive Care Units (ICUs), it is often associated with barotrauma and MV^{4,5}. Whatever the cause, BPF is difficult to treat, considering that the patients receive positive pressure, which tends to hinder closure of the fistula. Significant air leakage results in high morbidity and the mortality rate of 18% to 50%^{4,6}.

Patients with BPF may significantly worsen the ventilation/perfusion balance and arterial blood gases. BPF causes well described changes such as leakage of gases, reduction of the airway pressure, reduced alveolar ventilation per minute, alveolar collapse, arterial hypoxemia, respiratory acidosis, barotrauma or volutrauma in the contralateral lung as a complication of MV, difficulty in maintaining the positive end-expiratory pressure (PEEP) and self-cycling^{4,7}.

The success in handling BPF depends on treatment strategies, tailored according to individual needs of patients. The conventional treatment consists of organ support, intercostal catheters, chest drainage and MV and surgical or bronchoscopic definitive therapies⁴.

Since the '70s, various noninvasive methods have been used to solve or lessen the effects of positive pressure MV on BPF, most of them consisting of different methods of pressurizing the chest drainage flask. However, no controlled clinical study or trial has been documented.

The aim of this study was to describe a new adjustable inspiratory occlusion valve (aIOV) used to reduce the deleterious effects caused by BPF, acting directly on the air leakage, improving pulmonary ventilation and blood gases, but without causing hemodynamic derangements.

Methods

This study was approved by the Ethics Committee on Animal Experimentation of the Institute of Biology, Universidade de Campinas (Protocol n° 1685-1 A).

We used six large white pigs weighing 25kg each which, after general anesthesia, underwent endotracheal intubation (6mm),

and mechanically ventilation. The endotracheal tube and the mechanical ventilator circuit were connected through the sensor of volumetric capnography (CO₂SMO Plus DX-8100® Dixtal/Novamatrix), which was calibrated before the beginning of each experiment. The software (APlus^o) used to capture and store data online and offline enabled the measurement (in mL) of BPF output, which was calculated by subtracting the expired volume (Ve) from the inspired volume (Vi). The percentage of fistula output was defined as the result of this subtraction (Vi - Ve) divided by the Vi.

The respiratory rate, tidal volume and F_IO₂ in the MV remained the same throughout the experiment and was possible observed an increase in PaCO₂ and slightly decrease in PaO₂, but not statistically significant, probably resulting from alveolar hypoventilation.

A pulmonary artery catheter (PAC) was introduced through the femoral vein. Mean arterial pressure (MAP) was recorded continuously (Multiparameter Monitor Dixtal DX-2020; AJIBP-0). Data from arterial and venous blood gases and hemoximetry were collected before (baseline), after creation of BPF and after each experimental setting.

The animals received a continuous infusion of saline (0.9%) as well as anesthetics, sedatives and neuromuscular blockers as needed.

Surgical procedure

Through a left thoracotomy, a resection of the lingula was performed leaving the bronchial stump open in order to create a BPF with an output exceeding 50% of the inspired volume. The chest cavity was closed and drained into the water sealed system for initial observation of the high output BPF (Figure 1).

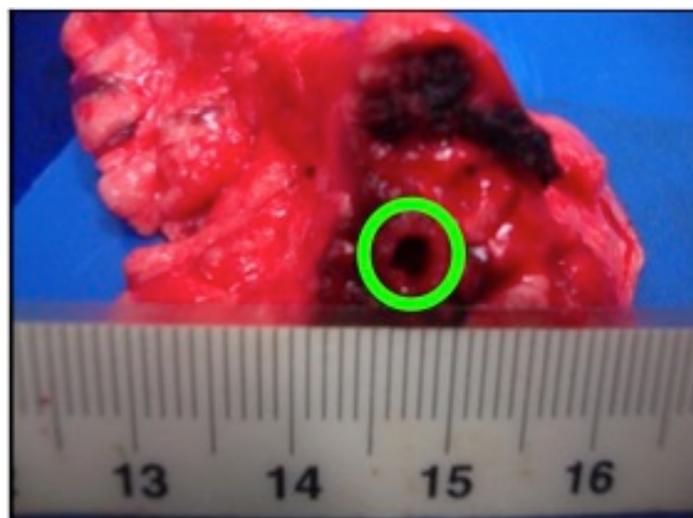


FIGURE 1 - Adjustable inspiratory occlusion valve (aIOV).

This device, called adjustable inspiratory occlusion valve (deposit number BR 10 2012 021143 2 and BR 13 2013 032098 5 patents), which must be connected to the outer extremity of the chest drain, consists of a nipple valve upon which a flexible diaphragm has been superimposed. The diaphragm is activated by proximal pressure (pressure generated in the respiratory system) via a flexible tube connected to the terminal “Y” of the patient (inspiratory pathway). Depending on the size of the nozzle and of the diaphragm, there is a 1:2 relationship between the proximal pressure and the closing pressure of the drain. That is, when the proximal pressure is 10cmH₂O, the occlusion pressure in the drain is 20cmH₂O. In order to allow finer adjustments in the occlusion pressure, we used a needle valve that allowed for a controlled escape flow. The larger the proximal escape flow, the lower the working pressure of the diaphragm. This way, we were able to perform appropriate adjustments in the release pressure of the chest drain, preventing unwanted pressurization of the pleural space. In short, this device is a pressure-stabilizing valve that keeps the pleural pressure slightly below the intrapulmonary pressure, reducing the fistula outflow and allowing for the controlled clearance of pleural air, thus preventing the creation of a tension pneumothorax. The pressure gradient is expected to be 2 to 3cmH₂O (Figure 2).

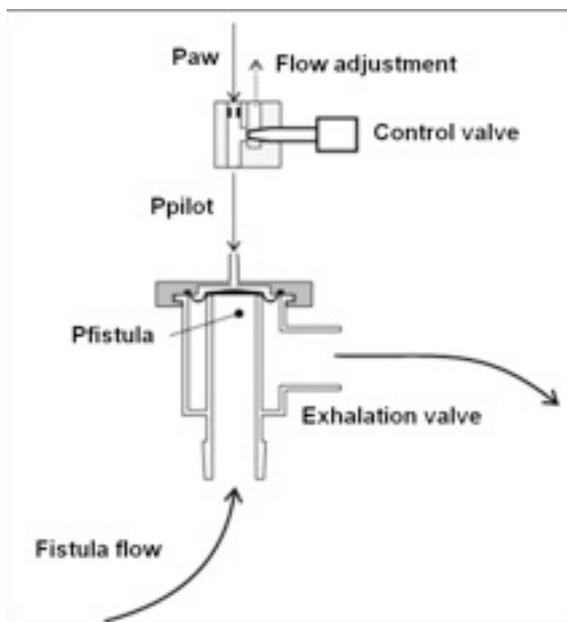


FIGURE 2 - Experimental protocol of mechanical ventilation.

The MV protocol consisted of Volume Controlled Ventilation (VCV), with a Tidal Volume (V_T) of 8ml/Kg, Fraction of Inspired Oxygen ($F_{I}O_2$) of 0.21, Inspiratory time *versus* Expiratory time (I:E ratio) = 1:2, Respiratory Rate (RR) of 22 bpm, Positive End Expiratory Pressure (PEEP) of 5 cmH₂O. Using these ventilatory parameters, it was possible to maintain the end-tidal CO₂ (PetCO₂) around 45mmHg.

Data from arterial blood gases were collected before (baseline), after creation of BPF and after each experimental treatment. A treatment was defined as a 10-minute period of ventilation with the adjustable inspiratory occlusion valve (aIOV) set in different aleatory positions of bronchopleural fistula output (BPFO) from highest to lowest rate of fistula. The treatment 0 corresponds to simple water-sealed drainage of the thorax. There were four treatments with the valve regulated, aleatorially, in different percentages of BFPO: Treatment 1 (corresponding to 69.6±20.0% of BPFO); Treatment 2- corresponding to 61.0±19.5% of BPFO); Treatment-3 (corresponding to 16.8±10.1% of BPFO); Treatment 4 - valve in the closed position (corresponding to 9.7±6.2% of BPFO).

A statistical analysis was performed for comparison of the continuous variables Cardiac Output (CO), Bronchopleural fistula Output (BPFO), Mean Arterial Pressure (MAP), End Tidal CO₂ (PetCO₂), Arterial Partial Pressure of O₂ (PaO₂), Arterial Partial Pressure of CO₂ (PaCO₂), Arterial Oxygen Saturation (SaO₂), and Alveolar Tidal Volume (V_T alv) between treatments that began with the water seal and progressed with the use of the valve until it was almost completely closed.

The statistical analysis was carried out comparing only treatments 0 to 4 using analysis of variance, considering each pig as an experimental block. Fixed the significance level at 5%, if the p-value is significant, then at least one pair of treatments has statistical different means. To check if there is difference between two treatments, a Tukey's honest difference test was performed.

Results

The results of changes in ventilation and hemodynamic recorded in pre-fistula (baseline) and after the creation of the BPF (treatments 0, 1, 2, 3 and 4) and the p-value correspondent to the ANOVA for comparison of the treatments 0 to 4 are arranged in Table 1.

TABLE 1 - Data of volumetric capnography, arterial blood gas and hemodynamic variables expressed as mean and standard deviation.

	Baseline	Treatment 0	Treatment 1	Treatment 2	Treatment 3	Treatment 4	p-value
BPFO (%)	NP	42.3±10.8 a,b,c,d	69.6±20.0 a,e,f	61.0±19.5 b,g,h	16.8±10.1 c,e,g	9.7±6.2 d,f,h	<0.0001
PetCO ₂	43.2±1.8	51.0±9.5	51.3±9.4	55.7±12.7	54.5±12.2	52.0±11.5	0.7042
PaCO ₂	46.0±3.8	54.6±12.3 a,b,c,d	66.4±12.7 a	67.7±16.0 b	63.4±16.1 c	63.1±18.4 d	<0.0001
V _T alv	173.5±34.9	92.0±25.7 a,b	55.0±25.4 c,d	60.6±28.8 e,f	139.3±36.0 a,c,e	156.0±29.1 b,d,f	<0.0001
PaO ₂	79.5±11.9	63.3±21.3	49.6±14.6	55.7±16.7	54.1±13.8	56.5±13.6	0.0836
Sat.O ₂	88.6±7.1	68.9±23.9	51.9±22.7	54.6±24.5	56.6±23.4	57.8±25.4	0.0992
MAP	86.7±17.6	115.2±19.5	128.2±20.5	125.5±22.1	118.0±9.2	112.8±13.2	0.3038
CO	3.7±0.8	4.0±0.9 a	4.9±1.6 a,b	4.4±1.2	4.1±1.2	3.8±1.1 b	0.0138

BPFO (%): Bronchopleural fistula output; PetCO₂ (mmHg): pressure of end-tidal CO₂; PaCO₂ (mmHg): partial pressure of CO₂ in arterial blood; V_T alv (ml): alveolar tidal volume; PaO₂ (mmHg): partial pressure of O₂; Sat.O₂ (%): oxygen saturation in arterial blood; MAP (mmHg): mean arterial pressure; CO (L/min): cardiac output. NP: not performed (baseline)

The significant differences between two treatments by Tukey’s test are represented by the same letters below their means. Fistula output: Treatment 0 when compared to treatments 1 and 2 resulted in statistically significant increase in the fistula output (Tukey, p=0.0001; p=0.0071, respectively), however the treatment 0 when compared to treatments 3 and 4 resulted in statistically significant decreased in the fistula output (Tukey, p=0.0003 and p<0.0001; respectively).

Arterial partial pressure of CO₂: In treatments 1 to 4 there was observed greater values of PaCO₂ when compared to treatment 0 (Tukey; p=0.0008; p=0.0002; p=0.0109 and p=0.0135, respectively).

Alveolar volume: Treatments 3 and 4 presented statistically greater values when compared to treatment 0 (Tukey; p=0.0083 and p=0.0004, respectively).

Arterial partial pressure of O₂ and oxygen saturation: The values observed in treatments 1 to 4 are smaller than treatment 0, but not significant. (ANOVA for PaO₂ and SatO₂ respectively: p=0.0836 and p=0.0992; Table 1).

Mean arterial pressure: There is no significant difference between treatments 0 to 4 (ANOVA p=0.3038; Table 1).

Cardiac output: There is a significant increase from treatment 0 to treatment 1 (Tukey, p=0.0472). However, there are no significant decreases between treatments 1 to 4 when compared to treatment 0.

The Figure 3 displays a representative model of volumetric capnography curves, during the respective treatments: water seal (0), 1, 2, 3 and 4. Note the significant improvement of the alveolar volume during the treatments.

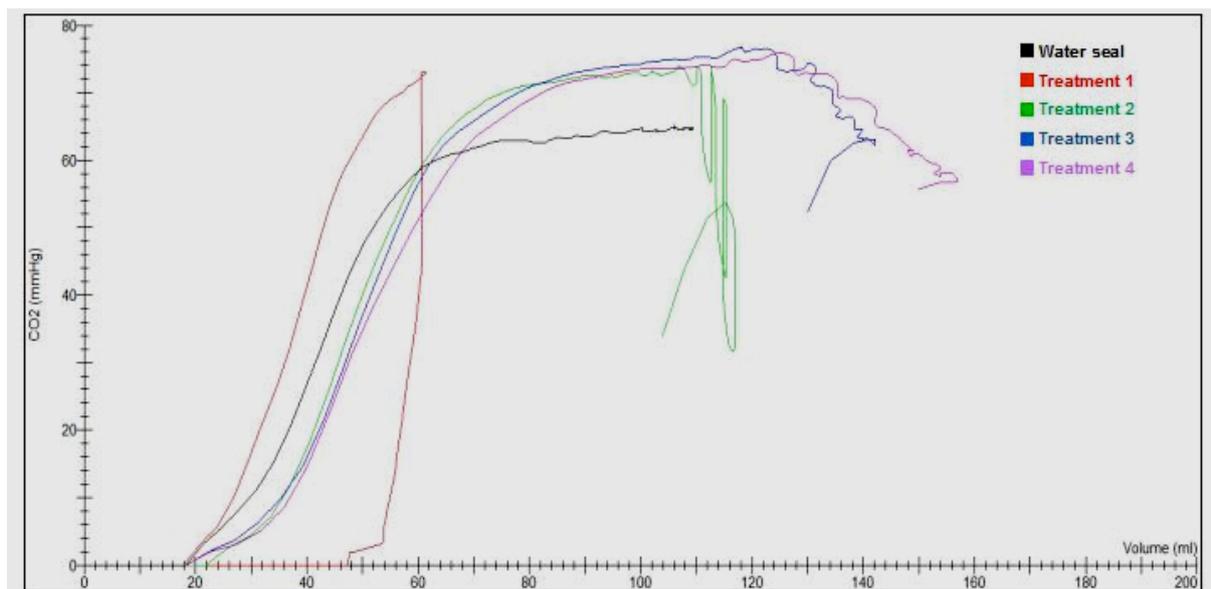


FIGURE 3 - Representative figure of Volumetric Capnography during treatments. In the “x” axis, tidal volume (mL) and the “y” axis, end-tidal CO₂ (mmHg). Note that alveolar volume behaves better during treatments 3 and 4.

Discussion

Despite the need to reduce morbidity and mortality of BPF therapy, particularly when associated with mechanical ventilation, little has been advanced in this field in the last decades. This study proposes a new method of reducing the output of a surgically created broncho-pulmonary fistula during mechanical ventilation, that improves alveolar volume, and, most importantly, does not cause any decrease in cardiac output or mean arterial blood pressure when compared with conventional water sealed drainage. The increased in cardiac output between Treatment 0 and 1 is probably due to the fact of increased preload and decreased after load of right ventricle (Table 1).

Several studies have described strategies to control BPF output during MV. However, these studies are mostly case reports and reviews, which failed to present an adequate solution to complications such as pneumothorax, hemodynamic instability, persistent air leak and severe hypoxemia. Published studies describe various forms of treatment, such as pressurization methods^{8,9} ventilatory strategies and surgical techniques such as stent placement in the bronchial tree to try to stop the leak¹⁰⁻¹². This demonstrates the heterogeneous nature of the problem and partially explains the non-standardization of therapy in BPF.

According to the majority of authors, the ideal treatment of BPF should not include the use of positive pressure^{1,8}. However, this is often necessary, especially in cases of high output BPF^{4,8,13}.

The increased mortality in patients with BPF under MV is the result of hypoventilation and consequent hypoxia. Minimizing the effects of air leakage while maintaining adequate arterial oxygenation may represent a conflicting demand imposed on MV¹.

Accordingly, we have developed an Adjustable Inspiratory Occlusion Valve (aIOV) that aims to treat high output BPF in patients undergoing positive pressure MV, specifically by reducing fistula output and improving ventilation without compromising hemodynamic parameters. In this study we have tried to measure its efficacy in pigs having a surgically created, high output BPF.

The assessment of efficacy was performed by volumetric capnography, a method that simplifies control of the ventilation by providing real-time, bedside data for alveolar ventilation. The volumetric capnography is widely applied in other diseases such as COPD^{14,15}, cystic fibrosis and noncystic fibrosis bronchiectasis¹⁶⁻¹⁸, asthma¹⁹, pulmonary embolism²⁰⁻²⁶.

Each step of the experiment was conducted for no more than ten minutes, in order to avoid the hypoxia, hypercapnia and

hemodynamic instability that were observed during the pilot study, when this time was extended. Mainly, because we did not increase inspiratory fraction of oxygen. It is believed that those problems were secondary to the high output BPF itself, and not to other methodological factors such as surgical incision or surgical time²⁷. Leite *et al.*²⁸, using an experimental model of lung re-expansion after bronchial occlusion, found an acute lung inflammatory response, which has been shown to be more pronounced in long periods of bronchial occlusion in terms of cytokine inflammatory response. In addition, the magnitude of this inflammatory response also can be detected systemically^{28,29}.

In the present study we did not try, to establish a valve setting that would apply to every case of BPF under MV. Instead we believe that the use of volumetric capnography, by providing respiratory mechanics data in real time, allows for customization of the valve setting to each patient, expressing the individualized character of this therapy. It is however clear by the data presented that higher settings of the valve were associated with a better recovery of the respiratory mechanics.

Arterial blood gas analysis did not show the same behavior as alveolar ventilation. A possible explanation lies in the fact that the time between treatments (10 minutes) and the cumulative effect of previous treatments, might have not allowed complete normalization of the blood gases. In the present experiment, the $F_{I}O_2$ was kept at 0.21, in order to investigate the actual effectiveness of the method under atmospheric conditions. It is noticeable however that, the use of the valve was not associated with any significant worsening of oxygenation when compared to treatment with water seal.

Several strategies have been tried to treat patients with high output BPF needing MV. Oliveira *et al.*³⁰ using an experimental model of high output BPF demonstrated that a simple insertion of a water-sealed thoracic drain resulted in reduction in bronchopleural fistula output and better CO_2 clearance without any drop in cardiac output or significant changes in mean arterial pressure. Shekar *et al.*⁴ maintained the airway pressure below the opening pressure of the BPF, and then optimized the pleural suction pressure thus preventing aggravations. Additionally, Kempainem and Pierson³ considered the use of low tidal volume and increased inspiratory/expiratory ratio, as a protective strategy of FBP under VM, because it reduces the peak pressure and avoids auto-PEEP. These authors proposed, in order to reduce the output of the FBP, the use of minimal levels of expiratory pressure, short inspiratory time, low tidal volume and low frequency⁴.

Other ventilatory strategies include high frequency MV (HF MV), which improves alveolar ventilation with consequent

increase in arterial oxygen saturation, and independent lung ventilation by selective intubation^{3,4}.

Although some publications show clear benefits of HFV, such as better ventilation, lower peak pressure and lower mean airway pressure, this technique is not widely applied and is restricted to specialized centers³¹. Furthermore, there are evidences that gas exchange might not be as satisfactory when the HFV is used in pulmonary diseases that concur with low pulmonary compliance².

Alternative strategies such as the occlusion of the chest tube may preserve the PEEP and reduce air leakage during inspiration, while allowing air to escape during the expiratory phase. This can be used in combination with the application of PEEP in the chest tube. Although these measures may help to maintain a small difference in transpulmonary pressure and reduce the risk of pulmonary collapse, they might also compromise the drainage of the pleural cavity and should be used with caution.

Some authors suggest the use of the suction of the drainage flask. However, the negative pressure applied to the chest tube to assist in drainage of the pleural space may increase transpulmonary pressure, resulting in an increase in the fistula output^{3,4}.

In patients with significant comorbidities or poor response to conservative treatment, non-surgical interventions to decrease the leak may provide temporary treatment, while the patient is stabilized for surgery^{3,4}.

Given the difficulties presented by the lack of standardized therapy to treat patients with BPF under MV and it's high mortality in the ICU, this study recommends a strategy that might be used in the presence of acute respiratory disorders arising from the fistula, to avoid additional complications while awaiting for better clinical conditions, that would permit surgical closure of fistula. Maung and Kaplan³² reported that patients with injuries such as BPF, require mechanical ventilation to control not only the primary respiratory failure, but also as a complement to manage other conditions.

According to Shekar *et al.*⁴, the success of therapy in cases of BPF will require strategies tailored to the individual patient needs. Accordingly, the method in question (volumetric capnography and occlusion valve), besides demonstrating the effectiveness of this valve, includes the concept of individualized therapy. In summary, this study demonstrated that it is possible, with the use of the adjustable inspiratory occlusion valve (aIOV), to reduce the leak of a BPF, with consequent improvement in alveolar volume, without compromising hemodynamic parameters, making this device a promising therapeutic tool for the treatment of BPF in patients on

MV. The aIOV accepts different settings, going from 100% closed to 100% open, allowing it to be customized, in real time, to the hemodynamic needs and blood gases of the particular patient.

Conclusion

The occlusion valve decreased the bronchopulmonary fistula output, improved alveolar volume, without compromising the hemodynamic status when compared with conventional treatment (simple water-seal drainage).

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Acknowledgements

To the team of the Center for Experimental Medicine and Surgery, Faculty of Medical Sciences, UNICAMP, especially to biologists Willian Adalberto Silva and Ana Cristina Moraes.

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Received: Apr 11, 2015

Review: June 14, 2015

Accepted: July 15 2015

Conflict of interest: none

Financial source: FAPESP (Process nº 04610-2/2009)

¹Research performed at Center for Experimental Medicine and Surgery, Faculty of Medical Sciences, Universidade de Campinas (UNICAMP), Brazil.