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Biphasic cuirass ventilation is better than bag-valve mask ventilation for resuscitation following organophosphate poisoning

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ABSTRACT

Objective: Exposure to organophosphates (OP) may lead to a life threatening cholinergic crisis with death attributed to a rapidly progressive respiratory failure. In a toxicological mass casualty event involving organophosphate exposure, many of the victims may depend on immediate short-term ventilation to overcome the respiratory distress which may exhaust life supporting resources. In addition, the mandatory use of personal protective gear by first responders emphasizes the need for a noninvasive, easy-to-operate ventilation device. Our objective was to assess the efficacy of MRTX, a Biphasic Cuirass Ventilation device, in comparison with standard bag-valve mask ventilation following acute organophosphate poisoning.

Methods: Pigs were exposed to paraoxon poisoning (1.4 LD_{50}), and treated 8 min later with atropine (0.05 mg/kg). The control group received no further support ($n = 9$), the two experimental groups received ventilation support initiated 15 min post exposure and lasted for 25 min: one group was ventilated with the commonly used bag-valve mask (Mask group, $n = 7$) and the other was ventilated with the Biphasic Cuirass Ventilation device (Cuirass group, $n = 7$). Clinical signs and physiological parameters were monitored during the first hour, and mortality up to 24 h post exposure was recorded.

Results: No mortality was observed in the Cuirass group following OP poisoning, while mortality in the Control and in the Mask groups was high (67% and 71%, respectively). Mouth excretions of the cuirass-ventilated animals were frothy white as in deep suctioning, as opposed to the clear saliva-like appearance of secretions in the other two groups. No further group differences were recorded.

Conclusions: The noninvasive, easy-to-operate Biphasic Cuirass Ventilation device was effective in reducing OP-induced mortality and might be advantageous in an organophosphate mass casualty event. This finding should be validated in further investigations.

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1. Introduction

Exposure to organophosphates (OP) results in a cholinergic crisis manifested as a dose dependent hypersecretion, fasciculation, tremor, convulsions, coma, respiratory failure and death [1–7]. Immediate treatment with an anticholinergic drug such as atropine sulfate and an oxime counteract some of the poisonous effects [6,8]. To ameliorate OP-induced centrally mediated seizure activity that can progress to status epilepticus and result in permanent brain damage, an anti-convulsing drug is also required [9–13]. The immediate cause of death following OP poisoning is a rapidly progressive respiratory failure caused by a complex pathophysiology, characterized by bronchoconstriction, profuse salivation, bronchorrhoea, respiratory muscle paralysis, and depression of the respiratory centers in the brain [14–17].

In an OP toxicological mass casualty event, be it an accident or a terrorist attack, several challenges are expected to impact casualty management, including a shortage of trained medical personnel, difficulties in performing intubations due to excess salivation, bronchoconstriction and convulsions, operator inexperience, poor patient positioning (often on floor), and limitations imposed by wearing the cumbersome personal protective gear [3,18]. Under these circumstances, a lightweight, easy to operate, portable and non-invasive ventilator could be highly advantageous.

The MRTX is a Biphasic Cuirass Ventilation device (Fig. 1a) that provides a non-invasive support based on a light cuirass tightly fit around the patient's chest. The MRTX is simple to operate, even while wearing personal protective gear [19,20], it can be used within seconds by minimally trained personnel and, if needed, on fully dressed casualty. It is a portable device and operates using rechargeable batteries. The device is unique in that it controls not only inspiration but expiration as well, which is of critical importance when having bronchoconstriction and paralysis as in OP poisoning.

The aim of the present study was to compare the Cuirass ventilation technique with the commonly used bag-valve mask ventilation device in terms of survival and clinical score, in a well-established pig model of OP poisoning. Bag-valve mask ventilation is a positive pressure ventilation technique expected to be widely used on-scene in an OP mass casualty event. The pig model used here exhibits prolonged respiratory distress following exposure to the organophosphate paraoxon. The model enabled the study of the beneficial effects of ventilation support following OP poisoning and the characterization of alterations in physiological parameters [21].

2. Methods

2.1. Animals

The study was approved by the IIBR Animal Ethics Committee, according to the recommendations of the *Guide for the Care and Use of Laboratory Animals*, National Academy Press, Washington DC, 1996. White domestic female pigs (Laboratory animals farm, Lahav, Israel), weighing 18–20 kg were used for this study, following 2–3 days of acclimatization in the animal facility.

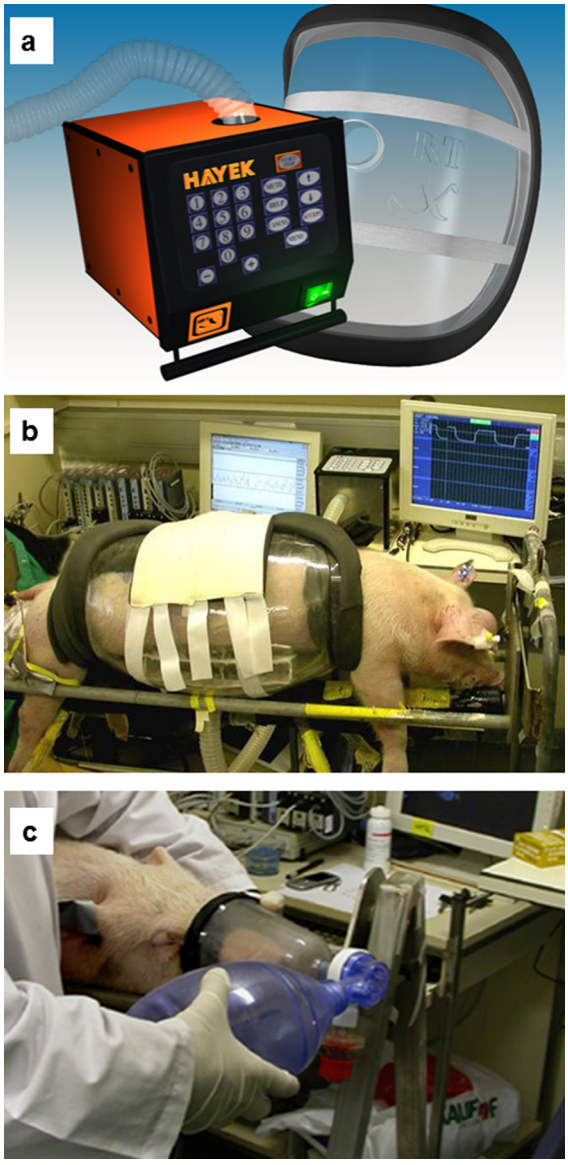

Fig. 1. (a) The MRTX device. The cuirass (b) and mask (c) were specially designed for pigs.

Animals were housed individually in a temperature ($21 \pm 2\,^{\circ}C$) and humidity ($50 \pm 10\%$) controlled animal quarters, and maintained on 12 h light–dark cycles (light on at 0600 am).

2.2. Materials and devices

Paraoxon and atropine sulphate (Sigma chemicals, Israel) and propofol 1% (Taro Pharmaceutical Industries Ltd, Israel) were used. ECG, heart rate and O_2 saturation recordings were performed using AcqKnowledge Software and Biopac Hardware Facility (Biopac Systems Inc., USA). The saturation probe was placed on the animals' tails, with reliableand consistent readings throughout the study. Arterial

pO_2, arterial pCO_2, arterial pH and base excess (BE) were analyzed using the Osmotech OPTI CCA Blood Gas Analyzer (Osmotech Incorporated, USA). An MRTX ventilator (MediVent International LTD, UK) was used with a cuirass specially designed and manufactured by the company to fit the chest wall of a pig (Fig. 1a and b).

2.3. Study design and setting

2.3.1. Preliminary study

Pigs were restrained on a specifically designed apparatus throughout the experiment. The adjustment of the two ventilation devices and the feasibility of their use were tested on two pigs anesthetized with Propofol (3.5 mg/kg, iv). One animal was ventilated by a standard bag-valve device with a specially-designed face-mask and with no intubation (Fig. 1c). The bag-valve mask device was adjusted to the animal's snout in order to establish a good seal. This was important in order to prevent delivery of high tidal volumes which may lead to high intrathoracic pressures and cardiovascular collapse and possible barotrauma. The bag-valve device did not have a pressure limit valve. We used a 1 l bag size. The MRTX with its cuirass was set on −25 negative and +5 positive pressures. Inspiratory: expiratory ratio was set on 1:1, based on prior clinical experience (this causes less atelectasis). Although we did not expose the pigs to OP in this preliminary study, we followed local clinical recommendations for the treatment of OP casualties, which includes hyperventilation, to reduce OP-induced hypercapnia. In both cases respiratory rate was kept on 30 breaths per minute, and ventilation lasted for 25 min, with no oxygen supplementation.

Both devices were effective in ventilating the animals. Physiological parameters were monitored continuously and no significant changes were observed. Vital signs included heart rate derived from ECG, O_2 saturation by pulse-oximetry placed on the animals' tails, non-invasive blood pressure and $EtCO_2$. Ventilation was monitored by watching chest wall movement and blood saturation.

2.3.2. Main study

Restrained pigs were fitted with an intravenous line and anesthetized using Propofol (3.5 mg/kg, iv) to enable the insertion of an arterial cannula into the pigs' ear. About 40 min later, when the pig regained full neck muscle tone, exposure to paraoxon was performed. An intramuscular dose of 600 μg/kg paraoxon (the equivalent of 1.4 LD_{50}) was followed 8 min later by a single administration of atropine (0.05 mg/kg, i.m.) alone, to simulate a realistic scenario, in which severe respiratory distress is likely to develop [21].

Following the paraoxon exposure three possible treatments were evaluated: Ventilation support using the biphasic cuirass device (Cuirass group, $n = 7$), ventilation support using a bag-valve mask (Mask group, $n = 7$) and a control group that received no ventilation support (Control, $n = 9$). No oxygen enrichment was provided ($FiO_2 = 0.21$). Ventilation was initiated 15 min following exposure and regardless of clinical manifestations was terminated 25 min later.

Rate of ventilation was kept at 30 breaths per minute in both groups, with the same MRTX settings as in the preliminary study.

Animals were closely observed for chest wall movement and post exposure signs. The following parameters were monitored continuously for 1 h after paraoxon exposure: ECG, Heart rate (derived from ECG), O_2 saturation by pulse-oximetry placed on the animals' tails, and blood pressure by using an arterial line placed in the animals' ear. Arterial blood gases (arterial pO_2, arterial pCO_2, arterial pH and BE) were collected from the arterial line before poisoning (0′) and 10, 20, 30, 40, and 50 min following exposure. The following clinical signs were recorded every 10 min during the first hour post exposure and 24 h later: fasciculation, salivation, teeth clenching, tremor, dermal patches, convulsion, and respiratory distress. The score ranged from 0 (no effect) to 3 (severe effect). Time of death within the 24 h was also recorded.

All animals were allowed to recover with no further help, for a period of 24 h. After 24 h all animals were euthanized using i.v. overdose of sodium pentobarbital (200 mg/ml).

2.4. Statistical analysis

The physiological data is presented as mean ± SE. Survival is presented as percentage and the differences were analyzed using the non-parametric Kaplan–Meier analysis (SPSS® computer program version 22, IBM).

3. Results

3.1. Clinical observations

Typical OP-induced symptoms were seen following exposure to paraoxon. Fasciculation, tremor, teeth clenching and salivation appeared within 5–10 min after paraoxon injection, followed by respiratory distress and tonic–clonic convulsions. All animals showed signs of significant respiratory distress within 15 min of exposure, manifested as tachypnea, cyanosis and gasping. If no ventilation support was provided, the clinical condition of the animals deteriorated rapidly and most of the animals died within 1 h of exposure (Control group: 67%, 6 out of 9 died within 24 h). In the bag-valve Mask group, the animals survived the 25 min of ventilation, but shortly after ventilation was terminated, the mortality rate resembled that of the control group (Mask group: 71%, 5/7). In contrast, no mortality was recorded following 25 min ventilation with the cuirass, and the pigs recovered better and faster (Cuirass group: 0%, 0/7). Survival analysis (Kaplan–Meier, Fig. 2) showed significant differences between groups ($\chi^2_{(2)} = 8.32$, $p < 0.016$), and pairwise comparison showed no differences between Control and Mask but both groups differ from the Cuirass group ($p < 0.009$).

A key observation relates to oropharyngeal secretions: Mouth excretions of the cuirass-ventilated animals were frothy white as in deep suctioning, as opposed to the clear saliva-like appearance of secretions in the other two groups. No other clinical differences between the bag-valve group and the Cuirass group, and no changes in

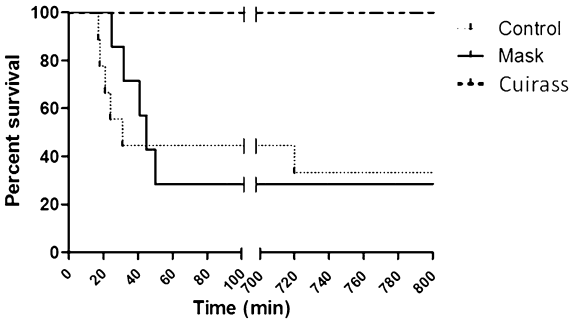

Fig. 2. Kaplan–Meier plot of mortality of the three groups. Time "0" depicts the beginning of ventilation in the Mask and the Cuirass groups. Ventilation lasted for 25 min.

hemodynamic parameters were observed (see below). In surviving animals, no significant differences were found between the three groups in any of the clinical signs observed (data not shown). 24 h following paraoxon exposure, most surviving pigs still showed ataxia, tremors at exertion and low mobility. At that time, 3 of the Cuirass group, and 1 of the surviving Mask group showed minor to no toxicity signs.

3.2. Physiological parameters

Pre-exposure mean values of the physiological parameters were within normal limits for all three study groups (data not shown).

Following exposure to paraoxon all three groups exhibited 30% reduction in hemoglobin saturation together with an increase in arterial pCO_2 and a decrease in arterial pO_2, compared to baseline. Reduction in both BE and blood pH were found in all three groups studied (an average decrease in BE of 15.3 ± 1.6 mEq/l in the Cuirass group, 16.3 ± 2.7 in the Mask group, and an average reduction of pH from 7.5 to 7.14 in the Cuirass and Mask groups, respectively). Sinus bradycardia (30–35% decrease) peaked at 20–30 min post exposure (113 ± 11 bpm in the Cuirass group) and was slightly lower in the Control and the Mask groups (95 ± 9 bpm).

4. Discussion

In OP poisoning, the immediate respiratory failure is mostly due to central respiratory mechanisms, with secondary effects of high dynamic airflow obstruction from secretions and bronchoconstriction, as well as from flaccid paralysis [22,23]. The pig model of paraoxon poisoning used here exhibited reproducible prolonged respiratory distress and delayed mortality, with signs and symptoms characteristic of organophosphate poisoning [21].

The most important finding in the present study was the dramatic effect of Cuirass technique in reducing the paraoxon-induced mortality (Fig. 2). This Cuirass technique was found to be superior to bag-valve mask ventilation, a common ventilation procedure, expected to be used following both single exposure and on-scene mass casualty event.

Earlier studies have demonstrated that respiratory failure was the predominant cause of death in nerve agent poisoning and that significant cardiovascular depression occurred only after cessation of respiration [24,25]. This emphasizes the importance of respiratory support over cardiovascular support during early stages following OP poisoning.

Biphasic Cuirass Ventilation has been reported as an easily-adopted and rapidly-applied method suitable for use by non-medical personnel, even while wearing protective gear [20]. In addition, Ben-Abraham et al. [19] have indicated that physicians wearing full personal protective gear applied the cuirass and instituted ventilation faster than performing endotracheal intubation followed by positive pressure ventilation.

Unfortunately, as we have shown here for the first time, the bag-valve mask ventilation did not sufficiently improve the impact of OP exposure unless continuously implemented. While animals survived during ventilation, shortly after its termination the animals died and mortality rates resembled that of the non-ventilated Control group. In contrast, ventilation with the cuirass for the same period of time prevented 24 h mortality and the animals recovered better and faster with no deterioration following cessation of ventilation.

An additional advantage of the Cuirass relates to airway management. In pre-hospital ventilation, a jaw thrust into the BVM is required to avoid the tongue occluding the airway, assuming the supine position of the casualty. This adds to the difficulties of using BVM in the pre-hospital setting of a chemical event. When using the cuirass there is no need for a jaw thrust, as the use of a guedel is enough. In our study there was no need for that since the animals were in a prone position.

In recent years several studies described a successful use of supraglottic airways and intubation in the pre-hospital setting [26–29]. Endotracheal intubation is still regarded as the golden standard, and supraglottic airways are regarded a bridge until definite airway control is achieved [30]. When looking at the success rates, supraglottic airways are easier to manage, including in a chemical event [26–30]. However, since supraglottic airways will be still connected to a bag-valve device, the results may be similar to that described in the present study. Other limitations of supraglottic airways in a chemical event is the difficulties in performing suction, it does not prevent aspirations, and high-pressure ventilation which is important in preventing acute lung injury is not possible [30].

Several observations should be highlighted:

1. In the present study, the excretions of the cuirass-ventilated animals were frothy white, similar to that seen after deep suctioning. In the Control and Mask groups, secretions were clear, saliva-like in appearance. In a study testing the use of Biphasic Cuirass Ventilation in OP-exposed cats, the device enabled clearance of bronchial secretions, saving the need for active suctioning of the airways [31]. The use of bag-valve mask ventilation requires further support against airway constriction combined with the vast secretions following

OP poisoning. Active suction of these secretions is an important supportive measure [7].

2. A major aspect of acute lung injury is the regulation of alveolar fluid clearance. Under normal conditions, molecular and cellular mechanisms regulate the active transport of solutes and fluids across the alveolar epithelium, thus enabling optimal gas exchange [32–34]. In OP poisoning as is with other pathologies involving respiratory failure and non-cardiogenic pulmonary edema, flooding of the alveolar air spaces with proteinaceous fluid which the epithelium cannot rapidly remove is evident [33,35–37]. This represents a pathological process of a failure to maintain proper airway fluid balance. Furthermore, exposure of the alveolar epithelium to hypoxic conditions has significant adverse effects on epithelial function [34]. We hypothesize that cuirass use improved alveolar fluid clearance and by doing so, may have preserved its critical role in attenuating the development of acute lung injury. This hypothesis deserves further study since lung secretions and lung tissues were not analyzed in this study.
3. The use of the cuirass may help in preventing recurrent alveolar collapse and reopening, and in achieving alveolar recruitment, by reducing tidal volumes and applying positive end-expiratory pressure [38–40]. It is generally thought that the use of positive pressure ventilation may cause further harm due to over-distention with barotrauma, as may be the case in bag-valve mask ventilation [38,41–43]. Failure in opening all atelectatic areas using the bag-valve mask technique may even contribute to the OP-induced damage. The cuirass technique, which better resembles the physiological way of ventilation, avoids this problem [44].
4. Most OP studies in animals focus on pharmacological interventions for the primary goal of preventing immediate death. Only few of them were dedicated to pre-hospital respiratory support (e.g. [45]). Because of the acute nature of OP poisoning and the relatively good response to the antidotes, ventilatory support is required immediately and for a relatively short period of time [46]. In light of the present results, the methods of ventilation following various OP nerve agents exposure should be further evaluated, in addition to the available antidotal treatment. It should be noted that exposure to other chemical agents such as phosgene, may result in acute respiratory distress syndrome (ARDS) that will require longer ventilation times [47]. In the current study we compared the cuirass to bag-valve mask ventilation only, since it is the more common mode of ventilation on-site. Although the use of an endotracheal intubation may improve success rate of bag-valve ventilation, the need for sedation and skilled personnel impede its use in mass casualty event and hence was not included in our study.
5. The cuirass technique was previously shown to have beneficial effects on the cardiovascular system too, i.e. decreasing intra-thoracic pressures and increasing venous return and cardiac output [44,48,49]. In these studies, the cuirass technique offered ventilation support similar to that of positive pressure ventilation, with the addition of improved cardiac output. Acute cardiovascular effects following OP poisoning appear only after respiratory failure is already apparent [24,25]. We did not observe significant differences in both respiratory and cardiovascular parameters between the experimental groups in the present study. Thus, the benefit of the cuirass technique is unlikely to be attributed to cardiovascular effects. However, we did not measure cardiac output in our study.

5. Conclusions

The current study demonstrates the efficacy of the cuirass device in severe respiratory distress induced by paraoxon exposure in a pig model. The minimal antidotal treatment applied here was sufficient to ensure 24 h survival if the cuirass technique was implemented. Without this cuirass ventilation high mortality rate was seen.

We conclude that the MRTX, a noninvasive, easy-to-operate Biphasic Cuirass Ventilation device might be advantageous on-scene in an OP mass casualty event. This finding should be validated in further investigations.

Transparency document

The Transparency document associated with this article can be found in the online version.

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