Efficacy of continuous positive airway pressure in casualties suffering from primary blast lung injury: A modeling study

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Abstract— **Primary blast lung injury is the most important component of a multisystem syndrome of injury that results from exposure to an explosive shockwave. The majority of such casualties require ventilation in an intensive care unit. We describe the use of a novel primary blast lung injury simulator to evaluate the potential efficacy of continuous positive airway pressure in 6 *in silico* casualties over 24 hours after injury. Our results suggest that primary blast lung injury is a form of acute lung injury that can be effectively managed with continuous positive airway pressure. In austere environments or in circumstances where medical resources are overwhelmed, continuous positive airway pressure using ambient air may be of benefit.**

I. Introduction

Detonation of a high-explosive creates a supersonic shock wave. As it dissipates its energy, a unique multi-system syndrome of injury known as primary blast injury (PBI) is generated in casualties [1]. Primary blast lung injury (PBLI) consists of parenchymal hemorrhage, air-space rupture and an inflammatory cascade. This may result in acute respiratory distress syndrome (ARDS). PBLI is a particular feature of the confined space explosions characteristic of terrorist attacks on public transport networks. PBLI was seen in 63% of the critically injured casualties suffered in the Madrid train bombings [2] and 13 of the 24 critically injured casualties in the London train bombings [3]. Life threatening cases will be apparent by the time the casualty reaches hospital and will present with respiratory distress and haemoptysis. Pneumothoraces and pneumatoceles are common. The majority of casualties suffering PBLI will require mechanical ventilation in an intensive care unit (ICU) facility [4].

Intensive care represents the most resource dependent part of a hospital or medical treatment facility (MTF), both in terms of manpower and equipment. Many intensive care units operate at or near full capacity, whilst in the developing world or areas of conflict, access to such a resource is extremely limited or non-existent. In mass casualty events or remote locations, oxygen may be unavailable or clinicians may be reliant on oxygen concentrating devices in order to deliver oxygen enriched air [5]. Continuous positive airway pressure (CPAP) is administered via a tight fitting face mask and is effective in reducing hypoxia resulting from excess extravascular lung water or atelectasis [6]. It achieves this by maintaining the functional residual capacity, reducing the mechanical work of breathing and improving alveolar ventilation [7]. It is effective in the management of hypoxia resulting from cardiogenic pulmonary oedema, muscle fatigue and blunt chest trauma [8, 9], but not pneumonia. Its efficacy has also been demonstrated in the pre-hospital environment [10], and is currently used by several European emergency medical services [11]. It can be administered to patients with respiratory failure outside of the intensive care setting and requires significantly less medical manpower and resources to manage. Ambient-air CPAP could thus be quickly and cheaply applied in the pre-hospital environment by first responders and possibly even by the casualties themselves. Ambient-air CPAP has recently demonstrated utility as a pre-hospital first aid measure following phosgene induced lung injury in an animal model [12]. This porcine study applied CPAP for 24 hours after injury and demonstrated improved survival and reduced lung injury. Here, we investigate the potential value of applying early ambient-air CPAP and 40% oxygen enriched CPAP as a means of limiting disease progression and reducing the need for higher level medical care in PBLI casualties.

II. Methods

The violent and sporadic nature of this disease means that research into novel modes of clinical care is generally dependent on either animal or *in silico* modeling [13]. This study utilizes a bespoke, high-fidelity computerized simulator of primary blast lung injury that has been developed to specifically meet this need [14]. The model has been described in detail in [14]. In summary, it consists of the amalgamation of detailed physiological data collected from a large animal model of severe but sub-lethal blast lung injury [15,16] and an in-silico model of human cardiovascular and respiratory physiology [17,18,21,22]. The cardiopulmonary component of the model is validated as a mathematical representation of human cardiac and respiratory physiology and represented graphically in Fig. 1. A genetic algorithm has been used to parameterize the model such that it robustly replicates the mean physiological parameters collected from the *in vivo* model. This underlying iterative model mathematically describes the relevant human cardio-respiratory physiology and repeats a complete mathematical iteration every 10 milliseconds. The results of

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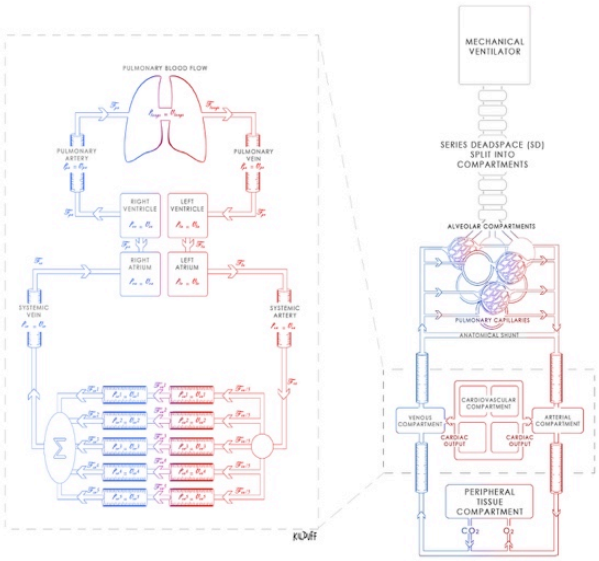
one iteration then determines the starting point for the next. Model parameterization and simulation was performed using the 'Minerva' high performance computing cluster provided by the University of Warwick (396 nodes, each with 2 × hexa-core 2.66 GHz 24 GB RAM) running MATLAB (2015a).

A moderate PBLI was applied to six in-silico young adult males (each weighing 70kg and in good health). Each subject was then studied in each of three arms whilst breathing spontaneously, with no intervention (no CPAP), with 5 cmH_2O of CPAP (low dose) and with 10 cmH_2O of CPAP (high dose) applied one hour after injury. The study was then repeated with the subjects breathing oxygen enriched air with an FiO_2 of 40%. The following respiratory parameters were measured at 4 hourly intervals in all arms of the study; arterial oxygen saturation (SpO_2), partial pressures of arterial oxygen and carbon dioxide (PaO_2, $PaCO_2$), respiratory rate (RR) and arterial pH. The following cardiovascular parameters were measured in the ambient air group only; cardiac output (CO), mean arterial pressure (MAP) and extra-vascular lung water (EVLW).

Figure 1. Graphical representation of the primary blast lung injury simulator.



III. Results

Tables 1 and 2 show the mean results and 95% confidence intervals at the end of the study period. Fig. 2(a-i) depicts the results as they develop over 24 hours. Compared to the no intervention group, application of ambient air CPAP increased mean arterial oxygenation (8.4 kPa (5 cmH_2O) and 9.4 kPa (10 cmH_2O) vs 6.6 kPa) and decreased mean respiratory rate (12 bpm (5 cmH_2O) and 11 bpm (10 cmH_2O) vs 18 bpm). Ventilation of carbon dioxide was also enhanced by the application of CPAP (5.8 kPa (5 cmH_2O) and 5.5 kPa (10 cmH_2O) vs 6.8 kPa) with a consequent improvement in arterial pH (7.4 (5 cmH_2O) and 7.5 (10 cmH_2O) vs 7.2). Application of 40% oxygen in combination with CPAP raised arterial oxygenation compared to the no intervention group as well as to the 40% oxygen only group (11.0 kPa (5 cmH_2O) and 11.9 kPa (10 cmH_2O) vs 9.1 kPa). The use of oxygen enriched air did not alter the remaining respiratory parameters to a clinically important extent. Increasing CPAP improved cardiovascular parameters with both an increasing mean arterial pressure and cardiac output and decreasing extravascular lung water.

TABLE I. Respiratory Results at 24 Hours

Parameter	Air *No CPAP*	Air *5 cmH_2O CPAP*	Air *10 cmH_2O CPAP*	40% *0 cmH_2O CPAP*	40% *5 cmH_2O CPAP*	40% *10 cmH_2O CPAP*
PaO_2 (kPa)	6.6 (6.1-7.0)	8.4 (7.7-9.1)	9.4 (8.9-9.9)	9.1 (8.7-.5)	11.0 (10.4-11.6)	11.9 (11.4-12.3)
$PaCO_2$ (kPa)	6.8 (6.2-7.3)	5.8 (5.2-6.4)	5.5 (5.1-5.8)	6.4 (6.1-6.8)	5.5 (4.9-6.1)	5.2 (4.8-5.7)
SpO_2 (%)	93 (91- 94)	94 (93- 95)	95 (94-96)	95 (94-96)	97 (96- 98)	98 (97- 98)
RR (bpm)	18 (16 – 20)	12 (10 – 15)	11 (10 – 13)	13 (11 – 15)	10 (10 – 10)	10 (10 – 10)
pH	7.2 N/A	7.4 N/A	7.5 (7.4-7.5)	7.3 (7.1-7.4)	7.5 (7.3-7.6)	7.5 (7.3-7.6)

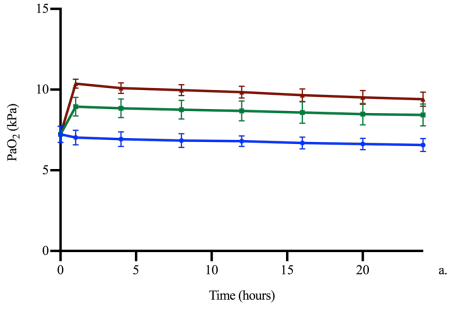
Values in brackets represent 95% confidence intervals. Arterial oxygen saturation (SpO2), partial pressures of arterial oxygen and carbon dioxide (PaO2, PaCO2), respiratory rate (RR), arterial pH

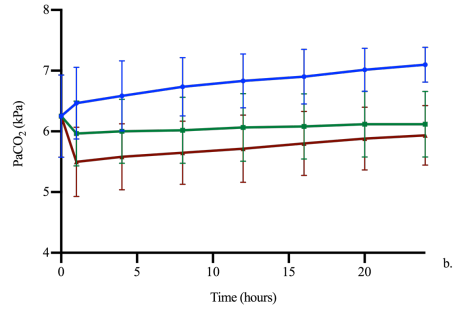
TABLE II. Cardiovascular Results at 24 Hours

Parameter	Air *No CPAP*	Air *5 cmH_2O CPAP*	Air *10 cmH_2O CPAP*
MAP (mmHg)	72 (63-80)	76 (69-84)	78 (72-85)
CO (L/min)	6.5 (4.0-9.0)	7.0 (4.1-9.9)	7.2 (4.8-9.6)
MPAP (mmHg)	25 (20-30)	22 (17-27)	22 (16-27)
EVLW (ml)	374 (313-435)	350 (296-404)	322 (266-377)

Values in brackets represent 95% confidence intervals. Cardiac output (CO), mean artery & pulmonary artery pressure (MAP, MPAP), Extra-vascular lung water (EVLW).

Figure 2. Study results over 24 hours at different levels of CPAP: 0 cmH_2O (blue), 5 cmH_2O (green) and 10 cmH_2O (red). a) Partial pressure of arterial oxygen in ambient air, b) Partial pressure of arterial carbon dioxide in ambient air, c) Respiratory rate in ambient air, d) Partial pressure of arterial O2 with 40% FiO_2, e) Partial pressure of arterial CO_2 with 40% FiO_2, f) Respiratory rate with 40% FiO_2, g) Extra-vascular lung water (EVLW), h) Cardiac Output, i) Mean Arterial Pressure.





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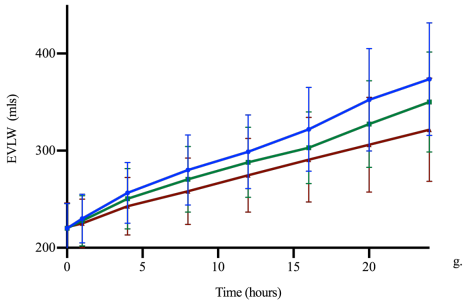

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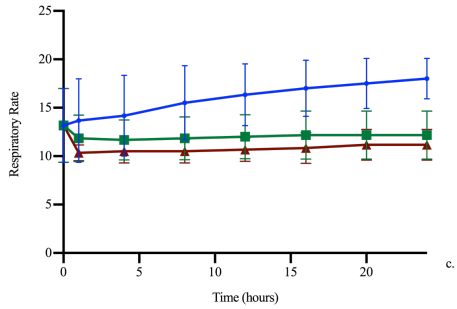

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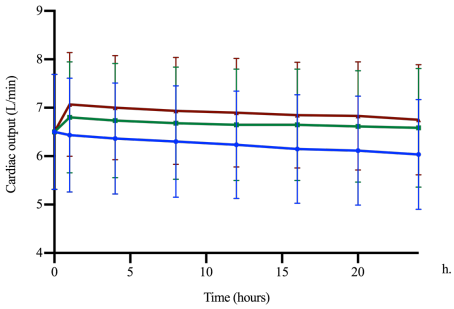

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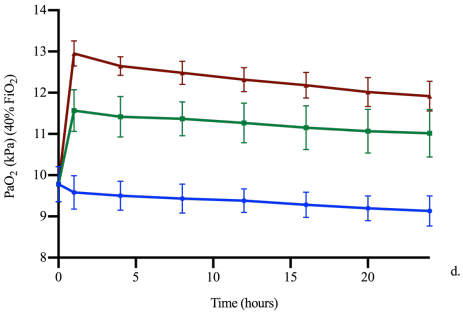

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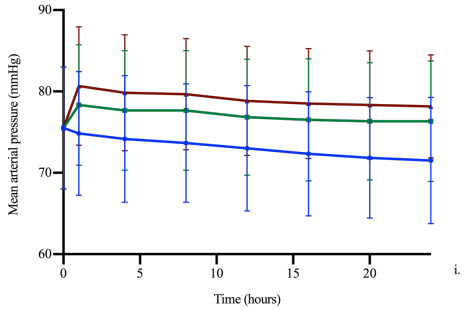

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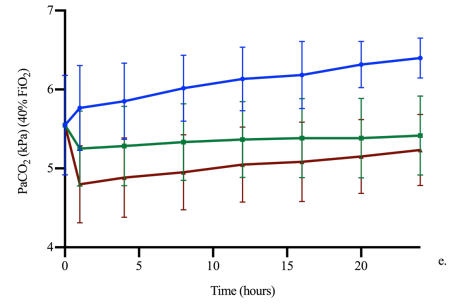

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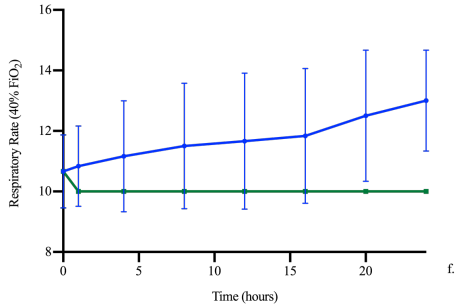

f.

IV. Discussion

This study suggests that there is the potential for benefit through the early application of ambient air CPAP in casualties with PBLI. The two most important respiratory parameters, partial pressure of oxygen and respiratory rate are both markedly improved by the application of low dose CPAP and high dose CPAP. This effect is predictably augmented by the use of oxygen enriched air. Additionally, the ventilation of carbon dioxide is improved, leading to a resolution of respiratory acidosis. Whilst a progressive decrease in extravascular lung water is seen with increasing CPAP, this does not appear to be a large enough effect to account for the improvements in oxygenation in isolation. This could also be explained by faster and easier attainment of alveolar threshold opening pressure (TOP) resulting in greater alveolar ventilation.

Intensive care intervention is normally considered when, despite best standard medical care, arterial oxygenation falls below 8 kPa or the work of breathing is so great (evidenced by an increasing respiratory rate) that the patient will become exhausted. In this study, application of ambient air

low dose CPAP keeps these parameters above this “ICU threshold” and maintains them at a level that allows the patient to be managed in the absence of significant medical infrastructure. The application of ambient-air high dose CPAP in this study resulted in further improvements in respiratory function compared to the low dose group. This effect however, appears to be limited compared to the improvement seen between the no-intervention group and the low dose group. In the conscious and spontaneously breathing casualty, low dose CPAP is more comfortable and better tolerated than high dose, potentially resulting in much better compliance with treatment.

Unlike most other forms of acute lung injury, PBLI is frequently complicated by traumatic pneumothoraces and pneumatoceles. There is traditional reluctance amongst clinicians to administer CPAP to patients with pneumothoraces out of fear that they may be exacerbated by the application of positive airway pressure. Such concerns are not evidence based, however, and attitudes are changing with a growing appreciation that this is not the case. In fact, the evidence suggests that even mechanically ventilated patients with traumatic pneumothoraces do not routinely need to be drained [19]. This is reflected in the current guidelines published by the Eastern Association for the Surgery of Trauma [20]. It is very unlikely that the application of 5 cmH_2O of CPAP in a spontaneously ventilating patient will lead to harm.

V. Conclusions

This in-silico study demonstrates potentially important clinical benefits from the application of CPAP in conscious and haemodynamically stable casualties with PBLI. In austere environments or in the context of a mass casualty event, applying low dose ambient-air CPAP may attenuate the evolving lung injury and reduce or delay the need for more sophisticated medical resources.

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