BJA

LABORATORY INVESTIGATION

Pre-hospital continuous positive airway pressure after blast lung injury and hypovolaemic shock: a modelling study

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Abstract

Background: In non-traumatic respiratory failure, pre-hospital application of CPAP reduces the need for intubation. Primary blast lung injury (PBLI) accompanied by haemorrhagic shock is common after mass casualty incidents. We hypothesised that pre-hospital CPAP is also beneficial after PBLI accompanied by haemorrhagic shock.

Methods: We performed a computer-based simulation of the cardiopulmonary response to PBLI followed by haemorrhage, calibrated from published controlled porcine experiments exploring blast injury and haemorrhagic shock. The effect of different CPAP levels was simulated in three *in silico* patients who had sustained mild, moderate, or severe PBLI (10%, 25%, 50% contusion of the total lung) plus haemorrhagic shock. The primary outcome was arterial partial pressure of oxygen (Pa_{O_2}) at the end of each simulation.

Results: In mild blast lung injury, 5 cm H_2O ambient-air CPAP increased Pa_{O_2} from 10.6 to 12.6 kPa. Higher CPAP did not further improve Pa_{O_2}. In moderate blast lung injury, 10 cm H_2O CPAP produced a larger increase in Pa_{O_2} (from 8.5 to 11.1 kPa), but 15 cm H_2O CPAP produced no further benefit. In severe blast lung injury, 5 cm H_2O CPAP inceased Pa_{O_2} from 4.06 to 8.39 kPa. Further increasing CPAP to 10—15 cm H_2O reduced Pa_{O_2} (7.99 and 7.90 kPa, respectively) as a result of haemodynamic impairment resulting from increased intrathoracic pressures.

Conclusions: Our modelling study suggests that ambient air 5 cm H_2O CPAP may benefit casualties suffering from blast lung injury, even with severe haemorrhagic shock. However, higher CPAP levels beyond 10 cm H_2O after severe lung injury reduced oxygen delivery as a result of haemodynamic impairment.

Keywords: computer simulation; continuous positive airway pressure; hypovolaemic shock; mathematical modelling; primary blast lung injury

Editor's key points

- In non-traumatic respiratory failure, pre-hospital application of CPAP reduces the need for intubation.
- The authors modelled whether pre-hospital CPAP may also be beneficial after primary blast lung injury accompanied by haemorrhage.

- The modelling was validated using physiological data obtained from a porcine model of blast lung injury accompanied by haemorrhage.
- Modelling demonstrated that ambient air CPAP improved Pa_{O_2} even with severe haemorrhagic shock, unless 10—15 cm H_2O was applied after severe blast injury.

- This modelling study suggests that the clinical benefits of pre-hospital ambient air CPAP may extend to mass casualty scenarios where blast lung injury is common.

The application of pre-hospital CPAP for the emergency treatment of acute respiratory failure (ARF) is increasingly used by emergency medical services.[1] In non-traumatic ARF, pre-hospital application CPAP via a tight-fitting mask reduces ventilatory frequency and the need for subsequent intubation.[2–4] Additionally, porcine data suggest the potential for decreased mortality, decreased pulmonary oedema, and increased arterial oxygen saturation after toxic lung injury when ambient-air CPAP is administered shortly after injury.[5] Computerised modelling of blast lung injury suggests that the use of ambient-air CPAP improves arterial oxygenation, increases gas exchange, and reduces ventilatory frequency and pulmonary oedema.[6] This study assumes that CPAP in the range used (between 5 and 10 cm H_2O) will not exacerbate pre-existing pneumothoraces in spontaneously breathing individuals, in accordance with current published guidelines.[7] The authors of both studies supported the use of ambient-air CPAP as a first-aid or self-aid measure after such injury patterns.

The combination of shock and blast lung injury is particularly relevant to the pre-hospital management of casualties in a mass casualty scenario. Before application of CPAP under such circumstances, the effect of raising intrathoracic pressure in casualties that are haemodynamically compromised as a result of blood loss must be determined to confirm efficacy and safety. However, the design and implementation of RCTs to answer these questions during mass casualty scenarios is unlikely to be feasible. In this study, we use an existing computerised model of blast lung injury and introduce the capacity to replicate haemorrhagic shock. We then simulate three casualties, each with identical shock state but with increasing degrees of blast lung injury. We assume that the casualties do not have access to pressurised oxygen in the pre-hospital phase, but are able to self-administer or 'buddy-administer' first-aid CPAP masks. Each casualty is then exposed to different levels of ambient-air CPAP, and the subsequent effects on oxygenation and haemodynamics are quantified.

Methods

Study design

This was a computer simulation study, performed on a 64-bit Quad-Core Intel Core i7 2.7 GHz personal computer manufactured by Apple running Matlab (R2020a) in London, England.

In silico model of blast lung injury

The primary blast lung injury (PBLI) simulator used in this study consists of a bespoke computational model that can represent mechanical ventilation, spontaneous ventilation, or both,[8–10] trauma-induced acute lung injury,[11,12] and ventilator-induced lung injury.[13–15] The pulmonary model comprises conducting airways and a respiratory zone of 100 parallel alveolar compartments, with a related set of parameters accounting for alveolar compliance, and airway and perialveolar vascular resistances. The integrated cardiovascular model consists of 19 variably compliant compartments, with pulsatile blood flow and ventilation affected transalveolar blood flow. All components are built from mass-conserving functions and solved as algebraic equations, obtained or approximated from the published literature, experimental data, and clinical observations. Equations are solved iteratively in series, with each iteration representing a physiological time of 5 ms.

Spontaneous breathing is simulated by incorporating a non-linear pressure signal acting on the lungs that induces a negative pressure gradient between the lungs and the upper respiratory tract, driving the flow of air (see[13] for further details). The applied pressure at the nasal passage and mouth is assigned to be 0 cm H_2O (relative to the atmospheric pressure) during unassisted spontaneous ventilation and adjusted to appropriate pressures during CPAP ventilation. Lung trauma as a result of a blast is simulated in the model by varying two parameters: (1) extrinsic pressure (P_{ext}, cm H_2O) represents the effective net pressure operating on each alveolar compartment, attributed to factors including alveolar interdependence, presence of adequate levels of pulmonary surfactant, or the accumulation of interstitial fluid, and (2) threshold opening pressure (TOP, cm H_2O), represents the threshold of the airway pressure below which an airway to an alveolar compartment will remain collapsed. As would be expected,
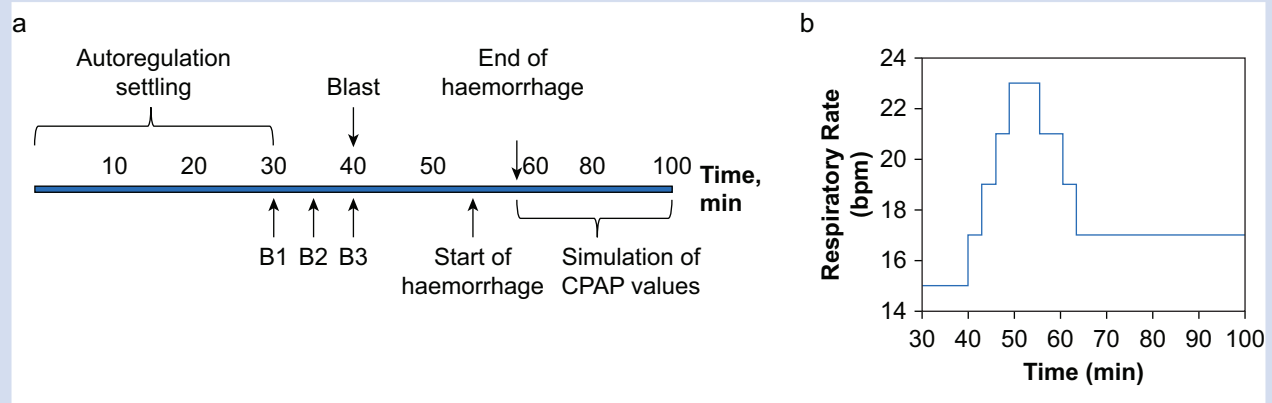

Fig 1. Simulation protocol. (a) The timeline of the implemented simulation protocol. (b) The values of ventilatory frequency implemented during the simulation protocol.

the source data also detail acute changes in mean ventilatory frequencies in response to both blast and haemorrhage (Fig. 1b), which have been integrated into the simulations.

Haemorrhage model

In order to model haemorrhage, a cardiovascular control module is implemented that produces a realistic baroreflex-based autoregulation response, targeting cardiovascular homeostasis. In response to deviation in MAP from a reference value (MAP_R), the control module adjusts θ, representing three variables of the cardiovascular system: HR, ventricular contractility, and peripheral systemic resistance. The value of θ at time t (θ_t) with respect to its value at the preceding time instant, $\theta_{\bar{t}}$, is given by

$$\theta_t = \begin{cases} \theta_t + \left[\alpha_\theta \{\theta_{max} - \theta_t\} \dfrac{(MAP_R - MAP)}{20} \right], & \text{if } MAP < MAP_R \\ \theta_t - \left[\alpha_\theta \{\theta_t - \theta_R\} \right], & \text{if } MAP \geq MAP_R \end{cases}$$

For this study, MAP_R is set to 85 mm Hg. θ_{max} and θ_R define the maximum and reference values of the related variable θ, respectively. α_θ allows for the calibration of the rate of response and is used to match the model outputs to data. Based on the available data, the autoregulatory response has been scaled to reflect measured parameters after both blast exposure and severe haemorrhage, as shown in Table 1. The model iteratively adopts blast and then haemorrhagic physiological parameters, as these injuries are suffered by the casualty.

Model validation

The source data used to calibrate and validate the above model were provided by collaborators at the Defence Science and Technology Laboratories, Porton Down, UK. Twelve anaesthetised pigs were exposed to blast and haemorrhagic shock under controlled conditions, resulting in a moderate blast lung injury.[16] Figure 2 compares the model response with the source data. Baseline partial pressure of oxygen (Pa_{O_2}) values are somewhat lower in the pig data than in our *in silico* subjects, consistent with the fact that the pigs are studied after laparotomy and breathing air spontaneously while

anaesthetised. Model responses to PBLI for Pa_{O_2} and partial pressure of carbon dioxide (Pa_{CO_2}) show a good agreement with the data for both the mild and moderate lung injury. In the severe lung injury casualty, Pa_{O_2} values are lower and Pa_{CO_2} values higher than the source data—the increase in Pa_{CO_2} demonstrated by the model can be explained by the simulated increase in ventilatory frequency (see Fig. 1) being insufficient to counteract the effect of the PBLI in this case. Model responses to PBLI for the haemodynamic variables show an excellent match to the data in all cases (note the differences in baseline HR between the porcine and human models, as expected). The large reduction of MAP after haemorrhage seen in the porcine data is reinforced by the Barcroft-Edholm reflex,[17] characterised by the reduction of peripheral resistance and HR. This reflex is replicated in our model, producing a reduction of MAP to 55 mm Hg. After the initiation of this reflex, cardiovascular autoregulatory mechanisms in the model react to try to increase MAP by increasing HR and systemic vascular resistance. However, despite HR recovering, MAP continues to decrease to 35 mm Hg owing to the slow recovery of systemic vascular resistance, the large volume of blood loss, and persistent myocardial impairment (reduced contractility as a result of the blast injury).[17] Overall, the range of responses generated by the computational model provide a realistic spectrum of severity of PBLI and associated responses that agree well with the experimental data from Garner and colleagues.[16]

Modelling study protocol

Figure 1a illustrates the simulation protocol implemented in this study. Three *in silico* casualties (healthy young adult males) are created and are initially allowed to reach a physiological steady state within the model for 40 min. From this time point up to 55 min, the simulation follows the blast injury trial protocol as detailed in the source *in vivo* data (explained briefly below).[16] At 30, 35, and 40 min, three baseline readings are taken. The effects of mild, moderate, and severe blast lung injury are then simulated in each of the *in silico* casualties, respectively. This results in an increasing contusional injury (10, 25, and 50% of the total lung), reflecting the various degrees of direct lung insult that has been observed in survivors with blast lung injury. Alveolar TOPs in the contused lung were randomly assigned within a normal distribution to give values consistent with published values.[18,19] At 55 min, each casualty suffers a loss of 30% of their blood volume over a 4 min period. From 60 to 100 min, ambient-air CPAP is applied to each casualty replicating a potential first-aid measure in the event of a major incident overwhelming the emergency medical services. The simulation is repeated for each casualty such that they are trialled with 5, 10, and 15 cm H_2O of CPAP.

Data collection

Throughout the simulation, we recorded HR, MAP, arterial Pa_{O_2} and Pa_{CO_2}, and cardiac output (CO). Additionally, the effect of CPAP was evaluated using shunt fraction (derived using the shunt equation) and tissue oxygen delivery (DO_2).

Primary modelling outcome

The primary outcome was the arterial Pa_{O_2} at the end of each simulation modelling mild, moderate, and severe primary blast injury (10, 25, 50% lung contusion, respectively).

Table 1 Parameters of the cardiovascular control model.

θ	θ_{max}	θ_R	Scenario	α_θ
HR	200 beats min^{-1}	70 beats min^{-1}	Normal	0.0005
			Haemorrhage	0.00002
			Blast trauma	0.00003
Contractility	20 mm Hg ml^{-1}	2.95 mm Hg ml^{-1}	Normal	0.01
			Haemorrhage	0.0001
			Blast trauma*	—
Systemic resistance	0.2 mm Hg s ml^{-1}	0.09 mm Hg s ml^{-1}	Normal	0.01
			Haemorrhage†	0.0001
			Blast trauma	0.01

* In the case of blast trauma, ventricular contractility is reduced by 5.7 mm Hg ml^{-1}, reflecting the myocardial impairment attributable to a blast.
† The data from the porcine study indicates a decrease in cardiac output despite an increase in HR, suggesting another autonomous reflex overriding the baroreflex. This is likely to be the Barcroft-Edholm reflex,[17] a reduction in HR and a vasodilatory response to sudden onset of blood loss, which is included here as a one-off reduction in peripheral resistance at the beginning of haemorrhage.
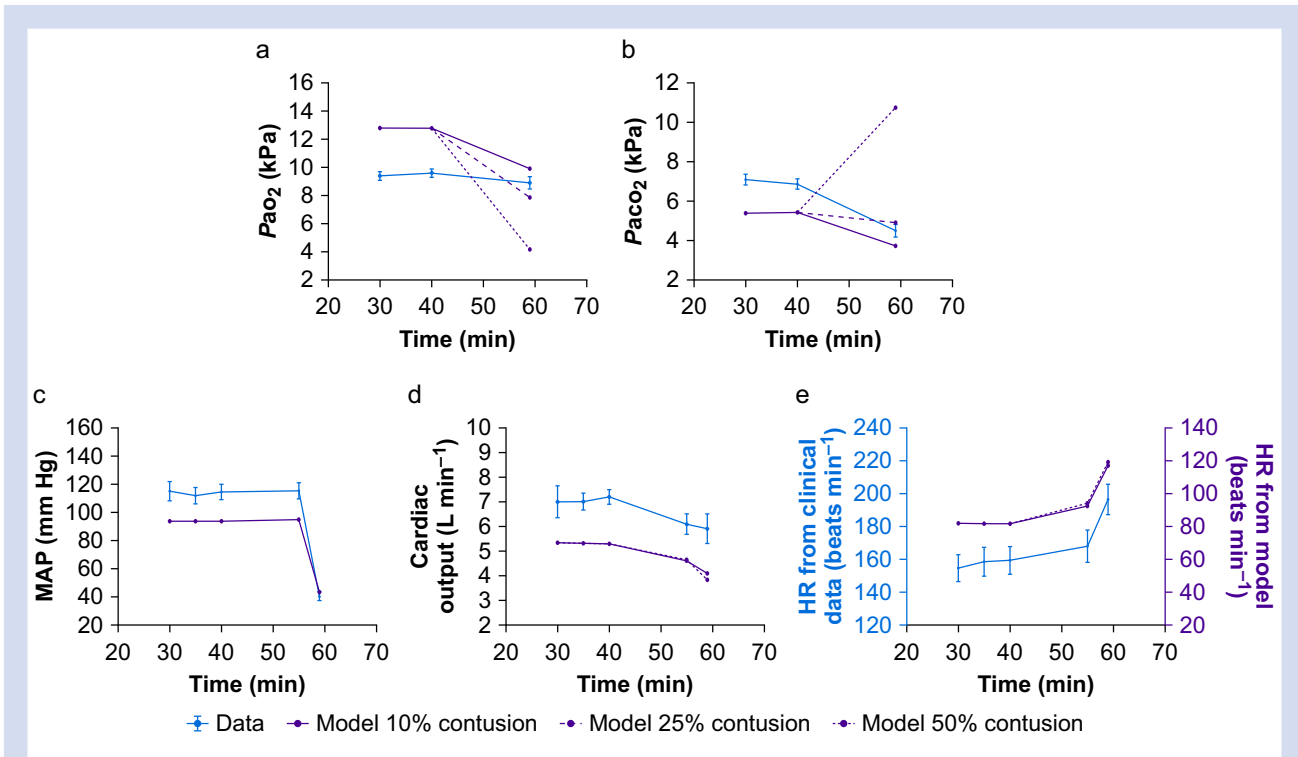
Fig 2. Model validation. Modelled patients' responses to varying levels of severity of primary blast lung injury (PBLI) and haemorrhage of 30% total blood volume, compared with responses of 12 pigs to PBLI and haemorrhage of 30% total blood volume (mean [standard deviation]).[16] Refer to Figure 1 for simulation protocol. (a) Partial pressure of oxygen (cm H_2O), (b) partial pressure of carbon dioxide (cm H_2O), (c) MAP (mm Hg), (d) cardiac output (ml min^{-1}), (e) HR (beats min^{-1}).

Statistics

Because of the deterministic nature of the modelling, where the outcome is independent of number of modelling runs unless we change the parameters or modelling boundaries, statistical analysis was not undertaken.

Results

Model validation

Baseline Pa_{O_2} values were lower in the published pig data than in our *in silico* subjects, consistent with the fact that the pigs are studied after laparotomy and breathing air spontaneously while anaesthetised (Fig. 2). Model responses to PBLI for Pa_{O_2} and Pa_{CO_2} show a good agreement with the data for both the mild and moderate lung injury. In the severe lung injury casualty, Pa_{O_2} values are lower and Pa_{CO_2} values higher than the source data—the increase in Pa_{CO_2} demonstrated by the model can be explained by the simulated increase in ventilatory frequency (see Fig. 1) being insufficient to counteract the effect of the PBLI in this case.

Model characteristics

Our modelling shows that once haemorrhage stops after 59 min, haemodynamic recovery is characterised by the autoregulation of systemic vascular resistance and HR

compensating for the reduction of MAP caused by blood loss and persistent myocardial impairment as a result of the blast injury (Figs 3—5). HR increases rapidly and systemic vascular resistance more slowly, with recovery of MAP (although the pre-haemorrhage MAP is not attained).

Mild lung injury

After 10% total lung contusion (Fig. 3), 5 cm H_2O ambient-air CPAP increased Pa_{O_2} from 10.6 to 12.6 kPa. Higher levels of CPAP did not further improve Pa_{O_2} and slightly reduced CO and DO_2.

Moderate lung injury

After 25% total lung contusion (Fig. 4), application of 10 cm H_2O CPAP produced a larger increase in Pa_{O_2} (from 8.5 to 11.1 kPa) than 5 cm H_2O, but a further increase to 15 cm H_2O produced no further benefit.

Severe lung injury

After 50% total lung contusion (Fig. 5), 5 cm H_2O CPAP increased Pa_{O_2} from 4.06 to 8.39 kPa. Further increasing CPAP to 10 and 15 cm H_2O resulted in slightly reduced values of Pa_{O_2} (7.99 and 7.90 kPa, respectively) because of haemodynamic impairment (note smaller increases in CO and DO_2).
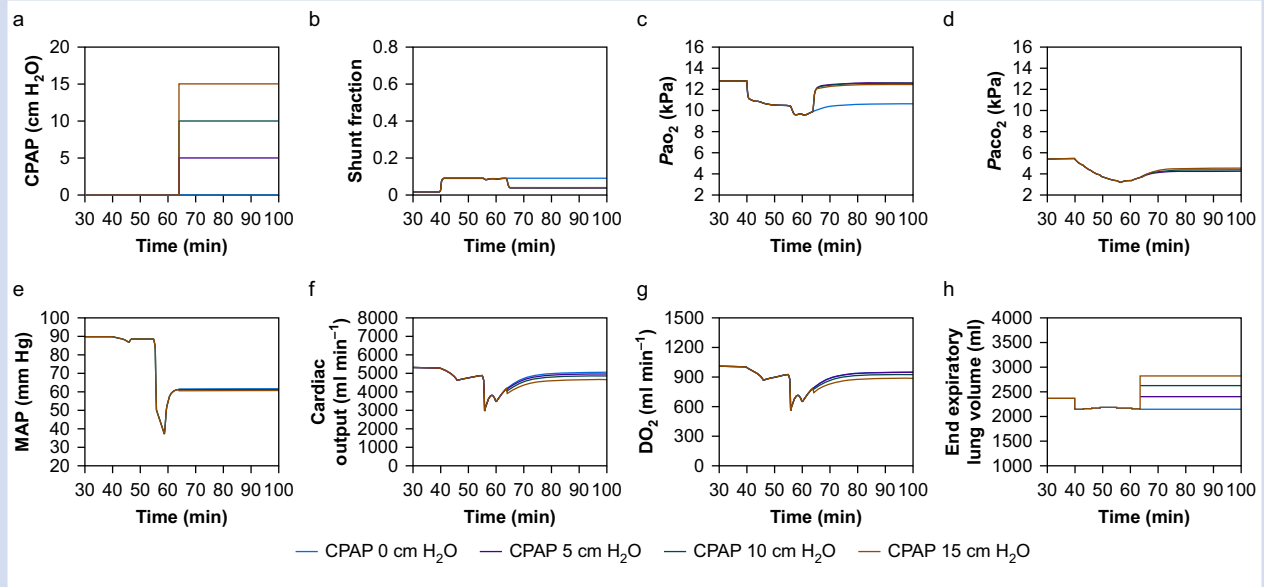
Fig 3. Refer to Figure 1 for simulation protocol. (a) Level of CPAP with ambient air (cm H_2O) implemented at 64 min into the simulation protocol, (b) shunt fraction, (c) partial pressure of oxygen (cm H_2O), (d) partial pressure of carbon dioxide (cm H_2O), (e) MAP (mm Hg), (f) cardiac output (ml min^{-1}), (g) delivered oxygen (ml min^{-1}), (h) end expiratory lung volume (ml). DO_2, oxygen delivery.

Discussion

Ambient-air CPAP is considered to be of significant clinical benefit to casualties suffering lung injury in the pre-hospital environment. This modelling study suggests that this benefit also extends to casualties suffering from blast lung injury with severe haemorrhagic shock. However, high airway pressures can be detrimental to CO through a combination of rising pulmonary vascular resistances increasing right ventricular afterload and diminishing venous return reducing right ventricular preload.[20] This leads to reduced right ventricular output and left ventricular filling. Consequently, improvement in oxygenation can be outweighed by positive pressure
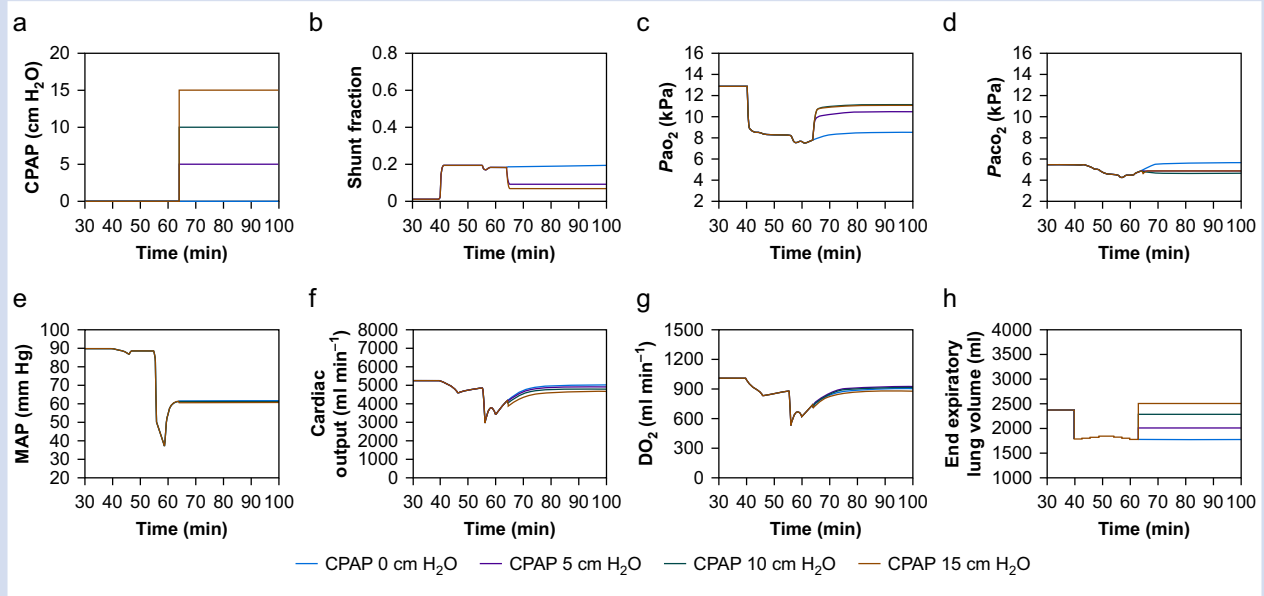

Fig 4. Patient responses to varying levels of CPAP for 25% lung contusion (moderate primary blast lung injury) and haemorrhage of 30% total blood volume. Refer to Figure 1 for simulation protocol. (a) Level of CPAP with ambient air (cm H_2O) implemented at 64 min into the simulation protocol, (b) shunt fraction, (c) partial pressure of oxygen (cm H_2O), (d) partial pressure of carbon dioxide (cm H_2O), (e) MAP (mm Hg), (f) cardiac output (ml min^{-1}), (g) delivered oxygen (ml min^{-1}), (h) end expiratory lung volume (ml). DO_2, oxygen delivery.
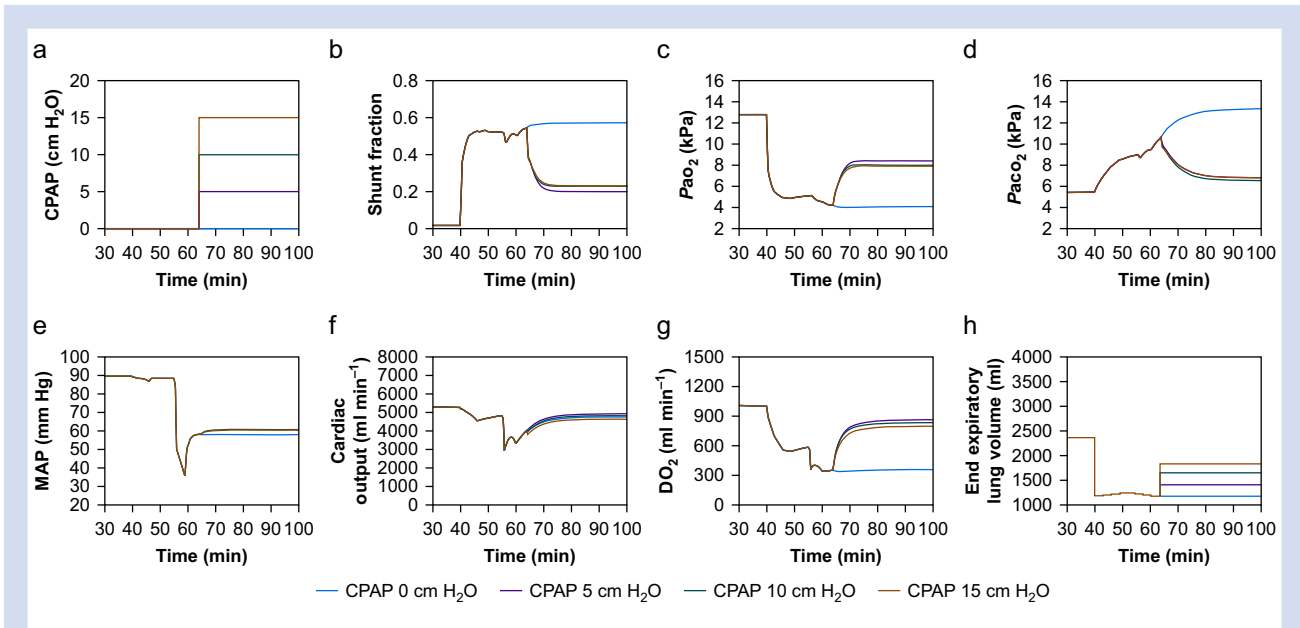
Fig 5. Patient responses to varying levels of CPAP for 50% lung contusion (severe primary blast lung injury) and haemorrhage of 30% total blood volume. Refer to Figure 1 for simulation protocol. (a) Level of CPAP with ambient air (cm H_2O) implemented at 64 min into the simulation protocol, (b) shunt fraction, (c) partial pressure of oxygen (cm H_2O), (d) partial pressure of carbon dioxide (cm H_2O), (e) MAP (mm Hg), (f) cardiac output (ml min^{-1}), (g) delivered oxygen (ml min^{-1}), (h) end expiratory lung volume (ml). DO_2, oxygen delivery.

ventilation-induced reduction in CO leading to poor tissue DO_2.[21] Our results suggest that increasing CPAP levels beyond 5−10 cm H_2O does not lead to clinically important improvements in arterial oxygenation, and in our most severely injured casualty model such increases in CPAP began to negatively affect DO_2 because of haemodynamic impairment.

Our model showed similar characteristics to an experimental model of porcine lung blast injury and haemorrhage. Model responses to PBLI for the haemodynamic variables show an excellent match to the data in all cases, other than the expected differences in baseline HR between the porcine and human models. The large reduction of MAP after haemorrhage seen in the porcine data is reinforced by the Barcroft-Edholm reflex,[19] characterised by the reduction of peripheral resistance and HR. This reflex is replicated in our model, producing a reduction of MAP to 55 mm Hg. After the initiation of this reflex, cardiovascular autoregulatory mechanisms in the model react to try to increase MAP by increasing HR and systemic vascular resistance. However, despite HR recovering, MAP continues to decrease to 35 mm Hg owing to the slow recovery of systemic vascular resistance, the large volume of blood loss, and persistent myocardial impairment (reduced contractility as a result of the blast injury).[19] Overall, the range of responses generated by the computational model provide a realistic spectrum of severity of PBLI and associated responses that agree well with the experimental data from Garner and colleagues.[16]

Our model has a number of limitations. Data from human patients with which the model could be calibrated are scarce, and we therefore relied heavily on data from animal experiments. The model also does not currently include a representation of casualties with pneumothoraces, a limitation that we are currently working to remove. The application of a CPAP mask is intended for fully conscious casualties only. This study therefore applies only to casualties with non-significant head injury who are sufficiently haemodynamically stable to maintain normal cerebration. We recognise that clinical validation of our findings will be difficult given the context, but we feel that this only further emphasises the usefulness of using a computational modelling approach. Further development of the model and validation against additional datasets will allow us to simulate larger numbers of casualties with finer granularity and broader age ranges. However, the results described above represent the best evidence currently available on this subject for healthcare professionals working in the pre-hospital environment and concerned with the management of mass casualty scenarios.

In summary, our results suggest that in the event of a major incident involving polytraumatised young adults, provision of ambient-air masks providing 5 cm H_2O CPAP should be considered to reduce the need for invasive ventilatory support.

Authors' contributions

Principal modeller: SM
Modeller and technical reviewer: AD
Original concept, study design: TES, DGB, JGH
All authors contributed to the drafting of the manuscript.

Declaration of interest

JGH is associate editor-in-chief of the *British Journal of Anaesthesia*. The other authors declare that they have no conflicts of interest.

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