Influence of negative expiratory pressure ventilation on hemodynamic variables during severe hemorrhagic shock

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Objective: **Outcome after trauma with severe hemorrhagic shock is still dismal. Since the majority of blood is present in the venous vessels, it might be beneficial to perform venous recruiting via the airway during severe hemorrhagic shock. Therefore, the purpose of our study was to evaluate the effects of negative expiratory pressure ventilation on mean arterial blood pressure, cardiac output, and short-term survival during severe hemorrhagic shock.**

Design: **Prospective study in 21 laboratory animals.**

Setting: **University hospital research laboratory.**

Subjects: **Tyrolean domestic pigs.**

Interventions: **After induction of controlled hemorrhagic shock (blood loss ~45 mL/kg), 21 pigs were randomly ventilated with either zero end-expiratory pressure (0 PEEP; n = 7), 5 cm H_2O positive end-expiratory pressure (5 PEEP; n = 7), or negative expiratory pressure ventilation (up to −30 cm H_2O at the endotracheal tube during expiration; n = 7).**

Measurements and Main Results: **Mean (±SD) arterial blood pressure was significantly higher in the negative expiratory pressure ventilation swine when compared with the 0 PEEP (38 ± 5 vs. 27 ± 3 mm Hg; $p = .001$) and the 5 PEEP animals (38 ± 5 vs. 20 ± 6 mm Hg; $p < .001$) after 5 mins of the experiment. Cardiac output was significantly higher in the negative expiratory pressure ventilation swine when compared with the 0 PEEP (3.1 ± .4 vs. 1.9 ± .9 L/min; $p = .001$) and 5 PEEP animals (3.1 ± .4 vs. 1.2 ± .8 L/min; $p < .001$) after 5 mins of the experiment. All seven negative expiratory pressure ventilation animals, but only three of seven 0 PEEP animals ($p = .022$), survived the 120-min study period, whereas all seven of seven 5 PEEP animals were dead within 35 mins ($p < .001$). Limitations include that blood loss was controlled and that the small sample size limits the evaluation of survival outcome.**

Conclusions: **When compared with pigs ventilated with either 0 PEEP or 5 PEEP, negative expiratory pressure ventilation during severe hemorrhagic shock improved mean arterial blood pressure and cardiac output. (Crit Care Med 2006; 34:2175–2181)**

Key Words: negative expiratory pressure; hemorrhage; shock; ventilation

Management of trauma patients in severe hemorrhagic shock is a challenging aspect of trauma care. Although there is an ongoing discussion regarding beneficial vs. adverse effects of fluid resuscitation during uncontrolled hemorrhagic shock, new approaches such as vasopressin to manage severe bleeding are entering the debate as well (1–4). However, both drugs and fluid resuscitation need to be administered intravenously to be effective. Unfortunately, especially in those patients who need therapy the most since blood pressure is collapsing, obtaining rapid intravenous access may be very difficult. A strategy to improve cardiocirculatory function even before an intravenous access can be obtained could be extremely beneficial in these patients.

Since the majority of blood is present in the venous vessel system, it may be helpful to perform venous recruiting when managing a patient in severe hemorrhagic shock, until a venous access can be obtained. Previous studies described positive effects of an inspiratory impedance threshold valve during cardiopulmonary resuscitation and hemorrhagic shock (5–8) in regard to optimizing right and left atrial filling and, therefore, cardiac output and mean arterial blood pressure. Although the venous recruiting concept of the inspiratory threshold valve is intriguing, it can only be used during cardiopulmonary resuscitation or spontaneous ventilation; however, extrapolating this concept to mechanical ventilation would be desirable. In that case, endotracheal intubation could be used to achieve a secured airway, oxygenation, and additionally venous recruiting with negative expiratory pressure.

The purpose of this study was therefore to assess the effects of negative expiratory pressure ventilation with positive pressure ventilation with zero cm H_2O PEEP (0 PEEP) and with positive pressure ventilation with 5 cm H_2O PEEP (5 PEEP), respectively. The tested primary study outcome was the improvement of mean arterial blood pressure, and secondary study outcomes were cardiac output and short-term survival.

MATERIALS AND METHODS

This project was approved by the Austrian Federal Animal Investigational Committee, and the animals were managed in accordance with the American Physiologic Society, institutional guidelines, and the position of the American Heart Association on Research Ani-

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Supported, in part, by the Austrian National Bank grants 9513 and 11448, Vienna, Austria, and the Department of Anesthesiology and Critical Care Medicine, Innsbruck Medical University, Austria.

The authors have not disclosed any potential conflicts of interest.

DOI: 10.1097/01.CCM.0000229886.98002.2B

mal Use, as adopted on November 11, 1984. Animal care and use were performed by qualified individuals, supervised by veterinarians, and all facilities and transportation comply with current legal requirements and guidelines. Anesthesia was used in all surgical interventions, all unnecessary suffering was avoided, and research would have been terminated if unnecessary pain or fear resulted. Our animal facilities meet the standards of the American Association for Accreditation of Laboratory Animal Care.

Surgical Preparations and Measurements. This study was performed on 21 healthy, 12- to 16-wk-old swine weighing 35–45 kg. The animals were fasted overnight but had free access to water. The pigs were premedicated with azaperone (4 mg/kg intramuscularly, neuroleptic agent, Janssen, Vienna, Austria) and atropine (0.01 mg/kg intramuscularly) 1 hr before surgery. Anesthesia was induced with a single bolus dose of ketamine (20 mg/kg intramuscularly), propofol (1–2 mg/kg intravenously), and piritramid (30 mg intravenously, opioid with ~4–8 hrs half time, Janssen, Vienna, Austria) given via an ear vein. The animals were placed in a supine position, and their trachea was intubated during spontaneous ventilation. After intubation, pigs were ventilated with a prototype volume-controlled ventilator (CAREvent, O-Two-Systems, Mississauga, ON, Canada) with 35% oxygen at 12 breaths/min and with a tidal volume adjusted to maintain normocapnia; furthermore, a PEEP of 5 cm H_2O was applied during preparation and hemorrhage. The ventilator is a pneumatically powered, time-cycled, square-wave generator. The negative pressure was generated using an oxygen-powered Venturi vacuum generator. The Venturi vacuum generator was turned on at the end of the inspiratory phase, remained on for the full duration of the expiratory phase, and was turned off at the commencement of the next inspiratory phase (Fig. 1). Respiratory variables were measured and analyzed using a pulmonary monitor (CP-100, Bicore Monitoring System, Irvine, CA) attached to a variable orifice pneumotachograph (Varflex, Allied Health Products, Riverside, CA) and an esophageal balloon catheter (Smart Cath, Allied Health Products, Riverside, CA). The esophageal balloon catheter was 2 mm (7-Fr) in diameter, 70 cm long, and constructed from medical-grade polyurethane. The inflated balloon was 0.9 cm in diameter and 10 cm long. The frequency response was 30 Hz. The esophageal balloon catheter was connected directly to the catheter port on the Bicore system. The Bicore system automatically performs a vacuum leak test and fills the esophageal balloon with 0.8 mL of air. The pneumotachometer was connected directly to the proximal end of the airway tube. Airway pressure and flow were measured at the pneumotachometer. The CO_2 sampling port was sited above the flow transducer. The position of the esophageal balloon catheter was checked and adjusted where necessary by observation of the cardiac artifact on the esophageal waveform, as recommended by the manufacturer.

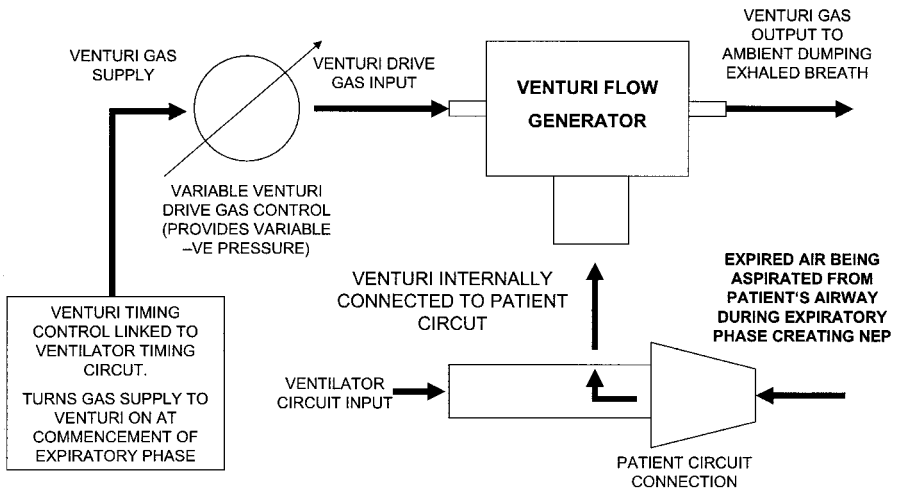

Figure 1. Venturi powered vacuum generator for negative expiratory pressure ventilation.

Anesthesia was maintained with propofol (6–8 mg/kg/hr intravenously) and a single injection of piritramid (15 mg intravenously). Lactated Ringer's solution (10 mL/kg/hr intravenously) was administered in the preparation phase, resulting in ~500 mL of fluid replacement in all animals before initiation of the experimental protocol (9). A standard lead II electrocardiogram was used to monitor cardiac rhythm; depth of anesthesia was judged according to arterial blood pressure and heart rate. If cardiovascular variables during the preparation phase indicated a reduced depth of anesthesia, additional propofol and piritramid were given. Body temperature was maintained at 38.5–39.5°C.

A 7-Fr saline-filled catheter was advanced via femoral cutdown into the right atrium for measurement of right atrial pressure, and two catheters were advanced via bilateral femoral cutdown into the abdominal aorta for measurement of aortic blood pressure, withdrawal of blood to induce hemorrhagic shock, and arterial blood samples. A 7.5-Fr pulmonary artery catheter was placed in the pulmonary artery via the internal jugular vein to measure cardiac output with the thermodilution technique. The intravascular catheters were attached to pressure transducers (1290A, Hewlett Packard, Boeblingen, Germany) that were aligned at the level of the right atrium. All pressure tracings were recorded with a data acquisition system (Dewetron port 2000, Graz, Austria; and Datalogger, custom-made software, Peter Hamm, departmental technician). Blood gases were measured with a blood gas analyzer (Chiron, Walpole, MA); end-tidal carbon dioxide was measured using an infrared absorption analyzer (Multicap, Datex, Helsinki, Finland).

Experimental Protocol. After assessing baseline hemodynamic values and blood gases, propofol infusion was adjusted to 2 mg/kg/hr and infusion of lactated Ringer's solution was stopped. Muscle paralysis was achieved with 0.2 mg/kg/hr pancuronium to prevent spontaneous or agonal breathing. Animals were ventilated with 100% oxygen and were bled ~45 mL/kg (estimated 65% of their calculated blood volume) (10) via an arterial catheter over a period of 30 mins to simulate controlled hemorrhagic shock. Subsequently, 21 animals were randomized into three groups and then ventilated with either up to −30 cm H_2O negative expiratory pressure ventilation (n = 7), 0 cm H_2O PEEP (n = 7), or 5 cm H_2O PEEP (n = 7; investigators were blinded to the treatment protocol; Fig. 2) Besides the end-expiratory pressure level, no other variable was changed in the ventilator setting. One blinded researcher collected all blood gases and another blinded researcher measured cardiac output. Blood gases and cardiac output were measured every 10 mins during the first 60 mins. No fluids were administered during the first 60 mins of the study period; after this time point, fluid resuscitation (25 mL/kg lactated Ringer's and 25 mL/kg 3% gelatin solution, a colloid fluid used as a volume expander) was performed in all surviving pigs. After fluid resuscitation was started, blood gases and cardiac output were measured every 15 mins.

From this point in time, animals were ventilated with the same ventilator settings before randomization; no recruitment maneuver was performed. Animals were declared dead if mean arterial blood pressure fell below 10 mm Hg. At

the end of the 120-min study protocol, the surviving animals were killed with an overdose of fentanyl, propofol, and potassium chloride.

Statistical Analysis. Values are expressed as mean ± SD. Shapiro Wilks tests were used to test for normality distribution. Baseline data for hemodynamic variables and arterial blood gases were tested with one-way analysis of variance if Gaussian-distributed and with Kruskal-Wallis test if not Gaussian-distributed. Statistical investigation was performed only for baseline data before and after hemorrhage, cardiac output, mean arterial blood pressure, and short-term survival. We did not statistically analyze other variables in order to avoid overinterpretation of the data. To evaluate differences in mean arterial blood pressure and cardiac output between groups, analysis for repeated measurements was used. Because all animals in the 5 PEEP group died before the end of the intervention, differences between the negative expiratory pressure ventilation group and the 5 PEEP group were only tested until 10 mins after start of the intervention (otherwise until the end of the experimental phase). Survival rates were compared using Kaplan-Meier methods with log rank (Mantel Cox) comparison of cumulative survival by treatment groups. We considered $p < .05$ to be statistically significant. No corrections were made for multiple comparisons. All statistical calculations were performed using SPSS, version 11.5, for Windows.

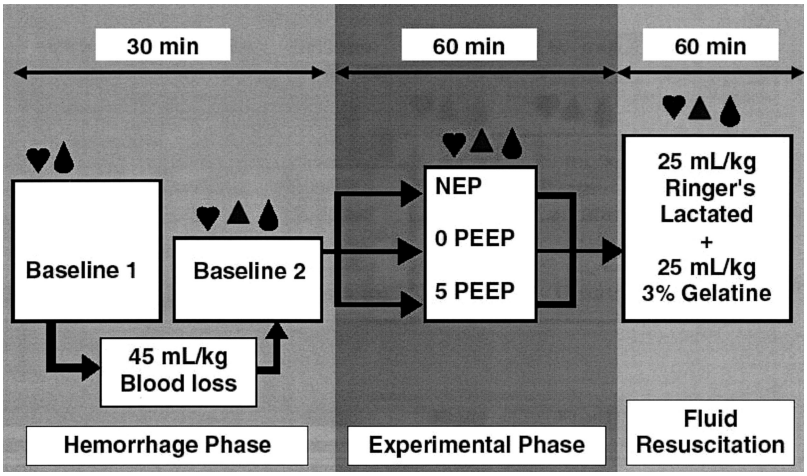

Figure 2. Flowchart of the experiment. *Hearts*, measurement of hemodynamic variables; *triangles*, measurement of airway pressures, tidal volumes, and flow rates with a pneumotachometer; *teardrops*, sampling of blood gases; *PEEP*, positive end-expiratory pressure; *NEP*, negative expiratory pressure.

RESULTS

Before induction of hemorrhagic shock, there were no differences in study end points between groups (Tables 1, 2). After induction of hemorrhagic shock, mean arterial blood pressure, cardiac output, and mean right atrial pressure were considerably decreased when compared with baseline values but were comparable between

Table 1. Hemodynamic variables during the hemorrhage phase, the experimental phase, and fluid resuscitation

	Hemorrhage Phase		Experimental Phase					Fluid Resuscitation	
Variable	BL 1	BL 2	5 Mins	10 Mins	20 Mins	30 Mins	60 Mins	90 Mins	120 Mins
End-tidal CO_2, mm Hg									
NEP	36 ± 1	20 ± 5	37 ± 3	38 ± 3	39 ± 2	41 ± 3	41 ± 2	41 ± 1	38 ± 4
0 PEEP	37 ± 1	19 ± 7	25 ± 6	25 ± 5	24 ± 8	30 ± 4	29 ± 9	37 ± 4	35 ± 1
5 PEEP	36 ± 2	23 ± 4	20 ± 7	22 ± 7	21 ± 6	16 ± 5	—	—	—
Heart rate, beats/min									
NEP	88 ± 5	184 ± 46	217 ± 20	219 ± 19	227 ± 18	230 ± 20	235 ± 21	183 ± 36	187 ± 57
0 PEEP	82 ± 8	183 ± 26	200 ± 28	204 ± 33	198 ± 43	222 ± 19	187 ± 22	184 ± 65	153 ± 36
5 PEEP	90 ± 4	186 ± 36	181 ± 30	186 ± 25	177 ± 14	163 ± 4	—	—	—
Mean right atrial blood pressure, mm Hg									
NEP	90 ± 4	186 ± 36	181 ± 30	186 ± 25	177 ± 14	163 ± 4	90 ± 4	186 ± 36	181 ± 30
0 PEEP	8 ± 1	2 ± 1	1 ± 1	1 ± 1	1 ± 1	1 ± 1	2 ± 2	8 ± 1	5 ± 3
5 PEEP	7 ± 1	3 ± 4	5 ± 2	3 ± 1	3 ± 1	3 ± 1	—	—	—
Mean pulmonary artery blood pressure, mm Hg									
NEP	18 ± 1	10 ± 1	5 ± 5	6 ± 1	7 ± 2	7 ± 1	7 ± 2	18 ± 2	19 ± 3
0 PEEP	18 ± 2	11 ± 2	11 ± 2	11 ± 2	11 ± 2	13 ± 1	12 ± 1	20 ± 2	18 ± 1
5 PEEP	20 ± 3	10 ± 2	10 ± 2	12 ± 1	11 ± 0	10 ± 2	—	—	—
Pulmonary artery occlusion pressure, mm Hg									
NEP	8 ± 2	2 ± 2	0 ± 1	1 ± 1	0 ± 1	−1 ± 3	0 ± 1	8 ± 3	8 ± 2
0 PEEP	8 ± 2	3 ± 3	6 ± 3	4 ± 3	3 ± 3	4 ± 1	5 ± 2	8 ± 2	8 ± 2
5 PEEP	9 ± 2	2 ± 2	4 ± 3	5 ± 1	5 ± 1	7 ± 3	—	—	—
Cardiac output, L/min									
NEP	3.7 ± 0.4	1.1 ± 0.4	3.1 ± 0.4[a,b]	3.2 ± 0.3[a,b]	3.2 ± 0.5[b]	3.5 ± 0.4[b]	4.0 ± 0.6[b]	6.0 ± 1.2	7.5 ± 1.4
0 PEEP	3.8 ± 0.5	1.1 ± 0.4	1.9 ± 0.9	2.0 ± 1.0	1.9 ± 0.7	2.5 ± 0.6	2.3 ± .8	6.2 ± 0.1	6.1 ± 1.2
5 PEEP	4.3 ± 0.9	1.0 ± 0.2	1.2 ± 0.8	0.9 ± 0.9	2.0 ± 0.3	0.4	—	—	—

BL 1, baseline 1, measurements before hemorrhage; BL 2, baseline 2, measurements after controlled hemorrhage (≈45 mL/kg blood loss); NEP, negative expiratory pressure ventilation; 0 PEEP, ventilation with 0 cm H_2O positive end-expiratory pressure; 5 PEEP, ventilation with 5 cm H_2O positive end-expiratory pressure; —, not measured due to death of all animals.

Values are given as mean ± SD of the mean.

[a] $p < .001$ for negative pressure ventilation vs. 5 PEEP; [b] $p = .001$ for negative pressure ventilation vs. 0 PEEP; since all animals in the 5 PEEP group died before the end of the intervention, differences between the negative expiratory pressure ventilation group and the 5 PEEP group where only tested until 10 mins after start of the intervention. No statistical comparison was performed for all other variables in order to avoid overinterpretation of the data.

Table 2. Arterial blood gases during the hemorrhage phase, the experimental phase, and fluid resuscitation

	Hemorrhage Phase		Experimental Phase					Fluid Resuscitation	
Variable	BL 1	BL 2	5 Mins	10 Mins	20 Mins	30 Mins	60 Mins	90 Mins	120 Mins
Arterial pH									
NEP	7.50 ± 0.02	7.50 ± 0.06	7.40 ± 0.09	7.31 ± 0.06	7.31 ± 0.05	7.30 ± 0.02	7.32 ± 0.04	7.37 ± 0.05	7.44 ± 0.06
0 PEEP	7.51 ± 0.02	7.49 ± 0.07	7.41 ± 0.09	7.33 ± 0.08	7.33 ± 0.07	7.28 ± 0.06	7.27 ± 0.15	7.38 ± 0.12	7.45 ± 0.05
5 PEEP	7.50 ± 0.03	7.49 ± 0.05	7.40 ± 0.07	7.34 ± 0.05	7.32 ± 0.06	7.34 ± 0.03	—	—	—
Arterial P_{CO_2}, mm Hg									
NEP	38 ± 2	34 ± 3	34 ± 5	43 ± 5	43 ± 3	45 ± 2	45 ± 4	41 ± 2	38 ± 4
0 PEEP	38 ± 1	33 ± 4	30 ± 6	34 ± 5	33 ± 8	42 ± 2	43 ± 5	39 ± 5	38 ± 1
5 PEEP	38 ± 2	34 ± 3	32 ± 4	33 ± 3	34 ± 6	29 ± 1	—	—	—
Arterial P_{O_2}, mm Hg									
NEP	144 ± 12	443 ± 55	384 ± 58	337 ± 64	283 ± 56	307 ± 32	326 ± 36	397 ± 81	417 ± 62
0 PEEP	151 ± 21	375 ± 57	352 ± 57	355 ± 84	381 ± 50	394 ± 65	353 ± 48	441 ± 50	415 ± 38
5 PEEP	178 ± 93	424 ± 85	393 ± 80	373 ± 62	436 ± 48	390 ± 67	—	—	—
Arterial base excess, mmol/L									
NEP	6 ± 2	4 ± 4	−4 ± 4	−5 ± 3	−5 ± 3	−4 ± 2	−3 ± 2	−2 ± 2	1 ± 3
0 PEEP	6 ± 2	2 ± 3	−5 ± 4	−7 ± 4	−4 ± 9	−7 ± 4	−7 ± 6	−2 ± 5	1 ± 3
5 PEEP	6 ± 2	2 ± 3	−5 ± 3	−8 ± 3	−8 ± 1	−10 ± 1	—	—	—
Arterial lactate, mmol/L									
NEP	1.8 ± 0.5	4.7 ± 1.2	8.8 ± 1.8	7.8 ± 1.6	7.6 ± 1.4	7.5 ± 1.6	6.5 ± 1.9	6.1 ± 2.1	4.6 ± 1.9
0 PEEP	1.8 ± 0.4	5.8 ± 1.2	10.0 ± 2.5	9.8 ± 2.0	10.2 ± 2.2	10.1 ± 3.0	9.3 ± 2.6	7.8 ± 2.5	5.7 ± 1.9
5 PEEP	1.8 ± 0.6	5.6 ± 1.6	10.0 ± 2.3	10.4 ± 3.2	11.4 ± 5.0	9.4 ± 4.6	—	—	—

BL 1, baseline 1, measurements before hemorrhage; BL 2, baseline 2, measurements after controlled hemorrhage (≈45 mL/kg blood loss); NEP, negative expiratory pressure ventilation; 0 PEEP, ventilation with 0 cm H_2O positive end-expiratory pressure; 5 PEEP, ventilation with 5 cm H_2O positive end-expiratory pressure; —, not measured due to death of all animals.

Values are given as mean ± SD of the mean. No statistical comparison was performed in order to avoid overinterpretation of data.

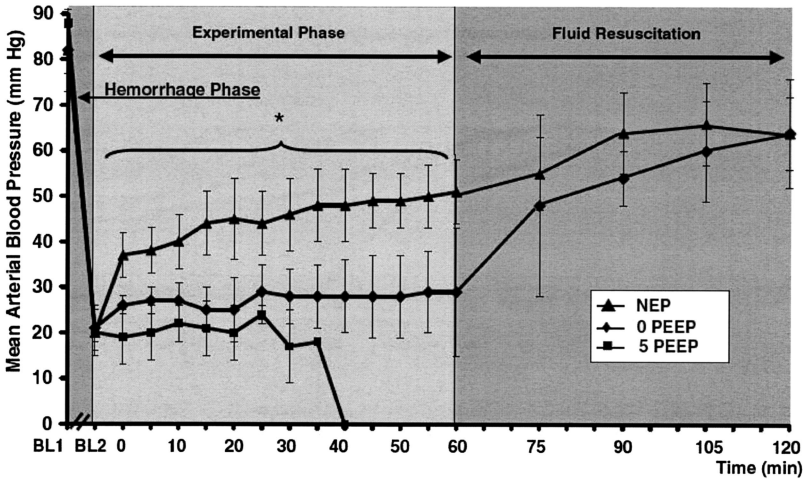

Figure 3. Mean ± SD mean arterial blood pressure during ventilation with negative expiratory pressure ventilation (*NEP; triangles*), 0 cm H_2O positive end-expiratory pressure (*0 PEEP; diamonds*), and 5 cm H_2O PEEP (5 PEEP; *squares*). *BL 1*, baseline 1 before blood withdrawal; *BL 2*, baseline 2 after 45 mL/kg blood loss. Note that the time line between BL 1 and BL 2 is not subject to scale. Fluid resuscitation indicates infusion of 25 mL/kg lactated Ringer's solution and 25 mL/kg 3% gelatin solution. *$p = .001$ between negative expiratory pressure and 0 cm PEEP, respectively.

groups. Also, total blood loss was comparable between groups.

Main Results. Mean arterial blood pressure was significantly higher in the negative expiratory pressure ventilation swine when compared with the 0 PEEP ($p = .001$) and 5 PEEP animals ($p < .001$). Cardiac output was significantly higher in negative expiratory pressure ventilation swine when compared with the 0 PEEP ($p = .001$) and 5 PEEP animals ($p < .001$; Table 1, Fig. 3), Seven of seven negative expiratory pressure ventilation animals, but only three of seven 0 PEEP swine, survived the 120-min study period, whereas seven of seven 5 PEEP pigs were dead within 35 mins. There was a statistically significant difference in cumulative survival between the negative expiratory pressure ventilation swine vs. the 0 PEEP pigs ($p = .022$) and between the negative expiratory pressure ventilation swine vs. the 5 PEEP pigs ($p < .001$; Fig. 4).

Secondary Results. During the shock phase, ventilation with negative expiratory pressure resulted in decreased mean airway pressure and increased delta esophageal pressure and delta airway pressure when compared with the 0 PEEP and 5 PEEP animals. (Table 3). When compared with the 0 PEEP and 5 PEEP group, end-tidal carbon dioxide was notably higher during the experiment, but arterial oxygen partial pressure was considerably lower in the negative expiratory pressure ventilation animals after 20 mins of the shock protocol. Representative tracings of mean arterial pressure and right atrial pressure tracings are given in Figures 5 and 6.

DISCUSSION

In this model of severe hemorrhagic shock, negative expiratory pressure ventilation ensured survival of seven of seven pigs for 60 mins without administration of vasopressors or fluid resuscitation and subsequently allowed 60 mins of hemodynamic stabilization with fluid resuscitation. In contrast, only three of seven 0 PEEP animals survived the 120-min

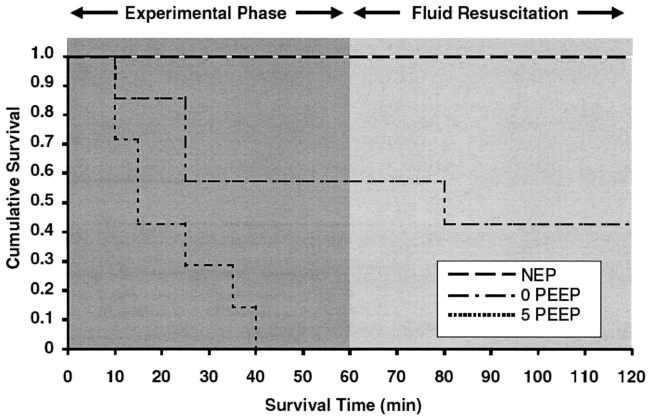

Figure 4. Kaplan-Meier survival curves in animals being ventilated with either negative expiratory pressure ventilation (*NEP*), 0 positive end-expiratory pressure (*PEEP*), or 5 PEEP. Note that the hemorrhage phase is not presented.

Table 3. Secondary results

	NEP	0 PEEP	5 PEEP
Baseline 2			
Expiratory tidal volume, mL	603 ± 44	661 ± 81	657 ± 92
Respiratory rate, per min	12 ± 0	12 ± 0	12 ± 0
Peak airway pressure, cm H_2O	34 ± 2	33 ± 3	32 ± 4
Mean airway pressure, cm H_2O	15 ± 0	14 ± 0	14 ± 1
Peak inspiratory flow rate, mL/sec	572 ± 59	626 ± 96	583 ± 70
Δ PES, cm H_2O	6 ± 4	9 ± 2	8 ± 3
Δ PAW, cm H_2O	28 ± 2	26 ± 3	25 ± 4
Experimental phase			
Expiratory tidal volume, mL	617 ± 66	683 ± 65	684 ± 97
Respiratory rate, per min	12 ± 0	12 ± 0	12 ± 0
Peak airway pressure, cm H_2O	29 ± 2	29 ± 3	35 ± 6
Mean airway pressure, cm H_2O	0 ± 0	12 ± 1	15 ± 1
Peak inspiratory flow rate, mL/sec	581 ± 57	594 ± 83	563 ± 63
Δ PES, cm H_2O	24 ± 12	10 ± 2	8 ± 2
Δ PAW, cm H_2O	58 ± 4	27 ± 3	26 ± 4
Fluid resuscitation			
Expiratory tidal volume, mL	644 ± 61	700 ± 57	—
Respiratory rate, per min	12 ± 0	12 ± 0	—
Peak airway pressure, cm H_2O	35 ± 4	31 ± 5	—
Mean airway pressure, cm H_2O	16 ± 1	15 ± 1	—
Peak inspiratory flow rate, L/sec	594 ± 62	645 ± 36	—
Δ PES, cm H_2O	7 ± 3	9 ± 2	—
Δ PAW, cm H_2O	28 ± 4	24 ± 5	—

NEP, negative expiratory pressure ventilation; 0 PEEP, ventilation with 0 cm H_2O positive end-expiratory pressure; 5 PEEP, ventilation with 5 cm H_2O positive end-expiratory pressure; Baseline 2, measurements after controlled hemorrhage (45 mL/kg blood loss); Δ PES, pressure change in the esophagus due to ventilation; Δ PAW, peak airway pressure minus the minimum airway pressure during each breath; —, not measured due to death of all animals.

Values are given as mean ± SD of the mean. No statistical comparison was performed in order to avoid overinterpretation of data.

study period, and seven of seven 5 PEEP animals died within 35 mins.

We withdrew ~65% of the calculated blood volume in order to simulate severe hemorrhagic shock. Our pigs had a mean arterial blood pressure of ~20 mm Hg immediately before randomization, indicating a critically decreased brain perfusion. A patient in this condition is most likely unconscious and should be immediately intubated and ventilated at the accident site according to the Advanced Trauma Life Support guidelines (11). Our prototype ventilator producing positive pressure during inspiration, and negative pressure during expiration, thus mimicking a "normal" ventilation cycle with reversed pressure ratios, may thus combine the advantage of ensuring ventilation plus enhancing venous return and perfusion. We deliberately withheld vasopressors and fluid resuscitation for the first 60 mins of the experiment in order to investigate the effects of different ventilation strategies over a prolonged period of time. Fluid resuscitation was then started to simulate further shock management and to determine whether the shock state was reversible or refractory.

Since spontaneous inspiration decreases intrathoracic pressure and induces decreases in right atrial blood pressure, venous return increases (12). Mechanical ventilation reverses this effect, since positive airway pressure and PEEP ventilation increase intrathoracic pressure, causing venous return to decrease (12). In contrast to current Advanced Trauma Life Support treatment concepts, this may be of considerable clinical importance during management of severe hemorrhagic shock. For example, in a porcine study simulating severe hemorrhagic shock, positive pressure ventilation with 5 or 10 PEEP significantly decreased cardiac output and mean arterial blood pressure, resulting in death within 5–30 mins (13). In contrast, an inspiratory threshold valve maintains and prolongs a vacuum created within the thorax during inspiration. This results in increased venous return and vital organ blood flow during cardiopulmonary resuscitation with an active compression decompression device and during controlled hemorrhagic shock (14, 15). Unfortunately, the innovative inspiratory threshold valve concept to recruit venous return cannot be applied after mechanical ventilation is initiated; thus, severely injured patients who usually require both airway and blood pressure management may be unable to benefit of this novel technique.

By analogy, noninvasive negative pressure ventilation also influences the cardiovascular system. Cuirass negative pressure ventilation significantly improved cardiac output in children after cardiac surgery (16, 17). It has been therefore discussed as adjunctive hemodynamic therapy in patients with a low cardiac output (18). As demonstrated in our animals, negative expiratory pressure ventilation decreased mean airway pressure, and subsequently mean right atrial blood pressure, as well as mean pulmonary artery blood pressure. Accordingly, cardiac output almost tripled in the negative expiratory pressure ventilation animals and was even comparable to prehemorrhage levels. This was accompanied by significantly higher end-tidal carbon

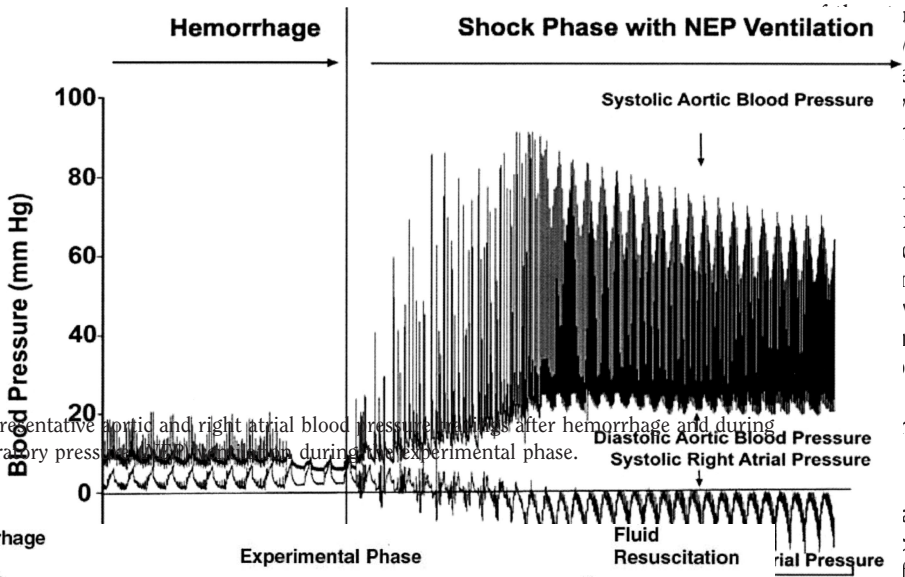

Figure 5. Representative aortic and right atrial blood pressure tracings after hemorrhage and during negative expiratory pressure ventilation during the experimental phase.

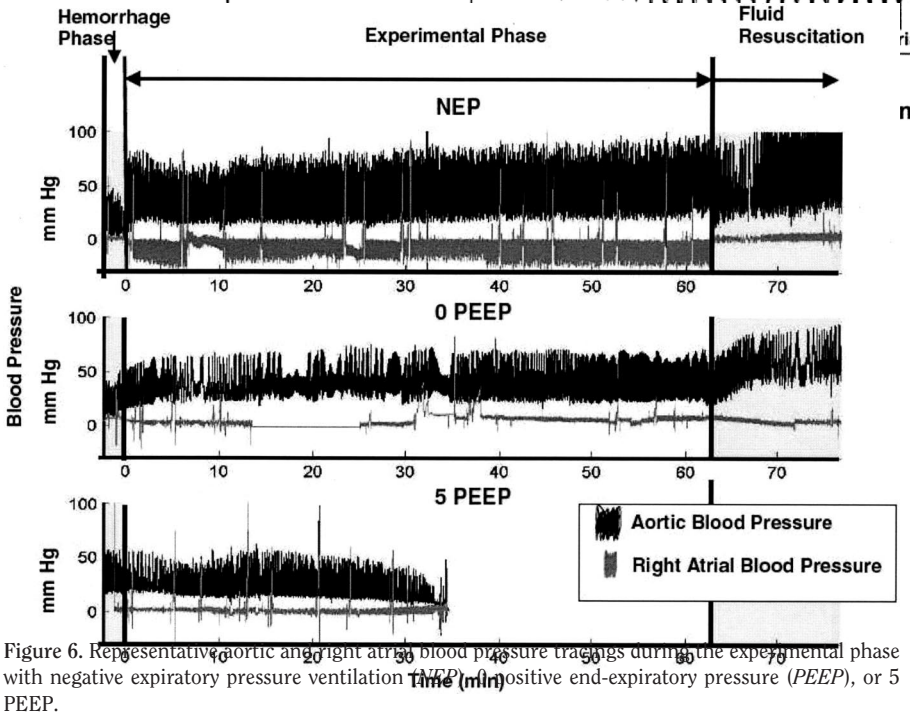

Figure 6. Representative aortic and right atrial blood pressure tracings during the experimental phase with negative expiratory pressure ventilation (*NEP*), 0 positive end-expiratory pressure (*PEEP*), or 5 PEEP.

dioxide levels when compared with the 0 and 5 PEEP animals, indicating a stabilization of hemodynamic status.

Negative expiratory pressure ventilation resulted in a lower, but not hypoxic, arterial oxygen partial pressure when compared with the 0 and 5 PEEP animals. Although speculative, this may be due to formation of atelectasis and increased pulmonary shunting; however, arterial oxygen partial pressure improved after the ventilator settings were changed to preshock parameters. Furthermore, no recruitment maneuver was necessary. Fluid resuscitation showed that shock was reversible, and pH, lactate, and base excess improved in the 1-hr observation period both in the negative expiratory pressure ventilation and also in the remaining 0 PEEP animals. Taken together, negative expiratory pressure ventilation may be a strategy to immediately improve cardiac output, which may be especially beneficial in trauma patients with collapsing blood pressure (19).

Limitations include that we withheld fluid resuscitation. Second, the small sample size limits the evaluation of survival outcome. Blood loss was controlled; and the effect of negative expiratory pressure ventilation in uncontrolled bleeding needs to be determined. Also, intubation with no subsequent fluid resuscitation may be contradictory to the Advanced Trauma Life Support guidelines but was used because of the experimental design

ıdy. We used young and healthy with flexible ribcages; therefore, e possible that the observed ef- be less profound in the elderly ıore rigid chest wall. Further- cannot report about the degree ɔnal residual capacity reduction xtent of atelectasis formation. did not perform a histologic ex- n of the lungs. Further, negative ventilation is a very stressful in- n for the lung. We do not know ıpens with pulmonary mediator and whether possible changes eversible after return to positive ventilation. Since we do not potentially detrimental effects, a negative pulmonary pressure could occur during normovol- fourth group of normovolemic entilated with negative pressure ve been interesting. We do not know if this mode of ventilation could trigger an acute respiratory distress syndrome.

CONCLUSIONS

When compared with pigs ventilated with either 0 PEEP or 5 PEEP, negative expiratory pressure ventilation during severe hemorrhagic shock improved mean arterial blood pressure and cardiac output.

ACKNOWLEDGMENTS

We are indebted to Kathrin Ebert and Kevin Bowden for technical assistance.

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