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Hyperventilation-Induced Hypotension During Cardiopulmonary Resuscitation

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Background—A clinical observational study revealed that rescuers consistently hyperventilated patients during out-of-hospital cardiopulmonary resuscitation (CPR). The objective of this study was to quantify the degree of excessive ventilation in humans and determine if comparable excessive ventilation rates during CPR in animals significantly decrease coronary perfusion pressure and survival.

Methods and Results—In humans, ventilation rate and duration during CPR was electronically recorded by professional rescuers. In 13 consecutive adults (average age, 63±5.8 years) receiving CPR (7 men), average ventilation rate was 30±3.2 per minute (range, 15 to 49). Average duration per breath was 1.0±0.07 per second. No patient survived. Hemodynamics were studied in 9 pigs in cardiac arrest ventilated in random order with 12, 20, or 30 breaths per minute. Survival rates were then studied in 3 groups of 7 pigs in cardiac arrest that were ventilated at 12 breaths per minute (100% O_2), 30 breaths per minute (100% O_2), or 30 breaths per minute (5% CO_2/95% O_2). In animals treated with 12, 20, and 30 breaths per minute, the mean intrathoracic pressure (mm Hg/min) and coronary perfusion pressure (mm Hg) were 7.1±0.7, 11.6±0.7, 17.5±1.0 ($P<0.0001$), and 23.4±1.0, 19.5±1.8, and 16.9±1.8 ($P=0.03$), respectively. Survival rates were 6/7, 1/7, and 1/7 with 12, 30, and 30+ CO_2 breaths per minute, respectively ($P=0.006$).

Conclusions—Professional rescuers were observed to excessively ventilate patients during out-of-hospital CPR. Subsequent animal studies demonstrated that similar excessive ventilation rates resulted in significantly increased intrathoracic pressure and markedly decreased coronary perfusion pressures and survival rates. **(*Circulation*. 2004;109: 1960-1965.)**

Key Words: cardiopulmonary resuscitation ■ death, sudden ■ heart arrest ■ ventilation ■ hypotension

Despite widespread cardiopulmonary resuscitation (CPR) training, survival rates after cardiac arrest remain dismal for most patients.[1] Recent experimental data suggest that there may be deleterious effects of rescue breathing, in part because ventilations interrupt chest compression and thereby reduce vital organ perfusion.[2] Positive-pressure ventilation may also be deleterious because it prohibits the development of negative intrathoracic pressure during chest wall recoil, inhibiting venous blood return to the right heart and thereby decreasing the hemodynamic effectiveness of CPR.[3]

This translational research initiative focused on the potential deleterious effects of excessive ventilation during CPR. At present, the American Heart Association (AHA) recommends 12 to 15 breaths per minute in patients with secured airways during the performance of CPR by healthcare professionals.[4] The purpose of the present clinical observational study was to objectively and electronically record actual ventilation frequency, duration, and the percentage of time in which a positive intrathoracic pressure was recorded in the lungs during CPR performed by emergency medical services (EMS) personnel at the scene of patients with an out-of-hospital cardiac arrest. The results of this study demonstrated that rescuers consistently hyperventilated patients at the scene of out-of-hospital cardiac arrest. On the basis of these clinical

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results, animal studies were performed to determine the potential hemodynamic and survival rate consequences of excessive ventilation rates.

Methods

Clinical Observational Study

This study was performed with an exception from informed consent requirements for emergency research (21 §CFR Part 50.24) after community consultation and public notification. It was part of but unrelated to another study for which the Food and Drug Administration had approved an investigational device exemption. The Human Research Review Committee at the Medical College of Wisconsin approved the study.

The clinical observational study was performed in the City of Milwaukee, where basic life support and advanced life support EMS personnel respond in a tiered manner. Care is provided according to AHA guidelines. For the study, an additional research team including a physician and paramedic were dispatched to the scene of each patient. Entry criteria for the study were (1) adult patients (presumed or known to be ≥21 years) believed to be in cardiac arrest of presumed cardiac cause and (2) patients who were successfully intubated with an endotracheal tube who were undergoing CPR at the time of scene arrival of the research team. A portable pressure monitor (Propaq, Welch Allyn Protocol, Inc) was used for electronic measurement of airway pressures, a surrogate for intrathoracic pressures. After arrival at the scene and after patient intubation, the research team connected the noninvasive intrathoracic pressure sensor between the endotracheal tube and the bag-valve resuscitator. Ventilations were then continuously recorded until resuscitation attempts were discontinued or the patient was resuscitated. There are a variety of factors that may affect ventilation rate throughout the resuscitation efforts, including the practice of hyperventilating immediately before and after intubation. For this reason, we sought to determine the maximum ventilation rate, defined as the highest ventilation rate recorded during CPR over a 16-second period occurring at least 2 minutes after intubation. The ventilation frequency, duration, and percentage of time in which a positive pressure was recorded in the lungs were then calculated with a digital caliper.

The first 7 consecutive cases constitute group 1. After recognizing that rescuers were consistently hyperventilating patients in cardiac arrest, investigators immediately retrained all EMS personnel to provide ventilations at a rate of 12 breaths per minute during CPR after establishment of a secured airway. The duration of each ventilation was not addressed during retraining. The subsequent 6 consecutive cases (after retraining) constitute group 2. Data were also analyzed by combining groups 1 and 2 (group 3). Differences between the means of groups 1 and 2 were statistically analyzed by ANOVA. A probability value of <0.05 was considered statistically significant. All data are expressed as mean±SEM.

Results: Clinical Observational Study

The average age of the 13 consecutive patients (6 women, 7 men) was 63±5.8 years (range, 34 to 96); 3 patients had an initial rhythm of ventricular fibrillation (VF), 5 had pulseless electrical activity, and 5 had asystole. Overall, the maximum ventilation rate was observed an average of 18.8±11.9 minutes after intubation (range, 2 to 39 minutes). No patient survived. The average maximum ventilation rate for group 1 patients was 37±4 breaths per minute (range, 19 to 49), ventilation duration was 0.85±0.07 seconds/breath, and the percentage of time in which a positive pressure was recorded in the airway was 50±4% (Table 1). After retraining, 3 of 6 group 2 patients had ventilation rates ≥26 breaths per minute. The ventilation rate for these 6 patients was slower than in group 1 patients, at 22±3 breaths per minute (range, 15 to 31). However, ventilation duration was significantly longer than in group 1 patients (1.18±0.06 versus 0.85±0.07 seconds/breath, respectively, $P<0.05$). As a result, the percentage of time in which a positive pressure was recorded in the airway was similar in group 2 and group 1 patients (44.5±8.2% versus 50±4%, respectively) (P=NS). Combining groups 1 and 2 (group 3), the ventilation rate for all 13 patients was 30 breaths per minute (twice the AHA-recommended rate).

TABLE 1. Clinical Observational Study: Maximum Ventilation Rate, Duration, and Percentage of Time in Which a Positive Pressure Was Recorded in the Lungs (Mean±SEM)

Group	Ventilation Rate (Breaths per Minute)	Ventilation Duration (Seconds per Breath)	% Positive Pressure
Group 1	37±4*	0.85±0.07†	50±4%
Group 2	22±3*	1.18±0.06†	44.5±8.2%
Group 3	30±3.2	1.0±0.7	47.3±4.3%

*$P<0.05$; †$P<0.05$; group 1, first 7 consecutive cases; group 2, subsequent 6 consecutive cases (after retraining); group 3, groups 1 and 2 combined.

Individual recordings provide insight into the rate and duration of ventilations provided by professional rescuers. Figure 1A represents delivery of CPR relatively close to AHA guidelines. Only one such case was observed. Figure 1, B, C, and D illustrate representative examples of hyperventilation observed in the majority of cases before retraining. After retraining, slower ventilation rates were seen in group 2 patients, but ventilation duration was more prolonged (Figure 1E). As a result, the percentage of time in which a positive pressure was recorded in the airway was not significantly different between groups 1 and 2.

Animal Studies

The porcine hemodynamic and survival studies were approved by the Committee of Animal Experimentation at the University of Minnesota. The animals received care in compliance with the 1996 Guide for the Care and Use of Laboratory Animals by the National Research Council. The animal preparation and surgical techniques have been previously described in detail.[3] Briefly, each animal received 10 mL (100 mg/mL) of intramuscular ketamine HCl for initial sedation, followed by intravenous propofol (2.3-mg/kg bolus and then a constant intravenous infusion of 165 μg/kg per minute). During the preparatory phase, animals were ventilated with room air by a positive-pressure ventilator (Harvard Apparatus Co). The rate and tidal volume were adjusted to maintain an arterial carbon dioxide ($PaCO_2$) at 40 mm Hg and oxygen saturation >90%, based on analysis of arterial blood gases (IL Synthesis, Instrumentation Laboratory).

Central aortic and right atrial pressures were recorded continuously using a micromanometer-tipped catheter (Mikro-Tip Transducer, Millar Instruments). All animals were treated with heparin (100 U/kg IV) as a single bolus once catheters were in place. Intrathoracic pressures were measured continuously with a micromanometer-tipped catheter positioned within the trachea, 2 cm below the tip of the endotracheal tube at the level of the carina. End-tidal carbon dioxide ($ETCO_2$) was recorded continuously (CO_2SMO Plus, Novametrix Medical Systems).

Resuscitation Protocols

Ventricular fibrillation was induced by using a 5F bipolar pacing catheter (St Jude Medical Corp) placed into the right ventricle, with alternating current at 7 V and 60 Hz. As soon as VF was induced, the positive-pressure ventilator was disconnected from the animal. After 6 minutes of untreated VF, closed-chest standard CPR was performed continuously with a pneumatically-driven automatic piston device (CPR Controller, AMBU International).[3] The compression rate was 100 per minute with a 50% duty cycle, and the compression depth was 25% of the anterior-posterior diameter of the chest wall. After each compression, the chest wall was allowed to recoil completely and without any impedance from the compression device. Pressure-controlled, synchronous ventilations were performed with a semiautomatic ventilator (Demand Valve Model L063–05R, Life Support Products Inc) at a constant flow rate of 160 L/min. Ventilation was initiated during the decompression phase of CPR, and each breath was delivered over a 1-second period of time.

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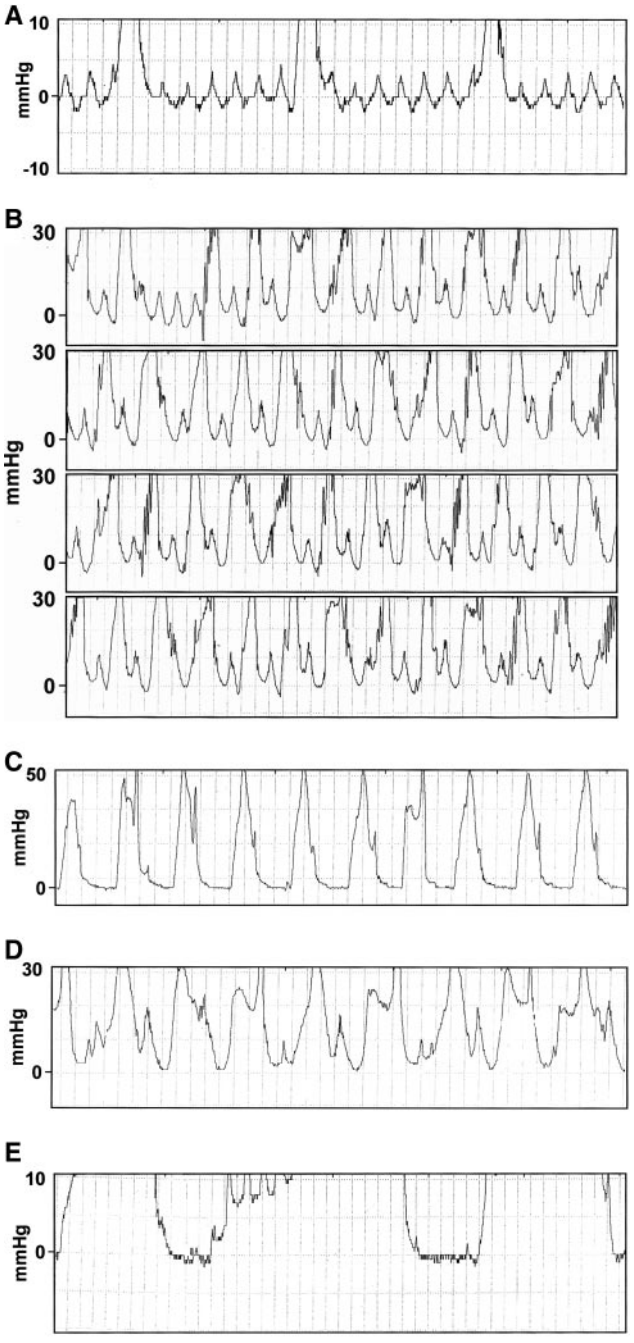

Figure 1. A, This 16-second intrathoracic pressure recording depicts CPR performed relatively close to AHA guidelines. Large-amplitude waves represent ventilations (11 breaths per minute). Small-amplitude waves represent chest compressions (90 compressions per minute). B, This 64-second intrathoracic pressure recording (from group 1) demonstrates a ventilation rate of 47 breaths per minute. C, This 16-second intrathoracic pressure recording (from group 1) represents a ventilation rate of 38 breaths per minute. D, This 16-second intrathoracic pressure recording (from group 1) represents a ventilation rate of 34 breaths per minute. E, After retraining, this 16-second recording from a group 2 patient demonstrates a slower ventilation rate (11 breaths per minute) but increased ventilation duration (over 4 seconds/breath), leaving little time (20%) during CPR for development of low or negative intrathoracic pressure.

During the first 2 minutes of CPR, a compression-to-ventilation ratio of 5:1 was used on all animals.

Hemodynamic Protocol (Protocol I)

After the initial 2 minutes of CPR, each animal received 3 different ventilation rates (12, 20, and 30 breaths per minute) in a computer-generated random order, with each phase lasting for 2 minutes. These 3 different ventilation rate interventions were delivered in an asynchronous manner, either every 5 seconds (12 per minute), every 3 seconds (20 per minute), or every other second (30 per minute), with each breath delivered over a period of 1 second.

During CPR, aortic, right atrial, and intrathoracic pressures were continuously recorded. $ETCO_2$ and O_2 saturation were also measured continuously and recorded every minute. Arterial blood gases were collected before induction of VF and at the end of each ventilation rate phase (after minute 8, 10, 12, and 14 of cardiac arrest).

Survival Protocol (Protocol II)

Ventilation during the first 2 minutes of CPR was delivered synchronously with a 5:1 compression-to-ventilation ratio. After the initial 2 minutes of CPR, each animal was randomized to receive 4 minutes of CPR with 1 of 3 different ventilation modes: (1) 12 breaths per minute with 100% O_2; (2) 30 breaths per minute with 100% O_2; or (3) 30 breaths per minute with 5% CO_2 and 95% O_2. Five percent CO_2 was added to inspiratory gases in the third group to evaluate the effect of hyperventilation on survival in the absence of hypocarbia. During these interventions, ventilations were delivered in an asynchronous manner every 5 seconds (12/min) or every other second (30/min), with each ventilation delivered over a period of 1 second.

During CPR, aortic, right atrial, and intrathoracic pressures as well as $ETCO_2$ and O_2 saturation were continuously recorded. Arterial blood gas samples were assessed before induction of VF and at the end of each ventilation phase.

At the end of each protocol, the animals were shocked with a biphasic defibrillator (M Series, Zoll Medical Corp) using 150 J, up to 3 times, as needed.[5] If resuscitation was successful, animals were ventilated with a ventilator and supplemental oxygen. Return of spontaneous circulation (ROSC) was defined as a palpable pulse over 5 minutes. Survival was defined as a stable blood-perfusing rhythm generating a measurable blood pressure over the first hour of observation after resuscitation. No other therapeutic interventions were performed after ROSC.

At the end of each study protocol, the animals were euthanized with an intravenous bolus of 60 mg propofol and then 10 mL potassium chloride.

All values are expressed as mean±SEM. Coronary perfusion pressure was calculated as the difference between aortic diastolic and right atrial diastolic pressures. For each animal, 10 measurements were performed for both aortic diastolic and right atrial diastolic pressures, and the average difference was used as the representative value for each animal. Mean intrathoracic pressure was measured as the time-averaged value from continuous measurements acquired over a 10-second period. Comparison between groups was done by ANOVA and paired t test. Survival was calculated with χ^2 and Fisher's exact tests. A probability value of <0.05 was considered statistically significant.

Results

Animal Hemodynamic Studies

Increased ventilation rate was associated with significantly higher mean intrathoracic pressures ($P<0.0001$) and significantly lower coronary perfusion pressures ($P=0.03$) and significantly higher arterial pH, but no change in PaO_2 (Table 2). There was also an increase in right atrial diastolic pressure with increased ventilation rate (Figure 2). This was only significantly lower in the 12–breaths/min versus 30–breaths/min groups (3.5±1.1 versus 7.3±1.0 mm Hg, $P=0.02$). The

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TABLE 2. Animal Protocol I: Changes in Hemodynamics and Arterial Blood Gases With Three Different Ventilation Rates Delivered in Random Order (Mean±SEM)

	Ventilation Rate, Breaths per Minute			
	12	20	30	*P*
Hemodynamics				
SAP, mm Hg	68.8±4.7	62.7±4.2	60.1±3.6	0.33
CPP, mm Hg	23.4±1.0	19.5±1.8	16.9±1.8	0.03
MIP, mm Hg per minute	7.1±0.7	11.6±0.7	17.5±1.0	<0.0001
Arterial blood gases				
pH	7.34±0.02	7.45±0.03	7.52±0.03	0.0006
$Paco_2$, mm Hg	22.7±2.7	15.6±2.2	11.6±1.5	0.005
Pao_2, mm Hg	340.9±40.7	403.3±47.0	403.7±48.0	0.59

SAP, Systolic aortic pressure; CPP, coronary perfusion pressure; MIP, mean intrathoracic pressure.

Statistical analysis was done by ANOVA. A value of $P<0.05$ was considered statistically significant.

ROSC rate was 3 of 9 pigs; 2 of 3 pigs that survived received 12 ventilations per minute as the terminal ventilation rate sequence.

Animal Survival Studies

The survival rate in pigs ventilated at 12 breaths per minute (100% O_2) was 6 of 7 (86%), compared with a survival rate of 1 of 7 (17%) at a rate of 30 breaths per minute (100% O_2), and 1/7 (17%) at a ventilation rate of 30 breaths per minute (5% CO_2/95% O_2) ($P=0.006$) (Figure 3). Mean intrathoracic pressures were significantly higher with the higher ventilation rates ($P<0.0001$), and coronary perfusion pressures were lower (Table 3). Changes in arterial blood gases and $ETCO_2$ with hyperventilation are shown in Table 4. Pigs ventilated at

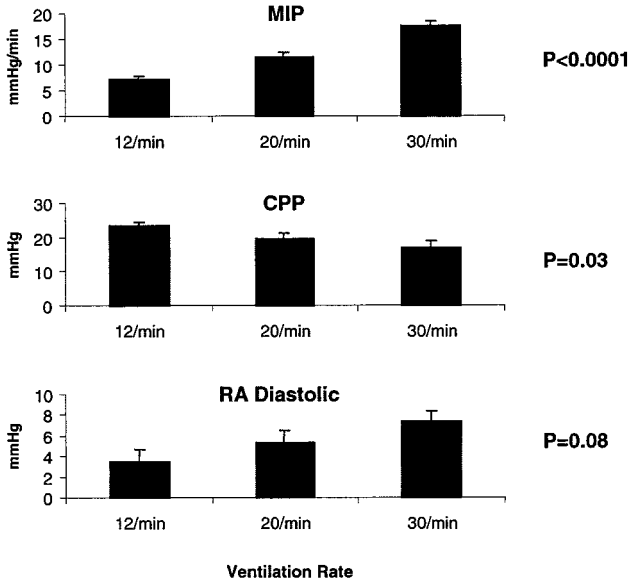

Figure 2. Hemodynamic Study (n=9). Changes in mean intrathoracic pressure (MIP), coronary perfusion pressure (CPP), and right atrial diastolic pressure (RA diastolic) with different ventilation rates during resuscitation in a porcine model of cardiac arrest. Probability value of <0.05 was considered statistically significant, based on ANOVA analysis of the 3 groups.

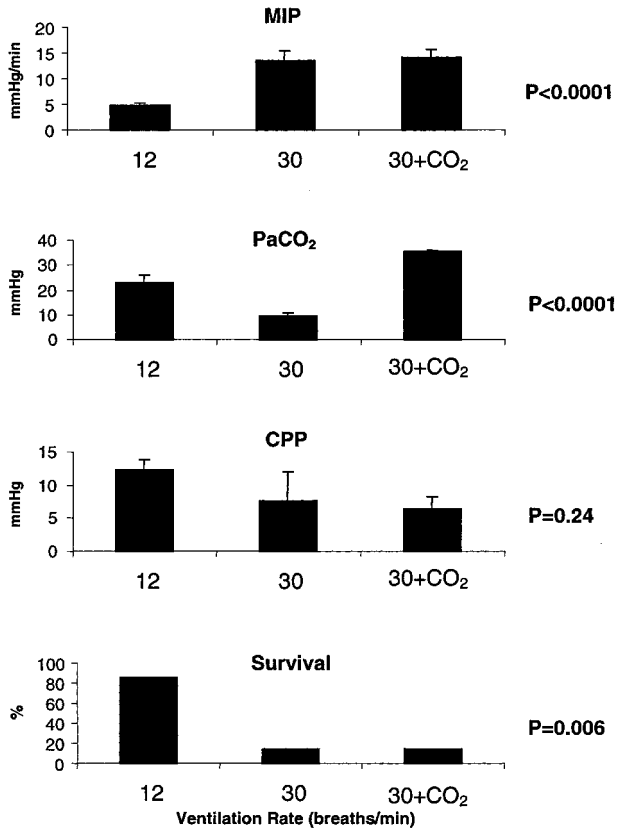

Figure 3. Survival Study (n=7 pigs per group). Changes in mean intrathoracic pressure (MIP), arterial CO_2 ($Paco_2$), coronary perfusion pressure (CPP), and survival rate, with hyperventilation and correction of hypocapnia (+CO_2). Probability value of <0.05 was considered statistically significant, based on ANOVA analysis of the 3 groups.

30 breaths per minute (100% O_2) had lower levels of $Paco_2$ (Table 4). Supplemental CO_2 resulted in correction of hypocapnia (Figure 3 and Table 4).

Discussion

These results demonstrate that ventilation rates during the prehospital application of CPR in a city with well-trained EMS personnel were observed to be far in excess of those recommended by the AHA. To our knowledge, this represents the first time that ventilation frequency, duration, and percent positive airway pressure have been objectively and electronically recorded during CPR performed by professional rescuers at the scene of out-of-hospital cardiac arrests. Both rapid-rate, short-duration ventilations and slow-rate, long-duration ventilations contributed to a high percentage of time that pressure in the chest was increased. As confirmed by the porcine hemodynamic and survival studies, excessive ventilation rates during CPR resulted in increased positive intrathoracic pressures, decreased coronary perfusion, and decreased survival rates.

During the decompression phase of standard CPR, a small vacuum is created within the chest relative to the rest of the body every time the chest wall recoils back to its resting position.[10] This draws venous blood back into the right heart.[10] Accentuating this small vacuum with use of an

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TABLE 3. Animal Protocol II: Changes in Aortic Systolic Blood Pressure, Coronary Perfusion Pressure, and Mean Intrathoracic Pressure With Hyperventilation and Correction of Hypocapnia (Mean±SEM)

	Ventilation Rate, Breaths per Minute Inhalation Gas			
	12 100% O_2 (n=7)	30 100% O_2 (n=7)	30 95% O_2/5% CO_2 (n=7)	*P*
Heart rate, beats/min				
Baseline	157.7±8.5	160.0±12.1	157.7±8.0	NS
Aortic systolic pressure, mm Hg				
Baseline	98.0±5.6	107.7±4.9	108.9±7.5	NS
8 minutes	67.8±2.2	71.8±7.7	62.8±9.8	NS
11.5 minutes	57.4±2.7	62.1±8.4	61.9±7.2	NS
Coronary perfusion pressure, mm Hg				
Baseline	71.6±5.5	75.5±6.6	82.0±6.6	NS
8 minutes	22.7±2.2	21.8±4.1	17.6±5.7	NS
11.5 minutes	12.3±1.4	7.6±3.7	6.3±1.9	0.24
Mean intrathoracic pressure, mm Hg/min				
8 minutes	5.6±0.5	6.5±0.9	5.7±0.8	NS
11.5 minutes	4.9±0.4	13.6±1.8	14.1±1.5	0.0001

Statistical analysis was done by ANOVA. A value of $P<0.05$ was considered statistically significant.

inspiratory impedance valve has been shown to significantly increase vital organ blood flow,[11] coronary perfusion pressure,[11] and survival.[3] Conversely, the physiological consequences of hyperventilation and of prolonged ventilation intervals result in a persistently positive intrathoracic pressure during the decompression phase of CPR, thereby decreasing cardiac preload[6] and cardiac output[7] and impeding right ventricular function.[8] Increased tidal volume is also known to adversely affect cardiac output.[9] In the present study, the mean intrathoracic pressure was significantly elevated in animals treated with higher ventilation rates. We speculate that the elevated mean intrathoracic pressures caused by excessive ventilation inhibited venous blood flow back to the right heart, as there was insufficient time to allow for the development of negative intrathoracic pressure between compressions. It is important to note that intrathoracic pressures never went below 0 mm Hg when ventilation rates were 30 per minute. The current results also support the contention that hypocapnia was not the cause of decreased coronary perfusion pressure and death in animals ventilated at 30 breaths per minute. When supplemental CO_2 at 5% was delivered to one group of pigs at a concentration identical to that found in expiratory gases to prevent hypocapnia without causing hypercarbia, the $PaCO_2$ level did not fall below 35.4±0.6 mm Hg, and survival rates (1/7) were identical to pigs hyperventilated with 100% O_2.

The data demonstrate that any incidence of hyperventilation is likely to have detrimental hemodynamic and survival consequences during low flow states such as CPR. Unrecognized and inadvertent hyperventilation may be contributing to the currently dismal survival rates from cardiac arrest. Similar detrimental effects of hyperventilation have recently been described in the setting of hemorrhagic shock.[12] Although the extent to which this clinical observation applies to other EMS systems needs to be determined through additional study, based on the current study, we strongly encourage medical directors to assess whether hyperventilation during CPR is inadvertently occurring in the care systems under their medical direction.

This study also demonstrates a significant difference between CPR performance by EMS personnel in the classroom and performance during an actual cardiac arrest as well as a potential direct relation between the quality of CPR delivered and victim survival. These observations have significant implications for the interpretation and design of resuscitation research, CPR guidelines, education, clinical practice, the development of future CPR devices, and EMS quality assurance.

There are several important limitations to this study. First, the clinical observations were only made in a single city and with a limited number of patients. We believed it was unethical to continue to collect data once we recognized the potential lethal nature of the observed hyperventilation. We found only one other published report in which ventilation rates for patients with an in-hospital cardiac arrest were as high as 70 times per minute.[13] Nonetheless, we do not know how widespread this problem is, and further study is warranted to characterize its prevalence nationally and internationally. Second, the animal hemodynamic studies focused on coronary perfusion pressures and intrathoracic pressures. The physiological effects of excessive ventilation rates may be underestimated by not measuring actual blood flow. Finally, animal survival studies were not performed at ventilation rates of <12 breaths per minute. The optimal ventilation rate

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TABLE 4. Animal Protocol II: Changes in Arterial Blood Gases and $ETCO_2$ With Hyperventilation and Correction of Hypocapnia (Mean±SEM)

	Ventilation Rate, Breaths per Minute Inhalation Gas			
	12 100% O_2 (n=7)	30 100% O_2 (n=7)	30 95% O_2/5% CO_2 (n=7)	*P*
pH				
Baseline	7.44±0.01	7.44±0.01	7.42±0.01	NS
8 minutes	7.43±0.03	7.49±0.07	7.28±0.03	0.03
11.5 minutes	7.36±0.04	7.53±0.06	7.22±0.03	0.0013
Pao_2, mm Hg				
Baseline	66.3±2.7	65.0±5.7	78.1±9.7	NS
8 minutes	314.5±64.9	377.8±35.8	406.1±28.1	NS
11.5 minutes	309.3±67.9	374.8±71.6	449.6±15.4	NS
$Paco_2$, mm Hg				
Baseline	38.7±1.1	37.4±0.6	39.6±0.8	NS
8 minutes	26.2±3.8	20.0±3.5	43.0±2.6	NS
11.5 minutes	22.7±3.4	9.3±1.6	35.4±0.6	<0.0001
Oxygen saturation, %				
Baseline	93.3±0.6	94.1±0.9	94.1±1.1	NS
8 minutes	97.2±2.8	100.0±0.0	100.0±0.0	NS
11.5 minutes	94.6±3.8	99.5±0.5	100.0±0.0	NS
$ETCO_2$, mm Hg				
Baseline	40.9±1.0	39.4±0.6	40.3±0.5	NS
8 minutes	16.0±1.7	16.3±2.0	40.8±0.7	0.0014
11.5 minutes	16.0±1.4	7.1±1.4	42.6±0.4	<0.0001

Statistical analysis was done by ANOVA. A value of $P<0.05$ was considered statistically significant.

for patients in cardiac arrest has yet to be defined and may well be lower than 12 breaths per minute.

Conclusions

Despite seemingly adequate training, EMS personnel consistently hyperventilated patients during out-of-hospital CPR. Subsequent hemodynamic and survival studies in pigs demonstrated that excessive ventilation rates significantly decreased coronary perfusion pressures and survival rates, despite supplemental CO_2 in one study group to prevent hypocapnia. This translational research initiative demonstrates an inversely proportional relationship between mean intrathoracic pressure and coronary perfusion pressure during CPR. Additional education of CPR providers is urgently needed to reduce these newly identified and deadly consequences of hyperventilation during CPR. These findings also have significant implications for the interpretation and design of resuscitation research, CPR guidelines, education, clinical practice, the development of future CPR devices, and EMS quality assurance.

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