Original Contributions

Comparison of a 10-Breaths-Per-Minute Versus a 2-Breaths-Per-Minute Strategy During Cardiopulmonary Resuscitation in a Porcine Model of Cardiac Arrest

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BACKGROUND: Hyperventilation during cardiopulmonary resuscitation (CPR) is harmful. METHODS: We tested the hypotheses that, during CPR, 2 breaths/min would result in higher cerebral perfusion pressure and brain-tissue oxygen tension than 10 breaths/min, and an impedance threshold device (known to increase circulation) would further enhance cerebral perfusion and brain-tissue oxygen tension, especially with 2 breaths/min. RESULTS: Female pigs (30.4 ± 1.3 kg) anesthetized with propofol were subjected to 6 min of untreated ventricular fibrillation, followed by 5 min of CPR (100 compressions/min, compression depth of 25% of the anterior-posterior chest diameter), and ventilated with either 10 breaths/min or 2 breaths/min, while receiving 100% oxygen and a tidal volume of 12 mL/kg. Brain-tissue oxygen tension was measured with a probe in the parietal lobe. The impedance threshold device was then used during an 5 additional min of CPR. During CPR the mean ± SD calculated coronary and cerebral perfusion pressures with 10 breaths/min versus 2 breaths/min, respectively, were 17.6 ± 9.3 mm Hg versus 14.3 ± 6.5 mm Hg (p = 0.20) and 16.0 ± 9.5 mm Hg versus 9.3 ± 12.5 mm Hg (p = 0.25). Carotid artery blood flow, which was prospectively designated as the primary end point, was 65.0 ± 49.6 mL/min in the 10-breaths/min group, versus 34.0 ± 17.1 mL/min in the 2-breaths/min group (p = 0.037). Brain-tissue oxygen tension was 3.0 ± 3.3 mm Hg in the 10-breaths/min group, versus 0.5 ± 0.5 mm Hg in the 2-breaths/min group (p = 0.036). After 5 min of CPR there were no significant differences in arterial pH, P_{O_2}, or P_{CO_2} between the groups. During CPR with the impedance threshold device, the mean carotid blood flow and brain-tissue oxygen tension in the 10-breaths/min group and the 2-breaths/min group, respectively, were 102.5 ± 67.9 mm Hg versus 38.8 ± 23.7 mm Hg (p = 0.006) and 4.5 ± 6.0 mm Hg versus 0.7 ± 0.7 mm Hg (p = 0.032). CONCLUSIONS: Contrary to our initial hypothesis, during the first 5 min of CPR, 2 breaths/min resulted in significantly *lower* carotid blood

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flow and brain-tissue oxygen tension than did 10 breaths/min. Subsequent addition of an impedance threshold device significantly enhanced carotid flow and brain-tissue oxygen tension, especially in the 10-breaths/min group. *Key words: respiration, cardiac arrest, cardiopulmonary resuscitation, CPR, impedance threshold device, circulation, hyperventilation, cerebral perfusion pressure, brain-tissue oxygenation.* [Respir Care 2008;53(7):862–870. © 2008 Daedalus Enterprises]

Introduction

Recent research indicates that an excessive ventilation rate during cardiopulmonary resuscitation (CPR) can be harmful, if not deadly.[1] Though this has resulted in evidence that supports less frequent delivery of positive-pressure ventilation during CPR, what remains unknown is the optimal number of breaths per minute needed to provide adequate gas exchange but not reduce circulation to the vital organs. A high ventilation rate during CPR is dangerous because it reduces venous blood return to the heart, increases lung volume, increases pulmonary vascular resistance, and reduces cardiac output. The increase in intrathoracic pressure associated with positive-pressure ventilation also increases intracranial pressure, which reduces cerebral perfusion pressure.[2,3]

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By contrast, little is known about the potential injurious effects of a very low ventilation rate during CPR. The recent 2005 American Heart Association Guidelines recommended a ventilation rate of 8–10 breaths/min during advanced cardiac life support,[4] but it is possible that a lower ventilation rate would be adequate and further improve circulation to the heart and brain. To begin to address the basic question of what is the minimum ventilation rate needed to optimize circulation and tissue oxygen supply to the vital organs during CPR, we tested 3 hypotheses:

1. Reducing the CPR ventilation rate from 10 breaths/min to 2 breaths/min would increase the coronary and cerebral perfusion pressures because of fewer interruptions in venous return to the heart during the chest-decompression phase,[5,6] but would not alter arterial oxygen content or carbon dioxide removal.

2. The lower ventilation rate would increase the end-tidal carbon dioxide concentration (P_{ETCO_2}) and the brain oxygen tension.

3. Adding an impedance threshold device (ITD) would increase the coronary and cerebral perfusion pressures during ventilation with either 2 breaths/min or 10 breaths/min.

The ITD we studied lowers intrathoracic pressure during the chest-wall-recoil phase of CPR and thereby enhances cardiac preload and lowers intracranial pressure.[3,7]

Our results support the unexpected conclusion that reducing the CPR ventilation rate from 10 breaths/min to 2 breaths/min markedly reduces blood flow through the lungs, thereby reducing the coronary and cerebral perfusion pressures and the brain oxygen tension. These findings provide new insight into the fundamental mechanism of blood flow during CPR and the optimal way to use this ITD.

Methods

The study was approved by the Institutional Animal Care Committee of the Minneapolis Medical Research Foundation of Hennepin County Medical Center, and all animals received treatment in compliance with the National Research Council's 1996 Guide for the Care and Use of Laboratory Animals. All studies were performed by a qualified, experienced research team, with female farm pigs.

Surgical Preparation

The anesthesia, surgical, preparation, and data monitoring and recording procedures were previously described.[8] All surgical procedures were performed under aseptic conditions. The initial sedation was achieved with intramuscular ketamine (7 mL of 100 mg/mL, Ketaset, Fort Dodge Animal Health, Fort Dodge, Iowa) followed by intravenous propofol anesthesia (2.3 mg/kg bolus and then 160 μg/kg/min, PropoFlo, Abbott Laboratories, North Chicago, Illinois). While spontaneously breathing but sedated, each pigs was intubated with a size 7.0 endotracheal tube, then additional propofol (1 mg/kg) was administered, followed by a propofol infusion of 160 μg/kg/min. At that point the pig became completely apneic and required positive-pressure ventilation for the remainder of the study. While sedated and mechanically ventilated, a burr hole was made half way between the left eyebrow and the posterior bony prominence of the skull. Through the burr hole we placed an intracranial pressure transducer (Camino, IntraLife Sciences, Plainsboro, New Jersey), a temperature probe, and an oxygen tension sensor (Licox, IntraLife Sciences, Plainsboro, New Jersey). The systolic, diastolic, and mean intracranial pressures were recorded every minute. Using a similar approach on the contralateral side, a micromanometer-tipped (Mikro-Tip Transducer, Millar Instruments,

Houston, Texas) catheter was placed to enable real-time recording of intracranial pressure. The left common carotid artery was then surgically exposed and a Doppler flow probe (Transonic 420 series multichannel, Transonic Systems, Ithaca, New York) was placed to quantify common carotid blood flow. The animal's temperature was carefully maintained at $37 \pm 0.5°C$, with a warming blanket (Bair Hugger, Augustine Medical, Eden Prairie, Minnesota).

The animals were placed supine, and unilateral femoral artery cannulation was performed. Central aortic blood pressure was recorded continuously with a micromanometer-tipped (Mikro-Tip Transducer, Millar Instruments, Houston, Texas) catheter. A similar central venous catheter was placed in the right external jugular vein, and all animals received an intravenous heparin bolus (100 units/kg). The animals were then ventilated with room air, with a volume-control ventilator (Narkomed 2A, Dräger Medical, Telford, Pennsylvania), with a tidal volume of 12 mL/kg and a respiratory rate adjusted to continually maintain a P_{aCO_2} of 40 mm Hg and P_{aO_2} of > 80 mm Hg (blood oxygen saturation $> 95\%$), as measured from arterial blood (Gem 3000, Instrumentation Laboratory, Lexington, Massachusetts) to adjust the ventilator as needed. Airway pressure was measured continuously with a micromanometer-tipped catheter positioned 2 cm above the carina. Surface electrocardiographic recordings were also made continuously. All data were recorded with a digital recording system (Superscope II version 1.295, GW Instruments, Somerville, Massachusetts, and a Power Macintosh G3 computer, Apple Computer, Cupertino, California). P_{ETCO_2}, tidal volume, minute ventilation, and blood oxygen saturation were continuously measured with a respiratory monitor (CO$_2$SMO Plus, Novametrix Medical Systems, Wallingford, Connecticut).

Measurements and Recording

All the variables (aortic, right atrial, airway, intracranial, coronary perfusion, and cerebral perfusion pressures, and common carotid blood flow) were analyzed with the data from the 4th, 5th, 9th, and 10th minutes of CPR. Coronary perfusion pressure during CPR was calculated during the decompression phase of CPR, based on the nadir of right-atrial pressure and coincident aortic pressure. Three consecutive decompression measurements before the delivery of a positive-pressure ventilation were averaged. These measurements were repeated 3 times within each minute studied, and the average of the 3 mean values is reported as the mean coronary perfusion pressure during each minute. Cerebral perfusion pressure was calculated as the difference between the mean values of aortic pressure and intracranial pressure, using the mean value of the digitized aortic and intracranial pressure tracings at

minutes 5 and 8. Common carotid blood flow, for minutes 5 and 8, was calculated by numerically integrating values for the forward minus the retrograde flow recorded over 1 minute. Brain tissue oxygen content was measured every 30 seconds. Arterial and mixed venous blood gas samples were collected at baseline and at minutes 4.5 and 9.5 of CPR.

Experimental Protocol

Upon completion of the surgical preparation and when oxygen saturation was $> 90\%$ and P_{ETCO_2} was stable between 35–42 mm Hg for 5 min, ventricular fibrillation was induced by delivering direct current via a temporary pacing wire (Daig Division, St Jude Medical, Minnetonka, Minnesota) positioned in the right ventricle. At that time, treatment assignment was made with a computer-generated randomization list. The ventilator was disconnected from the endotracheal tube and the dose of propofol was reduced to 100 μg/kg/min. After 6 min of untreated ventricular fibrillation, closed-chest standard CPR was performed with a pneumatically driven automatic piston device (Pneumatic Compression Controller, Ambu International, Glostrup, Denmark), as previously described.[7] The compression rate was 100 compressions/min, with a 50% duty cycle and a compression depth of 25% of the anterior-posterior chest diameter. The anterior chest wall was allowed to recoil passively but completely; the piston was actively pulled upward to 1 mm off the chest after each compression. During CPR positive-pressure ventilations were delivered asynchronously, to simulate Advanced Life Support with a manual resuscitator bag (Smart Bag, O$_2$ Systems, Toronto, Ontario, Canada). The fraction of inspired oxygen was 1.0, the tidal volume was approximately 400 mL, the peak airway pressure was 20 mm Hg, and the respiratory rate was either 2 breaths/min or 10 breaths/min, depending on the randomized sequence. During 2-breaths/min ventilation the objective was to maintain P_{ETCO_2} at approximately 40 mm Hg. If P_{ETCO_2} increased to > 40 mm Hg, we increased the ventilation rate by 2 breaths/min every 1 min until P_{ETCO_2} was ≤ 40 mm Hg.

Following 5 min of CPR with the randomized ventilation rate, the ITD (ResQPod, Advanced Circulatory Systems, Eden Prairie, Minnesota) was added, and 5 more minutes of CPR were performed with the same ventilation rate. Then CPR was terminated. Similar to during the 2-breaths/min ventilation period without the ITD, once the ITD was added, the ventilation rate was increased if necessary to keep $P_{ETCO_2} \leq 40$ mm Hg.

Statistical Analysis

All values are expressed as mean $\pm$ SD. The primary end point, determined a priori, was carotid artery blood

Table 1. Baseline Hemodynamic Values*

	CPR Respiration Rate	
Hemodynamic Variable	2 breaths/min	10 breaths/min
Systolic blood pressure (mm Hg)	105.6 ± 13.3	110.8 ± 20.0
Diastolic blood pressure (mm Hg)	82.7 ± 13.1	84.4 ± 15.4
Right atrial systolic pressure (mm Hg)	0.2 ± 2.1	1.7 ± 2.4
Right atrial diastolic pressure (mm Hg)	0.2 ± 2.3	−0.2 ± 3.9
Mean airway pressure (mm Hg)	0.1 ± 0.4	−0.3 ± 0.7
Intracranial systolic pressure (mm Hg)	21.5 ± 4.5	21.8 ± 5.8
Intracranial diastolic pressure (mm Hg)	18.9 ± 3.4	20.3 ± 5.4
Carotid flow (mL/min)	115.0 ± 46.9	123.7 ± 36.2

*Values are mean ± SD. There are no statistically significant differences between the groups.
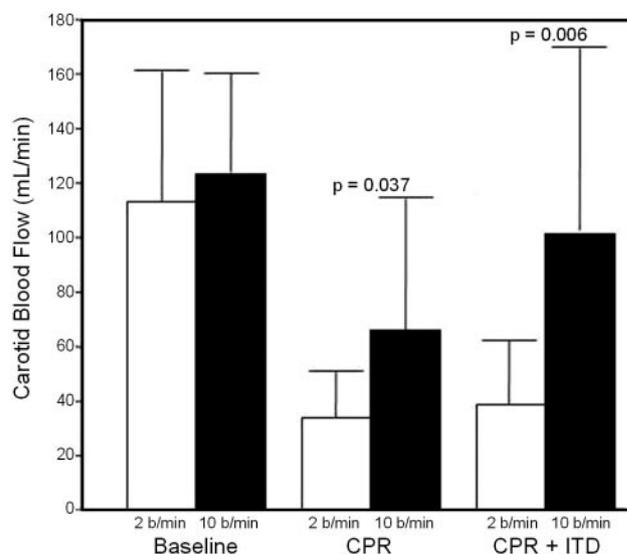CPR = cardiopulmonary resuscitation

Fig. 1. Mean ± SD carotid brain flow during cardiopulmonary resuscitation (CPR) with ventilation rates of 2 breaths/min (b/min) and 10 b/min. The p values represent the comparison of the 2-b/min group to the 10-b/min group. Carotid brain flow was also significantly higher with the addition of the impedance threshold device (ITD) in the 10 b/min CPR-plus-ITD subgroup compared to the 10 b/min CPR-without-ITD subgroup (p = 0.03). There was no statistically significant effect when the ITD was added to the 2 b/min subgroup.

flow. Based on pilot studies, it was estimated that to demonstrate a 50% difference in carotid blood flow, approximately 11 animals per group would be needed to detect a significant difference between the 2-breaths/min group and the 10-breaths/min group with 90% power and p = 0.05. Repeated-measurements analysis of variance and the unpaired t test were used to compare the 2 ventilation rates. A paired t test was used to evaluate the differences in a given animal with and without the ITD. A p value < 0.05 was considered statistically significant.

Results

There were 11 pigs per group. All the pigs weighed between 28 and 32 kg. The baseline hemodynamics, brain oxygen content, and blood gas values were similar between the 2 groups (Table 1). P_{ETCO_2} during CPR was similar between the 2-breaths/min group and 10-breaths/min group.

At baseline the carotid blood flow was similar between the groups: 115.0 ± 46.9 mL/min in the 2-breaths/min group, and 123.7 ± 36.2 mL/min in the 10-breaths/min group (p = 0.35). Figure 1 shows the differences in carotid blood flow between the 2-breaths/min group and the 10-breaths/min group. In the 2-breaths/min group, during CPR the carotid blood flow was 34.0 ± 17.1 mL/min, versus 65.0 ± 49.6 mL/min in the 10-breaths/min group (p = 0.037). In the 2-breaths/min group the ITD nonsignificantly increased carotid blood flow, from 34.0 ± 17.1 mL/min to 38.8 ± 23.7 mL/min (p = 0.20 for ITD vs no ITD). In the 10-breaths/min group the ITD increased flow from 65.0 ± 49.6 mL/min to 102.5 ± 67.9 mL/min (p = 0.03 for ITD vs no ITD). Expressed as a percentage of baseline carotid flow, ventilation at 2 breaths/min with the ITD was approximately 34% of the pre-cardiac-arrest flow, whereas at 10 breaths/

min with the ITD it was approximately 82% of the pre-cardiac-arrest flow.

To determine if the carotid flow was physiologically significant, tissue brain oxygen content was measured with a recently developed tissue oxygen tension sensor placed in the parietal lobe. Figure 2 shows that the baseline brain oxygen tensions were similar between the groups. At 2 breaths/min the brain oxygen tension was 0.5 ± 0.5 mm Hg, and at 10 breaths/min it was 3.0 ± 3.3 mm Hg (p = 0.036). Moreover, the ITD inconsequentially increased brain oxygen in the 2-breaths/min group, to 0.7 ± 0.7 mm Hg, whereas in the 10-breaths/min group the ITD increased brain oxygen to 4.5 ± 6.0 mm Hg (p = 0.12 for ITD versus no ITD in the 2-breaths/min group, and p = 0.11 for ITD versus no ITD in the 10-breaths/min group).

Table 2 shows additional hemodynamic data during CPR with and without the ITD. The right atrial systolic pressure was statistically lower at 2 breaths/min than at 10 breaths/min. No gasping was observed in either group during the study or on review of the intrathoracic pressure tracings, with the anesthetic regimen we used.

Table 3 shows the blood gas measurements. The mixed venous saturation values (an indirect measure of circulation) were higher in the 10 breaths/min (36 ± 14%) than in the 2-breaths/min group (19 ± 8%) (p = 0.002). These differences are internally consistent with the hemodynamic measurement differences between the groups.
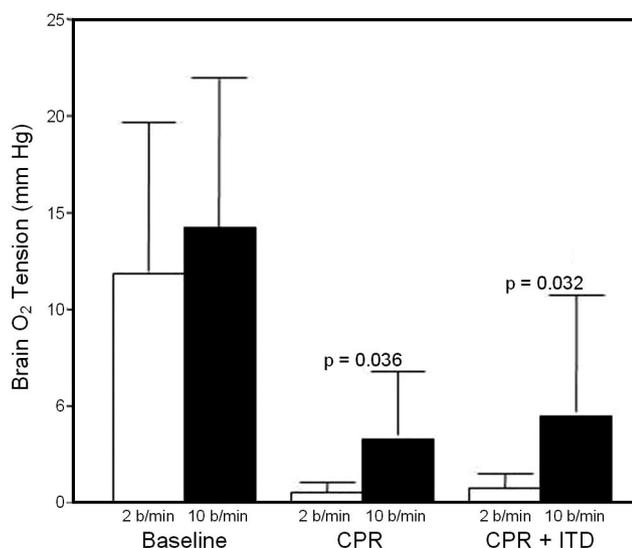
Fig. 2. Mean ± SD brain oxygen tension during cardiopulmonary resuscitation (CPR) with ventilation rates of 2 breaths/min (b/min) and 10 b/min. The p values represent the comparison of the 2-b/min group to the 10-b/min group. There was no statistically significant change in brain oxygen content with the addition of the impedance threshold device (ITD) in either group.

The ITD significantly changed the arterial pH, P_{aCO_2}, P_{aO_2}, base excess, oxygen saturation, and P_{ETCO_2} in the 10-breaths/min group, and significantly changed arterial pH and P_{aCO_2} in the 2-breaths/min group. Consistent with other measurements, arterial pH was significantly higher with the ITD: pH was 7.17 ± 0.10 at 2 breaths/min with the ITD, and 7.26 ± 0.11 at 10 breaths/min with the ITD (p = 0.035).

Addition of the ITD, though relatively late in the sequence of events, resulted in statistically significant changes in key physiologic variables, but only when comparing the 2 breaths/min with or without ITD subgroups or the 10 breaths/min with or without ITD subgroups (see Table 2 and Figs. 1 and 2). Airway pressure was significantly lower during the decompression phase with the ITD in both groups. The lowest intrathoracic pressure during the decompression phase was measured on a beat-to-beat basis: though the difference is not statistically significant, the vacuum created in the airway during the decompression phase at 2 breaths/min was −3.1 ± 1.1 mm Hg versus −4.8 ± 3.2 mm Hg at 10 breaths/min (p = 0.058).

The ITD increased P_{ETCO_2} immediately in the 2-breaths/min group. Within 1 min P_{ETCO_2} was > 40 mm Hg in the 2-breaths/min group. By contrast, P_{ETCO_2} never exceeded 40 mm Hg in the 10-breaths/min group. When P_{ETCO_2} rose above 40 mm Hg, we increased the ventilation rate by 2 breaths/min each minute, per the protocol, to try to maintain P_{ETCO_2} at ≤ 40 mm Hg. Thus, the ventilation rate in the 2-breaths/min group was adjusted upward after the addition of the ITD, and at the end of the 5-min period

of CPR with the ITD the average ventilation rate in the 2-breaths/min group was 2.9 ± 1.1 breaths/min (range 2–5 breaths/min). The ITD also slightly decreased the diastolic intracranial pressure in both the 2-breaths/min group and 10-breaths/min group.

Discussion

Cardiopulmonary interactions play a fundamental role in the delivery of circulation to the heart and brain during CPR. This study was designed to test the hypothesis that a low ventilation rate (2 breaths/min) would provide greater cerebral circulation than a higher ventilation rate (10 breaths/min), because (1) venous blood flow back to the heart would be less frequently interrupted by positive-pressure ventilations, which increase intrathoracic pressure and reduce venous return, and (2) the higher P_{CO_2} associated with the lower ventilation rate would increase cerebral vasodilation secondary to cerebral autoregulatory mechanisms. Our 2-breaths/min strategy was selected to test this hypothesis, but not necessarily as an optimal minimal clinical ventilation rate.

This study demonstrates that cardiopulmonary interactions play a fundamental role in the delivery of blood flow and oxygen to the brain. Reducing the ventilation rate from 10 breaths/min to 2 breaths/min had a profound and potentially harmful effect on carotid blood flow, brain-tissue O_2, and cardiac output. Our data reveal, for the first time, the harmful physiologic effects of a low ventilation rate during the initial minutes of CPR. The lower ventilation rate provided adequate arterial blood oxygen and pH levels but was associated with a potentially dangerous thoraco-cerebral interaction that should be avoided. In other words, even though the arterial blood gas values were similar between the groups, the lower ventilation rate altered cerebral circulation. The animals ventilated at 2 breaths/min in the initial minutes of CPR had significantly lower carotid-artery blood flow and brain-tissue oxygen than did those ventilated at 10 breaths/min. When combined with recent data that showed the harmful, if not deadly, effects of hyperventilation during CPR, these results support the conclusion that there is an ideal range of ventilation rate during CPR, and both too many and too few breaths per minute are dangerous. Markedly higher and lower rates result in physiologically detrimental cardiopulmonary and thoraco-cerebral interactions that substantially reduce the effectiveness of CPR. Importantly, our results also indicate that the ITD is more effective as a circulatory enhancer at 10 breaths/min than at 2 breaths/min.

Contrary to our original hypothesis, the lower ventilation rate did not enhance venous return of blood flow to the right heart, coronary or cerebral perfusion pressure, carotid blood flow, or cerebral oxygenation. Instead, our

Table 2. Hemodynamic Values During CPR

	Pressure (mean ± SD mm Hg)*			
Hemodynamic Variable	At 2 breaths/min	At 2 breaths/min + ITD	At 10 breaths/min	At 10 breaths/min + ITD
Systolic blood pressure	44.3 ± 18.4[a,c]	45.3 ± 13.2[a,d]	56.8 ± 23.0[b,c]	59.7 ± 29.2[b,d]
Diastolic blood pressure	19.7 ± 7.1[e,g]	17.2 ± 6.0[e,h]	20.9 ± 9.3[f,g]	17.8 ± 10.9[f,h]
Right atrial systolic pressure	35.8 ± 12.9[i,k]	45.2 ± 18.9[i,l]	54.6 ± 18.9[j,k]	63.0 ± 22.1[j,l]
Right atrial diastolic pressure	5.4 ± 5.2[m,o]	4.3 ± 5.1[m,p]	4.4 ± 2.9[n,o]	1.7 ± 2.8[n,p]
Mean airway pressure	−1.1 ± 0.8[q,s]	−3.1 ± 1.1[q,t]	−0.9 ± 1.7[r,s]	−4.8 ± 3.2[r,t]
Intracranial systolic pressure	27.9 ± 4.3[u,w]	27.9 ± 3.8[u,x]	32.6 ± 2.4[v,w]	31.3 ± 11.3[v,x]
Intracranial diastolic pressure	17.5 ± 3.0[y,aa]	16.2 ± 3.1[y,bb]	20.0 ± 7.4[z,aa]	19.5 ± 9.1[z,bb]
Mean airway pressure	14.3 ± 6.5[cc,ee]	13.4 ± 5.3[cc,ff]	17.6 ± 9.3[dd,ee]	16.8 ± 9.9[dd,ff]
Cerebral perfusion pressure	9.3 ± 12.5[gg,ii]	8.9 ± 9.1[gg,jj]	16.0 ± 9.5[hh,ii]	18.3 ± 11.5[hh,jj]

* Each superscripted letter (or double-letter combination) corresponds to one of the p values in the list below. The first superscripted letter in a row corresponds to the comparison of the first data column and the second data column in that row (eg, in the first row, "a" represents the comparison of 44.3 to 45.3). The next (in alphabetical order) superscripted letter in the row corresponds to the comparison of the third data column and the fourth data column (eg, in the first row, "b" represents the comparison of 56.8 to 59.7). The third (in alphabetical order) superscripted letter in the row corresponds to the comparison of the first data column and the third data column (eg, in the first row, "c" represents the comparison of 44.3 to 56.8). The fourth (in alphabetical order) superscripted letter in the row corresponds to the comparison of the second data column and the fourth data column (eg, in the first row, "d" represents the comparison of 45.3 to 59.7).
[a] $p = 0.318$, [b] $p = 0.274$, [c] $p = 0.093$, [d] $p = 0.086$, [e] $p = 0.113$, [f] $p = 0.058$, [g] $p = 0.365$, [h] $p = 0.440$, [i] $p = 0.015$, [j] $p = 0.130$, [k] $p = 0.007$, [l] $p = 0.031$, [m] $p = 0.013$, [n] $p = 0.025$, [o] $p = 0.309$, [p] $p = 0.098$, [q] $p < 0.001$, [r] $p < 0.001$, [s] $p = 0.391$, [t] $p = 0.058$, [u] $p = 0.487$, [v] $p = 0.210$, [w] $p = 0.157$, [x] $p = 0.184$, [y] $p = 0.007$, [z] $p = 0.304$, [aa] $p = 0.072$, [bb] $p = 0.142$, [cc] $p = 0.320$, [dd] $p = 0.428$, [ee] $p = 0.197$, [ff] $p = 0.163$, [gg] $p = 0.472$, [hh] $p = 0.377$, [ii] $p = 0.254$, [jj] $p = 0.042$.
ITD = impedance threshold device

Table 3. Blood Gas Values and P_{ETCO_2}*

	Pressure (mean ± SD mm Hg)*			
Variable	At 2 breaths/min	At 2 breaths/min+ITD	At 10 breaths/min	At 10 breaths/min+ITD
Arterial				
pH	7.33 ± 0.14[a,c]	7.17 ± 0.10[a,d]	7.41 ± 0.15[b,c]	7.26 ± 0.11[b,d]
P_{aCO_2} (mm Hg)	42 ± 14[e,g]	56 ± 13[e,h]	35 ± 15[f,g]	49 ± 18[f,h]
P_{aO_2} (mm Hg)	169 ± 81[i,k]	155 ± 82[i,l]	149 ± 52[j,k]	126 ± 58[j,l]
HCO_3^- (mEq/L)	21.5 ± 2.7[m,o]	20.2 ± 1.8[m,p]	20.9 ± 4.1[n,o]	20.1 ± 3.2[n,p]
Base excess (mEq/L)	−4.4 ± 3.9[q,s]	−8.2 ± 3.0[q,t]	−3.2 ± 4.0[r,s]	−6.9 ± 3.7[r,t]
O_2 saturation (%)	98 ± 3[u,w]	94 ± 9[u,x]	99 ± 1[v,w]	95 ± 7[v,x]
P_{ETCO_2} (mm Hg)	29 ± 9[y,aa]	39 ± 11[y,bb]	26 ± 13[z,aa]	33 ± 10[z,bb]
Venous				
pH	7.19 ± 0.09[cc,ee]	7.11 ± 0.07[cc,ff]	7.22 ± 0.09[dd,ee]	7.15 ± 0.07[dd,ff]
P_{CO_2} (mm Hg)	73 ± 25[gg,ii]	86 ± 12[gg,jj]	79 ± 22[hh,ii]	79 ± 13[hh,jj]
P_{O_2} (mm Hg)	21 ± 4[kk,mm]	24 ± 17[kk,nn]	25 ± 6[ll,mm]	28 ± 7[ll,nn]
HCO_3^- (mEq/L)	29.4 ± 3.0[oo,qq]	26.5 ± 3.0[oo,rr]	31.5 ± 2.6[pp,qq]	26.9 ± 3.4[pp,rr]
Base excess (mEq/L)	−2.0 ± 3.9[ss,uu]	−3.9 ± 3.6[ss,vv]	−0.7 ± 2.9[tt,uu]	−4.3 ± 3.2[tt,vv]
O_2 saturation (%)	19 ± 8[ww,yy]	23 ± 12[ww,zz]	36 ± 14[xx,yy]	36 ± 15[xx,zz]

*Each superscripted letter (or double-letter combination) corresponds to one of the p values in the list below. The first superscripted letter in a row corresponds to the comparison of the first data column and the second data column in that row (eg, in the first row, "a" represents the comparison of 7.33 to 7.17). The second (in alphabetical order) superscripted letter in the row corresponds to the comparison of the third data column and the fourth data column (eg, in the first row, "b" represents the comparison of 7.41 to 7.26). The third (in alphabetical order) superscripted letter in the row corresponds to the comparison of the first data column and the third data column (eg, in the first row, "c" represents the comparison of 7.33 to 7.41). The fourth (in alphabetical order) superscripted letter in the row corresponds to the comparison of the second data column and the fourth data column (eg, in the first row, "d" represents the comparison of 7.17 to 7.26).
[a] $p < 0.001$, [b] $p < 0.001$, [c] $p = 0.107$, [d] $p = 0.035$, [e] $p = 0.007$, [f] $p = 0.004$, [g] $p = 0.153$, [h] $p = 0.152$, [i] $p = 0.271$, [j] $p = 0.017$, [k] $p = 0.262$, [l] $p = 0.182$, [m] $p = 0.075$, [n] $p = 0.080$, [o] $p = 0.356$, [p] $p = 0.183$, [q] $p < 0.001$, [r] $p < 0.001$, [s] $p = 0.248$, [t] $p = 0.193$, [u] $p = 0.111$, [v] $p = 0.029$, [w] $p = 0.183$, [x] $p = 0.463$, [y] $p < 0.001$, [z] $p = 0.027$, [aa] $p = 0.288$, [bb] $p = 0.041$, [cc] $p < 0.001$, [dd] $p < 0.001$, [ee] $p = 0.211$, [ff] $p = 0.074$, [gg] $p = 0.044$, [hh] $p = 0.420$, [ii] $p = 0.277$, [jj] $p = 0.115$, [kk] $p = 0.131$, [ll] $p = 0.016$, [mm] $p = 0.034$, [nn] $p = 0.084$, [oo] $p < 0.001$, [pp] $p < 0.001$, [qq] $p = 0.077$, [rr] $p = 0.87$, [ss] $p < 0.001$, [tt] $p < 0.001$, [uu] $p = 0.079$, [vv] $p = 0.124$, [ww] $p = 0.142$, [xx] $p = 0.485$, [yy] $p = 0.002$, [zz] $p = 0.021$.
ITD = impedance threshold device
P_{ETCO_2} = end-tidal carbon dioxide pressure

results suggest that there is another important but often overlooked regulator of cardiac output during cardiac arrest and CPR, that is, blood flow through the lungs. At 2 breaths/min the lungs functioned as though transpulmo-

nary circulation was reduced. Also, at 2 breaths/min the vacuum generated during the chest-recoil phase of CPR was less, which suggests a reduction in the transmission of the energy from the elastic chest-wall recoil during CPR, probably due to greater atelectasis. This interpretation is consistent with the work of Markstaller et al, who found with computed tomography that there is a marked increase in atelectasis in the absence of ventilation during CPR.[9] We further speculate that infrequent ventilation decreases lung volume, which increases pulmonary vascular resistance, consistent with the classic U-shaped relationship between pulmonary vascular resistance and low lung volumes: during hypoventilation the lungs become more atelectatic, pulmonary vascular resistance increases, and transpulmonary blood flow decreases. In addition, these unanticipated findings in the 2-breaths/min group were further unmasked with the use of the ITD. Though the difference in airway pressure at the carina (an indirect measure of intrathoracic pressure) was not statistically significant between the groups, the airway pressure trended more negative with the ITD. These small differences must be viewed in the context of the normal diastolic right atrial pressure, which under normal physiologic conditions ranges from zero to -2 mm Hg. These subtle but important differences in decompression-phase intrathoracic pressure resulted in lower intracranial pressure and higher cerebral perfusion pressure with the ITD, especially in the 10-breaths/min group.

Part of our initial hypothesis was that higher P_{aCO_2} (presumed to be associated with a lower ventilation rate) would result in greater cerebral blood flow, because of the known effects of P_{aCO_2} on cerebral vascular autoregulation.[10] We therefore anticipated that we would observe higher P_{ETCO_2} and P_{aCO_2} in the 2-breaths/min group. In the protocol we attempted to maintain P_{ETCO_2} at approximately 40 mm Hg by increasing the ventilation rate (though the rate was always at least 2 breaths/min), and when P_{ETCO_2} rose above 40 mm Hg, we increased the ventilation rate by 2 breaths/min each minute. At 2 breaths/min the P_{aCO_2} was higher than at 10 breaths/min, yet this did not result in greater blood flow to the brain or higher brain oxygen level. However, these data are consistent with other investigations, which found that it is likely that with such low blood flow the cerebral autoregulatory effects of P_{aCO_2} are either absent or diminished, because carotid blood flow and brain oxygen tension was clearly dissociated from P_{aCO_2} and P_{ETCO_2}.[11] These data further suggest that fluid mechanics, including the relative pressures and resistances of the vascular beds in the thorax and brain, are more important than we expected in cerebral blood flow. The mixed venous oxygen saturation levels provide further support for the lower circulation rate in the 2-breaths/min group. More specifically, the markedly higher mixed venous saturation (an indicator of circulation) and the higher carotid flow in

the 10-breaths/min group support the conclusion that circulation is substantially impaired at 2 breaths/min.

Other investigators have suggested[3,5,6,8,12-16] that a lower ventilation rate improves hemodynamics, so why were our findings different? Perhaps the biggest difference between the current study and previous animal studies[5,6] is related to the hypothesis and the choice of anesthetic. In our study the pigs were fully anesthetized and did not gasp during CPR. Though gasping does occur in humans and is associated with a favorable outcome, it typically occurs only during the first couple of minutes of CPR.[17-20] In the current study propofol was administered intravenously, and with the dose we used, there was no gasping. This is similar to other reports from our laboratory.[2,7,8,16,17] By contrast, the inhaled agent isofluorane can be difficult to deliver in a regulated manner during CPR, unless the ventilation rate is constant or the pig is allowed to gasp and simultaneously spontaneously inhale the anesthetic. Pigs will gasp for long periods with external chest-wall stimulation in the absence of adequate anesthesia (personal observations by KGL) during CPR and thereby provide autorespiration. Moreover, gasping lowers intrathoracic pressure, thus simultaneously enhancing venous return, lowering intracranial pressure, and increasing cerebral perfusion pressure.[17,18] Thus, we speculate that prior animal studies that indicated beneficial effects from hypoventilation in the initial several minutes of CPR may have not controlled for gasping. This important difference in experimental design underlies the difference between our results and those from other experimental laboratories, and this theory should be investigated by eliminating spontaneous gasping with a pharmacologic intervention.

We also recognize that much of the impetus for studies on no-ventilation CPR had to do with unwillingness of bystanders to perform mouth-to-mouth ventilation, which is considered objectionable by many and thus a roadblock to bystander CPR. Therefore, we agree that chest compressions alone are preferred to no CPR at all, when CPR is performed by lay untrained or unwilling rescuers. The purpose of the present study was not to find fault with studies that have supported chest-compression-only CPR when trained CPR providers are not available, but rather to examine the physiology associated with hypoventilation during CPR.

It is well known that CPR with approximately 10 breaths/min results in only about 15% of normal blood flow to the heart and approximately 20% of normal blood flow to the brain.[7] Thus, part of the rationale for the current study was to find ways to enhance cardio-cerebral blood flow during CPR. However, at present, the mechanisms underlying the striking differences in carotid-artery blood flow and cerebral oxygen content at 2 breaths/min versus 10 breaths/min, with and without the ITD, remain unknown. Based on the present results we speculate that with only 2 breaths/

min the normal architecture of the lungs fails to support adequate transpulmonary blood flow and reduces the transfer of kinetic energy generated by the elastic recoil of the chest wall during the decompression phase of CPR. The vacuum created during the decompression phase is transferred nearly instantaneously throughout the various intrathoracic chambers and the brain, presumably via the paravertebral sinuses.[21] The present data further suggest that with infrequent positive-pressure ventilations the lungs simply collapse, yet the blood in the lungs is adequately oxygenated and carbon dioxide is sufficiently exchanged because of the slower transit time through the lungs, even though overall flow is reduced. In addition, the data suggest that the effectiveness of the ITD is muted because the pressures cannot be transmitted as effectively from one self-enclosed intrathoracic chamber (eg, heart chambers, vena cavae, lung parenchyma, bronchioles, heart and lung vasculature) to the next, including the generation and transmission of the intrathoracic vacuum to the brain. In other words, the data suggest that periodic lung inflation maintains the structural integrity of the lungs and lowers pulmonary vascular resistance, thereby improving blood flow through the lungs: 2 breaths/min is too few to support adequate forward flow. It is also likely that the periodic inflation of the lungs helps to propel blood forward, in a manner analogous to wringing out a wet sponge. Further studies are needed to more clearly elucidate the mechanisms associated with transpulmonary blood flow in the setting of severe hypoventilation. A better understanding of these mechanisms may lead to improvements in the overall effectiveness of CPR. For example, it may be possible to use the physiologic changes associated with different ventilation rates to alter key physiologic variables, such as intrathoracic pressure, to optimize blood flow to the heart and brain during CPR.

This study has 3 important limitations. First, only 2 initial ventilation rates were studied. It is possible that the optimal CPR ventilation rate is somewhere between 2 breaths/min and 10 breaths/min. However, our intent was to examine the relationship between different ventilation rate strategies and blood flow to the brain. The effects of 2 breaths/min are not unlike the harmful effects of an excessive ventilation rate during CPR; that is, there is also a lower limit to the ventilation rate, and when that limit is crossed, there are negative consequences of hypoventilation. Though ventilation rates between 2 breaths/min and 10 breaths/min should be evaluated, it is clear that low or no ventilation during CPR can be dangerous and should not be recommended except in circumstances where untrained CPR providers are not willing to perform mouth-to-mouth.

Second, vital-organ blood flow, pulmonary vascular resistance, and survival were not measured. These measurements are needed to fully understand the impact of a low ventilation rate on the effectiveness of CPR, and such

studies are planned. However, this study links together, for the first time, the carotid blood flow and brain oxygen tension, and the impact of hypoventilation on these important physiologic variables. The results suggest that there is a nonlinear, but direct, relationship between the amount of blood delivered to the brain via the carotid arteries and the amount of tissue oxygen available for metabolism. The mixed venous oxygen saturation data further support a nonlinear relationship between cardiac output or circulation and oxygen delivery to the brain in the setting of a very low ventilation rate. Moreover, despite more than adequate P_{aO_2}, the delivery of oxygen to the brain was clearly related to carotid flow and delivery of blood to the brain. A better understanding of these relationships may improve cardiac arrest outcomes.

Finally, the ITD was added relatively late in the protocol, which potentially caused us to underestimate its optimal effectiveness. Despite placing it after 5 min of CPR, blood flow to the brain and brain oxygen content were highest at 10 breaths/min with the ITD.

Conclusions

Contrary to our original hypothesis, a very low CPR ventilation rate was associated with lower blood flow to the brain, lower brain-tissue P_{O_2}, and lower mixed venous oxygen saturation. Considered along with the results of studies that indicated harmful effects from hyperventilation during CPR, it is clear that the ideal CPR ventilation rate is one that allows for adequate venous return during the chest-wall-recoil phase but also optimizes blood flow through the lungs. The data support the conclusion that a low ventilation rate decreases lung volume, increases pulmonary vascular resistance, and decreases transpulmonary blood flow and pressure transfer within the thorax. These effects decrease blood flow to the left heart and the brain. Though the ITD worked with both 2 breaths/min and 10 breaths/min, 10 breaths/min with the ITD resulted in markedly higher carotid blood flow and brain-tissue oxygenation than 10 breaths/min without the ITD. Finally, this study sheds new light on the importance of both cardiopulmonary and thoraco-cerebral interactions and the need for future research to optimize the balance between ventilation and circulation during the initial phase of CPR.

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