

Emergency Medical Services Authority

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**REQUEST FOR APPROVAL
TRIAL STUDY**

EMS MEDICAL DIRECTOR: **Angelo Salvucci, MD**

DATE: **8/29/2008**

LOCAL EMS AGENCY: **Santa Barbara County & Ventura County**

NAME OF PROPOSED PROCEDURE OR MEDICATION: **See attached study proposal. The King Airway and ResQpod will be used by BLS & ALS providers.**

1. DESCRIPTION OF THE PROCEDURE OR MEDICATION REQUESTED:
See attached study proposal.

2. DESCRIPTION OF THE MEDICAL CONDITIONS FOR WHICH THEY WILL BE UTILIZED:
Adult patients in cardiac arrest.

3. ALTERNATIVES(Please describe any alternate therapies considered for the same conditions and any advantages and disadvantages): **Standard 30:2 CPR without an ITD.**

4. AN ESTIMATE OF FREQUENCY OF UTILIZATION:
350/year

5. OTHER FACTORS OR EXCEPTIONAL CIRCUMSTANCES:
none

PLEASE ATTACH:

6. ANY SUPPORTING DATA, INCLUDING RELEVANT STUDIES AND MEDICAL LITERATURE.
See Attached

7. RECOMMENDED POLICIES/PROCEDURES TO BE INSTITUTED REGARDING USE, MEDICAL CONTROL, TREATMENT PROTOCOLS, AND QUALITY ASSURANCE OF THE PROCEDURE OR MEDICATION.
See Attached. All cardiac arrest cases are and will be reviewed.

8. DESCRIPTION OF THE TRAINING AND COMPETENCY TESTING REQUIRED TO IMPLEMENT THE PROCEDURE OR MEDICATION.
BLS and ALS personnel will be trained in device use in a hands on environment.

Patient pulseless and apneic or with agonal respirations.
CPR (see note 6), BLS airway management, Monitor, document rhythm strip, Determine Cardiac Rhythm ^{1,2}

PRIOR TO BASE HOSPITAL CONTACT																		
<p>VFIB/V-TACH* (Persistent) WHILE ON SCENE</p> <ol style="list-style-type: none"> DEFIBRILLATE**** Monophasic - 360 J* 5 cycles (2 minutes) CPR⁵ IV access during CPR Reassess cardiac rhythm. If VFib/Vtach³ remain: DEFIBRILLATE - 360 J* & resume CPR. EPINEPHRINE: May repeat q 3-5 min IVP: 1:10,000 1.0 mg If NO IV, give ET: 1:10,000 2.0 mg** IL: 1:1,000 1.0 mg Reassess cardiac rhythm. If VFib/Vtach³ remain: DEFIBRILLATE - 360 J* & resume CPR. ***Lidocaine IVP: 1.5 mg/kg or ET: 3 mg/kg** Defibrillate - 360 J* ALS airway management.⁴ Repeat Epi q 3-5 minutes Defibrillate - 360 J* Repeat Lidocaine 1.5 mg/kg in 3-5 minutes (to total dose of 3 mg/kg) Defibrillate - 360 J* 	<p>ASYSTOLE</p> <ol style="list-style-type: none"> IV access EPINEPHRINE May repeat q 3-5 min IVP: 1:10,000 1.0 mg If NO IV, give ET: 1:10,000 2.0 mg** IL: 1:1,000 1.0 mg Reassess Cardiac Rhythm. If any question in rhythm, confirm in 2 leads. If still ASYSTOLE, give ATROPINE: IVP: 1.0 mg IVP ET: 2.0 mg** IL: 1.0 mg (1 mg/ml) ALS Airway management.⁴ Repeat Epi q 3-5 minutes Repeat Atropine q 3-5 minutes to a total dose of 0.04 mg/kg (3 mg in a 75 kg patient) 	<p>BRADYCARDIC PEA***</p> <ol style="list-style-type: none"> ASSESS/TREAT CAUSE IV access EPINEPHRINE May repeat q 3-5 min IVP: 1:10,000 1.0 mg If no IV, give ET: 1:10,000 2.0 mg** IL: 1:1,000 1.0 mg Reassess cardiac rhythm. If still BRADYCARDIC PEA, give ATROPINE: IVP: 1.0 mg ET: 2.0 mg** IL: 1.0 mg (1 mg/ml) ALS airway management.⁴ Repeat Epi q 3-5 minutes Repeat Atropine q 3-5 minutes to a total dose of 0.04 mg/kg (3 mg in a 75 kg patient) 	<p>NON BRADYCARDIC PEA***</p> <ol style="list-style-type: none"> ASSESS/TREAT CAUSE: Medical vs. Trauma. Treat Hypovolemia if present IF TRAUMA OR HYPOVOLEMIA, STAT TRANSPORT AS SOON AS AIRWAY IS SECURED IV access (Wide Open if hypovolemic) EPINEPHRINE May repeat q 3-5 min IVP: 1:10,000 1.0 mg If No IV, ET: 1:10,000 2.0 mg** IL: 1:1000 1.0 mg ALS Airway Management.⁴ Reassess Cardiac Rhythm. If Non-Bradycardic PEA remains, continue treatment of likely cause. Repeat Epi q 3-5 minutes 															
<p>* Or biphasic waveform defibrillation at energy level approved by service provider medical director. ** For ET administration, dilute in 5-10 ml NS. *** If defibrillation → narrow complex rhythm > 50, not in 2nd or 3rd degree block, and Lidocaine not already given, give Lidocaine 1.5 mg/kg IVP or ET 3 mg/kg (if no IV). **** if collapse before dispatch, 5 cycles CPR before defibrillation.</p>		<p>LIKELY CAUSES OF PEA</p> <table border="0"> <tr> <td>Acidosis</td> <td>Pulm Embolism</td> <td>Drug OD</td> </tr> <tr> <td>Hyperkalemia</td> <td>Massive MI</td> <td>Tricyclics</td> </tr> <tr> <td>Tamponade</td> <td>Digitalis</td> <td>Beta Blockers</td> </tr> <tr> <td>Hypovolemia</td> <td>Tension Pneumo</td> <td>Profound Hypothermia</td> </tr> <tr> <td>Hypoxemia</td> <td></td> <td>Ca Channel Blockers</td> </tr> </table>		Acidosis	Pulm Embolism	Drug OD	Hyperkalemia	Massive MI	Tricyclics	Tamponade	Digitalis	Beta Blockers	Hypovolemia	Tension Pneumo	Profound Hypothermia	Hypoxemia		Ca Channel Blockers
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<p>Base Hospital Contact (if unable, initiate transport and continue efforts to contact)</p>																		
BASE HOSPITAL ORDERS ONLY																		
<ol style="list-style-type: none"> Consider Na Bicarb 1 mEq/kg IVP Defibrillate - 360 J Consider MgSO₄ 1-2 GM IVP Defibrillate - 360 J or biphasic waveform defibrillation at energy level approved by service provider medical director. 	<ol style="list-style-type: none"> Consider Na Bicarb 1 mEq/kg IVP 	<ol style="list-style-type: none"> Consider Na Bicarb 1 mEq/kg IVP ***PEA: Pulseless Electrical Activity 	<ol style="list-style-type: none"> Consider Na Bicarb 1 mEq/kg IVP 															

- NOTES:**
- Early BH contact is recommended in unusual situations, e.g., renal failure, Calcium channel blocker OD, tricyclic OD, Beta blocker OD and Torsade. BH to consider:
 - CaCl₂ and Bicarb in renal failure,
 - early Bicarb in Tricyclic OD,
 - early CaCl₂ in Ca channel blocker OD,
 - Glucagon in beta blocker OD and calcium channel blocker OD, and
 - MgSO₄ in Torsade.
 - Dosages
 - Calcium Chloride: 10 ml of 10% solution, may repeat X1 in 10 minutes
 - Glucagon: 1-5 mg IVP as available
 - Magnesium: 2 g slow IVP over 2 minutes
 - Sodium Bicarbonate: 1 mEq/kg followed by 0.5 mEq/kg q 10 minutes
 - In cases of normothermic adult patients with unmonitored cardiac arrest with adequate ventilation, vascular access, and persistent asystole or PEA despite 20 minutes of standard advanced cardiac life support; the base hospital should consider termination of resuscitation in the field. If transported, the patient may be transported Code II. If unable to contact base hospital, resuscitative efforts may be discontinued and patient determined to be dead.
 - V-Tach = Ventricular Tachycardia with rate > 150/min.
 - If unable to adequately ventilate with BLS measures, insert advanced airway earlier.
 - If organized narrow complex rhythm > 50, not in 2nd or 3rd degree block after 2 minutes post-shock CPR, IV access, lidocaine 1.5 mg/kg IVP.
 - For all rhythms, in patients 18 y/o and above, start compressions at 100/min. Insert King Airway as soon as practical. Place ITD in airway circuit. Once King Airway inserted, continue chest compressions at 100/min without interruption and ventilate with 1 breath every 10 compressions. If unable to place King Airway use standard 30/2 CPR with the ITD placed on the mask. If ROSC the ITD will be taken out of the airway circuit.

Effective Date: June 1, 2007
Review Date: June, 2009
C:\Documents and Settings\emsus095\Local Settings\Temporary Internet Files\OLK5EB0705_Carr_Arr_Adult_080829_Study.doc

VCEMS Medical Director

Deleted: start CPR w/ BVM at 30 compressions and 2 ventilations.

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DRAFT 8/13/08

Study Proposal: Comparison of Cardiac Arrest Outcomes with Early Advanced Airway and Impedance Threshold Device to Standard 2005 AHA CPR in the Out-of-Hospital Setting

Hypothesis: The combination of uninterrupted compressions and early use of an impedance threshold device will increase survival to hospital discharge neurologically intact in the adult out-of-hospital cardiac arrest patient^{1,2,3,4}.

Study Design: Current standard 2005 guideline CPR will be modified. Rather than 30/2 compression/ventilation ratio with pauses for ventilations, compressions will be started continuously at 100 per minute upon recognizing cardiac arrest. The airway will be managed with a King LTS-D Airway and a ResQPOD will immediately be placed in the airway circuit. When the King Airway is placed asynchronous ventilations will be started at 10 per minute⁵. Data will be recorded using an Utstein template for 15 months and compared to the prior 15 months data when "standard AHA CPR guidelines" were used. The primary endpoint will be hospital discharge with a Cerebral Performance Category of one or two. The study population will be all adult cardiac arrest patients for which resuscitation was/is attempted by EMS personnel in Ventura and Santa Barbara Counties working for agencies that have accurate retrospective outcome data.

Study Power: To achieve a significance level of 0.05 it is estimated that 424 subjects per arm of the study will be required.

Consent: Due to the nature of the study waiver of consent is required. California State EMS Authority approves the King Airway. The ResQPOD is a category 2A recommendation of the AHA. Compression rates and ventilation rates are consistent with AHA 2005 guidelines. The study uses a historical control group. There is no sham or placebo arm of the study. All subjects will be treated actively per current perceived "Best Practice" standards.

References:

1. JAMA. 2008 Mar 12;299(10): 1158-65. Minimally interrupted cardiac resuscitation by emergency medical services for out-of-hospital cardiac arrest. Bobrow, et al.
2. AHA 2007 Scientific Session. A Tale of Seven EMS Systems: An Impedance Threshold Device and Improved CPR Techniques Double Survival Rates After Out-of-Hospital Cardiac Arrest. Aufderheide, et al.
3. Ann Emerg Med 2008;51(4):475. Implementation of the 2005 Cardiopulmonary Resuscitation Guidelines and Use of an Impedance Threshold Device Improve Survival from Inhospital Cardiac Arrest. Thigpen, et al.
4. Europace (2007) 9, 2-9. Acute Management of Sudden Cardiac Death in Adults Based Upon the New CPR Guidelines. Yannopoulos, et al.

5. J. Respiratory Care (In press 2008) Comparison of a 10-Breaths-Per-Minute Versus 2-Breaths-Per-Minute Strategy During CPR in a Porcine Model of Cardiac Arrest. Lurie, et al.

dgcmd 8/13/08

Minimally Interrupted Cardiac Resuscitation by Emergency Medical Services for Out-of-Hospital Cardiac Arrest

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OUT-OF-HOSPITAL CARDIAC arrest is a major public health problem and a leading cause of death.¹⁻⁴ Unfortunately, in large metropolitan cities, the outcomes are poor for patients with out-of-hospital cardiac arrest.⁵⁻⁷ Although early defibrillation with automated external defibrillators improves survival, early defibrillation is rare and few patients with out-of-hospital cardiac arrest survive.⁵⁻⁸ In 2004, the average survival of patients with out-of-hospital cardiac arrest was 3% in the state of Arizona.⁹

Minimally interrupted cardiac resuscitation (MICR), also referred to as cardiocerebral resuscitation, is a new approach to out-of-hospital cardiac arrest for emergency medical services (EMS) personnel developed at the University of Arizona Sarver Heart Center, and first instituted in Tucson, Arizona, in late 2003.¹⁰⁻¹² Minimally interrupted cardiac resuscitation focuses on maximizing myocardial and cerebral perfusion through a series of coordinated interventions. This approach is intended to minimize interruption of chest compressions,

Context Out-of-hospital cardiac arrest is a major public health problem.

Objective To investigate whether the survival of patients with out-of-hospital cardiac arrest would improve with minimally interrupted cardiac resuscitation (MICR), an alternate emergency medical services (EMS) protocol.

Design, Setting, and Patients A prospective study of survival-to-hospital discharge between January 1, 2005, and November 22, 2007. Patients with out-of-hospital cardiac arrests in 2 metropolitan cities in Arizona before and after MICR training of fire department emergency medical personnel were assessed. In a second analysis of protocol compliance, patients from the 2 metropolitan cities and 60 additional fire departments in Arizona who actually received MICR were compared with patients who did not receive MICR but received standard advanced life support.

Intervention Instruction for EMS personnel in MICR, an approach that includes an initial series of 200 uninterrupted chest compressions, rhythm analysis with a single shock, 200 immediate postshock chest compressions before pulse check or rhythm reanalysis, early administration of epinephrine, and delayed endotracheal intubation.

Main Outcome Measure Survival-to-hospital discharge.

Results Among the 886 patients in the 2 metropolitan cities, survival-to-hospital discharge increased from 1.8% (4/218) before MICR training to 5.4% (36/668) after MICR training (odds ratio [OR], 3.0; 95% confidence interval [CI], 1.1-8.9). In the subgroup of 174 patients with witnessed cardiac arrest and ventricular fibrillation, survival increased from 4.7% (2/43) before MICR training to 17.6% (23/131) after MICR training (OR, 8.6; 95% CI, 1.8-42.0). In the analysis of MICR protocol compliance involving 2460 patients with cardiac arrest, survival was significantly better among patients who received MICR than those who did not (9.1% [60/661] vs 3.8% [69/1799]; OR, 2.7; 95% CI, 1.9-4.1), as well as patients with witnessed ventricular fibrillation (28.4% [40/141] vs 11.9% [46/387]; OR, 3.4; 95% CI, 2.0-5.8).

Conclusions Survival-to-hospital discharge of patients with out-of-hospital cardiac arrest increased after implementation of MICR as an alternate EMS protocol. These results need to be confirmed in a randomized trial.

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www.jama.com

provide immediate preshock chest compressions for prolonged ventricular fibrillation (VF), delay or eliminate endotracheal intubation, minimize positive pressure ventilations, and decrease

the time interval to intravenous epinephrine administration.¹⁰⁻¹⁵

Implementation of MICR was associated with substantially improved survival for patients with out-of-hospital

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Departments of Medicine (Drs Ewy and Kern), Emergency Medicine (Dr Sanders), and Pediatrics (Dr Berg), University of Arizona College of Medicine, Tucson, Arizona.

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For editorial comment see p 1188.

cardiac arrest in rural settings.¹⁴ We investigated whether MICR would improve survival from out-of-hospital cardiac arrest in a large urban setting. First, we report an analysis of before and after training of EMS personnel in 2 metropolitan fire departments in Arizona. Second, we investigated whether survival would be different in patients who actually received MICR (as defined by 4 compliance criteria) compared with patients who did not receive MICR in the 2 metropolitan and 60 additional fire departments throughout the state.

METHODS

The Save Hearts in Arizona Registry and Education (SHARE) program of the Bureau of Emergency Medical Services and Trauma System was established as part of the Arizona Department of Health Services to address the public health problem of sudden out-of-hospital cardiac arrest. This statewide program collects data from multiple EMS systems in rural, suburban, and urban settings. Because cardiac arrest has been identified as a public health issue in Arizona, these incidents are exempt from the Health Insurance Portability and Accountability Act of 1996. Approval was obtained from the Arizona Department of Health Services Human Subjects Review Committee and permission to publish deidentified data was obtained through the University of Arizona Institutional Review Board.

Arizona has approximately 6.3 million citizens living in 15 counties.¹⁶ Our study includes data for out-of-hospital cardiac arrest from 62 EMS agencies, representing approximately 75% of the state's population. Prehospital triage, treatment, and transport protocols vary by local jurisdiction and region.

Data Collection and Definitions

An Utstein-style database for out-of-hospital cardiac arrests was initiated for all 62 participating fire departments.¹⁷ The Utstein-style EMS incident reports collect information on patient demographics, event circumstances, response intervals, presenting rhythm, treatment and procedures, and initial

outcomes.¹⁷ Final outcomes were obtained through local hospitals and the Bureau of Public Health Statistics in the Arizona Department of Health Services.

Cardiac arrest was defined as the absence of cardiac mechanical activity determined by the absence of a pulse and the lack of normal breathing. Patients included all patients with out-of-hospital cardiac arrest on whom resuscitation was initiated. Cardiac arrest rhythms included asystole, pulseless electrical activity, and VF/pulseless ventricular tachycardia. Individuals with obvious signs of death (eg, rigor mortis, lividity) or with do not resuscitate documentation on EMS arrival were excluded because resuscitation efforts were not initiated per standard protocol. Other exclusion criteria were age (<18 years), cardiac arrest in adults witnessed by EMS personnel, and cardiac arrest secondary to trauma, drowning, or other noncardiac causes.

Intervention

Before and After Analysis. Minimally interrupted cardiac resuscitation was presented as an alternate treatment strategy for out-of-hospital cardiac arrest by 3 authors (B.J.B., L.L.C., and G.A.E.) to the EMS fire chiefs and medical directors. We provided MICR training with verbal and visual (slide presentation) instructions, psychomotor skill training for trainers (by B.J.B. and L.L.C.), and written supporting material (developed by the University of Arizona Sarver Heart Center Cardiopulmonary Resuscitation Research Group). A train-the-trainer model was used to disseminate the MICR protocol to fire department EMS personnel, and approximately 2000 EMS firefighters were trained in the new approach.

The MICR protocol for prehospital personnel includes an initial 200 uninterrupted chest compressions at 100 compressions per minute, rhythm analysis with a single shock when indicated, immediately followed by 200 postshock chest compressions before any pulse check or rhythm reanalysis. Endotracheal intubation is delayed until after 3 cycles of chest compressions and rhythm analysis. Intravenous epi-

nephrine (1 mg) is administered as soon as possible during the protocol and again with each cycle of chest compressions and rhythm analysis.^{12,14,15,18}

Minimally interrupted cardiac resuscitation discourages early and excessive ventilation by advocating passive oxygen insufflation with the placement of an oral-pharyngeal airway, a nonrebreather face mask, and high-flow oxygen rather than positive pressure ventilation.¹⁴ However, because this approach to ventilation was such a dramatic change for the EMS personnel, bag-valve-mask ventilation was still permitted by paramedics and firefighters at an encouraged rate of 8 ventilations per minute. No patient received post-resuscitation hypothermia.

For the before and after analysis, we report data collected between January 1, 2005, and June 30, 2007. Six months of baseline data, referred to as "before MICR" (January 1, 2005-June 30, 2005), were collected from the fire departments in the 2 largest metropolitan cities in Arizona. During the before MICR period, these departments followed the EMS protocol set forth in the 2000 American Heart Association (AHA) and the International Liaison Committee on Resuscitation Guidelines.¹⁹

Data collection for the "after MICR" training period began on the date that MICR training was first implemented. In the first fire department (site 1), MICR training was implemented on July 21, 2005. In the second fire department (site 2), MICR training was implemented on January 1, 2006. For the before and after analysis, data collection concluded in both fire departments on June 30, 2007. The before and after analysis was based on the principles of intention to treat and the analysis included all patients in the 2 time periods, regardless of whether they received MICR or not.

Protocol Compliance Analysis. In the protocol compliance analysis, we compared outcomes from patients who actually received MICR (all 4 compliance criteria present) with those who did not receive MICR between January 1, 2005, and November 22, 2007. The pro-

OUT-OF-HOSPITAL CARDIAC ARREST

toloc compliance analysis included patients from the initial 2 fire departments plus an additional 60 fire departments in Arizona. Twelve of the total 62 fire departments were trained in MICR; the other 50 had no MICR training. In the protocol compliance analysis, the MICR training described in the before and after analysis was provided in a similar manner for the 10 other fire departments between 2005 and 2007.

The MICR protocol compliance was assessed by the presence of all 4 of the

following criteria: (1) 200 preshock chest compressions, (2) 200 postshock chest compressions, (3) delayed endotracheal intubation for 3 cycles of 200 compressions and rhythm analysis, and (4) patients who received intravenous epinephrine in the first or second cycle of chest compressions.

Main Outcome Measures

The primary outcome measure in both the before and after analysis and the protocol compliance analysis was sur-

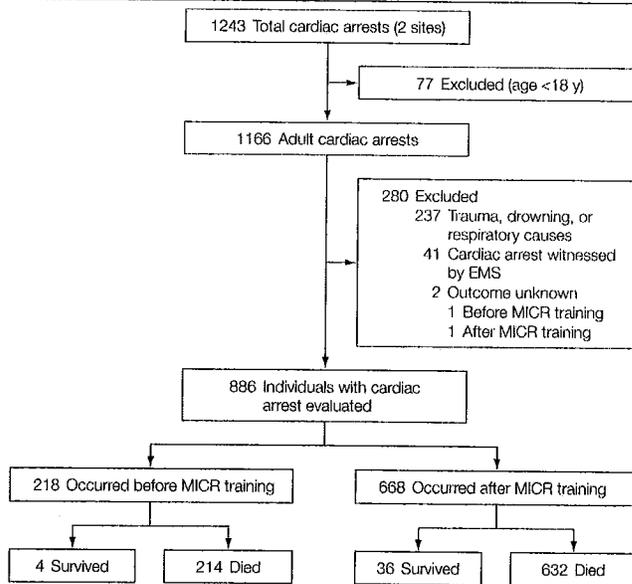
vival-to-hospital discharge for all patients with cardiac arrest and for the subgroup of patients with witnessed collapse and a shockable rhythm. Secondary outcome measures were favorable neurological outcome among survivors, return of spontaneous circulation, and survival-to-hospital admission.

To assess neurological outcome, survivors were contacted by mail and asked if they were willing to participate in a telephone interview or complete a questionnaire. The survivors also had the option of refusing to participate. A telephone interview was conducted or a questionnaire was sent to those patients consenting to assess their neurological status with the Cerebral Performance Categories (CPC) score on discharge from the hospital.¹⁷ A CPC score of 1 indicates good cerebral performance (conscious, alert, able to work, might have mild neurological or psychological deficit); score 2, moderate cerebral disability (conscious, sufficient cerebral function for independent activities of daily life; able to work in sheltered environment); score 3, severe cerebral disability (conscious, dependent on others for daily support because of impaired brain function; ranges from ambulatory state to severe dementia or paralysis); score 4, coma or vegetative state (any degree of coma without the presence of all brain death criteria; unawareness, even if appears awake [vegetative state] without interaction with environment; may have spontaneous eye opening and sleep/wake cycles; cerebral unresponsiveness); and score 5, brain death (apnea, areflexia, electroencephalographic silence). For our analysis, CPC scores of 1 or 2 were considered favorable neurological outcome with sufficient cerebral function for independent activities.

Statistical Analyses

Data were entered into Microsoft Access (Microsoft Corp, Redmond, Washington) and transported into SPSS version 15.0 for statistical analysis (SPSS Inc, Chicago, Illinois). Continuous variables were presented as mean (SD) and

Figure 1. Flow Diagram of Patient Enrollment in the Before and After Analysis



EMS indicates emergency medical services; MICR, minimally interrupted cardiac resuscitation. The before and after analysis consisted of before and after MICR training of EMS personnel in 2 metropolitan fire departments in Arizona, with data collection between January 1, 2005, and June 30, 2007. For cardiac arrests occurring before MICR training at both sites, data were collected between January 1 and June 30, 2005. For cardiac arrests occurring after MICR training, data were collected at site 1 between July 21, 2005, and June 30, 2007, and at site 2 between January 1, 2006, and June 30, 2007.

Table 1. Patient Demographics and Event Characteristics in the Before and After Analysis^a

Characteristics	Before MICR Training (n = 218)	After MICR Training (n = 668)	P Value
Age, mean (SD), y	65.0 (14.9)	66.0 (15.3)	.37
Men	143 (65.6)	459 (68.7)	.39
Home location	154 (70.6)	495 (74.1)	.32
Bystander CPR performed	75 (34.4)	262 (39.2)	.20
Witnessed	89 (40.8)	302 (45.2)	.26
Ventricular fibrillation	69 (31.7)	200 (29.9)	.63
EMS dispatch-to-arrival time, mean (SD), min	5.6 (2.6)	5.2 (2.0)	.12
Endotracheal intubation	90 (41.3)	437 (65.4)	<.001

Abbreviations: CPR, cardiopulmonary resuscitation; EMS, emergency medical services; MICR, minimally interrupted cardiac resuscitation.

^aData are presented as No. (%) unless otherwise specified.

analyzed by *t* test or Mann-Whitney *U* test. For the before and after analysis, the proportion of patients who survived to hospital discharge in the before MICR training and the after MICR training groups was compared with χ^2 or Fisher exact tests. A step-wise logistic regression analysis was used to determine the survival association of patients in the after MICR training group compared with those in the before MICR training group, adjusted for potential confounders. A base model was adjusted for age, sex, location of cardiac arrest, witnessed arrest, bystander cardiopulmonary resuscitation, VF, endotracheal intubation, and entire EMS dispatch-to-arrival time. A dummy variable was created to adjust for site differences and was included in the base model. The final

model included only statistically significant covariates ($P < .05$). Odds ratios (ORs) for survival and 95% confidence intervals (CIs) were determined. The sample size was not planned. For the protocol compliance analysis, similar statistical tests were conducted comparing survival-to-hospital discharge for those patients who did and did not receive MICR. Neurological outcomes were calculated by using the CPC scale.¹⁷

RESULTS

Before and After Analysis

Of 1243 cardiac arrests during the data collection period, 886 met the inclusion criteria (218 occurred before MICR training and 668 occurred after MICR training) and underwent further evaluation (FIGURE 1). There were no sig-

nificant differences between patients in the before MICR training group and the after MICR training group, regarding age, sex, location of cardiac arrest, presence of an initial shockable rhythm (VF), or EMS dispatch-to-arrival time. During the after MICR training period, more patients received endotracheal intubation ($P < .001$) (TABLE 1).

Among the 886 patients with cardiac arrest, survival-to-hospital discharge was found in 4 of 218 patients (1.8%) in the before MICR training group and in 36 of 668 patients (5.4%) in the after MICR training group (adjusted OR, 3.0; 95% CI, 1.1-8.9) (TABLE 2). In the subgroup of 174 patients with a witnessed cardiac arrest and a shockable rhythm, survival was found in 2 of 43 patients (4.7%) in the before MICR training group and

Table 2. Comparison of Major Outcomes in the Before and After Analysis

Outcomes	No./Total No. (%) of Patients		Odds Ratio (95% CI)		Significant Covariates in Final Model ^a
	Before MICR Training	After MICR Training	Unadjusted	Adjusted	
	Primary outcomes				
Survival-to-hospital discharge	4/218 (1.8)	36/668 (5.4)	3.0 (1.1-8.6)	3.0 (1.1-8.9)	Witnessed arrest and VF
Survival with witnessed VF	2/43 (4.7)	23/131 (17.6)	4.4 (1.0-19.1)	8.6 (1.8-42.0)	Endotracheal intubation
Secondary outcomes					
Return of spontaneous circulation	34/218 (15.6)	154/668 (23.1)	1.6 (1.1-2.4)	1.3 (0.8-2.0)	Witnessed arrest, VF, endotracheal intubation, and site
Survival-to-hospital admission	35/218 (16.1)	113/668 (16.9)	1.1 (0.7-1.6)	0.8 (0.5-1.2)	Bystander CPR performed, witnessed arrest, VF, endotracheal intubation, entire EMS dispatch-to-arrival time

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; MICR, minimally interrupted cardiac resuscitation; VF, ventricular fibrillation.
^aInitial model included age, sex, location of cardiac arrest, bystander CPR performed, witnessed arrest, VF, endotracheal intubation, entire EMS dispatch-to-arrival time, and site. The final model included only significant covariates, as indicated.

Table 3. Compliance and Outcomes in the Before and After Analysis by Site and 6-Month Time Intervals^a

	Before MICR Training	After MICR Training	6-Month Intervals After MICR Training			
			1	2	3	4
Site 1 (n = 393)						
Compliance, %		70.4	60.3	81.1	69.2	65.2
Overall survival	3/119 (2.5)	18/274 (6.6)	3/58 (5.2)	11/95 (11.6)	1/52 (1.9)	3/69 (4.3)
Witnessed VF survival	2/23 (8.7)	11/52 (21.2)	2/11 (18.2)	7/17 (41.2)	1/6 (16.7)	1/18 (5.6)
Return of spontaneous circulation	16/119 (13.4)	77/274 (28.1)	17/58 (29.3)	29/95 (30.5)	13/52 (25.0)	18/69 (26.1)
Survival-to-hospital admission	15/119 (12.6)	50/274 (18.2)	10/58 (17.2)	20/95 (21.1)	9/52 (17.3)	11/69 (15.9)
Site 2 (n = 493)						
Compliance, %		54.6	57.6	54.3	50.0	
Overall survival	1/99 (1.0)	18/394 (4.6)	11/172 (6.4)	5/116 (4.3)	2/106 (1.9)	
Witnessed VF survival	0/20 (0)	12/79 (15.2)	7/32 (21.9)	4/26 (15.4)	1/21 (4.8)	
Return of spontaneous circulation	18/99 (18.2)	77/394 (19.5)	37/172 (21.5)	25/116 (21.6)	15/106 (14.2)	
Survival-to-hospital admission	20/99 (20.2)	63/394 (16.0)	24/172 (14.0)	21/116 (18.1)	18/106 (17.0)	

Abbreviations: MICR, minimally interrupted cardiac resuscitation; VF, ventricular fibrillation.

^aData are presented as No./Total No. (%), unless otherwise specified. There was no compliance in the before MICR training at both sites because MICR was not performed. At site 2, there was no after MICR training interval 4. For site 1, the after MICR training interval 1 was between July 21, 2005, and December 31, 2005; interval 2: between January 1, 2006, and June 30, 2006; interval 3: between July 1, 2006, and December 31, 2006; and interval 4: between January 1, 2007, and June 30, 2007. For site 2, the after MICR training interval 1 was between January 1, 2006, and June 30, 2006; interval 2: between July 1, 2006, and December 31, 2006; and interval 3: between January 1, 2007, and June 30, 2007.

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in 23 of 131 patients (17.6%) in the after MICR training group (adjusted OR, 8.6; 95% CI, 1.8-42.0). Overall, 61.1% (408/668) of cardiac arrests treated after MICR training met the 4 MICR compliance criteria.

In TABLE 3, the primary outcome measures and compliance are reported in the before and after analysis by site and 6-month time intervals. At site 1, overall survival-to-hospital discharge increased from 2.5% before MICR training to 6.6% after MICR training, with a compliance of 70.4% after MICR training.

In addition, survival among patients with witnessed cardiac arrest and VF increased from 8.7% to 21.2%. At site 2, overall survival-to-hospital discharge increased from 1.0% before MICR training to 4.6% after MICR training, with a compliance of 54.6% after MICR training. Furthermore, survival among patients with witnessed VF at site 2 increased from 0% to 15.2%.

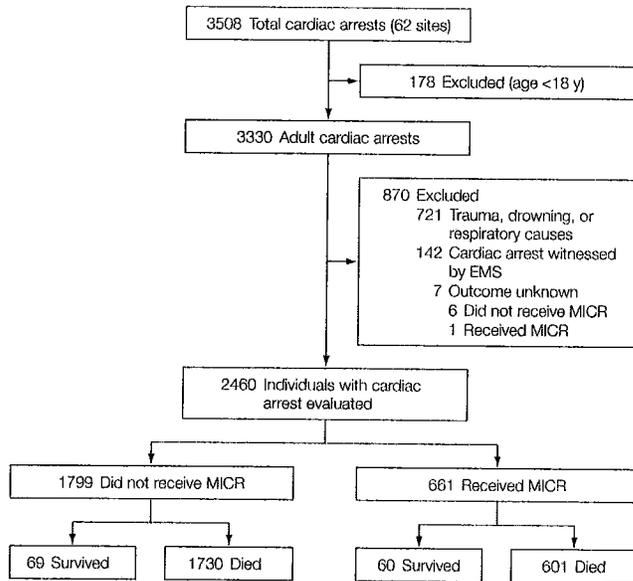
Protocol Compliance Analysis

FIGURE 2 shows the enrollment data for the protocol compliance analysis, an as-

essment of outcomes for patients who actually received MICR vs those who did not receive MICR in the 2 metropolitan cities and in the 60 additional Arizona fire departments. Overall, 3508 patients in cardiac arrest were assessed from January 1, 2005, to November 22, 2007, with 2460 included in the analysis. A total of 1799 patients did not receive MICR and 661 patients received MICR. Baseline characteristics of each group are shown in TABLE 4. In the group that received MICR, there were more men, endotracheal intubation was more frequent, and the patients were slightly younger.

TABLE 5 shows the major outcomes for the protocol compliance analysis. Overall survival-to-hospital discharge was found in 69 of 1799 patients (3.8%) who did not receive MICR and in 60 of 661 (9.1%) who received MICR (adjusted OR, 2.7; 95% CI, 1.9-4.1). Survival with witnessed VF cardiac arrest was found in 46 of 387 patients (11.9%) who did not receive MICR and in 40 of 141 patients (28.4%) who received MICR (adjusted OR, 3.4; 95% CI, 2.0-5.8). Neurological outcome data was available for 84 of 129 survivors (65.1%). Favorable neurological outcomes with CPC scores of 1 or 2 were noted among 81.6% of patients who did not receive MICR and 80.0% of patients who received MICR (TABLE 6).

Figure 2. Flow Diagram of Patient Enrollment in the Protocol Compliance Analysis



EMS indicates emergency medical services; MICR, minimally interrupted cardiac resuscitation. The protocol compliance analysis included patients from the initial 2 metropolitan fire departments plus an additional 60 fire departments in Arizona (total 62 fire departments: 12 trained in MICR and 50 not trained in MICR), with data collection between January 1, 2005, and November 22, 2007.

Table 4. Patient Demographics and Event Characteristics in the Protocol Compliance Analysis^a

Characteristics	Did Not Receive MICR (n = 1799)	Received MICR (n = 661)	P Value
Age, mean (SD), y	67.8 (15.0)	65.7 (15.4)	.002
Men	1169 (65.0)	462 (69.9)	.02
Home location	1276 (70.9)	494 (74.7)	.06
Witnessed	797 (44.3)	298 (45.1)	.73
Bystander CPR performed	707 (39.3)	267 (40.4)	.62
Ventricular fibrillation	561 (31.2)	211 (31.9)	.73
EMS dispatch-to-arrival time, mean (SD), min	5.6 (3.2)	5.2 (2.3)	.32
Endotracheal intubation	1032 (57.4)	414 (62.6)	.01

Abbreviations: CPR, cardiopulmonary resuscitation; EMS, emergency medical services; MICR, minimally interrupted cardiac resuscitation.

^aData are presented as No. (%) unless otherwise specified.

COMMENT

The before and after analysis demonstrated that survival-to-hospital discharge after out-of-hospital cardiac arrest in a metropolitan setting improved from 1.8% to 5.4% after 2 fire departments delivering EMS were taught the MICR protocol. The greatest improvement in survival occurred in the subgroup of patients most likely to survive: those with documented witnessed cardiac arrest and a shockable rhythm. Those patients had a 4.7% survival rate before MICR training vs 17.6% after MICR training.

The study by Kellum et al¹⁴ reported a tripling (from 15% to 48%) in neurologically intact survival for patients in a

Table 5. Comparison of Major Outcomes in the Protocol Compliance Analysis

Outcomes	No./Total No. (%) of Patients		Odds Ratio (95% CI)		Significant Covariates in Final Model ^a
	Did Not Receive MICR	Received MICR	Unadjusted	Adjusted	
Primary outcomes					
Survival-to-hospital discharge	69/1799 (3.8)	60/661 (9.1)	2.5 (1.7-3.6)	2.7 (1.9-4.1)	Age, bystander CPR performed, witnessed arrest, VF, endotracheal intubation, and entire EMS dispatch-to-arrival time
Survival with witnessed VF	46/387 (11.9)	40/141 (28.4)	2.9 (1.8-4.7)	3.4 (2.0-5.8)	Age, bystander CPR performed, endotracheal intubation, and entire EMS dispatch-to-arrival time
Secondary outcomes					
Return of spontaneous circulation	312/1799 (17.3)	185/661 (28.0)	1.9 (1.5-2.3)	1.9 (1.5-2.3)	Sex, witnessed arrest, VF, endotracheal intubation, and entire EMS dispatch-to-arrival time
Survival-to-hospital admission	271/1799 (15.1)	145/661 (21.9)	1.6 (1.3-2.0)	1.5 (1.2-2.0)	Age, sex, bystander CPR performed, witnessed arrest, VF, endotracheal intubation, and entire EMS dispatch-to-arrival time

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; MICR, minimally interrupted cardiac resuscitation; VF, ventricular fibrillation. ^aInitial model included age, sex, location of cardiac arrest, bystander CPR performed, witnessed arrest, VF, endotracheal intubation, and entire EMS dispatch-to-arrival time. The final model included only significant covariates, as indicated.

rural setting who had witnessed out-of-hospital cardiac arrest and a shockable rhythm after EMS implementation of cardiocerebral resuscitation. We found a similar magnitude of improvement in survival in a metropolitan setting.

In the before and after analysis, 61.1% of the resuscitations after MICR training met all 4 compliance criteria. EMS personnel received only 1 training session in MICR. Perhaps survival rates would have been even better with more training, retraining, and feedback, resulting in higher MICR compliance rates. In the protocol compliance analysis, we analyzed data from 2 fire departments in metropolitan cities and 60 additional Arizona fire departments and compared outcomes of patients who actually received MICR with those who did not receive MICR. In this latter analysis, overall survival was 3.8% in patients not receiving MICR vs 9.1% in patients receiving MICR, with approximately 80% of survivors in both groups having favorable neurological outcomes.

Why should MICR be associated with improved outcomes after out-of-hospital cardiac arrest? One major contributor to the poor survival rates of patients with out-of-hospital cardiac arrest is prolonged inadequate myocardial and cerebral perfusion. During resuscitation efforts, the forward blood flow produced by chest compressions is so mar-

ginal that any interruption of chest compressions is extremely deleterious, especially for favorable neurological outcomes.²⁰⁻²² Excessive interruptions of chest compressions by prehospital personnel are common.^{23,24} Therefore, MICR emphasizes uninterrupted chest compressions.^{11,12}

A second contributor to suboptimal survival of adults with out-of-hospital cardiac arrest is that defibrillation is typically provided after 5 or more minutes of VF cardiac arrest, the "circulatory" phase of VF arrest²⁵ when preshock and/or postshock myocardial perfusion are necessary for attaining return of spontaneous circulation.^{26,27} Prolonged VF (the circulatory phase) is different from short-duration VF in regard to myocardial bioenergetics, cellular electrophysiology, whole-organ myocardial electrophysiology, and response to therapy.^{13-15,18,19,22,28} Substantial, progressive depletion of myocardial high-energy phosphates occur during prolonged VF.^{19,22} Moreover, characteristic changes occur in the VF waveform during prolonged VF from a coarse waveform initially to a fine waveform over time. As the duration of VF increases and the waveform becomes fine, defibrillation into a perfusing rhythm is less likely. Experimental and clinical studies indicate that preshock chest compressions for prolonged VF can

Table 6. Cerebral Performance Category (CPC) Scores Among Survivors^a

CPC Score	Did Not Receive MICR	
	(n = 69)	Received MICR (n = 60)
1	20 (40.8)	18 (51.4)
2	20 (40.8)	10 (28.6)
3	7 (14.3)	7 (20.0)
4	2 (4.1)	0
5	0	0

Abbreviation: MICR, minimally interrupted cardiac resuscitation.
^aSee "Methods" section for explanation of CPC scores 1 through 5. Some participants were missing a CPC score (20 who did not receive MICR and 25 who received MICR).

"coarsen" the VF waveform and improve the rate of successful resuscitation.^{1,13-16,20,21} Furthermore, a recent clinical investigation demonstrated that even 10- to 20-second pauses in preshock compressions decrease defibrillation success.²³ Preshock and postshock immediate uninterrupted chest compressions are emphasized with MICR.^{11,12,14}

A third potential contributor is that stacked or 3 sequential shocks¹ with an automated external defibrillator increase the "hands-off" time due to repeated automated rhythm analyses and shock advisories, thereby leading to inadequate myocardial and cerebral perfusion during this circulatory phase of VF cardiac arrest. Therefore, single shocks are used in MICR.^{11,12,14}

A fourth potential contributor to the poor survival of patients with out-of-hospital cardiac arrest who are treated

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with standard cardiopulmonary resuscitation and advanced cardiac life support is that positive pressure ventilations during cardiac arrest may be harmful because they increase intrathoracic pressure, thereby decreasing venous return and subsequent myocardial and cerebral blood flow.²⁹ Probably due to the excitement and stress of resuscitation efforts, excessive ventilations by both physicians and EMS personnel are common.^{29,30} Positive pressure ventilations are discouraged with MICR in the crucial early resuscitation period.^{14,18,31}

Although endotracheal intubation was discouraged in the after MICR training group until after 3 cycles of shocks in the before and after analysis and was not permitted before completion of 3 cycles of shocks for inclusion as MICR in the protocol compliance analysis, more patients overall in the after MICR training group in the before and after analysis and in the MICR group in the protocol compliance analysis received endotracheal intubation. This apparent anomaly presumably occurred because the EMS protocol initiated with MICR training specifically included endotracheal intubation for all unresponsive patients before arrival at an emergency department.

The MICR approach may seem to downplay the importance of oxygen uptake from the lungs and delivery to the tissues. In fact, adequate tissue oxygen delivery is critically important for survival from a cardiac arrest, and chest compressions without rescue breaths can provide adequate oxygen delivery.^{21,32,33} Immediately after a sudden VF cardiac arrest, aortic oxygen and carbon dioxide concentrations do not vary from the prearrest state because there is no blood flow and oxygen consumption is minimal. Therefore, when chest compressions are initiated, the blood flowing from the aorta to the coronary and cerebral circulations provides adequate oxygenation at an acceptable pH. At that time, myocardial oxygen delivery is limited more by blood flow than oxygen content. Adequate oxygenation and ventilation can continue without rescue

breathing because the lungs serve as a reservoir of oxygen that allows adequate oxygen exchange with the limited pulmonary blood flow during cardiopulmonary resuscitation (only approximately 10%-15% of pulmonary blood flow during normal sinus rhythm). In addition, substantial ventilation occurs from chest compression-induced gas exchange (ie, small volumes exhaled with each compression and inhaled with chest recoil) and spontaneous gasping by the patient in cardiac arrest during cardiopulmonary resuscitation.^{32,33}

Despite increases in survival-to-hospital discharge, there was no demonstrable difference in rates of return of spontaneous circulation or survival-to-hospital admission between the before MICR training and after MICR training periods. This observation is important because it is not uncommon for studies of out-of-hospital cardiac arrest to use the intermediate outcome of return of spontaneous circulation or hospital admission as an end point.

In our before and after analysis, 16% of both groups survived to hospital admission, and yet survival to discharge was significantly greater in the after MICR training group. This finding suggests that initial cardiac resuscitation occurs in an equal percentage of patients receiving and not receiving MICR. However, our data also suggest that MICR provides perfusion sufficient for longer-term survival. Similar findings were observed in the protocol compliance analysis assessment of outcomes for patients who actually received MICR vs those who did not receive MICR.

The limitations of our observational study include the fact that the MICR intervention was not tested in a randomized controlled trial. We encourage others to conduct randomized controlled trials to confirm these results. However, an observational approach has been used effectively during the past few decades to advance resuscitation science, and this method will probably continue to be a major contributor to future advances in resuscitation.³⁴ The before and after observational design was intended to minimize

selection bias by assessing the same population in the same 2 cities treated by the same fire departments and with the same hospitals before and after implementing MICR instruction. Also, our patient populations were similar in the before MICR and after MICR training periods. It is possible that other factors, such as postresuscitation care, changed during the study period. However, none of the patients in the before and after analysis or the protocol compliance analysis received in-hospital therapeutic hypothermia. Furthermore, the protocol compliance analysis was consistent with the before and after analysis despite the ongoing inclusion of many patients who did not have MICR in the last year of the protocol compliance analysis study (2007).

We cannot exclude the possibility that the MICR training in the 12 fire departments motivated EMS personnel to provide better care independent of the specific MICR protocol (ie, the Hawthorne effect). However, none of the periodic changes in EMS protocols associated with new cardiopulmonary resuscitation and advanced cardiac life support guidelines during the past few decades has resulted in such a dramatic improvement in survival of patients with witnessed out-of-hospital cardiac arrest.

Another limitation of our study is that we compared MICR with the approach used by fire departments in our community during a time period when the AHA Guidelines were updated. Therefore, some of the non-MICR fire departments were following the 2000 AHA Guidelines while others were following the 2005 AHA Guidelines. The study by Rea et al³⁵ demonstrated that instituting some of the major changes of the 2005 guidelines for advanced cardiac life support (single shock and 200 chest compressions immediately after the shock rather than stacked shocks) was associated with increased survival-to-hospital discharge. A single shock followed by 200 uninterrupted chest compressions rather than stacked shocks is an important component of MICR.¹²

Outcome data are unknown for 2 patients in the before and after analysis

(1 in the before MICR training group and 1 in the after MICR training group) and for 7 patients in the protocol compliance analysis (6 in the did not receive MICR group and 1 in the received MICR group). Neurological outcomes are unknown in 35% of the survivors in the protocol compliance analysis. Nevertheless, the missing data are evenly distributed among the study groups, and we have no reason to believe that this represents a systematic bias.

In the protocol compliance analysis, we compared outcomes between patients who actually received MICR and those who had not to extend our observations to a larger population. We cannot exclude ascertainment biases in this analysis. Perhaps the most enthusiastic and skilled EMS personnel provided MICR and the least enthusiastic or least skilled EMS personnel did not. Furthermore, EMS personnel may have preferentially provided MICR to the patients most likely to survive. Nevertheless, our findings in the protocol compliance analysis were consistent with the data in the before and after analysis.

CONCLUSION

In this study, survival-to-hospital discharge of patients with an out-of-hospital cardiac arrest improved significantly after implementation of MICR as an alternate EMS protocol. These findings require confirmation in randomized trials.

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Study concept and design: Bobrow, Clark, Ewy, Sanders, Berg, Richman, Kern.

Acquisition of data: Bobrow, Clark.

Analysis and interpretation of data: Bobrow, Clark, Ewy, Chikani, Sanders, Berg.

Drafting of the manuscript: Bobrow, Clark, Ewy, Chikani, Sanders, Berg, Richman.

Critical revision of the manuscript for important intellectual content: Bobrow, Clark, Ewy, Sanders, Berg, Kern.

Statistical analysis: Chikani.

Administrative, technical, or material support: Bobrow, Clark, Ewy, Sanders, Berg, Kern.

Study supervision: Bobrow.

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**A TALE OF SEVEN EMS SYSTEMS:
AN IMPEDANCE THRESHOLD DEVICE AND IMPROVED CPR TECHNIQUES DOUBLE SURVIVAL
RATES AFTER OUT-OF-HOSPITAL CARDIAC ARREST**

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Introduction: Maximizing outcomes after cardiac arrest depends on optimizing a sequence of interventions from collapse to hospital discharge. The 2005 American Heart Association (AHA) Guidelines recommended many new interventions during CPR ('New CPR') including use of an Impedance Threshold Device (ITD).

Hypothesis: The combination of the ITD and 'New CPR' will increase return of spontaneous circulation (ROSC) and hospital discharge (HD) rates in patients with an out-of-hospital cardiac arrest.

Methods: Quality assurance data were pooled from 7 emergency medical services (EMS) systems (Anoka Co., MN; Harris Co., TX; Madison, WI; Milwaukee, WI; Omaha, NE; Pinellas Co., FL; and Wake Co., NC) where the ITD (ResQPOD®, Advanced Circulatory Systems; Minneapolis, MN) was deployed for >3 months. Historical or concurrent control data were used for comparison. The EMS systems simultaneously implemented 'New CPR' including compression/ventilation strategies to provide more compressions/min and continuous compressions during Advanced Life Support. All sites stressed the importance of full chest wall recoil. The sites have a combined population of ~ 3.2 M. ROSC data were available from all sites; HD data were available as of June 2007 from 5 sites (MN, TX, Milwaukee, NE, NC).

Results: A total of 893 patients treated with 'New CPR' + ITD were compared with 1424 control patients. The average age of both study populations was 64 years; 65% were male. Comparison of the ITD vs controls (all patients) for ROSC and HD [Odds ratios (OR), (95% confidence intervals), and Fisher's Exact Test] were: 37.9% vs 33.8% [1.2, (1.02, 1.40), $p=0.022$] and 15.7% vs 7.9% [2.2, (1.53, 3.07), $p<0.001$], respectively. Patients with ventricular fibrillation had the best outcomes in both groups. Neurological outcome data are pending. Therapeutic hypothermia was used in some patients (MN, NC) after ROSC.

Conclusion: Adoption of the ITD + 'New CPR' resulted in only a >10% increase in ROSC rates but a doubling of hospital discharge rates, from 7.9% to 15.7%, ($p<0.001$). These data represent a currently optimized sequence of therapeutic interventions during the performance of CPR for patients in cardiac arrest and support the widespread use of the 2005 AHA CPR Guidelines including use of the ITD.

Session Info: Resuscitation Science Symposium: Best of the Best (Oral Abstract Presentations Part II) – Presented: Sunday, November 04, 2007 @ 08:00 AM in Room W230ab

IMPLEMENTATION OF THE 2005 CARDIOPULMONARY RESUSCITATION GUIDELINES AND USE OF AN IMPEDANCE THRESHOLD DEVICE IMPROVE SURVIVAL FROM INHOSPITAL CARDIAC ARREST

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Study Objective: The 2005 American Heart Association guidelines recommended many new interventions during cardiopulmonary resuscitation (CPR), including a Level IIa recommendation for an impedance threshold device (ITD), which is intended to further optimize circulation during CPR. To date, all data published supporting use of an ITD have been following prehospital cardiac arrest. This study's objective was to determine the effect that implementing new CPR guidelines, which included use of an ITD, would have on survival to hospital discharge following in-hospital cardiac arrest.

Methods: Quality assurance data from adult patients (≥ 18 years) experiencing an in-hospital cardiac arrest at a 571-bed, acute care hospital were analyzed. Survival rates from a historical (control) period (01/2006 – 09/2006) were compared to matched patients in a prospective period (10/2006 – 08/2007) during which the new CPR guidelines and use of an ITD (ResQPOD®, Advanced Circulatory Systems; Minneapolis, Minnesota) were implemented. Per hospital protocol, the ITD was used on both a facemask and/or endotracheal tube in patients regardless of cardiac arrest etiology, unless specifically overridden by physician.

Results: In both study populations, patients, on average, were 67 years and 49% were male. The results were as follows:

Table: Survival Following In-hospital Cardiac Arrest

	Historical (n=157)	Prospective (n=136)	Odds Ratio	95% Confidence Intervals	Fischer's Exact Test
Return of Spontaneous Circulation	52/157 (33.1%)	79/136 (58.1%)	2.80	1.69, 4.64	p<0.001
Survival to Hospital Discharge	27/157 (17.2%)	38/136 (27.9%)	1.87	1.03, 3.41	P=0.034

Conclusion: Adoption of the new CPR guidelines and an ITD resulted in a 75% increase in initial arrest survival rates and a 62% increase in survival to hospital discharge rates. This first known reporting of data demonstrating the impact of new CPR plus and an ITD following in-hospital cardiac arrest represent a currently optimized sequence of therapeutic interventions and support widespread adoption of these therapies.



REVIEW

Acute management of sudden cardiac death in adults based upon the new CPR guidelines

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resuscitation;
Circulation;
Ventilation

Purpose of the review The aim of this article is to provide a comprehensive description of interventions that can improve outcomes in adults with sudden cardiac death. The new American Heart Association 2005 Guidelines introduced a number of changes for the initial management of cardiorespiratory arrest based on new data that accumulated over the last 5 years.

Acute management of sudden cardiac death Appropriate interventions targeting the three phases of cardiopulmonary resuscitation (CPR) (electrical, circulatory, and metabolic) should be implemented. Early defibrillation in early witnessed arrest with one shock is very effective and can improve survival outcomes. When resuscitation efforts are delayed and CPR is performed by paramedics, 2 min of CPR before shock is recommended. Emphasis has been placed on fast and forceful continuous compressions with minimal interruptions, adequate decompression, and decrease in the rate of ventilations to 8-10/min for intubated patients with two rescuers and a universal increase in compression to ventilation ratio to 30:2 for lone rescuers. Mechanical adjuncts to improve circulation have been adapted in the recommendations. The inspiratory impedance threshold device that enhances negative intrathoracic pressure and improves venous preload has been recommended for application in intubated and bag-mask ventilated patients. Owing to the difficulty of endotracheal intubation, airway management devices (Combitube and Laryngeal Mask Airway) can be used as alternatives with minimal extra training. **Conclusion** The new guidelines for CPR have focused on early defibrillation, uninterrupted compressions, complete decompression, fewer ventilations, and simplification and uniformity of the process.

Introduction

Approximately 1 000 000 sudden cardiac deaths occur yearly in the USA and Europe.^{1,2} Despite a dramatic improvement in many aspects of treatment strategies for emergency clinical situations, the survival from both out-of-hospital and in-hospital cardiac arrest remains poor. Even in the most advanced emergency medical systems in Western societies,^{1,3} neurologically intact survival rates remain <20%. On the basis of the large body of scientific advances in the arena of cardiopulmonary resuscitation (CPR), the American Heart Association and European Resuscitation Council have developed new guidelines for CPR and emergency management of sudden cardiac death.⁴

This article is focused on the major and critical interventions that have been proposed for the initial management of cardiac arrest. Special emphasis will be given to the basic

simple ways to improve circulation and vital organ perfusion pressures in an effort to improve the grave prognosis of sudden cardiac death. Most of this article is focused on relatively simple ways to increase the blood flow to the heart and brain during CPR to improve the overall chances of meaningful survival.

The complexity of cardiac arrest has led to the generation of a theory for its study, which divides cardiac arrest into three phases. Although the existence of those three phases is not scientifically proved, they are widely used as a basis for research. Specific treatments targeting the pathophysiology of each phase increase the chances of a meaningful recovery.⁵ The first phase, the electrical, where most patients have ventricular fibrillation, lasts ~4 min after the initial collapse and is characterized by a high degree of responsiveness to early defibrillation. The second phase, the circulatory, lasts from min 4 to 10, depending on the surrounding temperature and conditions. Good quality CPR, with emphasis given to improve delivery of oxygenated blood to brain and the heart before

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defibrillation, is of paramount importance and techniques that increase circulation have been shown to improve outcomes. The third phase, the metabolic, usually starts after 10 min. Current treatments are poor. These late efforts generally target the metabolic effects of prolonged ischaemia. Survival is inversely related to the time of untreated cardiac arrest. Most of the victims of cardiac arrest get professional assistance during the second phase of cardiac arrest, namely, the circulatory phase. This is one of the reasons that the new guidelines have placed extra emphasis on ways to improve circulation and to simplify the delivery of compressions and ventilations.

Immediate resuscitation

The earlier the intervention after the cardiac collapse, the higher the chances of survival. On the basis of the idea that most of the victims of cardiac arrest are initially approached by laypersons, a specific emphasis has been placed, increasing the rate of bystander CPR. Specifically, the new guidelines recommend that radio dispatchers should encourage chest-compressions-only CPR when there is unwillingness to provide rescue breathing in order to facilitate rapid initiation of chest compression. Fear of disease transmission from mouth-to-mouth ventilation and the challenges of trying to teach mouth-to-mouth by telephone dispatch have shifted the emphasis of pre-emergency medical service (EMS) arrival phone instructions to focus rescuers on chest compressions only. For lay rescuers interested in learning traditional CPR, a new and effective home-instruction self-learning programme was developed to teach basic life support (BLS) and automatic external defibrillator (AED) techniques in 30 min rather than the traditional 4 h course.

In the new guidelines, early defibrillation is re-emphasized as an essential therapy for the electrical phase of cardiac arrest. Direct current defibrillation can restore a perfusing rhythm in 80% of patients within 1-2 min. However, after 10 min, the success rate falls to <5% without CPR. That is the reason that broad deployment of public access defibrillators for layperson use has been encouraged. In a study that tested early defibrillation in US casinos, the survival of patients suffering from ventricular fibrillation was 50% overall. Patients who received defibrillation within 3 min of collapse had a 75% hospital discharge rate.⁶ The new 2005 guidelines give a Class I recommendation for early defibrillation in a witnessed arrest, reinforcing the previous 2000 guidelines.⁷⁻¹² A Class I or IIa recommendation is given to techniques and devices that have been shown in clinical trials to be effective and considered acceptable and useful.

The type of waveform recommended for defibrillation has also been changed. Biphasic electrical counter-shocks have been shown to decrease defibrillation thresholds when compared with monophasic shock. Although there are no clinical data demonstrating improved short- (1 h) or long-term survival rates between the monophasic and biphasic waveforms for the treatment of ventricular fibrillation during the electrical phase of cardiac arrest, a single high energy (150-200 J) biphasic defibrillation shock was recommended, Class IIa, for the treatment of both in-hospital and out-of-hospital ventricular fibrillation.¹³ Class IIa recommendations are given in the guidelines when the level of evidence or the consensus of expert opinion (when evidence is absent)

suggests a benefit without harm from any particular recommendation. Nearly, all new external defibrillators are currently manufactured to deliver biphasic shocks, but the AEDs need to be reprogrammed to minimize the time when there is no CPR or circulation to the heart and brain.¹³

Improving circulation

Most of the pre-hospital cardiac arrests cannot be treated within 4 min of the electrical phase. During this phase, there is a need for immediate compressions to generate blood flow and partially replete the membrane's energy required for generation of an organized rhythm. It has been recently shown that when the time between the emergency call and the paramedic arrival is longer than 4-5 min, CPR first, before shock, improves survival rates.¹⁴⁻¹⁶ If the time to defibrillation was <5 min, there were no differences in survival. When the time from the emergency call to the arrival of the ambulance was >5 min, CPR first improved survival and hospital discharge rates five-fold (4-22%).¹⁵

The new guidelines focus on more compressions and fewer ventilations. They call for immediate chest compressions and, once an advanced airway has been established, continuous chest compressions without interruption for ventilations. For BLS, the compression to ventilation ratio was increased from 15:2 to 30:2 in order to provide fewer interruptions of compressions for ventilation. During CPR, even in the best of circumstances, the generated cardiac output is <20% of normal.¹⁷ Each positive pressure ventilation immediately decreases the blood flow to the heart and brain.¹⁸ Moreover, respiratory exchange is adequate with less than normal minute ventilation, in part, because gas exchange is limited by the severely reduced pulmonary flow.

This change in the guidelines was based upon a consensus of experts in CPR. However, it has been recently shown in pigs that with the shift from a 15:2 to 30:2 compression:ventilation ratio, there is doubling of the common carotid blood flow and a 25% increase in cardiac output without any compromise in oxygenation and acid-base balance¹⁹ (Figure 1).

During advanced life support (ALS), uninterrupted compressions with a rate of 100/min are recommended. The rescuers who are responsible for the ventilation should deliver 8-10 breaths/min with special care not to hyperventilate. Rescuers should rotate frequently (every 2-3 min) to avoid excessive fatigue, which is known to diminish the quality of CPR (discussed subsequently).

Ventilations

Periodic ventilation during CPR is important to provide oxygen to the blood and tissues. However, a fundamental shift in the new guidelines is to prevent excessive ventilation rates, which have been shown to be life-threatening, if not deadly.²⁰ As in the prior recommendation, obtaining an open airway is of paramount importance, which for endotracheal intubation is recommended as Class I intervention. For the same reason, the use of a Combitube, that is placed in the oropharyngeal cavity and allows for non-selective airway isolation for the purpose of ventilation, and the Laryngeal Mask Airway (LMA), are recommended as a Class IIa intervention in the new guidelines. Neither has been shown to alter outcomes after cardiac arrest, but both provide a means to maintain airway patency. More

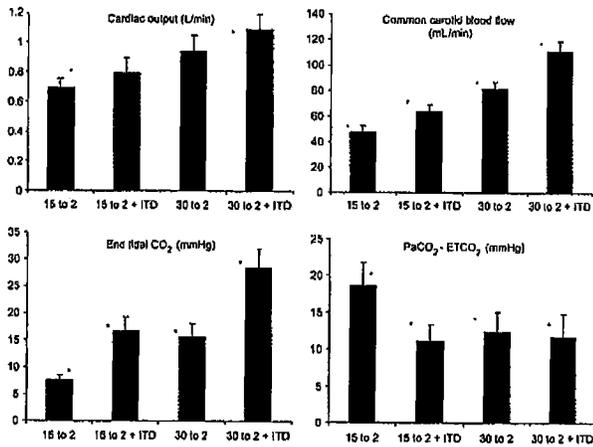


Figure 1 After 6 min of untreated ventricular fibrillation, 6 min of either 15:2 or 30:2 compression to ventilation ratio CPR was performed. At the end, the inspiratory ITD was added for another 4 min. There was a significant increase in cardiac output, common carotid artery flow, end tidal CO₂ in the animals that received 30:2 C/V ratio. There was a further increase with the addition of an ITD, although it was applied late. PaCO₂-EtCO₂ is a marker of pulmonary ventilation/perfusion matching. Asterisk means statistical significant difference compared with the ratio of 15:2 ($P < 0.05$).

importantly, however, the guidelines stress the importance of reducing the frequency of ventilation during CPR, along with the importance of delivering a breath rapidly to minimize the duration of positive airway pressures. Each time intrathoracic pressure is increased with a positive pressure ventilation, venous return to the heart is inhibited and intracranial pressure is increased.²¹ As such, the benefits of positive pressure ventilation must be weighed against the harm associated with too much ventilation (*Figure 2*).

Hyperventilation increases intrathoracic and intracranial pressures and concomitantly decreases coronary perfusion and mean arterial pressures and survival rates in animals.¹⁹ Intracranial pressures are regulated, in part, by intrathoracic pressures: each time ventilation is delivered, there is a rise in the pressure inside the thorax and the brain, which reduces cardiac and cerebral perfusion pressures^{18,21} (*Figure 3*). A simple change in the compression to ventilation ratio from 15:2 to 15:1 resulted in an increase in diastolic aortic pressure and higher cerebral perfusion pressure in pigs.^{18,22}

Based in part upon this rediscovered physiology, the new guidelines recommend a reduced ventilation rate during BLS of two breaths after 30 continuous compressions and of only 8–10 breaths/min for ALS. Moreover, each BLS and ALS breath should be delivered with a tidal volume of only ~500 cc and over a period of only 1 s.^{23–25} These subtle, but fundamental, changes in ventilation technique assure optimal circulation during conventional manual closed chest CPR.

Compressions

Generation of blood flow during compression results from an increase in intrathoracic pressure (thoracic pump theory), the mechanical effect of compressing the heart between

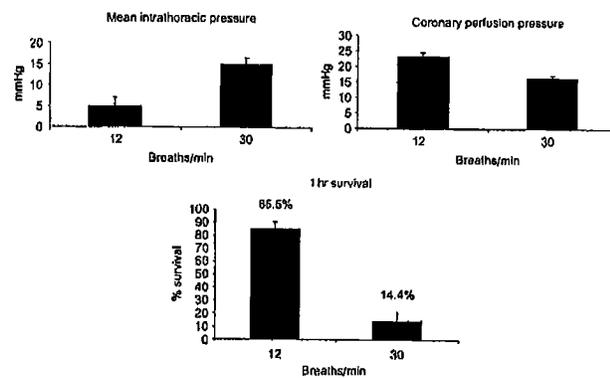


Figure 2 When after 6 min of untreated ventricular fibrillation pigs received CPR with either 12 or 30 breaths/min (as observed frequently in a clinical trial), the mean intrathoracic pressure was inversely related to coronary perfusion pressure and 1 h survival rates ($P < 0.05$).

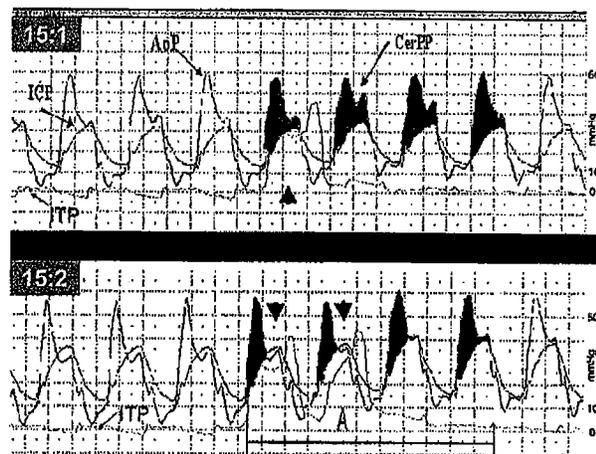


Figure 3 Representative real-time tracings from a single animal during 15:1 and 15:2 compression to ventilation ratios. Aortic pressure and intracranial pressure are shown as well as intrathoracic pressure at the level of the carina. Filled with black is the cerebral perfusion pressure area. Notice the significant decrease in the area when two breaths instead of one are delivered. There is an increase in intracranial pressure with positive pressure ventilation and it more pronounced with the 15:2 ratio. ICP, intracranial pressure; AoP, aortic pressure; CerPP, cerebral perfusion pressure; ITP, intrathoracic pressure. Arrow heads show when the positive pressure ventilation is delivered.

the sternum and the spine (cardiac pump theory), and the cardiac valvular system that allows mainly unidirectional flow. The new guidelines, recognizing the importance of compressions during CPR, recommend pushing 'hard and fast'. A depth of 1.5–2 in. (5 cm) is considered adequate compression depth.^{17,26}

The rate should be 100 compressions/min as lower rates decrease forward blood flow.^{27,28} Interruptions should be minimized, because every time compressions are stopped, it takes a significant amount of time to re-establish adequate aortic and coronary perfusion pressures.²⁹ For example, pulse checks should not last more than 10 s. In observational studies, the average time without

compressions during resuscitation varies from 25 to 50%.^{25,26} This can be extremely detrimental as no compressions means no perfusion. Studies, in animals and humans,³⁰⁻³² have shown that for the initial few minutes of CPR, uninterrupted chest compressions only are an alternative to standard CPR that has the advantage to be performed by any layperson who is not willing to perform mouth to mouth ventilation.

An important change in the new guidelines is that uninterrupted chest compressions should be delivered both before and immediately after the delivery of a shock. Chest compressions for 90 s to 3 min before defibrillation help to prime the pump, making successful return of spontaneous circulation most likely after defibrillation. Chest compressions for 60 s to 2 min immediately after defibrillation are thought to help prevent the hypotension and asystole often observed when a defibrillation shock is delivered. As a result, rather than check for a pulse after a defibrillatory shock in a patient who has been in ventricular fibrillation for >4 min, the guidelines recommend the rescuers immediately resume CPR to maintain circulation, even if the heart is spontaneously beating. It is important to note that this recommendation was based upon a consensus of experts rather than a clinical trial demonstrating increased short- or long-term survival rates with this new approach. Despite the theoretical risk of re-inducing fibrillation with chest compression, there are no human data to support a significant risk in performing a 2-3 min of CPR before checking for rhythm and pulses after defibrillation.

Decompressions

Newly emphasized in the guidelines is the importance of the decompression phase. With each chest wall recoil, the negative intrathoracic pressure naturally generated by the elastic recoil properties of the chest wall acts to promote venous return to the heart, thereby increasing preload for the next compression cycle. Incomplete decompression, such as hyperventilation, is a common mistake that also decreases blood flow to the heart and brain during CPR. Fatigue and ineffective technique, as well as inappropriate hand positioning, can result in incomplete chest wall recoil. From a recent randomized trial, it was shown that many rescuers fail to decompress completely. This results in a sustained end-diastolic increase in intrathoracic pressure. This phenomenon, when examined in a porcine model of cardiac arrest, revealed two fundamental effects. First, incomplete chest wall recoil caused a significant decrease in mean arterial pressure, an increase in right atrial pressure, and thus decreased coronary perfusion pressures. Secondly, incomplete chest wall recoil caused an increase in intracranial pressure leading to a significant decrease in cerebral and systemic perfusion pressures.^{21,33} Strikingly, when incomplete decompression and positive pressure ventilation occurred simultaneously, cerebral perfusion ceased: the cerebral perfusion gradient was essentially zero for at least three to four compression-decompression cycles (*Figure 4*). Thus, the guidelines re-emphasize the importance of full chest wall recoil after each compression to avoid the deleterious effects of incomplete chest wall recoil and the combined and dangerous effects of hyperventilation and incomplete decompression.

Alternative hand positioning has been described in order to eliminate incomplete decompression.³³

Devices

Inspiratory impedance threshold device

The dynamic energy of the expanding chest wall during the decompression phase can be harnessed in order to increase venous return, lower intracranial pressure, and increase circulation to the heart and brain. The inspiratory impedance threshold device (ITD) regulates the entry of air through the airways into the chest during the decompression phase of CPR. It causes a decrease in intrathoracic pressure to -5 to -10 mmHg and thereby helps to generate a greater intrathoracic vacuum to draw blood back to the heart during the recoil phase of CPR.³⁴⁻³⁹ Although this device is attached to an airway, it is used during CPR to enhance circulation. The ITD has been shown repeatedly to improve blood flow to vital organs and survival in animal and human studies.^{19,22,34-38,40} In clinical studies, the ITD doubles the systolic blood pressure during CPR and increases the chances of short-term survival. This is the only CPR device with a Class IIa level of recommendation in the new guidelines, and it is recommended as a way to enhance circulation during CPR and to increase the chances of successful resuscitation and a return of spontaneous circulation. The ITD needs to be applied early and it can be used both with intubated patients connected to the endotracheal tube and with a facemask and a good seal (*Figure 5*).

Oesophageal-tracheal Combitube, laryngeal mask airway, and facemask ventilation

Owing to the practical issues of adequate training for endotracheal intubation, the Combitube has been recognized as a reasonable alternative when endotracheal intubation is not possible or feasible. This device isolates the oesophagus and allows for airway isolation for ventilation and avoidance of gastric inflation. One of the most important issues for prevention of potentially fatal complications is the correct identification of the distal port.^{39,41,42}

Laryngeal mask airway has been shown in many clinical non-cardiac arrest situations to be simple to use and to provide a safe alternative to intubation. The new guidelines recommend its use in a manner similar to the Combitube, when endotracheal intubation is not possible or feasible. The only disadvantage is that a small percentage of patients cannot be adequately ventilated and an alternative airway management technique should be available. Both these airway adjuncts have been recommended as a Class IIa interventions by the new AHA 2005 guidelines.⁴³⁻⁴⁵

As in earlier guidelines, two-person technique is recommended when using a facemask for ventilation. One person should maintain the correct head position, the complete seal, and a jaw thrust to maintain airway patency and the second person should squeeze the resuscitator bag. This approach can be used for more prolonged period of time when sufficient personnel is available as it enables rescuers to perform high quality CPR without stopping compressions and interrupting circulation to place an advanced airway device. One of the hallmarks of the new guidelines is to maintain continuous chest compressions without interruptions. Delaying intubation by providing a

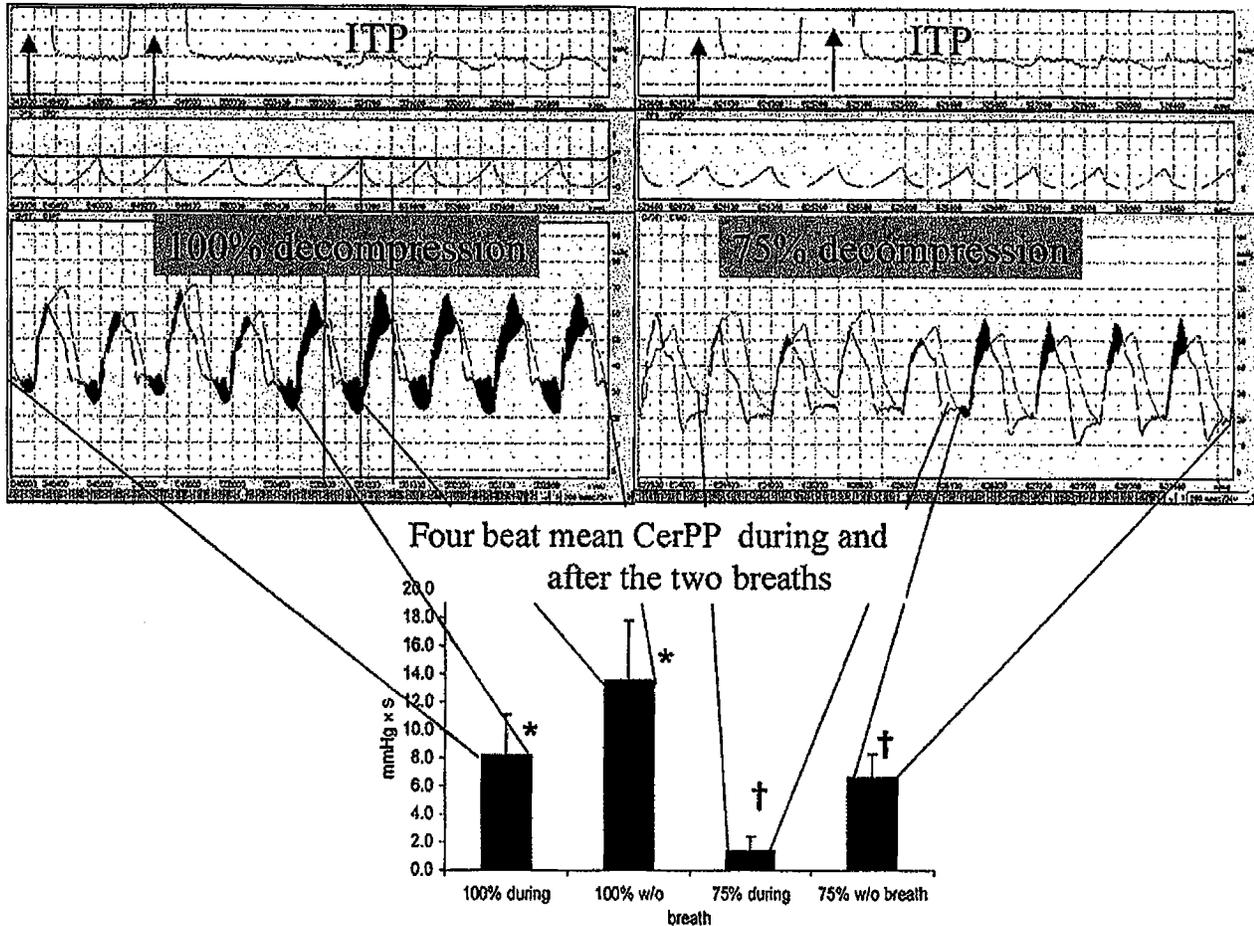


Figure 4 The effect of positive pressure ventilation and incomplete decompression on CerPP is shown. The first tracing shows real-time aortic and ICP waveforms from a pig with full chest wall recoil after a ventilation cycle, whereas the second tracing shows the aortic and ICP waveforms with incomplete chest wall recoil after a ventilation cycle. Positive pressure gradient (Ao-ICP) is shown in black. Note the marked difference in total area during each compression-decompression cycle with and without a positive pressure breath. The bar graph shows the mean four beat area of all animals during and after a ventilation cycle. The mean \pm SEM values during 100 and 75% decompression are illustrated. Arrows show when the positive pressure ventilations are delivered. ITP, intrathoracic pressure.

good facemask ventilation technique is an important way to maximize chest compression time.

Impedance threshold device (ITD)

- **Concept.** Lower intrathoracic pressure in the chest during the decompression phase of CPR enhances venous return to the thorax.
- **Design.** Each time the chest wall recoils following a compression, the ITD transiently blocks air/oxygen from entering the lungs, creating a small vacuum in the chest, resulting in improved pre-load.



Figure 5 Concept and design of the inspiratory ITD. ITD can be placed on an endotracheal tube or on a specially designed facemask for bag-mask ventilation provided that a good air seal is applied. Timing lights flash at a rate of 10/min to guide ventilations and compressions (10 compressions between 2 flashes).

Compression devices

Several chest compression devices were again evaluated in the new guidelines. The Autopulse, an automated band-compression device, has shown significant improvement in vital organ perfusion and systemic pressures in animals and humans.⁴⁵⁻⁴⁷

This device was given a Class IIb level of recommendation, suggesting that it is probably of benefit. However, a recent randomized trial (ASPIRE) showed that the use of the Autopulse increased mortality rates.⁴⁸ As such, this trial was prematurely stopped. There are concerns about the device, including weight and delays associated with placement. At the time of writing, it is not clear whether the increased death rate associated with the use of the Autopulse is caused by the way the device performs CPR or whether it is due to a device implementation issue, or both.

Active compression-decompression (ACD) CPR devices were recommended with a Class IIb for in-hospital use and

Class indeterminate (more data needed) for pre-hospital use. Two in-hospital studies with this device have shown an increase in short-term survival rates.^{49,50} Multiple out-of-hospital survival studies have been performed with ACD CPR.⁵¹⁻⁵⁶ Some have shown significant improvements in up to 1-year survival, whereas others have shown no significant benefit with the device.

Another ACD device is the Lund University Compression Assist Device or LUCAS device. There are no randomized controlled trials with this device. Thus, it too was given a Class indeterminate level of recommendation.

Therapeutic hypothermia

During the metabolic phase of cardiac arrest, decreasing core body temperature has been shown to have protective effect on the myocardium from reperfusion injury (deep hypothermia 25°C)^{57,58} Hypothermia also protects the brain, possibly by lowering intracranial pressures^{59,60} and by protecting the brain from ischaemic injury.⁶¹⁻⁶⁴ In two large randomized human trials, mild-to-moderate hypothermia (32-34°C), post-resuscitation, resulted in an improvement (16-23% absolute risk reduction) for poor neurological outcomes in patients who had a witnessed ventricular fibrillation arrest. There was a significant improvement in 6-month survival rates in the hypothermic groups.^{65,66} In resuscitated victims of cardiac arrest, especially after prolonged resuscitation efforts, hypothermia should be considered and implemented when possible. The new guidelines have given hypothermia a Class IIa level of recommendation for comatose patients with ventricular fibrillation arrest.

For all other presenting rhythms of cardiac arrest, hypothermia was given a IIb recommendation. Recent studies have shown that it is possible to cool during CPR before reperfusion is achieved to minimize tissue damage before it occurs. Cooling during CPR in animals with venovenous access systems or with cold IV saline and use of ACD CPR plus the ITD may eventually offer a means of rapidly decreasing cerebral temperatures during CPR and improving neurological outcomes.^{67,68} On the basis of the data in support of therapeutic hypothermia, the guidelines recommend cooling of comatose patients after successful resuscitation when possible, as long as there is a protocol in place to assure careful monitoring of core temperatures and haemodynamics, prevention of shivering, and maintenance of adequate perfusion pressures during the recommended 24 h period of cooling. Further study is needed to evaluate the therapeutic potential of very early cooling and to investigate the best way of achieving cerebral hypothermia in a timely and practical manner.

Pharmacological management

There were very few major changes in the pharmacological management of patients in cardiac arrest.

Vasoactive medications

Evidence for the broad use of vasoactive medication during CPR comes primarily from animal studies. There are no placebo-controlled trials that have demonstrated long-term benefit of either adrenaline or vasopressin. As such, the new

guidelines recommend the use of either of these agents as Class IIb.

Adrenaline is the most commonly used vasopressor during CPR. The beneficial haemodynamic effects of adrenaline during CPR are due to its potent alpha-adrenergic effects. The significant increase in central aortic pressures results in significant increase in coronary and cerebral perfusion pressures and possibly rates of successful resuscitation.^{69,70}

However, on the basis of the multiple clinical trials, the use of high dose adrenaline is contraindicated and harmful in patients in cardiac arrest (Class III). The guidelines continue to recommend 1 mg of adrenaline every 3-5 min (Class IIb) for adults in cardiac arrest. If no venous access has been obtained, endotracheal or intra-osseous administration can be also effective.

Vasopressin is recommended as an alternative vasopressor during CPR. It too has potent vasoconstricting properties. No study has shown that vasopressin use will result in an increase in hospital discharge rates when used in patients in cardiac arrest. A recent study showed that the combination of adrenaline plus vasopressin resulted in higher rates of resuscitation, no increase in long-term survival rates, but a strong trend towards worsening of neurological outcomes, except in those with an initial rhythm of asystole arrest.^{71,72} On the basis of these findings, 40 U of vasopressin can be used instead of the first or second dose of adrenaline during CPR (guidelines recommendation: Class indeterminate). The authors of this article recommend that one to two doses of adrenaline are used prior to vasopressin given the lack of definitive data and levels of recommendation in the new guidelines.

There is no good treatment for asystole. Atropine, a vagolytic medication, has no known untoward effects in patients with asystole and can be given for severe bradycardia and asystole with doses of 1 mg IV every minute to a total dose of 3 mg. (Class indeterminate). There is no randomized animal or human study to support the administration of atropine for the improvement of outcomes.

Anti-arrhythmic agents

As with the other intravenous medications, there were insufficient data or consensus among the experts regarding the use of anti-arrhythmic agents during CPR. Amiodarone is now considered the drug of choice and as an intravenous bolus of 150-300 mg for ventricular fibrillation or pulseless ventricular tachycardias that are unresponsive to the initial sequences of CPR-shock-CPR-vasoconstrictors. The recommendation is based on limited clinical trials^{73,74} showing improvement in hospital admission, but no definitive increase in hospital discharge rates when compared with placebo or lignocaine. Given the lack of definitive data, lignocaine (initial dose of 1-1.5 mg/kg IV) can also be used in patients in cardiac arrest (Class indeterminate).

Summary

In the new 2005 AHA CPR guidelines, significant emphasis has been placed on early defibrillation, quality and continuity of compressions, less frequent ventilations, and adequate decompression. In order to simplify CPR

performance, a unifying 30:2 compression to ventilation ratio has been introduced for all single rescuers. Adjuncts to improve circulation during CPR, such as the inspiratory ITD, have also been recommended, although the evidence for their effectiveness has still to be determined. Comatose patients with ventricular fibrillation arrest could be treated with mild therapeutic hypothermia as long as the infrastructure needed to support the patients is promptly available.

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

Keith G Lurie MD, Demetris Yannopoulos MD, Scott H McKnite, Margot L Herman, Ahamed H Idris MD, Vinay M Nadkarni MD, Wanchun Tang MD, Andrea Gabrielli MD, Thomas A Barnes EdD RRT, and Anja K Metzger PhD

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 \pm 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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Keith Lurie MD, Scott H McKnite, Margot Herman, and Anja K Metzger work for Advanced Circulatory Systems, which makes the ResQPod impedance threshold device used in this study. The authors report no other conflicts of interest in the content of this paper.

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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):1-*. © 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}

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 perfu-

sion 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 μ g/kg/min, Propoflo, Abbott Laboratories, North Chicago, Illinois). While spontaneously breathing but sedated, each pig was intubated with a size 7.0 endotracheal tube, then additional propofol (1 mg/kg) was administered, followed by a propofol infusion of 160 μ g/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

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Systems, Ithaca, New York) was placed to quantify common carotid blood flow. The animal's temperature was carefully maintained at $37 \pm 0.5^\circ\text{C}$, 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 (CO₂SMO Plus, Novamatrix 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 oxygen tissue 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 $\mu\text{g}/\text{kg}/\text{min}$. 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, O₂ 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 was 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 $P_{\text{ETCO}_2} \leq 40$ mm Hg.

Statistical Analysis

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

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Table 1. Baseline Hemodynamic Values*

Hemodynamic Variable	CPR Respiration Rate	
	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)	113.0 ± 47.9	123.7 ± 36.2

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

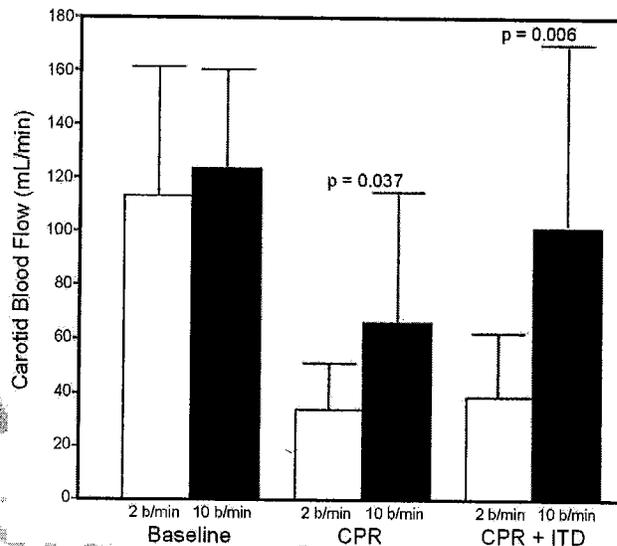


Fig. 1. Mean ± SD carotid brain flow during cardiopulmonary resuscitation (CPR) with ventilation rates of 2 breaths/min (b/min) and 10 b/min. The p values represent the comparison of the 2-b/min group to the 10-b/min group. Carotid brain flow was also significantly higher with the addition of the impedance threshold device (ITD) in both the 2-b/min group (p = 0.036 for 2 b/min CPR-plus-ITD subgroup compared to the 2 b/min CPR-without-ITD subgroup) and the 10-b/min group (p = 0.030 for the 10 b/min CPR-plus-ITD subgroup compared to the 10 b/min CPR-without-ITD subgroup).

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 < 0.02 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. When ventilated 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 ± 6.02 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.

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

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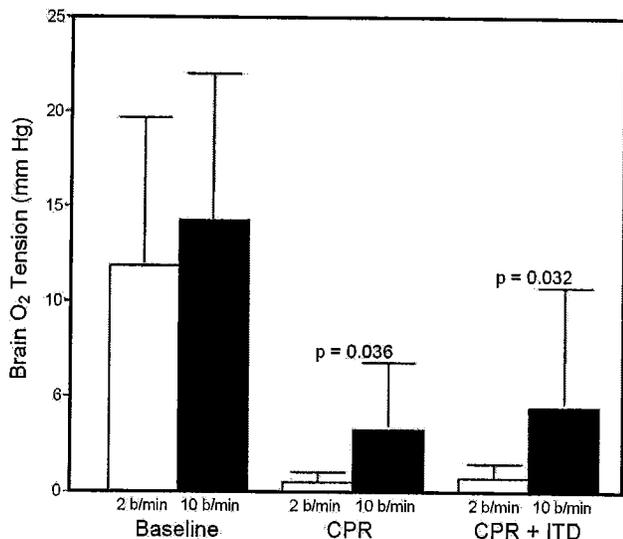


Fig. 2. Mean \pm SD brain oxygen tension during cardiopulmonary resuscitation (CPR) with ventilation rates of 2 breaths/min (b/min) and 10 b/min. The p values represent the comparison of the 2-b/min group to the 10-b/min group. There was no statistically significant change in brain oxygen content with the addition of the impedance threshold device (ITD) in either group.

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 di-

astolic 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. The current 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, the present 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 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

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Table 2. Hemodynamic Values During CPR

Hemodynamic Variable	Pressure (mean ± SD mm Hg)*			
	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,c}	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,ii}	16.0 ± 9.5 ^{hh,ii}	18.3 ± 11.5 ^{hh,ii}

* 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_{ETCO₂}*

Variable	Pressure (mean ± SD mm Hg)*			
	At 2 breaths/min	At 2 breaths/min + ITD	At 10 breaths/min	At 10 breaths/min + ITD
Arterial				
pH	7.33 ± 0.14 ^{ac}	7.17 ± 0.10 ^{a,d}	7.41 ± 0.15 ^{b,c}	7.26 ± 0.11 ^{b,d}
P _{aCO₂} (mm Hg)	42 ± 14 ^{e,g}	56 ± 13 ^{e,h}	35 ± 15 ^{f,g}	49 ± 18 ^{f,h}
P _{aO₂} (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 _{ETCO₂} (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 _{CO₂} (mm Hg)	73 ± 25 ^{gg,ii}	86 ± 12 ^{gg,ii}	79 ± 22 ^{hh,ii}	79 ± 13 ^{hh,ii}
P _{O₂} (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_{ETCO₂} = end-tidal carbon dioxide pressure

2 breaths/min the lungs functioned as though transpulmonary 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

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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 only occurs 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 gasping. This is similar to other reports from our laboratory.^{2,7,8,16,17} By contrast, the inhaled agent isoflurane 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 auto-respiration. 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 trans-

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fer 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 in the current study 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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