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HeartRescue
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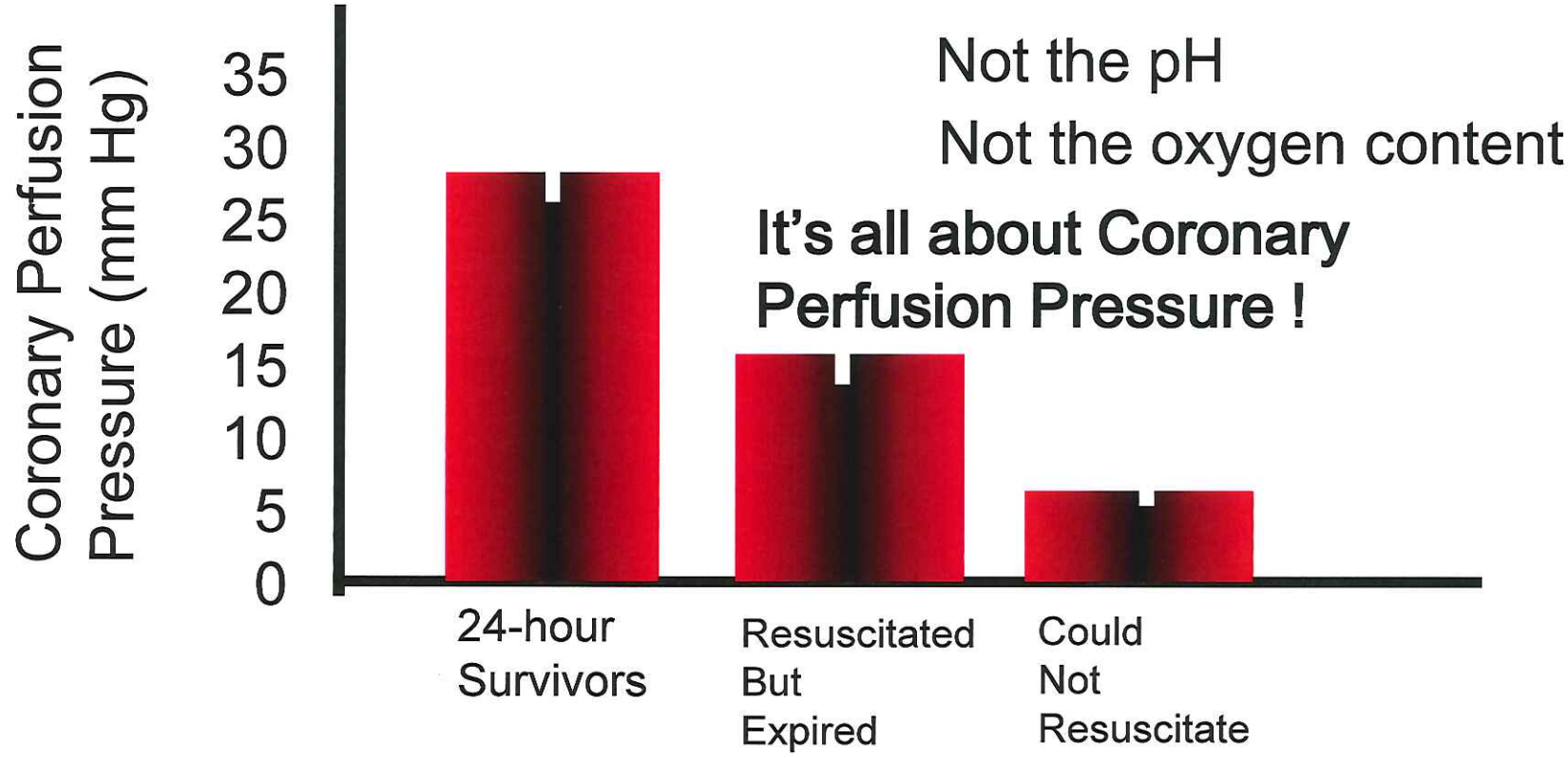
Bringing Science to the Pit Crew:
High-Functioning EMS CPR Teams

"The Science"

Survival is related to arterial pressures generated by chest compressions



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Paradis *et al. JAMA* 1990; 263:1106

Adverse Hemodynamic Effects of Interrupting Chest Compressions for Rescue Breathing During Cardiopulmonary Resuscitation for Ventricular Fibrillation Cardiac Arrest

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Background—Despite improving arterial oxygen saturation and pH, bystander cardiopulmonary resuscitation (CPR) with chest compressions plus rescue breathing (CC+RB) has not improved survival from ventricular fibrillation (VF) compared with chest compressions alone (CC) in numerous animal models and 2 clinical investigations.

Methods and Results—After 3 minutes of untreated VF, 14 swine (32±1 kg) were randomly assigned to receive CC+RB or CC for 12 minutes, followed by advanced cardiac life support. All 14 animals survived 24 hours, 13 with good neurological outcome. For the CC+RB group, the aortic relaxation pressures routinely decreased during the 2 rescue breaths. Therefore, the mean coronary perfusion pressure of the first 2 compressions in each compression cycle was lower than those of the final 2 compressions (14±1 versus 21±2 mm Hg, $P<0.001$). During each minute of CPR, the number of chest compressions was also lower in the CC+RB group (62±1 versus 92±1 compressions, $P<0.001$). Consequently, the integrated coronary perfusion pressure was lower with CC+RB during each minute of CPR ($P<0.05$ for the first 8 minutes). Moreover, at 2 to 5 minutes of CPR, the median left ventricular blood flow by fluorescent microsphere technique was 60 mL · 100 g^{-1} · min^{-1} with CC+RB versus 96 mL · 100 g^{-1} · min^{-1} with CC, $P<0.05$. Because the arterial oxygen saturation was higher with CC+RB, the left ventricular myocardial oxygen delivery did not differ.

Conclusions—Interrupting chest compressions for rescue breathing can adversely affect hemodynamics during CPR for VF. **(*Circulation*. 2001;104:2465-2470.)**

Key Words: cardiopulmonary resuscitation ■ heart arrest ■ hemodynamics ■ fibrillation ■ ventilation

Defibrillation is the treatment of choice for ventricular fibrillation (VF).[1] Until a defibrillator is available, maintenance of myocardial viability with cardiopulmonary resuscitation (CPR) can be lifesaving. Although this approach has resulted in survival rates of 25% to 30% in Seattle, dismal survival rates of <5% are generally reported elsewhere.[1–3] One contributing factor to the very low survival rates in 3 relatively recent studies may be the disappointingly low rates of bystander-initiated CPR: 16%, 28%, and 22%.[1–3] Although the reasons for such low bystander CPR rates are not fully known, mouth-to-mouth rescue breathing is apparently a barrier to the performance of bystander CPR.[1–4]

Numerous animal investigations and 2 clinical studies suggest that bystander CPR with chest compressions alone (CC) is as effective as chest compressions plus rescue breathing (CC+RB) for VF cardiac arrest.[5–14] This technique is attractive because it is simpler than standard CPR and easier to teach, learn, remember, and perform.[2–4,14]

Hypoxia and hypercarbia, however, are important mediators of poor outcome from VF.[10,15] Experimental investigations comparing CC with CC+RB have established that CC can maintain adequate arterial oxygen saturation for 4 to 10 minutes.[5–10,16] Nevertheless, CC results in lower arterial oxygen saturation and more severe hypercarbic acidosis than CC+RB. Therefore, CC has been presumed to be less effective at delivering oxygen to the myocardium than CC+RB.

In a recent animal investigation, qualitative retrospective review of the aortic and right atrial pressure waveforms during simulated single-rescuer CPR demonstrated substantial decreases in the aortic diastolic pressures and coronary perfusion pressures (CPPs) during the 4-second interval for the 2 rescue breaths.[11] The aortic pressure and CPP promptly increased during the first 3 to 7 chest compressions of the next series of 15 consecutive compressions. Perhaps adverse

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effects of rescue breathing on CPR hemodynamics counterbalance the improved arterial oxygenation.

This investigation was undertaken to evaluate and quantify the effects of simulated rescue breathing on myocardial hemodynamics and oxygen delivery during simulated bystander CPR for VF cardiac arrest. We hypothesized that CC+RB would improve arterial oxygen saturation and worsen myocardial perfusion compared with CC alone. We further hypothesized that myocardial oxygen delivery would not differ in the 2 groups, resulting in similar successful resuscitation rates.

Methods

Animal Preparation

Experimental protocols were approved by The University of Arizona Institutional Animal Care and Use Committee and followed the guidelines of the American Physiological Society. Healthy domestic pigs (32±1 kg) were subjected to masked anesthesia with isoflurane, followed by oral endotracheal intubation. They were mechanically ventilated with a volume-limited, time-cycled Harvard ventilator (model 661, Harvard Apparatus, Inc) on a mixture of room air and titrated isoflurane (generally 0.5% to 1.5% inspired concentration). The tidal volume was initially set at 15 mL/kg and the ventilator rate at 12 breaths per minute; ventilator settings were adjusted to maintain end-tidal carbon dioxide at 35 to 40 mm Hg.

After a surgical plane of anesthesia had been achieved, introducer sheaths were placed in the right internal and external jugular veins, right carotid artery, and right femoral artery by cutdown technique. High fidelity, solid-state, micromanometer-tipped catheters (MPC-500, Millar Instruments) were advanced through the carotid artery into the left ventricle and through the femoral artery and external jugular vein into thoracic locations. Catheter placements were performed under fluoroscopic guidance.

Measurements

Right atrial pressure and aortic pressure, as well as ECG and end-tidal P_{CO_2} measurements (model 47210A, Hewlett Packard), were continuously displayed and recorded on a laptop computer (Fujitsu Lifebook 530T) with specialized data acquisition software (Windaq, Dataq Instruments Inc) throughout the experiment until the 1-hour simulated intensive care unit period ended. CPP during CPR was calculated by subtracting mid-diastolic right atrial pressure from mid-diastolic aortic pressure. The integrated CPP (iCPP), or positive area under the curve, was also measured during each minute of CPR. Arterial blood gas specimens were obtained from the thoracic aorta at baseline (before cardiac arrest) and 5 and 15 minutes after cardiac arrest (2 and 12 minutes after chest compressions were started). Oxygen saturation, P_{CO_2}, P_{O_2}, pH, and hemoglobin were measured with a blood gas analyzer (IL-1306 with model 482 co-oximeter, Instrumentation Laboratories). Minute ventilation during minute 7 of CPR was determined with a heated pneumotachometer (Fleisch size 0, Instrumentation Associates) attached to a well-sealed nose cone mask.

Left ventricular myocardial blood flow and cardiac output were determined with a fluorescent, nonradioactive, color-microsphere technique at baseline (before cardiac arrest), between minutes 2 and 5 of CPR (5 to 8 minutes after VF), and between minutes 9 and 12 of CPR (12 to 15 minutes after VF).[9,10,17] Fluorescent, colored polystyrene–divinyl benzene microspheres, 12±2 μm (E-Z Trac), were injected as a bolus (≈10×10^6 spheres) into the left ventricle. Reference aortic blood samples were obtained over 2 minutes 35 seconds at a rate of 10 mL/min by automatic screw pump (Harvard Apparatus, Inc). The left ventricle was sectioned and microspheres were counted as previously reported.[9,10,17]

Experimental Protocol

After baseline data were collected, a pacing electrode was positioned in the right ventricle. Isoflurane was discontinued and the aortic pressure allowed to return to baseline (systolic pressure >80 mm Hg). VF was then induced with a 60-cycle alternating current to the endocardium and confirmed by the ECG waveform and precipitous decline in aortic pressure. Ventilation was discontinued. A 3-minute interval of untreated VF, mimicking a bystander recognizing cardiac arrest and calling for help, was followed by 12 minutes of basic life support. Animals were randomly assigned to (1) the CC group, provided with a metronome-guided rate of 100 compressions per minute, punctuated each minute with a brief rest period for the rescuer to take 2 deep breaths, or (2) the CC+RB group, provided with 2 manual rescue breaths followed by 15 manual chest compressions at the metronome-guided rate of 100 compressions per minute, repeated sequentially. The rescue breaths were provided with a gas mixture of 17% oxygen and 4% carbon dioxide, simulating expired air from a rescuer.[2] Endotracheal tubes remained in place during CPR to protect the airway and avoid gastric distention with rescue breaths. The same research technician performed chest compressions in all animals. He compressed the pig's chest approximately one third of the anteroposterior diameter. All animals in both groups gasped during CPR.

At the end of this simulated bystander CPR period, 15 minutes after VF was induced, all animals received advanced cardiac life support according to American Heart Association algorithms for VF, as if the paramedic unit had arrived at the scene.[1] Electrical shock therapy was provided, starting with 120 J (≈4 J/kg) on the first 2 shocks and 200 J (≈6 J/kg), if necessary, on the third and all subsequent shocks. CPR by this simulated paramedic team included ventilation with 100% oxygen on a volume-cycled ventilator at a rate of 15 breaths per minute and chest compressions manually at a rate of 100 per minute. Restoration of spontaneous circulation was defined as unassisted pulse with a systolic arterial pressure >50 mm Hg and a pulse pressure >20 mm Hg lasting >1 minute. If the animal did not attain return of spontaneous circulation with the first set of shocks, epinephrine (0.02 mg/kg) was immediately administered intravenously. After each epinephrine administration, CPR was continued for 1 minute to allow for circulation of the epinephrine before further attempts to defibrillate.

All successfully resuscitated animals were supported aggressively for 1 hour in a simulated intensive care setting. All pigs received 40 mL/kg IV of normal saline during the intensive care period, because they had received no fluids the previous night and suffered "third space" losses from their significant cardiovascular and surgical insults. Mechanical ventilation was provided with 100% oxygen and adjusted to obtain an end-tidal carbon dioxide of 30 to 40 mm Hg. At the end of 1 hour, all animals were weaned off pharmacological and ventilatory support. Throughout the intensive care period, isoflurane was administered, as necessary, to maintain adequate analgesia and anesthesia. Animals that survived the intensive care period were transferred to observation cages for the next 24 hours.

Outcome and Neurological Evaluation

Survival and neurological status were evaluated at 24 hours after the initial cardiac arrest. To provide objective neurological evaluation, swine cerebral performance categories were assessed.[5,6,9–11] Briefly, swine cerebral performance category is a global assessment of neurological function. Category 1 was assigned to pigs that appeared normal on the basis of level of consciousness, gait, feeding behavior, response to an approaching human, and response to human restraint. Category 2, mildly abnormal, was assigned when the pigs had subtle dysfunction with regard to these characteristics. Category 3, severely disabled, referred to more severe dysfunction, such as inability to stand, walk, or eat. Category 4, vegetative state or deep coma, referred to pigs with minimal response to noxious stimuli. Category 5 referred to animals with no response to their environment. Categories 1 and 2 were considered good neurological outcome.

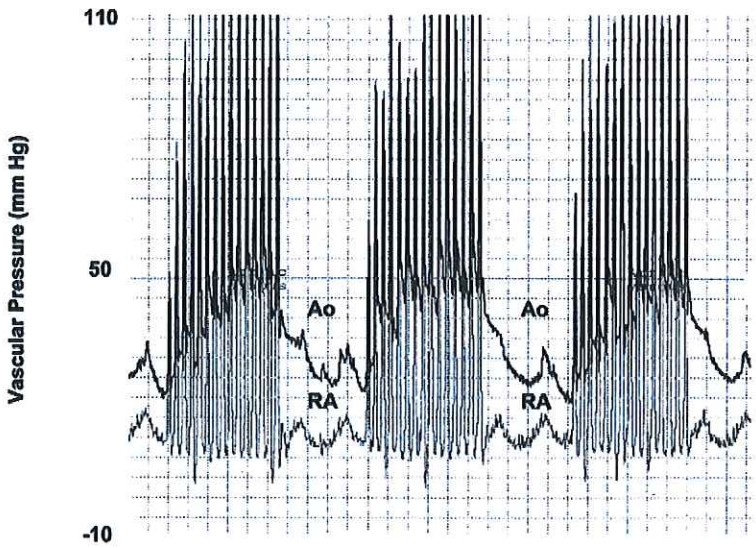

Figure 1. Aortic (Ao, dark band) and right atrial (RA, light band) pressures during standard CPR, CC+RB, with a 15:2 compression:ventilation ratio. Aortic relaxation, or diastolic, pressure (lower border of dark band) decreases during each set of 2 breaths, resulting in lower CPP during first several compressions of next cycle. Right atrial relaxation, or diastolic, pressure is most inferior border. Difference between Ao and RA relaxation pressures is CPP.

Data Analysis

Continuous variables such as blood pressures, CPP, iCPP, and blood gas analyses were evaluated by 2-tailed, unpaired Student's *t* test and described as mean±SEM. Continuous variables that were not normally distributed (myocardial blood flows, cardiac outputs, and oxygen deliveries) were evaluated by Mann-Whitney *U* test and described as median (25%, 75%). In the CC+RB group, we compared the mean CPP during the first 2 compressions of each 15-compression cycle with the last 2 compressions by paired Student's *t* test. Comparisons of discrete variables, such as rate of return of spontaneous circulation, 1-hour ICU survival, swine cerebral performance categories, 24-hour survival, and 24-hour good neurological outcome were evaluated by Fisher's exact test.

Results

For the CC+RB group, the aortic relaxation ("diastolic") pressures routinely decreased during the interval of 2 rescue breaths when no compressions were provided, thereby also decreasing the CPPs (Figure 1). Therefore, the mean CPP of the first 2 compressions in each compression cycle was lower than that of the final 2 compressions (14±1 versus 21±2 mm Hg, respectively, $P<0.001$). This difference was demonstrable independently at each minute of the 12 minutes of CPR (Figure 2).

Thirteen of the 14 animals survived 24 hours with good neurological outcome. Six of the 7 CC animals and 5 of the 7 CC+RB animals were in cerebral performance category 1 at 24 hours (ie, normal); 1 in each group was in cerebral performance category 2, mildly abnormal; and 1 CC+RB animal was in cerebral performance category 3, severely disabled. All 13 animals with good neurological outcome could stand, walk, feed themselves, and actively resist restraint. Animals in cerebral performance category 1 performed these tasks normally; animals in cerebral performance category 2 had slightly wobbly gaits, lethargy, or sluggish response to restraint. The only animal in category 3 could not walk and responded quite sluggishly to restraint but would drink.

At baseline, the CC and CC+RB groups did not differ in weight, hemoglobin concentration, heart rate, blood pressure, or central venous pressure. Aortic and right atrial compression pressures during each minute of CPR did not differ between the 2 groups (Table 1). At each minute of CPR, the

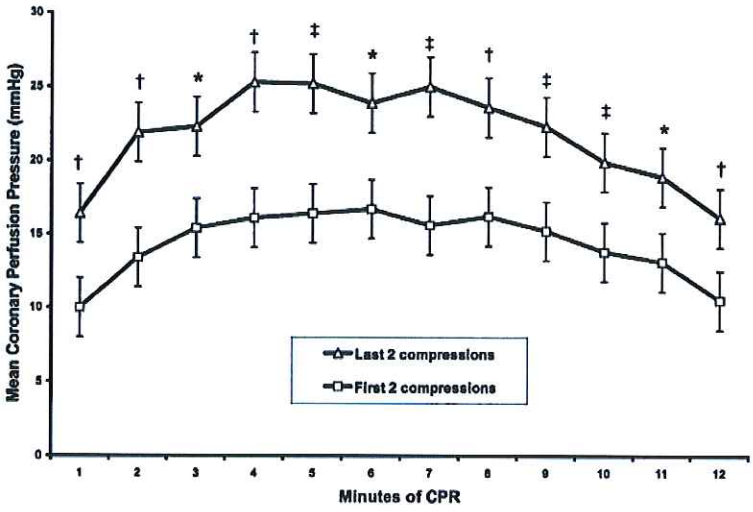

Figure 2. Mean CPP of first 2 compressions (bottom line) and last 2 compressions (top line) of each 15-compression cycle during CPR with CC+RB at a compression:ventilation ratio of 15:2. Mean CPP difference: *$P<0.05$; †$P<0.01$; ‡$P<0.001$.

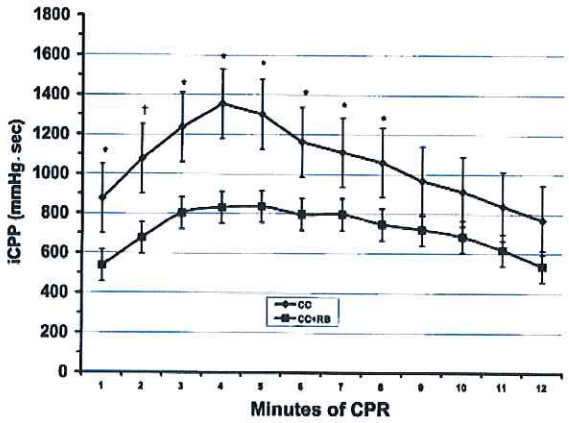

Figure 3. iCPP over each minute in CC and CC+RB groups. iCPP difference: *$P<0.05$; †$P<0.01$.

CPP at the end of the 15-compression cycle with CC+RB did not differ from the CPP with CC (Table 1). None of the animals received inotropic or vasopressor support after return of spontaneous circulation.

During each minute of CPR, the number of chest compressions delivered was lower in the CC+RB group (62±1 versus 92±1 mm Hg, $P<0.001$). Because of metronome guidance, these compression rates were remarkably consistent during each minute of CPR. The iCPP was lower with CC+RB during each minute of CPR, $P<0.05$ for each of the first 8 minutes of CPR (Figure 3).

There were no differences in cardiac output, left ventricular myocardial blood flow, or left ventricular myocardial oxygen delivery between the 2 groups at baseline (Table 1). Median left ventricular blood flow early in CPR, during the interval between minutes 2 and 5 of CPR, however, was 96 (62, 130) mL · 100 g^{-1} · min^{-1} with CC versus 60 (20, 100) mL · 100 g^{-1} · min^{-1} with CC+RB, $P<0.05$. After more prolonged CPR, during the interval between minutes 9 and 12 of CPR, left ventricular myocardial blood flow was 79 (27, 131) mL · 100 g^{-1} · min^{-1} with CC versus 52 (27, 77) mL · 100 g^{-1} · min^{-1} with CC+RB, $P=0.11$. The concomitant left ventricular myocardial oxygen deliveries and cardiac outputs at these times did not differ (Table 1, Figure 4).

There were no differences in arterial blood gases between the 2 groups at baseline. The arterial oxygen saturation and pH were higher and P_{CO_2} lower in the CC+RB group 5 and 15 minutes after VF (ie, after 2 and 12 minutes of CPR), respectively (Table 2). Minute ventilation in the CC group after 7 minutes of CPR was 2650±670 mL/min, and gasping accounted for 41±9% of the minute ventilation.

Discussion

This investigation establishes that interrupting chest compressions for rescue breathing can adversely affect myocardial hemodynamics during CPR for VF. Compared with CC, CC+RB resulted in worse myocardial perfusion, yet better oxygen content of the blood that perfused the myocardium. The net result was no substantial difference in myocardial oxygen delivery. Not surprisingly, once again this study confirmed that successful resuscitation and neurological outcome are comparable after CC or CC+RB for VF cardiac arrest.[5–14] More importantly, this investigation highlights the hemodynamic importance of continuous chest compressions during CPR.

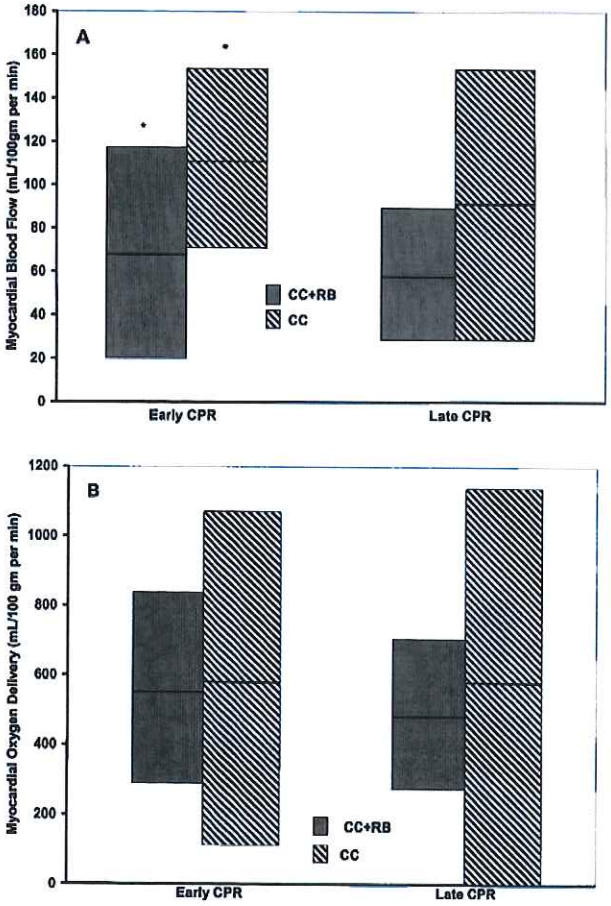

Figure 4. A, Median left ventricular myocardial blood flow in CC vs CC+RB groups with 25% and 75%. Early CPR refers to interval from 2 to 5 minutes of CPR (5 to 8 minutes after VF); late CPR refers to interval from 9 to 12 minutes of CPR (12 to 15 minutes after VF). Blood flow difference: *$P<0.05$. B, Median left ventricular myocardial oxygen delivery in 2 groups, as in A.

The relative time for rescue breathing and compression during single-rescuer CPR is a "zero-sum" game.[2] Indeed, the number of compressions was nearly 50% greater with CC than with CC+RB in this experiment. Moreover, we previously published qualitative data of aortic and right atrial pressure tracings during CC+RB, suggesting substantial decreases in the aortic diastolic pressures and CPPs during the 2 rescue breaths (ie, during the 4-second interval between compressions).[11] The aortic pressure and CPP promptly increased during the first 3 to 7 chest compressions of the next series of 15 consecutive compressions. The present investigation confirms this finding with quantitative data indicating that the mean CPP decreased by 7 mm Hg during the 2 rescue breaths. Most importantly, the median left ventricular myocardial blood flow was markedly lower during early CPR with CC+RB than with CC.

The mechanism responsible for the decreases in aortic diastolic pressure during the 2 rescue breaths was not delin-

TABLE 1. Hemodynamics at Baseline and During CPR

	AoS, mm Hg	AoD, mm Hg	RAS, mm Hg	RAD, mm Hg	CPP	CO, L/min	MBF, mL · 100 g^{-1} · min^{-1}	MDO_2, mL · 100 g^{-1} · min^{-1}
Baseline								
CC+RB	92±4	67±5		7±1		3.3 (1.9, 4.7)	76 (3, 149)	720 (130, 1310)
CC	91±2	63±3		8±1		3.8 (2.0, 5.6)	70 (35, 105)	740 (490, 990)
Early CPR								
CC+RB	88±8	38±4	116±11	13±1	26±3	0.60 (0.3, 0.9)	60 (20, 100)*	560 (290, 830)
CC	92±9	41±6	108±22	13±1	29±6	0.90 (0.4, 1.4)	96 (62, 130)*	590 (110, 1070)
Late CPR								
CC+RB	83±6	35±4	107±6	14±2	21±4	0.50 (0.2, 0.8)	52 (27, 77)	490 (280, 700)
CC	86±5	31±5	110±10	12±1	18±4	0.70 (0.3, 1.1)	79 (27, 131)	590 (0, 1140)

AoS indicates aortic systolic pressure; AoD, aortic diastolic pressure; RAS, right atrial systolic pressure; RAD, right atrial diastolic pressure; CO, cardiac output; MBF, left ventricular myocardial blood flow; MDO_2, left ventricular myocardial oxygen delivery; Baseline, before VF; Early CPR, pressures at 4 minutes of CPR and flows (CO, MBF, MDO_2) during 2–5 minutes of CPR; and Late CPR, pressures at 11 minutes of CPR and flows during 9–12 minutes of CPR. All pressures are mean±SEM; all flows are median (25%, 75%).

*$P<0.05$ between groups.

eated. Presumably, the longer pause between compressions resulted in greater "runoff" of blood from the aorta, thereby decreasing the aortic volume and pressure.

Because of lower compression rates and lower CPP during the initial part of the compression cycle with CC+RB, the "true" mean CPP during each of the first 8 minutes of CPR was higher in the CC group, as confirmed by the iCPP data. Notably, these iCPP differences were demonstrable even though the CPP at the end of the 15-compression cycle with CC+RB did not differ from the corresponding CPP with CC (Table 1). In previous animal investigations, we consistently evaluated the CPP in 3 consecutive representative compression-relaxation cycles during each minute of CPR. The rapidly changing CPP during the first several compressions in the CC+RB group was not regarded as representative. Therefore, the calculated mean CPP in the CC and CC+RB groups did not differ in any of those studies.

Consistent with previous investigations, this study confirms that CC+RB with CPPs of 20 to 30 mm Hg can result in left ventricular myocardial blood flow >50% of prearrest baseline despite cardiac outputs 15% to 25% of prearrest baseline.[9,18,19] Peripheral vasoconstriction and coronary vasodilation preferentially direct blood flow through the coronary arteries. Impressively, this study establishes that left ventricular myocardial blood flow during CC can be nearly the same as prearrest baseline in the setting of excellent compressions, nearly maximally dilated coronary arteries, and no coronary artery disease (Table 1).

TABLE 2. Arterial Blood Gases During CPR

Arterial Blood Gas	CC+RB	CC	*P*
Baseline, before VF			
So_2, %	93±1	95±2	0.49
pH	7.48±0.01	7.48±0.01	0.77
Pco_2, mm Hg	38±1	40±1	0.34
HCO_3^-, mmol/L	29±1	30±1	0.27
After 2 min of CPR			
So_2, %	93±1	67±9	0.01
pH	7.57±0.02	7.40±0.02	0.0002
Pco_2, mm Hg	25±1	42±6	0.02
HCO_3^-, mmol/L	23±1	26±2	0.17
After 12 min of CPR			
So_2, %	93±2	70±11	0.05
pH	7.48±0.03	7.33±0.06	0.04
Pco_2, mm Hg	22±2	43±10	0.05
HCO_3^-, mmol/L	16±1	20±2	0.06

Some aspects of this study protocol tend to bias the data in favor of the CC+RB group compared with real prehospital single-rescuer CPR. It is unlikely that excellent chest compressions and mouth-to-mouth rescue breathing would be provided by a single rescuer in the field. Transitions from rescue breathing to compressions and vice versa are likely to be much more difficult for a single rescuer than for our experienced, multi-individual research team. In fact, video data of CPR performance on resuscitation manikins immediately after a CPR course demonstrated substantially fewer chest compressions with single-rescuer CC+RB than in our experiment because of time spent on rescue breathing and the attendant transitions.[4] Those single-rescuer subjects compressed the chest only 39 times per minute, mostly because the average pause from compressions to position the head and provide 2 rescue breaths was 16 seconds. In contrast, the interval for 2 rescue breaths was only 4 seconds in our swine study, consistent with American Heart Association recommendations.[1]

Other important limitations include lack of blinding and applicability to human cardiac arrest victims. By its very nature, this study could not be blinded. Strict adherence to standardized resuscitation and postresuscitation protocols, however, was intended to minimize treatment bias. In addition, the comparability of aortic and right atrial compression pressures in the 2 groups suggests that the force of chest compressions was similar for both groups.

Compared with human CPR studies, animal CPR experiments allow for stricter experimental control and more consistent measurement of relevant physiological variables,

thereby more effectively elucidating the mechanisms of different interventions. Nevertheless, human outcome data are the "gold standard" for resuscitation interventions. A prospective study of 3053 prehospital cardiac arrests suggests that our findings are applicable to humans.[12,13] Long-term survival was comparable among those treated with good-quality chest compressions alone (17 of 116, or 15%) and those treated with good-quality chest compressions plus mouth-to-mouth rescue breathing (71 of 443, or 16%). The outcomes with either of these techniques were superior to those receiving no CPR (123 of 2055, or 6%, $P<0.001$).

A recent study from Seattle also suggests that bystander-initiated CPR is as effective with CC as CC+RB.[14] In a randomized manner, emergency medical system telephone dispatchers gave bystanders CPR instructions for CC or CC+RB. Successful initial resuscitation resulting in hospital admission was not different (97 of 241 [40%] with CC versus 95 of 279 [34%] with CC+RB, $P=0.15$). Similarly, survival to hospital discharge was not different (35 of 240 [15%] with CC versus 29 of 278 [10%] with CC+RB, $P=0.18$).

In summary, this investigation establishes that interrupting chest compressions for rescue breathing can adversely affect hemodynamics during CPR. We postulate that avoiding these interruptions is a mediator of the excellent outcomes with CC CPR in experimental models and clinical investigations of CPR for VF.

Acknowledgment

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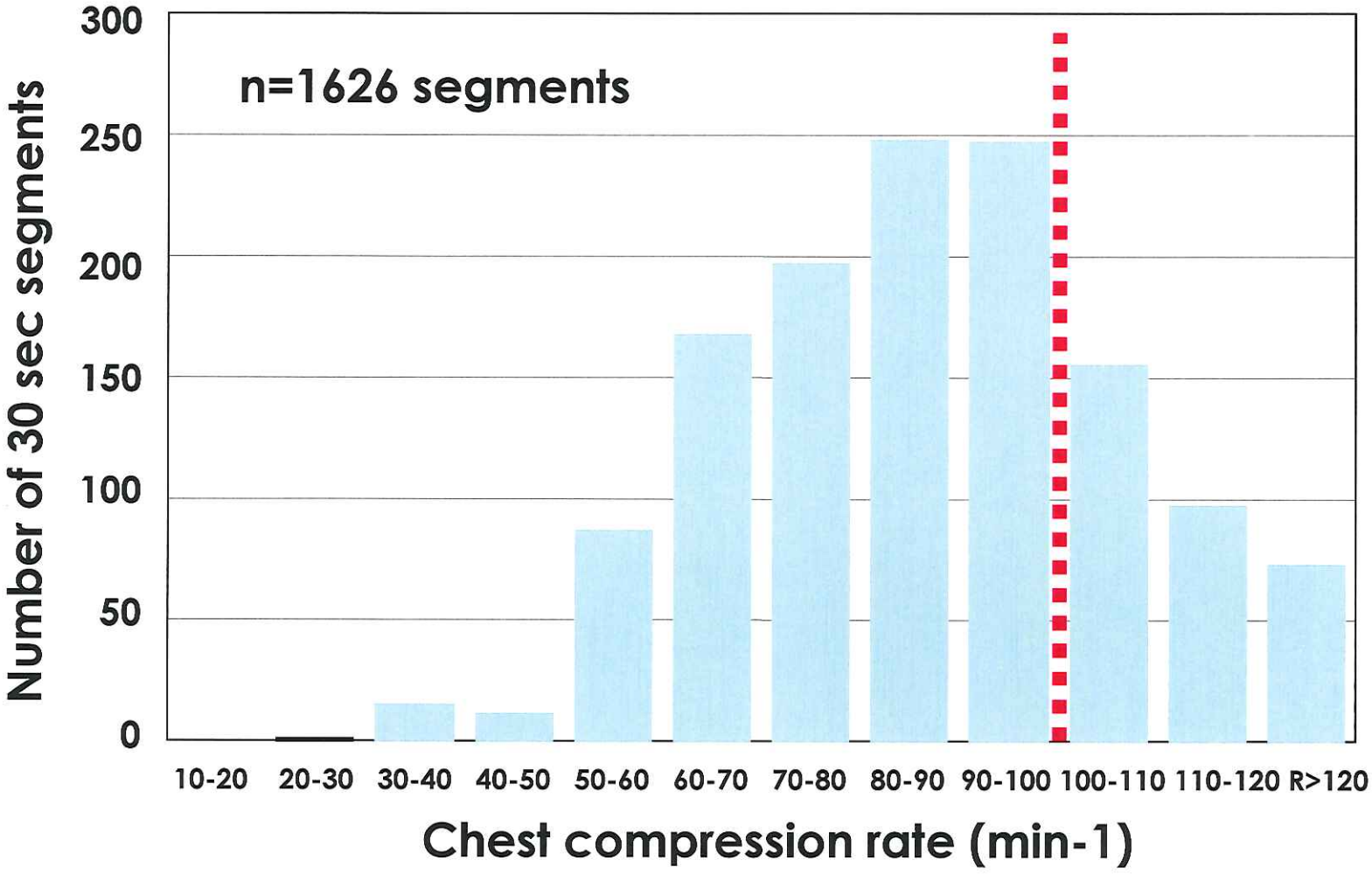
Chest compression rates



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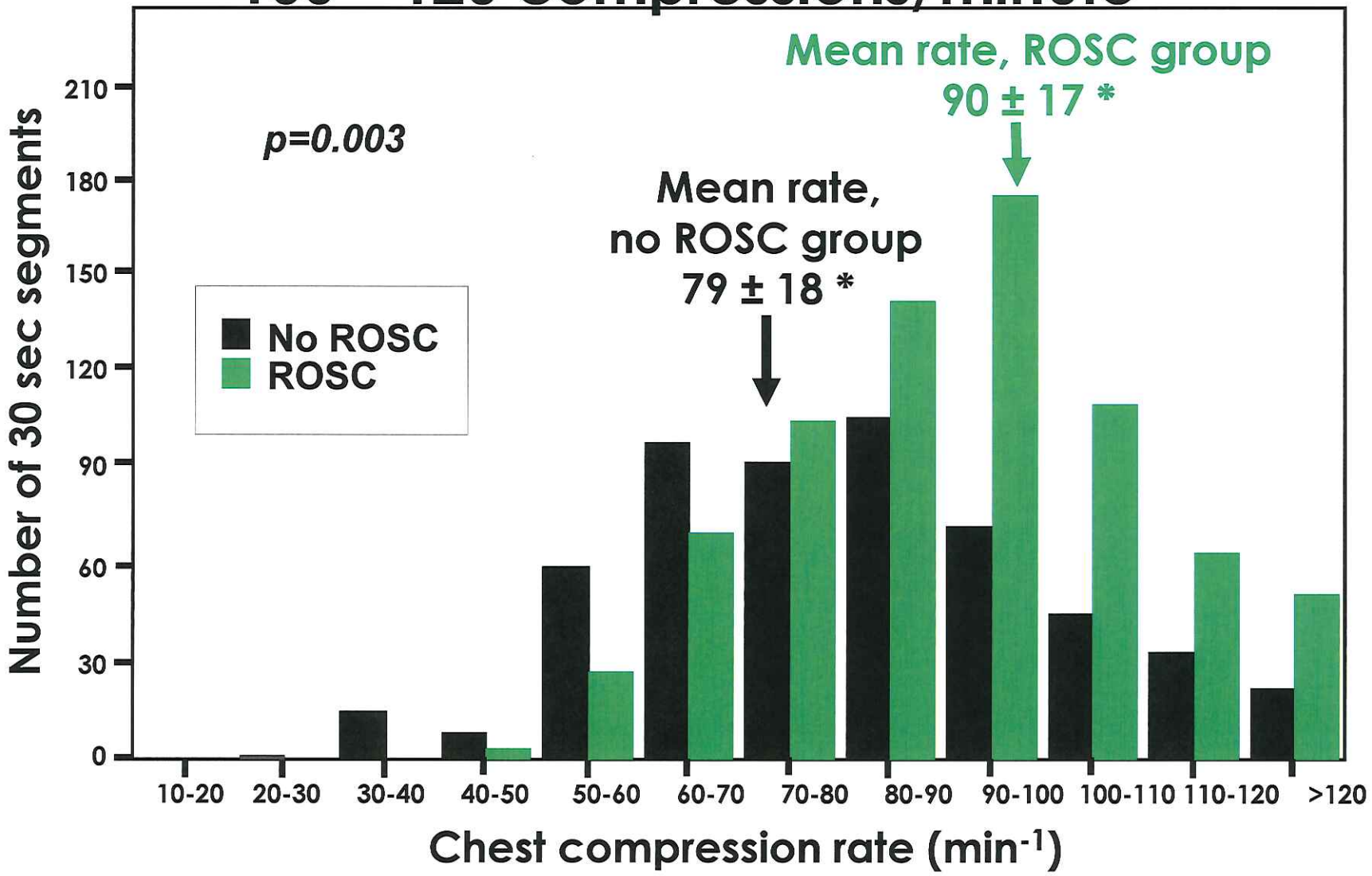
Survival better with compression rate of 100 – 120 compressions/minute



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Chest Compression Rates During Cardiopulmonary Resuscitation Are Suboptimal

A Prospective Study During In-Hospital Cardiac Arrest

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Background—Recent data highlight a vital link between well-performed cardiopulmonary resuscitation (CPR) and survival after cardiac arrest; however, the quality of CPR as actually performed by trained healthcare providers is largely unknown. We sought to measure in-hospital chest compression rates and to determine compliance with published international guidelines.

Methods and Results—We developed and validated a handheld recording device to measure chest compression rate as a surrogate for CPR quality. A prospective observational study of adult cardiac arrests was performed at 3 hospitals from April 2002 to October 2003. Resuscitations were witnessed by trained observers using a customized personal digital assistant programmed to store the exact time of each chest compression, allowing offline calculation of compression rates at serial time points. In 97 arrests, data from 813 minutes during which chest compressions were delivered were analyzed in 30-second time segments. In 36.9% of the total number of segments, compression rates were <80 compressions per minute (cpm), and 21.7% had rates <70 cpm. Higher chest compression rates were significantly correlated with initial return of spontaneous circulation (mean chest compression rates for initial survivors and nonsurvivors, 90 ± 17 and 79 ± 18 cpm, respectively; $P=0.0033$).

Conclusions—In-hospital chest compression rates were below published resuscitation recommendations, and suboptimal compression rates in our study correlated with poor return of spontaneous circulation. CPR quality is likely a critical determinant of survival after cardiac arrest, suggesting the need for routine measurement, monitoring, and feedback systems during actual resuscitation. (***Circulation.*** **2005;111:428-434.)**

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

Survival rates from cardiac arrest remain poor despite the development of both cardiopulmonary resuscitation (CPR) and electrical defibrillation as treatment modalities over the past 50 years.[1,2] Approximately 1% to 6% of patients suffering out-of-hospital cardiac arrest ultimately survive the event, and although survival rates are somewhat better for in-hospital arrest patients, a recent comprehensive report observed that only 17% of these patients were discharged alive.[3–5]

In an effort to improve cardiac arrest outcomes, recent investigations have focused on the timing and quality of CPR. For example, a study of in-hospital resuscitation showed that even short delays in the initiation of CPR correlated with poor outcomes.[6] Another out-of-hospital investigation demonstrated that pauses in chest compressions reduce the chance of subsequent defibrillation success.[7] Although CPR is traditionally composed of chest compressions interspersed with ventilations, recent work suggests that increasing the ratio of chest compressions to ventilations may improve the probability of the return of spontaneous circulation (ROSC), ie, the return of a viable rhythm and pulse.[8,9] One study found that chest compression without ventilation yielded improved survival over chest compression with intermittent ventilation.[9] The notion of chest compression–only CPR (without ventilations) has begun to accumulate support from both clinical and animal investigations.[10] An important challenge to the current resuscitation paradigm was issued by Wik et al,[11] who recently showed that out-of-hospital arrest patients who received 3 minutes of CPR before defibrillation had higher survival rates than those who were immediately defibrillated.

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This study, along with a prior investigation with similar results from Seattle,[12] suggests the paramount importance of chest compression in the framework of CPR and resuscitation. Most recently, Aufderheide et al[13] have demonstrated that out-of-hospital arrest patients are hyperventilated during arrest, and parallel animal experiments confirmed that this hyperventilation can decrease coronary perfusion pressures during resuscitation efforts and worsen survival.

These investigations collectively support the notion that high-quality CPR is vital for survival after cardiac arrest. Chest compressions are central to the performance of CPR, yet very few data exist on how well rescuers perform this important therapy. Resuscitation guidelines published in the United States and Europe recommend that chest compressions be performed at a rate of 100 compressions per minute (cpm).[14] We undertook a multicenter investigation to determine whether CPR-certified rescuers actually perform chest compressions at the guideline-specified rate during in-hospital arrest. We designed a custom-programmed data collection tool to allow observation and recording of real-time chest compression rates for the duration of resuscitation efforts. In this fashion, we studied a readily quantifiable metric (chest compression rate) as a surrogate measure for CPR quality.

Methods

Study Design

Our study protocol was approved by the Institutional Review Boards (IRBs) of the 3 study hospitals. Waiver of consent was used for cardiac arrest patients after appropriate measures were taken to satisfy the use of waiver provisions, including community and staff notification before initiation of our study. This included several advertised meetings in the hospital and clinics at which patients and physicians were presented with the study design and given an opportunity to comment. Data collection was structured to carefully comply with all relevant Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations.

Cardiac arrests were observed by investigators at University of Chicago Hospitals (UCH), a 600-bed academic medical center; Lutheran General Hospital (LGH), a 600-bed referral hospital; and MacNeal Hospital (MNH), a 400-bed community hospital. Investigator observation teams were organized to provide coverage in their respective hospitals during equally proportioned day, evening, and overnight shift periods. In this fashion, cardiac arrests were recorded at each site from April 2002 to October 2002 (UCH) and from April 2003 to October 2003 (LGH and MNH). Trained observers were registered nurses (UCH, MNH) or respiratory therapists (LGH). All observers were previously certified in basic life support and had prior experience in cardiac resuscitation. Trained observers were linked to hospital paging systems to be alerted to each cardiac arrest, and they recorded chest compression data continuously from their arrival at the arrest scene throughout the duration of the arrest efforts. At all 3 hospitals, staff members performing CPR included nurses, resident physicians, and medical students; at a minimum, all were certified in basic life support.

Cases were excluded if the patients experiencing arrest were <18 years of age or if the arrests occurred in operating rooms or emergency departments. Arrests were also excluded if the trained observers arrived at the arrest before sufficient personnel were present, so that their direct assistance in patient care was required. True arrest cases were defined by the loss of a pulse and the delivery of chest compressions by hospital staff. On arrival at a cardiac arrest, observers made all reasonable efforts to record compressions using the data collection tool without alerting resuscitation providers to their presence.

Data Collection Tool

A novel tool was developed to record real-time chest compression rates with a personal digital assistant (PDA; Palm Pilot m500, Palm, Inc) programmed with the assistance of a Visual Basic application platform (AppForge Professional Edition 2.1.1, AppForge, Inc). The PDA application was designed to record such events as arrival at arrest, chest compression given, and end of event by pressing different buttons on the device. Investigators were trained to press the "chest compression given" button in a synchronized 1-to-1 fashion with each compression delivered. Events were automatically time stamped to the nearest 10 milliseconds and stored on a memory card (SD Card, SanDisk Inc). Clinical data such as age, sex, race, and outcome were also recorded for each event on the device. To comply with IRB and HIPAA requirements, these clinical data were collected in aggregate fashion only, with outcome (ROSC or no ROSC) as the only patient characteristic linked to the actual event. Observers were trained to indicate ROSC if a detectable pulse and perfusing rhythm were maintained for ≥5 minutes. Similarly, data were collected only for the cardiac arrest event; patients were not followed up to hospital discharge.

Observers received several hours of training and were tested with a simulated cardiac arrest before the study. Additionally, during the study period, observers were tested against a standard videotaped arrest simulation with variable known compression rates. This allowed us to assess correct performance and validate the recording protocol (see below).

Data Analysis

Data were analyzed with a spreadsheet application (Excel, Microsoft Corp). Arrest recordings were divided into 30-second segments for analysis, and chest compression rates were computed for each segment from this formula: rate = (compressions per 30-second segment) × 60 / (30 − total pause time in 30-second segment), where pause time indicates periods of time in which ≥4 seconds pass without chest compressions, suggesting that some noncompression action such as a pulse check or shock is taking place. Analysis of our data using pause time thresholds from 2 to 5 seconds did not significantly change our results (data not shown). Thus, calculated compression rates are relatively unaffected by pauses for pulse checks and rescuer change or other brief times without compressions. Average chest compression rates for each arrest were also calculated. Mean chest compression rate data (to determine the significance between ROSC and non-ROSC cohort subsets) were compared by use of the 2-tailed Student t test, with significance set at $P<0.05$. The frequency of ROSC was tabulated for each quartile of average chest compression rates. The quartile groups were then compared by use of the χ^2 test with Bonferroni adjustment for 6 pairwise comparisons, yielding a required significance level (α) of 0.0083.

Validation of Data Recording

To determine whether trained observers could accurately record chest compressions using our handheld device, we performed validation testing on each of the observers at the 3 hospital sites (18 total observers). A carefully simulated cardiac arrest with realistic chest compression rates and rate variation was videotaped. Each observer recorded this arrest using the handheld device, and data were analyzed against the "true" chest compression data for the same event derived by study authors by freeze-frame analysis of the simulation video with millisecond time stamping. Validation data were evaluated with Pearson correlation coefficient analysis.

Results

Observer Validation

Each observer was tested with a videotaped cardiac arrest simulation during the study period to ensure correct data recording performance (see Methods). This validation of our data collection tool and trained observers is shown in Figure 1. The mean correlation coefficient calculation for our 18

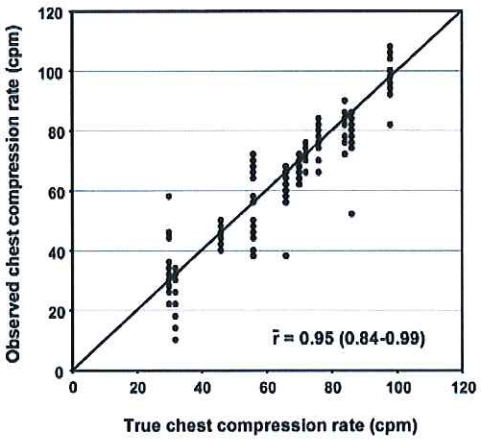

Figure 1. Validation of observer chest compression recording method with Pearson correlation coefficient analysis. Observers were tested against videotaped simulated cardiac arrest, and chest compression rates were compared with known rates of simulation derived by digital time stamping. Mean correlation coefficient for all data points is shown, with range of coefficients in parentheses.

observers revealed $r=0.95$, demonstrating that observers could collect chest compression data reproducibly and reliably.

Study Population

Over the study period, 813 minutes of resuscitation was observed at the 3 hospitals during 97 cardiac arrest events. IRB-approved aggregate demographic data are shown in the Table. The average age of the patients was 73.1 years; 49 of 97 (51%) were female. Cardiac arrests occurred in intensive care settings (53 of 97, 55%), hospital ward beds (31 of 97, 32%), or other locations such as radiology areas (13 of 97, 13%). Initial survival (ROSC) was attained in 61 of 97 patients (63%). Differences in demographic data between the 3 hospitals reflected their different patient populations. Age, setting of cardiac arrest, and survival data are generally consistent with other reports of in-hospital arrest.[15,16]

Chest Compression Rate Analysis

An example cardiac arrest data set is shown in Figure 2A. Chest compression rates were calculated for each 30-second segment (see Methods) and are shown in the figure. In this arrest record, as in other arrests in our cohort, chest compression rates often fell to <100 cpm, the rate recommended during standard CPR by the American Heart Association and European Resuscitation Council.[14] Many arrest records demonstrated significant time intervals during which no chest compressions were performed, representing interventions such as intubation or periods when compressions were held because a pulse may have been detected. Shorter pauses, for pulse checks or change of rescuer, were excluded in the calculation of 30-second compression rates because these pauses would artificially lower the true rates when compressions were actually being delivered. The average chest compression rates over resuscitation time are shown in Figure 2B.

Characteristics of Patient Cohort

		Hospital		
	All Sites	UCH	LGH	MNH
Cohort size				
Time recorded, min	813	638	109	66
Events recorded, n	97	71	14	12
Age (mean), y	73.1*	72.4*	75.7±18.9	74.2±13.6
Gender, n (%)				
Female	49/97 (51)	38/71 (56)	6/14 (43)	5/12 (42)
Male	48/97 (49)	33/71 (44)	8/14 (57)	7/12 (58)
Race, n (%)				
Black	38/97 (39)	35/71 (52)	1/14 (7)	2/12 (17)
White	48/97 (49)	29/71 (46)	12/14 (86)	7/12 (58)
Other	11/97 (11)	7/71 (2)	1/14 (7)	3/12 (25)
Location, n (%)				
Intensive care	53/97 (55)	40/71 (64)	8/14 (57)	5/12 (42)
Ward	31/97 (32)	23/71 (26)	4/14 (29)	4/12 (33)
Other	13/97 (13)	8/71 (10)	2/14 (14)	3/12 (25)
Arrest characteristics				
Initial ROSC, n (%)	61/97 (63)	46/71 (65)	8/14 (57)	7/12 (58)
Event duration (mean), min	8:23±6:42	9:00±6:34	7:48±8:35	5:33±4:15
Event duration, range, min	0:08–26:11	0:40–23:56	0:08–26:11	0:52–14:32

"Other" locations included cardiac catheterization and radiology areas. "Other" race included patients of Hispanic or Asian descent. "Event duration" refers to time duration of recorded resuscitation efforts.

*Given IRB requirements at this hospital to aggregate demographic data, we cannot calculate an SD for this data set.

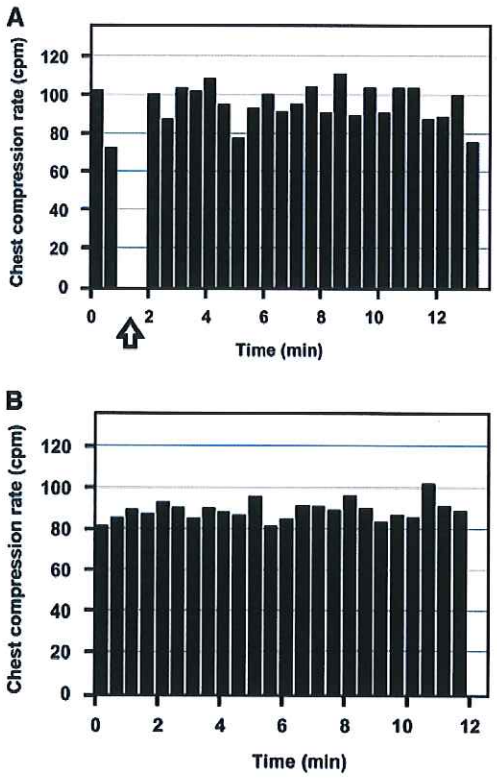

Figure 2. A, Example of chest compression rate data from one cardiac arrest event. Each bar represents average chest compression rate for 30-second time segment. Note the pause during first 2 minutes of resuscitation marked by arrow; during this time, intubation was performed. B, Average chest compression rates for entire cohort during each time segment. Each bar represents average of all chest compression rates at that point in time for entire cohort. First 12 minutes of arrest time is shown. Because some resuscitation efforts ended before 12 minutes, number of arrests included in each average declines over time. Similarly, some resuscitations lasted >12 minutes; for simplicity, data from beyond 12 minutes are not shown. It does not appear that chest compression rates decay significantly over this time interval in the resuscitation cohort.

Chest compression rates in our cohort showed great variation and often fell well below 100 cpm (Figure 3). In fact, rates were at 100±10 cpm in only 31.4% of segments and were <80 cpm in 36.9% of segments. When data from each individual hospital were compared, similar distributions of chest compression rates were seen, supporting the notion that poor rate compliance is not a hospital-specific issue (data not shown). A variety of medical staff, specifically nurses, residents, and medical students, performed chest compressions at each study hospital, and all were CPR-certified via basic life support or advanced cardiopulmonary life support training courses.

Chest Compression Rate and Outcome

The distribution of chest compression rates was plotted separately for the patients who attained ROSC and for those who did not survive initial resuscitation efforts (Figure 4). The data show that patients who attained ROSC were given chest compressions at higher rates. Mean chest compression rate for initial survivors was 90±17 cpm; for nonsurvivors, 79±18 cpm (P=0.0033). Average total resuscitation times for the 2 groups were 450±403 and 595±390 seconds, respectively, suggesting that poor compression rate may not reflect performer bias against patients thought to have little chance of resuscitation (see Discussion). Two additional analyses also revealed better compression rates for initial survivors than nonsurvivors. First, when average chest compression rates were calculated for the 2 groups at each time segment during resuscitation (ie, at segment 1, segment 2), average chest compression rates among the ROSC group were higher than among the nonsurviving group during the vast majority of time segments (data not shown). Second, a quartile analysis was performed in which all arrests were grouped into 4 groups ranked by chest compression rate (Figure 5). ROSC was scored for each of these groups. The quartile of arrests with the lowest chest compression rates had a ROSC rate of 42%, whereas the quartile with the highest chest compression rates had a ROSC rate of 75% (P=0.0083). Given the small number of arrests with average chest compression rates >100 cpm, we could not discern a significant drop in ROSC rate for overly high compression rates in separate analysis (data not shown).

Discussion

Using a custom-designed data collection system, we have performed the first comprehensive evaluation of chest compression rates during cardiac arrest. After observing 97 cardiac arrests, we have concluded that chest compressions are often delivered at rates much lower than recommended. The frequency of suboptimal compression rates was similar in all 3 hospitals, suggesting that poor chest compression rates may be a widespread problem. Our work confirms and extends a small pilot study that found low chest compression rates when manually counted for 45 seconds during a convenience sample of 12 in-hospital arrests for a total of 8 minutes of observation time at one hospital site.[17]

When resuscitation outcomes were evaluated, we found that higher average chest compression rates correlated with higher rates of ROSC. Perhaps most interesting is the quartile analysis in Figure 5, which demonstrates that the group of arrests with the lowest chest compression rates had a greatly reduced rate of initial survival compared with the group of arrests with the highest chest compression rates. The 2 upper quartiles have similar ROSC rates, suggesting that a "threshold" effect may be evident; ie, survival may be diminished only if the chest compression rate falls below a certain critical value. Our analysis suggests that such a threshold may exist at a rate between 80 and 90 cpm. We did not design our study with the expected power necessary to detect differences in ROSC rates, yet these differences are statistically significant by both direct comparison and quartile analysis.

There are 2 possible explanations for this intriguing finding. Low rates of chest compression may contribute to resuscitation failure; therefore, our findings may reveal an important aspect of CPR performance by trained personnel. This would suggest that improvements in chest compression rates might improve outcomes. This hypothesis is consistent with animal data on CPR quality. Alternatively, low chest compression rates may reflect bias of the resuscitation team

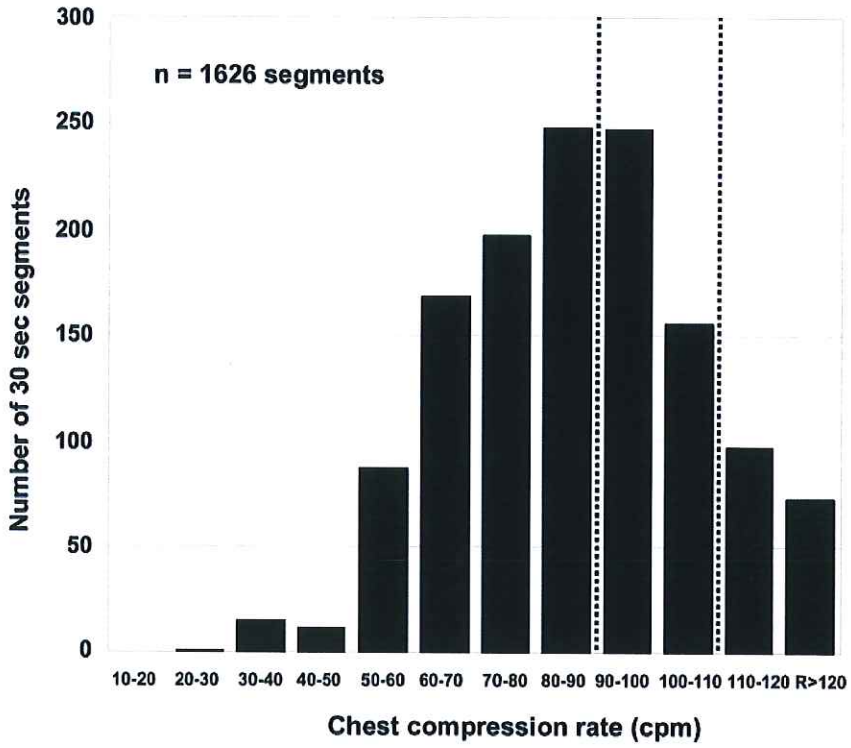

Figure 3. Distribution of chest compression rates at 3 study hospitals. Aggregated data for all 30-second segments during which compressions were delivered show wide distribution of rates. Note that standard guidelines for CPR recommend a rate of 100 cpm. Percentage of segments within 10 cpm of guideline recommendations is shown, with dotted lines on histogram representing this range.

toward probable outcome. That is, patients thought to have little chance of recovery may receive poor resuscitation efforts, intentionally or not. A surrogate marker for team effort during arrest, namely duration of resuscitation efforts, suggests that bias may not play a role because patients who died received longer resuscitation efforts than patients who lived (Figure 4). If a team correctly identifies patients who will not survive despite resuscitation, one might expect shorter resuscitation durations in the population that did not attain ROSC. This is by no means conclusive, however. Given IRB constraints on linking patient data such as age or morbidities to our compression data (see Methods), a careful analysis comparing ROSC and non-ROSC cohorts is limited.

Effectiveness of chest compressions depends on several components and certainly includes variables that go beyond simple rate such as depth, pressure, and technique.[18,19] Prior laboratory investigations have shown that slow rates of compression do not generate sufficient flow to sustain resuscitation[20] and that higher chest compression rates are associated with improved measures of perfusion.[21] In this preliminary study, we have not considered depth of compressions or rate and depth of ventilation. Effectiveness of CPR is most

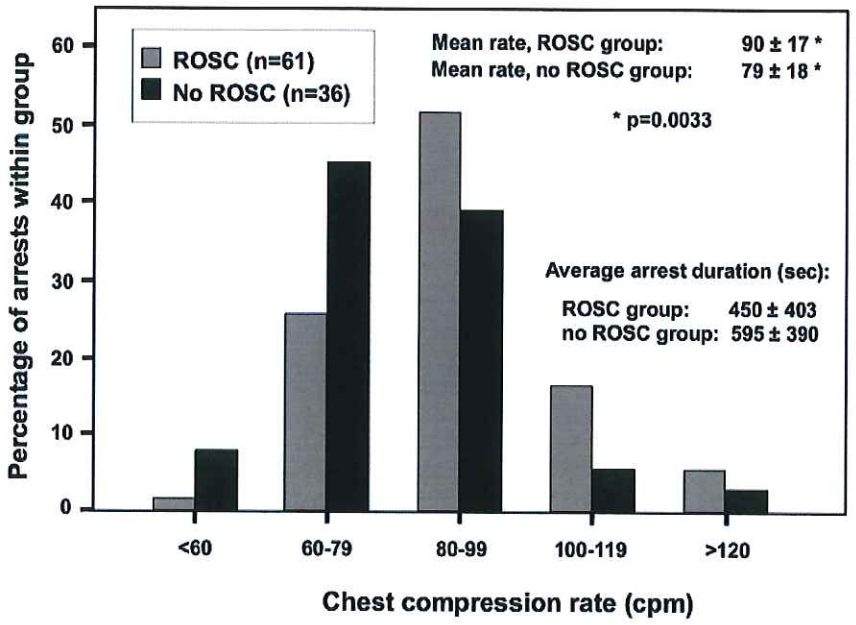

Figure 4. Chest compression rates correlate with initial resuscitation outcome. Subgroup of patients attaining ROSC is shown in gray; subgroup that did not, in black. Note 2 overlapping but distinct distributions, with mean rates for each group shown. Also note mean durations of resuscitation for 2 groups, demonstrating that the group that expired received longer resuscitation efforts on average, arguing against a "slow-code" bias (see Discussion). Asterisk denotes statistical significance from 2-tailed *t* test as shown.

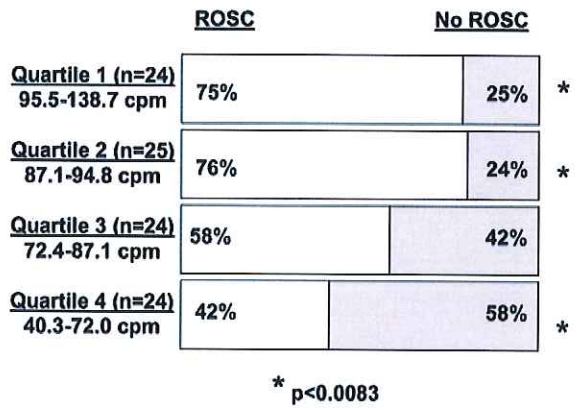

Figure 5. Quartile analysis of chest compression rate and survival. Arrest cohort was divided into 4 groups based on mean chest compression rates (ie, quartile 1 had highest compression rates, quartile 4 had lowest compression rates). ROSC was then compared among these groups. Asterisks denote statistical significance comparing either first or second quartile with last quartile (P=0.000925 and P=0.000371, respectively); comparison of third and fourth quartiles was not statistically significant (P=0.0997). We used χ^2 analysis with Bonferroni adjustment for 6 pairwise comparisons to calculate significance.

likely limited by poor performance in any of its components; thus, inadequate rate, even in the presence of sufficient depth and technique, likely reduces the effectiveness of compressions.

Current research into CPR methodology suggests that ventilations may require less priority than assumed previously.[8–11] Concentrating on compressions alone (especially in the out-of-hospital CPR context where the lay public and paramedics serve as rescuers) may improve both the rate of participation in rescue attempts[22] and the quality of compressions.[10] Animal investigation has shown that even brief pauses in chest compressions adversely affect hemodynamics during resuscitation efforts.[23] If our data are also considered, it is also possible that chest compression rates (and therefore rates of ROSC) might improve if ventilation rates were reduced during CPR.

One limitation of our study is that data were collected via an observer, so human error might affect our findings. We have attempted to address this concern in several ways. First, observers undertook several hours of training with the recording device and were tested before the study began. Second, we validated our data collection via testing of each observer during the study period using a videotaped arrest simulation (Figure 1) that provided evidence that accurate data could be collected. These arguments notwithstanding, a more objective measurement of CPR quality would be a welcome advancement. After all, it is possible that some overcounting or undercounting of chest compressions might have occurred in our study despite observer training.

Another possible study limitation in the generalizability of our findings is the small number of hospital sites. We chose 3 contrasting hospitals with different philosophies of care, patient mix, and staff composition to achieve a representative sample of in-hospital CPR performance. We suspect that a variety of universal human factors contribute to poor CPR quality. These include the difficulty of performing CPR during stressful and chaotic cardiac arrest conditions, the lack of an internal sense of chest compression rate, rescuer fatigue,[24] and infrequent CPR recertification. Therefore, we believe that our results are likely to reflect an endemic problem among healthcare providers.

There are at least 2 possible solutions to the problem of poor CPR quality. The first involves mechanical devices that can provide chest compressions reliably at a set rate and depth.[25] These devices have the potential to generate better hemodynamic characteristics than manual chest compressions.[26] Nevertheless, they have remained unpopular in the clinical arena because they are often cumbersome to use and awkward to work around if other patient instrumentation is required. The other solution is to improve monitoring and feedback to reduce human error during manual CPR. Our data support the importance of additional instrumentation such as end-tidal CO_2 monitors[27] and "smart defibrillators," which can sense CPR characteristics and alert rescuers to errors such as incorrect chest compression rate or depth.[28]

Our results suggest that relatively highly trained hospital personnel often fall short of CPR guidelines during resuscitation efforts. Most cardiac arrests take place in the out-of-hospital setting, where bystanders and paramedics are the primary providers of CPR.[29] It is possible that the quality of community CPR may be even more variable than what we have found in the present study of trained providers.

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Disclosures

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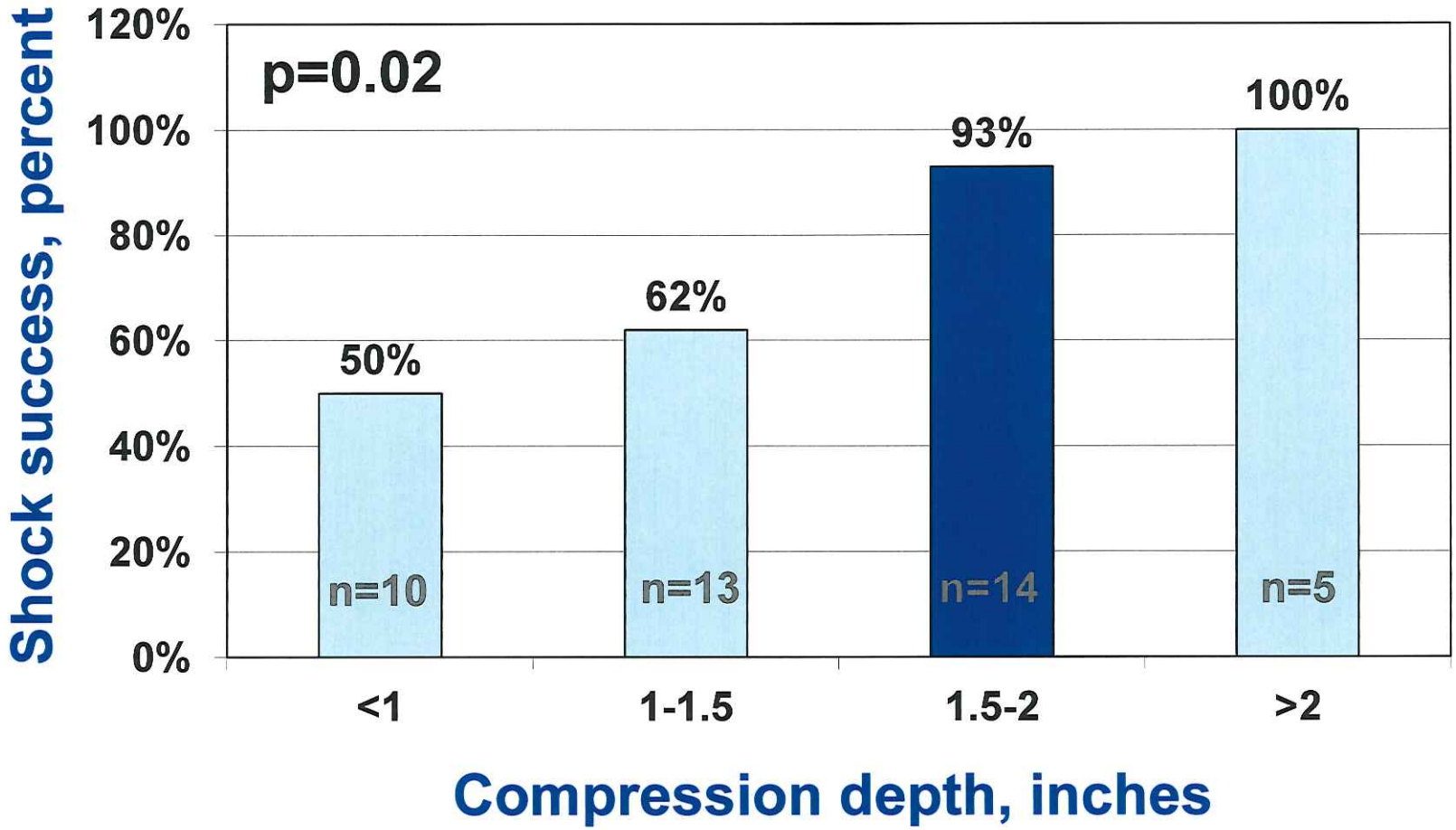
Shock success by compression depth



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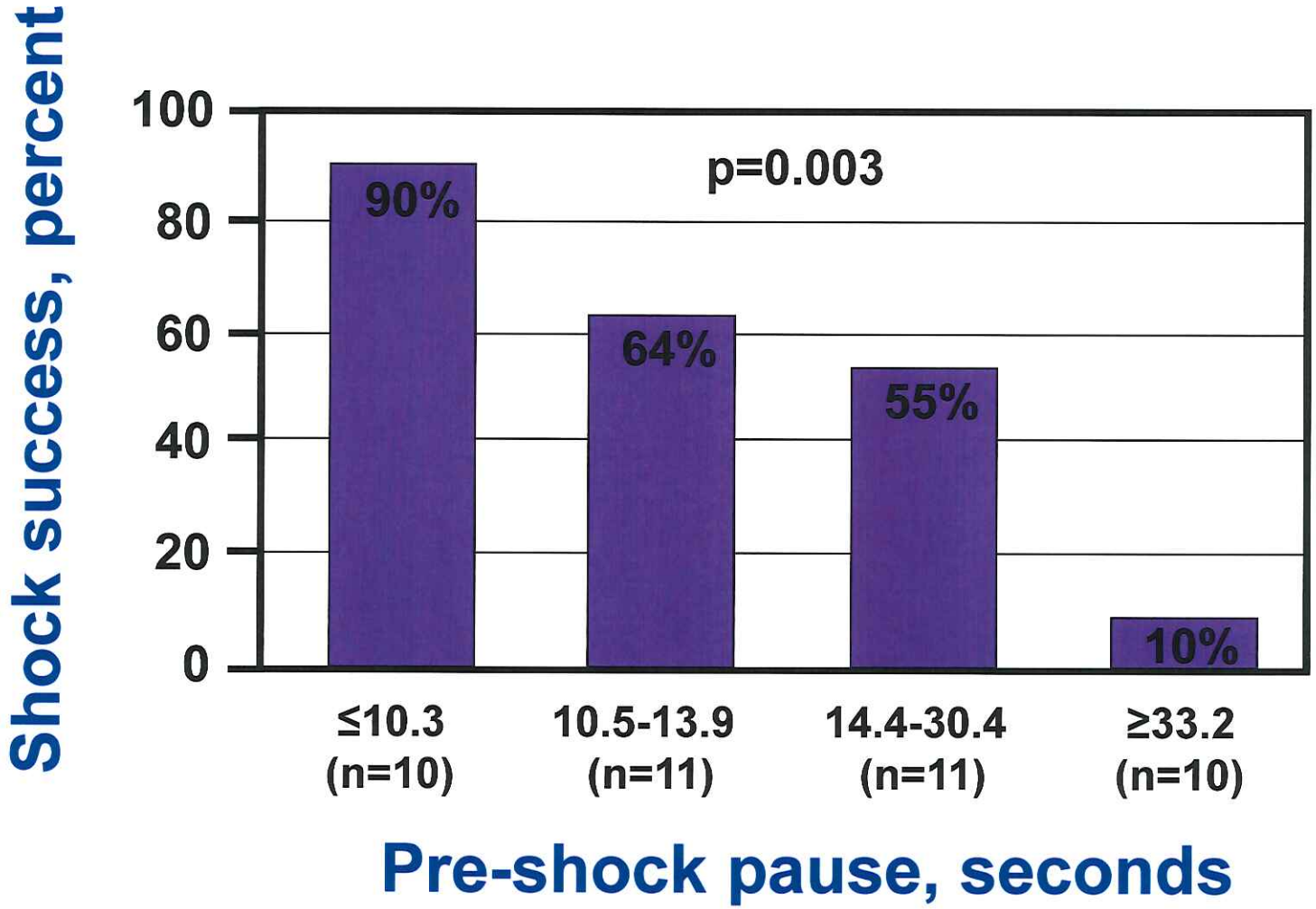
Shock success by pre-shock pauses



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CLINICAL PAPER

Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest☆

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KEYWORDS
Heart arrest;
Cardiopulmonary resuscitation;
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Chest compression

Summary
Background: Cardiopulmonary resuscitation (CPR) and electrical defibrillation are the primary treatment options for ventricular fibrillation (VF). While recent studies have shown that providing CPR prior to defibrillation may improve outcomes, the effects of CPR quality remain unclear. Specifically, the clinical effects of compression depth and pauses in chest compression prior to defibrillation (pre-shock pauses) are unknown.
Methods: A prospective, multi-center, observational study of adult in-hospital and out-of-hospital cardiac resuscitations was conducted between March 2002 and December 2005. An investigational monitor/defibrillator equipped to measure compression characteristics during CPR was used.
Results: Data were analyzed from 60 consecutive resuscitations in which a first shock was administered for VF. The primary outcome was first shock success defined as removal of VF for at least 5 s following defibrillation. A logistic regression analysis

☆ A Spanish translated version of the summary of this article appears as Appendix in the online version at 10.1016/j.resuscitation.2006.04.008.

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demonstrated that successful defibrillation was associated with shorter pre-shock pauses (adjusted odds ratio 1.86 for every 5 s decrease; 95% confidence interval 1.10–3.15) and higher mean compression depth during the 30 s of CPR preceding the pre-shock pause (adjusted odds ratio 1.99 for every 5 mm increase; 95% confidence interval 1.08–3.66).

Conclusions: The quality of CPR prior to defibrillation directly affects clinical outcomes. Specifically, longer pre-shock pauses and shallow chest compressions are associated with defibrillation failure. Strategies to correct these deficiencies should be developed and consideration should be made to replacing current-generation automated external defibrillators that require long pre-shock pauses for rhythm analysis.

Introduction

Although rapid defibrillation remains the cornerstone of treatment for ventricular fibrillation (VF), a number of studies have supported the notion that cardiopulmonary resuscitation (CPR), especially in the time preceding defibrillation, may also play a key therapeutic role.[1,2] However, the effect of CPR quality on clinical outcomes remains poorly understood.

Recent work, relying on new technology capable of sensing compression rate and depth, has shown that CPR quality is inconsistent in actual clinical practice, with frequent pauses and shallow compression depth.[3,4] Using this technology, the effects of these CPR variables on clinical outcomes can now be evaluated. Of particular interest are the duration of time from the end of chest compressions until the defibrillation shock is given (i.e., the pre-shock pause) and the measured depth of chest compressions preceding defibrillation. Both have been shown to have significant impact on outcomes in animal studies,[5–8] yet neither has been rigorously investigated in the clinical setting.

Understanding the effects of these variables has significant public health and policy implications. Pre-shock pauses are particularly important as automated external defibrillators (AEDs), that generally require long pre-shock pauses for rhythm analysis,[8–10] have gained widespread acceptance and have been implemented in a variety of settings.[11–14] Additionally, understanding the relative importance of these variables of CPR quality on outcomes will have implications for resuscitation guidelines and training. We therefore examined whether pre-shock pause and compression depth, two likely determinants of blood flow preceding defibrillation, affect the ability of a shock to terminate VF.

Methods

Study design

An international, multi-center, observational study of in-hospital and out-of-hospital cardiac arrests occurring between March 2002 and December 2005 was conducted. Approval was granted by the Institutional Review Board of the University of Chicago Hospitals and the regional ethics committee in Akershus, with mechanisms to satisfy waiver of consent provisions at both sites. Additionally, an oral consent process was used for rescuers in Chicago.

Details of the study design and methods have been described previously.[3,4] An investigational monitor/defibrillator (FDA IDE # G020121) was used during resuscitation from cardiac arrest. This device is a modification of a standard biphasic monitor/defibrillator with additional sensing capabilities to detect chest compression rate and depth, ventilation rate and volume, and presence of a pulse. Chest compression measurements were obtained using a chest compression pad outfitted with both an accelerometer and force detector while ventilations and pulse were detected by changes in chest wall impedance. Measurements of these variables have been validated elsewhere.[15–18]

Study setting and population

Consecutive adult in-patients at the University of Chicago Hospitals between December 2002 and December 2005 and out-of-hospital patients in Akershus, Norway, between March 2002 and August 2003 were enrolled in the study if they suffered a cardiac arrest, as defined by the loss of a pulse, requiring the delivery of chest compressions. In-hospital patients were excluded if they were arrested in the emergency department or operating

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room environments. Additionally a small number of patients did not receive treatment with the study defibrillator and were therefore excluded from analysis. These were rare and sporadic occurrences, related to local team response and not to specific patient characteristics. Only those patients whose first shock was received for VF were considered in this analysis.

CPR was provided by resident physicians certified in Advanced Cardiovascular Life Support (ACLS) with assistance from respiratory technicians, nurses, and medical students in Chicago and by paramedics from the emergency medical system in Akershus. The CPR-sensing monitor/defibrillator was used in manual mode in both locations and all rescuers received training in its use. In Akershus, a modified protocol required paramedics to provide 3 min of CPR prior to defibrillation. Data from the investigational devices were collected on memory cards and subsequently downloaded by study personnel.

Measurements

All arrest transcripts with shocks were analyzed and annotated manually for rhythm prior to and immediately following defibrillation attempts. The time interval of the last 30 s of CPR preceding the pre-shock pause was also annotated. The duration for CPR quality assessment was chosen to remain consistent with our earlier work evaluating CPR quality in 30 s segments[3,4,19] and in order to evaluate the immediate effect of CPR quality on shock outcomes. Further quantitative analysis was then performed to determine the pre-shock pause duration and variables of CPR quality. All rhythms and pause times were confirmed manually independently by two physician investigators (DPE, BSA).

Pre-shock pauses were measured from the end of the last chest compression to the start of defibrillation (Figure 1). Shocks were deemed successful if VF was terminated for at least 5 s, consistent with the prevailing definition in the literature.[10,20,21] Return of spontaneous circulation (ROSC) was defined by the presence of an organized rhythm with a palpable pulse and measurable blood pressure for at least 20 min, as documented in the medical record.

Three measures of CPR quality were considered in this analysis. Compression depth was the calculated mean depth of all compressions administered during the 30 s segment of CPR preceding the pre-shock pause, measured in millimeters. No flow time (NFT) was the number of seconds during that same time period in which no compressions were

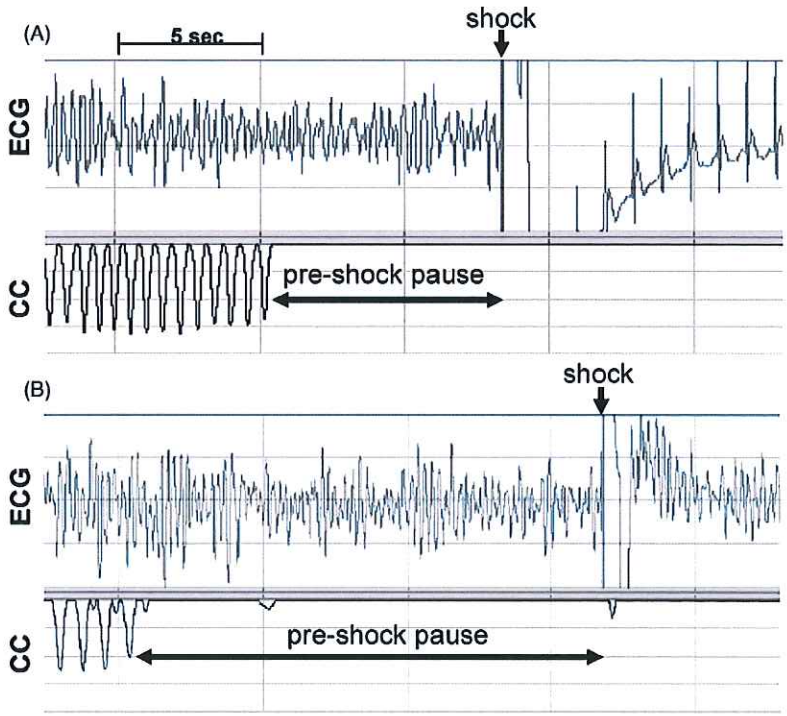

Figure 1 Examples of defibrillation attempts. (A) Successful shock preceded by an 8-s pre-shock pause and deep chest compressions. (B) Unsuccessful shock preceded by a 16 s pre-shock pause and shallower chest compressions. ECG, electrocardiogram; CC, chest compressions.

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being administered. Compression rate was calculated as the compression count*60/(30-NFT) and represented the rate of compressions/min during the fraction of the 30 s segment in which compressions were being provided. Ventilation rate was determined by multiplying the number of ventilations provided during the 30 s by two.

Patient demographic and outcome data were extracted from a subsequent review of medical records. Time to shock was measured from the time the defibrillator was turned on until the first shock was administered. This is only a proxy for arrest time but was chosen for consistency due to lack of time synchronization between defibrillators and other clocks used for reporting arrest intervals. This dilemma has been reported by other investigators.[22]

Data analysis

All calculations were performed using a statistical software application (Stata Version 9.0, College Station, TX). Skewed data, such as times and total shocks, were reported as medians with interquartile ranges and compared using a Wilcoxon rank sum test. Means were compared with a two-sided student's *t*-test and binary variables were compared via chi-squared analysis. A logistic regression analysis was undertaken to adjust for possible confounding variables. Additionally, trends in proportions were analyzed with an ordinal trend test. Significance was set at $p < 0.05$ for all values. As this manuscript represents a post hoc study of a collected data set, there were no interim analyses and all patients who met inclusion criteria for this analysis were included.

Table 1 Baseline patient characteristics ($n = 60$)

Age (year), mean (SD)	65 (16)
Male sex, *n* (%)	38 (63)
Out-of-hospital arrest location, *n* (%)	33 (55)
Time to first shock (min), median (IQR)	3.7 (2.2–5.7)
Total shocks per patient, median (IQR)	5 (2–8)
First shock success, *n* (%)	44 (73)
Return of spontaneous circulation, *n* (%)	28 (53)
Survival to hospital discharge, *n* (%)	4 (7)

S.D., standard deviation; IQR, interquartile range.

Results

A total of 60 patients received a first electrical shock for VF during the study period. Table 1 summarizes the baseline characteristics of the entire cohort. Characteristics of successful and unsuccessful shocks are compared in Tables 2 and 3. There were no statistically significant differences

Table 2 Patient characteristics by first shock success

Characteristic	Success ($n = 44$)	Failure ($n = 16$)	*p*-Value
Age (year), mean (SD)	67 (16)	61 (16)	0.23
Male sex, *n* (%)	30 (68)	8 (50)	0.20
Out-of-hospital arrest location, *n* (%)	27 (61)	6 (38)	0.10
Time to first shock (min), median (IQR)	3.8 (2.7–5.3)	3.3 (1.7–11.2)	0.96
Outcomes			
Return of spontaneous circulation, *n* (%)	24 (55)	4 (25)	0.04
Survival to discharge, *n* (%)	4 (9)	0 (0)	0.21

S.D., standard deviation; IQR, interquartile range.

Table 3 CPR quality prior to the first shock by shock outcome

	Success	Failure	Overall	*p*-Value
Pre-shock pause (s), median (IQR) [$n = 53$]	11.9 (6.8–19.4)	22.7 (15.6–37.7)	15.3 (8.3–23.5)	0.002
[a]No flow time (s), median (IQR) [$n = 49$]	4.8 (0.6–13.8)	0.0 (0.0–9.1)	4.5 (0.0–13.3)	0.15
[a]Compression rate (min^{-1}), mean (S.D.) [$n = 49$]	114 (17)	120 (23)	116 (19)	0.31
[a]Compression depth (mm), mean (S.D.) [$n = 47$]	39 (11)	29 (10)	36 (11)	0.004
[a]Ventilation rate (min^{-1}), mean (S.D.) [$n = 39$]	16 (9)	16 (11)	16 (10)	0.99

[a] During the 30 s of CPR preceding the pre-shock pause. IQR, interquartile range.

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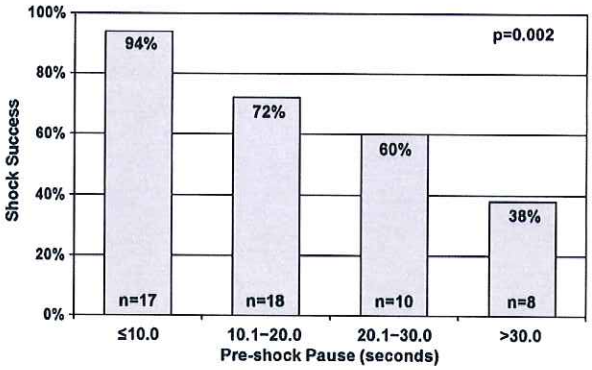

Figure 2 Association between pre-shock pause and shock success. Cases are grouped by pre-shock pause in 10 s intervals. Note that longer pre-shock pauses are significantly associated with a smaller probability of shock success.

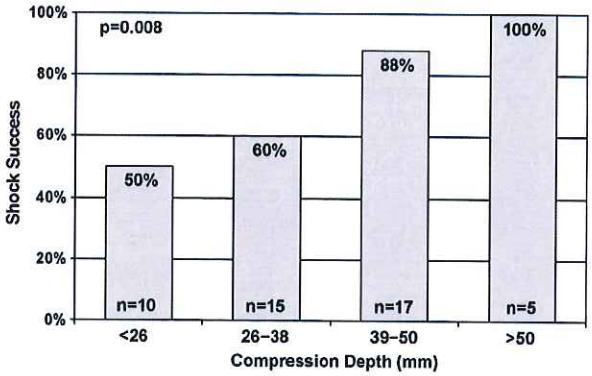

Figure 3 Association between chest compression depth and shock success. Cases are grouped by 30 s average compression depth in approximately 11 mm (0.5 in.) intervals. Chest compression depth of 38–50 mm (1.5–2 in.) represents current CPR guidelines recommendations. Deeper chest compressions are significantly associated with increased probability of shock success.

in age, sex, arrest location or time to shock by first shock success. However, successful shocks were associated with a shorter median pre-shock pause duration (11.9 s versus 22.7 s; $p = 0.002$) and higher mean chest compression depth in the 30 s of CPR preceding the pre-shock pause (39 ± 11 mm versus 29 ± 10 mm, $p = 0.004$). The other features of CPR quality, including ventilation rate, chest compression rate and no flow time, were similar between the two groups.

When pre-shock pause time and compression depth were divided into categories, a statistically significant dose-response effect for each was seen on first shock success. Figure 2 shows the relationship between increasing pre-shock pause and probability of shock success. In this model, 10-s increments were chosen for simplicity and comparability to an established animal model.[6] A similar relationship was seen between compression depth in the 30 s preceding the pre-shock pause and the probability of shock success (Figure 3). For compression depth evaluation, half-inch increments (converted into millimeters) were assessed to allow those patients who received the ACLS recommended compression depth of 1.5–2 in. (38–50 mm) to fall into one category.[23]

The effects of pre-shock pause and compression depth on shock success were seen independently in both the in-hospital and the out-of-hospital setting (data not shown). However, in order to account for this possible confounder (as well as age, sex, and time to shock), a logistic regression model was used. The results are shown in Table 4. After adjusting for these factors, a 5 s decrease in pre-shock pause was associated with an 86% increase in the odds of shock success ($p = 0.02$) while a 5 mm increase in compression depth was associated with a 99% increase in the odds of shock success ($p = 0.03$).

While there was no statistically significant effect of either pre-shock pause or compression depth on ROSC or survival to hospital discharge, patients with first-shock success were more likely to achieve ROSC at some point during the resuscitation (55% versus 25%; $p = 0.04$) and trended toward a higher survival to hospital discharge rate (9% versus 0%, $p = 0.21$), as shown in Table 2.

Of the 60 patients, CPR quality could not be collected in 11 patients who received a shock without first receiving at least 30 s of monitored CPR. Seven

Table 4 Logistic regression of factors affecting first shock success ($n = 47$)

Factor	OR	95%CI	*p*-Value
Pre-shock pause (5 s decrease)	1.86	1.10–3.15	0.021
Compression depth (5 mm increase)	1.99	1.08–3.66	0.028
Out-of-hospital location	7.47	0.90–62.41	0.063
Male sex	1.10	0.17–7.12	0.919
Age (1 year increase)	1.01	0.96–1.07	0.616
Time to shock (1 min increase)	0.88	0.76–1.02	0.095

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of those 11 patients received no compressions prior to defibrillation and therefore a pre-shock pause could not be calculated. Additionally, two patients were excluded from compression depth analysis due to technical difficulties with the compression pad. Of the seven patients who did not have measurable pre-shock pauses, two had a perfusing rhythm within 20 s of the shock while the other five were shocked soon after pad placement. In the latter cases a pre-shock pause could be estimated to be at least as long as the pads were in place prior to defibrillation. We performed a revised analysis including these estimated values, and the results did not change significantly (data not shown).

Discussion

Using technology that measures multiple variables of CPR quality accurately, our international study group has gathered data that demonstrate a significant association between termination of VF and two variables that have received little formal evaluation during human cardiac arrest, pre-shock pause duration and compression depth. Specifically, we have shown that each 5 mm increase in compression depth and each 5 s decrease in pre-shock pause portend an approximate two-fold increase in the likelihood of shock success after adjusting for arrest location, age, sex and time to shock. Given that both pre-shock pause and compression depth affect blood flow during cardiac arrest, these new data provide additional insight into the importance of high-quality CPR during attempted resuscitation.

Our findings on the inverse relationship between the duration of pre-shock pause and shock success have not been reported previously in the clinical setting, although increasing pre-shock pause intervals have been correlated with decreased survival in several animal studies.[6–8] Additionally, Eftestøl et al. demonstrated that VF waveforms in human subjects deteriorated during pre-shock pauses, correlating with a predicted decrease in the likelihood of achieving ROSC.[24] Pre-shock pauses are especially relevant to the use of AEDs. Several studies have shown improved outcomes with the use of these devices in VF.[11–13] However, the required pre-shock pause needed for an AED to perform rhythm analysis is quite variable among different models.[8–10] For example, one study of seven popular AEDs demonstrated pre-shock pauses ranging from 5.2 to 28.4 s, with only one of the devices achieving an interval of less than 10 s.[9] In light of our findings, the duration of pre-shock pause mandated by AEDs on the market may have important consequences.

While compression rate has previously been shown to correlate with outcomes in humans,[19] compression depth has not. ACLS guidelines currently specify a target compression depth of 1.5–2 in. or 4–5 cm.[23] However, scant experimental data support this recommendation. In 1960, Kouwenhoven et al. described in detail what are now recognized as modern-day chest compressions and recommended a compression depth of 3–4 cm.[25] Subsequently, Babbs et al. demonstrated in a canine model that cardiac output increases linearly with chest compression depth between 2.5 and 6 cm.[5] To our knowledge, the current study represents the first objective evidence relating compression depth to clinical outcomes from defibrillation. The 100% shock success rate seen in the five patients who received a mean chest compression depth greater than 50 mm in the 30 s preceding defibrillation (Figure 3) raises interesting questions about the upper limit of appropriate depth. While the segments evaluated in the current study reflected only short periods of CPR, these five patients had comparable rates of ROSC and survival to hospital discharge compared to the group as a whole (data not shown). However, it is too few patients to draw any conclusions and future work should seek to improve the definition of the ideal chest compression depth in humans.

It is interesting to note that shallow chest compressions may be physiologically indistinguishable from a pause in CPR if the compressions are too shallow to generate a functional cardiac output. Thus, compressions preceding the pre-shock pause that are below a certain threshold (i.e., the 2.5 cm threshold noted by Babbs et al.[5]) are likely to have the same clinical effects as a longer pre-shock pause.

The first shock success rate of 73% in this study is lower than that reported in other studies of biphasic defibrillation.[21,26–28] However, those studies included only out-of-hospital cardiac arrests and our current investigation includes both in-hospital and out-of-hospital arrests. Our logistic regression analysis suggests that out-of-hospital location may be an independent predictor of shock success. This may be due to underlying differences in patient population or more specifically to the different resuscitation protocols between the two groups in our work, as the out-of-hospital group received 3 min of CPR prior to defibrillation. Since this protocol was unique to the out-of-hospital subgroup, it is not possible to separate the effects of the CPR prior to defibrillation from other differences between the two groups but other work has suggested a threshold value for duration of chest compressions to improve chances for successful defibrillation.[29]

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A key feature of our study was the use of new technology for objective recording of multiple CPR quality variables. This is important since few of the individual variables that comprise CPR have yet been subjected to rigorous evaluation. As CPR represents a complicated set of actions, particularly for lay rescuers, many important questions remain about what specific components to prioritize. Accurate data on the relationship between CPR quality variables and outcomes will be required to address these issues. Now that CPR-sensing technology is available, it will allow the evaluation of CPR quality as an independent and potentially confounding variable in future clinical studies of cardiac arrest. As this technology becomes more widespread and available on many devices, we believe that important insights are likely to be gained from actual human cardiac arrest data. These will include methods to optimize the practice of CPR itself as well as to evaluate drugs and devices that are unlikely to work if CPR is deficient.

There are several important limitations to our study. The primary limitation is that we do not have sufficient numbers of patients to demonstrate whether pre-shock pause and compression depth correlate with survival. While shock success has been a commonly reported outcome,[10,20,21] the termination of VF does not necessarily translate into survival to hospital discharge or neurological recovery. However, our data do show a significant correlation between first-shock success and ROSC, as well as a trend towards survival to discharge. And, although shock success is less definitive than survival, it remains a crucial outcome measure since the absence of shock success invariably portends death.

An additional limitation is that our study was not a randomized, controlled trial of pre-shock pauses or compression depth. However, such a trial would not be ethically feasible. Although it is not possible to prove that there were no systematic biases in compression depth and pre-shock pause (such as delivery of suboptimal CPR in a patient whose prognosis is deemed poor), we believe such bias to be unlikely since all the patients in this study had VF, a rhythm which often portends a better chance of resuscitation than other rhythms such as asystole. Additionally, our evaluation of only first shocks further reduces the risk of this bias, as only the first brief period of CPR was analyzed, before the resuscitation prognosis may have become evident to the resuscitation team.

Future studies of pre-shock pause and compression depth need to be performed with larger sample sizes to better define the relationship between these variables and survival. Additionally, methods to minimize pre-shock pause and optimize compression depth should be developed and investigated. Potential technological solutions that are being pursued already involve the use of mechanical compression devices that can provide consistent full-force compressions throughout shock delivery without fear of electrical injury to CPR providers[30–32] as well as software that can filter out compression artifact for analysis of underlying rhythm without a requirement for pauses in chest compressions.[33] Other possibilities include audio feedback during CPR[34] and stand-alone chest compression monitoring devices.[35]

Conclusions

Using objective measurements of CPR quality during actual cardiac arrest, we have found that longer pre-shock pauses and shallower chest compressions are correlated significantly with decreased shock success. The opportunity to improve the quality of CPR in clinical practice is now practically available and may significantly improve resuscitation success. Approaches to minimize (or eliminate) pre-shock pauses and optimize compression depth should be made and consideration should be given to the use of newer-generation AEDs with shorter (<10 s) analysis times.

Conflict of interest

The sponsor had no role in data collection, interpretation of results or drafting of the manuscript. One author at the study sponsor (Mr. Myklebust) was involved in study conception and design. Drs. Abella and Becker have received honoraria and research support from Philips Medical Systems (Andover, MA) and Laerdal Medical Corporation (Stavanger, Norway) while Drs. Steen, Wik and Kramer-Johansen have received research support from Laerdal Medical Corporation (Stavanger, Norway).

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resuscitation team at the University of Chicago. This work was supported by a grant from the Laerdal Medical Corporation (Stavanger, Norway).

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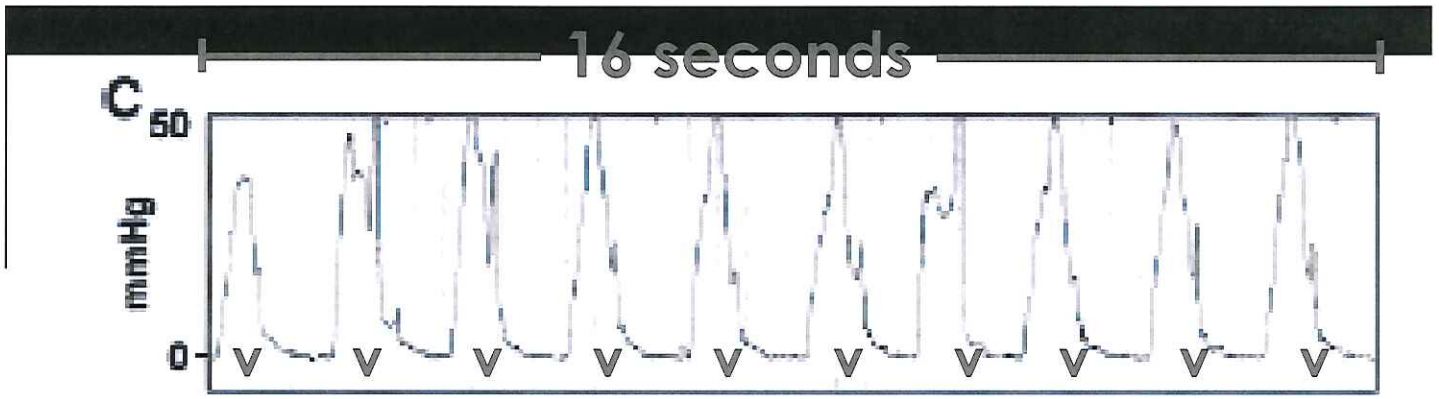
Patients can be hyperventilated to DEATH!



mean ventilation rate: 30 ± 3.2

first group: 37 ± 4 → after retraining: 22 ± 3

Aufderheide et al, 2004

Hyperventilation-Induced Hypotension During Cardiopulmonary Resuscitation

Tom P. Aufderheide, MD; Gardar Sigurdsson, MD; Ronald G. Pirrallo, MD, MHSA; Demetris Yannopoulos, MD; Scott McKnite, BA; Chris von Briesen, BA, EMT; Christopher W. Sparks, EMT; Craig J. Conrad, RN; Terry A. Provo, BA, EMT-P; Keith G. Lurie, MD

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

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

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

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

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

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

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

Methods

Clinical Observational Study

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

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

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

Results: Clinical Observational Study

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

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

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

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

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

Animal Studies

The porcine hemodynamic and survival studies were approved by the Committee of Animal Experimentation at the University of Minnesota. The animals received care in compliance with the 1996 Guide for the Care and Use of Laboratory Animals by the National Research Council. The animal preparation and surgical techniques have been previously described in detail.[3] Briefly, each animal received 10 mL (100 mg/mL) of intramuscular ketamine HCl for initial sedation, followed by intravenous propofol (2.3-mg/kg bolus and then a constant intravenous infusion of 165 μg/kg per minute). During the preparatory phase, animals were ventilated with room air by a positive-pressure ventilator (Harvard Apparatus Co). The rate and tidal volume were adjusted to maintain an arterial carbon dioxide ($Paco_2$) at 40 mm Hg and oxygen saturation >90%, based on analysis of arterial blood gases (IL Synthesis, Instrumentation Laboratory).

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

Resuscitation Protocols

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

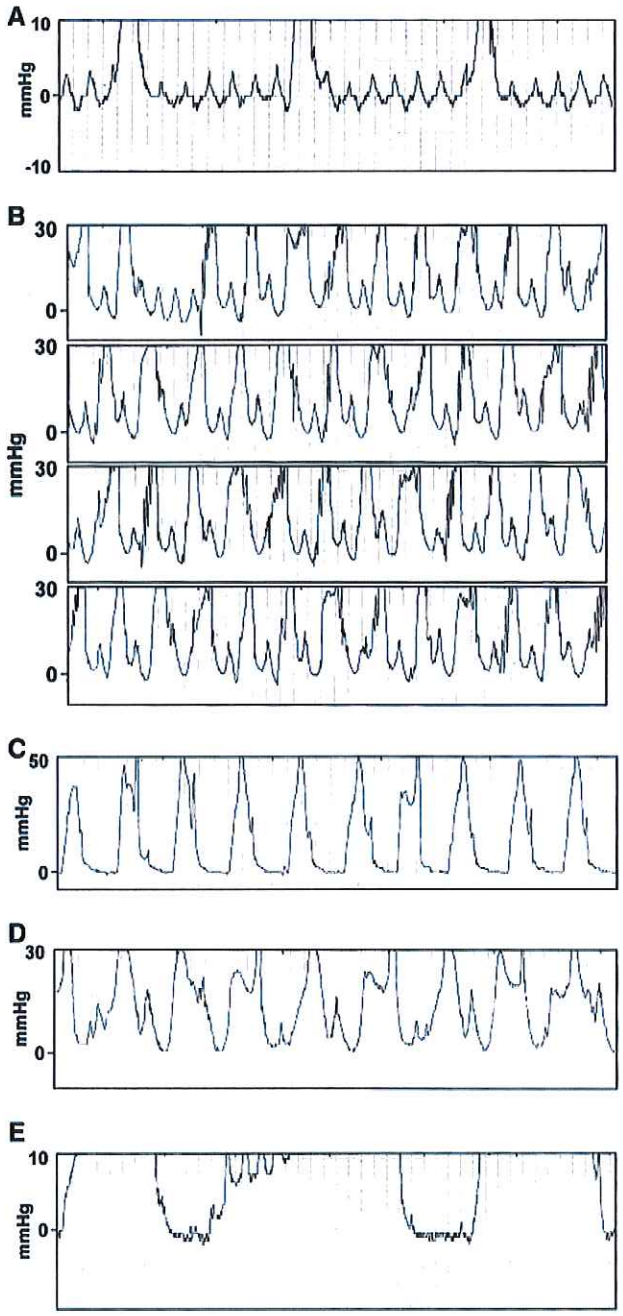

Figure 1. A, This 16-second intrathoracic pressure recording depicts CPR performed relatively close to AHA guidelines. Large-amplitude waves represent ventilations (11 breaths per minute). Small-amplitude waves represent chest compressions (90 compressions per minute). B, This 64-second intrathoracic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

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

Hemodynamic Protocol (Protocol I)

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

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

Survival Protocol (Protocol II)

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

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

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

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

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

Results

Animal Hemodynamic Studies

Increased ventilation rate was associated with significantly higher mean intrathoracic pressures ($P<0.0001$) and significantly lower coronary perfusion pressures ($P=0.03$) and significantly higher arterial pH, but no change in Pao_2 (Table 2). There was also an increase in right atrial diastolic pressure with increased ventilation rate (Figure 2). This was only significantly lower in the 12–breaths/min versus 30–breaths/min groups (3.5±1.1 versus 7.3±1.0 mm Hg, $P=0.02$). The

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

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

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

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

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

Animal Survival Studies

The survival rate in pigs ventilated at 12 breaths per minute (100% O_2) was 6 of 7 (86%), compared with a survival rate of 1 of 7 (17%) at a rate of 30 breaths per minute (100% O_2), and 1/7 (17%) at a ventilation rate of 30 breaths per minute (5% CO_2/95% O_2) ($P=0.006$) (Figure 3). Mean intrathoracic pressures were significantly higher with the higher ventilation rates ($P<0.0001$), and coronary perfusion pressures were lower (Table 3). Changes in arterial blood gases and $ETCO_2$ with hyperventilation are shown in Table 4. Pigs ventilated at 30 breaths per minute (100% O_2) had lower levels of $Paco_2$ (Table 4). Supplemental CO_2 resulted in correction of hypocapnia (Figure 3 and Table 4).

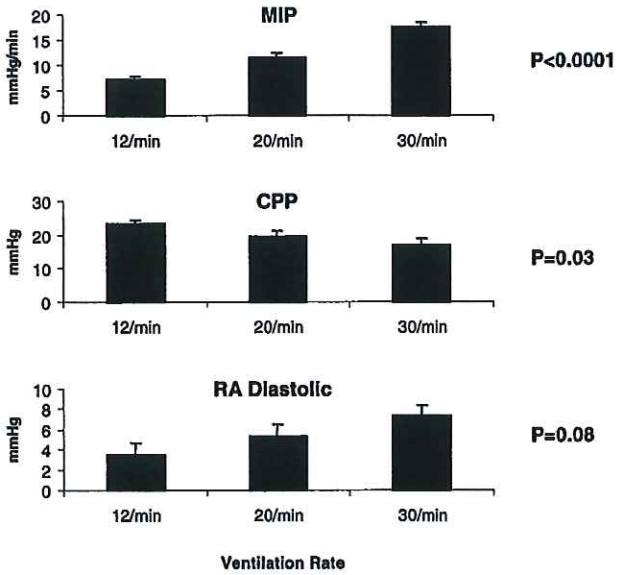

Figure 2. Hemodynamic Study (n=9). Changes in mean intrathoracic pressure (MIP), coronary perfusion pressure (CPP), and right atrial diastolic pressure (RA diastolic) with different ventilation rates during resuscitation in a porcine model of cardiac arrest. Probability value of <0.05 was considered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

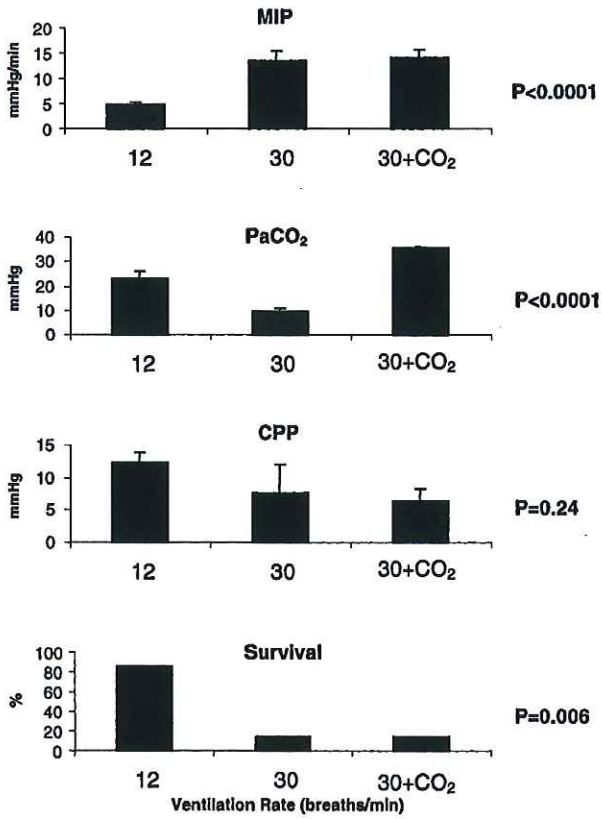

Figure 3. Survival Study (n=7 pigs per group). Changes in mean intrathoracic pressure (MIP), arterial CO_2 ($Paco_2$), coronary perfusion pressure (CPP), and survival rate, with hyperventilation and correction of hypocapnia (+CO_2). Probability value of <0.05 was considered statistically significant,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

Discussion

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

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

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

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

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

inspiratory impedance valve has been shown to significantly increase vital organ blood flow,[11] coronary perfusion pressure,[11] and survival.[3] Conversely, the physiological consequences of hyperventilation and of prolonged ventilation intervals result in a persistently positive intrathoracic pressure during the decompression phase of CPR, thereby decreasing cardiac preload[6] and cardiac output[7] and impeding right ventricular function.[8] Increased tidal volume is also known to adversely affect cardiac output.[9] In the present study, the mean intrathoracic pressure was significantly elevated in animals treated with higher ventilation rates. We speculate that the elevated mean intrathoracic pressures caused by excessive ventilation inhibited venous blood flow back to the right heart, as there was insufficient time to allow for the development of negative intrathoracic pressure between compressions. It is important to note that intrathoracic pressures never went below 0 mm Hg when ventilation rates were 30 per minute. The current results also support the contention that hypocapnia was not the cause of decreased coronary perfusion pressure and death in animals ventilated at 30 breaths per minute. When supplemental CO_2 at 5% was delivered to one group of pigs at a concentration identical to that found in expiratory gases to prevent hypocapnia without causing hypercarbia, the $Paco_2$ level did not fall below 35.4±0.6 mm Hg, and survival rates (1/7) were identical to pigs hyperventilated with 100% O_2.

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

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

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

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

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

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

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

Conclusions

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

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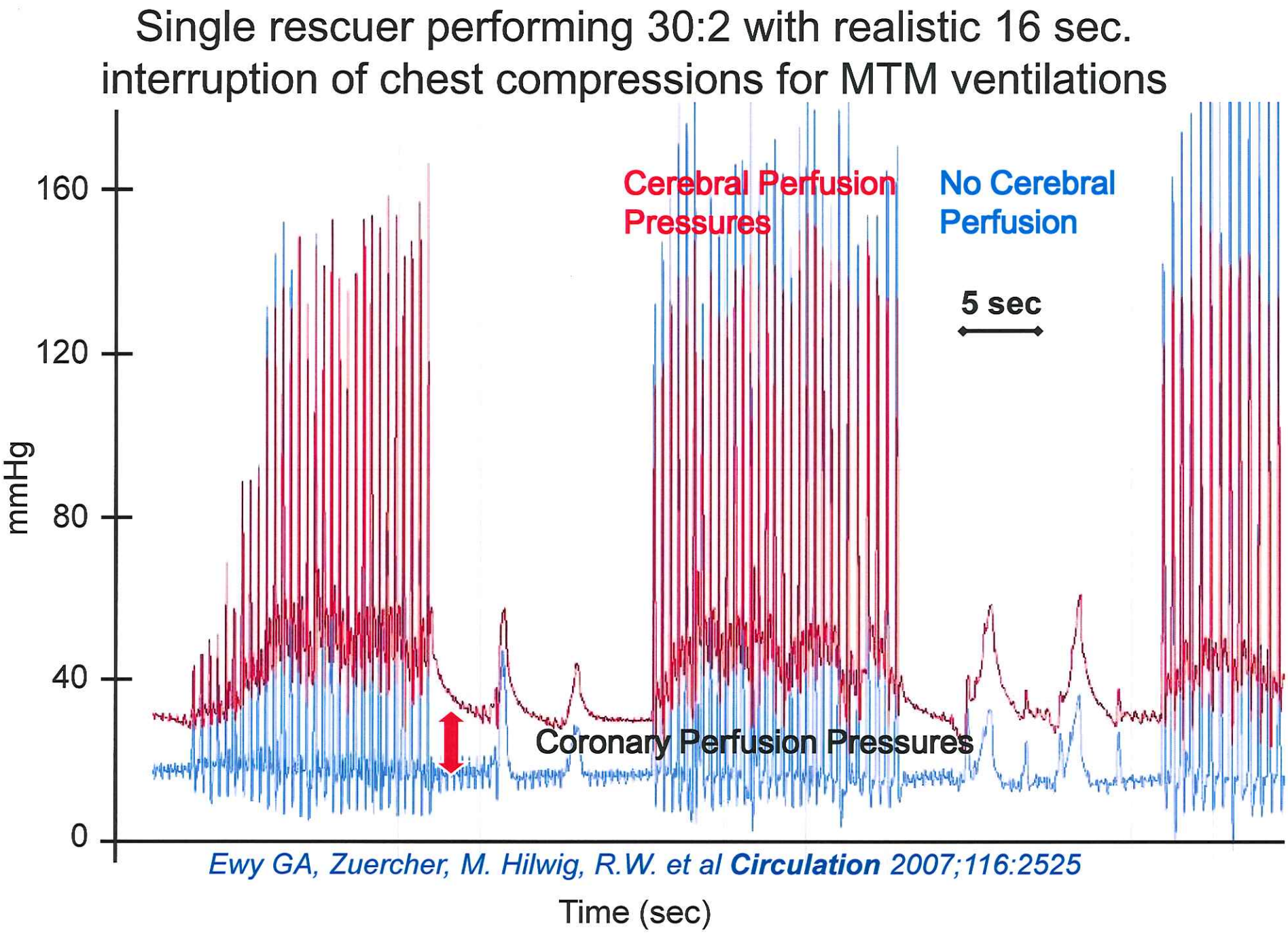
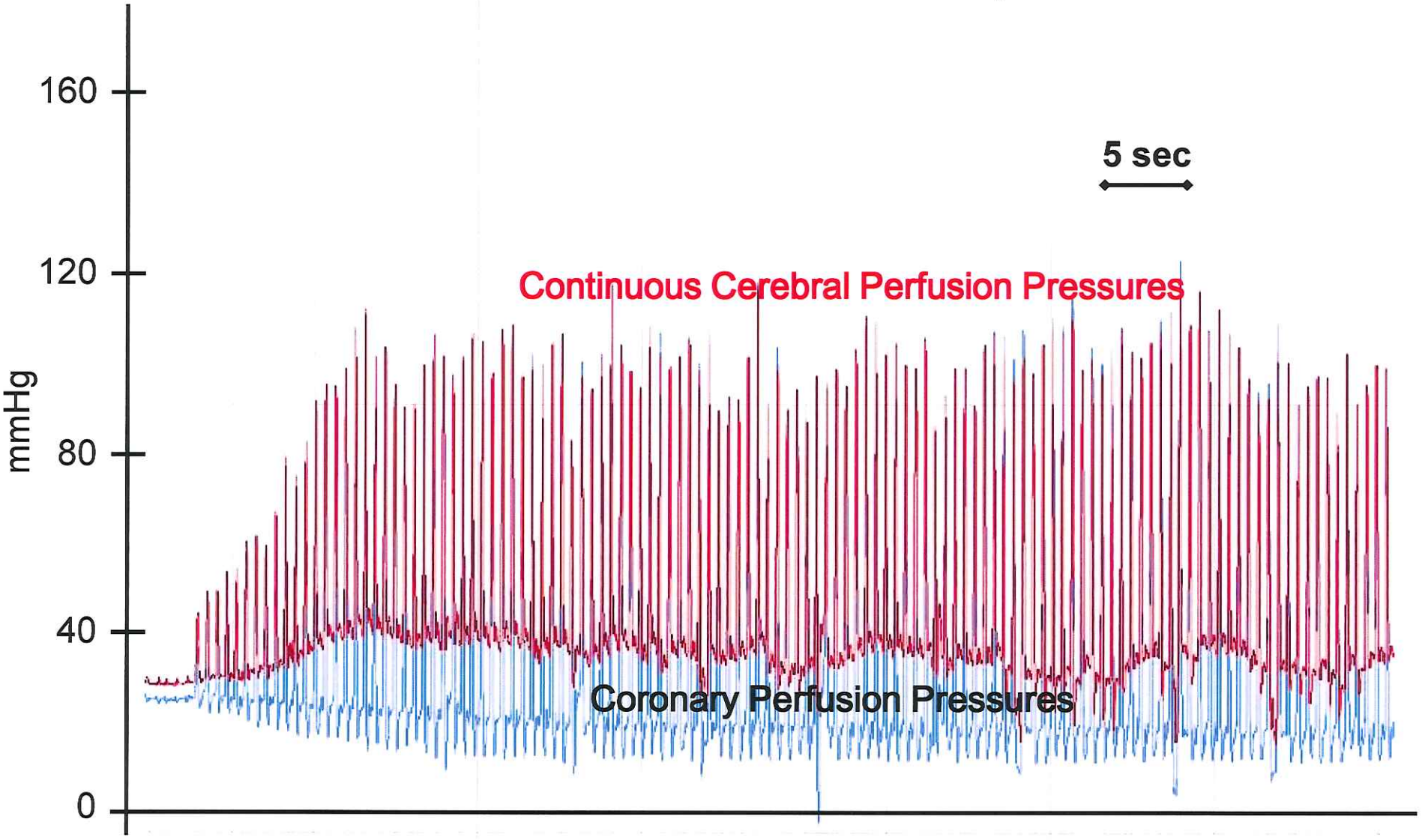

Single rescuer performing 30:2 with realistic 16 sec. interruption of chest compressions for MTM ventilations
160
120
80
40
0
mmHg
Cerebral Perfusion Pressures
No Cerebral Perfusion
5 sec
Coronary Perfusion Pressures
Ewy GA, Zuercher, M. Hilwig, R.W. et al Circulation 2007;116:2525
Time (sec)

Perfusion with continuous compressions



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Improved Neurological Outcome With Continuous Chest Compressions Compared With 30:2 Compressions-to-Ventilations Cardiopulmonary Resuscitation in a Realistic Swine Model of Out-of-Hospital Cardiac Arrest

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Background—The 2005 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care changed the previous ventilations-to-chest-compression algorithm for bystander cardiopulmonary resuscitation (CPR) from 2 ventilations before each 15 chest compressions (2:15 CPR) to 30 chest compressions before 2 ventilations (30:2 CPR). It was acknowledged in the guidelines that the change was based on a consensus rather than clear evidence. This study was designed to compare 24-hour neurologically normal survival between the initial applications of continuous chest compressions without assisted ventilations with 30:2 CPR in a swine model of witnessed out-of-hospital ventricular fibrillation cardiac arrest.

Methods and Results—Sixty-four animals underwent 12 minutes of ventricular fibrillation before defibrillation attempts. They were divided into 4 groups, each with increasing durations (3, 4, 5, and 6 minutes, respectively) of untreated ventricular fibrillation before the initiation of bystander resuscitation consisting of either continuous chest compression or 30:2 CPR. After the various untreated ventricular durations plus bystander resuscitation durations, all animals were given the first defibrillation attempt 12 minutes after the induction of ventricular fibrillation, followed by the 2005 guideline–recommended advanced cardiac life support. Neurologically normal survival at 24 hours after resuscitation was observed in 23 of 33 (70%) of the animals in the continuous chest compression groups but in only 13 of 31 (42%) of the 30:2 CPR groups ($P=0.025$).

Conclusions—In a realistic model of out-of-hospital ventricular fibrillation cardiac arrest, initial bystander administration of continuous chest compressions without assisted ventilations resulted in significantly better 24-hour postresuscitation neurologically normal survival than did the initial bystander administration of 2005 guideline–recommended 30:2 CPR. **(*Circulation*. 2007;116:2525-2530.)**

Key Words: resuscitation ■ cardiopulmonary resuscitation ■ heart arrest ■ ventricular fibrillation

The 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, hereafter referred to as the 2005 guidelines, changed the recommendations for single-rescuer cardiopulmonary resuscitation (CPR) from 2:15 ventilations-to-chest compressions (2:15 CPR) to 30:2 chest compressions-to-ventilations (30:2 CPR).[1] The rationale for these changes was to provide more chest compressions per minute.[1] It was stated that the new compression-to-ventilation ratio of 30:2 was selected on the basis of a consensus rather than clear evidence.[1]

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Clinical Perspective p 2530

In a realistic nonparalyzed swine model of prolonged ventricular fibrillation (VF) arrest, previous studies from our resuscitation research laboratory showed that continuous chest compression (CCC) without assisted ventilations was as effective as 2:15 CPR when the 2 ventilations interrupted chest compressions for only 4 seconds.[2–6] Although the previous guidelines recommended that each of the 2 breaths be delivered over a 2-second time interval,[7] manikin studies have demonstrated that lay individuals interrupt chest com-

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pressions for an average of 16 seconds to deliver the 2 breaths.[8] When realistic 16-second interruptions of chest compressions were applied to our swine model comparing the then-standard ventilation-to-compression ratio (2:15 CPR) with CCC, CCC resulted in significantly better neurologically normal survival.[9]

The purpose of the study reported here was to determine whether the 2005 guideline–recommended single-bystander 30:2 CPR results in equivalent or different 24-hour postresuscitation normal neurological function compared with CCC in a swine model of out-of-hospital VF cardiac arrest when realistic 16-second interruptions of chest compressions were used to provide the 2 breaths.

Methods

Outcomes

The primary outcome was 24-hour survival with normal neurological function. Secondary end points included return of spontaneous circulation (ROSC), the presence of a perfusing rhythm after the first defibrillation shock, and overall 24-hour survival. The purpose of studying progressively longer intervals before the initiation of resuscitation efforts was to determine whether the duration of untreated VF had an influence on the need for ventilation during basic cardiac life support.

Experimental Preparation and Design

This study was conducted with the approval of the University of Arizona Institutional Animal Care and Use Committee in accordance with the guidelines set forth in the *Position of the American Heart Association on Research Animal Use*. Sixty-four domestic swine of either sex weighing 28±4 kg were anesthetized with 5% isoflurane inhalation anesthetic in oxygen administered by nose cone. An endotracheal tube was placed per os, and anesthesia was maintained using 1.5% to 3% isoflurane in room air until induction of VF. The ventral neck area was prepared in standard fashion for sterile cutdown procedures to place vascular introducer sheaths (5F to 7F, Cordis Corp, Miami, Fla) into selected vessels. ECG leads were placed on the limbs to continuously monitor heart rate and rhythm. An infrared capnometer (47210A, Hewlett Packard Co, Palo Alto, Calif) and a pneumotachometer (MP45–871, Validyne Engineering Corp, Northridge, Calif) were placed in the airway to measure the end-tidal partial pressure of carbon dioxide (P_{ETCO_2}) and tidal volume, respectively. Ventilation was provided by a rate- and volume-regulated ventilator/anesthesia machine (Narkomed 2A, North American Drager, Telford, Pa). The initial ventilation rate was 12 rpm, and tidal volume was 15 mL/kg. Rate and/or volume were altered to maintain P_{ETCO_2} at 40±3 mm Hg. Solid-state pressure transducers (MPC-500, Millar Instruments, Houston, Tex) were placed, one via a common carotid artery sheath into the descending aorta to measure its pressure, and the other via an external jugular vein into the right atrium to measure its pressure. The animals were placed in a dorsal recumbent position in a V tray, and adhesive defibrillator pads (Quik-Combo, Medtronic, PhysioControl, Redmond, Wash) were adhered to the chest.

Data Acquisition

Data, consisting of aortic pressure, right atrial pressure, tidal volume, ECG, and Peak end-tidal CO_2 (P_{ETCO_2}), were continuously displayed on a physiological recorder (Gould Ponemah Physiology Platform, model P3 Plus, LDS Life Science, Valley View, Ohio) and stored on a laptop computer for later analyses. Coronary perfusion pressure during CPR and CCC administration was calculated as the difference between aortic pressure and right atrial pressure in the midrelaxation phase of chest compressions. All animals had normal sinus rhythm, arterial blood gases, oxygen saturations, and blood pressures before induction of VF.

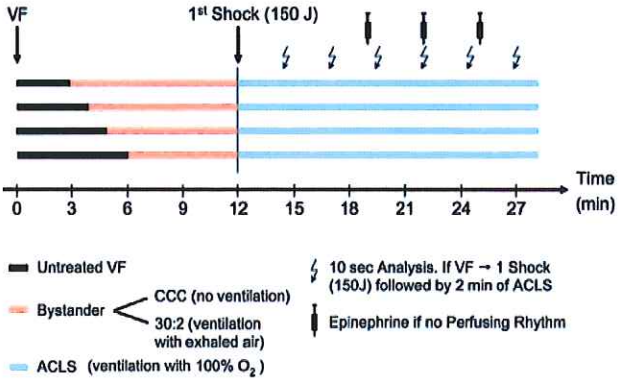

Figure 1. Experimental protocol timeline. The initial biphasic defibrillator shock of 150 J was given after 12 minutes of VF. The crooked arrows indicate the onset of a 10-second pause in chest compressions for rhythm analysis and a single 150-J shock if indicated. The syringe indicates the administration of epinephrine if a perfusing rhythm was not present. Black bars indicate the duration of untreated VF; hatched red bars, CCC or 30:2 CPR bystander resuscitation; light blue bars, ACLS according to the 2005 guidelines.

Baseline data were collected; then, VF was induced with a pacing electrode temporarily placed in the right ventricle. The presence of VF was confirmed by the characteristic ECG waveform and the precipitous fall in aortic pressure. Assisted ventilation was discontinued, and the animals underwent a period of untreated VF to simulate the time it might take a bystander to recognize the problem, try to arouse the victim, perhaps call for help, phone the emergency medical service, and begin resuscitation efforts.

Experimental Protocol

The animals were assigned to 1 of 4 experimental groups relative to the time before simulated bystander resuscitation was begun randomly with either CCC without assisted ventilations or 30:2 CPR. Groups 1 through 4 sustained untreated VF for periods of 3, 4, 5, and 6 minutes, respectively, before initiation of the resuscitation protocols (Figure 1). Within each group, the animals were randomly assigned to receive either CCC without assisted ventilations or 30:2 CPR using exhaled gas for 2 equally spaced mouth-to-endotracheal tube ventilations of 2 seconds each during the 16-second interruption of chest compressions. All chest compressions were administered manually at a metronome-directed rate of 100 per minute. Care was taken to ensure that the hands of the rescuer were completely elevated from the chest during the relaxation phase of compressions to allow recoil of the chest. These resuscitation efforts continued until simulated emergency medical services arrival at 12 minutes after arrest. A single biphasic defibrillation shock of 150 J was delivered at this time (LifePak 12, Medtronic Emergency Response Systems, Redmond, Wash), and advanced cardiac life support (ACLS) per the 2005 guidelines was begun immediately after the shock with no pause for automated external defibrillator rhythm analysis.[1] Ventilations with 100% oxygen were delivered manually by Ambu bag. After each 2 minutes of standard CPR, a 10-second pause was interjected to simulate automated external defibrillator rhythm analysis. If after the defibrillation shock a perfusing rhythm (peak aortic systolic pressure >50 mm Hg) was achieved, the animals were connected to the mechanical ventilator and given 100% oxygen at an initial rate of 12 breaths per minute and a tidal volume of 15 mL/kg. Rate and/or tidal volumes were subsequently adjusted as needed to return P_{ETCO_2} to normal values. Isoflurane was added if and when the animals began to stir. No further chest compressions were administered unless the animals had recurrent VF.

ROSC was defined as a peak aortic pressure of >50 mm Hg and pulse pressures of >20 mm Hg sustained for 1 minute. If either VF or pulseless electrical activity was present after the defibrillation shock, an additional 2 minutes of ACLS was given before the next

Table 1. Baseline Data

	CCC	30:2 CPR	*P*
n	33	31	
Gender, F/M	19/14	10/21	0.042
Weights, kg	27±3	28±4	0.159
Heart rate, bpm	101±24	106±18	0.714
Mean systolic BP, mm Hg	80±16	81±14	0.607
Diastolic BP, mm Hg	54±12	55±10	0.430
Cardiac output, L/min	2.5±0.4	2.6±0.7	0.304
Arterial Po_2, mm Hg	75±12	78±22	0.920
Arterial saturation, %	40±2	39±2	0.463
Arterial Pco_2, mm Hg	92±2	92±4	0.651

BP indicates blood pressure.

10-second pause to simulate automated external defibrillator rhythm analysis. This procedure was continued until a perfusing rhythm was attained or until 19 minutes after arrest, when epinephrine (0.02 mg/kg IV) was given. If required, epinephrine administration was repeated at 3-minute intervals, and ACLS was continued as previously until successful ROSC or 3 doses of epinephrine were administered. If VF or pulseless electrical activity was still present at 28 minutes after arrest (3 minutes after the last epinephrine dose), resuscitation efforts were discontinued.

Animals that had a positive ROSC were reconnected to the ventilator/anesthesia machine and underwent a 1-hour intensive care period during which they were given intravenous fluids to restore third-space fluid losses. With the exception of 1 jugular vein sheath that was used for fluid administration, all other vascular sheaths were removed. The animals were allowed to recover from anesthesia, placed in observation cages, and monitored over the ensuing hours until 24 hours after resuscitation, when a neurological examination was performed as previously described.[3,5,10] Briefly, a score of 1 is normal, 2 is abnormal (eg, not eating or drinking normally, unsteady gait, or slight resistance to restraint), 3 is severely abnormal (the animal is recumbent, unable to stand, and only partially responsive to stimuli), 4 is comatose, and 5 is dead. After the neurological examination, the animals were humanely euthanized by intravenous injection of a commercial euthanasia solution (Fatal+, Vortech Pharmaceuticals, Dearborn, Mich).

Data Analysis

The data were transported into SPSS 15.0 for Windows for statistical analysis (SPSS, Inc, Chicago, Ill). Continuous variables are presented as mean±SD and were analyzed by Student's *t* test or the Mann–Whitney *U* test for nonnormal distribution. The primary and secondary outcomes in different groups were compared with the χ^2 test or Fisher's exact test. A logistic regression analysis was used to determine the odds of 24-hour postresuscitation normal neurological function in the CCC group compared with the 30:2 CPR group with adjustment for differences in the time lags.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The 2 major groups were comparable at baseline (Table 1). Because of a randomization error, 33 swine were in the CCC groups and 31 swine in the 30:2 CPR groups. The number of neurologically normal survivors 24 hours after resuscitation was significantly greater in the CCC groups (23 of 33, 70%) compared with the 30:2 CPR groups (13 of 31, 42%; $P=0.025$; Table 2 and Figure 2). With longer duration of untreated VF before the initiation of resuscitation efforts, fewer animals survived with good neurological outcomes, and more animals had significant neurological deficits (Figure 2). In the combined 4, 5, and 6 minutes of untreated VF groups, 16 of 17 in the CCC groups and 6 of 11 in the 30:2 CPR groups survived with normal neurological function ($P=0.022$, Fisher exact test). In the combined 5 and 6 minutes of untreated VF groups, 10 of 10 in the CCC groups but only 4 of 9 in the 30:2 CPR groups survived with normal neurological function ($P=0.011$, Fisher exact test). The odds of neurologically normal 24-hour postresuscitation survival was significantly greater for the CCC groups (odds ratio, 3.7; 95% confidence interval, 1.2 to 11.3) compared with the 30:2 CPR groups with adjustment for differences in the time lag. The odds ratios for ROSC and 24-hour survival were not significant between the 2 groups.

Table 2. Outcomes

	CCC	30:2 CPR	*P*
n	33	31	
Normal 24-h neurological score	23/33	13/31	0.025
24-h Survival	24/33	18/31	0.217
ROSC	26/33	19/31	0.126
Perfusing rhythm after first shock	21/33	9/31	0.006

A significant difference was found between the 2 resuscitation techniques relative to the cardiac rhythm following the first defibrillation shock. A perfusing rhythm followed the first defibrillation in 21 of 33 animals (64%) in the CCC groups and in 9 of 31 animals (29%) in the 30:2 CPR groups ($P=0.006$; Table 2). This outcome contributed to a significant difference between groups in the greater need for epinephrine administration during ACLS resuscitation efforts (12 of 33 in the CCC groups versus 20 of 31 in the 30:2 CPR groups; $P=0.024$; Table 3).

The hemodynamic data during resuscitation are shown in Table 3. The mean integrated coronary perfusion pressure during basic life support was 20±10 mm Hg with CCC and 14±10 mm Hg with 30:2 CPR ($P=0.028$). The mean integrated coronary perfusion pressure in the 24-hour survivors with normal neurological function was 23±8 mm Hg but only 10±7 mm Hg in animals with severe neurological deficits ($P=0.001$). There was no difference in the mean integrated coronary perfusion pressure between the survivors with severe neurological deficits and nonsurvivors. The mean number of chest compressions delivered during the bystander resuscitation period was 746±112 in the CCC groups and 385±63 in the 30:2 CPR groups ($P=0.001$; Table 3). The mean arterial blood oxygen saturation after 12 minutes of VF, just before the first defibrillation shock, was 79±29% for the CCC group versus 88±7% for the 2:30 CPR group ($P=0.288$; Table 3). No significant differences existed in arterial Po_2 or Pco_2 between groups at the completion of the bystander resuscitation period (eg, after 12 minutes of VF) (Table 3).

Discussion

This is the first reported study comparing CCC without assisted ventilations with the 2005 American Heart Associa-

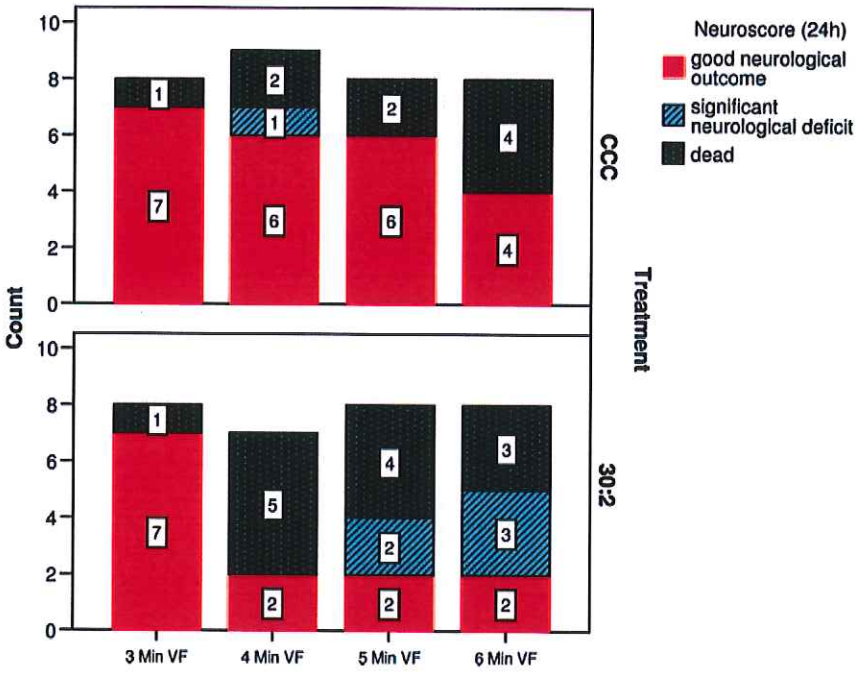

Figure 2. Outcomes of all 64 animals in the experiments. Top, Outcomes of the animals receiving CCC without assisted ventilations. Bottom, Outcomes of the animals given 30:2 CPR. The individual columns represent durations in minutes of untreated VF. Red bars indicate normal neurological outcomes at 24 hours; hatched blue bars, 24-hour survival with significant neurological deficits; and dotted black bars, animals that did not survive.

tion guideline recommendations for basic cardiac life support of 30 chest compression before each 2 ventilations during simulated single-bystander resuscitation for out-of-hospital VF arrest. When all untreated VF times were combined, there was a significant difference favoring CCC over 30:2 CPR for 24-hour neurologically normal survival (23 of 33 [70%] versus 13 of 31 [42%]; $P=0.025$). When the duration of untreated VF exceeded 3 minutes before the initiation of simulated bystander resuscitation, 16 of 17 of the surviving animals in the CCC groups were neurologically normal at 24 hours after resuscitation compared with 6 of 11 in the 30:2 CPR groups ($P=0.022$; Figure 2).

It has been shown in experimental models that a major determinant of survival after cardiac arrest is coronary perfusion pressure (ie, the difference between the aortic and right atrial pressures during the release phase of chest compression).[11] Uninterrupted chest compressions produced higher integrated coronary perfusions pressures relative to the 30:2 CPR groups because of the required pauses in compressions in the latter group to provide breaths (Table 3). Furthermore, CCC generated more consistent arterial systolic pressures, which provided cerebral perfusion and presumably contributed to the better neurologically normal survival in this group (Figure 3).

Table 3. Intraresuscitation Parameters

	CCC	30:2 CPR	*P*
n	33	31	...
Epinephrine administration,	12/33	20/31	0.045
Chest compressions delivered, n	746±112	385±63	0.0001
Mean CPP, mm Hg	20±10	14±10	0.028
Mean aortic "systolic" pressures, mm Hg	95±31	93±40	0.368
Mean aortic "diastolic" pressures, mm Hg	29±11	24±11	0.0001
Mean RA "systolic" pressures, mm Hg	89±44	90±36	0.323
Mean RA "diastolic" pressures, mm Hg	11±5	11±4	0.064
Mean arterial Po_2 at 12 min of VF, mm Hg	59±24	60±13	0.829
Mean arterial Pco_2 at 12 min of VF, mm Hg	32±18	34±11	0.477
Mean arterial So_2 at 12 min VF, %	79±29	88±7	0.384

CPP indicates coronary perfusion pressure; RA, right atrial.

Typically, out-of-hospital resuscitation efforts are delayed for some time after collapse. The present study suggests that perfusion should take precedence over ventilations for postresuscitation neurologically normal survival when resuscitation efforts are not initiated within 4 minutes after collapse. Although ventilation might become essential during the treatment of very prolonged VF, this study indicates that assisted ventilations apparently are not necessary during the first 12 minutes of VF even if initiation of bystander resuscitation is delayed for as long as 6 minutes after the onset of VF.

The change in the 2005 guidelines from 2:15 CPR to 30:2 CPR was based in part on the fact that the revised ratio would produce more chest compressions per unit of time and theoretically would improve perfusion.[1] The increased number of chest compressions delivered using 30:2 CPR has been validated.[12] However, that experimental study comparing 2:15 CPR with 30:2 CPR did not evaluate 24-hour survival or neurological outcome.[12] A before-and-after clinical study among municipal firefighters who originally used 15:2 CPR and then were retrained to perform 30:2 CPR was reported from Pittsburgh.[13] No differences in any outcome measures were found.[13]

Our study has several potential limitations. The conclusions of the study may not apply to bystander CPR performed by 2 rescuers when the interruptions for chest compressions

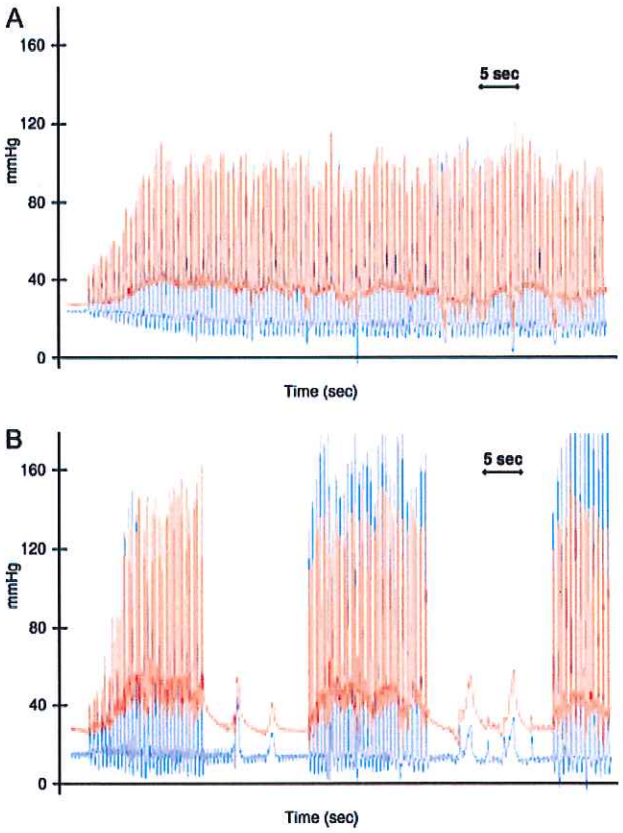

Figure 3. A, Initiation of CCC during VF. B, Initiation of 30:2 CPR during VF. Aortic pressure is in red; right atrial pressure is in blue.

to deliver the 2 recommended ventilations after each 30 compressions would not be as long.

The nature of this study precluded the investigators from being blinded to the procedures. To ensure that bias did not influence the depth or force of manual chest compressions, the mean arterial systolic blood pressures were measured during the last 10 seconds of the first 4 compressions cycles during 30:2 CPR and compared with analogous time frames during CCC. Table 3 shows that these means were not different. This study was done in young healthy swine with compliant chests and without discernible coronary artery disease. The neurological examinations were conducted by experienced study personnel, including a veterinarian with substantial experience evaluating swine neurological status. Observer bias was minimized by the clearly defined and easily assessed swine cerebral performance categories.

Another potential limitation is that this study was done with an endotracheal tube in place. In previous animal studies, we have demonstrated substantial passive gas exchange during chest compressions even when the endotracheal tube was removed before the provision of chest compressions.[4,5,10] We also have shown that animals were effectively resuscitated by chest compressions alone with clamped endotracheal tubes.[6] Moreover, many adults have gasping breaths before and during resuscitation efforts.[14] Finally, humans without endotracheal tubes can have better outcomes after bystander chest compressions alone compared with chest compressions with rescue breathing.[15]

For a variety of reasons, the question of the relevance of swine studies to human resuscitation is always an issue. However, our previous finding[9] of improved survival in swine with CCC versus 2:15 CPR has recently been confirmed by an observational study in humans (Cardiopulmonary Resuscitation by Bystanders With Chest Compression Only [SOS-KANTO]).[15,16]

Conclusions

In a realistic swine model of single-bystander out-of-hospital VF cardiac arrest in which defibrillation was first attempted at 12 minutes of the arrest, CCC resulted in more 24-hour neurologically normal survivors than did the 2005 guideline–recommended 30:2 CPR.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In the absence of early defibrillation, prompt initiation of resuscitation by bystanders is a major determinant of neurologically intact survival after out-of-hospital sudden cardiac arrest. Unfortunately, some bystanders do not initiate resuscitation because of an aversion to mouth-to-mouth ventilation. This study assessed neurological outcomes in a porcine model of cardiac arrest treated with continuous chest compressions without interruption for ventilation compared with chest compressions interrupted for ventilation. Neurological outcomes were better with chest compressions only. Although this study was conducted in a nonparalyzed swine model, recent human observations support the applicability of this model to humans with important implications. In contrast to secondary cardiac arrest resulting from severe hypoxia, "rescue breathing" may be unnecessary in patients with primary cardiac arrest. During chest compressions, perfusion is marginal, so that stopping compressions even briefly for ventilation (except for prompt defibrillation) is potentially harmful. Furthermore, positive pressure ventilation decreases venous return to the chest and subsequently perfusion of the heart and the brain. The findings of this study support continuous chest compressions as a new bystander approach to saving patients with cardiac arrest.

CPR before defibrillation may increase survival (when CA not witnessed by EMS)

Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation

24% (155/639) 30% (142/478) *p=0.04*

Defib first	CPR (90 sec) first, then defib
42 months	**36 months**

Cobb et al, 1999

Meier et al. BMC Medicine 2010, 8:52
http://www.biomedcentral.com/1741-7015/8/52

BMC Medicine

RESEARCH ARTICLE Open Access

Chest compressions before defibrillation for out-of-hospital cardiac arrest: A meta-analysis of randomized controlled clinical trials

Pascal Meier[1,2*], Paul Baker[3], Daniel Jost[4], Ian Jacobs[5], Bettina Henzi[6], Guido Knapp[7], Comilla Sasson[8]

Abstract

Background: Current 2005 guidelines for advanced cardiac life support strongly recommend immediate defibrillation for out-of-hospital cardiac arrest. However, findings from experimental and clinical studies have indicated a potential advantage of pretreatment with chest compression-only cardiopulmonary resuscitation (CPR) prior to defibrillation in improving outcomes. The aim of this meta-analysis is to evaluate the beneficial effect of chest compression-first versus defibrillation-first on survival in patients with out-of-hospital cardiac arrest.

Methods: Main outcome measures were survival to hospital discharge (primary endpoint), return of spontaneous circulation (ROSC), neurologic outcome and long-term survival.
Randomized, controlled clinical trials that were published between January 1, 1950, and June 19, 2010, were identified by a computerized search using SCOPUS, MEDLINE, BIOS, EMBASE, the Cochrane Central Register of Controlled Trials, International Pharmaceutical Abstracts database, and Web of Science and supplemented by conference proceedings. Random effects models were used to calculate pooled odds ratios (ORs). A subgroup analysis was conducted to explore the effects of response interval greater than 5 min on outcomes.

Results: A total of four trials enrolling 1503 subjects were integrated into this analysis. No difference was found between chest compression-first versus defibrillation-first in the rate of return of spontaneous circulation (OR 1.01 [0.82-1.26]; $P = 0.979$), survival to hospital discharge (OR 1.10 [0.70-1.70]; $P = 0.686$) or favorable neurologic outcomes (OR 1.02 [0.31-3.38]; $P = 0.979$). For 1-year survival, however, the OR point estimates favored chest compression first (OR 1.38 [0.95-2.02]; $P = 0.092$) but the 95% CI crossed 1.0, suggesting insufficient estimate precision. Similarly, for cases with prolonged response times (> 5 min) point estimates pointed toward superiority of chest compression first (OR 1.45 [0.66-3.20]; $P = 0.353$), but the 95% CI again crossed 1.0.

Conclusions: Current evidence does not support the notion that chest compression first prior to defibrillation improves the outcome of patients in out-of-hospital cardiac arrest. It appears that both treatments are equivalent. However, subgroup analyses indicate that chest compression first may be beneficial for cardiac arrests with a prolonged response time.

Background

There are an estimated 294,851 emergency medical services (EMS)-assessed out-of-hospital cardiac arrests (OHCA) in the United States each year [1,2]. The most common underlying arrhythmias of witnessed arrests are ventricular tachycardia and ventricular fibrillation [3]. Despite major attempts to improve the chain of survival, survival rates for OHCA remain the same at 7.6% for over 30 years [4]. Average rates of survival to hospital discharge are as low as 0.3% in some communities [5,6] and depend strongly not only on the time to initiation of chest compressions but also on the time until defibrillation and the underlying rhythm [3]. While the first two factors can be influenced, they cannot be performed simultaneously. Controversy about priority has resulted from experimental and clinical data.

Current guidelines of the European Resuscitation Council (ERC) and the American Heart Association

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(AHA) were last updated in 2005 and emphasize the importance of early defibrillation. The International Liaison Committee on Resuscitation (ILCOR), ERC and AHA clearly prioritize early defibrillation [7,8]. However, the AHA guidelines state that in cases of nonwitnessed events, one cycle of cardiopulmonary resuscitation (CPR)/chest compressions may be considered before defibrillation (class IIb recommendation) [7]. The interval from compression to defibrillation is highly critical as impaired myocardial oxygenation distinctively decreases defibrillation success rates while myocardial preoxygenation may improve outcome [9,10].

There is, however, clinical equipoise whether professional chest compression only promptly followed by defibrillation could increase myocardial "readiness" for defibrillation. Data from the first randomized clinical trials (RCT) have shown conflicting results, but most studies were limited in size and underpowered to allow definite conclusions. A recent large-scale observational study indicated potential benefit for preshock chest compressions [11].

This is the first meta-analysis to systematically review the current research on chest compression first as compared to defibrillation first on outcomes in patients with OHCA.

Methods

The study was performed according to PRISMA guidelines (Additional file 1) [12]. Planning and study design were done by two authors (CS, PM), including creation of an electronic database with variables of interest (Microsoft Excel). Primary and secondary endpoints, variables of interest and search strategy (databases, sources for unpublished data) were defined in a strategy outline which can be obtained from study authors on request.

Data Sources and Searches

A search was conducted of SCOPUS, MEDLINE (via PubMed), BIOS, EMBASE, the Cochrane Central Register of Controlled Trials, International Pharmaceutical Abstracts database, and Web of Science from January 1, 1950, to June 19, 2010, supplemented by the conference proceedings of the American Heart Association (2006-2009), the American College of Cardiology (2006-2010), the European Society of Cardiology (2001-2009), the symposium on Transcatheter Cardiovascular Therapeutics (2006-2009), the World Congress of Cardiology (2006-2009) and the European Resuscitation Council Scientific Symposium (2006-2009). We also considered published review articles, editorials, and Internet-based sources of information (http://www.tctmd.com, http://www.theheart.org, http://www.europcronline.com, http://www.cardiosource.com, http://www.crtonline.com and Google scholar). For details on search strategy for MEDLINE, see Additional file 2. Similar but adapted search terms were used for the other literature databases.

Study selection

In a two-step selection process, two investigators (PM, BH) independently reviewed the titles and abstracts of all citations to identify potentially relevant studies and to exclude duplicates. The corresponding publications were reviewed in full text by three investigators (CS, PM, BH) to assess whether studies met the following inclusion criteria: 1) randomized treatment assignment to chest compression first versus defibrillation first, 2) human study and 3) included outcome data on one of the four following clinical outcomes: return of spontaneous circulation, survival to hospital discharge, neurological outcome at discharge or survival at 1 year (Figure 1). Reviewers were not blinded to study authors or outcomes. Final inclusion of studies was based on the agreement of three investigators (CS, PM, BH).

Data extraction and quality assessment

Relevant information from the articles, including baseline clinical characteristics of the study population and outcome measures, were extracted by two reviewers (PM, BH) using the prepared standardized extraction database (MS Excel); data on outcome (see endpoint definition below), total patient numbers per group, and covariables of interest (average age, gender, witnessed arrest, bystander CPR, response time upon arrival of emergency medical service EMS as defined by each study) were extracted. The quality of each trial was assessed using the Jadad scale to ensure sufficient quality but was not implemented in the analysis due to relevant limitations of such approaches [13,14]. Absolute numbers were recalculated when percentages were reported. All corresponding authors of included trials were contacted to ensure accuracy of the data extraction and in an attempt to obtain more information and individual patient level data.

Endpoints

The primary endpoint of this analysis was survival to hospital discharge. However, the endpoints are presented in a chronologic order as follows:

1. Return of spontaneous circulation (ROSC)
2. Survival to hospital discharge
3. Favorable neurologic outcome at discharge (cerebral performance category (CPC) score 1 or 2)
4. Long-term outcome (survival at 1 year)

"Favorable neurological outcome" was defined as a CPC score of 1 or 2 (no or moderate cerebral disability).

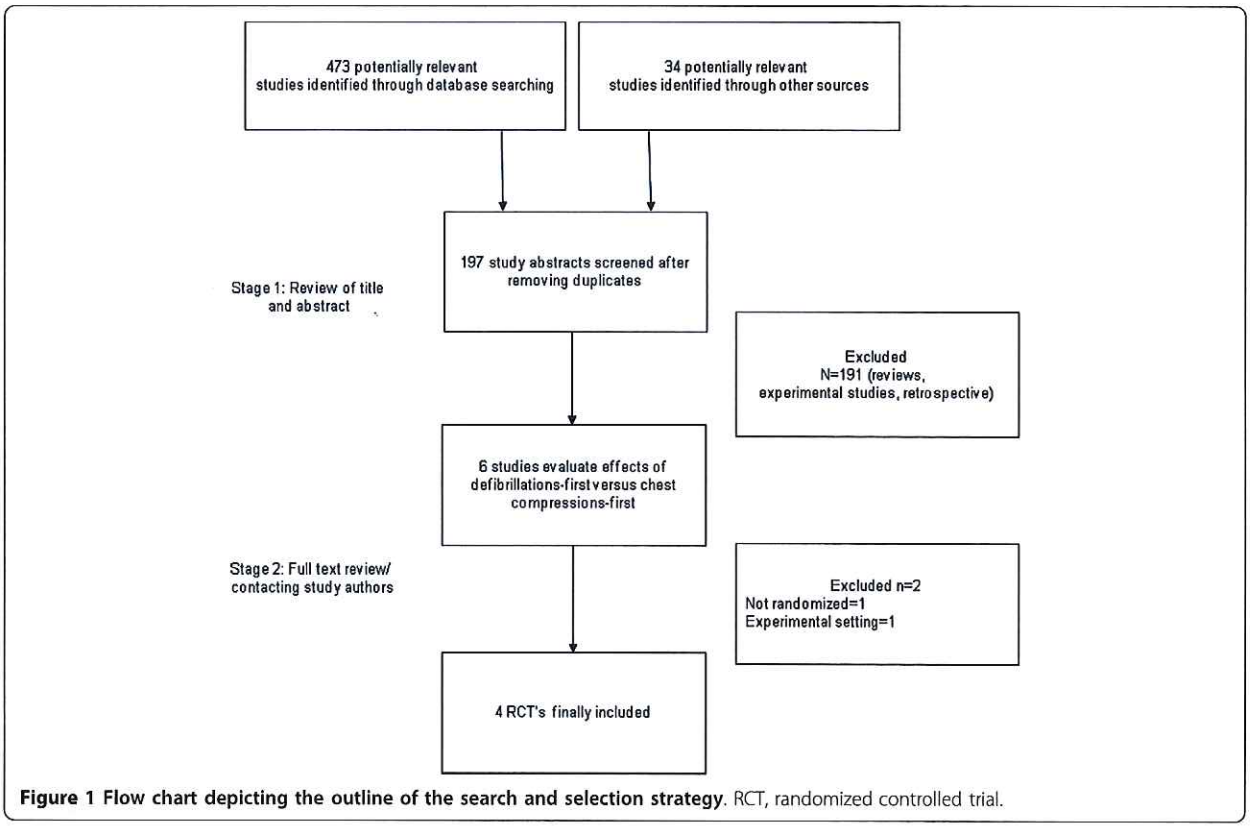

Figure 1 Flow chart depicting the outline of the search and selection strategy. RCT, randomized controlled trial.

Definition of a "clinically relevant" change for the primary endpoint

We regarded a relative change of at least 20-25% as clinically relevant. Power analyses of prospective randomized trials evaluating interventions for OHCA (predefibrillation chest compression, therapeutic hypothermia) used variable definitions for "clinically relevant" differences in survival, ranging from 32-550% [15-19]. Therapeutic hypothermia as one of few measures with proven benefits in OHCA showed a 35% increase in survival in a recent meta-analysis of randomized trials [20]. Since survival is such an essential endpoint, we regard a relative change of at least 20-25% as already clinically relevant, while on the other hand, a lower threshold would not be very meaningful in the context of the general low survival to discharge rate for OHCA (average 7.6%) [4]. This would increase the risk to detect incidental differences.

Data synthesis and analysis

All analyses were performed on an intent-to-treat basis. Data of included studies were combined to estimate the pooled treatment effect (odds ratio, OR) for the chest compression-first compared to the defibrillation-first groups. Calculations were based on a DerSirmonian and Laird random effects model [21]. Sensitivity analyses were conducted using alternative meta-analytical approaches such as the Hartung-Knapp method, which tends to be more conservative, and by meta-regression analyses (mixed-effects model) for the subgroups as defined below (R package "metafor") [22,23]. Continuity correction was used when no event occurred in one group to allow calculation of an odds ratio [24]. We used the rank correlation test to assess the risk for publication bias [25,26]. Heterogeneity among trials was quantified with Higgins's and Thompson's I^2. I^2 can be interpreted as the percentage of variability due to heterogeneity between studies rather than sampling error. On the basis of findings in a previous observational study, an *a priori* subgroup analysis of response time from event to EMS arrival (≤5 min versus >5 min) was also conducted [27]. Further, a meta-regression analysis was performed on the basis of the mean response intervals of each study using a mixed-effects model. Weighted average incidence of events for the chest compression-first and the defibrillation-first groups were calculated on the basis of a random effect analysis using a Freeman-Tukey double arcsine transformation and the inverse variance method [28]. Findings are presented as point estimates and 95% confidence intervals. Analyses have been performed by two investigators independently (GK, PM). All analyses were performed with R version 2.10.1 (packages "meta," "rmeta," and "metafor") [29].

Results

Description of included studies

A total of 245 abstracts were reviewed, and 79 of those were subsequently reviewed as full text articles; finally, four randomized trials enrolling 1503 subjects satisfied the predetermined inclusion criteria (Figure 1) [15-18]. Tables 1, 2, 3 summarize the characteristics and quality scores of the four trials.

Outcomes

Return of spontaneous circulation (ROSC)

The pooled analysis did not reveal a relevant difference in the overall chance for ROSC between the chest compression-first and the defibrillation-first approach (OR 1.01 [0.82-1.26]; $P = 0.979$; heterogeneity: $I^2 = 0\%$, $P = 0.79$) (Figure 2a). The weighted average proportion of patients in whom ROSC was achieved was 39.2% [19.8-60.5%] for the chest compression-first group and 37.3% [17.0-60.2%] for the defibrillation-first group.

Survival to hospital discharge

As summarized for all response times in Figure 2b, the direct comparison between the chest compression-first and the defibrillation-first approach did not reveal a relevant difference (OR 1.10 [0.70-1.70]; $P = 0.686$; heterogeneity: $I^2 = 34.4\%$, $P = 0.206$). The average weighted proportion of patients able to leave the hospital after cardiac arrest was 12.0% [6.4-19.1%] for the chest compression-first group as compared to 11.4% [7.1-16.6%] for the defibrillation-first group.

Favorable neurologic outcome

The average weighted proportion of patients with favorable neurological status was 13.7% [4.9-25.9%] after chest compression first and 13.3% [9.0-18.3%] after defibrillation first. As seen in Figure 2c, patients who were treated with chest compression first did not show an increased likelihood of a "favorable neurologic outcome" (as defined by a CPC score of 1 or 2) compared to those with defibrillation first (OR 1.02 [0.31-3.38]; $P = 0.979$; heterogeneity: $I^2 = 74.9\%$, $P = 0.05$).

One-year survival

As shown in Figure 2d, the OR point estimates favored a chest compression-first approach (OR 1.38 [0.95-2.02]; $P = 0.092$; heterogeneity: $I^2 = 0\%$, $P = 0.647$). However, the 95% confidence intervals crossed 1.0, indicating insufficient precision of the effect size estimation and resulting in statistical nonsignificance. The average weighted proportion of patients able to leave the hospital after cardiac arrest with chest compression first it was 11.0% [4.8-19.5%] as compared to 8.6% [4.8-13.4%] for patients treated with defibrillation first.

Figure 3 summarizes the chance of survival of patients involved in the included trials after cardiac arrest up to 1 year after the event. As mentioned above, ROSC was achieved in approximately 40% of patients with OHCA included in these trials, chance for survival to hospital discharge was around 12.0% and similar between both treatment groups, while the survival chance at 1 year was 11.0% with chest compression first and 8.6% with defibrillation first.

Subgroup Analyses Based on Response Intervals (Call to EMS Arrival)

In Figure 4, the studies are ordered according to their average EMS response times. OR point estimates of studies with shorter EMS response times favored a defibrillation-first approach. The longer the EMS response times, the OR point estimates favored chest compression first followed by defibrillation. However, for all these OR estimates, the 95% confidence intervals crossed 1.0; thus, none of the differences were statistically significant.

Table 1 Characteristics of included studies

Author	Year	Location	Group	Patients (n)	Age (yrs)	Male (%)	Witnessed (%)	Bystander CPR performed (%)	Response time (min)
Jost [15]	2010	France	Defi.-first	424	62	79	86	21	10:54
			Compr.-first	421	65	78	87	21	10:30
Baker [16]	2008	Australia	Defi -first	105	66*	80	79	58	08:14
			Compr.-first	97	65*	84	84	59	07:41
Jacobs [17]	2005	Australia	Defi -first	137	62	80	74	54	09:00
			Compr.-first	119	64	80	80	64	09:20
Wik [18]	2003	Norway	Defi -first	96	80*	89	94	56	11:42
			Compr.-first	104	71*	85	91	62	12:00

*Median; Compr-first: chest compressions before defibrillation; Defi.-first: immediate defibrillation before chest compressions; response time: time-to arrival of ambulance.

Table 2 Characteristics of included studies

Author	Year	Group	CPR pretreatment (sec)	Compression to ventilation ratio	No. of consecutive shocks
Jost	2010	Defi -first		Cardio-pump*	3
		Compr.-first	60	Cardio-pump*	1
Baker	2008	Defi -first			3
		Compr.-first	180	15:2	3
Jacobs	2005	Defi -first			3
		Compr.-first	90	5:1	3
Wik	2003	Defi -first			3
		Compr.-first	180	5:1	3

* Trademark (manufacturer: Ambu, Denmark). Compr-first: chest compressions before defibrillation;
Defi.-first: immediate defibrillation before chest compressions; sec: seconds

Response Interval ≤5 minutes

ROSC As shown in Figure 5a, for response time ≤5 minutes, the OR to achieve ROSC was not significantly different between chest compression first and defibrillation first (OR 1.05 [0.58-1.88]; P = 0.872; heterogeneity: I^2 = 0%, P = 0.73).

Survival to discharge The point estimates of the OR for this outcome were in disfavor of predefibrillation chest compressions (OR 0.69 [0.36-1.32]; P = 0.263; heterogeneity: I^2 = 0%, P = 0.954) (Figure 5b). The 95% confidence interval crossed 1.0, indicating inadequate precision of the effect estimate, resulting in statistical nonsignificance.

Neurologic outcome As Figure 5c shows, the OR point estimate was in disfavor of predefibrillation chest compression approach (OR 0.57 [0.23-1.43]; P = 0.300 (heterogeneity: 0%; P = 0.370). Again, the 95% confidence interval crossed 1.0, and the difference was therefore not statistically significant.

5 minutes",1,0,2,0,0pc,0pc,0pc,0pc>Response Interval >5 minutes

ROSC No relevant differences were found for patients with a response time >5 minutes in ROSC (Figure 6a), the OR was 1.10 [0.67-1.78]; P = 0.705 (heterogeneity: 62.4%; P = 0.0712).

Survival to discharge The point estimate for the OR pointed toward superiority of chest compression first, but the confidence interval crossed 1.0; thus, the finding was not statistically significant (OR 1.45 [0.66-3.20]; P = 0.353; heterogeneity: 59.1%; P = 0.062) (Figure 6b).

Neurologic outcome As Figure 6c illustrates, there was no relevant difference between the two groups (OR 1.02 [0.31-3.38]; P = 0.879; heterogeneity: I^2 = 84.2%; P = 0.012).

Meta-regression analysis based on mean response intervals

This analysis showed a significant effect of the mean response interval of each study in the control arm on the effect of predefibrillation chest compression; the point estimates of the OR pointed toward inferiority of predefibrillation chest compression for studies with short mean response intervals but toward superiority for studies with longer mean response intervals (Additional file 3; Supplementary Figure 1). This response interval effect was statistically significant. The slope of the meta-regression was 0.0051 [0.0004-0.0097]; P = 0.033. That is, for every absolute increase of 1 time unit (1 second) in the response time, the log odds ratio increased by 0.0051 (in direction to superiority of a chest compression-first approach). At around 600 seconds (10 min) response time, the regression line crosses OR 1.0 (equipoise between the two interventions). Additional file 4, Supplementary Table 6 gives an overview of variable response intervals with corresponding predicted odds ratios.

Sensitivity analyses

The analysis performed with the Hartung-Knapp meta-analytical approach and by a mixed-effects meta-regression analysis revealed almost identical results (see Additional file 5, Supplementary Tables 3-5. Also, a sensitivity analysis was conducted without the study by Jost et al. [15], as this study did not exclusively test

Table 3 Quality of included studies (Jadad score)

Author	Randomized	Appropriate randomization	Double blind	Appropriate blinding (single blind)	Drop outs appropriately declared	Score
Jost	Yes	Yes	No	Yes	Yes	4/5
Baker	Yes	Yes	No	Yes	Yes	4/5
Jacobs	Yes	Yes	No	Yes	Yes	4/5
Wik	Yes	Yes	No	Yes	Yes	4/5

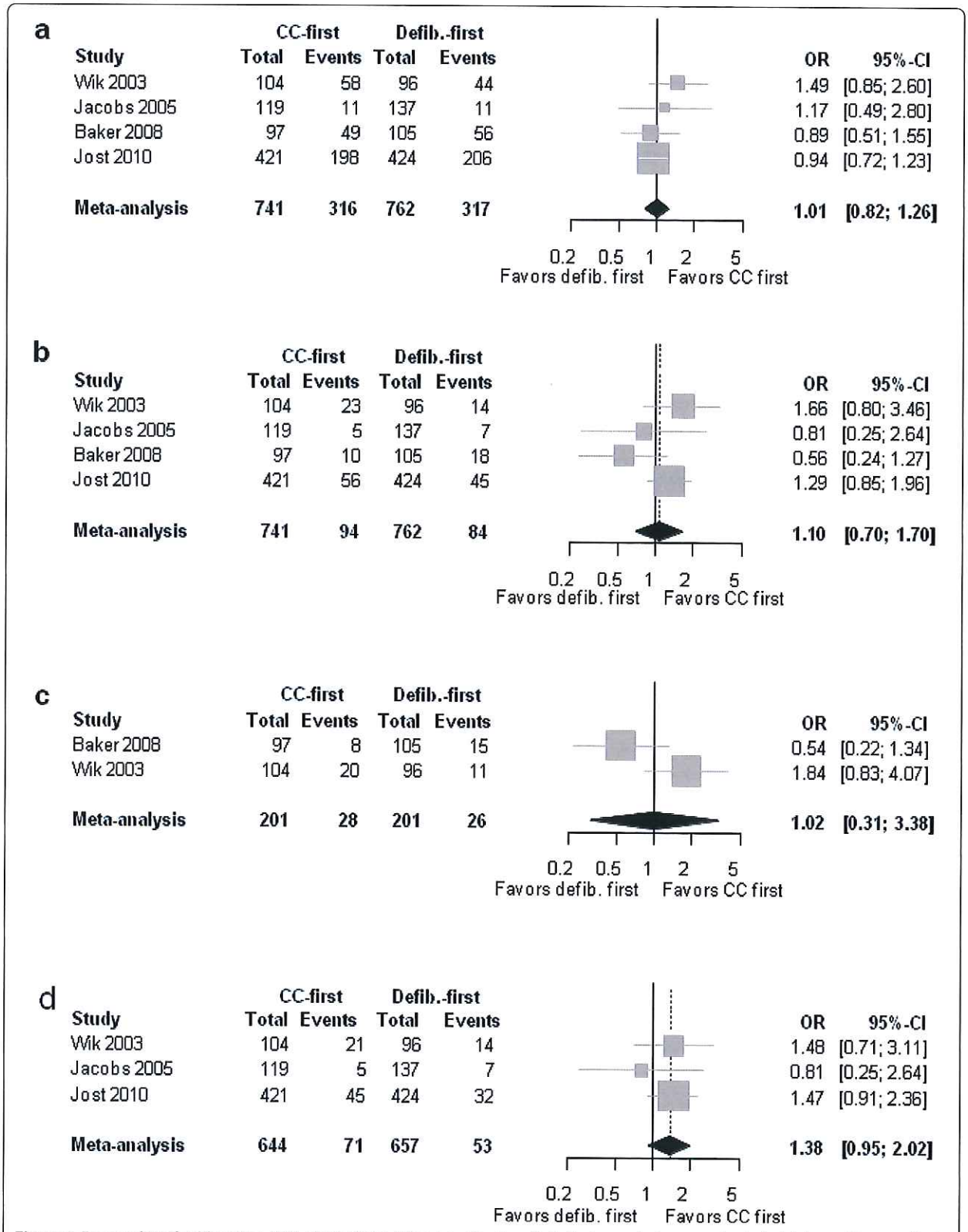

Figure 2 Forest plot of odds ratios (OR) of (a) ROSC, (b) survival to hospital discharge (primary endpoint), (c) favorable neurologic outcome, and (d) 1-year survival. Horizontal bars indicate 95% confidence intervals. Size of markers represents study weight in meta-analysis.

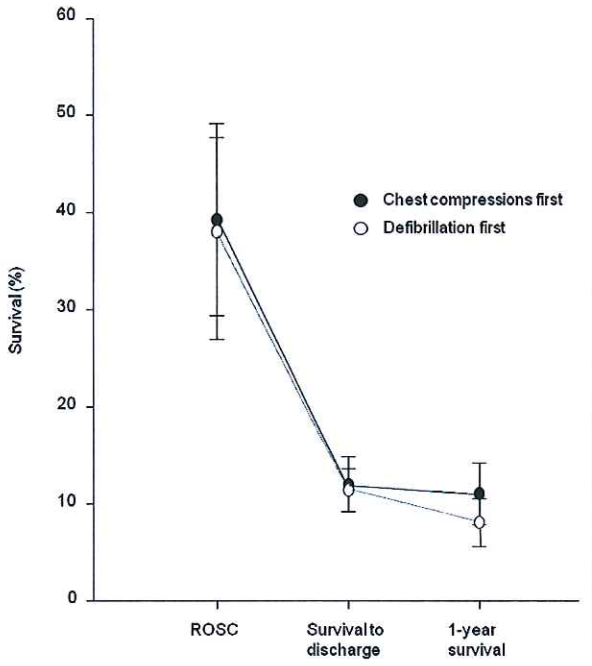

Figure 3 Survival of enrolled patients after cardiac arrest (average percentage and 95% confidence intervals).

the effect of chest compression first, but also the effect of three consecutive shock applications versus a single shock at a time. Also, most patients did not receive bystander CPR; CPR was initiated in most cases by firefighters using a CPR device instead of manual compressions. When excluding this study, the results did not change despite the considerable weight (study size) of this study in this analysis (data not presented).

Publication bias assessment

Regarding the primary endpoint, the rank correlation test was not suggestive for publication bias, $P = 0.588$.

Discussion

This is the first meta-analysis evaluating the effect of chest compression first versus defibrillation first in patients having out-of-hospital cardiac arrest. We included four randomized, controlled clinical trials with 1503 subjects. Overall, our findings suggest that there was no significant difference between the two groups in general. However, our subgroup analyses of patients with a response interval >5 min found point estimates that pointed toward superiority of a chest compression-first approach and vice versa for the subgroup with response interval ≤5 min. The point estimate for the 1-year survival results pointed toward a lower 1-year mortality for chest compression-first patients, which was mainly driven by studies with longer EMS response times [15,18]. However, the 95% confidence intervals of these subgroup and long-term analyses crossed 1.0, indicating insufficient precision of the effect estimates and resulting in statistical nonsignificance. These analyses were based on smaller patient numbers.

Rational for Chest Compressions Prior to Defibrillation

Chest compressions serve to empty the right ventricle (RV) and to avoid RV distension during VF, which helps to reduce the risk of occurrence of "nonperfusing" post-defibrillation rhythms (e.g., pulseless electrical activity or asystole) [30,31]. Two experimental animal studies on ventricular defibrillation have demonstrated that chest compression first may improve defibrillation success in comparison to the standard defibrillation first approach. A randomized study in swine conducted by Berg et al. and a study by Niemann et al. in dogs both showed higher efficiency for chest compression prior to defibrillation [32,33]. Data from a study conducted on humans showed that even short preshock pauses were found to strongly correlate with lower defibrillation success [34]. Accordingly, a large observational study by Cobb et al. demonstrated improved survival for patients treated for out-of-hospital cardiac arrest after implementation of chest compression-first protocol compared to the preceding 42 months with the standard defibrillation-first approach [27]. Similarly, a study including 886 patients of Bobrow et al. performed in Arizona implementing a protocol of 200 uninterrupted chest compressions before defibrillation (single shock) showed a remarkable increase in survival-to-hospital discharge, from 1.8% to 5.4% after protocol implementation [35,36]. Yet, despite all of the above data from experimental and observational studies, our meta-analysis based on randomized clinical trials in humans shows that both treatments appear to be equivocal, with point estimates that favor chest compression first regarding long-term outcomes.

Several aspects could explain this controversy. First, findings from experimental animal studies may not apply to humans, especially since most models use electrical induction of ventricular fibrillation, which may not appropriately reflect the majority of cardiac arrests in humans [37]. In a more recent study in swine using an acute myocardial ischemia model, 24-hr survival with a favorable neurological outcome was less likely when chest compressions were performed prior to defibrillation [38]. Second, observational studies [27,35] are more prone to confounding than randomized trials. Because we decided *a priori* to include only randomized, controlled trials in our meta-analysis, our results may differ from these large observational studies. Finally, it may be that the treatment effect of chest compression first may be dependent on the response interval from the time of call to EMS response. Further research, with patient-

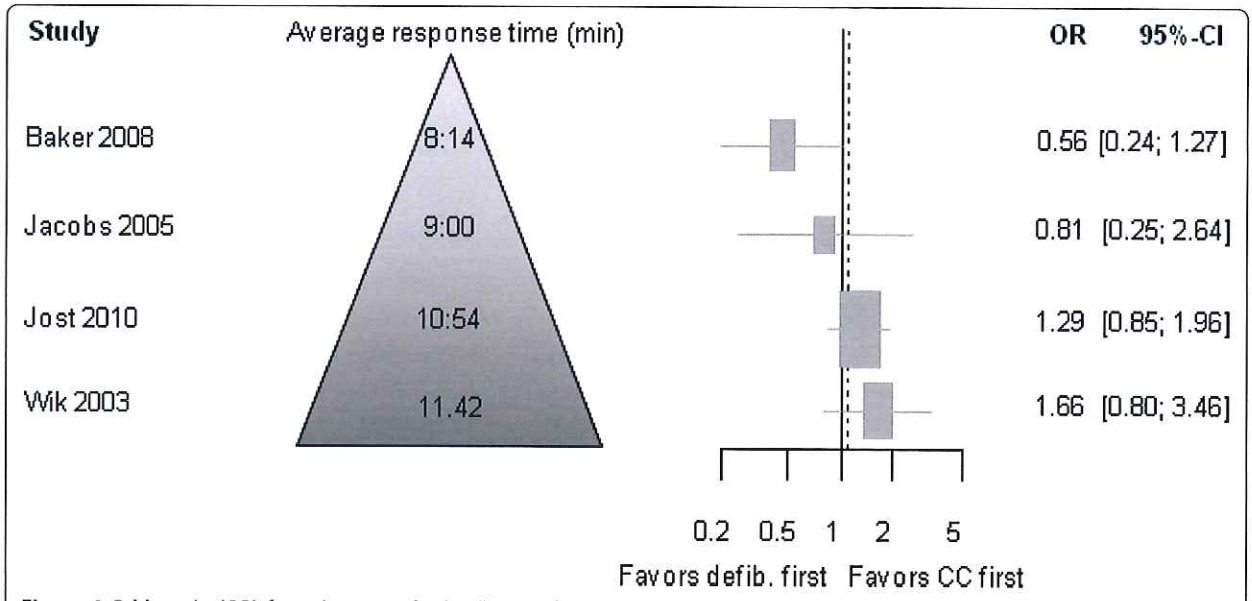

Figure 4 Odds ratio (OR) for primary endpoint "survival to hospital discharge" and response time. Horizontal bars indicate 95% confidence intervals. Size of markers represents study weight in meta-analysis.

level data, will need to be conducted to assess whether this finding is consistent.

Short- versus longer-duration cardiac arrest

The possible difference in treatment effect for longer-lasting (response interval >5 min) makes plausible sense from a pathophysiological standpoint. Cardiac arrest (due to ventricular tachycardia/fibrillation (VT/VF)) is definitively not a static event. Rather, it is a dynamic process with sometimes continuous transitions starting with VT, transforming into coarse and then into fine amplitude VF and finally into asystole; these different electrocardiogram morphologies are obviously associated with different degrees of defibrillation success [39]. During the course of VF high-energy phosphates are progressively depleted, which also decreases the chances for successful defibrillation [40].

Niemann et al. demonstrated the superiority chest compression first in a dog model [33], but found better outcomes for defibrillation first in a subsequent study [41]. In this second study, VF duration was relevantly shorter (5 min versus 7.5 min in the first study). Another study conducted in dogs specifically evaluated different VF durations, showing differential results based on the duration of VF. For short-lasting VF arrests (< 3 min), defibrillation first was superior to chest compression first [42]. It has to be considered, however, that most experimental animal studies used electrical induction of VF, which may not be identical to ischemia-induced VF [37]. The study by Cobb et al. included in our analysis showed the most prominent benefit for chest compression first if response time was >4 min [27].

In 2002, Weisfeldt et al. proposed a three-phase time-sensitive model for treatment of sudden cardiac arrest: the electrical phase (early phase during the first around 0-4 min where immediate defibrillation may be optimal, the circulatory phase (4-10 min) where predefibrillation chest compressions could be meaningful, and the metabolic phase (> 10 min), where survival rates are poor in general [39]. The authors stated in their editorial that "phase-specific research is needed to extend knowledge of the importance of time on resuscitation, such as testing early defibrillation and public access defibrillation programs during the electrical phase and testing chest compression and vasoconstrictors first during the circulatory phase." [39]. Our findings support the view of Weisfeld et al. as illustrated in Figure 4 and as shown in the subgroup analyses of patients with longer versus those with shorter response intervals.

Limitations of this study

It has to be considered that nonstratified overall results showed odds ratios very close to 1.0; that is, no treatment effect with fairly narrow confidence (precision) intervals and with very little heterogeneity. In contrast, OR point estimates pointed toward superiority of predefibrillation chest compressions for those cardiac arrests with prolonged EMS response, while in patients with shorter EMS intervals these OR estimates pointed toward superiority of a defibrillation-first approach (Figures 5 and 6). Owing to the smaller sample sizes in

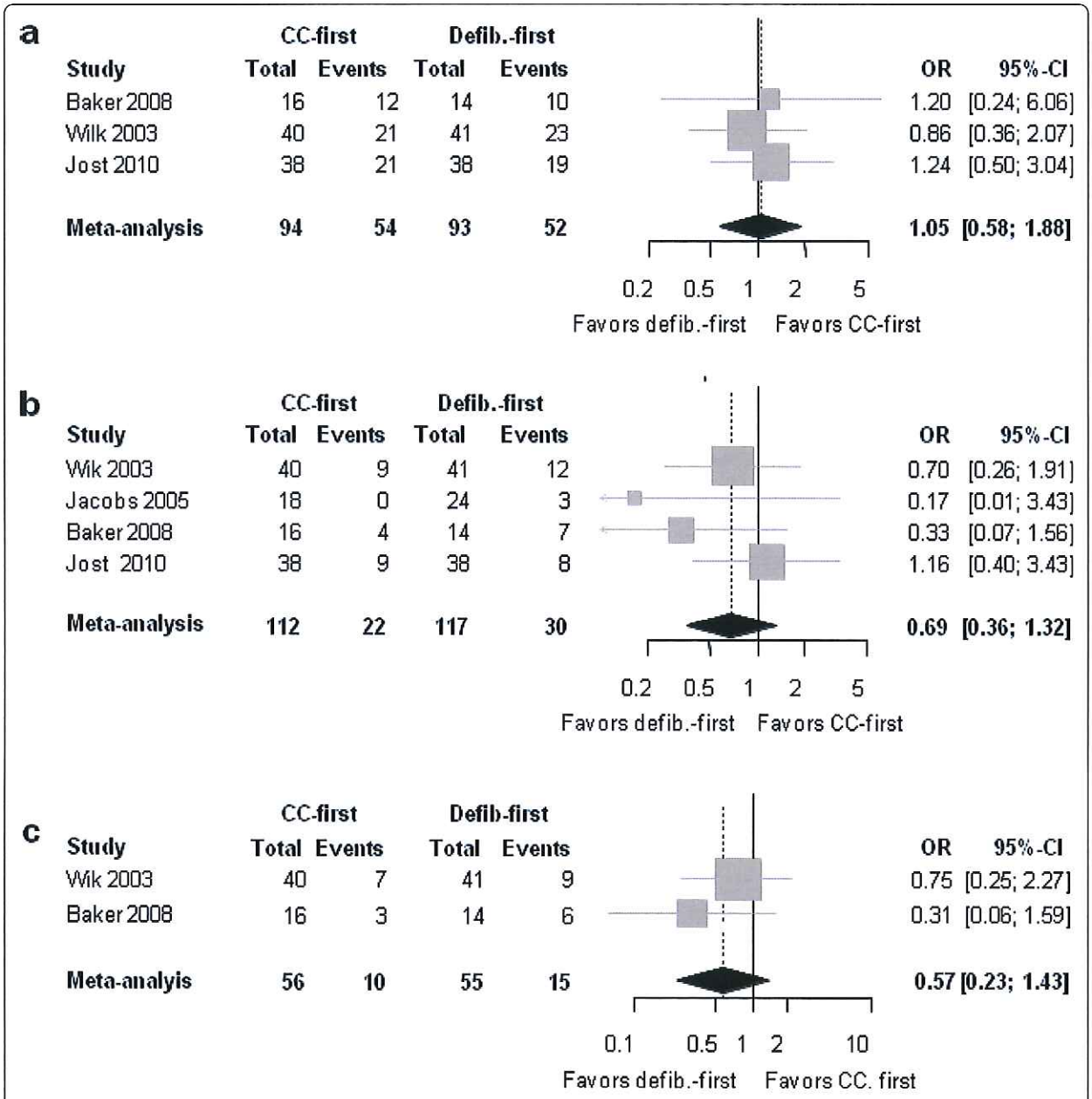

Figure 5 Forest plot of odds ratios (OR) of the subgroup of patients with response time ≤5 min for (a) ROSC, (b) survival to hospital discharge, and (c) favorable neurologic outcome. Horizontal bars indicate 95% confidence intervals. Size of markers represents study weight in meta-analysis.

these subgroups, confidence intervals were wider due to reduced precision of these estimates. The confidence intervals for these subgroup analyses crossed 1.0; i.e., the result was statistically not significant. It is possible that there is in fact a difference that was not detected by our analysis due to limited statistical power. An interaction between optimal treatment and response time is further supported by the observation that the odds ratios were influenced by the average response intervals of the individual studies (Figure 3 and Additional file 1). However, the meta-regression analysis (Additional file 1), even though in line with the findings of the subgroup analyses, has to be interpreted with care because it is based on summary measure (mean response intervals of each study) and not on individual response intervals. Meta-analyses are useful for synthesizing the literature and to explore areas for further exploration rather than to provide a definitive

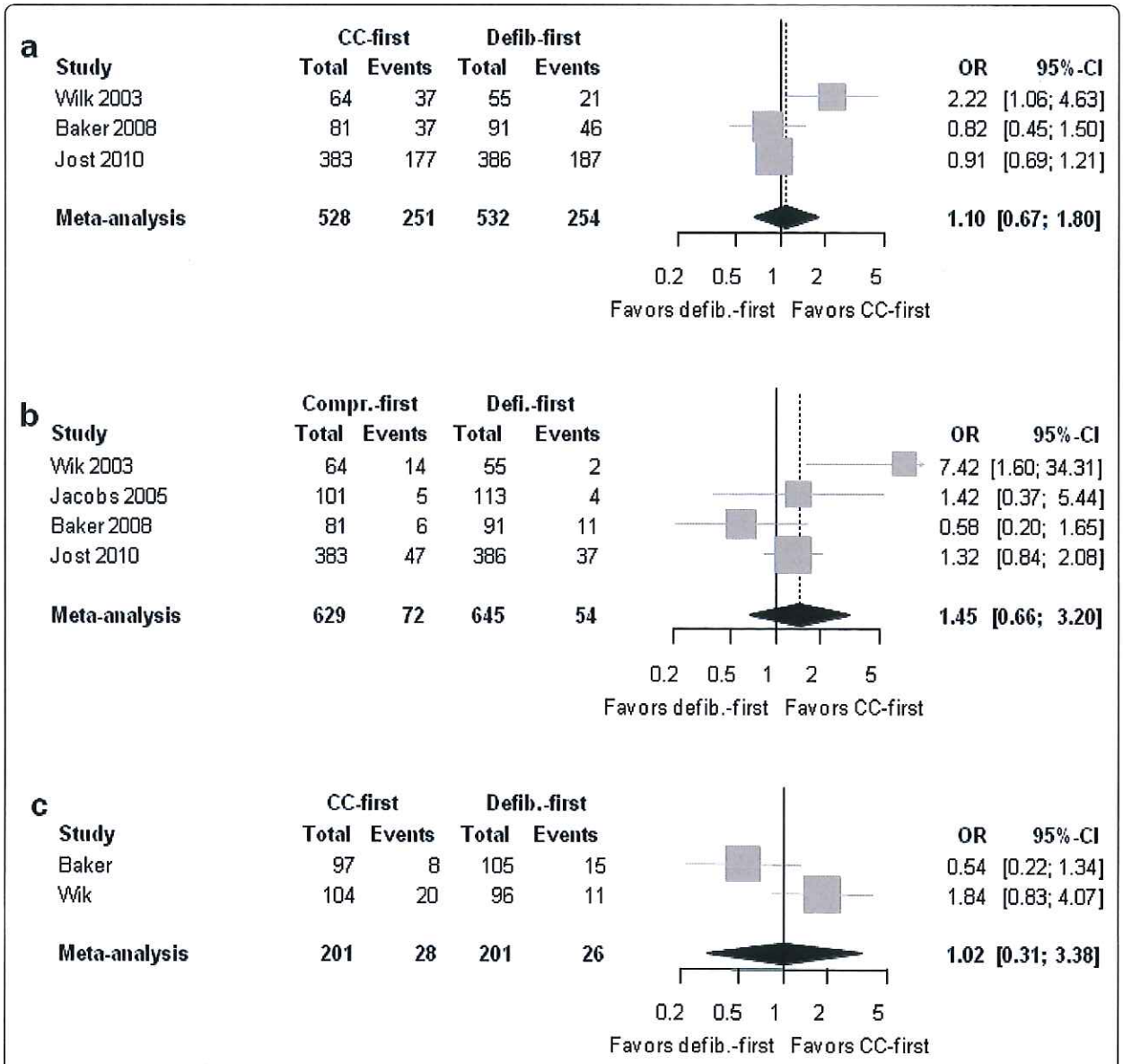

Figure 6 Forest plot of odds ratios (OR) of group with response time >5 min for (a) ROSC, (b) survival to hospital discharge and (c) good neurologic outcome. Horizontal bars indicate 95% confidence intervals. Size of markers represents study weight in meta-analysis.

conclusion. Future research based on this meta-analysis could be conducted with patient-level data to assess whether the overall pooled results are consistent with the individual-level data.

RCT data are considered the "golden standard" and superior to observational studies. Clearly, the latter are more prone to be biased by confounding, and, accordingly, we considered RCT exclusively in this meta-analysis. Nevertheless, there are caveats for RCT also [43]; this is especially true in the context of human emergency medicine research. The vast majority of patients assessed for inclusion in these trials were finally not eligible because of predefined exclusion criteria or owing to logistical reasons. Thus, the patient selection associated with RCT potentially complicates generalizability of findings into routine clinical practice. For example, bystander CPR rate ranged from 54-64% in three of the included trials, while the AHA estimates the average bystander CPR rate in the United States to be 31.4% [1]. Future research will need to be conducted on communities that may be more generalizable than the study populations in this analysis.

A further limitation of this study is the heterogeneity of the study protocols. Three of the four included trials

use the 2000 guidelines with a "three-shock protocol" [16-18],

while one study utilized a single shock application (as advocated in the current 2005 guidelines) in the chest compression first group [15]. All four studies did not control for the quality of chest compressions. The quality of chest compressions has a key impact on outcome and is often insufficient, even for in-hospital cardiac arrests [34] and even in some experimental studies [44]. We cannot exclude that the quality of compressions in the included studies was insufficient, and as a consequence, the studies were unable to show a benefit. Because of the differences in study protocols, we chose to use a random effects model rather than a fixed-effect model for data analysis.

Finally, we did not have the complete set of individual patient data, and our analyses are thus based on study-level data. Therefore, we could not adjust the analysis for covariables. For example, the 1-year survival data for the study by Jost et al. [15] are based on Kaplan-Meier survival estimates, which showed a survival probability of 10.6% in the intervention group and 7.6% in the control group ($P = 0.45$).

Conclusions

The results of this meta-analysis demonstrate that survival is equivocal for the chest compression-first group as compared to the defibrillation-first group. Thus, current guidelines emphasizing early defibrillation still appear appropriate. However, the study revealed signals toward possible superiority of predefibrillation chest compressions for patients with a response interval of >5 min; the statistical power of this study was insufficient for such subgroup analyses, and none reached statistical significance. These signals suggest that the optimal treatment of cardiac arrest patients may depend on the duration of the event and the timeliness of the response. Future research will need to be conducted to assess whether this differential effect is seen in patients treated for out-of-hospital cardiac arrest. This may lead to different treatment guidelines based on the duration of the arrest and the interval of the response.

Additional material

Additional file 1: Supplementary table 1. PRISMA statement checklist.

Additional file 2: Supplementary table 2. Detailed literature search strategy with search terms used for Medline.

Additional file 3: Supplementary figure 1. Meta-regression plot. Meta-regression plot of odds ratios (OR) versus response interval (seconds). Size of circles indicate study weights in a mixed-effects model.

Additional file 4: Supplementary table 6. Predicted odds ratios for variable response intervals.

Additional file 5: Supplementary tables 3 - 5. Sensitivity analyses with different meta-analytical approaches.

Abbreviations

AHA: American Heart Association; CPR: Cardiopulmonary resuscitation; ERC: European Resuscitation Council; EMS: Emergency medical services; ILCOR: International Liaison Committee on Resuscitation; OHCA: Out-of-hospital cardiac arrests; OR: Odds ratio; RCT: Randomized clinical trials; ROSC: Return of spontaneous circulation.

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Authors' contributions

PM, CS conceptualized and designed this meta-analysis. PM, BH, CS were substantially involved in data acquisition (literature search, study selection and data abstraction). PM, GK, CS performed the analyses and were substantially involved in data interpretation. PB, DJ, IJ provided data used for the analysis and relevantly contributed to the interpretation and intellectual content of the manuscript. PM and CS drafted the manuscript. All authors revised the manuscript critically for important intellectual content. All authors approved the final version.

Competing interests

The authors declare that they have no competing interests to disclose. PM is supported by a postdoctoral fellowship grant from the Swiss National Research Foundation, Switzerland. The funding organizations had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

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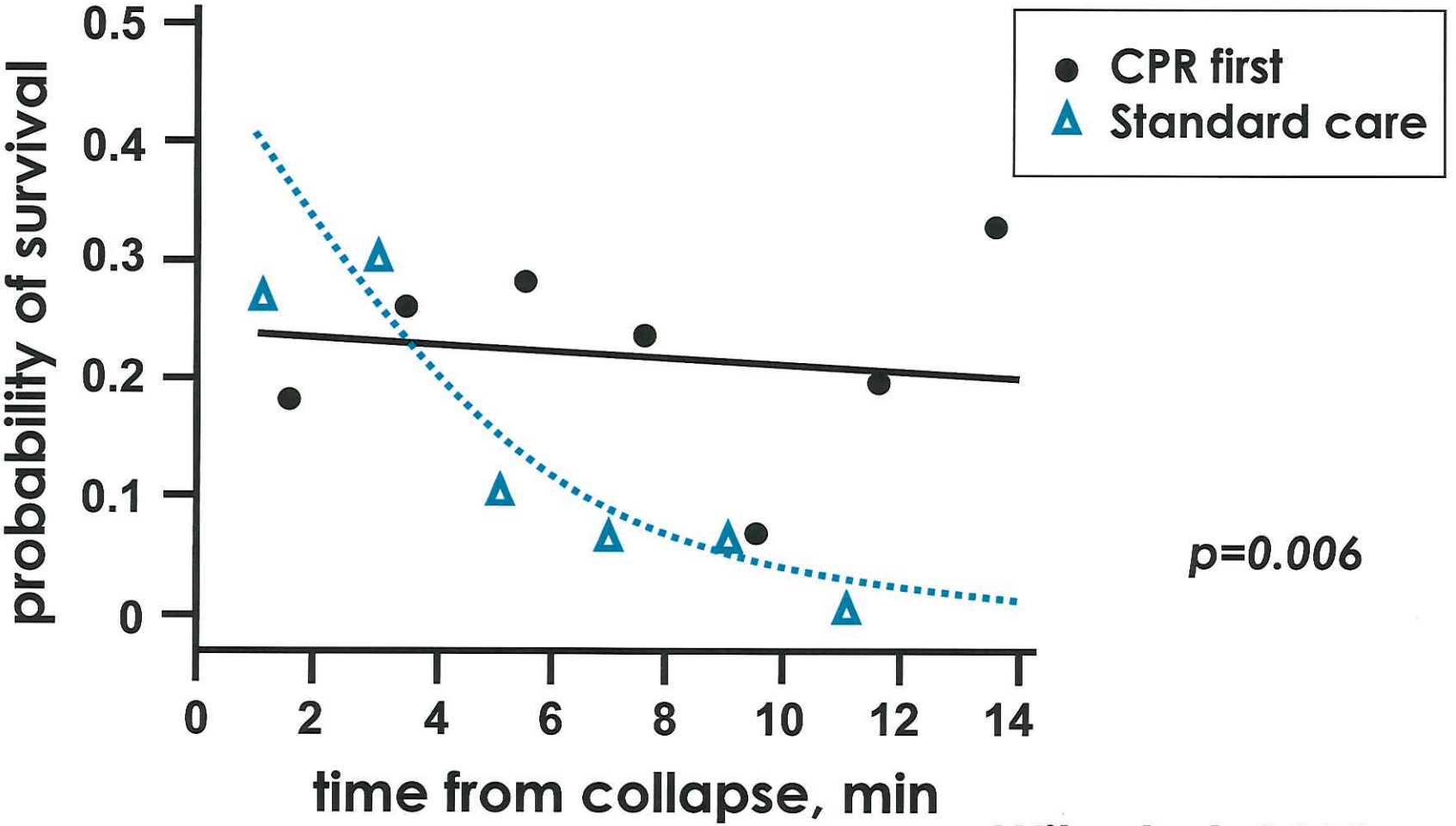
CPR first may improve survival: RCT



Wik et al, 2003

Delaying Defibrillation to Give Basic Cardiopulmonary Resuscitation to Patients With Out-of-Hospital Ventricular Fibrillation

A Randomized Trial

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Context Defibrillation as soon as possible is standard treatment for patients with ventricular fibrillation. A nonrandomized study indicates that after a few minutes of ventricular fibrillation, delaying defibrillation to give cardiopulmonary resuscitation (CPR) first might improve the outcome.

Objective To determine the effects of CPR before defibrillation on outcome in patients with ventricular fibrillation and with response times either up to or longer than 5 minutes.

Design, Setting, and Patients Randomized trial of 200 patients with out-of-hospital ventricular fibrillation in Oslo, Norway, between June 1998 and May 2001. Patients received either standard care with immediate defibrillation (n=96) or CPR first with 3 minutes of basic CPR by ambulance personnel prior to defibrillation (n=104). If initial defibrillation was unsuccessful, the standard group received 1 minute of CPR before additional defibrillation attempts compared with 3 minutes in the CPR first group.

Main Outcome Measure Primary end point was survival to hospital discharge. Secondary end points were hospital admission with return of spontaneous circulation (ROSC), 1-year survival, and neurological outcome. A prespecified analysis examined subgroups with response times either up to or longer than 5 minutes.

Results In the standard group, 14 (15%) of 96 patients survived to hospital discharge vs 23 (22%) of 104 in the CPR first group ($P=.17$). There were no differences in ROSC rates between the standard group (56% [58/104]) and the CPR first group (46% [44/96]; $P=.16$); or in 1-year survival (20% [21/104] and 15% [14/96], respectively; $P=.30$). In subgroup analysis for patients with ambulance response times of either up to 5 minutes or shorter, there were no differences in any outcome variables between the CPR first group (n=40) and the standard group (n=41). For patients with response intervals of longer than 5 minutes, more patients achieved ROSC in the CPR first group (58% [37/64]) compared with the standard group (38% [21/55]; odds ratio [OR], 2.22; 95% confidence interval [CI], 1.06-4.63; $P=.04$); survival to hospital discharge (22% [14/64] vs 4% [2/55]; OR, 7.42; 95% CI, 1.61-34.3; $P=.006$); and 1-year survival (20% [13/64] vs 4% [2/55]; OR, 6.76; 95% CI, 1.42-31.4; $P=.01$). Thirty-three (89%) of 37 patients who survived to hospital discharge had no or minor reductions in neurological status with no difference between the groups.

Conclusions Compared with standard care for ventricular fibrillation, CPR first prior to defibrillation offered no advantage in improving outcomes for this entire study population or for patients with ambulance response times shorter than 5 minutes. However, the patients with ventricular fibrillation and ambulance response intervals longer than 5 minutes had better outcomes with CPR first before defibrillation was attempted. These results require confirmation in additional randomized trials.

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EARLY DEFIBRILLATION IS CRITICAL for survival from ventricular fibrillation. The survival rate decreases by 3% to 4% or 6% to 10% per minute depending on whether basic cardiopulmonary resuscitation (CPR) is performed.[1,2] Another major factor known to influence survival in patients with ventricular fibrillation is whether CPR is performed prior to when a defibrillator is available.[1] It has been assumed that the blood flow generated by CPR decreases the rate of deterioration of the heart and brain cells,[3] but is insufficient to improve the state of the tissues. If tissue perfusion could be improved, withholding defibrillation for a short period while administering CPR might improve the results for patients with depleted myocardial levels of high-energy phosphates,[3] severe acidosis,[4] and a ventricular fibrillation frequency spectrum indicating a low chance of defibrillation success.[5,6]

In an experimental study, defibrillation was more successful following basic CPR and high-dose epinephrine than immediate defibrillation in dogs with

For editorial comment see p 1434.

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7.5 minutes of untreated ventricular fibrillation.[7] In a nonrandomized human study, Cobb et al[8] reported that 90 seconds of CPR by ambulance personnel before defibrillation improved survival to hospital discharge compared with a historic control group. We therefore designed this clinical trial to determine whether CPR prior to defibrillation (CPR first) would improve outcomes in patients with out-of-hospital ventricular fibrillation.

METHODS

Study Design

The Regional Committee for Medical Research Ethics, which is an independent but nationally coordinated committee of members who are appointed by the Minister of Education, Research, and Church Affairs based on recommendations from the Research Council of Norway, approved the study protocol. Informed consent for inclusion in the study was waived as decided by this committee in accordance with paragraph 26 in the Helsinki Declaration,[9] but was required for including 1-year follow-up data.

The study was conducted in the Oslo emergency medical service (EMS) system, which covers a land area of 427 km^2 and a population of approximately 500000. Of this population, 48% were men and 16% were older than 65 years. The study was a randomized, controlled trial involving patients older than 18 years with ventricular fibrillation or pulseless ventricular tachycardia in whom the ambulance personnel had not witnessed the cardiac arrest. On-site randomization after defibrillator electrocardiogram verification of ventricular fibrillation/ventricular tachycardia was performed by opening a sealed study envelope that contained the treatment assignment. The ambulance personnel could not be blinded thereafter. Hospital personnel were blinded, including the physicians responsible for assessing the neurological outcome at hospital discharge. The study was monitored by a physician not involved in the care of any patients or in data collection. This physician received all case records and the sealed randomization list after 6, 18, and 30 months, and performed interim analyses of outcome. If significant differences in survival were detected ($P<.05$), the study would have been stopped. Subgroups of patients with response times either up to or longer than 5 minutes were also included in the monitoring.

Treatment Protocol

The patients were attended by either 1 ambulance with an anesthesiologist and 2 paramedics, or 2 ambulances with 2 ambulance personnel each and a minimum of 1 paramedic per ambulance. The equipment, drugs, and procedures were identical on all units including the physician-staffed unit. Advanced cardiac life support was provided according to the guidelines of the European Resuscitation Council[10] except for the duration of CPR (defined as chest compressions and ventilation) prior to a defibrillation attempt, which was the intervention studied. When the ambulance arrived, a monophasic automated defibrillator (LIFEPAK 12, Medtronic Physio-Control, Redmond, Wash) was immediately applied to the patient by 1 EMS staff member and all patients with ventricular fibrillation/pulseless ventricular tachycardia were included. The other rescuer intubated the patient as soon as possible without disturbing the electrocardiographic analysis.

In the standard group, a defibrillating shock of 200 J was given immediately. If unsuccessful, defibrillation was repeated once with 200 J, and if necessary once more with 360 J. If return of spontaneous circulation (ROSC) was not achieved, 1 minute of CPR was given for ventricular fibrillation/ventricular tachycardia or 3 minutes for nonventricular fibrillation/ventricular tachycardia before a new rhythm analysis and the shock and CPR sequence was repeated as indicated with all shocks at 360 J. All patients were ventilated with 100% oxygen and given 1 mg of epinephrine intravenously every 3 minutes until ROSC or termination of the resuscitation attempt. Epinephrine should be administered in the beginning of a chest compression-ventilation interval, and was therefore not given before the first defibrillation attempt in either group due to the time required before an intravenous line with a continuous drip of 500 mL of Ringer acetate could be established.

The CPR first group was treated identically except that CPR was given for 3 minutes prior to the first defibrillation attempt, and if CPR was needed thereafter, it was given for 3 minutes both for ventricular fibrillation/ventricular tachycardia and nonventricular fibrillation/ventricular tachycardia. Countershock refractory ventricular fibrillation or recurrent ventricular fibrillation was treated according to the 1998 European Resuscitation Council guidelines.[10] A standard 100-mg dose of lidocaine was given intravenously only after 9 defibrillation attempts. Other antiarrhythmics, such as amiodarone, were not given.

Data Collection

Data were collected according to the Utstein style.[11] Out-of-hospital data were based on the digital dispatcher database, the ambulance records, and the Utstein data collection sheets. These data included the therapy administered, whether the cardiac arrest was witnessed, application of bystander-initiated CPR, location of the cardiac arrest, and response-time intervals calculated from time of dispatch of the first ambulance to arrival of the first ambulance as registered on-line by a central computer system in the dispatch center. A computer board and screen in the ambulance were connected to this central computer, and enabled the ambulance personnel to log the time of arrival directly on this computer, which was the same one that dispatched the ambulance, thus avoiding a time synchronization problem. The time of patient collapse was estimated by the ambulance personnel based on the information they received from bystanders, and manually synchronized with the time on the computer screen. Time intervals from arrival at the patient's location until direct current shock and ROSC were taken from the defibrillator and did not need to be synchronized with the other time points.

Survival and neurological status at hospital discharge were obtained from the hospital record. Neurological status was assessed according to the Glasgow-Pittsburgh outcomes, which consist of the cerebral performance category (CPC) and the overall performance category (OPC) with CPC/OPC of 1 indicating a good cerebral/good overall performance; CPC/OPC of 2, moderate cerebral/moderate overall disability; CPC/OPC of 3, severe cerebral/severe overall disability; CPC/OPC of 4, coma/vegetative state; and CPC/OPC of 5, brain death/death.[12] One-year follow-up data were collected from a questionnaire (available from the authors on request) sent to patients or their relatives during May 2002.

All data were stored in a database (FileMaker Pro, Version 4.1, FileMaker Inc, Santa Clara, Calif) and analyzed using an SPSS statistical package (Version 11.0, SPSS Inc, Chicago, Ill).

Outcomes

The primary outcome was survival to hospital discharge. Secondary outcomes were ROSC and survival to hospital, overall status scored as OPC and neurological status scored as CPC at discharge, and 1-year survival with neurological status.

Statistical Analysis

Prior to analyzing the outcomes, we postulated that any resultant survival benefit would be most evident in cases with longer response intervals based on the report by Cobb et al,[8] which was published while our study was still ongoing. We decided prior to data analysis to analyze subgroups with response times either up to or longer than 5 minutes.[13,14] Cobb et al[8] used a response interval of 4 minutes. These response times are longer than those used in Seattle,[8] and we expected that we would have too few patients in a group with response intervals shorter than 4 minutes. This decision was made by the 2 main authors (L.W. and P.A.S.) alone and communicated to the other authors, but not to any other personnel involved in the study.

A power analysis using Sigmastat statistical software (Version 2.03, SPSS Inc) provided a power of 80 for α of .05 with 250 patients in each group for an increased survival from 15% for the standard group to 25% for the CPR first group. The survival of ventricular fibrillation patients has been 16% to 18% in previous studies of standard advanced cardiac life support in this EMS system.[13,14]

Categorical data were analyzed by the χ^2 (alternatively the Fisher-Irwin) test and numerical data by the Mann-Whitney U test. We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) using SPSS statistical software. $P<.05$ was considered significant.

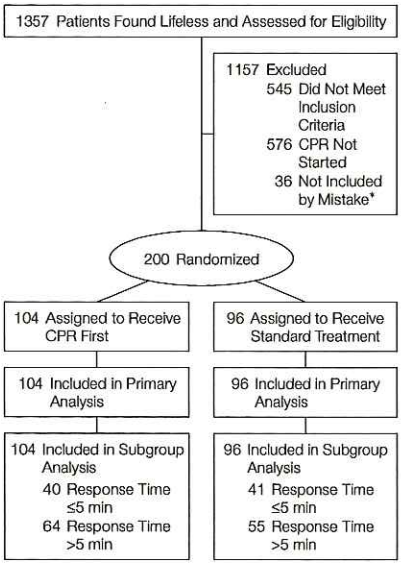
To assess differences between the standard treatment and the CPR first groups, a logistic regression analysis was performed. The dependent variable of discharged alive was regressed on the independent variables of group, age, sex, whether cardiac arrest was witnessed, whether CPR was performed by a bystander, location of cardiac arrest, and response time interval. The interaction term between group and response time interval was also included. This term represents differences between the standard and the CPR first groups, with respect to probability of survival to hospital discharge as a function of response time, and it may specifically be used to test the hypothesis generated by Cobb et al[8] that a CPR first strategy only benefits patients with longer response times.

RESULTS

Study Population

Between June 1998 and May 2001, 1357 patients were found lifeless and advanced CPR was started on 781 patients; 466 had asystole and 55 had pulseless electrical activity. Of 260 cardiac arrests with ventricular fibrillation as the first documented rhythm, 24 were witnessed by EMS personnel and were therefore excluded. The randomization envelope was missing in 2 cases. Thirty-four patients were not included in the study because EMS personnel failed to enroll them even though they met study criteria (FIGURE 1).

Figure 1. Flow Diagram of CPR First and Standard Care



CPR indicates cardiopulmonary resuscitation. Asterisk indicates emergency medical service personnel failed to enroll patients even though they met study criteria; the randomization envelope was missing for 2 patients.

The baseline characteristics of the 200 patients included in the study are shown in TABLE 1. There were no significant differences between the study groups in terms of age, sex, EMS response times, location of the cardiac arrest, proportion of cardiac arrests that were witnessed, or times CPR was performed by a bystander. The physician-manned ambulance was dispatched to 25 (24%) of 104 patients in the CPR first group and to 22 (23%) of 96 patients in the standard treatment group. There was no difference in the use of epinephrine or lidocaine in the 2 groups.

Outcome

There was no difference between the CPR first group and the standard group in the survival rate to hospital discharge (22% [23/104] vs 15% [14/96]; $P=.17$); ROSC rates (56% [58/104] vs 46% [44/96]; $P=.16$); or 1-year survival (20% [21/104] vs 15% [14/96]; $P=.30$) (TABLE 2). Of 37 patients discharged alive, 33 (89%) were re-

ported to have made a good neurological recovery at hospital discharge (CPC/OPC of 1 or 2) with no difference between the groups at discharge or when evaluated by the patient or a relative 1 year after cardiac arrest (TABLE 3). As of May 2002, 29 patients were still alive and 27 patients or their relatives responded to the follow-up survey. Two patients did not respond (1 patient in each group; both had been in the interval of ≤5 minutes).

For the 81 patients with ambulance response times of 5 minutes or less, there were no differences in ROSC, survival to hospital discharge, 1-year survival, or neurological outcome of survivors (Table 2 and Table 3).

Table 1. Baseline Characteristics of Patients

Characteristic	No. (%) CPR First (n = 104)	No. (%) Standard (n = 96)	P Value
Age, median (range), y	71 (18-88)	70 (18-96)	.57
Men	88 (85)	85 (89)	.42
Cardiac arrest observed by others	95 (91)	90 (94)	.52
Bystander performed CPR	64 (62)	54 (56)	.41
Location of cardiac arrest			
Home	51 (49)	42 (44)	.39
Public place	36 (35)	42 (44)	
Other	17 (16)	12 (12)	
Time, mean (95% CI), min			
Collapse to ambulance arrival	12.0 (10.7-13.4)	11.7 (10.7-12.7)	.76
Arrival to first defibrillation attempt	3.8 (3.4-4.2)	1.9 (1.6-2.2)	<.01
First defibrillation attempt to ROSC	12.9 (9.2-16.5)	14.4 (11.5-17.3)	.22
Collapse to ROSC	26.9 (23.4-30.4)	26.7 (23.6-29.8)	.74
Dose of epinephrine, mean (95% CI), mg	5.3 (4.3-6.4)	5.0 (4.2-5.9)	.74
Lidocaine given intravenously	22 (21)	21 (22)	>.99

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ROSC, restoration of spontaneous circulation.

Table 2. Rates of Discharge From Hospital, ROSC, and 1-Year Survival*

Group	No. (%) CPR First (n = 104)	No. (%) Standard (n = 96)	OR (95% CI)†	P Value‡
Total				
Discharged from hospital	23 (22)	14 (15)	1.66 (0.80-3.46)	.20
ROSC	58 (56)	44 (46)	1.49 (0.85-2.60)	.20
1-Year survival	21 (20)	14 (15)	1.48 (0.71-3.11)	.35
≤5 min				
	(n = 64)	(n = 55)		
Discharged from hospital	9 (23)	12 (29)	0.70 (0.26-1.91)	.61
ROSC	21 (52)	23 (56)	0.87 (0.36-2.08)	.82
1-Year survival	8 (20)	12 (29)	0.60 (0.22-1.69)	.44
>5 min				
	(n = 40)	(n = 41)		
Discharged from hospital	14 (22)	2 (4)	7.42 (1.61-34.3)	.006
ROSC	37 (58)	21 (38)	2.22 (1.06-4.63)	.04
1-Year survival	13 (20)	2 (4)	6.76 (1.42-31.4)	.01

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; OR, odds ratio; ROSC, return of spontaneous circulation.
*Patients received ventricular fibrillation posthospitalization and 3 minutes of CPR before defibrillation vs standard treatment with immediate defibrillation.
†ORs and 95% CIs were calculated by logistic regression.
‡Calculated from the Fisher exact test.

For the 119 patients with response times longer than 5 minutes, more patients in the CPR first group than in the standard group achieved ROSC (58% [37/64] vs 38% [21/55]; $P=.04$); survival to hospital discharge (22% [14/64] vs 4% [2/55]; $P=.006$); and 1-year survival (20% [13/64] vs 4% [2/55]; $P=.01$) (Table 2).

In logistic regression analysis, both forward and backward stepwise variable selection procedures resulted in a model with the predictor variables of age (OR, 0.97; 95% CI, 0.94-0.99), CPR performed by a bystander (OR, 3.75; 95% CI, 1.49-9.42), response time (OR, 0.68; 95% CI, 0.52-0.90), and the interaction term between group and response time present (OR, 1.41; 95% CI, 1.03-1.94).

Specifically, the interaction term is significant ($P=.03$). The term group is also included since it is involved in a significant interaction. Leaving it out implies only minor differences in the results. FIGURE 2 shows the estimated probability of survival to hospital discharge plotted against response time. The significant interactions between group and response time means that the shapes of the curves are significantly different. The estimated survival with CPR first vs standard therapy is a function of the response time interval formula ($-1.305+0.346\times$Time), indicating a higher chance of survival with CPR first for response time intervals longer than 4 minutes.

The calculated OR for survival with CPR before defibrillation increased from 0.4 (95% CI, 0.08-1.80) for a less than 1-minute response interval to 3 (95% CI, 1.06-8.79) for a 7-minute interval, and 6.1 (95% CI, 1.34-27.80) for a 9-minute interval.

COMMENT

In this study, there were no overall differences in survival for patients with out-of-hospital ventricular fibrillation who received standard care vs CPR first prior to defibrillation. However, for patients with longer ambulance response times (>5 minutes), the hospital discharge and 1-year survival rates were higher for patients who had re-

Table 3. Overall Performance Categories and Cerebral Performance Categories of Patients at Hospital Discharge and at 1-Year Survival

	No. Received Treatment, All Patients				No. Received Treatment, ≤5 min				No. Received Treatment, >5 min			
	CPR First (n = 104)		Standard (n = 96)		CPR First (n = 40)		Standard (n = 41)		CPR First (n = 64)		Standard (n = 55)	
Outcome	At Discharge	1 Year	At Discharge	1 Year	At Discharge	1 Year*	At Discharge	1 Year	At Discharge	1 Year	At Discharge	1 Year
Overall performance category												
1	11	8	9	9	3	2	7	7	8	6	2	2
2	9	7	4	3	4	2	4	3	5	5	0	0
3	1	0	1	0	0	0	1	0	1	0	0	0
4	2	0	0	0	2	0	0	0	0	0	0	0
5 (Dead)	81	82	82	82	31	32	29	29	50	50	53	53
Unknown*	0	7	0	2	0	4	0	2	0	3	0	0
Cerebral performance category												
1	14	6	7	7	4	3	5	5	10	3	2	2
2	6	9	4	4	3	1	4	4	3	8	0	0
3	1	0	1	1	0	0	1	1	1	0	0	0
4	2	0	0	0	2	0	0	0	0	0	0	0
5 (Dead)	81	83	82	83	31	33	29	30	50	50	53	53
Unknown*	0	6	2	1	0	3	2	1	0	3	0	0

Abbreviation: CPR, cardiopulmonary resuscitation.
*There are no differences between the groups when comparing patients surviving (overall performance category and cerebral performance category 1 through 4) to either hospital discharge or 1 year after cardiac arrest. In both the CPR first and the standard treatment group, 1 patient with response time of 5 minutes or less failed to answer the questionnaire. The other patients with unknown scores lived longer than 1 year, but died before the questionnaire was sent out in May 2002.

ceived 3 minutes of CPR prior to defibrillation and then 3-minute intervals of CPR (instead of 1 minute) between defibrillation attempts. This finding is in agreement with Cobb et al[8] who found 27% survival to hospital discharge with 90 seconds predefibrillation CPR vs 17% in a historic control group without predefibrillation CPR for response times of 4 minutes or longer.

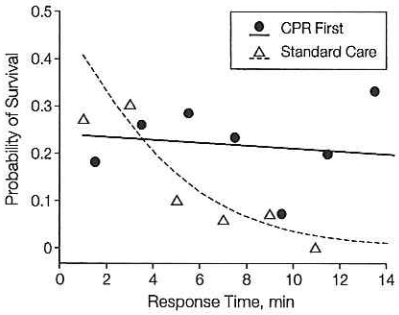
The hospital admission rate of 46% and discharge rate of 15% in the standard group in our study are similar to previously reported results for patients with ventricular fibrillation of 39% to 47% and 16% to 18% even in retrospective studies from this same EMS system.[13,14] When considering these rates along with the fact that cardiac arrest results continuously receive specific focus in this EMS system, we believe a Hawthorne effect (important in prospective clinical research[15]) is unlikely to specifically affect the results in our study.

Robinson et al[16] reported ROSC in 16% of unwitnessed out-of-hospital cardiac arrests with a 4% overall survival rate to hospital discharge. All patients were given CPR for at least 2 minutes prior to first shock, and the principle of defibrillation first was questioned as these investigators found their survival rate compared favorably with reports from systems using the defibrillation first strategy.

Some experimental studies of ventricular fibrillation demonstrate that CPR increases the defibrillation success rate.[7,17,18] In dogs with 7.5 minutes of initially untreated ventricular fibrillation, the defibrillation success was higher after predefibrillation CPR and high-dose epinephrine than after immediate defibrillation.[7] The same laboratory later reported better results with immediate defibrillation than CPR first in swine with 5 minutes of initially untreated ventricular fibrillation.[19] In a study of dogs, immediate defibrillation was effective for episodes of fibrillation if it was limited to approximately 3 minutes.[17]

There may be a cut-off time also in patients below which defibrillation first is best. Immediate defibrillation is highly effective in monitored patients treated within the first minute or two.[1,20,21] Such patients have excellent outcomes as shown by many years of experience in coronary care units and in other situations in which defibrillators are immediately available.[22]

Figure 2. Estimated Probability of Survival to Hospital Discharge Plotted Against Response Time



Average fraction of surviving patients for each 2-minute interval. Lines indicate logistic regression models with time as independent variable fitted separately for each of the 2 groups.

Similar to the results of Cobb et al,[8] we did not find a higher survival rate with CPR prior to defibrillation for patients with short response times, but nor was survival worse. We cannot exclude that this could be due to a type II error, and a much larger study with a finer division of the response times may give better survival with immediate defibrillation for short response times. The best average cut-off time for CPR first vs de-

fibrillation first is therefore not presently known. From our calculations based on this limited material, we hypothesized this to be around a 4- to 5-minute response time.

There did not appear to be a difference in outcome in the CPR first group between patients with response times either up to or longer than 5 minutes. The probability of being discharged alive tended to decrease with time when estimated in a logistic regression model (Figure 2), but the fall-off rate with time before defibrillation was much more apparent in the standard group, which is consistent with previously suggested rates.[2] However, even though the 5-minute cut point was prespecified in this study, the findings are based on nonrandomized subgroups, and therefore require confimation in future clinical trials.

There is no contrast between our study and studies concluding that time to defibrillation is the most important factor for survival.[1,23,24] In those studies, defibrillation was attempted as soon as possible, while deliberately delaying defibrillation to provide CPR was not evaluated. Also, the response time in the present study and thus the time before defibrillation was an important factor for survival, but the analysis indicates that there was an interaction between time and whether the ambulance personnel performed defibrillation prior to CPR. The delay before defibrillation is still important. The outcome from ventricular fibrillation is better with response times of 3 minutes than of 7 or 10 minutes. For response times longer than 5 minutes, the outcomes appear to improve if defibrillation is delayed to perform CPR first. Other evidence from both clinical and animal studies suggests that electroshock of prolonged ventricular fibrillation commonly is unsuccessful,[17] with an increased probability of converting ventricular fibrillation to a more resuscitation-refractory rhythm, such as asystole or pulseless electrical activity.[17]

The basis for the worsened electrical and mechanical cardiac function with prolonged ventricular fibrillation[6] seems related to the relatively high metabolic requirements for ventricular fibrillation, lack of oxygen supply, and an ultimate depletion of metabolic substrates and high-energy phosphate stores.[3] Cardiopulmonary resuscitation might provide a critical amount of cardiac perfusion and improve the metabolic state of the myocytes in patients with ventricular fibrillation, with a potentially more favorable response to defibrillation.

In our study, defibrillation prior to CPR by the ambulance personnel had an effect on outcomes, even though more than half the patients had received CPR performed by a bystander, which also was associated with survival. Previous studies have indicated that the effects of CPR performed by a bystander depends on the quality.[25] In a study from Oslo,[13] only 47% of the CPR performed by a bystander was rated as good.

Cobb et al[8] used 1.5 minutes of CPR, Robinson et al[16] used 2 minutes, and we used 3 minutes of CPR before defibrillation. The optimal duration of delaying defibrillation to perform CPR may be difficult to define, and most likely depends on the condition of the myocardium, which is dependent on the duration of the cardiac arrest and the quality of CPR performed by a bystander. Ideally, whether CPR should be started and defibrillation postponed should be determined by the frequency spectrum of the electrocardiogram, which can predict the probability of ROSC after defibrillation.[5]

In this study, we also increased the duration of CPR between defibrillation series from 1 to 3 minutes. The probability of ROSC after defibrillation as judged from spectral analysis of the electrocardiogram appears to deteriorate rapidly in the absence of CPR.[6] In patients with a median probability of ROSC of 50%, there was a decrease to a median of 8% after 20 seconds without CPR.[6] A series of 3 defibrillation attempts usually takes approximately 45 seconds, and it was hypothesized that 3 minutes of CPR might be more appropriate than the traditional 1 minute if the myocardium can be improved with CPR.

In this study, the neurological outcome was good in survivors in both groups. The concern that a strategy that results in a higher rate of ROSC after longer periods of cardiac arrest would generate more survivors with severe neurological damage did not occur. There was no difference in neurological outcome in the patients who survived in the 2 groups, and the results compare favorably with previous research.[8,26] In the study by Cobb et al,[8] there was a tendency toward improved neurological outcome ($P<.11$) in the group who received defibrillation prior to CPR.

Use of the Glasgow-Pittsburgh outcomes (CPC and OPC) is recommended in the international Utstein guidelines for reporting results after cardiac arrest.[11] Most outcome studies only report CPC and OPC at the time of hospital discharge, and the accuracy of this for predicting the function and quality of life later after discharge has been challenged by Hsu et al,[27] who reported that a CPC score of 1 at hospital discharge had a sensitivity of 78% and a specificity of 43% for predicting that quality of life at a later date was the same as or better than prior to cardiac arrest. They also found poor correlation between the CPC and a functional status questionnaire, and stated that part of problem might be caused by the CPC and OPC being scored by physicians and not patients, and that physicians appear to be inaccurate judges of patient function.[27] In the present study, we are reporting 1-year follow-up and the basis of the scores is the patient or relative's own evaluation of function, mood, and memory compared with abilities prior to cardiac arrest. In May 2002 when the follow-up questionnaire was sent out, 29 patients were still alive. Twenty-seven patients or their relatives answered the follow-up questionnaire. With a response rate of 93%, we believe it is unlikely that this can have created much of a bias in the results.

In most cardiac arrest studies, the time intervals from patient collapse are only estimates, but probably are fairly reasonable estimates in our study because 93% were witnessed. This high percentage of cardiac arrests that were witnessed probably explains why this was not an independent predictor of sur-

vival in this study. The high proportion of men in our study (87%) is somewhat higher than previously reported in the same EMS service (76%)[28] or that reported in a large Swedish study with 10 966 patients (72%).[29] We have no specific explanation—it could be due to chance.

While defibrillation is the essential intervention in ventricular fibrillation, defibrillation alone does not ensure return of an organized cardiac rhythm, restoration of circulation, or long-term survival, particularly when the start of treatment has been delayed. Providing CPR prior to delivery of a precordial shock for ventricular fibrillation is not novel. For a number of years it was considered useful to apply CPR to "coarsen ventricular fibrillation." However, that policy was abandoned in favor of defibrillation as soon as possible for all patients with ventricular fibrillation.[30,31] Lack of improvement in survival rate and outcome after sudden cardiac arrest despite global, systematic implementation of current resuscitation guidelines, and based on the study by Cobb et al[8] and our data, signal the need for reevaluation of the recommendations. Weisfeldt and Becker[32] have recently proposed a 3-phase time-sensitive model for treatment of ventricular fibrillation. An approximately 4-minute electric phase with immediate defibrillation, followed by a circulatory phase from approximately 4 to 10 minutes with CPR prior to defibrillation, and a third metabolic phase when circulating metabolic factors, can cause additional injury beyond the factors of the local ischemia.

In summary, our findings support previous experimental and clinical work suggesting that CPR prior to defibrillation may be of benefit when there has been several minutes' delay before defibrillation can be delivered to patients with out-of-hospital ventricular fibrillation. Further trials are needed to evaluate this resuscitation strategy and to determine the optimal duration of CPR first in patients with ventricular fibrillation.

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