Preshock Cardiopulmonary Resuscitation Worsens Outcome From Circulatory Phase Ventricular Fibrillation With Acute Coronary Artery Obstruction in Swine

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Background—Some clinical studies have suggested that chest compressions before defibrillation improve survival in cardiac arrest because of prolonged ventricular fibrillation (VF; ie, within the circulatory phase). Animal data have also supported this conclusion, and we have previously demonstrated that preshock chest compressions increase the VF median frequency and improve the likelihood of a return of spontaneous circulation in normal swine. We hypothesized that chest compressions before defibrillation in a swine model of acute myocardial ischemia would also increase VF median frequency and improve resuscitation outcome.

Methods and Results—Twenty-six swine were subjected to balloon occlusion of the left anterior descending coronary artery for 2 hours. The balloon was removed and VF was induced and untreated for 8 minutes. Swine were then treated with up to 3 stacked defibrillation shocks (n=13, shock-first group) or 3 minutes of chest compressions before shock (n=13, preshock cardiopulmonary resuscitation group). In the preshock cardiopulmonary resuscitation group, median frequency was increased from 7.0±0.8 to 13.9±1.6 Hz after chest compressions (P=0.002). Despite the improved median frequency in the preshock cardiopulmonary resuscitation group, 24-hour survival with favorable neurological status was significantly worse in the preshock cardiopulmonary resuscitation group (1/13) compared with the shock-first group (8/13, P=0.01).

Conclusions—In a swine model of prolonged VF in acute myocardial ischemia, 24-hour survival with favorable neurological status was more likely when defibrillation was performed first without preceding chest compressions. Myocardial substrate is an important factor in determining the optimal resuscitation strategy.

Key Words: cardiopulmonary resuscitation ▪ myocardial infarction ▪ heart arrest ▪ ventricular fibrillation ▪ defibrillation

More than 150 000 Americans experience a cardiac arrest each year, mostly in the prehospital setting, with approximately 60 000 cases attributed to ventricular fibrillation (VF).1 Patients with VF are more likely to survive an arrest compared to patients with other rhythms,2 and successful resuscitation from VF is time dependent.3,4 Unfortunately, emergency medical service providers are generally not on site until more than 5 minutes after collapse from VF, and defibrillation from such prolonged VF typically results in a nonperfusing rhythm (pulseless electric activity or asystole).3,4,6–8 Animal and human data indicate that successful resuscitation from these nonperfusing rhythms depends on prompt effective cardiopulmonary resuscitation (CPR).3,4,6,7 Because shocks alone frequently result in successful resuscitation from short duration VF, whereas preshock or postshock circulatory support is generally necessary for prolonged VF, Weisfeldt and Becker proposed that short duration VF (<5 minutes) is the electric phase of VF and that longer duration VF (5 to 15 minutes) is the circulatory phase.2,5

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Some animal and human data indicate that preshock chest compressions can improve outcome from circulatory phase VF compared with a “shock-first” strategy.3,4,6,7,9–11 Other human data do not support these findings.12 Importantly, it is currently unknown whether underlying myocardial substrate, such as acute myocardial ischemia and infarction, may influence the effectiveness of the strategy of preshock chest compressions compared with a strategy of shock first. We hypothesized that a strategy of preshock chest compressions

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would improve 24-hour survival with favorable neurological outcome from circulatory phase VF compared with a shock-first strategy in a swine model of prolonged VF after acute myocardial ischemia. We also hypothesized that preshock chest compressions would increase the VF waveform median frequency and improve the likelihood of achieving a return of spontaneous circulation (ROSC).

Methods

Experimental protocols were approved by the University of Arizona Institutional Animal Care and Use Committee. Twenty-six domestic female swine (27 ±1 kg) were anesthetized with 5% isoflurane in 100% oxygen delivered by a nose cone, followed by oral endotracheal intubation. A surgical plane of anesthesia was maintained with 1.5% to 3% isoflurane in air until the electric induction of VF. An infrared capnometer (47210A, Hewlett Packard Co) and pneumotachometer (3700, Hans Rudolph) were placed in-line to measure end-tidal concentration of carbon dioxide and minute ventilation, respectively. Mechanical ventilation was supplied via a rate- and volume-regulated ventilator (Narkomed 2A, North American Drager) using an initial rate of 12 breaths per minute and a tidal volume of 15 mL/kg. Rate and tidal volume were adjusted to maintain an end-tidal carbon dioxide level of 40 ±4 mm Hg. The lowest concentration of anesthetic that prevented movement during surgical instrumentation was used. Vascular introducer sheaths (5 to 7 F, Cordis Corp) were placed in the right internal and external jugular veins and right carotid artery by a sterile cutdown technique. Micromanometer-tip, Millar solid state pressure transducers (MCP-500, Millar Instruments) were placed in the descending aorta and right atrium. A Swan-Ganz thermistor catheter (Baxter Healthcare Corp) was placed in the pulmonary artery to determine cardiac output (CO) by thermodilution. A pressure transducer was periodically placed in the left ventricle to measure dP/dt. Correct catheter placement was verified by fluoroscopy. ECG, right atrial pressure, and aortic pressure were continuously recorded (P3P Ponemah Instrumentation Platform, Data Sciences International). Hemoglobin was measured with a blood gas analyzer (IL-1306 with 482 cooximeter, Instrumentation Laboratories). A pacing catheter electrode was placed into the right ventricle to induce VF with a 100 Hz alternating current. Ventricular fibrillation was confirmed by the ECG waveform and a precipitous decline in aortic pressure. Ventilation was discontinued, and a continuous ECG was obtained for the duration of untreated VF. Electrocardiographic signals (lead II) were filtered over a bandpass of 0.5 to 30 Hz. Median frequency and VF amplitude were computed from the power spectrum obtained by a fast Fourier transformation analysis over a 5-second interval, with the same techniques as previously used.9,10 This analysis was obtained at 8 minutes of VF and before the first defibrillation shock.

Acute myocardial ischemia was induced by placement of a coronary balloon catheter in the left anterior descending artery just beyond the second diagonal branch. The balloon was inflated and radioopaque contrast was injected to confirm total occlusion of the vessel. The balloon was kept inflated for 2 hours. After this period of time, the balloon was removed and VF was induced with a 100 Hz alternating current from the pacing catheter in the right ventricle.

The resuscitation protocol was initiated after 8 minutes of untreated VF (Figure 1). Resuscitation commenced with either 3 minutes of uninterrupted chest compressions (100 compressions/min) and rescue breathing with mechanical ventilation with 100% oxygen followed by defibrillation (preshock CPR) or immediate shock (shock first). Up to 3 sequential defibrillation shocks were delivered (stacked shocks) with the first 2 shocks at 200 J and the third and any subsequent defibrillation shocks at 300 J (monophasic waveform). If VF persisted, chest compressions were continued for 1 minute before the next defibrillation attempt. Mechanical ventilation with 100% oxygen was continued throughout the resuscitation. ROSC was defined as an unassisted pulse with a peak systolic aortic pressure greater than 50 mm Hg and a pulse pressure of at least 20 mm Hg lasting for at least 1 minute. Resuscitation was continued until ROSC was achieved and was terminated if ROSC could not be achieved by 25 minutes. Epinephrine (0.02 mg/kg) was administered at 20 minutes postarrest if defibrillation or pulseless electric activity had not been successfully terminated. Swine that were successfully resuscitated were observed in the laboratory for 1 hour, and then returned to the observation pen for an additional 24 hours of surveillance and assessment of neurological status. Neurological status was evaluated by swine cerebral performance categories.9,10 Category 1 was assigned to animals with normal levels of consciousness, gait, and feeding behavior; response to an approaching human, and response to human restraint. Category 2 was assigned to animals with mild dysfunction in any of these areas, category 3 to more severe dysfunction including an inability to stand, walk, or eat. Category 4 was assigned to animals in coma with minimal response to noxious stimuli, and category 5 was assigned to dead animals. Categories 1 and 2 were regarded as a favorable neurological state. The following outcome variables were assessed: (1) termination of VF with the first shock, (2) ROSC achieved with the first set of shocks, (3) ROSC achieved after the first set of shocks with up to 3 minutes of postshock chest compressions, (4) ROSC achieved by the end of the resuscitation protocol, (5) 24-hour survival, and (6) 24-hour survival with favorable neurological state.

Statistics

Continuous variables were evaluated by Student t test or ANOVA and reported as mean ±SD. Repeated observations were assessed by a paired Student t test. Comparison of discrete variables was accomplished by a Fisher exact test. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

A total of 26 acute MI swine were studied: 13 animals in the preshock CPR group and 13 animals in the shock-first group. Baseline characteristics are provided in Table 1. Right atrial pressure was higher in the preshock CPR group (Table 1). However, there were no significant differences in weight,
The median frequency at 8 minutes of untreated VF was similar in the preshock CPR group (7.0±0.8 Hz) and shock-first group (9.1±0.7 Hz, \( P=\text{NS} \)). The 3 minutes of preshock CPR improved the VF median frequency in the preshock CPR group to 13.9±1.6 Hz (\( P=0.002 \)). Therefore, before the first defibrillation shock attempt, VF frequency was higher in animals with preshock CPR (13.9±1.6 Hz versus 9.1±0.7 Hz in the shock-first group, \( P=0.01 \)). The VF amplitude was similar in the 2 groups at 8 minutes of untreated VF (46.0±1.4 mV shock-first group versus 45.0±0.8 mV preshock CPR group), and after 3 minutes of preshock CPR the amplitude increased to 49.1±2.4 mV (\( P=\text{NS} \)).

Twenty-four–hour survival with favorable neurological outcome was significantly more likely to occur in shock-first animals: 8 of 13 compared to 1 of 13 animals in the preshock CPR group (\( P=0.01 \), Table 2). Other outcome variables were not significantly different between groups but tended to favor the shock-first group of animals. Termination of VF with the first shock (with or without a perfusing rhythm to follow) occurred in 11 of 13 shock-first animals and 6 of 13 preshock CPR animals. With up to 3 minutes of chest compressions after the first shock, a perfusing rhythm was restored in 5 of 13 shock-first animals and in 1 of 13 preshock CPR animals. There was also a trend for improved survival at 24 hours in the shock-first group (8 of 13) compared with the preshock CPR group (3 of 13, \( P=0.11 \)).

Of the 11 animals that survived 24 hours, 8 animals required 1 shock only during resuscitation, and 3 animals required multiple shocks (range, 4 to 10 shocks), including shocks needed to treat recurrent VF. Only 1 animal that survived 24 hours (in the preshock CPR group) required epinephrine. Animals that survived 24 hours required an average of 5.7 minutes of resuscitation (range, 1 to 11.25 minutes).

## Discussion

These data demonstrate that 24-hour survival with favorable neurological outcome was substantially more likely with a shock-first strategy compared with a preshock CPR strategy in a swine model of prolonged VF after acute myocardial ischemia. These findings are in stark contrast to previous results from our laboratory and other laboratories showing that preshock CPR is a superior strategy for prolonged (circulatory phase) VF among swine without acute myocardial ischemia. Although VF waveform frequency improved after 3 minutes of preshock chest compressions in these swine with VF after acute myocardial ischemia, the VF waveform frequency improvements did not translate into higher rates of initial successful resuscitation or 24-hour survival.

In previous swine studies without prearrest acute myocardial ischemia, we have shown that preshock CPR improved VF median frequency and improved myocardial readiness for successful resuscitation and thereby improved the response to initial defibrillation attempts compared with a shock-first strategy in both 10-minute untreated VF\(^{9}\) and 8-minute untreated VF models.\(^{10}\) These previous findings were consistent with earlier animal studies by others also indicating that preshock CPR could improve initial defibrillation success compared with a shock-first strategy for prolonged VF of \( \geq 8 \) minutes, but not for VF \( \leq 5 \) minutes.\(^{11,13,14}\) These animal studies suggest that between 5 and 8 minutes the myocardium without prearrest ischemia transitions from the electric to circulatory phase, where chest compressions before defibrillation are beneficial.

In contrast, we find in animals with prearrest myocardial ischemia, 24-hour survival with favorable neurological outcome was significantly decreased with a preshock CPR treatment strategy. Furthermore, these animals rarely attained ROSC with the first shocks regardless of treatment strategy: 1 of 13 animals with preshock CPR and 0 of 13 animals with shock first. Why did animals with prearrest acute myocardial ischemia have worse outcomes with a preshock CPR strategy in contrast to the animals without prearrest myocardial ischemia that conversely had benefited from the preshock CPR? Our data cannot answer this important question. It is possible that in acute myocardial ischemia the onset of the circulatory phase is shifted to a later time, such that at 8 minutes swine may still be within the electric phase. Perhaps the prearrest balloon dilation of the coronary arteries and acute myocardial ischemia provided a preconditioning that allowed the myocardium to remain in the electric phase longer and to respond more favorably to the initial defibrillation attempts. The benefits of the additional 3 minutes of preshock CPR in preparing the myocardium for successful initial response to defibrillation may have been overshad-
owed by the benefits of preconditioning, and the adverse effects of 3 more minutes before the first shock may have been unmasked.

Another possibility is that the difference in outcomes in these 2 experiments after 8 minutes of untreated VF is related to the duration of chest compressions, which was increased from 90 seconds in the previous studies without myocardial ischemia to 3 minutes in this study with prearrest myocardial ischemia. However, we have previously demonstrated benefits of preshock CPR after 3 minutes of chest compressions. In that study, we compared preshock CPR versus shock first after 10 minutes of untreated VF. In addition, human studies have demonstrated improved outcomes after either 90 seconds or 3 minutes of preshock CPR compared with shock first. Therefore, we do not believe that the longer duration of CPR with the acute myocardial infarction model is responsible for the differences in outcome compared with our previous preshock CPR study after 8 minutes of untreated VF without myocardial ischemia.

It has been proposed that ischemic preconditioning results in protection of the myocardium from subsequent ischemic insults by activation of a transcription factor, hypoxia-inducible factor (HIF-1). In a murine model of repetitive coronary occlusion to achieve ischemic preconditioning, activation of HIF-1 was associated with cardioprotection with smaller infarct sizes from subsequently induced ischemia, whereas the suppression of HIF-1 abolished this cardioprotective effect. Activation of this transcription factor or some other factor during myocardial ischemia in our swine model may have maintained the myocardium in the electric phase during VF and improved the likelihood of successful defibrillation to a perfusing rhythm.

**Clinical Significance**

What is the clinical relevance of this novel observation that preshock CPR can have adverse effects in the setting of acute myocardial ischemia? Landmark studies in Seattle and Norway have demonstrated that chest compressions before the first defibrillation shock can improve outcomes from out-of-hospital VF when emergency services providers arrive greater than 45 or 516 minutes after the initial emergency service call. These 2 clinical studies and the previous animal investigations are the basis for the current paradigm: prearrest CPR is recommended for prolonged VF.2,5

In a more recent randomized controlled trial, Jacobs and colleagues found no significant difference in achieving ROSC among the patients who were randomized to preshock CPR or to shock first. Survival to hospital discharge was also not significantly different between preshock CPR and shock-first patients. Unlike the 2 other studies, there was no tendency of differential results with brief duration VF versus prolonged duration VF. However, none of these 3 clinical studies addressed the issue of concomitant coronary obstruction with acute myocardial ischemia or infarction. The clinical significance of this swine study of acute myocardial ischemia is that it offers a possible explanation for the contradictory results of human studies, if the population studied by Jacobs included more patients with acute myocardial ischemia. In addition, these data suggest that a shock-first strategy may be superior to a preshock CPR strategy for patients with clear evidence of prearrest acute myocardial infarction even when the duration of VF is greater than 5 minutes.

**VF Waveform**

The VF waveform data from our swine acute myocardial infarction study raise another important question: does the myocardial substrate need to be considered for appropriate interpretation of the VF waveform. Animal and human data have established that higher VF median frequencies are associated with successful defibrillation to ROSC. However, the higher median frequencies attained in this study with preshock CPR did not translate into an improved outcome. Perhaps the optimal VF waveform for successful defibrillation and resuscitation with favorable neurological outcome is dependent on myocardial substrate, in particular the presence of prearrest myocardial ischemia. Consistent with this concept are previous observations indicating that VF waveforms and responses to shocks are influenced by myocardial substrate.27–29

The proportion of sudden cardiac death attributable to ventricular fibrillation in the setting of acute myocardial infarction is unclear, with autopsy studies demonstrating acute coronary thrombosis in 80% of young victims, whereas other studies have suggested lower percentages of 50% or even 15%. Of patients with acute myocardial infarction, it is estimated that approximately 20% develop VF within the first 15 hours. Among patients who do survive to hospital admission, 48% were found to have acute coronary occlusion and successful angioplasty was an independent predictor of survival. Thus, a model of prearrest acute myocardial ischemia and infarction is a clinically relevant model to investigate, particularly if the majority of sudden cardiac arrest attributable to VF is related to myocardial ischemia. Further investigation is warranted to determine the influence of resuscitation interventions and myocardial substrate on the predictability of defibrillation. We speculate that the predictability of successful resuscitation based on a VF waveform will require additional consideration of the duration of VF; the previous resuscitation efforts that have occurred, and the underlying myocardial substrate of the fibrillating myocardium.

**Limitations**

In our experimental model, VF was induced electrically in young healthy swine after removal of the balloon catheter. This model allowed for reperfusion of the vessel at the time of VF induction. This process is presumably relevant to clinical scenarios, such as myocardial ischemia resulting from coronary vasospasm or other acute coronary syndromes with postarrest coronary artery perfusion. However, this method of temporary coronary occlusion with a balloon catheter may not replicate the clinical situation of acute coronary occlusion attributable to plaque rupture and coronary thrombosis. In the latter situation, coronary reperfusion may not occur without pharmacological or percutaneous coronary intervention, although VF arrest may occur after such reperfusion. We chose to deflate the balloon before VF induction so that ongoing cardiogenic shock related to myocardial infarction would not confound our results, particularly with regard to assessing 24-hour neurological outcome. Also, this model may result in preconditioning that might not occur in many patients with
acute VF cardiac arrests. However, it is possible that preconditioning occurs in humans who have an acute myocardial infarction before VF. Despite these limitations, animal models with acute myocardial ischemia have advantages in representing clinical VF compared with nonischemic models.

We also acknowledge that by performing statistical tests to assess multiple outcomes there is a chance for a type I statistical error, and that the probability values that we obtain should ideally be adjusted. However, adequately correcting for this “multiple comparisons–like” effect is not feasible, as the statistical test used, the Fisher exact test, is already a highly conservative test, and a standard Bonferroni correction would likely yield an overly aggressive correction for this uncertainty. Importantly, the most clinically relevant outcome, 24-hour survival with favorable neurological outcome, was substantially more likely in the shock-first group, even though the differences did not reach statistical significance.

Conclusions
In this swine model of prolonged VF with prearrest acute myocardial ischemia, the 24-hour survival rate with favorable neurological outcome was better with a strategy of shock first compared with preshock chest compressions. This study suggests that myocardial substrate is an important factor in determining the optimal resuscitation strategy. The clinical relevance of these findings warrants further investigation.

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Disclosures
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References
CLINICAL PERSPECTIVE

Population studies have shown inconsistent results concerning the utility of delaying the first defibrillation shock to perform chest compressions first in cardiac arrest due to prolonged ventricular fibrillation. Animal studies in normal swine, however, have shown that preshock chest compressions improve the likelihood of attaining a perfusing rhythm after defibrillation. It is also known that an altered myocardial substrate, such as acute myocardial ischemia due to coronary occlusion, may complicate resuscitation. This study investigated whether preshock chest compressions improve resuscitation outcome in the state of acute myocardial ischemia in a swine model of cardiac arrest due to ventricular fibrillation. In swine subjected to balloon occlusion of the left anterior descending artery prior to the induction of ventricular fibrillation, 24-hour survival with favorable neurological status was significantly worse in swine that receive chest compressions prior to the first defibrillation compared with swine treated with shocks first. This study suggests that a shock-first strategy may be superior to a preshock chest compression strategy for patients with clear evidence of prearrest acute myocardial infarction, even when the duration of ventricular fibrillation is more than 5 minutes. These findings warrant further investigation.
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