“Bystander” Chest Compressions and Assisted Ventilation Independently Improve Outcome From Piglet Asphyxial Pulseless “Cardiac Arrest”

Robert A. Berg, MD; Ronald W. Hilwig, DVM, PhD; Karl B. Kern, MD; Gordon A. Ewy, MD

Background—Bystander cardiopulmonary resuscitation (CPR) without assisted ventilation may be as effective as CPR with assisted ventilation for ventricular fibrillatory cardiac arrests. However, chest compressions alone or ventilation alone is not effective for complete asphyxial cardiac arrests (loss of aortic pulsations). The objective of this investigation was to determine whether these techniques can independently improve outcome at an earlier stage of the asphyxial process.

Methods and Results—After induction of anesthesia, 40 piglets (11.5±0.3 kg) underwent endotracheal tube clamping (6.8±0.3 minutes) until simulated pulselessness, defined as aortic systolic pressure ≤50 mm Hg. For the 8-minute “bystander CPR” period, animals were randomly assigned to chest compressions and assisted ventilation (CC+V), chest compressions only (CC), assisted ventilation only (V), or no bystander CPR (control group). Return of spontaneous circulation occurred during the first 2 minutes of bystander CPR in 10 of 10 CC+V piglets, 6 of 10 V piglets, 4 of 10 CC piglets, and none of the controls (CC+V or V versus controls, P<0.01; CC+V versus CC and V combined, P=0.01). During the first minute of CPR, arterial and mixed venous blood gases were superior in the 3 experimental groups compared with the controls. Twenty-four-hour survival was similarly superior in the 3 experimental groups compared with the controls (8 of 10, 6 of 10, 5 of 10, and 0 of 10, P<0.05 each).

Conclusions—Bystander CPR with CC+V improves outcome in the early stages of apparent pulseless asphyxial cardiac arrest. In addition, this study establishes that bystander CPR with CC or V can independently improve outcome.

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Key Words: cardiopulmonary resuscitation ■ heart arrest ■ ventilation ■ asphyxia ■ pediatrics

Bystander cardiopulmonary resuscitation (CPR) improves survival from prehospital ventricular fibrillatory (VF) cardiac arrest, even though it is only a bridge until defibrillation.1-3 For asphyxial cardiac arrests, bystander CPR can be definitive therapy.1 Nevertheless, in 2 recent studies, there were no attempts at bystander CPR for 74% and 61% of children with prehospital cardiac arrests.4,5

Single-rescuer bystander CPR includes mouth-to-mouth rescue breathing and chest compressions (CC), complex psychomotor tasks that are difficult to teach, learn, remember, and perform.1,6 Animal and clinical investigations suggest that bystander CPR without assisted ventilation (ie, no mouth-to-mouth rescue breathing) may be as effective as CPR with assisted ventilation for VF cardiac arrests.2,3,7-12 However, rescue breathing is considered especially important for children in cardiac arrest because a respiratory problem so often initiates the event and VF is relatively uncommon.1,4,13

In a recent swine study of simulated pediatric asphyxial cardiac arrest (no aortic pulsations), chest compressions plus assisted ventilation (CC+V) resulted in markedly superior outcome compared with no “bystander” CPR or CC without (V).14 Clinical and epidemiological data suggest that some children with apparent cardiac arrest respond to bystander CPR with CC alone or rescue breathing alone.2,15-17 Perhaps these patients are apneic, unresponsive, and apparently pulseless but not yet in complete cardiac arrest. They may have had inadequate blood pressure without total loss of aortic pulsation (asphyxial shock).18

The purpose of this investigation was to determine whether CC alone and V alone (V) can independently improve outcome at an early stage of apparent asphyxial cardiac arrest (systolic BP<50 mm Hg) in piglets. In a previous piglet study, CC and V did not improve outcome from complete asphyxial cardiac arrest (no aortic pulsations).14 Our hypotheses were that bystander CPR with CC or V would be...
superior to no bystander CPR, and each would be inferior to CC+V earlier in the asphyxial process.

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 2- to 3-month-old domestic piglets 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 (0.5% to 1.5%). The tidal volume was initially set at 15 mL/kg and ventilator rate at 12 breaths per minute; ventilator settings were adjusted to maintain end-tidal carbon dioxide at 35 to 40 mm Hg (4.7 to 5.3 kPa).

After a surgical plane of anesthesia had been achieved, introducer sheaths were placed in the right external jugular vein, right carotid artery, and left external jugular vein by cutdown technique. High-fidelity, solid-state, micromanometer-tipped Millar catheters were advanced through the carotid artery and external jugular vein into thoracic locations. A fluid-filled balloon-tipped flotation catheter was placed in the main pulmonary artery through the right external jugular introducer sheath. Catheter placements were performed under fluoroscopic guidance.

Measurements
Right atrial and thoracic aortic pressure waveforms, as well as ECG and end-tidal PCO2 measurements (model 47210A, Hewlett Packard), were continuously monitored and recorded on the 4-channel Gould ES1000 recorder throughout the experiment until the 1-hour simulated intensive care unit period ended. Coronary perfusion pressure during CPR was calculated by subtracting right atrial relaxation (midaortic) pressure from simultaneous aortic relaxation pressure at a single point during 3 consecutive compression-relaxation cycles. Arterial blood gas specimens were obtained from the thoracic aorta and mixed venous specimens from the main pulmonary artery at baseline (before cardiac arrest) and 1 minute after cardiac arrest. Oxygen saturation, PCO2, PO2, pH, and hemoglobin were measured with a blood gas analyzer (IL-1306 with model 482 co-oximeter, Instrumentation Laboratories).

Experimental Protocol
After baseline data were collected, the endotracheal tube was clamped and the piglet was asphyxiated until simulated pulselessness, as defined by an aortic systolic pressure <50 mm Hg (Figure). For the 8-minute simulated bystander CPR period, animals were randomly assigned to group 1, chest compressions and simulated mouth-to-mouth ventilation (CC+V); group 2, chest compressions only (CC); group 3, simulated mouth-to-mouth ventilation only (V); or group 4, no bystander CPR (control group). CC plus simulated mouth-to-mouth ventilation was provided in a manner consistent with standard single-rescuer CPR for children as described by the American Heart Association (AHA).1 This included ventilation with a simulated rescued exhaled gas mixture (FiO2 0.17 and FICO2 0.04) for 2 breaths followed by 15 manual CCs at a rate of 100 per minute, repeated sequentially. The research technician providing the manual ventilation alone was provided as a simulated expired gas mixture (FiO2 0.17 and FICO2 0.04), delivered via bag-valve–endotracheal tube at 12 to 15 breaths per minute. For the control group, the endotracheal tubes remained clamped, and no ventilation or CCs were provided during this bystander CPR period. The experimental bystander CPR technique was discontinued when evidence of successful resuscitation occurred, such as spontaneous respirations, vigorous motor activity, and substantial increases in the aortic blood pressure. Otherwise, the bystander CPR technique was continued throughout the simulated bystander CPR period.

For animals that did not attain return of spontaneous circulation (ROSC) during the 8-minute bystander CPR period, full advanced life support was provided as if the paramedic unit had arrived at the scene. All CC piglets without ROSC underwent endotracheal intubation during the last minute of the bystander CPR period and were then ventilated with 100% oxygen beginning at 8 minutes of CPR. CCs were provided at a rate of 100 per minute and rescue breaths at a rate of 12 to 15 per minute. Intravenous epinephrine (0.02 mg/kg) was administered 2 minutes after the simulated paramedic team arrived and was repeated every 3 minutes, as necessary. The 2-minute interval is consistent with the amount of time for a typical paramedic team to obtain intravenous access.10 The epinephrine dose of 0.02 mg/kg was administered rather than the AHA-recommended dose of 0.01 mg/kg because of its established use in swine experiments.11-12 When VF occurred, defibrillation was attempted with 50 J. If unsuccessful, the second defibrillation attempt was also with 50 J, and the third and subsequent attempts were with 100 J. ROSC was defined as unassisted aortic pulse with a systolic blood pressure >50 mm Hg and pulse pressure >20 mm Hg for ≥1 minute.

All successfully resuscitated animals were supported aggressively for 1 hour in a simulated intensive care setting. Systolic blood pressure was maintained at >80 mm Hg with dopamine and/or volume administration as clinically indicated. All piglets received normal saline 10 mL/kg IV during the intensive care period. Ventricular arrhythmias were treated with electroshocks or lidocaine as necessary. Mechanical ventilation was provided with 100% oxygen and adjusted to obtain an end-tidal carbon dioxide of 30 to 40 mm Hg (4.0 to 5.3 kPa). Recurrent cardiac arrest was treated with standard advanced life support according to the AHA decision trees. Throughout the intensive care period, isoflurane was administered as necessary to maintain adequate analgesia and anesthesia. At the end of 1 hour, all animals were weaned off pharmacological support, ventilatory support, and anesthesia and 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.7,9-12 Briefly, swine cerebral performance category is a global assessment of neurological function. Category 1 was assigned to piglets 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 piglets 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 piglets 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. After the 24-hour evaluation, survivors were killed by infusion of pentobarbital sodium/phenytoin sodium.

Data Analysis
Systolic and diastolic aortic pressures, right atrial pressures, and ECGs were collected from the graphic records at 1-minute intervals, every 2 minutes after endotracheal tube clamping (before cardiac arrest), and during the simulated bystander CPR period. Bystander CPR hemodynamic data were excluded after animals had returned spontaneous circulation.

Continuous variables such as blood pressures, coronary perfusion pressures, and blood gases analyses were evaluated by ANOVA. For all variables with significant differences by ANOVA, post hoc comparisons were evaluated by Fisher’s protected least significant difference test. Comparisons of blood pressures and blood gases during bystander CPR between the CC and CC+V groups were also evaluated by unpaired Student’s t test because the available data from the other 2 groups were not comparable physiologically owing
to absence of CC. Continuous variables are described as mean±SEM. Comparisons of discrete variables, such as rate of return of spontaneous circulation, 1-hour intensive care unit survival, 24-hour survival, and good neurological outcome were evaluated by Fisher’s exact test.

Results

Forty animals were studied (weight, 11.5±0.3 kg). The 4 groups did not differ with respect to baseline weights, hemodynamics, or hemoglobin concentrations (Table 1). Baseline arterial and mixed venous $\text{PO}_2$, $\text{SO}_2$, pH, and $\text{PCO}_2$ were also not different among the 4 groups (Table 2).

The mean time interval from endotracheal tube clamping until simulated pulselessness was 6.8±0.3 minutes and did not differ among the groups (Figure). Thirty-nine of the 40 animals exhibited pulseless electrical activity with bradycardia or sinus rhythm at the time pulselessness was declared. One animal had ventricular tachycardia; none had VF. The rhythm deteriorated to VF in 17 of 40 piglets at some point during the experiment. Thirteen of the animals went into VF during the bystander period (4 CC, 3 V, and 6 controls); 2 of these 13 converted to asystole before simulated arrival of emergency medical services. Eleven of the 40 (27%) were in VF as the “paramedics” arrived. An additional 4 piglets went into VF during the paramedic resuscitation. Only 1 of the 17 piglets with VF at any time during the experiment survived for 24 hours, compared with 19 of 23 that did not have VF, $P<0.001$.

After 1 minute of the bystander CPR period, arterial and mixed venous $\text{PO}_2$, $\text{SO}_2$, $\text{PCO}_2$, and pH were markedly better in the 3 experimental groups than the control group (Table 2). Similarly, the hemodynamic profiles (aortic blood pressures and coronary perfusion pressures) were generally superior in the CC+V and CC groups compared with the V and control groups during the first 30 seconds of CPR (Table 3). The aortic compression (systolic) pressures in the CC+V and CC groups did not differ during the initial 30 seconds of CPR (before the CC+V piglets attained return of spontaneous circulation (ROSC)), suggesting that the force of compressions was comparable in the 2 groups.

The important outcome data are in Table 4. Most of the animals attained ROSC. All of the CC+V animals were successfully resuscitated during the first 2 minutes of the bystander period, as were nearly half of the animals in each of the other 2 experimental groups. All piglets that attained ROSC during the bystander period of this experiment did so within the first 2 minutes. Eighteen of the 20 piglets with ROSC during the first 2 minutes of bystander CPR survived for 24 hours, compared with only 1 of 20 piglets that did not attain ROSC during the bystander CPR period, $P<0.001$. Each of the 3 experimental groups had better survival rates than the control group. Both CC+V and V had improved 24-hour good neurological survival compared with the control group, and there was a similar trend toward improvement in the CC group as well. The rate of ROSC during the bystander CPR period was superior in the CC+V group to

<table>
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<tr>
<th>TABLE 2. Blood Gas Analyses</th>
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<td>V</td>
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<td>Control</td>
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MV indicates mixed venous (pulmonary arterial); Baseline, before asphyxia; and CPR 1 min, 1 minute after "bystander" CPR started.

*P<0.05 vs control; †P<0.01 vs control; ‡P<0.01 vs V.
TABLE 3. Hemodynamics During First 30 Seconds of CPR

<table>
<thead>
<tr>
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<th>CPP, mm Hg</th>
<th>AoD, mm Hg</th>
<th>RAD</th>
<th>AoS, mm Hg</th>
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<tr>
<td>CC</td>
<td>23±3*</td>
<td>33±2†</td>
<td>10±1</td>
<td>81±9§</td>
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<td>CC + V</td>
<td>29±3†</td>
<td>36±3†</td>
<td>7±1</td>
<td>89±10§</td>
</tr>
<tr>
<td>V</td>
<td>16±2</td>
<td>23±2</td>
<td>7±1</td>
<td>45±3</td>
</tr>
<tr>
<td>Control</td>
<td>9±2</td>
<td>21±3</td>
<td>10±3</td>
<td>42±3</td>
</tr>
</tbody>
</table>

CPP indicates coronary perfusion pressure; RAD, right atrial diastolic pressure (mm Hg). Other abbreviations as in Table 1.

*P<0.01 vs control; †P<0.01 vs V; ‡P<0.001 vs control; §P<0.001 vs V.

That in the combined CC and V groups (10 of 10 versus 10 of 20, P=0.01). There was a nonsignificant tendency toward superior good neurological survival rate in the CC+V group compared with the combined CC and V groups (8 of 10 versus 10 of 20, P=0.24).

Twenty piglets attained ROSC within 2 minutes of bystander CPR; 18 survived 24 hours, 17 with good neurological outcome. Six piglets did not attain ROSC until after paramedic arrival; 5 did not survive 24 hours. Of the 26 piglets with ROSC, 7 did not survive 24 hours. Four of these piglets were from the control group; 2 died of progressive cardiorespiratory failure <1 hour after the ICU period, and the other 2 were in severe cardiorespiratory distress and severely neurologically impaired by then. One of the 6 with ROSC from the CC group was similarly neurologically impaired, exhibited moderate cardiorespiratory distress <1 hour after the ICU period, and did not survive 24 hours. Two animals from the CC+V group inexplicably died before 24 hours despite apparent cardiorespiratory stability and good neurological status (ie, alert, walking, and eating) 2 hours after ROSC.

Nine of the 10 CC+V piglets, 4 of 10 CC piglets, 6 of 10 V piglets, and 0 of 10 control animals were walking, drinking, and acting nearly normal within 2 hours of the pulseless arrest (ie, good neurological outcome at 2 hours). Among piglets that survived for 2 hours after ROSC, 17 of 19 with good neurological outcome at that time survived 24 hours with good neurological outcome (2 died), yet only 1 of 5 with bad neurological status at 2 hours attained good 24-hour neurological outcome, P<0.01.

Difficulty with resuscitation and ICU management was further estimated by comparing the 4 groups in terms of number of epinephrine doses during resuscitation and the need for dopamine after resuscitation. Because all of the CC+V piglets and approximately half of the CC and V piglets had return of spontaneous circulation during the bystander CPR period, all 3 experimental groups needed fewer epinephrine doses than the control group (0.2±0.2 versus 1.3±0.5 versus 1.2±0.5 versus 2.8±0.4 doses, respectively, P<0.001). Dopamine administration did not differ among the 4 groups (1 of 10 CC+V, 1 of 10 CC, 0 of 10 V, and 2 of 10 controls).

Discussion

This study of simulated bystander CPR in a swine model of pediatric asphyxial pulseless cardiac arrest establishes that V alone or CC alone can independently improve outcome at this stage of the asphyxial process. Both techniques also improved arterial and mixed venous blood gases during the first minute of CPR compared with the control group. Furthermore, CC+V (standard single-rescuer bystander CPR) led to superior initial successful resuscitation rates (ROSC during bystander CPR) compared with V and CC.

This study is consistent with prehospital pediatric cardiac arrest experiences. Outcomes are dismal when the child is still in cardiac arrest by the time paramedics arrive, but excellent outcomes are typical when the child is successfully resuscitated before paramedic arrival.4,5,13,15–17,20–24 Successful resuscitation techniques have included mouth-to-mouth rescue breathing alone, CC alone, and CC plus mouth-to-mouth rescue breathing; however, authors have retrospectively questioned whether these patients needed resuscitation.2,5,15,16 This controlled swine study demonstrates that such bystander CPR techniques can result in prompt successful resuscitation during sufficiently severe asphyxia that resuscitation is needed.

A previous swine asphyxial cardiac arrest investigation established that CC+V improves outcome after asphyxial cardiac arrest with absence of aortic pulsations compared with CC, V, or no bystander CPR for 8 minutes.14 The experimental design was essentially identical to the present investigation except that the animals’ asphyxia was continued until complete loss of aortic pulsations, a later phase in the asphyxial process (8.9±0.4 minutes of endotracheal tube clamping versus 6.8±0.3 minutes in the present study). The severe hypoxemia and acidosis with resultant severe cardiac and neurological insults limited the effectiveness of CC or V in that study. However, earlier in the asphyxial process (the present study), CC and V are each independently more effective than no bystander CPR.

In contrast to these asphyxial studies, simulated bystander CPR with CC has been as effective as CC+V in clinically relevant animal models of fibrillatory cardiac arrests.7–12 Those studies included brief untreated cardiac arrest intervals (30 seconds and 2 minutes) with excellent outcomes (90% to 100% survival rates) and longer untreated cardiac arrest intervals (5 minutes) with ~50% survival rates.

Consistent with the VF animal studies is a prospective uncontrolled investigation of prehospital bystander CPR (mostly adults).2,3 Long-term survival was comparable among those treated with good-quality CC alone (17 of 116, or 15%) and those treated with good-quality CC plus mouth-to-mouth ventilation (71 of 443, or 16%). The outcomes were

TABLE 4. Outcome Data

<table>
<thead>
<tr>
<th></th>
<th>CC+V</th>
<th>CC</th>
<th>V</th>
<th>No CPR</th>
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<tbody>
<tr>
<td>ROSC (&lt;2 min)</td>
<td>10/10</td>
<td>6/10</td>
<td>6/10</td>
<td>4/10</td>
</tr>
<tr>
<td>ROSC (&lt;2 min)</td>
<td>10/10</td>
<td>6/10</td>
<td>6/10</td>
<td>4/10</td>
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<tr>
<td>1-h survival</td>
<td>10/10</td>
<td>6/10</td>
<td>6/10</td>
<td>4/10</td>
</tr>
<tr>
<td>24-h survival</td>
<td>8/10</td>
<td>5/10</td>
<td>6/10</td>
<td>0/10</td>
</tr>
<tr>
<td>24-h neurologically normal</td>
<td>8/10</td>
<td>4/10</td>
<td>6/10</td>
<td>0/10</td>
</tr>
</tbody>
</table>

ROSC (<2 min) indicates ROSC during first 2 minutes of bystander CPR. Values are number of animals.

*P=0.05 vs No CPR; †P=0.01 vs No CPR; ‡P=0.001 vs No CPR; §P<0.01 vs CC and V combined.
superior with either of these techniques compared with those receiving no CPR (123 of 2055 survival, or 6%), P<0.001.

Because oxygenation and ventilation are clearly important for survival from fibrillatory cardiac arrest,25,26 why is assisted ventilation not necessary in VF models, yet quite important in asphyxial models? Immediately after an acute fibrillatory cardiac arrest, aortic oxygen and carbon dioxide concentrations do not vary from the prearrest state because there is no blood flow and aortic oxygen consumption is minimal. Therefore, when CCs are initiated, the blood flowing from the aorta to the coronary circulation provides adequate oxygenation at an acceptable pH. At that time, myocardial oxygen delivery is limited more by blood flow than oxygen content. Over the next several minutes, arterial oxygenation and pH become increasingly important for effective resuscitation.25,26 Adequate oxygenation and ventilation can continue without assisted ventilation because of chest compression–induced gas exchange and gasping ventilation during CPR.8–11,27 Assisted ventilation was not necessary in the fibrillatory arrest experiments because arterial oxygenation and pH and myocardial oxygen delivery were adequate with CC.

During asphyxia, oxygen consumption and carbon dioxide and lactate production continue for many minutes after endotracheal tube clamping before pulselessness or cardiac arrest. In addition, continued pulmonary blood flow after endotracheal tube clamping presumably depletes the pulmonary oxygen reservoir. In contrast to VF, asphyxia results in significant arterial hypoxemia and acidemia before resuscitation, which may not be essential for initial cardiopulmonary resuscitation.8–11,27 Assisted ventilation does not improve outcome in a porcine model of single-rescuer bystander cardiopulmonary resuscitation.19,28 These issues tend to bias the data in favor of the CC+V group.

A potential limitation of this study is that the experimental groups received excellent CC and rescue breathing. It is unlikely that excellent CC and rescue breathing can be provided by a single rescuer in the field. Even during 2-rescuer CPR, attention to rescue breathing may be counterproductive with respect to optimal CC.12,27 These CC+V animals benefited from optimal airway management and endotracheal tube placement before cardiac arrest. Mouth-to-mouth rescue breathing in a prehospital setting is unlikely to be nearly as controlled, effective, or safe. Rescue breathing before endotracheal intubation frequently causes gastric distension, which can lead to impairment of adequate ventilation and/or aspiration of gastric contents.1,27,28 These issues tend to bias the data in favor of the CC+V group.

Our clinical experience and research data regarding CPR in children, adults, and animals suggest that most bystanders perform CC poorly.29–31 We believe that outcomes from clinical cardiac arrests would improve with excellent CPR technique.

In conclusion, the outcomes in this experiment are consistent with epidemiological studies of prehospital CPR for apneic, unresponsive, pulseless children. Bystander CPR improves outcome, and many of the long-term survivors are successfully resuscitated by the bystanders before the paramedics arrive. Moreover, this study establishes that CC alone or V alone can independently improve outcome in early stages of apparent pulseless asphyxial cardiac arrest. Finally, the findings from our 2 investigations of piglet pulseless cardiac arrest support the present recommendations for bystander treatment of pediatric asphyxial cardiac arrest victims: CC+V is the treatment of choice, but either alone is better than no resuscitation attempt.1,14,27

Acknowledgment

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References


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