EXPERIMENTAL PAPER

A swine model of pseudo-pulseless electrical activity induced by partial asphyxiation

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Summary
Background: The incidence of pulseless electrical activity (PEA) as a presenting rhythm during cardiac arrest is increasing. The current animal models of PEA arrest, post-countershock or total asphyxiation, unreliably generate PEA for a specific time period. Neither of these models predictably generate pseudo-PEA. The purpose of this study was to create an animal model of pseudo-PEA that will allow for a prolonged time period in this arrest state for future research.

Methods: In a laboratory setting, five ventilated swine on inhaled anesthesia and 100% oxygen with continuous EKG recordings were instrumented with central aortic and venous pressure-transducing catheters. Animals were then switched to intravenous anesthesia while being ventilated with a 16% oxygen/84% nitrogen mix. Continuous EKG, aortic and venous pressures were recorded to a computerized data collection program. Arterial blood gas samples were taken every 10 min. Time until onset of pseudo-PEA, duration of pseudo-PEA, and cardiac rhythm during pseudo-PEA were recorded.

Results: Mean time to onset of pseudo-PEA was 80.6 ± 47.3 min. Mean duration of pseudo-PEA was 18.6 ± 6.2 min. Mean arterial pH at pseudo-PEA onset was 7.20 ± 0.05 with a mean associated base excess of −11.4 ± −5.94. No significant differences were noted in other recorded variables.

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Introduction

The incidence of pulseless electrical activity (PEA) as an initial presenting out-of-hospital cardiac arrest rhythm appears to be increasing.\(^1\)-\(^4\) The rise in the incidence of PEA is associated with a relative decrease in the incidence of out-of-hospital ventricular fibrillation (VF).\(^3\),\(^4\) This phenomenon may be due to earlier diagnosis and intervention in patients with coronary artery disease.\(^3\),\(^6\) As the incidence of PEA arrest increases, the need to further study PEA and to create new therapies that address this clinical condition becomes more apparent.

PEA is not a heterogeneous clinical entity. Patients in PEA have various levels of physiologic derangement, with associated blood pressures ranging from completely absent without cardiac wall motion (true PEA) through states of severe hypotension without clinically detectable pulses but with residual cardiac activity (pseudo-PEA).\(^5\) Some studies have found that a large percentage of the subset of patients who present in PEA are actually in pseudo-PEA, with blood pressures and pulses undetectable by routine clinical exam.\(^5\),\(^6\) Emergency department cardiac ultrasonography has further helped to establish this phenomenon, as cardiac wall motion is often detectable during resuscitation from PEA cardiac arrest using this modality.\(^6\),\(^7\)

At this point, there are no well-defined animal models that create a stable time window during which pseudo-PEA can be studied in a laboratory setting. Current accepted animal models of true PEA include a total asphyxial model or a post-countershock model, both of which can create a relatively stable but brief time window of PEA arrest.\(^5\),\(^9\) One study using the total asphyxial animal model of PEA has addressed the concept of pseudo-PEA in a defined fashion. Spreng et al., addressed the issue of pseudo-PEA while investigating the use of an esophageal Doppler probe in cardiac arrest. They found the duration of pseudo-PEA to be approximately 106 s from loss of femoral pulses (onset of pseudo-PEA) to loss of aortic fluctuations detected by the probe.\(^1\),\(^2\) They also noted that cardiac arrest was associated with a relative decrease in the incidence of out-of-hospital VF.

Conclusion: Partial asphyxiation using a 16% oxygen/84% nitrogen mix is a reliable laboratory method to create a prolonged state of pseudo-PEA in a swine model. The mechanism generating pseudo-PEA is hypoxemia-induced systemic acidosis. This model will allow sufficient time in this low-flow cardiac state for future research to be conducted.

Methods

The animal protocol was approved by the institutional animal care and use committee of the University of Colorado at Denver and Health Sciences Center. Five mature 35–50 kg swine were sedated using ketamine (15 mg/kg) and acepromazine (0.2 mg/kg). The animals were placed under general anesthesia using 2–3% isoflurane and 100% O\(_2\). The animals were endotracheally intubated and placed on a volume-controlled ventilator (Draeger EV-A). The animals were ventilated with a tidal volume of 10 cm\(^3\)/kg and a respiratory rate of 12–14 breaths per minute. End tidal CO\(_2\) was continuously monitored and minute ventilation was adjusted to maintain eucapnia. Appropriate baseline ventilation was confirmed by arterial blood gas analysis. Isoflurane was adjusted to maintain an adequate plane of surgical anesthesia as assessed by blood pressure and pulse rate.

The animals were instrumented with a microprocessor-tipped pressure-transducing catheter (Millar Instruments, Houston, TX, Model SPC-450) placed into the descending aorta above the diaphragm via a surgical cutdown of a femoral artery. A right atrial pressure-transducing catheter (Millar Instruments, Houston, TX, Model SPC-450) was placed either through a surgical cutdown of the external jugular vein or the femoral vein. Correct placement was confirmed by measurement and appropriate pressure waveform. A rectal temperature probe was placed and the animals were kept euthermic with a warming blanket. Continuous 3-lead EKG, aortic pressures, right atrial pressures, calculated coronary perfusion pressure (CPP) and temperature were recorded using a computerized software program (Chart 5, Powerlab, AD Instruments, Sydney, Australia) and saved to disc at 400 Hz.

After instrumentation, the animals were converted to continuous intravenous anesthesia using ketamine (50 mg/kg/min) and fentanyl (0.45 μg/kg/min). Isoflurane was gradually discontinued, and depth of anesthesia was maintained as determined by baseline blood pressure and heart rate readings. The animals remained in this plane of anesthesia for 15 min to allow isoflurane washout and to establish a stable level of continuous IV anesthesia prior to initiation of the arrest protocol. The animals were administered intravenous heparin (100 μg/kg) to prevent catheter clotting and pancuronium (0.1 mg/kg) for paralysis to prevent gasping during respirations. Intermittent boluses of ketamine (2 mg/kg), fentanyl (0.1 mg/kg), and pancuronium (0.5 mg/kg) were administered if needed to maintain adequate anesthesia and paralysis.

Once adequate anesthesia was obtained, the animals were ventilated with a hypoxic gas mixture of 16% oxygen/84% nitrogen for the duration of the experiment. Gas concentration was measured using an oxygen concentration analyzer (Oxygen Analyzer S-3A/I, Applied Electrochemistry, VMETEK). Arterial blood gas (pH, pCO\(_2\), pO\(_2\), HCO\(_3\), %saturation), serum sodium, serum potassium, serum glucose, hemoglobin, hematocrit, serum ionized calcium, and base excess (BE) were measured and recorded every 10 min (i-STAT CGB, Abbott Laboratories, East Windsor, New Jersey). The time to onset of pseudo-PEA was defined as the time from initiation of ventilations with the hypoxic gas mixture until an aortic systolic pressure waveform ≤ 60 mm Hg.
was recorded by the aortic catheter in the presence of an organized cardiac rhythm. The duration of pseudo-PEA was recorded and defined as the time from onset of pseudo-PEA until the absence of aortic pressure waveform fluctuations. Once the animal developed true PEA, the experiment was discontinued and the animal was euthanized.

**Results**

The mean time to onset of pseudo-PEA after initiation of the hypoxic gas mixture was 80.6 ± 47.3 min (mean ± S.D.). The mean duration of pseudo-PEA was 18.6 ± 6.2 min. The mean arterial pH at the time of pseudo-PEA onset was 7.20 ± 0.05 with a mean associated BE of −11.4 ± −5.94. Cardiac rhythm at the time of onset of pseudo-PEA was variable, but generally bradycardic without ventricular ectopy (see Figure 1).

No clinically significant changes were noted in core body temperature, serum sodium, serum potassium, serum glucose, serum ionized calcium, or hematocrit levels. Mean arterial blood gas analyses for the five animals at start of experimentation, at time of onset of pseudo-PEA, and at final time point prior to onset of true PEA are shown in Table 1, as well as significant electrolyte concentrations measured at each of these time points.

**Discussion**

Much of the past work related to cardiac arrest has been focused on resuscitation from ventricular fibrillation. As the demographics of cardiac arrest changes, there must also be a shift in the focus of research being done related to this field. PEA is becoming a more frequent presenting arrest rhythm to both EMS and emergency department providers, but ACLS algorithms used to treat this problem have undergone little change in the past decades. Only recently have new therapies started to address resuscitation from PEA and asystole. Devices and techniques such as the impedance threshold devise, pneumatic vest CPR, and active compression—decompression CPR may provide a survival benefit in patients presenting with PEA arrest, but studies are still ongoing.11—13

PEA is a heterogeneous clinical condition. Blood pressure is likely not clinically detectable below a systolic reading of 70 mmHg without invasive measures. Pseudo-PEA defines this state of clinically undetectable but present blood pressure with an associated cardiac rhythm on EKG monitoring. Theoretically, patients presenting with pseudo-PEA are more salvageable to hospital admission than those patients in true PEA. Few studies to date have examined the survival differences between these clinically different subgroups. Furthermore, no laboratory models have been created to study interventions for this clinical problem.

This hypoxic swine model is reliably able to generate a prolonged period of pseudo-PEA. The mechanism generating the pseudo-PEA event appears to be related to a hypoxemia-induced metabolic acidosis due to anaerobic metabolism as measured by serial ABG’s and BE levels. Although serum lactate levels were not directly measured in this experiment, the etiology of the acidosis is likely related...
to lactate production. Praise et al., reported on a comparison of lactate or BE during out-of-hospital cardiac arrest to determine metabolic acidosis. They found statistically significant correlations between lactate levels, BE levels, and pH. Their receiver–operator curve analysis showed that a cut-off point of 7 mmol/l lactate indicates a BE below –10 with a sensitivity of 96% and a specificity of 67%.

Using this model, we were able to recreate this increasingly important clinical condition in a laboratory setting while controlling for other common disturbances that are associated with PEA and pseudo-PEA arrest. These include hypothermia, hypercapnea, hyponatremia, hypo- and hyperkalemia, hypo- and hyper-glycemia, hypocalcemia, and electrically induced myocardial damage. This model will be used to examine interventions that will influence the ability to resuscitate animals from this clinical state as measured by changes in hemodynamic parameters related to survival. Interventions such as timing of chest compressions to influence CPP, the use of the external devices to maximize CPP, and drug administration to maximize CPP are all potential areas of investigation with this model. If interventions are found that improve CPP, survival studies would then need to be conducted.

Notably in this model there is variability in the time of onset and the duration of the pseudo-PEA event. The variability did not appear to be predictable and likely represents normal physiologic response differences and tolerance between the animals. This study is also limited by the small number of animals used, but appears generalizable as a methodology.

**Conclusion**

This hypoxic swine model is able to reliably generate relatively prolonged periods of pseudo-PEA prior to onset of true PEA. The PEA event is related to the development of hypoxemia-induce metabolic acidosis. This model may be useful for future studies related to the increasingly prevalent conditions of PEA and pseudo-PEA.

**Conflicts of interest**

None.

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