A comparison of electrically induced cardiac arrest with cardiac arrest produced by coronary occlusion

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KEYWORDS
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Left anterior descending coronary artery;
Ventricular fibrillation;
Ejection fraction;
Fractional area change

Summary
Objective: The present study was undertaken to compare an animal model of electrically induced VF with ischemically induced VF. In a preponderance of models of cardiac arrest and resuscitation in intact animals, ventricular fibrillation (VF) is induced by an alternating current delivered directly to the epicardium or endocardium. Yet, the applicability of such animal models has been challenged for it is not an electrical current alone but rather a current generated in the ischemic myocardium that triggers VF. Accordingly, a potentially more clinically relevant model was investigated in which spontaneous VF followed acute myocardial ischemia.

Methods: Twenty anesthetized pigs were randomized to either electrical fibrillation or myocardial ischemia following transient occlusion of the left anterior descending (LAD) coronary artery.

Results: VF was untreated for 7 min in both models after which mechanical ventilation and precordial compression were begun. Defibrillation was attempted after 5 min of CPR in both groups. VF appeared within 5.7 ± 2.0 min of LAD occlusion.

Conclusions: A significant increase in the number of post-resuscitation premature ventricular beats and recurrent VF followed ROSC and a significantly greater number of shocks was required for restoration of spontaneous circulation (ROSC) after LAD occlusion. Nevertheless, early post-resuscitation myocardial dysfunction, neurological recovery and 72 h survival were indistinguishable between the two models.

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Introduction

Sudden death due to cardiac arrest in patients is primarily due to underlying ischemic heart disease and especially in clinical settings of acute myocardial ischemia. Approximately one third of fatalities occur within the first 2 h after onset of symptoms of coronary insufficiency. Accordingly, ischemia and reperfusion have been implicated in the triggering of ventricular ectopic dysrhythmias and sudden cardiac death, often without evidence of acute coronary thrombosis or myocardial infarction. In animal studies, both Ouyang et al., and the research team headed by Ideker have reported that when VF was followed acute myocardial ischemia, significantly higher electrical energies were required for successful defibrillation in comparison with electrically induced VF. These studies have raised the question of whether electrically induced VF models are clinically relevant. However, when our group first defined post-resuscitation myocardial dysfunction, it did so in a porcine model in which VF was induced by an alternating current delivered to the endocardium of the right ventricle. Since then, appropriate support for the phenomenon of post-resuscitation myocardial dysfunction followed, followed by reports post-resuscitation myocardial dysfunction in human victims.

In further pursuit of this issue, we elected to compare electrically and ischemically induced VF in a large animal model. We focused specifically on differences in post-resuscitation myocardial function, neurological outcome, and survival. In accord with earlier reports, we hypothesized that cardiac arrest produced by transient occlusion of the left anterior descending (LAD) coronary artery would be less amenable to successful resuscitation with less favorable post-resuscitation and survival outcome.

Materials and methods

Twenty domestic male swine were randomized to one of two groups. In the first group of 10 animals, VF was induced by delivery of a 1.5 mA current to the right ventricular endocardium as previously described. In the second group of 10 animals, a balloon-tipped catheter was used to occlude the LAD coronary artery transiently. The study was approved by the Animal Care and Use Committee of the non-profit Weil Institute of Critical Care Medicine. All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and Published by the National Institutes of Health (NIH publication 86-32, revised 1985). The animal laboratories of the Weil Institute of Critical Care Medicine are fully accredited by American Association for Accreditation of Laboratory Animal Care (AAALAC) International.

Animal preparation

Animals weighing between 35 and 40 kg were fasted overnight but had free access to water. Anesthesia was induced by an intramuscular injection of ketamine (20 mg/kg) and completed by ear vein injection of sodium pentobarbital (30 mg/kg). Additional doses of sodium pentobarbital (8 mg/kg) were injected at intervals of 1h to maintain anesthesia. A cuffed tube was advanced into the trachea. Animals were mechanically ventilated with a volume-controlled ventilator (Model MA-1, Puritan-Bennett, Carlsbad, CA) with a tidal volume of 15 ml/kg, peak flow of 40 l/min, and FiO2 of 0.21.

For the measurement of left ventricular functions, a 5.5/7.5 Hz biplane with Doppler transesophageal echocardiographic transducer with 4-way flexure (Model 21363A, Hewlett-Packard Co., Medical Products Group, Andover, MA) was advanced from the incisor teeth into the esophagus for a distance of approximately 35 cm. Electrocardiographic frontal plane lead 2 was monitored continuously. For the measurement of aortic pressure, a fluid-filled catheter was advanced from the left femoral artery into the thoracic aorta. For the measurements of right atrial, pulmonary arterial pressures and blood temperature, a 7-French, pentalumen, thermodilution-tipped catheter (Model T123F7, Baxter Healthcare Corporation, Irvine, CA) was advanced from the left femoral vein and flow-directed into the pulmonary artery. A 7-French catheter was advanced from the left cephalic vein into the great cardiac vein for the measurement of great cardiac vein blood gases and lactate. For inducing VF in the first group, a 5-French pacing catheter (EP Technologies, Inc., Mountain View, CA) was advanced from the right cephalic vein into the right ventricle.

Model of myocardial ischemia

Myocardial ischemia was induced by intraluminal occlusion of the LAD coronary artery between the first and second diagonal branches. The right
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Figure 1

Representative coronary angiograms from LAD occlusion group. Angiograms demonstrated occlusion of the left main coronary artery (left), LAD prior to contrast (center), and LAD after contrast (right).

common carotid artery was isolated in the neck, and a 7-French balloon-tipped catheter (Model T123F7, Baxter Healthcare Corporation, Irvine, CA) connected with a transducer (Transpac® IV, Abbott Critical Care Systems, North Chicago, IL) was advanced from the carotid artery into the aorta and then into the left coronary artery with the aid of image intensification and guided by intermittent injection of radiographic contrast media (Renogafin®-76, Squibb Diagnostics, NJ). The catheter was advanced beyond the first diagonal branch of the LAD after which the balloon was inflated with 1 ml air. Complete occlusion was assumed when the coronary artery pressure distal to the occlusion declined to less than 40 mmHg in the absence of significant changes in mean arterial pressure (Figure 1). A bolus injection of 0.5 ml containing 2500 IU of heparin was then injected distal to the LAD occlusion to minimize the risk of thrombosis and infarction.

Experimental procedure

Animals were randomized by the sealed envelope method after completion of initial preparation and instrumentation excepting insertion of the right ventricular pacing catheter or the coronary occluding balloon catheter to either electrical or ischemic cardiac arrest. Cardiac arrest was induced electrically with 1—2 mA 60 cycle current delivered to the endocardium of the right ventricle. Mechanical ventilation was discontinued after onset of VF due to either electrical fibrillation or LAD occlusion. For ischemic cardiac arrest, the balloon was deflated after onset of VF and withdrawn into the proximal aorta prior to start of precordial compression. Compression was with the aid of a pneumatic piston-driven chest compressor (Thumper®, Model 1000, Michigan Instruments, Grand Rapids, MI). Coincident with the start of precordial compression, the animals were mechanically ventilated with a tidal volume of 15 ml/kg and FiO2 of 1.0. Precordial compression was programmed to provide 100 compressions per min and synchronized to provide a compression/ventilation ratio of 5:1 with equal compression—relaxation intervals, i.e., a 50% duty cycle. The compression force was adjusted to decrease the anterior—posterior diameter of the chest by 25%. After 5 min of precordial compression, defibrillation was attempted with a Hewlett-Packard defibrillator (MI1723A, Rosemont, IL) which delivered 150 J biphasic waveform shocks between the right infraclavicular area and the cardiac apex. If an organized cardiac rhythm with mean aortic pressure of more than 60 mm Hg persisted for an interval of 5 min or more, resuscitation of the animal was regarded as successful.

Measurements were continued for 4 h after successful resuscitation. The animals were returned to their cages after recovery from anesthesia. Post-resuscitation neurological alertness was scored according to the method described by Tang et al. and survival was observed over the ensuing 72 h. Animals were subsequently sacrificed painlessly by intravenous injection of 150 mg/kg pentobarbital.

Autopsy with gross examination of thoracic and...
abdominal organs was performed routinely to document possible injuries to the bony thorax and the thoracic or abdominal viscera.

**Measurements**

Dynamic data, including aortic, right atrial, pulmonary arterial, and coronary artery pressure distal to the occluding balloon were measured together with end-tidal PCO2 (PetCO2) and electrocardiographic lead 2. The data were recorded on a PC-based acquisition system, supported by CODAS/WINDAQ hardware/software (Dataq Instruments, Akron, OH) as described previously.15 The coronary perfusion pressure (CPP) was computed digitally as the difference between time coincident precompression aortic diastolic and right atrial pressure. Hemodynamic measurements and the electrocardiogram were displayed in real time.

Echocardiographic measurements were obtained by an observer blinded to the experiment with the aid of a Hewlett-Packard Sonos 2500 echocardiographic system, using a 5.5/7.5 Hz biplane Doppler transesophageal echocardiographic transducer with 4-way flexure. A 2- or 4-chamber long-axis view was obtained. Left ventricular end-systolic and -diastolic volumes were calculated by the method of discs (Acoustic Quantification Technology, Hewlett-Packard, Andover, MA). From these, ejection fractions (EF) and fractional area change (FAC) were computed.

Aortic, mixed venous and great cardiac vein blood gases, hemoglobin and oxyhemoglobin were measured from 200 μl aliquots of blood sampled simultaneously from each site. Measurements were obtained with a stat profile analyzer (ULTRA C, Nova Biomedical Corporation, Waltham, MA) adapted for porcine blood. Arterial and great cardiac venous blood lactate was measured with a lactic acid analyzer (Model 23L, Yellow Springs Instruments, Yellow Springs, OH). These measurements were obtained at 30 min prior to inducing cardiac arrest, 3 min after start of CPR and hourly after resuscitation for a total of 4 h. ST-T segment alterations in electrocardiographic lead 2 were measured manually at baseline and again immediately prior to inducing VF, at 5, 10, 20 and finally at 30 min following resuscitation. The cumulative number of premature, wide complex ectopic beats during the first 5 min following resuscitation were also counted manually. The number of shocks required prior to return of spontaneous circulation (ROSC) and the incidence of recurrent episodes of VF were also recorded over the 4-h interval following resuscitation. The quantitative neurological alertness score, which allows for a maximum score of 100 for fully alert animals with normal function and minimum score of 0 for unresponsive, comatose animals without spontaneous breathing, represents an objective grading of level of consciousness, respiration, posture, and food and water intake.14

**Statistical analyses**

All data were presented as mean ± S.D. Differences of hemodynamic and metabolic measurements among groups were analyzed by ANOVA using the Scheffe method for multiple comparison. A value of P < 0.05 was regarded as significant.

**Results**

Hemodynamic, blood gas, and lactate values did not differ significantly between the two groups prior to inducing cardiac arrest and at 60 min after success-

<table>
<thead>
<tr>
<th></th>
<th>Ischemia Baseline</th>
<th>PR 60</th>
<th>Electric Baseline</th>
<th>PR 60</th>
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</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>122.8 ± 16.3</td>
<td>200.8 ± 6.7</td>
<td>128.8 ± 11.4</td>
<td>194.0 ± 13.0</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>103.0 ± 12.0</td>
<td>97.3 ± 9.1</td>
<td>106.5 ± 14.4</td>
<td>104.0 ± 8.2</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>4.0 ± 2.5</td>
<td>6.6 ± 3.3</td>
<td>3.8 ± 1.3</td>
<td>6.6 ± 0.7</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>15.9 ± 2.8</td>
<td>17.9 ± 2.6</td>
<td>16.4 ± 1.8</td>
<td>18.7 ± 3.0</td>
</tr>
<tr>
<td>Art-PO2/FiO2</td>
<td>489.5 ± 20.1</td>
<td>342.3 ± 85.5</td>
<td>491.5 ± 32.3</td>
<td>333.3 ± 88.9</td>
</tr>
<tr>
<td>Art-lactate (mmol/l)</td>
<td>1.3 ± 0.7</td>
<td>5.2 ± 1.7</td>
<td>1.4 ± 1.2</td>
<td>5.9 ± 1.6</td>
</tr>
<tr>
<td>ET CO2 (mmHg)</td>
<td>37.7 ± 1.8</td>
<td>37.2 ± 1.1</td>
<td>38.3 ± 2.3</td>
<td>37.5 ± 2.1</td>
</tr>
<tr>
<td>PO2 (mmHg)-gcv</td>
<td>26.6 ± 2.2</td>
<td>39.7 ± 10.6</td>
<td>25.1 ± 1.8</td>
<td>39.9 ± 9.1</td>
</tr>
<tr>
<td>PCO2 (mmHg)-gcv</td>
<td>52.7 ± 3.9</td>
<td>57.8 ± 7.7</td>
<td>54.6 ± 4.8</td>
<td>57.0 ± 8.4</td>
</tr>
<tr>
<td>Lactate (mmol/l)-gcv</td>
<td>0.9 ± 0.7</td>
<td>4.5 ± 1.4</td>
<td>0.8 ± 0.4</td>
<td>4.8 ± 1.2</td>
</tr>
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HR, heart rate; bpm, beat per min; MAP, mean arterial pressure; RAP, right atrial pressure; PAP, mean pulmonary artery pressure; gcv, great cardiac vein.
A comparison of electrically induced cardiac arrest with cardiac arrest produced by coronary occlusion

Table 2 Myocardial function after resuscitation

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<thead>
<tr>
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<th>Ischemic</th>
<th>Electric</th>
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<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>62.0 ± 5.0</td>
<td>63.0 ± 2.0</td>
</tr>
<tr>
<td>PR 60</td>
<td>41.0 ± 4.0</td>
<td>43.0 ± 5.0</td>
</tr>
<tr>
<td>PR 120</td>
<td>41.0 ± 5.0</td>
<td>42.0 ± 7.0</td>
</tr>
<tr>
<td>PR 180</td>
<td>42.0 ± 5.0</td>
<td>41.0 ± 7.0</td>
</tr>
<tr>
<td>PR 240</td>
<td>41.0 ± 6.0</td>
<td>43.0 ± 7.0</td>
</tr>
<tr>
<td>Fractional area change (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>43.0 ± 2.0</td>
<td>45.0 ± 4.0</td>
</tr>
<tr>
<td>Electric</td>
<td>32.0 ± 6.0</td>
<td>30.0 ± 7.0</td>
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</tbody>
</table>

PR = Min following restoration of spontaneous circulation.

ful resuscitation (Table 1). After occluding the LAD, pressure distal to the intracoronary balloon occlusion was reduced from 120 ± 20 to 32 ± 5 mmHg (P < 0.01). Prior to onset of VF, progressive electrocardiographic ST segment elevation was observed in the LAD occlusion group (Figure 2). VF appeared within an interval of 5.7 ± 2.0 min (range 3—9 min) after start of occlusion. Immediately following successful defibrillation both the occlusion and the electrical groups manifested comparable elevations in ST segments as shown in Figure 2.

A significantly greater number of electrical shocks was required prior to ROSC in the ischemic group and significantly greater number of premature ventricular beats was associated with recurrent VF. The duration of CPR and the total energies delivered for defibrillation were significantly increased (Figure 3).

Measurements of EF and FAC obtained at hourly intervals following ROSC indicated no differences

Figure 2 ST-T segment elevation at 1 min prior to onset of VF with reversal over the 30 min interval that followed resuscitation.

Figure 3 After ischemically induced cardiac arrest, a significantly greater incidence of premature ventricular beats (PVB's), a greater incidence of recurrent VF, prolonged CPR, a need for a larger number, and therefore greater cumulative energy, of electrical shocks prior to successful resuscitation.
Table 3 Neurological Alertness Score after resuscitation

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<th>Ischemic</th>
<th>Electric</th>
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<tr>
<td>24 h</td>
<td>77.4 ± 15.5</td>
<td>72.8 ± 17.8</td>
</tr>
<tr>
<td>48 h</td>
<td>92.6 ± 5.4</td>
<td>94.5 ± 8.3</td>
</tr>
<tr>
<td>72 h</td>
<td>93.7 ± 6.3</td>
<td>93.6 ± 7.5</td>
</tr>
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</table>

between the two groups (Table 2). All animals survived and were normally active at 72 h after resuscitation. Accordingly, there were no significant differences in the post-resuscitation course after 60 min and specifically no differences in myocardial function, neurological alertness or survival (Table 3).

Except in one instance in which an aortic intramural hematoma measuring 0.7 cm in largest dimension was found in the intima immediately proximal to the junction of the left main coronary artery and the circumflex artery, no abnormalities were detected at autopsy.

Discussion

We confirmed the earlier reports of Ouyang et al., Walcott et al., and Qin et al., that ischemia induced VF which follows LAD occlusion required a larger number and therefore higher cumulative energy shocks prior to obtain ROSC. There was a significantly greater incidence of post-resuscitation premature ventricular beats and recurrent VF in the ischemic group. Nevertheless, no differences in post-resuscitation myocardial function, neurological recovery or 72 h survival were detected. Accordingly, other than the initial electrical instability that immediately followed reversal of ischemic VF, the post-resuscitation course was indistinguishable between electrically induced and coronary occlusion induced cardiac arrest.

Ideker and co-workers also found that significantly higher defibrillation energy was required for defibrillation in settings of ischemia. They viewed this higher defibrillation threshold as a fundamental difference in the mechanisms of cardiac arrest when VF occurs in settings of myocardial ischemia. They concluded that the myocardial ischemia model may be more relevant as an experimental analog to the clinical model of "sudden cardiac death" when compared with electrically induced VF.

In interpreting the present data, pre-cardiac arrest ST elevations after the LAD occlusion ushers in ischemic arrest. There is substantially greater difficulty in restoring spontaneous circulation. Our findings are supportive of earlier reports by the Ouyang and the Ideker and co-workers and the observation that in ischemic models there are recurrent wavebreaks, fragmentation of wavefronts, and consequently ectopic arrhythmias. In addition, variable VF cycle length in locally ischemic myocardium contrasts with that of the global myocardial ischemia of electrically induced VF.

These differences notwithstanding, post-resuscitation myocardial function and specifically, EF and FAC were comparable. In contrast to the model reported by Niemann et al., the LAD was occluded for less than 20 min. The likelihood of permanent myocardial cell damage and therefore cell death was unlikely. We did not in this initial study include markers of cell injury such as Troponin. The duration of coronary occlusion was 12.6 ± 2.0 min compared to 7 min in the electrical model. Accordingly, the critical time limit for irreversible ischemic injury terminating in cell death, was not exceeded in the present model such that the injury would comply with stunning of the myocardium.

Conclusions

The present study confirmed that when VF is induced by transient coronary occlusion, there are significantly greater numbers of ventricular ectopic beats, recurrent VF, and more prolonged CPR prior to resuscitation with larger numbers of electrical shocks prior to ROSC, in comparison with electrically induced VF and significantly greater total energy is required for defibrillation. However, post-resuscitation myocardial and neurological function and survival are comparable.

Conflict of interest statement

The authors report no conflict of interest.

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