The Myocardial Protection of Polarizing Cardioplegia Combined With Delta-Opioid Receptor Agonist in Swine

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Background. **The purpose of this study was to determine whether polarized arrest using adenosine/lidocaine cold crystalloid cardioplegia in combination with the hibernation inductor δ-opioid receptor agonist pentazocine would give satisfactory myocardial protection rather than using depolarized supranormal potassium cardioplegia, supranormal potassium cardioplegia with pentazocine, or adenosine/lidocaine cardioplegia.**

Methods. **Twenty pigs were randomly divided into four groups (n = 5 each) to receive the four types of cold crystalloid cardioplegia with an aortic cross-clamp time of 1 hour. Hemodynamic data were continuously measured, as was the left ventricular end-diastolic pressure (LVEDP), left ventricular end-systolic pressure (LVESP), plus or minus derivative of change in diastolic pressure over time (±dp/dt), cardiac output, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac troponin I, and left ventricular ultrastructure.**

Results. **Both the adenosine/lidocaine/pentazocine group and the adenosine/lidocaine group got significantly better results than the hyperkalemic and hyperkalemic pentazocine groups in improving hemodynamic values, pulmonary capillary wedge pressure, LVEDP, LVESP, ±dp/dt, cardiac output, cardiac troponin I values, and left ventricular ultrastructure. There were no statistical differences between the adenosine/lidocaine/pentazocine group and the adenosine/lidocaine group at 1 hour after cross-clamp removal; but at 2 hours after cross-clamp removal, the adenosine/lidocaine/pentazocine group stands out (LVEDP 3.3 ± 0.5, LVESP 122.5 ± 18.9, +dp/dt 2.9 ± 0.1, −dp/dt 2.0 ± 0.6, cardiac output 2.6 ± 0.4, and troponin I 4.9 ± 0.5), with significant differences from the adenosine/lidocaine group (LVEDP 5.8 ± 1.0, LVESP 98.5 ± 10.1, +dp/dt 2.5 ± 0.2, −dp/dt 1.0 ± 0.2, cardiac output 2.2 ± 0.2, troponin I 8.2 ± 0.8; $p < 0.05$). The defibrillation rate was largely decreased after the cross-clamp was released in the group containing pentazocine in cardioplegia.**

Conclusions. **Adenosine/lidocaine/pentazocine cold crystalloid cardioplegia gave satisfactory cardiac arrest and better myocardial protection than the other three groups, especially with regard to improving prolonged postoperative cardiac function.**

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Hyperkalemic cardioplegia (St. Thomas solution) has been the foundation of most myocardial protection strategies since its introduction more than 25 years ago. But apart from electrochemical arrest, these solutions are far from perfect. Myocardial membrane depolarization with potassium is associated with continued transmembrane ionic fluxes through sodium and calcium "window currents." It gives ionic imbalance, intracellular sodium and calcium overload, and continued energy expenditure, which subsequently may cause contracture and myocardial injury. Cardiomyocyte dysfunction and death, microvascular injury, coronary vasoconstriction and spasm, arrhythmias, and left ventricular stunning [1] may appear afterward.

Schwartz and colleagues [2] have represented that mammalian hibernation biology closely parallels the altered cardiac cellular physiology noted with hypothermic cardioplegic arrest. It may be induced in nonhibernators through δ-opioid peptides. During hibernation, the myocardial transmembrane electrical potential was in a polarized standing state, which locks the ion channels in a "closed" state [3]; therefore, ionic imbalance and subsequent consequences are likely to be avoided. Also, δ-opioid was noted as a hibernation induction trigger [4-6] to suppress cardiac metabolic rate, particularly myocardial oxygen. The contractile function of the heart was well preserved and proved to induce hibernation in active animals, and afford myocardial protection after ischemia-reperfusion injury. The exact chemical responsible for the induction of hibernation is elusive; however, a protoopiate nature is well established as hibernation can be reversed or retarded by opiate antagonists. The combination of adenosine and lidocaine is an alternative

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Abbreviations and Acronyms

AL = adenosine/lidocaine
ALP = adenosine/lidocaine/pentazocine
ATP = adenosine triphosphate
CPB = cardiopulmonary bypass
cTnI = cardiac troponin I
dp/dt = derivative of change in diastolic pressure over time
K = hyperkalemic cardioplegia
KP = hyperkalemic cardioplegia with pentazocine
LVEDP = left ventricular end-diastolic pressure
LVESP = left ventricular end-systolic pressure
MAP = mean arterial pressure
PAP = pulmonary artery pressure

method to achieve polarized arrest. Adenosine activates adenosine triphosphate (ATP)-sensitive potassium channels by A_1-receptor mediated mechanisms; lidocaine can prevent transmembrane depolarization and electrical activation by blocking sodium channels. Several studies have shown promising results with adenosine in combination with lidocaine in small-animal experiments [7-9]. Some clinical trials attempt to use adenosine and lidocaine (AL) in cardioplegia [10, 11] and intravenous treatment for acute myocardial infarction [12].

Given these reasons, we chose AL crystalloid cardioplegia combined with the δ-opioid receptor agonist pentazocine to replace traditional hyperkalemic cardioplegia in an open-chest pig model with global myocardial ischemia under cardiopulmonary bypass (CPB), hypothesizing that adenosine and lidocaine combined with pentazocine cardioplegia (ALP) would offer satisfactory cardiac arrest and less cardiac dysfunction, compared with the standard hyperkalemic group (K), hyperkalemic pentazocine group (KP), and AL group, respectively.

Material and Methods

All animals received humane care in compliance with the "Regulation for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources in Beijing, China, and published by the National Scientific Committee (revised 1997). Twenty male purebred Bama miniature pigs (from Guangxi, China) with mean body weight of 25 kg (K group, 27.7 ± 7.0; KP group, 23.0 ± 2.4; AL group, 23.0 ± 3.6; ALP group, 26.5 ± 6.6; $p = 0.494$) were fasted overnight with free access to water before the surgery.

The pigs were premedicated with intramuscular ketamine (20 mg/kg) and diazepam (0.85 mg/kg). A 20G catheter was placed in an ear vein, and general anesthesia was induced with ketamine (35 mg/kg) and diazepam (1.5 mg/kg) intravenously. The pigs were endotracheally intubated and placed in a supine position with their legs attached to the operating room table, and mechanically ventilated (Servo Ventilator 900C; Seimens, Erlangen, Germany) by 60% oxygen 15 times per minute to maintain a normal blood gas value. Anesthesia was maintained by intermittent infusion of ketamine (105 mg) and diazepam (4.5 mg) when necessary. Muscle relaxation was induced with 10 mg succinylcholine.

Mean arterial pressure (MAP) was measured from the descending aorta through the left ventricle catheter (5F [Cordis, Bridgewater, NJ]) placed in the right femoral artery. Central venous pressure was measured in the right atrium through a Swan-Ganz catheter (CCOmbo V; Edwards Lifesciences, Irvine, CA), which was also capable of measuring cardiac output, pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure. Nasopharyngeal temperature and a continuous electrocardiogram were measured for the entire procedure. The left ventricle pressure was monitored once the Cordis catheter was placed into the left ventricle. Central blood temperature was monitored through the Swan-Ganz catheter and maintained by warming or cooling within the normal range. After a median sternotomy, the pericardium was incised, the pigs received heparin 3 mg/kg, keeping an activated clotting time (ACT) of greater than 480 s.

During CPB, the pigs were cannulated through the aortic artery with an 18F pediatric arterial cannula (Kewei, China), and venous drainage was obtained from the superior vena cava (20F; Medtronic, Minneapolis, MN) and inferior vena cava (24F; Medtronic). A standard pediatric cardioplegia cannula (Tianjin, China) was placed in the ascending aorta. A roller pump (Stockert S2 heart-lung machine; Sorin, Milan, Italy), a membrane oxygenator (Kewei, China), and a nonheparin-coated polyvinylchloride tubing were employed. The priming solutions in the membrane oxygenator and cannular involve 500 mL colloid (polygeline) and 400 mL allogeneic whole blood transfusion. Superficial hypothermia CPB 32°C to 34°C was initiated with a flow similar to baseline cardiac output; MAP was maintained at 40 to 70 mm Hg by adjusting the arterial flow rate. The aorta was then cross-clamped for 1 hour. The cardioplegia (4°C) was given antegradely and intermittently, the first dose of 500 mL immediately after cross-clamping the aorta, and the second and third doses of 250 mL 20 and 40 minutes after cross-clamping the aorta; each dose was perfused in 4 to 5 minutes. The crystalloid cardioplegia was nearly all suctioned from the incision of the right atrium. Ice-slush was applied. After 1 hour of cold ischemic arrest, the aortic cross-clamp was released. Weaning from CPB was tried 20 minutes after cross-clamp release. If necessary, animals were allowed extended time of support before CPB was terminated. Sampling and measurements were collected at baseline, before anesthesia (T1), and 1 hour (T2) and 2 hours (T3) after cross-clamp removal. Animals were sacrificed after T3 with an overdose of intravenous potassium.

The pigs were randomly divided into four groups (n = 5 each) for the four kinds of cardioplegia. The compositions of the cardioplegia solutions are given in Table 1. The K group was the traditional St. Thomas solution group, the KP group was given 1 mg/kg pentazocine in the St. Thomas solution, the AL group used 1 mmol/L