Esmolol Added in Repeated, Cold, Oxygenated Blood Cardioplegia Improves Myocardial Function After Cardiopulmonary Bypass

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Objective: This study investigated if the β-receptor blocking agent esmolol, added to standard oxygenated blood cardioplegia, improved myocardial function after weaning from bypass.

Design: A block-randomized, blinded study.

Setting: A university laboratory.

Participants: Twenty anesthetized pigs, Norwegian Landrace.

Interventions: After cardiopulmonary bypass, cardiac arrest was induced with cold (12°C), oxygenated blood cardioplegia, enriched with either esmolol or vehicle, repeated every 20 minutes. After 100 minutes the heart was reperfused and weaned.

Measurements and Main Results: Left ventricular function was evaluated with pressure-volume loops, local myocardial function with multilayer strain and strain rate by epicardial short-axis tissue Doppler imaging. One hour after declamping, preload recruitable stroke work did not differ between groups, but increased to 72 ± 3 mmHg in esmolol-treated animals *v* 57 ± 4 mmHg ($p < 0.001$) in controls after 3 hours. Radial peak ejection strain rate also was increased by esmolol; 6.0 ± 1.0 s^{-1} *v* 2.9 ± 0.3 s^{-1} ($p < 0.001$) in subendocardium and 3.9 ± 0.5 s^{-1} *v* 2.3 ± 0.2 s^{-1} ($p < 0.005$) in the midmyocardium. Cardiac index was increased, 4.0 ± 0.2 L/min/m^2 by esmolol *v* 3.3 ± 0.1 L/min/m^2 for controls ($p < 0.05$). Isovolumetric relaxation time constant was reduced by esmolol, 23 ± 1 ms *v* 26±1 ms ($p < 0.025$). Troponin-T did not differ and was 339 ± 48 ng/L for the esmolol group and 357 ± 55 ng/L for the control group ($p = 0.81$).

Conclusions: Esmolol added to blood cardioplegia preserved systolic cardiac function during the first 3 hours after reperfusion in a porcine model with 100 minutes of cardioplegic arrest.

KEY WORDS: *esmolol, cardiac function, cardioplegia, cardiopulmonary bypass, beta-blockade*

IN NUMEROUS CLINICAL AND EXPERIMENTAL studies, β-adrenergic blocking agents are found to be protective both functionally and structurally in myocardium undergoing ischemia and reperfusion.[1–3] This cardioprotective effect also may be beneficial during cardiopulmonary bypass (CPB) and cardioplegic arrest. However, the cardiodepressive effects of these agents potentially may prolong weaning and lead to an inadequate cardiac response in the postoperative phase. Therefore, special attention has been drawn to the ultra short-acting β-blocker esmolol.

From a cardioprotective point of view, continuous myocardial perfusion with high concentrations of esmolol may be advantageous compared to potassium-based cardioplegia, to facilitate acceptable surgical conditions with little or no myocardial movement.[4–7] Use of lower systemic concentrations of esmolol before, during, or after CPB and cardioplegic arrest in combination with commonly used cardioplegic regimens also have been shown to be beneficial, both experimentally and clinically.[8–10] In isolated hearts both anoxia and ischemia release catecholamine stores, resulting in lipolysis and myocardial tissue damage.[11–13] Crystalloid cardioplegia preserves myocardial catecholamine stores.[14] Esmolol may further reduce the potential ischemic and reperfusion injury by inhibiting the effects of the endogenous release of catecholamines. When added to repeated oxygenated blood cardioplegia, direct intracoronary delivery of esmolol during the cardioplegic perfusions exposes the myocardium to esmolol with a reduced total systemic dose. To the authors' knowledge, only 1 study has used esmolol as an additive to cold blood cardioplegia. In patients urgently operated for unstable angina, the addition of esmolol did not affect myocardial tissue damage judged by troponin-I, CK-MB fraction, and lactate release.[15] However, postoperative cardiac function was not evaluated.

Repeated antegrade, cold, oxygenated, blood cardioplegia is often the preferred method used to facilitate cardioplegic arrest and myocardial protection.[16] In this experimental study, the authors hypothesized that esmolol as an additive to standard potassium-based blood cardioplegia would improve the postoperative cardiac function. Pigs were subjected to CPB and cardioplegic arrest for 100 minutes during tepid general hypothermia in a protocol mimicking a clinical setting. Cardiac function was evaluated with regional and global variables for the first 3 hours after aortic declamping and reperfusion.

METHODS

The experiments were performed using 24 pigs (Norwegian Landrace) of either sex weighing 43 ± 4 kg (SD). Animals were acclimated for at least 7 days. Before surgery animals were fasted overnight, but with access to water. All procedures were performed in accordance with international guidelines described in the European Communities Council Directive of 2010 (63/EU). The experimental protocol was approved by the Norwegian State Commission for Laboratory Animals (project No. 20092088).

After premedication with ketamine, 20 mg/kg, diazepam, 10 mg, and atropine, 1 mg IM, animals briefly were ventilated

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with isoflurane, 3% in oxygen, allowing cannulation of 2 ear veins. General anesthesia was induced and maintained by loading doses and continuous infusions of fentanyl, 0.02 mg/kg and 0.02 mg/kg/h, midazolam, 0.3 mg/kg and 0.3 mg/kg/h, vecuronium, 0.4 mg/kg and 0.2 mg/kg/h, and pentobarbital, 15 mg/kg and 4 mg/kg/h. A tracheotomy was performed and the lungs of each pig were ventilated (Julian, Dräger, Lübeck, Germany) with 57% N_2O and oxygen, with a tidal volume of 11 mL/kg. The end-tidal CO_2 was kept within the range of 5.0 to 5.7 kPa (38 to 43 mmHg) by respiratory rate adjustments. Further evaluation of this anesthetic protocol, justifying the safe use of a neuromuscular blocker in young pigs, can be found elsewhere.[17] At the end of the experiments, still under general anesthesia, animals were euthanized by saturated potassium chloride injected into the left atrium.

Surgical Preparation and Instrumentation

The right femoral artery and vein were exposed surgically and cannulated. A suprapubic urine catheter was inserted into the bladder. Following midline sternotomy and pericardiotomy, a band was placed loosely around the inferior caval vein, allowing dynamic preload reductions. A Portex catheter placed into the left atrium was used for microsphere injections. Sutures later needed for bypass cannulation were prepared. A Swan-Ganz catheter (139H-7.5F; Edward Lifesciences Inc., Irvine, CA) was advanced from the right internal thoracic vein to the pulmonary artery, connected to a continuous cardiac output computer (Vigilance I; Edward Lifesciences Inc.) and pressure transducers (SensoNor, Horten, Norway), obtaining central venous and pulmonary artery pressures. Central aortic pressure was measured by a pressure-tip catheter (MPC-500; Millar Corp., Houston, TX) placed in the proximal aorta from the left internal thoracic artery. The pressure-conductance catheter (SPR 788; Millar Corp.), connected to a signal conditioning unit (Sigma 5; CD Leycom, Zoetermeer, the Netherlands), was placed via the apex through the left ventricle and through the aortic valve. Correct position was confirmed by echocardiography (Vivid E9; GE Vingmed Ultrasound, Horten, Norway) and any distal conductance segments with paradox volume signals were excluded. All hemodynamic signals were digitized and recorded with a signal conditioner unit (ACQ-7700; Data Sciences International, St. Paul, MN). Animals were allowed to stabilize for 15 minutes before baseline data were obtained.

Cardiopulmonary Bypass

Animals were cannulated for CPB with an 18F arterial cannula (Medtronic Inc., Minneapolis, MN) in the brachiocephalic artery and a 29F cavoatrial 3-stage cannula (Medtronic Inc.) placed from the right atrial appendage. After tepid CPB flow (90 mL/min/kg) for a short time, mixing blood and prime volume (1200 mL Ringer's acetate), an arterial blood gas was drawn and the aorta was cross-clamped. Oxygenated cold blood cardioplegia, 7% of initial CPB flow (6.3 mL/min/kg), was administered in the aortic root with an initial "high dose" for 3 minutes followed by 2 minutes of "low dose" every 20 minutes (Table 1). Following the first cardioplegia infusion, a 17F left ventricular venting catheter was placed through the left atrium.

Table 1. Final Concentrations in Blood Cardioplegic Perfusate

	High Dose		Low Dose		Total Dose	
K^+	22	mM	14	mM	877	μmol/Kg
Mg^{2+}	16	mM	9	mM	719	μmol/Kg
Cl^-	134	mM	120	mM	2352	μmol/Kg
Procaine	0.8	mM	0.4	mM	37	μmol/Kg
Esmolol	34	μM	19	μM	1.6	μmol/Kg

The animal core temperature was allowed to drift. When reaching 35°C or no later than after 20 minutes, CPB flow was reduced to 72 mL/min/kg. Following the last cardioplegia infusion, CPB flow was reset to 90 mL/min/kg and rewarming was commenced. After 100 minutes the aorta was declamped, and animals weaned from CPB within 20 minutes. If needed, ventricular fibrillations were electroconverted. No other antiarrhythmic intervention was allowed in the protocol. The animals were monitored for 3 hours after aortic declamping.

Design

A block randomized controlled study was performed. Researchers were unaware of the randomization code both during surgery and analysis. Excluded animals were replaced by consecutive experiments until a total of 10 animals in each group were included. The cardioplegic concentrate (1000 mL) was enriched with 5 mL, 10 mg/mL, of esmolol (Brevibloc, Baxter AS, Oslo, Norway) for the intervention group or 5 mL of vehicle for the control group. A total of 0.467 mg/kg (1.6 μmol/kg) of esmolol was administered to pigs in the intervention group. The freshly mixed cardioplegic solution, 12°C, was delivered with a dual-head pump and separate cooling. This will expose the myocardium to concentrations avoiding significant influence from inhibition of L-type Ca^{2+} channels and fast Na^+ channels (Table 1).[18]

Measurements of Cardiac and Hemodynamic Function

Measurements were performed at baseline and 1, 2, and 3 hours after aortic declamping. At each point, arterial blood gases and serum for troponin-T measurements were drawn. Injections of fluorescent microspheres (Dye-Trak "F" ®, Triton Technology Inc., San Diego, CA) were performed with a concurrent sampling of reference arterial blood with a constant rate extraction pump for regional tissue blood flow measurements.[19] General hemodynamics were analyzed with Ponemah Physiology Platform v. 4.90 (Data Sciences International). PV-loop data were exported and analyzed with custom-made software. Hemodynamic variables were averaged over 5-8 consecutive heart beats during a stable situation. The time constant of isovolumetric relaxation, τ, was calculated according to Raff and Glantz.[20] From 6-10 consecutive cardiac cycles during a dynamic preload reduction, load-independent variables were obtained (Fig 1). Systolic function was described by the left ventricular end-systolic pressure-volume relationship (ESPVR) and preload-recruitable stroke work (PRSW). Correspondingly, diastolic compliance was expressed by the linear and the logarithmic end-diastolic pressure-volume relationships ($EDPVR_{lin}$ and β).[21,22] The median correlation coefficient for