Selective beta blockade improves the outcome of cardiopulmonary resuscitation in a swine model of cardiac arrest

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BACKGROUND AND OBJECTIVES: *Epinephrine has been the mainstay drug of choice for cardiac resuscitation for more than 30 years. Its vasopressor effects favoring initial resuscitation point to its β-adrenergic action. However, its β-adrenergic actions may have detrimental effects. The aim of the present experimental study was to evaluate the efficiency of co-administration of Esmolol, an ultra-short-acting beta-blocker, and of epinephrine in a swine model of cardiac arrest.*
MATERIALS AND METHODS: *Fourteen pigs (19±2 Kg) were anesthetized and instrumented. Ventricular Fibrillation (VF) was produced electrically. After induction of VF, the animals were left untreated for 5 minutes. Animals were randomized into two groups, control and study group. Six animals were used in the control group, and 8 in the study group. The control group received 10 ml of normal saline via a peripheral vein, while the study group received 0.4 mg/kg Esmolol in 10 ml dilution. Epinephrine was administered to all animals after the first unsuccessful defibrillation set, and all animals received standardized Advanced Life Support.*
RESULTS: *Seven animals (87.5%) restored cardiac rhythm compatible with a pulse in the Esmolol group, compared to 2 animals (33.3%) in the control group (p= 0.018). The average time until restoration of circulation was 16±3.2 minutes in our control group and 12.8±1.4 minutes in Esmolol group (p= 0.059). Coronary perfusion pressure (CPP) was significantly higher in the Esmolol group.*
CONCLUSIONS: *Esmolol improves significantly the outcome of cardiopulmonary resuscitation and the average time of restoration of circulation, while in the proposed dosage does not alter the CPP at the beginning of CPR. However, it augments CPP from the sixth minute of CPR and afterwards.*

KEY WORDS: Beta-blockade, Coronary perfusion pressure, Resuscitation, Return of spontaneous circulation, Ventricular fibrillation.

Introduction

The worldwide occurrence of Sudden Cardiac Death (SCD) is difficult to estimate, as it varies largely in accordance to the coronary heart disease prevalence in different countries [1].

Sudden cardiac death due to ventricular fibrillation is the most serious of the cardiac diseases. There is evidence that heightened sympathetic activity contributes to fatal arrhythmias, particularly in the presence of myocardial ischemia. The occurrence of sudden death peaks in the morning, and is triggered by events that are similar to those that trigger non-fatal myocardial infraction. This higher incidence of sudden cardiac death is reduced in subjects receiving beta blockers[2].
The American Heart Association in association with the International Liaison Committee on Resuscitation (ILCOR), recommends treatment with either epinephrine or vasopressin for patients in cardiac arrest due to

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ventricular fibrillation (VF), who are unresponsive to initial treatment with a defibrillator [3]. Epinephrine acts to increase blood pressure and blood flow to the heart and brai [4,5]. However, the efficacy and safety of epinephrine has been questioned in many studies [6,7].

There is increasing evidence that unusually heightened myocardial responsiveness to β_2-adrenoceptor agonists (epinephrine) increases susceptibility to VF [8], and may contribute to severe post resuscitation myocardial dysfunction [9,10].

The mechanism, by which epinephrine administered during cardiopulmonary resuscitation increases the severity of post resuscitation myocardial dysfunction after primary VF, points to its β_1-adrenergic actions, which are inotropic and chronotropic and thereby increase the excessive myocardial oxygen requirements of the fibrillating heart [11].

Observations in an isolated heart model, led to the conclusion that β- adrenergic stimulation in the presence of low coronary perfusion pressure could increase myocardial ischemic injury during VF [12]. The detrimental effects of, agonists were emphasized with evidence that the β-adrenergic actions of epinephrine increased the severity of myocardial ischemic injury and therefore the likelihood of reentrant [13,14,15] and ectopic ventricular arrhythmias [16].

In addition to the aforementioned facts, β-adrenergic stimulation increases myocardial oxygen consumption during VF and seems to have important implications concerning both pharmacologic intervention during cardiopulmonary resuscitation and the intense endogenous sympathetic activation in cardiac arrest, which result in extraordinary high endogenous epinephrine plasma concentrations [17].These high levels of epinephrine subsequently lead to excessive β stimulation resulting in oxygen demand increases [18].

Moreover, with the extremely high concentration of circulating endogenous catecholamines in cardiac arrest, it is difficult to imagine how a pure vasoconstrictor, such as epinephrine could increase coronary blood flow without increasing the β adrenergic stimulation in the heart. As a result, we hypothesized that the administration of an ultra-short-acting selective β_1 antagonist, such as Esmolol, would diminish the undesirable effects of epinephrine when given before it.

Materials and Methods

Preparation

The experimental protocol was approved by the General Directorate of Veterinary Services (permit no. K/954/2001), according to Greek legislation, regarding ethical and experimental procedures (Presidential Decree 160/1991, in compliance to the EEC Directive 86/609, and Law 2015/1992, in conformance to the European Convention "for the protection of vertebrate animals used for experimental or other scientific purposes, 123/1986"). After approval by the Directorate of Veterinary Services of the Prefecture of Athens, Attica, Greece, 14 Landrace piglets aged 10-15 weeks and with an average weight of 19 ± 2 kg were studied. The animals were acclimatized for a week in the facilities of our department, receiving humane care. They were fasted overnight, but had free access to water. Initial sedation in each animal was achieved with intramuscular Ketamine 10 mg/kg, Midazolam 0.5 mg/kg and Atropine 0.05 mg/kg. Propofol anesthesia 2.0 mg/ kg was also delivered as an intravenous bolus via the lateral auricular vein (BD Venflon 20GA 1.26IN 54ml/ min). While spontaneously breathing, but anaesthetized, the pigs were intubated with a 4.5 or 5.0 endotracheal tube (MLT ™ 4.5 or 5.0 Oral 27 mm Mallinckrodt Medical). Correct placement of the endotracheal tube was ascertained with inflation and auscultation in both lungs. Additional propofol 1mg/ kg and also cis-Atracurium 0,15mg/kg and Fentanyl 4Ìg/ kg were then administrated, followed by a propofol infusion of 150Ìg/ kg/ min.

Ventilations were delivered with an automatic ventilator (ventiPac Sims pneuPac) with a total tidal volume of 15 mL/Kg. End- tidal P_{CO} was monitored (Nihon Kohden Corp) and the respiratory frequency was adjusted to maintain P_{ETCO2} 35 to 40 mmHg.

Electrocardiographic monitoring (ECG, Mennen Medical, Envoy) was performed by leads I, II, III, aVF, aVR, aVL using self adhesive electrodes in order to assess the cardiac rhythm and the heart rate was also determined by the ECG signal. Cerebral oximetry (Somanetics INVOS Cerebral Oximeter, Model SPFB Pediatric Somasensor SOMANETICS) was also used, as well as Pulse oximetry (SpO2) (Vet/ Ox Plus 4700).

A femoral arterial catheter was inserted to monitor arterial pressure (IBP) (Mennen Medical, Envoy). Right and Left Internal Jugular Veins and Left Carotid Artery are dissected. 7F sheaths are inserted in the Right and Left Internal Jugular Veins for infusions and Pulmonary Artery catheter insertion. Through the Left External Carotid Artery a 6F pigtail catheter is forwarded to the Descending Throracic Aorta for Aortic Pressure monitoring. (Opticath 5.5 F, 75 cm Abbott, Ethicon Mersilk ™).

Protocol

After stabilization of the animals, blood was drawn for baseline analysis. A 5 F pacemaker catheter was inserted into the right ventricle and ventricular fibrillation was produced with a 9V ordinary lithium battery. After induction of VF, the animals were left untreated for 5 minutes and propofol infusion was stopped. Resuscitation procedures started with inspired oxygen concentration 100% followed by chest compressions for 3 minutes.

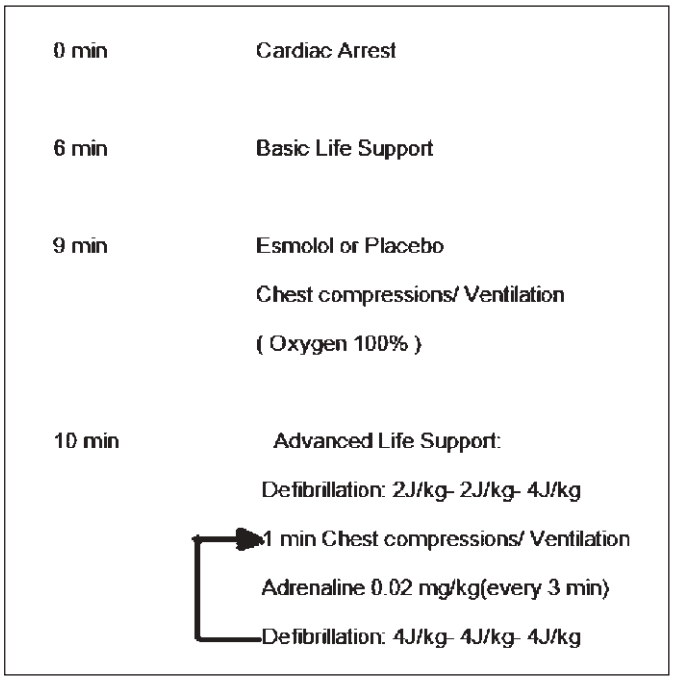

Fig. 1: Experimental Protocol.

Compressions were maintained at a rate of 100/min with equal compression β relaxation duration. Compression depth was equivalent to 30% of the anteroposterior diameter of the chest. During this period, rSO_2, SpO_2, right atrial pressure and IBP were monitored.

Animals were randomized into two groups, control and study group. Six animals were used in the control group and 8 in the study group. The investigators were blinded to the intervention until immediately before induction of VF, at which time the principal investigator opened a sealed envelope, the contents of which provided for randomization of the animal. The control group received 10 ml of normal saline from the peripheral vein, while the study group received 0.4 mg/kg Esmolol in 10 ml dilution. To ensure circulation, chest compressions were continued for one more minute. Chest Compressions were delivered at a rate of 100/min, with a compression depth equivalent to 30% of the anteroposterior diameter of the chest. Up to three shocks were given initially with energies of 2 J/Kg, 2 J/kg, and 4 J/Kg. While the defibrillator was recharged, the ECG monitor was observed for any changes in the rhythm. Blood was drawn and Adrenaline was administered peripherally. In case of failure to convert to a cardiac rhythm compatible with pulse, the typical Advanced Life Support (ALS) protocol was performed. This involved further defibrillation with energies 4 j/kg, 4 j/kg, 4 j/kg, and adrenaline administration every three minutes. Our experimental protocol is shown in the Fig. 1.

The animals that restored spontaneous circulation were monitored for 30 minutes, while anesthesia was maintained. Different parameters, such as IBP, the pressures of the right atrium, Aortic Systolic and Diastolic Pressures as well as SpO_2 were observed. These animals were euthanized by intravenous solution of thiopentale up to 1 gr. Autopsy was routinely performed to identify adverse effects of the interventions and especially traumatic injuries of thoracic and/or abdominal organs.

Statistical analysis

Data are expressed as mean ±1 standard deviation (S.D.). The Kolmogorov–Smirnov test was used to assess normality of the distributions. Comparisons of continuous variables were analyzed using the unpaired t-test and Mann-Whitney non-parametric test, as appropriate. Linear relationships between quantitative normally distributed parameters were assessed with Pearson's two way test, otherwise Spearmans' rho was used. All performed tests were two-sided. Differences were considered as statistically significant at the level of 5% ($p<0.05$).

Results

There was no difference in the baseline haemodynamics in the two groups, as illustrated in Table I.

Our results are summarized in Tables 2 to 7. Table II illustrates the successful outcomes for ROSC and the average time until restoration of a perfusing rhythm. Two out of 6 animals restored ROSC in the epinephrine group and 7 out of 8 animals in the Esmolol-epinephrine group ($p=0.018$)

The average time until the restoration of circulation was 16 minutes in our control group and 12.8 minutes in Esmolol group ($p=0.059$).

Coronary Perfusion Pressure (CPP) was defined as the arithmetic difference between diastolic aortic pressure minus the pressure of the right atrium. CPPs are sum-

TABLE I - *Baseline Haemodynamic Variables*

Variables	Epinephrine	Esmolol + Epinephrine
Aortic Systolic Pressure (mmHg)	101±6	103±8
Aortic Diastolic Pressure (mmHg)	67±6	65±7
Right Atrial Diastolic Pressure (mmHg)	7±3	7±4
Heart Rate (bpm)	112±14	114±19

TABLE II - *Outcomes versus Treatment*

	Epinephrine	Esmolol + Epinephrine	p
ROSC	2/6	7/8	0.036
Average time until restoration of perfusing rhythm	16 ±3.2 min	12.8±1.4 min	0.059

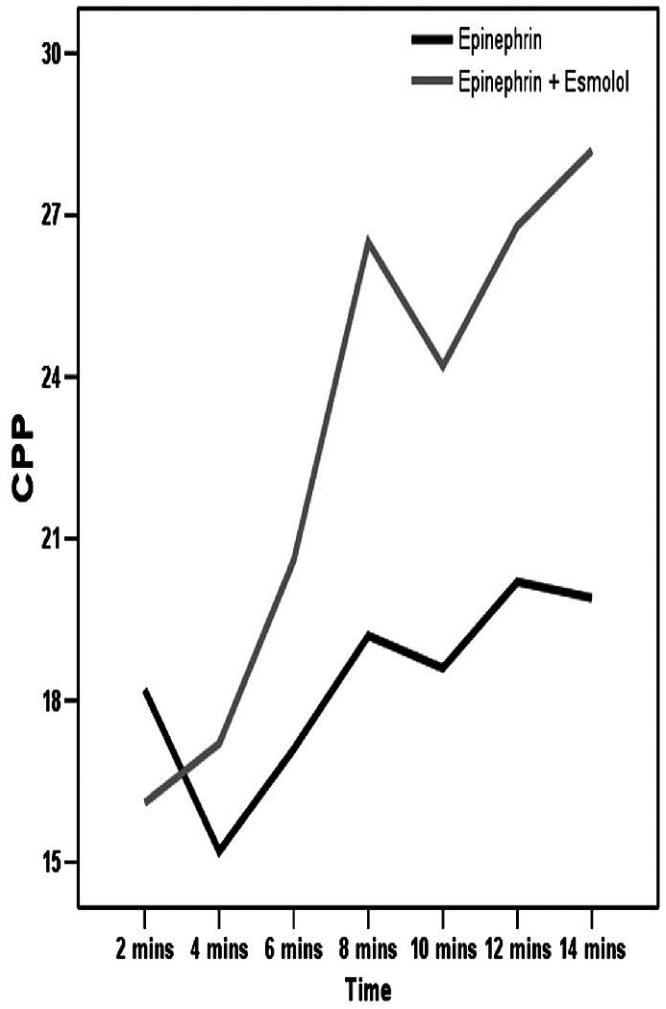

Fig. 2: Coronary Perfusion Pressure (CPP) changes in time.

marized in Table III. Coronary Perfusion pressures were significantly higher in the Esmolol+ Epinephrine group especially after 6 minutes of resuscitation, which is compatible to the better ROSC ratio in our study group. CPP changes in time are also illustrated in Fig. 2.
Tables IV and V summarize the same parameters at 11 min post arrest and 15 min post successful resuscitation. The heart rate was better controlled in the beta blocker group, as expected.

TABLE III - *Coronary Perfusion Pressures (mmHg) during CPR (*NS= Non-Significant)*

Min	Epinephrine	Esmolol +Epinephrine	P
2	18.2±1.5	16.1±2.4	NS*
4	15.2±1.3	17.2±2.1	NS*
6	17.1±0.9	20.6±2.1	0.003
8	19.2±1.9	26.5±3.1	<0.001
10	18.6±1.3	24.2±2.9	<0.001
12	20.2±2.5	26.8±3.2	<0.001
14	19.9±1.4	28.2±3.6	<0.001

TABLE IV - *Different Haemodynamic Variables 11 min post arrest (5 min VF+ 6 min CPR)*

Variables	Epinephrine	Esmolol+ Epinephrine
Aortic Systolic Pressure (mmHg)	87±17	89±14
Aortic Diastolic Pressure (mmHg)	34±5	42±7
Right Atrial Diastolic Pressure (mmHg)	16±4	15±6
Coronary Perfusion Pressure (mmHg)	17.1±0.9	20.6±2.1
Heart Rate (bpm)	100	100

TABLE V - *Haemodynamic variables 15 minutes Post Successful Resuscitation*

Variables	Epinephrine	Esmolol+ Epinephrine
Aortic Systolic Pressure (mmHg)	124±36	123±38
Aortic Diastolic Pressure (mmHg)	87±33	85±37
Heart Rate (bpm)	142±27	124±32

TABLE VI - *Number of Shocks and total energy of defibrillation*

Group	Number of shocks
Epinephrine	5.9±2.8
Epinephrine+Esmolol	1.4±0.8 (p<0.005)

TABLE VII - *Occurrence of Postresuscitation Dysrhythmias in the 2 different groups, in successfully resuscitated animals*

	Premature Ventricular Contractions	Salvos	Ventricular Tachycardia
Epinephrine	38±12	12±5	15±9
Epinephrine+Esmolol	18±7	3±2	1±0
p	<0.001	<0.001	<0.001

A significantly larger number of electrical shocks and total energy of defibrillation was required in the epinephrine group compared with the addition of esmolol, as can be seen on Table VI.
The numbers of premature ventricular contractions and salvos were significantly greater in the epinephrine-treated animals in the post resuscitation period. This contrasted with the Esmolol+Epinephrine group, after the β_1 effects of epinephrine were blocked (Table VII).

Discussion

In 1948, Ahliquist observed that there are two distinct types of adrenoceptors, which were α (excitatory) and β

(inhibitory). This classical subdivision was further expanded by Lands[20], and at present, nine adrenoceptor subtypes have been cloned. There are 3 α_1-subtypes (α_{1A}, $\alpha_{1B,}$ α_{1D}), 3α_2-subtypes (α_{2A}, $\alpha_{2B,}$ α_{2C}) and 3 β-subtypes (β_1, β_2, β_3) [21].

The structurally and functionally similar ,$_1$ and ,$_2$ adrenoceptors couple to GTP-binding proteins to elicit their biological effects, while β_1 and β_2 adrenoceptors both respond to the adrenal hormone epinephrine. In mammals, it is mostly the β_1-adrenoceptors that are involved in local sympathetic modulation of physiologic responses [22].

Epinephrine has a potent effect on both α and β receptors. β-adrenoceptors modulate myocardial contractility, heart rate, and peripheral vascular resistance. However, evidence suggests that its efficacy is due to the α- adrenergic peripheral vasoconstriction effect [5].

The search continues for the drug of choice in cardiopulmonary resuscitation. Although over the years, epinephrine remains the drug of choice, even with the newly published guidelines, concern has been expressed that it may actually worsen myocardial oxygen supply and demand balance. In previous studies, it has been demonstrated that comparing high dose epinephrine, high dose phenylephrine and combination of phenylephrine with beta blockade, improves the balance between myocardial oxygen supply and demand with the addition of the beta blocker [23,24]. Additionally, it has been showed that pretreatment with a beta-blocker prior to cardiac arrest followed by standard epinephrine therapy results in reduced myocardial injury during CPR without compromising successful defibrillation or post-resuscitation left ventricular function [25]. However, those studies did not examine the effect of beta blockade given prior to the administration of adrenaline during CPR. This study was designed to investigate the effect of intravenous selective beta blockers with standard dose epinephrine on the return of spontaneous circulation.

Our results are promising for the proposed dose of Esmolol, especially when the beta blockade agent was administered before epinephrine. The blocking of the beta-adrenergic effect of exogenous and endogenous catecholamines during resuscitation significantly improved the coronary perfusion pressure after six minutes of resuscitation. This finding was consistent with a previous study that nonselective β-adrenergic blockade propranolol pretreatment reduced myocardial injury CPR without compromising the likelihood of successful defibrillation or spontaneous post resuscitation left ventricular function. In the same study it was shown that nonselective β-blockade increases CPP during CPR, implying that β-adrenergic blockade can enhance vasoconstriction by allowing the unopposed α-adrenergic stimulation of vessels [25].

Those results could possibly explain the effect of what was demonstrated by another study in a rat CPR model where less post resuscitation myocardial impairment and prolonged survival could be produced, when epinephrine was combined with a short-acting β_1-adrenergic blocker. In one of the studies propranolol pretreatment combined with epinephrine procured greater cardiac output, suggesting improved myocardial contractility and left ventricular diastolic function.

The authors recognize several limitations in the interpretation of the present finding. The study was conducted on apparently healthy swine, therefore its direct application to human victims of cardiac arrest, the vast majority of which has underlying heart disease, remain to be proven. This study has not addressed any species differences. Nevertheless, within these limitations esmolol seem to exert a beneficial effect on the primary outcome of cardiopulmonary resuscitation.

Conclusion

Those experimental data suggest that selective β_1- blocking improves the Coronary Perfusion Pressures, therefore improving the overall rate of successful defibrillation in swine resuscitated from cardiac arrest. In view of these promising results, we believe that an area of research has been opened for β-blockade during cardiopulmonary resuscitation.

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Riassunto

La somministrazione di adrenalina fu per più di 30 anni la terapia d'elezione per la resuscitazione cardiopolmonare. L'azione vasocostrittiva di tale sostanza, desiderata ai fini della resuscitazione è di tipo α–adrenergico. Le sue azioni di tipo β–adrenergico però possono avere dei risultati catastrofici per il paziente. L'obiettivo del presente lavoro sperimentale è quello di valutare l'efficienza dell'esmololo, un farmaco β_1–bloccante ad azione breve a ridurre tali devastanti β–effetti dell'adrenalina se somministrata assieme ad essa in un modello sperimentale di arresto cardiaco indotto artificialmente in cuore suino.

Riportiamo il materiale utilizzato ed il metodo di studio, i risultati e le conclusioni tratte dalla nostra sperimentazione, le quali mettono in evidenza che l'utilizzo dell'esmololo in ambito di resuscitazione cardiopolmonare migliora chiaramente l'esito dei tentativi di resuscitazione ed inoltre diminuisce significativamente il tempo medio necessario al completo recupero perfusionale del modello sperimentale in seguito all'arresto.

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