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Prophylactic amiodarone and lidocaine improve survival in an ovine model of large size myocardial infarction

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Abstract

Background—Large animal models serve as a critical link in the translation of basic science to clinical practice. However, large animal models of MI, especially a large size MI, are associated with high mortality due to arrhythmia. The prophylactic effect of amiodarone and lidocaine were retrospectively reviewed in our ovine MI model.

Methods—One hundred-fourteen Dorset hybrid sheep with 25–30% MI were included in this study. Animals were prophylactically treated with amiodarone plus lidocaine before ligation of the 4–6 coronary artery branches supplying the apex of the heart (arrhythmia-prevention group, AP group, n=45) and with epinephrine (shock-prevention group, SP group, n=49), respectively. Animals without prophylactic treatment (no-prevention group, NP group, n=20) were used as the control group. The incidence of arrhythmia requiring treatment, mortality due to arrhythmias, hemodynamics and arterial blood gas values during the surgery were analyzed in these three groups.

Results—There was no significant difference in infarct size among the three groups. The incidence of arrhythmia requiring treatment was significantly decreased in the AP group compared to the NP or SP groups 4.4% (AP) vs. 35% (SP) or 45% (NP) $p<0.05$). The mortality due to lethal arrhythmia was 2.2% in the AP group, significantly lower than in the NP group (15%) or the SP group (18.4%). Besides heart rate (HR), hemodynamic data there were no significant differences between the AP and NP group. Metabolic acidosis was not observed in any group as indicated by pH and lactate values.

Conclusions—Prophylactic amiodarone plus lidocaine decreased the mortality due to lethal arrhythmia after acute myocardial infarction in our sheep model without significant negative effect on hemodynamics. However, epinephrine improved hemodynamics but also increased mortality due to lethal arrhythmia. Thus, prophylactic amiodarone plus lidocaine is recommended to improve the stability in a large MI animal model.

Keywords

animal model; myocardial infarction; ovine; arrhythmia; amiodarone; lidocaine

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Introduction

Acute myocardial infarction (MI) is a common and disabling condition. In 2011, there were 610,000 new cases and 325,000 recurrent cases in the US. The mortality of acute MI remains as high as 9% (1). MI is still the most common cause of heart failure (HF). With close approximation to human anatomy and physiology, large animal models of HF are a critical link in the translation of basic science to clinical practice. Large animal models of myocardial infarction have been used in experimental cardiology for many decades as they accurately model this devastating human disease. However the experimental MI procedure is associated with high mortality due to arrhythmias, ranging from 16% to 29% in ovine models (6,7,8), and even higher incidence in swine models. The incidence of ventricular fibrillation in pigs is 19% within the first 10 minutes after the occlusion of a coronary artery, increasing to 38% in 20 to 40 minutes after ischemia, with a mortality of 12.5% due to ventricular fibrillation (9). Thus the optimal drug regimen in large animal models of acute MI remains a critical factor in experimental heart studies. Selection of an appropriate perioperative treatment strategy requires consideration of cardiogenic shock, arrhythmia prevention, and possible side effects of the chosen drugs as well as maintaining clinical relevance. Amiodarone, lidocaine and epinephrine have been used to prevent arrhythmia or to increase cardiac output after acute MI. Although these three drugs have been shown to have both positive and negative effects in acute MI patients, their use in the animal model remains unclear. In the present study, we sought to investigate the prophylactic effects of amiodarone/lidocaine and epinephrine on the mortality rate in a large animal ovine MI model.

Materials and Methods

114 Dorset hybrid sheep were included in this study. Forty-five animals were prophylactically treated with amiodarone and lidocaine before ligation of the 4–6 coronary artery branches supplying the apex of the heart (arrhythmia-prevention group, AP group). Forty-nine animals, which were prophylactically treated with epinephrine, were used as a MI cardiogenic shock prevention group (SP group). Twenty animals without prophylactic treatment served as the MI control group (no prevention group, NP group). All animals in this study were treated in compliance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (National Institutes of Health publication 85–23, revised 1996). All surgical procedures were carried out according to protocol approved by the Institutional Animal Care and Use Committee of the University of Maryland, Baltimore.

Animal preparations and anesthesia

The animals were fasted for 12 to 16 hours prior to anesthetic administration but they were allowed free access to water. They were pre-anesthetized with atropine (0.01 – 0.02 mg/kg IM) and glycopyrrolate (0.01 – 0.02 mg/kg IM). Anesthesia was induced with Ketamine (5 ~ 15 mg/kg IM). An 8 Fr. catheter was placed in the left internal jugular vein. Anesthesia induction was continued with sodium thiopental (7–20mg/kg IV). Once induced, endotracheal intubation was performed by direct visualization using a laryngoscope. Anesthesia was maintained with isoflurane in 100% oxygen delivered through a precision vaporizer (North American Drager, Narkomed 2B, Telford, PA) at a concentration of 1–4%. Succinylcholine was administered in a single dose (1 mg/kg IV) to give temporary neuromuscular blockade prior to incision through the chest wall musculature. A left femoral artery catheter (5 Fr.) was placed using Seldinger technique for blood pressure monitoring. Surface ECG, pulse oximeter, and rectal temperature were continuously monitored during the surgical procedure. Arterial blood gas (ABG) was measured every 30–60 minutes. Animals received intravenous Ringer's lactate or saline solution throughout surgery. A

Swan-Ganz catheter was used for monitoring pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP). An ultrasound flow probe (Transonic Systems Inc., Ithaca, NY) was placed around the main pulmonary artery for monitoring cardiac output (CO).

Pre-MI medication

Prophylactic treatment with amiodarone and lidocaine was used in the AP group. Amiodarone was administered with loading dose of 1–3mg/kg IV 10–20 minutes before MI and then 1–1.5mg/kg/hr IV infusion. Lidocaine was given with loading dose of 1–2mg/kg IV and then 1–2mg/kg/hr IV infusion after thoracotomy and pericardiotomy. In the NP group, no medicine was given before MI induction. In the SP group, epinephrine was given at 240 µg/hr 10 minutes before coronary ligation and reduced by 60µg/hr every 5 minutes, with the final reduction being 20µg/hr. The dose was held at 40µg/hr for 10–20 minutes after ligation.

MI induction

A left lateral thoracotomy was performed through the 5th intercostal space and the left heart was exposed. Coronary artery branches feeding the ventricular apex were ligated at 2/3 distance from the base to apex, to produce an apical MI.

Post-MI treatment

Arrhythmias, including non-lethal: premature ventricular contractions (PVCs) (more than 10 times per minute, doublets, triplets, multi-formed) and atrial fibrillation (AF), and lethal: ventricular tachycardia (VT) and ventricular fibrillation (VF), were treated with amiodarone and/or lidocaine. Animals with PVCs were treated with 1–2mg/kg lidocaine IV. If PVCs persisted 3 minutes, treatment was repeated at a dose of 0.5 to 1 mg/kg IV to a maximum of 3.0 mg/kg, or / and IV infusion started at 1–3mg/kg/hr. Animals with AF were treated with 1–3mg/kg amiodarone IV. After 3 minutes, if AF persisted, treatment was repeated at a dose of 0.5 to 1.5 mg/kg IV. Treatment was repeated every 3 minutes if no return to sinus rhythm occurred. Animals with VT/VF were treated with 1–2mg/kg lidocaine IV plus 1–3mg/kg amiodarone IV. The surgeon directly squeezed the animal's heart by hand to assist contractions. If VT/VF persisted 1–2 minutes, animals were treated with the electrical cardioversion. Deviations from this recommended treatment protocol were at the discretion of the anesthesiologist. For the animals which experienced AF, only one animal required the electrical cardioversion. The energy level of the internal electrical cardioversion was set initially at 10 joules and progressively increased up to 50 joules as needed.

Data collection

Baseline observations were made when the animals were fully anesthetized. Hemodynamic data following MI was collected 15, 30, and 45 minutes after coronary ligation. The following measurements were recorded: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), cardiac output (CO), Mean pulmonary artery pressure (MPAP), PCWP and CVP. Isoflurane concentration and ventilation parameters were collected every 15 minutes. Ventilation and ABG parameters were collected at the same time points and 40–60 min after coronary ligation. At the time of termination, the heart from each animal was harvested. Infarct size was measured as the area ratio between fibrosis at the LV apex and the free LV wall by ImageJ software (National Institutes of Health, USA),

Statistics

All data are expressed as mean $\pm$ standard error of the mean (SEM). ANOVA was performed after multiple comparisons with the least significant difference (Bonferroni) correction. A *p* value of < 0.05 was considered statistically significant.

Results

General information of animal and anesthesia

There were no significant differences among the three groups in heart rates, respiration rates, rectal temperature, body weight before surgery or pre-medication, anesthesia introduction and maintenance, infusion and ventilation during surgery. The baseline data of the study animals are listed in Table 1.

Arrhythmia occurrence and mortality

Infarct size was similar among the three groups ($24.5 \pm 0.9\%$ in NP group, $23.7 \pm 1.1\%$ in SP group and $24.7 \pm 1.4\%$ in AP group). Arrhythmias were significantly lower in the AP group (4.4%) than in the NP group (35%) or the SP group (45%) ($p < 0.05$, Figure 1). The AP group had a lower mortality rate compared with the other two groups ($p < 0.05$). The mortality due to lethal arrhythmias in the AP group was 2.2%, which is significantly lower than in the NP group (15%) or the SP group (18.4%). All lethal arrhythmias were VT/VF. There were no mortalities in any group due to AF, heart block or other ectopy.

The death rate due to other factors (including: aspiration, hemorrhage, acute heart failure after MI, irreversible hypoxemia) was similar, 10%, 12.2% and 11.9% in the NP group, the SP group and the AP group, respectively (Figure 2).

Arrhythmia prophylaxis and treatment

The type and treatment of arrhythmia post-MI were outlined in Table 2. In the NP group, arrhythmia occurred in 7 animals among 20 cases (35%, 15% VT / VF). One animal was treated with amiodarone alone and 2 animals were treated with lidocaine alone, and 4 animals were treated with both amiodarone and lidocaine. The initial dose of amiodarone was $2.37 \pm 0.10\text{mg/kg}$ and the initial dose of lidocaine was $1.37 \pm 0.15\text{mg/kg}$. Three animals (1VT, 2VF) required electrical cardioversion with a mean energy of 27 ± 4 joules but they did not survive. In the SP group, arrhythmia occurred in 22 animals (45%, 20.4% VT / VF) out of 49 cases. 5 animals were given amiodarone and lidocaine. 13 animals were treated with amiodarone and lidocaine first, then with lidocaine infusion. 4 animals were treated with lidocaine infusion alone. The initial doses of amiodarone and lidocaine were $2.44 \pm 0.30\text{mg/kg}$ ($n=18$), $1.28 \pm 0.15\text{mg/kg}$ ($n=18$) respectively, and the infusion rate of lidocaine was $2.54 \pm 0.15\text{mg/kg/hr}$ ($n=17$). 11 of those animals (8VF, 2VT, 1AF) were treated with the electrical cardioversion with a mean energy of 28 ± 2 joules. 2 animals survived after the cardioversion (1VF and 1AF) and 9 died. In the AP group, there were only two (4.4%) incidents of lethal arrhythmia out of 45 cases. The loading doses of amiodarone and lidocaine were $2.38 \pm 0.08\text{mg/kg}$ ($n=42$) and $1.38 \pm 0.08\text{mg/kg}$ ($n=42$) respectively. Their infusion rates were $1.47 \pm 0.04\text{mg/kg/hr}$ and $1.52 \pm 0.07\text{mg/kg/hr}$ respectively. 2 animals (2VF) were defibrillated with a mean energy of 26 ± 7 joules. One animal survived and the other died after the cardioversion.

All the animals with VF or VT were defibrillated with internal paddles. For the animals which experienced AF, only one animal required the electrical cardioversion.

Hemodynamics

Table 3 summarizes hemodynamic parameters at baseline and after MI. The cases requiring post-MI antiarrhythmic medications were excluded. This reduced the NP group to 13, the SP group to 27 and the AP group to 43. In the NP group, HR did not change after MI compared to the baseline value. SBP, DBP, MAP and CO were significantly lower following MI compared to the baseline values. MPAP, PCWP, and CVP had no significant changes after MI. In the SP group, HR, SBP, DBP, MAP and CO increased after MI compared to the baseline values. MPAP, PCWP, and CVP were also increased after MI with the epinephrine infusion.

In the AP group, HR after MI was significantly lower compared to the baseline value or that of the NP group or the SP group. SBP, DBP, MAP and CO were significantly reduced following MI compared to the baseline values and were also lower than the pressures in the NP group after MI. MPAP, PCWP, and CVP increased after MI compared to baseline values in both the SP and AP groups, but had no significant difference compared to the NP group after MI.

Metabolism

There were no significant differences in ABG parameters between the three groups (Table 4). Under normal circumstances, the sheep's blood is alkaline ($\text{pH} \approx 7.5$). In the SP group, even though lactate acid slightly increased but there was no significant difference compared to the NP group and the AP group.

Discussion

Coronary artery disease is a leading cause of the death in many industrialized nations. In recent decades, improvements in the diagnosis and treatment of acute MI have led to an increasing number of patients surviving with a damaged myocardium and subsequent risk of developing heart failure (1,2,3,4). In spite of these advances in diagnostics and therapeutics, the morbidity and mortality rates of heart failure are still high which demand new and more effective therapeutic strategies. Large animal models can closely approximate human physiology, function, and anatomy. For this reason, a reproducible model of myocardial infarction in large animals is an essential step not only in the development of new therapies but also improved understanding of cell and molecular pathology following cardiac ischemia (5). Both in experimental animal models and patients, lethal arrhythmia is the leading cause of death following MI, accounting for 12.5–29.4% and 30–40% of mortality in large animal models and humans, respectively (6,7,8,9). In an effort to more closely approximate clinical scenarios and to decrease mortality of experimental animals, actively preventing arrhythmias following infarction is critical in large animal studies.

From our extensive experience with the ovine MI model, we have learned important lessons. The experiments with 114 sheep have helped to optimize our model and support the continuing practices. As the sheep is a calm animal, no sedative was needed preoperatively. In a few cases, an atropine dose of 0.02mg/kg/IM did not control salivation for the entire period of the operation, additional doses of 0.005–0.01mg/kg IV were necessary 1–2 times during the procedure. Ketamine 14–15mg/kg IM, without other sedatives, was a suitable dosage for anesthesia induction, keeping the animal quiet and cooperative for jugular vein catheter placement. Additionally, thiopental ~10mg/kg IV alone is sufficient to facilitate endotracheal intubation. Lately we have been using propofol to replace thiopental, 3–6mg/kg, because market availability restrictions of thiopental in the US. A 9 mm ET tube is suitable for most adult sheep. Tracheal intubation is easily achieved in the supine position. Sheep can have the mouth wide open and the laryngeal structures are easily viewed but often

the epiglottis can fold backward to cover the entrance of the larynx. The optimal drug regimen in large animal models of acute myocardial infarction remains uncertain. Selection of an appropriate perioperative treatment strategy requires consideration of cardiogenic shock and arrhythmia prevention, the possible side effects of the chosen drugs as well as maintaining clinical relevance.

Epinephrine has α - and β -adrenergic receptors with high affinity and positive cardiac inotropic function, increased heart rate, oxygen consumption, and increased vasoconstriction. Although helpful in treating shock, epinephrine may cause a transient lactic acidosis and arrhythmia (10,11). Our results show that the blood pressure and cardiac output following MI in the SP group were significantly higher than those in the NP and AP groups but there were no significant differences in MPAP, PCWP and CVP. There was no lactic acidosis in any groups as animals were sufficiently perfused and supplemented with oxygen during surgery. Incidence of lethal arrhythmia in the NP and the SP group was significantly higher than those in the AP group. All lethal arrhythmia were due to VT/VF. A significant increased mortality due to VT/VF is seen in the NP and the SP groups compared to the AP group. Both were significantly higher than the AP group.

Amiodarone is a class III antiarrhythmic agent, is also class I, II and IV activity, used for various types of cardiac dysrhythmias. Amiodarone is most effective for preventing recurrent ventricular tachyarrhythmias. In cardiac arrest survivors, empirical treatment with amiodarone is an effective method to improve survival by reducing lethal arrhythmias (12). In addition, amiodarone does not exacerbate heart dysfunction, is less pro-arrhythmic than other drugs and is better choice for patients with severe left ventricular failure (13). Sassi et al. reported that in patients receiving prophylactic antiarrhythmic treatment with amiodarone after acute MI, the mortality was 8.7% but was 24.2% when receiving placebo (14). Lidocaine is a class I antiarrhythmic agent used for mainly ventricular arrhythmias. Wyman et al. reported that the incidence of primary VF was 0.5% among the 4150 patients with suspected acute MI who received prophylactic lidocaine and 10% among the 104 who did not (15). We planned to combine amiodarone with lidocaine to complement each other. Side effects were reduced through close monitoring of hemodynamic changes and drug dosage adjustment accordingly. Our results show that only HR decreased following MI in the AP group compared to the NP group. The prophylactic use of amiodarone plus lidocaine significantly reduced arrhythmias and mortality after myocardial infarction in this sheep model. Increased understanding of the role of these three drugs in the prevention of sudden cardiac death after acute MI may provide anesthesiologists with strategies to improve outcome in addition to improving an important research model.

Our study has several potential limitations. It is not randomized or prospective in design. Additionally, we don't have an amiodarone alone group. As a "broad antiarrhythmic drug", amiodarone may suffice as anti-arrhythmic prophylaxis without adding the risk of hemodynamic instability of lidocaine (16). Dorian et al. reported (17) that when compared to lidocaine, amiodarone improves survival for out-of-hospital ventricular fibrillation, resistant to epinephrine and electrical cardioversion. Further studies are warranted to optimize hemodynamics following MI.

In conclusion, this study demonstrated that the prophylactic use of amiodarone plus lidocaine, dose adjustment based on hemodynamic parameters, was a simple and effective measure to significantly reduce arrhythmia and mortality after MI, to improve the moral acceptance and cost effectiveness of this important experimental model (18,19).

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Figure 1.

Figure 2.

Table 1

General information of animal and anesthesia

Animal Characteristics	HR (bpm)	95.3 ± 1.6
	RR (bpm)	36.4 ± 0.6
	RT (°C)	38.92± 0.06
	BW (kg)	54.1 ± 0.7
Pre-medication	Atropine (µg/kg)	20.3 ± 0.5
	Glycopyrrolate (µg/kg)	10.2 ± 0.3
Anesthesia introduction	Ketamine (mg/kg)	14.1 ± 0.2
	Pentothal (mg/kg)	9.2 ± 0.2
Anesthesia maintenance	Isoflurane (%)	1.98 ± 0.04
Infusion during surgery	Fluids (ml/kg/hr)	4.07 ± 0.15
Ventilation during surgery	MTV (ml/kg/min)	149.8 ± 3.4

HR: heart rate, RR: respiratory rate, RT: rectal temperature, BW: body weight, MTV: minute tidal volume.

Table 2

Type and treatment of arrhythmia post-MI

	Type of Arrhythmia Animals, n (%)	Treatment, n (%)				Deaths, n (%)
		Lidocaine IV	Lidocaine Infusion	Amiodarone IV	Defibrillation	
NP group (7/20 35%)	PVCs	2 (10)	2 (10)			
	AF	1 (5)		1 (5)		
	PVCs+AF	1 (5)	1 (5)	1 (5)		
	VT	1 (5)	1 (5)	1 (5)	1 (5)	1 (5)
	VF	2 (10)	2 (10)	2 (10)	2 (10)	2 (10)
SP group (22/49 45%)	PVCs	4 (8.2)	4 (8.4)			
	AF	0				
	PVCs+AF	8 (16.3)	8 (16.3)	8 (16.3)	1 (2)	
	VT	2 (4.1)	2 (4.1)	2 (4.1)	2 (4.1)	2 (4.1)
	VF	8 (16.3)	8 (16.3)	8 (16.3)	8 (16.3)	7 (14.3)
AP group (2/45 4.4%)	PVCs	0				
	AF	0				
	PVCs+AF	0				
	VT	0				
	VF	2 (4.4)			2 (4.4)	1 (2.2)

PVCs: premature ventricular contractions, AF: atrial fibrillation, VT: ventricular tachycardia, VF: ventricular fibrillation.

Table 3

Hemodynamic Parameters of Baseline and Post MI

	NP group (n=13)		SP group (n=27)		AP group (n=43)	
	Baseline	Post MI	Baseline	Post MI	Baseline	Post MI
HR (bpm)	96.5 ± 3.0	99.5 ± 2.5	103.6 ± 3.2	108.4 ± 3.4	102.9 ± 2.3	84.9 ± 1.8 * †
SBP (mm Hg)	97.3 ± 1.5	82.8 ± 2.0 *	100.8 ± 1.9	104.0 ± 2.0 †	99.4 ± 1.7	79.5 ± 1.1 * #
DBP (mm Hg)	72.4 ± 1.2	55.5 ± 1.0 *	71.8 ± 2.2	80.6 ± 2.1 * †	71.4 ± 1.8	53.5 ± 1.0 * #
MBP (mm Hg)	81.0 ± 1.0	65.6 ± 1.0 *	81.1 ± 1.7	90.9 ± 2.2 * †	83.2 ± 1.6	63.3 ± 0.9 * #
CO (L/min)	4.56 ± 0.21	4.06 ± 0.18	4.45 ± 0.15	5.24 ± 0.14 * †	4.37 ± 0.12	3.54 ± 0.14 * #
MPAP (mm Hg)	15.0 ± 0.6	16.3 ± 0.3	16.0 ± 0.3	18.9 ± 0.7 *	14.9 ± 0.4	17.9 ± 0.5 *
PCWP (mm Hg)	10.0 ± 0.6	10.3 ± 0.9	9.8 ± 0.7	11.1 ± 0.8 *	9.3 ± 0.4	10.9 ± 0.4 *
CVP (mm Hg)	3.7 ± 0.6	5.3 ± 0.6	5.0 ± 0.4	6.8 ± 0.4 *	4.5 ± 0.3	6.8 ± 0.3 *

HR: heart rate, SBP: systolic arterial blood pressure, DBP: diastolic arterial blood pressure, MBP: mean arterial blood pressure, CO: cardiac output, MPAP: mean pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, CVP: central venous pressure.

* p<0.05 vs. baseline,

† p<0.05 vs. post MI in NP group,

p<0.05 vs. post MI in NP group and SP group,

p<0.05 vs. post MI in SP group.

Table 4

ABG parameters

	NP group (n=20)	SP group (n=49)	AP group (n=45)	Total (n=114)
pH	7.49 ± 0.02 (n=7)	7.50 ± 0.01 (n=21)	7.51 ± 0.01 (n=31)	7.50 ± 0.01 (n=59)
PaCO ₂ (mm Hg)	41.9 ± 1.3 (n=7)	41.1 ± 1.8 (n=21)	39.5 ± 1.1 (n=31)	40.3 ± 0.9 (n=59)
HCO ₃ (mEq/L)	32.8 ± 1.4 (n=7)	33.7 ± 1.3 (n=21)	31.4 ± 0.6 (n=31)	32.4 ± 0.6 (n=59)
BE	7.52 ± 1.36 (n=7)	7.77 ± 0.88 (n=21)	7.66 ± 0.91 (n=31)	7.65 ± 0.59 (n=59)
Lac (mmol/L)	2.74 ± 0.60 (n=7)	3.14 ± 0.32 (n=13)	2.56 ± 0.39 (n=12)	2.83 ± 0.24 (n=32)