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Female sex is not associated with improved rates of ROSC or short term survival following prolonged porcine ventricular fibrillation

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Abstract

Objectives—There may be a survival benefit in female patients experiencing cardiac arrest, which could affect the interpretation of *in vivo* animal studies. We hypothesized that sex predicts return of spontaneous circulation (ROSC) and short-term survival (SURV) in porcine studies of prolonged ventricular fibrillation (VF).

Methods—Retrospective analysis of eight comparable experiments performed in our lab using mixed-breed domestic swine of either sex. All experiments included prolonged untreated VF, CPR, defibrillation, and drugs. We defined ROSC as systolic blood pressure $\geq$ 80 mmHg for one minute. Short-term survival was defined 20 or 60 minutes, depending on protocol. Categorical variables were compared with chi-square test and Fisher's exact test. Continuous variables were compared with two-sample t-test and one-way ANOVA. Multiple logistic regression determined predictors of ROSC and SURV, utilizing cluster analysis by experimental protocol. Candidate variables were sex, weight, anesthesia duration, VF duration, and CPR ratio.

Results—Of 263 swine analyzed (53.2% male), 58.6% of males and 68.3% of females had ROSC ($p=0.10$), whereas 50.0% of males and 61.0% of females experienced SURV ($p=0.07$). Neither sex nor any identified candidate variable predicted ROSC or SURV. Both models had acceptable fit with Hosmer-Lemeshow values of 0.35 and 0.31, respectively.

Conclusions—Sex predicts neither ROSC nor SURV in a swine model of prolonged VF.

Keywords

Cardiopulmonary resuscitation (CPR); Resuscitation; Heart Arrest; Animal Model; Drug Therapy; Swine

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Conflict of Interest Statement

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Introduction

Several studies have highlighted a gender discrepancy in outcomes following both out-of-hospital and in-hospital cardiac arrest, noting improved short-term survival among females compared to males. (1–7) Prior work has demonstrated that females are less likely to survive from pneumonia (8–11), burns (12), and penetrating trauma. (13) However, females appear to have improved outcomes following blunt trauma (13) and traumatic brain injury. (14,15) If female sex is associated with improved outcomes following cardiac arrest, the interpretation of *in vivo* animal studies utilizing mixed sex may be affected. Reviewing prior experiments in our large animal lab, we hypothesized that sex is associated with return of spontaneous circulation (ROSC) and short-term survival (SURV) in porcine studies of prolonged ventricular fibrillation (VF).

Materials and Methods

The care and handling of the animals were in accord with NIH guidelines. We conducted a retrospective analysis of the last eight comparable experiments performed in our lab using mixed-breed domestic swine of either sex. (16–21) The swine are between 12 and 16 weeks of age and our supplier has remained the same during the course of these experiments. Animal preparation methods have been previously described in detail and have remained consistent over the past 12 years, except as outlined below. (19) In all studies, we induced VF by delivering a three second, 60 Hz, 100 mA AC current externally across the thorax.

Depending on experimental protocol, chest compressions were delivered either manually or mechanically with a traditional, high-impulse, or continuous device. Manual compressions were delivered by one investigator (JJM) using the sound of the mechanical device as a metronome. Mechanical chest compressions were applied using an oxygen-driven resuscitation device (Thumper, Michigan Instruments, Grand Rapids, MI). High-impulse compressions were accomplished using a high-impulse Thumper (Model 1007, Michigan Instruments, Grand Rapids, MI). Continuous compressions with intermittent ventilations were performed using a LUCAS device (Jolife, Lund, Sweden). All compressions were performed in an anterior-posterior direction at a rate of 100 per minute with a compression depth of 2.0 inches and a duty cycle of 50%. The compression to ventilation ratio utilized in experiments evolved from 5:1 to 15:1 to 30:2 with corresponding changes in American Heart Association/International Liaison Committee on Resuscitation Emergency Cardiovascular Care guidelines that emphasized the importance of chest compressions. (22–24) Ventilation was performed with 100% FiO₂ for all experiments at a tidal volume of approximately 400 cc.

Our laboratory uses an impedance-compensating, truncated exponential biphasic defibrillation waveform (LifePak 12, 3-D, Medtronic-Physio-Control) with a fixed dose of energy of 150J. All countershocks were administered by one investigator (JJM) to eliminate intra-user variability.

All animals received high-dose epinephrine (0.1 mg/kg), propranolol (1 mg), vasopressin (40 IU) and bicarbonate (1 mEq/kg) as an initial drug cocktail. Thereafter, the animals may have received additional doses of epinephrine (0.015 mg/kg) every 3 minutes as the resuscitation wore on and pulses were not restored. If pulses were restored, sodium bicarbonate was administered for acidosis if necessary. Dosing of sodium bicarbonate was based on an arterial blood gas ($\text{NaHCO}_3 = 0.3 \text{ mEq} \times \text{weight in kgs.} \times \text{base deficit}$).

ROSC was defined as an organized electrical rhythm with a systolic blood pressure of at least 80mm Hg for at least 1 minute continuously at any time during the resuscitation effort. Short-term survival was defined as maintenance of ROSC for either 20 or 60 minutes,

depending on the protocol. Thereafter, the animal was euthanized with 40 mEq of potassium chloride. Resuscitation efforts were continued for 20 minutes in those animals that did not experience ROSC.

Data Analysis

Demographic data, including experimental study, sex, weight, CPR ratio (compressions to ventilations), pre-resuscitation anesthesia duration, VF duration, ROSC, and short-term survival were abstracted from the experiential records. We used Microsoft Excel 2011 (Microsoft Corporation, Redmond, WA) and STATA 12.0 (StataCorp, College Station, TX) to analyze the data. Categorical variables were compared with chi-square test and Fisher's exact test. Continuous variables were compared with a two-sample t-test and one-way ANOVA. Two logistic regression models were constructed to determine predictors of ROSC and short-term survival. Predictor variables were identified by either *a priori* potential confounding or univariate logistic regression with a $p \leq 0.1$ threshold for entrance into the multiple variable model. Candidate variables included: sex, weight, duration of anesthesia, duration of VF, and CPR ratio. Resuscitation protocol accounted for variation in the mechanical device utilized for CPR and timing of drug cocktail. Because animals were independent across experiments but not necessarily within experiments, the multiple variable logistic models utilized cluster analysis by experimental protocol. Variance inflation factor was calculated to assess for multicollinearity between variables. The Hosmer-Lemeshow test was used to determine goodness of fit. An alpha of 0.05 was used for both descriptive and predictive statistics. Receiver operator curves were generated from the final multiple variable models and the area under the curve (AUC) was analyzed.

Results

In total, 263 swine were included in the analysis, of which 140 (53.2%) were male. The total number of animals achieving ROSC was 166/263 (63.1%). The total number of animals achieving short-term survival was 145/263 (55.1%). Some baseline demographics did vary by study, notably weight, anesthesia time, untreated VF duration, and CPR ratio. (Table 1)

There were no significant differences in weight ($p = 0.67$), anesthesia time ($p = 0.85$), VF duration ($p = 0.98$), or CPR ratio ($p = 0.09$) between males and females. Distribution in experimental protocol did vary by gender ($p = 0.04$). There were no significant differences in ROSC ($p = 0.10$) or short-term survival (0.07) between males and females. (Table 2)

There were no significant differences in male gender ($p = 0.10$), weight ($p = 0.16$), anesthesia time ($p = 0.15$), and VF duration ($p = 0.55$) between animals with and without ROSC. Animals that experienced ROSC had a higher ratio of compressions to ventilations ($p < 0.001$). There were no significant differences in male gender ($p = 0.07$), weight ($p = 0.12$) and anesthesia time ($p = 0.19$) between animals that did and did not experience short-term survival. Animals that experienced short-term survival had a shorter VF duration ($p = 0.02$) and a higher ratio of compressions to ventilations ($p < 0.001$). The distribution of animals across experimental protocols was different for animals with and without ROSC ($p < 0.001$) and short-term survival ($p < 0.001$). (Table 3)

Based on univariate analysis, sex (OR 0.66; 95% CI 0.40, 1.10; $p = 0.1$) and increasing compression : ventilation ratio (OR 0.67; 95% CI 0.43, 1.04; $p = 0.07$) were candidates for multiple variable analysis predicting ROSC. However, weight, anesthesia duration, and untreated VF duration were also identified as potential confounders based on *a priori* analysis (Table 1). Based on univariate analysis, sex (OR 0.64; 95% CI 0.39, 1.05; $p = 0.08$) and VF duration (OR 0.92; 95% CI 0.85, 0.99; $p = 0.03$) were candidates for multiple variable analyses predicting SURV. However, weight, compression : ventilation ratio, and

anesthesia duration were also identified as potential confounders in *a priori* analysis (Table 1).

Multiple variable logistic regression analyses did not identify sex or any other potential confounder as significant predictors of either ROSC or short-term survival. (Table 4) Variance inflation factors were all < 2.5 for each independent variable and the mean variance inflation factor was 1.56. Both models had acceptable fit with Hosmer-Lemeshow values of 0.35 and 0.31 in the ROSC model and SURV model, respectively. Based on the receiver operating characteristic curves of the multiple variable regression models, sex had poor discrimination of ROSC (AUC 0.60) and short-term survival (AUC 0.60).

Discussion

This study finds no association between female sex and ROSC or short-term survival in our porcine model of out-of-hospital VF cardiac arrest. If further studies validate these results, *in vivo* experimentation utilizing swine of mixed sex do not require reinterpretation in light of observed clinical differences.

One possible explanation for observed clinical differences may be estrogen's effect on the regulation of the inflammatory cascade. Prior research by Adrie *et al.* described an inflammatory response similar to sepsis in the post-arrest patient. (25) They noted an increase in IL6 in resuscitated patients. IL6 is mediated by the cytochrome p450 system, which is in turn, mediated by estrogen. Interestingly, recent data from Tortorici *et al.* described decreased IL6 and cytochrome p450 activation during hypothermia. (26) These data suggest that one mechanistic pathway of hypothermia's effect is through decreased inflammation. This is buttressed by recent data demonstrating the effect of 17 β -estradiol on NF- κ B. (27) Estrogen and hypothermia may share a similar pathway in their effect on patients in the post-ROSC phase.

There have been several other proposed explanations for observed clinical differences besides hormonal effects. Biondi-Zoccai et al. have previously noted that female myocytes have a resistance to ischemic apoptosis when compared to male. (29) While the mechanism is unclear, suggested mechanisms include beta-adrenergic receptors, sodium/calcium exchange or through the renin-angiotensin system. Of note, both X-linked inhibitor of apoptosis and apoptosis-inducing factor are located on the X chromosome. Swartz, et al. found that gender differences in a rat model of spinal cord injury were not sex steroid dependent. (30) Spolarics, et al. have suggested that cellular mosaicism in females may result in a more balanced and adaptive system to accommodate challenges. (31) Future studies should determine the genetic and cellular mechanisms responsible for these sex differences.

Interestingly, the clinically observed improvement in outcome among females after cardiac arrest is not present in pediatric patients. A 2011 multi-center cohort study of out-of-hospital pediatric cardiac arrest found no difference in sex distribution between survivors and non-survivors to hospital discharge. (32) Approximately two-thirds of these patients were less than 8 years of age and presumably prepubescent. Additionally, a 2007 review of pediatric extracorporeal cardiopulmonary resuscitation found no difference in sex distribution between neurologically intact survival to hospital discharge. (33) The median age was 4.9 months (IQR: 0.8 – 25.8 months); again presumably pre-pubescent. If hormonal mechanisms are the primary reason for gender differences in cardiac arrest outcome, this may explain the discrepancy observed between adult and pediatric patients.

The swine utilized in our experiments were nearing estrus, but were not yet sexually mature. Prior research has demonstrated that although developing female swine do have periodic

measurable levels of estrogen, peak values occur with the onset of first estrus. (28) These swine were similar in age to those in this study. Given the retrospective nature of this study, we do not have the estrogen levels of these swine prior to arrest.

Our results suggest that in experiments utilizing pre-estrus swine of mixed gender, sex is not associated with ROSC or short-term survival. This is important because clinical data identified sex as a potential confounder of ROSC and short-term survival, two commonly used outcome measures in porcine models of cardiac arrest. If externally validated, future experiments utilizing pre-estrus swine may not need to adjust for confounding by sex. Our results do not apply to swine that are sexually mature. Future studies using sexually mature animals may wish to control for levels of sex hormones.

This study has several limitations. First, it is a retrospective review of our experiments and as such, is designed to generate hypotheses. Levels of estrogen in the animals were not assessed. Second, the animals used are young, healthy animals. The cardiovascular physiology of these animals may be different than that of many patients who experience out of hospital cardiac arrest. Finally, the outcomes assessed are ROSC and short-term survival. Our animal studies do not provide information on neurologically intact survival, which is the most relevant outcome from the perspective of the patient.

Conclusions

Despite clinical observations, sex is associated with neither ROSC nor short-term survival in our porcine model of prolonged ventricular fibrillation utilizing pre-estrus swine.

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Table 1

Demographics of individual studies included.

Experimental Study (n) [Reference]	% Male	Mean Weight $\pm$ SD (kg) *	CPR Ratio *	Mean Anesthesia Time $\pm$ SD (min) *	Mean Untreated VF duration $\pm$ SD (min) *	% ROSC *	% Short-term Survival *
1 (n = 36) [14]	63.9	25.7 $\pm$ 1.9	15:1	38.9 $\pm$ 7.0	11.0 $\pm$ 0	55.6	44.4
2 (n = 41) [15]	34.1	26.5 $\pm$ 2.2	15:1	36.8 $\pm$ 8.6	11.0 $\pm$ 0	65.9	56.1
3 (n = 28) [16]	64.3	27.8 $\pm$ 3.2	5:1	31.0 $\pm$ 4.2	11.0 $\pm$ 0	75.0	71.4
4 (n = 73) [17]	52.1	22.7 $\pm$ 1.7	5:1	42.9 $\pm$ 3.4	10.8 $\pm$ 5.6	82.2	69.9
5 (n = 2)	50.0	24.3 $\pm$ 1.0	5:1	47.5 $\pm$ 24.7	10.3 $\pm$ 1.1	100.0	100.0
6 (n = 22)	63.6	22.7 $\pm$ 1.9	5:1	41.6 $\pm$ 2.6	XX	27.3	27.3
7 (n = 43) [18]	44.2	26.6 $\pm$ 2.4	15:1	34.5 $\pm$ 6.0	7.2 $\pm$ 1.4	27.9	20.9
8 (n = 18) [19]	72.2	26.3 $\pm$ 1.7	30:2	40.3 $\pm$ 8.0	8.0 $\pm$ 0	100.0	100.0
n=263	53.2	25.2 $\pm$ 0.2		38.4 $\pm$ 0.5	10.0 $\pm$ 0.2	63.1	55.1

SD: standard deviation. CPR: cardiopulmonary resuscitation; VF: ventricular fibrillation; ROSC: return of spontaneous circulation; XX: data unavailable;

* p < 0.05 across studies.

Table 2Demographics and outcomes by sex. Data presented at mean $\pm$ standard deviation or n (%).

	Sex		p-value
	Male	Female	
n	140 (53.2%)	123 (46.8%)	
Weight (kg)	25.2 $\pm$ 2.8	25.1 $\pm$ 2.9	0.67
Anesthesia duration (min)	38.4 $\pm$ 7.3	38.5 $\pm$ 7.3	0.85
VF duration (min)	10.0 $\pm$ 3.3	10.0 $\pm$ 3.7	0.98
CPR Ratio (compressions : ventilations)			0.09
5:1	56 (55.4%)	45 (44.6%)	
15:1	56 (46.7%)	64 (53.3%)	
30:2	13 (72.2%)	5 (27.8%)	
Experimental Protocol			0.04
1	23 (63.9%)	13 (36.1%)	
2	14 (34.1%)	27 (65.9%)	
3	18 (64.3%)	10 (35.7%)	
4	38 (52.1%)	35 (47.9%)	
5	1 (50.0%)	1 (50.0%)	
6	14 (63.6%)	8 (36.4%)	
7	19 (44.2%)	24 (55.8%)	
8	13 (72.2%)	5 (27.8%)	
ROSC (%)	82 (49.4%)	84 (50.6%)	0.10
Short-term survival (%)	70 (48.3%)	75 (51.7%)	0.07

VF: ventricular fibrillation. CPR: cardiopulmonary resuscitation. ROSC: return of spontaneous circulation.

Table 3

Demographics by ROSC and short-term survival.

	ROSC			Short-term survival		
	Yes	No	p-value	Yes	No	p-value
n	166	97		145	118	
Male sex	82 (49.4%)	58 (59.8%)	0.10	70 (48.3%)	70 (59.3%)	0.07
Weight (kg)	25.0 ± 2.9	25.5 ± 2.8	0.16	24.9 ± 2.9	25.5 ± 2.8	0.12
Anesthesia time (min)	39.0 ± 7.5	37.6 ± 6.8	0.15	39.0 ± 7.3	37.8 ± 7.3	0.19
VF duration (min)	9.9 ± 3.6	10.2 ± 3.3	0.55	9.6 ± 3.5	10.6 ± 3.4	0.02
CPR ratio (compressions : ventilations)			< 0.001			< 0.001
5:1	81 (80.2%)	20 (19.8%)		71 (70.3%)	30 (29.7%)	
15:1	59 (49.2%)	61 (50.8%)		48 (40.0%)	72 (60.0%)	
30:2	18 (100.0%)	0 (0.0%)		18 (100.0%)	0 (0.0%)	
Experimental Protocol			< 0.001			< 0.001
1	20 (55.6%)	16 (44.4%)		16 (44.4%)	20 (55.6%)	
2	27 (65.9%)	14 (34.1%)		23 (56.1%)	18 (43.9%)	
3	21 (75.0%)	7 (25.0%)		20 (71.4%)	8 (29.6%)	
4	60 (82.2%)	13 (17.8%)		51 (69.9%)	22 (30.1%)	
5	2 (100.0%)	0 (0.0%)		2 (100.0%)	0 (0.0%)	
6	6 (27.3%)	16 (72.7%)		6 (27.3%)	16 (72.7%)	
7	12 (27.9%)	31 (72.1%)		9 (20.9%)	34 (79.1%)	
8	18 (100.0%)	0 (0.0%)		18 (100.0%)	0 (0.0%)	

ROSC: return of spontaneous circulation. **VF:** ventricular fibrillation. **CPR:** cardiopulmonary resuscitation.

Table 4

Multiple variable predictors of return of spontaneous circulation (ROSC) and short-term survival.

	ROSC			Short-term survival		
	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Male sex	0.70	0.38, 1.30	0.26	0.71	0.33, 1.53	0.38
Weight (kg)	0.94	0.85, 1.04	0.25	0.92	0.79, 1.06	0.25
Increasing CPR ratio	0.75	0.18, 3.19	0.70	0.81	0.17, 3.86	0.79
Anesthesia duration (min)	1.04	0.99, 1.09	0.13	1.03	0.97, 1.09	0.30
VF duration (min)	0.95	0.73, 1.23	0.69	0.90	0.71, 1.15	0.41

CI: confidence interval. **CPR**: ratio of compressions : ventilations. **VF**: ventricular fibrillation.