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Vasopressin improves survival compared with epinephrine in a neonatal piglet model of asphyxial cardiac arrest

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BACKGROUND: Epinephrine is a component of all resuscitation algorithms. Vasopressin is a pulmonary vasodilator and systemic vasopressor. We investigated the effect of epinephrine vs. vasopressin on survival and hemodynamics after neonatal porcine cardiac arrest (CA).

METHODS: A 4-min asphyxial CA was induced, after which cardiopulmonary resuscitation (CPR) was commenced. Animals were randomized to low- (LDE: 0.01 mg/kg) or high-dose epinephrine (HDE: 0.03 mg/kg), low- (LDV: 0.2 U/kg) or high-dose vasopressin (HDV: 0.4 U/kg), or control (saline). Clinical and echocardiography indexes were monitored.

RESULTS: Sixty-nine animals were randomized. Survival was greater in HDV (n = 8 (89%); $P < 0.05$ ANOVA) vs. control (n = 7 (43%)) and LDE (n = 5 (36%)) but not vs. HDE (n = 7 (64%)) or LDV (n = 6 (75%)). Animals resuscitated with LDE required more shocks (2.5 (interquartile range: 2–6); $P < 0.05$) and higher doses of energy (15 J (interquartile range: 10–20); $P < 0.05$). Left ventricular output was comparable between groups, but a greater increase in superior vena caval flow was seen after HDV ($P < 0.001$ vs. control, LDE, and HDE). Plasma troponin was greatest in the HDE group ($P < 0.05$ vs. control and HDV).

CONCLUSION: Vasopressin results in improved survival, lower postresuscitation troponin, and less hemodynamic compromise after CA in newborn piglets. Vasopressin may be a candidate for testing in human neonates.

The need for active neonatal resuscitation is common with an incidence of 5–10%, although there is likely to be regional variability (1). Guidelines for drug use in neonatal resuscitation guidelines are based on extrapolations from adult literature. Pressors, almost invariably epinephrine, are recommended as core therapy during cardiopulmonary resuscitation (CPR) in order to enhance systemic perfusion (especially cerebral and coronary perfusion) by maintaining vascular tone while forward flow is generated by chest compressions. Epinephrine, although an integral part of every published protocol for neonatal resuscitation, may be associated with adverse effects (2–6); similar concerns exist in pediatric and adult cardiac arrest (CA). However, because of concerns associated with epinephrine (2,7), vasopressin was studied in the setting of asystolic CA. Vasopressin is an intense systemic vasoconstrictor, which may explain why it increases cerebral (and systemic) perfusion during experimental cardiac massage, as well as increasing cerebral oxygenation, neurological outcome, and resuscitation success following experimental CPR (8–12).

Vasopressin was first proposed as a resuscitation agent after endogenous vasopressin levels were found to be higher in successfully resuscitated patients compared with those who died (13). Evidence from a large, adult, multicenter, randomized controlled trial suggests it to be superior to epinephrine, when the nature of the CA was primary asystole (14). For the following reasons, vasopressin may be a good candidate for pressor support during CPR. First, CA in neonates is almost always due to asphyxia, which most commonly causes asystolic CA, the type of arrest in which vasopressin appears more effective in adult studies. Second, pulmonary vascular resistance is characteristically more prominent in neonates, especially in those at risk of asphyxia arrest, and the combined pulmonary vasodilator and systemic vasoconstrictor properties of vasopressin may make it an ideal support drug in this context. We therefore performed a comparative evaluation of vasopressin and epinephrine in a neonatal porcine model of asphyxial CA.

RESULTS

Sixty-five neonatal piglets satisfied eligibility criteria and were randomized. Return of spontaneous circulation (ROSC) occurred in nine animals before allocation to treatment; these animals were excluded from final analysis. There were no between-group differences in baseline characteristics (see **Supplementary Table S1** online). Survival rate was higher following high-dose vasopressin (HDV) (n = 9/10 (90%)) vs. either control (n = 5/12 (43%); P = 0.03) or low-dose epinephrine (LDE) (n = 5/13 (38%); P = 0.006) (**Figure 1**). Comparisons with high-dose epinephrine (HDE) (n = 6/11 (54%)) and low-dose vasopressin (LDV) (n = 7/10 (70%)) and between all other groups were not significant.

Requirement for Defibrillation

In total, 21 (32%) animals were noted to have fine ventricular fibrillation (VF); specifically control = 3, LDE = 6, HDE

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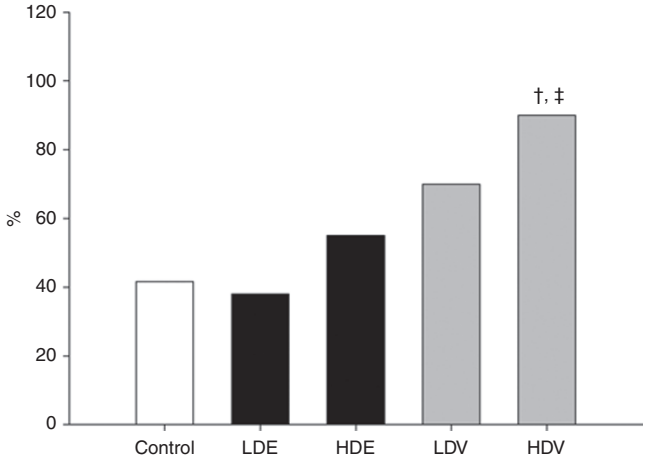

Figure 1. Survival rate in allocated groups demonstrating survival advantage in vasopressin-resuscitated animals. †$P < 0.05$ vs. control group; ‡$P < 0.05$ vs. low-dose epinephrine (LDE); white column fill, control-resuscitated animals; black column fill, epinephrine-resuscitated animals; gray column fill, vasopressin-resuscitated animals. HDE, high-dose epinephrine; HDV, high-dose vasopressin; LDV, low-dose vasopressin.

= 4, LDV = 4, and HDV = 4. Animals resuscitated with LDE required the greatest number of shocks ($P < 0.05$ vs. control) and the highest dose (J) of delivered shock ($P < 0.05$ vs. control) (**Figure 2**).

Cardiorespiratory Variables

The postresuscitation period was characterized by tachycardia ($P < 0.001$ vs. time, two-way repeat measures ANOVA (2rmANOVA)), higher arterial ($P < 0.001$ vs. time, 2rmANOVA) and central venous pressure ($P < 0.001$ vs. time, 2rmANOVA), higher coronary perfusion pressure ($P < 0.001$ vs. time, 2rmANOVA), higher mean airway pressure ($P < 0.001$ vs. time, 2rmANOVA), and lower core body temperature ($P < 0.001$ vs. time, 2rmANOVA) (**Table 1**). Although arterial pressure increased in the first 10 min, systolic arterial pressure remained was low by 120 min in LDE and LDV groups ($P < 0.05$ vs. baseline) only. Postresuscitation diastolic pressure was also low in LDV-resuscitated animals ($P < 0.05$ vs. baseline). An increase in airway pressure was seen in control, LDE, and HDE groups but not in either of the vasopressin-resuscitated groups. We found intergroup differences in heart rate ($P = 0.03$, 2rmANOVA) only, which was higher in all groups at 120 min vs. control ($P < 0.05$). Increased PaO_2 ($P < 0.001$ vs. time, 2rmANOVA), $PaCO_2$ ($P < 0.001$ vs. time, 2rmANOVA), and base excess ($P < 0.001$ vs. time, 2rmANOVA) with lower arterial pH ($P < 0.001$ vs. time, 2rmANOVA) were seen in all groups (**Table 2**). There were intergroup differences in base deficit in HDE, LDV, and HDV groups ($P < 0.05$ vs. control) at 60, 90, and 120 min.

Echocardiography Variables

Complete evaluations were obtained on all survivors.

Systemic hemodynamics. In all groups, the postresuscitation period was characterized by a fall in indexes of left heart preload (E wave V_{max} ($P = 0.002$ vs. time, 2rmANOVA); A wave

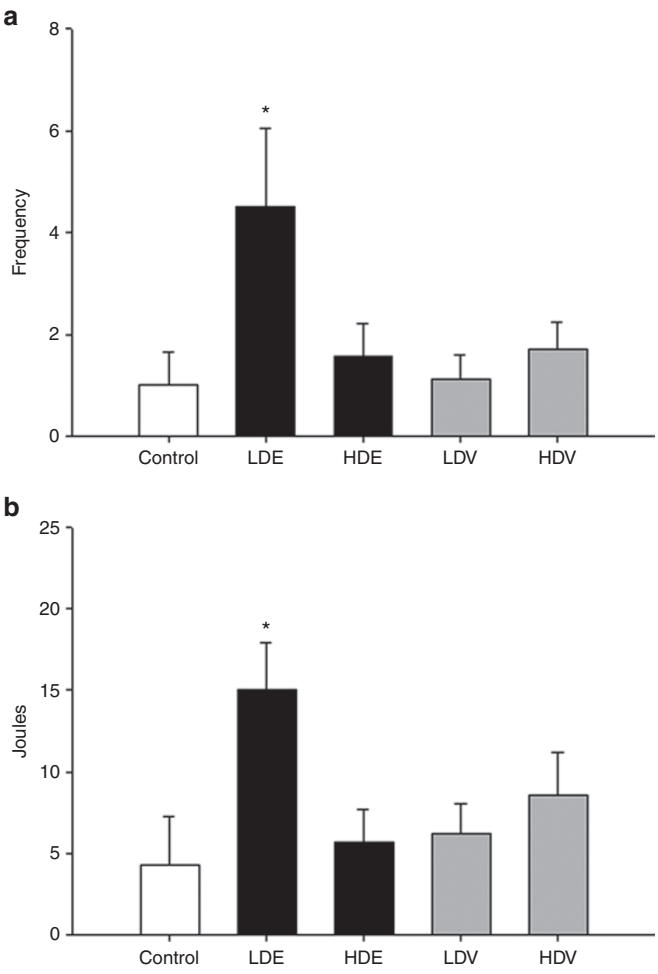

Figure 2. Need for defibrillation. (**a**) Frequency and (**b**) maximal dose of delivered shocks in survivors. *$P < 0.05$ vs. control group; white column fill, control-resuscitated animals; black column fill, epinephrine-resuscitated animals; gray column fill, vasopressin-resuscitated animals. HDE, high-dose epinephrine; HDV, high-dose vasopressin; LDE, low-dose epinephrine; LDV, low-dose vasopressin.

A_{max} ($P = 0.002$ vs. time, 2rmANOVA)), left ventricular (LV) systolic performance (fractional shortening ($P < 0.001$ vs. time, 2rmANOVA); mean velocity of circumferential fiber shortening ($P < 0.001$ vs. time, 2rmANOVA)), LV diastolic performance (isovolumic relaxation time; $P < 0.001$ vs. time, 2rmANOVA), and systemic flow (LV output (LVO) $P < 0.001$ vs. time, 2rmANOVA; superior vena caval flow ($P < 0.001$ vs. time, 2rmANOVA)). Although an increase in systemic vascular resistance was noted in all groups ($P < 0.001$), there was no change in end-systolic wall stress (**Table 3**). Epinephrine-resuscitated animals had lower superior vena caval flow ($P < 0.05$ vs. control), whereas HDV-resuscitated animals had higher superior vena caval flow. Prolongation of isovolumic relaxation time was also noted in both vasopressin-resuscitated groups ($P = 0.01$ vs. control), peaking at 60 and 90 min.

Pulmonary hemodynamics. A decrease in the inverse ratio of pulmonary artery acceleration time to right ventricular ejection time was noted in vasopressin-resuscitated animals

Table 1. Cardiorespiratory variables in survivors before and after resuscitation

Variable	Baseline	2 min	5 min	10 min	30 min	60 min	90 min	120 min	*P*
HR (bpm)									
Control	186±39	213±23	217±19	221±16	192±16	176±32	172±27	161±38	*P* < 0.001 vs. time,
LDE	186±22	219±33	224±26	218±20	204±31	190±37	184±39	173±39	2rmANOVA
HDE	197±34	209±26	230±32	186±22	202±17	201±25	196±31	210±34*	*P* = 0.03 vs. group,
LDV	184±37	200±34	221±32	212±34	169±5	147±18	137±4	186±22	2rmANOVA
HDV	187±42	207±45	217±25	215±15	193±33	203±5	184±22	137±33	
SBP(mm Hg)									
Control	98±10	124±23†	132±12†	136±12†	98±24	80±13	86±19	89±20	*P* < 0.001 vs. time,
LDE	97±10	115±16	109±23	115±9	87±10	69±8†	62±6†	69±11†	2rmANOVA
HDE	94±11	115±22	115±17	124±18†	84±16	77±10	86±26	84±17	p>.05 vs. group,
LDV	99±8	127±8	113±37	106±49	89±8	64±4	57±6†	57±10†	2rmANOVA
HDV	87±9	98±22	138±23†	138±13†	95±15	90±10	87±10	86±8	
DBP (mm Hg)									
Control	64±10	79±24†	92±12†	94±9	62±20	53±15	61±16	65±15	*P* < 0.001 vs. time,
LDE	67±7	86±17†	92±22†	95±14	64±17	51±12	49±10	55±9	2rmANOVA
HDE	65±10	82±16	76±15	79±12	43±17†	44±14†	54±17	58±13	*P* > 0.05 vs. group,
LDV	64±7	82±21	81±23	73±34	61±13	36±6†	36±11†	37±13†	2rmANOVA
HDV	58±10	69±23	94±20†	93±14†	62±22	65±10	59±19	58±16	
MBP (mm Hg)									
Control	79±10	98±24	110±12	112±10	76±23	65±16	72±17	76±16	*P* < 0.001 vs. time,
LDE	80±6	95±29	99±21	106±10†	71±8	58±9†	56±7†	62±11†	2rmANOVA
HDE	78±9	83±26	84±24	98±15	56±18	56±14†	62±11	67±14	*P* > 0.05 vs. group,
LDV	80±7	101±22	94±21	87±25	73±12	46±4†	43±11†	44±13†	2rmANOVA
HDV	72±9	74±29	96±25	96±21	76±20	77±10	70±16	70±13	
CVP (mm Hg)									
Control	6.4±0.8	9.2±2.5†	8.6±1.0†	8±1	6±1.1	6±0.8	6.3±1.3	6.7±1.1	*P* < 0.001 vs. time,
LDE	6.8±2.9	8.5±1.7	9±2.3	7.8±1.3	6.2±1.3	6.6±1.6	6.4±1.5	6.2±1.3	2rmANOVA
HDE	6.2±0.7	10±2.3†	8.5±2	7.1±2.1	6.1±1.7	6.4±2	6.4±2	6.1±1.9	*P* > 0.05 vs. group,
LDV	6±0.9	9±1.6†	10±1†	9.3±1.5†	7.3±0.7	7.5±1	7.1±1.1	8.5±2.2	2rmANOVA
HDV	7.7±1.8	9.5±2.6	9.8±1.9	8.6±1.8	6.7±1.5	5.3±1.7	7±1.6	6.5±1.3	
2rmANOVA CPP (mm Hg)									
Control	63±6	70±21	77±13	80±14	52±23	45±14	55±11	59±0	*P* < 0.001 vs. time,
LDE	61±2	77±17	91±18†	93±9†	62±7	53±12	62±16	65±17	2rmANOVA
HDE	61±9	72±16	72±19	70±22	55±15	45±14	47±20	46±17	*P* > 0.05 vs. group,
LDV	58±7	73±20	78±18†	82±11†	43±14	46±12	45±13	49±12	2rmANOVA
HDV	49±11	69±24	79±11†	84±19†	44±18	33±19	36±16	42±16	
AP (cm H_2O)									
Control	14±2	18±4†	20±5	18±4	16±3	16±3	16±2	16±2	*P* < 0.001 vs. time,
LDE	13±3	22±0.5†	21±2†	21±1†	18±1†	18±1†	17±1†	17±1†	2rmANOVA
HDE	14±2	21±3	21±2	21±1	18±1	18±0.8	18±1	17±1	*P* > 0.05 vs. group,
LDV	6±0.9	9±1.6†	10±1†	9.3±1.5†	7.3±0.7	7.5±1	7.1±1.1	8.5±2.2	2rmANOVA
HDV	7.7±1.8	9.5±2.6	9.8±1.9	8.6±1.8	6.7±1.5	5.3±1.7	7±1.6	6.5±1.3	
Temperature (°C)									
Control	37.4±0.8	36.8±1	36.6±0.5†	36.6±0.6†	36.2±0.4†	36±0.3†	35.9±0.4†	35.9±0.5†	*P* < 0.001 vs. time,
LDE	37.6±0.6	36.4±1.2†	36.7±0.9†	35.8±0.8†	35.3±0.5†	35.2±0.6†	35.4±0.7†	35.3±0.6†	2rmANOVA
HDE	37.6±0.8	36.7±1.1	37.2±0.8	37±0.8	36.6±1	36.2±0.8†	35.9±0.4†	35.8±0.3†	*P* > 0.05 vs. group,
LDV	37±0.7	36.3±0.9	35.4±0.5†	35.8±0.8†	35.7±0.7†	35.7±0.3†	35.6±0.6†	35.5±0.9†	2rmANOVA
HDV	37.2±0.6	36.5±0.8	36.1±1	36±1	35.9±0.8†	35.4±0.8†	35.8±0.6†	35.8±0.6†	

Data are presented as mean ± SD or median (interquartile range).
2rmANOVA, two-way repeat measures ANOVA; AP, airway pressure; CPP, coronary perfusion pressure; CVP, central venous pressure; DBP, diastolic blood pressure; HDE, high-dose epinephrine; HDV, high-dose vasopressin; HR, heart rate; LDE, low-dose epinephrine; LDV, low-dose vasopressin; MBP, mean blood pressure; SBP, systolic blood pressure.
†*P* < 0.05 vs. baseline. **P* < 0.05 vs. control.

Table 2. Arterial blood gas values in survivors before and after resuscitation

Variable	Baseline	5 min	10 min	30 min	60 min	90 min	120 min	*P*
pO_2 (mm Hg)								
Control	87 (76, 91)	239 (154, 344)†	301 (190, 384)†	68 (61, 161)	68 (59, 79)	74 (60, 96)	71 (60, 82)	$P < 0.001$ vs. time,
LDE	82 (73, 97)	198 (145, 229)†	188 (169, 287)†	66 (64, 73)	71 (66, 79)	75 (68, 77)	75 (69, 89)	2rmANOVA
HDE	73 (70, 86)	151 (119, 231)†	209 (138, 277)†	71 (66, 79)	71 (66, 79)	71 (66, 79)	71 (66, 79)	$P = 0.46$ vs. group,
LDV	83 (77, 88)	250 (102, 351)†	313 (133, 363)†	71 (55, 83)	74 (58, 79)	73 (49, 81)	71 (56, 76)	2rmANOVA
HDV	86 (71, 104)	181 (149, 222)†	235 (157, 279)†	71 (64, 73)	72 (68, 79)	70 (67, 74)	77 (72, 81)	
pCO_2 (mm Hg)								
Control	40 (36, 43)	75 (56, 92)†	61 (49, 70)†	53 (49, 62)	43 (40, 53)	40 (38, 41)	41 (39, 48)	$P < 0.001$ vs. time,
LDE	40 (37, 42)	66 (50, 77)†	66 (63, 74)†	56 (49, 60)	44 (43, 54)	42 (38, 50)	40 (35, 50)	2rmANOVA
HDE	40 (36, 46)	52 (42, 69)	57 (52, 68)†	50 (47, 64)†	45 (40, 54)	42 (39, 48)	41 (36, 45)	$P = 0.86$ vs. group,
LDV	40 (39, 44)	40 (36, 46)†	64 (45, 99)†	56 (48, 61)†	45 (43, 48)	42 (39, 47)	40 (38, 46)	2rmANOVA
HDV	41 (37, 43)	52 (44, 69)†	59 (54, 68)†	59 (51, 57)†	48 (43, 51)	43 (39, 46)	41 (38, 44)	
pH								
Control	7.45 ± 0.05	6.91 ± 0.15†	6.98 ± 0.12†	7.08 ± 0.08†	7.25 ± 0.07†	7.34 ± 0.08	7.36 ± 0.09	$P < 0.001$ vs. time,
LDE	7.43 ± 0.01	6.92 ± 0.09†	6.94 ± 0.06†	7.06 ± 0.06†	7.17 ± 0.07†	7.26 ± 0.09†	7.33 ± 0.09	2rmANOVA
HDE	7.41 ± 0.06	6.98 ± 0.10†	6.91 ± 0.11†	6.98 ± 0.10†	7.11 ± 0.14†	7.22 ± 0.15†	7.28 ± 0.10	$P = 0.61$ vs. group,
LDV	7.42 ± 0.05	6.90 ± 0.13†	6.91 ± 0.09†	7.04 ± 0.07†	7.17 ± 0.09†	7.25 ± 0.11†	7.32 ± 0.12	2rmANOVA
HDV	7.42 ± 0.04	6.96 ± 0.17†	7.05 ± 0.17†	7.01 ± 0.07†	7.13 ± 0.18†	7.23 ± 0.07	7.31 ± 0.17	
Base excess								
Control	3.4 (−0.5, 5.1)	−22 (−27, −17)†	−22 (−24, −14)†	−14 (−20, −3.2)	−7.3 (−11, −4.8)	−1.6 (−8.5, −0.4)	−0.9 (−3.9, 1.9)	$P < 0.001$ vs. time,
LDE	2.4 (0.5, 2.9)	−22 (−26, −19)†	−21 (−24, −17)†	−16 (−20, −12)	−9.5 (−16, −8.8)	−5 (−13.4, −3.2)	−2.4 (−8.7, 0.2)	2rmANOVA
HDE	1.7 (−2.1, 3.1)	−21 (−24, −20)†	−23 (−27, −19)†	−19 (−24, −16)†	−19 (−21, −9.7)*	−10 (−17, −3.7)*	−6.8 (−13.6, −1.8)*	$P = 0.03$ vs. group,
LDV	1.7 (−0.1, 5.3)	−23 (−26, −20)†	−23 (−25, −20)†	−17 (−18, −16)†	−12 (−16, −9)†,*	−8 (−12, −3)†,*	−5.6 (−10.2, 0.7)*	2rmANOVA
HDV	1.3 (−0.3, 2.6)	−22 (−24, −16)†	−23 (−25, −20)†	−20 (−21, −13)†	−15 (−17, −8)†,*	−11 (−12, −7)*	−5.4 (−7, −3.7)*	

Data are presented as mean ± SD or median (interquartile range).
2rmANOVA, two-way repeat measures ANOVA; HDE, high-dose epinephrine; HDV, high-dose vasopressin; LDE, low-dose epinephrine; LDV, low-dose vasopressin.
†$P < 0.05$ vs. baseline. *$P < 0.05$ vs. control.

($P < 0.05$ vs. control) suggestive of lower pulmonary vascular resistance, whereas an increased ratio was seen in control and LDE-resuscitated animals ($P < 0.05$ vs. control). There was a late fall in right ventricular output in both epinephrine-resuscitated groups ($P < 0.05$ vs. control), whereas right ventricular output was preserved in both vasopressin-resuscitated groups.

Catecholamine and Troponin Levels

An increase in plasma levels of norepinephrine, epinephrine, and dopamine (**Figure 3a–d**) was noted in all groups ($P < 0.001$ vs. baseline) although postresuscitation levels of dopamine were lower in the LDV group ($P < 0.05$ vs. control). While an increase in plasma troponin ($P < 0.05$ vs. baseline) was demonstrated in all groups, the magnitude of the rise in troponin level was greatest in HDE-resuscitated animals ($P < 0.05$ vs. control, 2rmANOVA) (**Figure 3b**). We found no difference in wet: dry ratio between groups ($P > 0.05$ vs. control, one-way ANOVA).

DISCUSSION

In a neonatal porcine model of asphyxia CA, vasopressin led to improved survival vs. the current standard of care, less myocardial injury, decreased need for defibrillation, and less compromise to upper body perfusion. This is the only randomized comparison of any resuscitation medication in the setting of neonatal resuscitation. These data amplify evolving concerns regarding the suitability of LDE as the resuscitation agent of choice in neonates.

Epinephrine May Lead to Harm in Neonates

Animals resuscitated with LDE were less likely to survive and more likely to need defibrillation, which may reflect direct myocardial toxicity or inadequate dosing. Higher doses of epinephrine are associated with hemodynamic effects (e.g., hypertension, tachycardia) known to be caused by elevated levels of circulating catecholamines. The increase in catecholamines in all groups in this experiment is consistent with previous reports, although the magnitude of the rise in plasma dopamine levels was less in LDV-resuscitated animals. It is worth noting that dopamine levels were highest, although not statistically significant, in LDE-resuscitated animals that also needed the greatest amount of defibrillation, whereas levels were lowest in LDV-resuscitated animals that needed the least amount of defibrillation. A recent observation in adult pigs noted differential changes in epinephrine or norepinephrine levels compared with

Table 3. Echocardiography characteristics in survivors before and after resuscitation

	Baseline	5 min	30 min	60 min	90 min	120 min	*P* value
Left ventricular performance							
E wave V_{max} (m/s)							
Control	0.58 ± 0.22	0.69 ± 0.07	0.69 ± 0.26	0.59 ± 0.23	0.59 ± 0.25	0.54 ± 0.2	$P = 0.002$ vs time,
LDE	0.62 ± 0.13	0.62 ± 0.15	0.58 ± 0.14	0.5 ± 0.13	0.38 ± 0.11	0.41 ± 0.15	2rmANOVA
HDE	0.59 ± 0.1	0.98 ± 0.3†	0.72 ± 0.31	0.57 ± 0.1	0.5 ± 0.11	0.44 ± 0.03	$P > 0.05$ vs group,
LDV	0.66 ± 0.16	0.62 ± 0.28	0.57 ± 0.14	0.65 ± 0.1	0.6 ± 0.13	0.62 ± 0.1	2rmANOVA
HDV	0.67 ± 0.17	0.66 ± 0.13	0.61 ± 0.13	0.5 ± 0.15	0.44 ± 0.21	0.4 ± 0.17	
A wave V_{max} (m/s)							
Control	0.63 ± 0.2	0.6 ± 0.16	0.67 ± 0.3	0.57 ± 0.2	0.6 ± 0.23	0.53 ± 0.2	$P = 0.01$ vs time,
LDE	0.6 ± 0.14	0.66 ± 0.23	0.57 ± 0.13	0.52 ± 0.1	0.4 ± 0.13	0.41 ± 0.11	2rmANOVA
HDE	0.62 ± 0.1	0.85 ± 0.5	0.83 ± 0.24	0.57 ± 0.11	0.53 ± 0.1	0.52 ± 0.1	$P > 0.05$ vs group,
LDV	0.71 ± 0.15	0.66 ± 0.22	0.61 ± 0.1	0.65 ± 0.05	0.6 ± 0.13	0.62 ± 0.1	2rmANOVA
HDV	0.75 ± 0.14	0.62 ± 0.2	0.62 ± 0.1	0.59 ± 0.1	0.57 ± 0.12	0.48 ± 0.07	
LVEDD (cm)							
Control	1.8 ± 0.2	1.8 ± 0.7	2 ± 0.3	2.2 ± 0.4	2.6 ± 0.6	2.1 ± 0.2	$P > 0.05$ vs time,
LDE	1.5 ± 0.1	2.1 ± 0.3	1.8 ± 0.1	1.5 ± 0.3	1.6 ± 0.1	2 ± 0.1	2rmANOVA
HDE	1.8 ± 0.1	1.7 ± 0.9	2 ± 0.3	1.8 ± 0.1	1.8 ± 0.2	1.7 ± 0.1	$P > 0.05$ vs group,
LDV	1.8 ± 0.3	2.2 ± 0.4	2.1 ± 0.2	1.9 ± 0.4	2.1 ± 0.4	2.1 ± 0.3	2rmANOVA
HDV	1.7 ± 0.3	1.9 ± 0.7	2 ± 0.5	2 ± 0.3	1.9 ± 0.5	1.8 ± 0.5	
LVFS (%)							
Control	45 ± 8	29 ± 15†	38 ± 7	25 ± 12†	28 ± 11†	25 ± 12†	$P < 0.001$ vs time,
LDE	42 ± 8	33 ± 14	50 ± 5	20 ± 4	25 ± 7	35 ± 7	2rmANOVA
HDE	42 ± 6	28 ± 11	33 ± 12	32 ± 8	31 ± 5	32 ± 13	$P > 0.05$ vs group,
LDV	41 ± 7	23 ± 11†	26 ± 15†	28 ± 13	25 ± 8†	21 ± 10†	2rmANOVA
HDV	43 ± 9	35 ± 15	32 ± 14	32 ± 8	27 ± 9	32 ± 8	
mVCFc							
Control	1.3 ± 0.4	1.6 ± 0.6	1.5 ± 0.3	0.9 ± 0.5	1 ± 0.4	1 ± 0.7	$P < 0.001$ vs time,
LDE	1.6 ± 0.7	2.1 ± 0.1	2.8 ± 0.6	0.9 ± 0.3	1.2 ± 0.5	1.1 ± 0.2†	2rmANOVA
HDE	1.5 ± 0.2	1.6 ± 0.1	1.3 ± 0.4	1.3 ± 0.3	1.2 ± 0.3	1.9 ± 1	$P > 0.05$ vs group,
LDV	1.7 ± 0.5	1.4 ± 0.8	1.1 ± 0.7	1.2 ± 0.5	1.1 ± 0.3	0.9 ± 0.5†	2rmANOVA
HDV	1.5 ± 0.3	1.7 ± 1.2	1.2 ± 0.6	1.3 ± 0.8	1.1 ± 0.8	1.6 ± 0.4	
IVRT (ms)							
Control	47 ± 9	45 ± 9	43 ± 5	44 ± 7	50 ± 7	54 ± 10	$P > 0.05$ vs time,
LDE	42 ± 14	38 ± 5	42 ± 4	35 ± 8	30 ± 2	46 ± 6	2rmANOVA
HDE	44 ± 17	51 ± 22	30 ± 11	55 ± 9	60 ± 14	52 ± 13	$P > 0.05$ vs group,
LDV	45 ± 14	45 ± 17	50 ± 6	68 ± 8†	73 ± 14†	61 ± 19	2rmANOVA
HDV	47 ± 18	54 ± 19	45 ± 16	71 ± 7†	73 ± 16†	56 ± 12	
LVO (ml/min/kg)							
Control	279 ± 64	234 ± 83	288 ± 52	202 ± 47	212 ± 45	188 ± 49	$P = 0.001$ vs time,
LDE	233 ± 92	184 ± 71	259 ± 86	211 ± 10	244 ± 17	214 ± 27	2rmANOVA
HDE	328 ± 99	311 ± 121	322 ± 156	261 ± 33	235 ± 72	215 ± 44	$P > 0.05$ vs group,
LDV	324 ± 128	207 ± 60	271 ± 90	226 ± 36	228 ± 98	214 ± 47	2rmANOVA
HDV	341 ± 106	178 ± 40	268 ± 90	216 ± 81	232 ± 22	232 ± 19	

Table 3. Continued on next page

Table 3. Continued

	Baseline	5 min	30 min	60 min	90 min	120 min	*P* value
SVCO (ml/min/kg)							
Control	127 ± 59	151 ± 101	124 ± 5	153 ± 12	125 ± 12	127 ± 30	$P > 0.05$ vs time,
LDE	105 ± 61	109 ± 86	127 ± 3	68 ± 22	120 ± 10	103 ± 17	2rmANOVA
HDE	112 ± 42	144 ± 37	126 ± 55	80 ± 18†	77 ± 37	112 ± 30	$P = 0.03$ vs group,
LDV	181 ± 96	125 ± 71	149 ± 84	143 ± 55	112 ± 32	142 ± 43	2rmANOVA
HDV	155 ± 57	128 ± 30	199 ± 54†,‡	182 ± 20‡	139 ± 47	123 ± 65	
Pulmonary hemodynamics							
$PAAT:RVET_{inv}$							
Control	4.3 ± 2.6	6.8 ± 4.6†	6.7 ± 1.6†	4.3 ± 1	4.7 ± 1	3.5 ± 2.2	$P < 0.001$ vs time,
LDE	3.4 ± 0.7	3.6 ± 0.8	5.1 ± 0.7	6.5 ± 0.1†	6.3 ± 0.2†	4.2 ± 0.1	2rmANOVA
HDE	4.6 ± 1.4	4.3 ± 1.1	4.6 ± 0.9	4.5 ± 1.1	3.3 ± 0.5	3.2 ± 0.3	$P > .05$ vs group,
LDV	4.1 ± 1.1	3.7 ± 1.0	3.1 ± 0.4†	3 ± 1.2	2.9 ± 0.9	3.2 ± 0.7	2rmANOVA
HDV	5.4 ± 2.2	3.6 ± 0.8	3.5 ± 1.1†	3.8 ± 0.4	3 ± 1.8	3.3 ± 0.6	
RVO (ml/min/kg)							
Control	346 ± 107	297 ± 124	376 ± 36	212 ± 31	265 ± 93	187 ± 33	$P = 0.004$ vs time,
LDE	300 ± 101	245 ± 78	296 ± 27	224 ± 17	249 ± 57	180 ± 17	2rmANOVA
HDE	359 ± 54	339 ± 184	283 ± 104	170 ± 5†	184 ± 51†	201 ± 154	$P > 0.05$ vs group,
LDV	402 ± 160	234 ± 62	330 ± 96	260 ± 93	291 ± 22	267 ± 20†	2rmANOVA
HDV	326 ± 167	199 ± 78	294 ± 67	245 ± 15	242 ± 25	218 ± 26	
RVSP (mm Hg)							
Control	10 (9, 16)	15 (13, 18)	17 (11, 27)	14 (9, 32)	13 (9, 37)	14 (9, 37)	$P > 0.05$ vs time,
LDE	15 (10, 17)	12 (11, 16)	20 (16, 24)	12 (7, 17)	14 (10, 17)	15 (8, 18)	2rmANOVA
HDE	10 (8, 22)	10 (9, 15)	11 (10, 28)	19 15, 24)	10 (7, 16)	9 (7, 21)	$P = 0.08$ vs group,
LDV	10 (9, 16)	19 (10, 65)	19 (9, 28)	20 (9, 30)	24 (12, 36)	20 (13, 24)	2rmANOVA
HDV	13 (7, 15)	16 (10, 34)	20 (11, 29)	15 (8, 25)	11 (10, 24)	18 (11, 20)	
Systemic afterload							
ESWS (10^3 dynes/cm^2)							
Control	51 ± 14	46 ± 21	70 ± 28	106 ± 48	74 ± 38	76 ± 24	$P > 0.05$ vs time,
LDE	33 ± 15	54 ± 24	43 ± 15	33 ± 5	58 ± 21	53 ± 16	2rmANOVA
HDE	71 ± 22	29 ± 13	62 ± 37	51 ± 34	46 ± 10	41 ± 8	$P > 0.05$ vs group,
LDV	56 ± 31	45 ± 10	103 ± 42	68 ± 35	70 ± 29	81 ± 29	2rmANOVA
HDV	39 ± 20	58 ± 19	82 ± 49	64 ± 33	65 ± 27	57 ± 34	
SVR (dynes/cm^5)							
Control	25 ± 5	46 ± 21†	25 ± 5	30 ± 6	29 ± 10	34 ± 14	$P < 0.001$ vs time,
LDE	31 ± 4	54 ± 24†	21 ± 4	18 ± 5	19 ± 2	17 ± 8	2rmANOVA
HDE	21 ± 7	49 ± 13†	19 ± 8	22 ± 12	22 ± 11	24 ± 8	$P > 0.05$ vs group,
LDV	22 ± 15	62 ± 10†	31 ± 3†	35 ± 5†	27 ± 11	27 ± 7	2rmANOVA
HDV	24 ± 14	58 ± 19†	37 ± 10†	31 ± 16	26 ± 5	27 ± 4	

Data presented as mean ± SD or median (interquartile range).
2rmANOVA, two-way repeat measures ANOVA; E and A wave, passive and active phases of transmitral flow; ESWS, end-systolic wall stress; HDE, high-dose epinephrine; HDV, high-dose vasopressin; IVRT, isovolumic relaxation time; LDE, low-dose epinephrine; LDV, low-dose vasopressin; LVEDD, left ventricular end-diastolic dimension; LVFS, left ventricle fractional shortening; LVO, left ventricular output; mVCFc, mean velocity of circumferential fiber shortening; PAAT, pulmonary artery acceleration time; RVET, right ventricular ejection time; RVO, right ventricular output; RVSP, right ventricular systemic pressure; SVCO, superior vena cava output; SVR, systemic vascular resistance.
†$P < 0.05$ vs. baseline.*$P < 0.05$ vs. control. ‡$P < 0.05$ vs. LDE.

dopamine levels after recurrent VF, suggesting a dichotomy of responsiveness in the face of myocardial toxicity (15). In addition, β-adrenergic–mediated cardiac toxicity, well described in animal (2,16–18) and human (adult (19), pediatric (20)) studies, may lead to postresuscitation myocardial dysfunction (2,16–18) and subsequent mortality. The hemodynamic consequences of

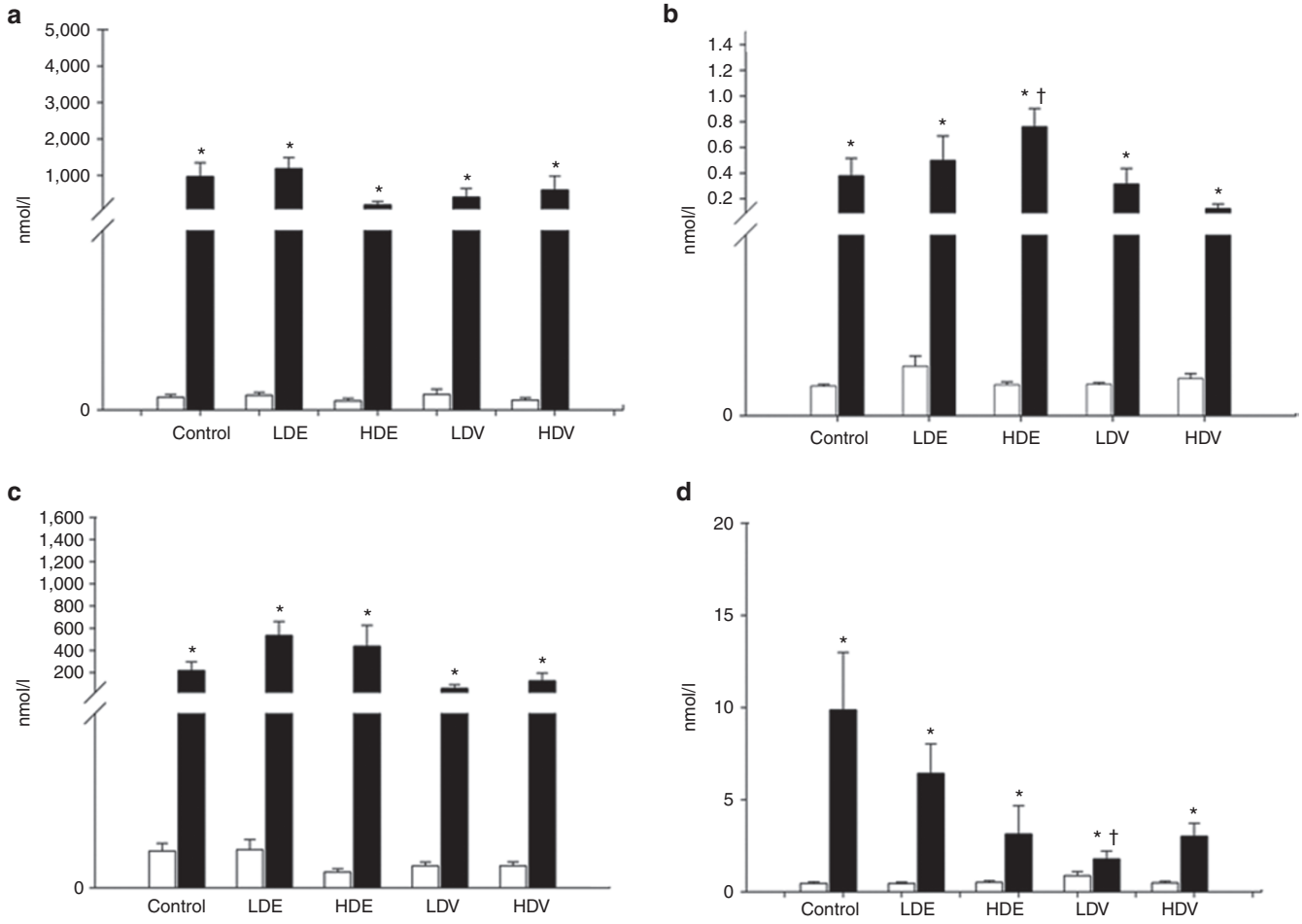

Figure 3. Circulating plasma (**a**) norepinephrine, (**b**) troponin, (**c**) epinephrine, and (**d**) dopamine levels in survivors before (white column fill) and after (black column fill) cardiac arrest. *$P < 0.05$ vs. baseline, †$P < 0.05$ vs. control group. HDE, high-dose epinephrine; HDV, high-dose vasopressin; LDE, low-dose epinephrine; LDV, low-dose vasopressin.

epinephrine were evident in this study, but we found no major difference between doses. A single study examining incremental doses of epinephrine in a neonatal ovine model of asphyxial CA demonstrated systemic hypertension and low cardiac output at a dose of 0.1 mg/kg (21). In the only prospective randomized controlled trial in children, a single dose of epinephrine (0.1 mg/kg^{-1}) did not increase the rate of ROSC and was associated with increased mortality (20). Nonetheless, in the absence of alternative data, epinephrine is still considered to be the resuscitation agent of choice in asystolic CA (3) despite the absence of appropriate clinical comparisons (22). Our findings of higher postresuscitation troponin and lower myocardial performance in the epinephrine-resuscitated groups are consistent with previous experimental reports (17,23). These effects are thought to be due to its cardiac β effects, causing a precipitous increase in myocardial oxygen demand leading to myocyte necrosis and myocardial dysfunction. There is evidence that the neonatal porcine myocardium, when compared with adult pigs, is more susceptible to catecholamine-induced cardiotoxicity (23). Such effects result in reduced myocardial compliance and are associated with sarcolemmal rupture and increased cytoplasmic calcium deposition. The increase in airway pressure in epinephrine-resuscitated animals may relate to LV diastolic dysfunction with secondary pulmonary venous hypertension leading to pulmonary edema, although we are not able to validate the physiology in this experimental design. Finally, the finding of increased need for defibrillation in LDE is novel and may also relate to myocardial toxicity and increased propensity to VF of an immature myocardium (24). It is worth noting that LDE-resuscitated animals had lower aortic diastolic perfusion pressure and LVO in the early postresuscitation phase, which may also further compromise coronary artery flow therein promoting myocardial fibrillation. The detection of fine VF in neonatal piglets is novel, but the frequency is surprising and warrants prospective investigation in human neonates.

Vasopressin Appears a Plausible Alternative to Epinephrine

Vasopressin is a 9-amino acid peptide, commonly known as anti-diuretic hormone, whose activity is modulated by three receptors, (V_{1-3}). The V_1 receptors are G-protein receptors mediating vascular smooth muscle contraction via inositol triphosphate and phospholipase C, thereby directly increasing systemic vascular resistance (25), which enhances coronary artery perfusion. Several adult animal experimental models,

of both asphyxial and VF induced CA, have demonstrated improved survival after intravenous vasopressin, compared with epinephrine, following CA (26–29). Vasopressin appears to be more effective than epinephrine, as adjunctive therapy, in the treatment of adults with VF and pulseless electrical activity. A recent large multicenter randomized controlled trial in adults found that for patients in whom the primary rhythm disturbance was asystole, vasopressin was superior to epinephrine with a higher proportion of victims surviving to reach hospital admission (29.0 vs. 20.0%; $P = 0.02$) and a higher rate of early hospital discharge (4.7 vs. 1.5%; $P = 0.04$) (14). In a recent case series of rescue vasopressin (0.4 U/kg) for witnessed CA (at least two doses of epinephrine) in children, ROSC was achieved in three of six cases. The improvement in survival in vasopressin-resuscitated neonatal piglets is striking and the benefit may result from the following effects. First, vasopressin will cause intense systemic vasoconstriction despite the presence of extreme acidosis, unlike epinephrine (30). Second, it acts directly on the coronary artery to induce vasodilation (31), which may be beneficial in enhancing coronary perfusion pressure during CA. Finally, in contrast to epinephrine, which significantly increases myocardial oxygen consumption through β_1-adrenergic receptor activation, vasopressin enhances myocardial oxygen delivery (32) and may increase contractility by preserving myocardial energetics (33). The V_1 receptor has also been shown to induce a negative inotropic effect due to an increase in calcium levels in the cardiac myocytes (33); however, we identified no adverse effect on systolic function, which may be a true lack of effect or may relate to sample size. In the clinical setting of perinatal asphyxia, where extremes of acidosis and pulmonary hypertension are common, vasopressin may be a more physiologically effective resuscitation agent.

Impact of Vasopressin on Myocardial Performance

In a porcine model of VF arrest, maximal organ blood flow was achieved with 0.8 U/kg of vasopressin (32). In a similar experimental design, 0.4 U/kg of vasopressin provided higher systemic blood pressure, lower pulmonary vascular resistance, and a reversible depressant effect on myocardial function, compared with epinephrine (27). In the current study, we found no depressant effect of vasopressin on myocardial systolic or diastolic function. There was, however, an overall decline in LVO, but no group differences were seen. There were, however, albeit transient, intergroup differences in superior vena caval flow; lower flow was seen in both epinephrine-resuscitated groups compared with HDV-resuscitated animals with peak changes at 30–60 min after successful ROSC. The latter observation may relate to redistribution in blood flow or an indirect effect of vasopressin on cerebral blood flow, although these observations are speculative. In a pediatric (porcine) model of VF arrest, vasopressin, alone or in combination with HDE, significantly improved total cerebral blood flow during CPR (28). The authors speculate that improvements in brain perfusion may relate to vasopressin-mediated nitric oxide release and cerebral vasodilation. The preservation of right ventricular output and lack of elevation of pulmonary vascular resistance observed in the current study may relate to the differential effect of vasopressin on the pulmonary vascular bed. Vasopressin has been shown to lower pulmonary arterial pressure in rats with hypoxic pulmonary hypertension, through activation of the V_1 receptor (34). It has been speculated that these pulmonary vasodilator properties may be mediated, in part, by modulation of nitric oxide release (35,36). Canine pulmonary arteries, mounted in an organ bath and preconstricted with phenylephrine, have been shown to vasodilate in response to vasopressin (37). It is possible that there may be independent effects of either agent on right ventricular function, but the latter is difficult to assess using echocardiography.

Limitations

It is possible that the beneficial effects on survival and myocardial function may be species specific due to variability in numbers and binding of receptors or other pharmacokinetic factors; therefore, caution must be exercised in generalization or extrapolation to human neonates. Second, the dose of

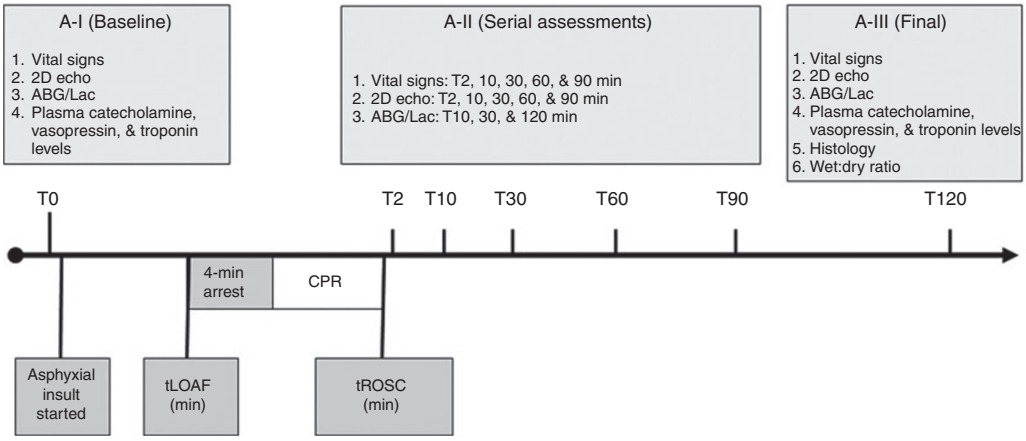

Figure 4. Schematic of cardiac arrest experimental paradigm detailing the times of baseline, postresuscitation, and final assessments of vital signs, laboratory measurements, and two-dimensional (2D) echocardiography. A, assessment; ABG, arterial blood gas; Lac, plasma lactate; T, time (min); tLOAF, time to loss of aortic fluctuation; tROSC, time to return of spontaneous circulation.

vasopressin chosen was extrapolated from adult human studies. Third, healthy term newborn piglets were used for this experimental paradigm, whereas in the clinical setting neonates would invariably have significant preexisting cardiopulmonary compromise. Next, it is important to recognize that this experimental model more closely resembles postnatal "in-NICU" CA and is not as reflective of the delivery room situation where transitional cardiac and lung physiology differ significantly. Finally, only short-term outcomes were studied; there may be long-term effects that are not addressed in this study design.

Conclusion

In the setting of a neonatal piglet model of asphyxia CA, vasopressin results in improved survival, less myocardial necrosis, and a lower requirement for defibrillation although the benefit to postresuscitation hemodynamics was inconsistent. The data also reaffirm prior concerns that higher doses of epinephrine do not improve resuscitation success or overall survival rates and may be associated with hyperadrenergic states and postresuscitation myocardial dysfunction. The identification of fine VF on the electrocardiograph and echocardiography is novel and requires future investigation in human neonates. Changes to standard resuscitation protocols must await evidence of either harm resulting from a therapeutic intervention or evidence of substantial benefit from an alternative therapy with an acceptable safety profile. These data may guide future studies in neonates preparing for testable hypotheses and if positive modification of resuscitation guidelines.

METHODS

Study Design

Prospective randomized blinded placebo-controlled study of intravenous epinephrine and vasopressin in a neonatal porcine model of asphyxial CA.

Hypothesis

The primary hypothesis was that vasopressin is a more effective resuscitation agent than epinephrine for neonatal asphyxial CA and would lead to improved survival. We also hypothesized that epinephrine is associated with hemodynamic instability and impaired postresuscitation myocardial performance leading to increased mortality.

Study Population

Healthy neonatal female Yorkshire piglets (3–4 kg, <3 d old) fasted (free access to water) overnight prior to experimentation. They were managed in accordance with the guidelines of the Canadian Council for Animal Care. Institutional ethics board approval was obtained from the animal care committee at the Hospital for Sick Children (Approval number 8203).

Specific Aims

The primary aim was to compare the effects of intravenous vasopressin (high vs. low dose) and intravenous epinephrine (high vs. low dose) on postresuscitation survival. The secondary aims were to compare the effects of each intervention on ROSC, pulmonary hemodynamics, myocardial performance, and biological indexes of myocardial toxicity.

Anesthesia. Animals were first premedicated intramuscularly with ketamine 22 mg/kg and acepromazine 1.1 mg/kg. Anesthesia was induced intravenously with pentobarbital 30 mg/kg and maintained at an infusion rate of 0.2 mg/kg/min. Neuromuscular blockade was achieved with pancuronium 0.1–0.2 mg/kg.

Instrumentation. Animals were intubated with a size of 3.0–3.5 endotracheal tube. Two 20-gauge catheters were inserted into ear veins, for maintenance of fluids and drug administration. A 3.5 F saline-filled catheter was inserted into the carotid artery for withdrawal of arterial blood samples and measurement of arterial blood pressure. Another 3.5 F saline-filled catheter was placed in the right atrium, via femoral cutdown, to measure right atrial pressure and for drug or fluid administration. Aortic and right atrial pressures were measured with the micromanometer catheters (Millar Instruments, Houston, TX) attached to transducers (model 1290A, Hewlett Packard, Palo Alto, CA) calibrated to atmospheric pressure at the level of the right atrium.

Prerandomization Stabilization and Monitoring

Piglets were ventilated in room air with a time-cycled, volume ventilator (model 683, Harvard Apparatus, South Natick, MA) for small animals (tidal volume (V_T: 8 ml/kg, positive end expiratory pressure: 4 cm H_20, rate: 40/min), adjusted to maintain normoxemia and normocapnia. Muscle relaxation was achieved with a bolus of pancuronium sulfate 0.1 mg/kg followed by a continuous infusion of 0.2 mg/kg/h. A Ringer's solution (Baxter, Mississauga, ON, Canada) (4 ml/kg/h) was infused in the preparation phase, before induction of the CA and during the postresuscitation phase. Core body temperature was monitored using an esophageal probe (model 50-7079-F, Harvard Apparatus) and maintained with a homeothermic blanket. Cardiac rhythm was monitored using a standard II lead electrocardiogram. Baseline heart rate, mean arterial pressure, and airway pressure were documented. An arterial blood gas was drawn for analysis, using an automated blood gas analyzer (ABL 700, Radiometer, Copenhagen, Denmark). Blood glucose was measured from the same sample to ensure that the animals were not hypoglycemic (data not presented).

Randomization and Treatment Allocation

Animals were randomized only after stable physiological parameters were met. Randomization was achieved using computer-generated random numbers and sealed envelopes. Both the resuscitator and sonographer were blinded to the treatment allocation. Animals (minimum of $n = 8$ per group to ensure at least five survivors per group) were randomized to receive an intravenous bolus of 0.1 ml/kg of one of the following groups: LDE (0.01 mg/kg), HDE (0.03 mg/kg), LDV (0.2 U/kg), HDV (0.4 U/kg), or control (0.9% saline). Blinding was achieved as follows: no drug (control) epinephrine (50 mg (0.01 mg/kg) or 150 mg (0.03 mg/kg)) or vasopressin (1,000 U (0.2 U/kg) or 2,000 U (0.4 U/kg)) were added to five (500 ml) bags of 0.9% saline labeled (A–E) by an independent person. This ensured the treatment allocation equates to a consistent volume of 0.1 ml/kg.

CA and Resuscitation Protocol

Following the completion of the baseline assessment, CA was induced by disconnecting the endotracheal tube from mechanical ventilation. The time of onset of CA was defined by a heart rate of less than 60 beats per minute and/or a mean arterial pressure <20 mm Hg, AND loss of aortic pressure waveform fluctuation, AND absence of cardiac output on two-dimensional echocardiography. The timed duration of CA was 4 min. The asphyxial time interval was therefore defined as the period between ventilator disconnection and the commencement of resuscitation efforts. CPR was commenced after the 4-min CA period by recommencing mechanical ventilation (FiO_2: 1.0, V_T: 8 ml/kg, positive end expiratory pressure: 4 cm H_20, rate: 40/min). After 30 s of uninterrupted mechanical ventilation, we initiated manual anteroposterior compression of the thorax, to one-third of its depth, at a rate of 120/min. Successful ROSC was defined by a mean arterial pressure of 40 mm Hg and a heart rate >100/min. If ROSC was not achieved by 3 min, the resuscitation medication, determined by random allocation, was administered. We chose a single time point for drug administration to ensure standardization of the methods. If there was no ROSC after an additional 2 min of resuscitation, brief echocardiography was performed to exclude pericardial effusion or fine VF as causes of failure of ROSC. In developing the experimental model, we noted that some animals had evidence of VF on echocardiography, although this was not detectable on electrocardiograph monitoring. Cardioversion was attempted if fine VF was identified

after failure to respond to a single dose of the resuscitation medication. The animals received incremental shocks of 2, 4, and 6 J/kg at intervals of 30 s. Resuscitative efforts were discontinued if ROSC did not occur within 6 min of commencement of cardiac compressions as the purpose of this study was to study a single dose of the resuscitation medications. The duration of the postresuscitation monitoring was 2 h (**Figure 4**).

Hemodynamic variables. Coronary perfusion pressure was defined as the difference between aortic and right atrial diastolic pressures (CPP = AoDP − RAP). Mean airway pressure, heart rate, blood pressure (systolic, diastolic, and mean), and right atrium pressure were recorded at specific intervals (2, 10, 30, 60, 90, and 120 min) after ROSC. Arterial pressures were recorded with reference to mid-chest.

Blood samples. Arterial blood gases were drawn at specific intervals (0, 10, 60, and 120 min). Plasma catecholamines and troponin I levels were obtained at baseline and 2 h postresuscitation in surviving animals from each treatment group. In total, samples were obtained from 24 animals, centrifuged, and stored at −70 °C. Catecholamines and troponin I levels were measured by enzyme immunoassay and plasma catecholamines by high-pressure liquid chromatography.

Two-dimensional echocardiography. Studies were performed using the Vivid 7 Advantage cardiovascular ultrasound system (GE medical systems, Milwaukee, WI) using a 7.5- to 12-MHz sector array scanning transducer. This system has a maximum frame rate of 250/min, which optimizes image quality in a small animal model and is fully digitalized. All two-dimensional echo studies were performed by the principal investigator (P.J.McN.), who is experienced with animal echocardiography (17–19). Animals were examined in the supine position, and the transducer was gently applied to the chest, with a depth and frame rate, chosen to obtain the highest quality images. Serial two-dimensional, M-mode, and Doppler tracings were acquired at baseline and then at 2, 10, 30, 60, 90, and 120 min after successful ROSC. All images were electronically stored using 3.5″ magneto optical disks and transferred to an electronic database for offline analysis using the EchoPac system. Specifically, measurements were taken to characterize LV performance, LVO, pulmonary hemodynamics, and LV afterload (see **Supplementary Table S2** online) using previously published methods (38–41).

Lung wet:dry ratio. After animal sacrifice, a sample of lung tissue from the right upper lobe was obtained and weighed to calculate the wet weight. The sample was reweighed after 7 d to obtain the dry weight. The wet:dry ratio was then calculated as a surrogate measure of pulmonary edema (42).

Data analysis. To detect an incremental mortality difference of 35% between saline-treated and epinephrine-treated animals, with an α of 0.05 and 80% power (Yates correction applied), a convenience sample of eight animals per group was required. This expected mortality difference is based on the mortality difference noted in our previous experiments (19) and previous pilot data. The primary outcome was survival. The effect of group on mortality was analyzed using χ^2 or Fisher's exact test, where appropriate. Secondary outcomes included hemodynamics (arterial pressure, coronary artery perfusion pressure, arterial blood gas), echocardiography, and biochemical (e.g., troponin, catecholamines) parameters. Descriptive data were used to characterize baseline animal cardiorespiratory variables. Details of the asphyxial insult (time to loss of aortic fluctuation, tROSC) were analyzed by ANOVA with multiple group comparisons. All continuous physiologic variables (heart rate), biochemical markers (e.g., plasma catecholamines, troponin) and echocardiography parameters (e.g., LVO) were analyzed by 2rmANOVA and Holm-Sidak testing. Nonparametric data were analyzed by repeated measures ANOVA for ranks to investigate the effect of time and group. Multiple intergroup comparisons were performed where a difference in group was identified. All data were analyzed using Sigma Stat (Version 11; Jandel, San Rafael, CA).

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

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P.J.McN. was responsible for securing funding, planning and executing the study, completing the analysis, writing the first draft of the manuscript, and obtaining feedback from all coauthors; D.E. was responsible for assisting with study planning and execution, data analysis, and reviewing and editing the manuscript; M.F. was responsible for assisting with study planning and execution, data analysis, and reviewing and editing the manuscript; K.A. was responsible for assisting with study planning and execution and editing the manuscript; and B.P.K. was responsible for assisting with study planning and execution and reviewing and editing the manuscript

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