Resuscitation (2007) **74**, 13—26

ELSEVIER

RESUSCITATION

www.elsevier.com/locate/resuscitation

REVIEW

Drug administration in animal studies of cardiac arrest does not reflect human clinical experience☆

Joshua C. Reynolds[a], **Jon C. Rittenberger**[b,*], **James J. Menegazzi**[b]

[a] *School of Medicine, University of Pittsburgh, Pittsburgh, PA, United States*
[b] *Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, PA, United States*

Received 4 August 2006; received in revised form 28 September 2006; accepted 2 October 2006

KEYWORDS
Cardiopulmonary resuscitation (CPR);
Cardiac arrest;
Resuscitation;
Drug therapy

Summary
Introduction: To date, there is no evidence showing a benefit from any advanced cardiac life support (ACLS) medication in out-of-hospital cardiac arrest (OOHCA), despite animal data to the contrary. One explanation may be a difference in the time to first drug administration. Our previous work has shown the mean time to first drug administration in clinical trials is 19.4 min. We hypothesized that the average time to drug administration in large animal experiments occurs earlier than in OOHCA clinical trials.
Methods: We conducted a literature review between 1990 and 2006 in MEDLINE using the following MeSH headings: swine, dogs, resuscitation, heart arrest, EMS, EMT, ambulance, ventricular fibrillation, drug therapy, epinephrine, vasopressin, amiodarone, lidocaine, magnesium, and sodium bicarbonate. We reviewed the abstracts of 331 studies and 197 full manuscripts. Exclusion criteria included: non-peer reviewed, all without primary animal data, and traumatic models. From these, we identified 119 papers that contained unique information on time to medication administration. The data are reported as mean, ranges, and 95% confidence intervals. Mean time to first drug administration in animal laboratory studies and clinical trials was compared with a *t*-test. Regression analysis was performed to determine if time to drug predicted ROSC.
Results: Mean time to first drug administration in 2378 animals was 9.5 min (range 3.0—28.0; 95% CI around mean 2.78, 16.22). This is less than the time reported in clinical trials (19.4 min, $p < 0.001$). Time to drug predicted ROSC (odds ratio 0.844; 95% CI 0.738, 0.966).
Conclusion: Shorter drug delivery time in animal models of cardiac arrest may be one reason for the failure of animal studies to translate successfully into the clinical arena.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at 10.1016/j.resuscitation.2006.10.032.

* Corresponding author at: Department of Emergency Medicine, University of Pittsburgh, 230 McKee Place, Suite 400, Pittsburgh, PA 15213, United States. Tel.: +1 412 647 9489; fax: +1 412 647 6999.
E-mail address: rittenbergerjc@upmc.edu (J.C. Rittenberger).

0300-9572/$ — see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.resuscitation.2006.10.032

Contents

Introduction

Despite numerous clinical trials, survival rates in out-of-hospital cardiac arrest (OOHCA) remain low. To date, there is no evidence that supports the use of ACLS drugs in this setting.[1–3] Animal studies, in contrast, have demonstrated superior survival rates with drug use.[4–13] One reason for failure of animal studies to translate to clinical practice may be the time at which the first drug is delivered. Previous work has demonstrated the average time to first drug administration in clinical trials is 19.4 min (range 13.3—25.0; 95% CI around the mean 12.8, 25.9) (Appendix A).[14] Thus, clinically, these drugs are given during the late metabolic phase of cardiac arrest. Consequently, it is not surprising they are ineffective. Based on our laboratory and clinical experience, we hypothesized that the average time to drug administration in large animal experiments occurs earlier than in OOHCA clinical trials.

Methods

We conducted a comprehensive literature review between 1990 and 2006 in MEDLINE using the following MeSH headings: swine, dogs, resuscitation, heart arrest, EMS, EMT, ambulance, ventricular fibrillation, drug therapy, epinephrine, vasopressin, amiodarone, lidocaine, magnesium, and sodium bicarbonate. We used no language restriction. We used OVID to search MEDLINE and obtain the abstracts. All abstracts were printed and two reviewers (JCR and JCR) jointly reviewed all abstracts. We eliminated the following from further review: small animal; non-peer reviewed; all without primary animal data (editorials, case reports, review articles, letters, practice guidelines); studies modeling trauma, sepsis, or burns; studies performed in vitro; those studies were no exogenous medications were given. We then reviewed independently the full manuscripts of all remaining papers for data describing the time to first medication administration. Both reviewers then compared the articles captured.

The type of animal, number of animals, time to first drug administration, route of medication administration, type of medication, method of delivery (bolus versus infusion), return of spontaneous circulation (ROSC) and short-term survival were abstracted from the articles. Unlike most meta-analyses where we compare the effect size as a function of treatment compared to control across the studies, our analysis compares the mean response time to the 'minimally acceptable' time. Consequently, our effect size is the sample mean and our goal is to combine the study results, derive a confidence interval for mean response time and compare that range to what the guidelines define as appropriate. Given that variances were not available for all studies, we used the weighted study sample sizes relative to the entire sample size across the 119 studies to estimate the effect size variance[15]: $\text{weight}_i = N_i$, where N_i is the sample size for each study and $\sum_{i=1}^{k} \text{weight}_i = N$ which is the total sample size across all the studies.

Due to the large differences in sample sizes across the studies (and obvious heterogeneity), we chose to analyze the results using the random effects model as recommended by Hunter and Smith.[16] This approach accounts for the variability between studies and is a more conservative method to estimate the confidence interval around the mean. We used Microsoft Excel XP 2002 (Redmond, WA) and STATA 9.0 (College Station, TX) to record and analyze the data. We report the mean times, ranges, and the respective 95% confidence intervals around the mean. We next compared the data from this review with that of our previous study in clinical trials to determine if time to drug predicted ROSC. A *t*-test was completed to determine if the mean time to drug administration was different between the clinical trial data and the animal trial data. Multivariate logistic regression was used to determine predictors of ROSC in the

Table 1 Time to drug administration (min) by study

Study	Number of subjects	Time to drug administration	First medication received
Krieter et al.[27]	10	8	Epinephrine
Loeckinger et al.[28]	8	7	Vasopressin
	10	7	Epinephrine
Krismer et al.[29]	7	7	Vasopressin
	6	7	Epinephrine
Little et al.[30]	13	13	Angiotensin II
	11	13	Epinephrine
	13	13	Angiotensin II + epinephrine
Johansson et al.[31]	24	7	Epinephrine
Bahlmann et al.[32]	14	18	Vasopressin
Behringer et al.[33]	11	9	Epinephrine
Voelckel et al.[34]	12	16	Vasopressin
	6	16	Vasopressin + epinephrine
Holzer M et al.[35]	19	10	Endothelin-1
	6	10	Epinephrine
Johansson et al.[36]	12	7	Vasopressin
	12	7	Epinephrine
Prengel et al.[7]	7	7	Epinephrine
	7	7	Vasopressin
	7	7	Vasopressin + epinephrine
Amann et al.[37]	16	7	Vasopressin
	9	7	Epinephrine
	11	7	Novel vasopressor
	12	4	Epinephrine
	11	4	Vasopressin
	2	10	Vasopressin
	3	10	Epinephrine
Adams et al.[38]	12	18	Vasopressin
Schwarz et al.[39]	7	18	Vasopressin
	7	28	Amiodarone
Vukmir et al.[40]	12	5	Epinephrine
	20	15	Epinephrine
Manning et al.[41]	5	10.5	Epinephrine
	5	10.5	Aortic occlusion + epinephrine
	5	10.5	Aortic occlusion + intraaortic epinephrine
Strohmenger et al.[42]	7	7	Epinephrine
	7	7	Vasopressin
Ayoub et al.[43]	8	10	Cariporide
	8	10	Epinephrine
	8	10	Cariporide + epinephrine
Stadlbauer et al.[44]	6	7	Epinephrine
	6	7	Epinephrine + vasopressin
Mayr et al.[45]	6	12	Epinephrine
	6	12	Vasopressin
	6	12	High-dose epinephrine + vasopressin
	6	12	Standard-dose epinephrine + vasopressin
Amann et al.[46]	11	7	Vasopressin
	5	7	Epinephrine
	5	12	Vasopressin
	4	12	Epinephrine
Hilwig et al.[47]	12	8	Standard-dose epinephrine
	12	8	Standard-dose epinephrine + β blocker
	10	8	High-dose epinephrine + β blocker
	10	8	Phenylephrine + β blocker
Nozari et al.[48]	11	7	Aortic occlusion + epinephrine
	12	7	Epinephrine IV

Table 1 (*Continued*)

Study	Number of subjects	Time to drug administration	First medication received
Seaberg et al.[9]	7	9	Combination therapy including epinephrine + novel cardiocerebral-protective agent
	9	9	Magnesium
	8	10	Epinephrine
Menegazzi et al.[13]	9	9	Standard-dose epinephrine
	9	12	Standard-dose epinephrine
	9	15	Standard-dose epinephrine
	9	12	Standard-dose epinephrine
	7	15	Standard-dose epinephrine
	9	8	High-dose epinephrine
	8	11	High-dose epinephrine
Prengel et al.[49]	8	5	Epinephrine
	8	5	Vasopressin
Wenzel et al.[50]	8	18	Vasopressin
	8	18	Vasopressin + epinephrine
Wenzel et al.[51]	7	7	Vasopressin
	7	7	Vasopressin + nitroglycerin
Lurie et al.[52]	12	8	Epinephrine + vasopressin
	12	8	Epinephrine
Berg et al.[53]	12	11	Epinephrine
Holzer et al.[54]	21	10	Endothelin-1
	6	10	Epinephrine
Prengel et al.[55]	6	6	Epinephrine
Bleske et al.[56]	7	5	Intra-nasal epinephrine
	6	5	Epinephrine IV
Tang et al.[57]	10	9	Epinephrine
Lindner et al.[58]	14	5.5	High-dose epinephrine
Lindner et al.[59]	7	7	Epinephrine
	21	7	Vasopressin
Idris et al.[60]	24	17	Epinephrine
Bar-Joseph et al.[61]	36	17	Epinephrine
Paradis et al.[62]	13	8	Epinephrine
Bleske et al.[63]	26	6	Epinephrine
Lindner et al.[64]	28	8	Epinephrine
Wolf et al.[65]	7	7	Epinephrine
	7	7	Norepinephrine
	7	7	Vasopressin
Blecic et al.[66]	6	9	Atropine
	6	9	Atropine
Prengel et al.[67]	8	5	Epinephrine
	8	5	Vasopressin
Berg et al.[68]	15	11	Standard-dose epinephrine
	15	11	High-dose epinephrine
Strohmenger et al.[69]	21	7	Vasopressin
Bleske et al.[70]	9	12	Bicarbonate
	9	13	Epinephrine
Menegazzi et al.[5]	9	8	Epinephrine
	9	9	Epinephrine
Manning et al.[71]	16	12	Epinephrine
Wenzel et al.[72]	9	18	Epinephrine
	9	18	Vasopressin
Mayr et al.[73]	7	3	Epinephrine
	7	3	Vasopressin
	7	3	Epinephrine + vasopressin

Table 1 (*Continued*)

Study	Number of subjects	Time to drug administration	First medication received
Gervais et al.[74]	7	8	Epinephrine
	7	8	Phenylephrine
	7	8	Epinephrine + β blocker
Nejman et al.[75]	6	13	Novel vasopressor
Achleitner et al.[76]	5	7	Vasopressin
	5	7	Epinephrine
	5	12	Vasopressin
	6	12	Epinephrine
Neimann et al.[6]	14	8	Epinephrine
	14	7.5	Epinephrine
Voelckel et al.[77]	12	7	Vasopressin
Lindner et al.[78]	7	7	Epinephrine
	7	7	Vasopressin
Gazmuri et al.[79]	8	8	Bicarbonate
	8	8	Carbicarb
Bleske et al.[80]	7	6	Intra-nasal epinephrine
Jameson et al.[81]	19	18	Epinephrine
Wenzel et al.[82]	7	7	Vasopressin IV
	9	7	Endobronchial vasopressin
Lindner et al.[83]	7	5	Epinephrine
	7	5	Norepinephrine
Angelos et al.[84]	8	15	Standard-dose epinephrine
	8	15	High-dose epinephrine
Prengel et al.[85]	7	7	Vasopressin
	7	7	Epinephrine
Littmann et al.[86]	20	6.5	Epinephrine
	20	6	Epinephrine
DeBehnke et al.[87]	8	15	High-dose epinephrine
	8	15	Standard-dose epinephrine
Manning et al.[88]	8	10	Epinephrine
Schleien et al.[89]	16	8	Epinephrine
Strohmenger et al.[90]	21	7	Epinephrine
Lindberg et al.[91]	6	6	Epinephrine
	6	6	Norepinephrine
Wenzel et al.[92]	6	7	Vasopressin
	6	7	Epinephrine
Menegazzi et al.[6]	8	9	Combination therapy including epinephrine + novel cardiocerebral-protective agent
	8	9	Epinephrine
	8	9	Lidocaine + bretylium
	8	9	Propanolol
	8	9	Novel cardiocerebral-protective agent
	8	10	Epinephrine
Suddath et al.[93]	10	10	Epinephrine
Nozari et al.[94]	11	13	Epinephrine
	11	13	Vasopressin
Krismer et al.[95]	14	4	Epinephrine
	14	4	Vasopressin
Idris et al.[96]	24	17	Epinephrine
Barton et al.[97]	4	12	Aortic occlusion + epinephrine
	4	12	Epinephrine
Berg et al.[98]	15	16	High-dose epinephrine
	15	16	Standard-dose epinephrine
Killingsworth et al.[99]	8	9	β Blocker
Cairns et al.[100]	14	8	Epinephrine

Table 1 (*Continued*)

Study	Number of subjects	Time to drug administration	First medication received
Rubertsson et al.[101]	8	11	Aortic occlusion + epinephrine
	8	11	Epinephrine IV
Wenzel et al.[102]	6	7	Vasopressin IV
	6	7	Intraosseous vasopressin
Jasani et al.[103]	36	9	Epinephrine
Rubertsson et al.[104]	22	9	Epinephrine
Wenzel et al.[105]	12	7	Epinephrine
Wenzel et al.[106]	8	18	Vasopressin
Voelckel et al.[107]	6	7	Vasopressin
	6	7	Epinephrine
Hoekstra et al.[108]	7	13	Norepinephrine
	7	13	Epinephrine
Leong et al.[109]	11	11	Epinephrine
	12	10	Epinephrine
Kornberger et al.[110]	6	7	Epinephrine
Schwarz et al.[111]	8	18	Vasopressin
Krismer et al.[112]	6	9	Epinephrine
	6	9	Epinephrine + novel K^+ channel blocker
Nozari et al.[113]	10	7	Aortic occlusion + vasopressin
	10	7	Vasopressin
Voelckel et al.[114]	6	16	Epinephrine
	6	16	Vasopressin
	6	16	Vasopressin + epinephrine
Roberts et al.[115]	6	3	Novel α_1-agonist
	6	3	Standard-dose epinephrine
	6	3	High-dose epinephrine
Prengel et al.[87]	7	7	Epinephrine
	7	7	Vasopressin
Brunette et al.[116]	10	15	Standard-dose epinephrine
	10	15	High-dose epinephrine
Klouche et al.[117]	7	9	Novel α_2-agonist
	7	9	Epinephrine
Hornchen et al.[118]	8	3	Standard-dose epinephrine
	8	3	High-dose epinephrine
Wenzel et al.[119]	6	7	Epinephrine
	6	7	Vasopressin
	6	12	Epinephrine
	6	12	Vasopressin
Bar-Joseph et al.[120]	38	17	Epinephrine
Hoekstra et al.[121]	10	13	Epinephrine
Angelos et al.[122]	8	10	Epinephrine
Hilwig et al.[123]	10	8	Endothelin-1 + epinephrine
	17	8	Epinephrine
DeBehnke et al.[124]	5	13	Endothelin-1
	6	13	Epinephrine
Kornberger et al.[125]	7	7	Epinephrine
	7	7	Vasopressin
Mulligan et al.[126]	11	8	Epinephrine
	7	8	Vasopressin
	11	8	Epinephrine + vasopressin
Gedeborg et al.[127]	13	10	Aortic occlusion + epinephrine
	13	10	Epinephrine
Babar et al.[128]	17	8	Epinephrine
	18	8	Vasopressin
Hornchen et al.[129]	8	3	Epinephrine
	8	3	Endobronchial epinephrine

Table 1 (*Continued*)

Study	Number of subjects	Time to drug administration	First medication received
Lindner et al.[130]	7	7	Angiotensin II
Kern et al.[131]	16	12.5	Epinephrine
	16	12.5	Vasopressin
	16	12.5	Vasopressin
Hornchen et al.[132]	8	3	Epinephrine IV
	8	3	Endobronchial epinephrine
Schindler et al.[133]	26	10	Epinephrine
Hornchen et al.[134]	16	3	Epinephrine
Hornchen et al.[135]	10	3	Norepinephrine IV
	10	3	Endotracheal norepinephrine
Hornchen et al.[136]	26	3	Epinephrine IV
	18	3	Endotracheal epinephrine
Liu et al.[137]	10	10	Aortic occlusion + vasopressin
	10	10	Aortic occlusion + epinephrine
	10	10	Epinephrine
Manning et al.[138]	12	12	Epinephrine

Subject group given for studies comparing interventions.

animal studies. Predictor variables included: time to drug, route of delivery (IV or ET), induction of hypothermia, and type of drug. Time to drug was analyzed as a continuous variable in this regression model. The Hosmer—Lemeshow test was used to assess goodness of fit.

Results

Our literature review yielded 332 abstracts. Of these, 197 were selected for review of the full manuscript. The reason for exclusion is presented in Figure 1. Of the 197 manuscripts, 119 contained

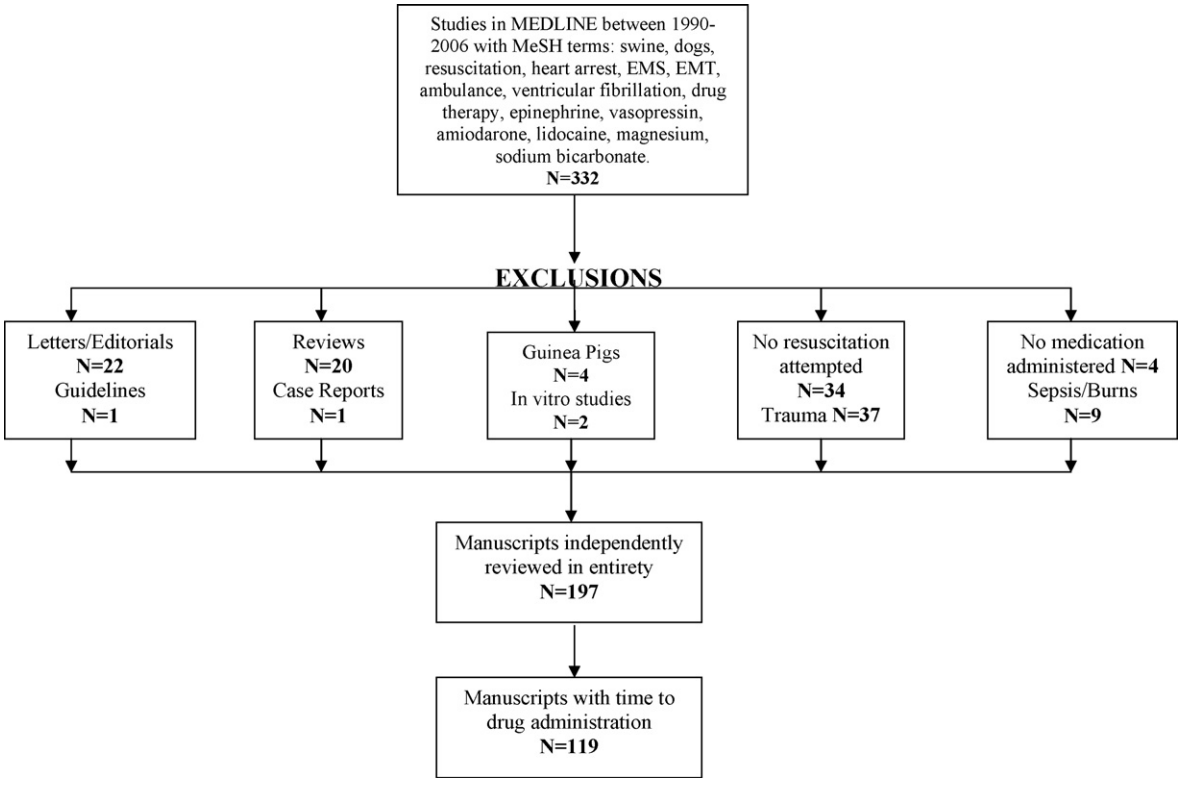

Figure 1 Results of decision algorithm used.

unique data on time to first drug administration. There was 100% agreement between both reviewers on which studies to include in our analysis (Table 1). The average time to first medication administration in these 2378 animals was 9.5 min (range 3.0—28.0; 95% CI around mean 2.78, 16.22). This was less than our previously reported clinical trial data (19.4 min; $p < 0.001$). In the regression analysis, time to drug was the lone predictor of ROSC (odds ratio 0.844; 95% CI 0.738, 0.966). This regression model had acceptable fit (Hosmer—Lemeshow value 0.195).

Discussion

Drugs are administered approximately 10 min earlier in animal studies than in clinical trials. Specifically, animal studies give drugs during the circulatory phase while clinical trials give drugs during the metabolic phase. This delay may be one reason animal studies have failed to translate to clinical practice.

Weisfeldt and Becker have proposed a three-phase model of cardiac arrest.[17] The first phase is electrical and lasts from 0 to 4 min. During this initial phase, ventricular fibrillation responds well to countershock. The second phase, from 4 to 10 min, is the circulatory phase. Both animal and human data support the initiation of CPR before attempting defibrillation to ensure adequate tissue oxygenation and perfusion. Data in this phase also supports supplementary administration of vasopressors with CPR. Immediate rescue shock alone has been ineffective during this phase.[13,18,19] The third phase of cardiac arrest occurs beyond 10 min. Little research has been conducted in this metabolic phase, even though it is usually during this phase that advanced life support is initiated and patients receive their first dose of medication. One study has suggested that cardiopulmonary bypass may be effective and result in neurologically intact survivors.[20] Using a swine model, we demonstrated recently that these phases may be extended through the use of an optimal resuscitation incorporating CPR and a drug cocktail prior to rescue countershock.[21] This model would predict a 21% probability of ROSC with drug administration at 19.4 min, and an 83% probability of ROSC with drug administration at 9.5 min.

The 2005 ILCOR guidelines downplay the import of medication administration.[22] In light of this literature review and our own experience with animal models, we believe that these drugs are not inert, but only effective when administered during the circulatory phase of cardiac arrest. These data suggest a shift in resuscitation care to improve drug delivery in the out-of-hospital setting. One method employed to decrease time to drug is system-wide changes in dispatch protocols. These changes have been shown to decrease time to medication administration by 3.5 min.[23] A second method to improve drug delivery time is to provide first responders with the ability to establish intraosseus access and give drugs. We have demonstrated previously that the use of an intraosseus needle by prehospital basic life support providers is feasible and compares favorably with prior studies of advanced life support intravenous catheter placement.[24,25] If drug delivery continues to occur late during resuscitative efforts, we are unlikely to find a benefit from any drug or cocktail of drugs in the clinical setting.

Our study has several limitations. First, it is limited to a retrospective review of the literature. There is the possibility that studies have been missed, but we believe this to have been minimized by our inclusive search criteria and extensive review. Second, the animals used are young, healthy animals. The cardiovascular physiology of these animals may be different than that of many people who experience OOHCA. Third, time to drug delivery is reliably and consistently recorded in animal studies. However, in clinical settings this data is limited due to being self-reported. The time from collapse to EMS activation is rarely known. Finally, the outcomes assessed are ROSC and short-term survival. Most animal studies do not provide information on neurologically intact survival, which is the most relevant outcome from the perspective of the patient. We note that previous studies showing short-term benefits have failed to translate to long-term survival.[26]

Conclusions

Time to first drug delivery in animal resuscitation studies occurs approximately 10 min earlier than in clinical trials. In animal trials, time to drug predicts ROSC. These data suggest that one reason for the failure of animal studies to translate into clinical practice may be delay to drug delivery. We suggest that an emphasis on gaining vascular access may improve drug effectiveness.

Conflict of interest statement

None of the authors have a conflict of interest to report.

Acknowledgements

Dr. Rittenberger and Dr. Menegazzi are supported by the Clinical Research Skills Development Core of the Resuscitation Outcomes Consortium through the National Heart, Lung and Blood Institute 5U01 HL077871-02. Dr. Menegazzi is also supported by the National Heart, Lung and Blood Institute 5R01 HL080483-2.

Appendix A

Time to medication administration (min) in clinical studies of cardiac arrest. Subject group given for studies comparing interventions. Grey shading indicates studies specifically evaluating time to study drug administration.

Study	Number of Subjects	Time to Medication Administration	Subject Group
Nolan J, *et al.*	309	14.7	Standard CPR
Nolan J, *et al.*	267	15.8	Active compression-decompression CPR
Eisenburger P, *et al.*	114	18.0	
Allegra J, *et al.*	58	13.3	Magnesium sulfate
Allegra J, *et al.*	58	14.7	Placebo
Mauer D, *et al.*	83	14.2	Active compression-decompression CPR
Mauer D, *et al.*	90	13.4	Standard CPR
Mader TJ, *et al.*	66	12.5	Aminophylline
Mader TJ, *et al.*	45	12.9	Control
Callaham M, *et al.*	286	16.0	High-dose epinephrine
Callaham M, *et al.*	260	17.0	Standard-dose epinephrine
Callaham M, *et al.*	270	16.0	Norepinephrine
Gueugniaud P, *et al.*	153	20.7	Standard-dose epinephrine
Gueugniaud P, *et al.*	173	20.6	High-dose epinephrine
Persse DE, *et al.*	24	18.8	Uniform response
Persse DE, *et al.*	181	15.2	Targeted response
Rudner R, *et al.*	171	10.0	Resuscitation not successful
Rudner R, *et al.*	17	10.0	Resuscitation successful
Martin DR, *et al.*	16	16.7	Countershock group
Martin DR, *et al.*	31	18.5	No countershock group
Schneider T, *et al.*	72	13.8	
Van der Hoeven JG, *et al.*	261	11.8	Before physician supervision
Van der Hoeven JG, *et al.*	218	13.9	After physician supervision
Kudenchuk PJ, *et al.*	123	21.4	Amiodarone
Kudenchuk PJ, *et al.*	179	20.5	Placebo
Dorian P, *et al.*	162	25.0	Amiodarone
Dorian P, *et al.*	148	24.0	Lidocaine
Wenzel V, *et al.*	589	17.5	Vasopressin
Wenzel V, *et al.*	597	18.1	Epinephrine
Brown CG, *et al.*	244	24.8	Standard-dose epinephrine
Brown CG, *et al.*	230	24.0	High-dose epinephrine

Bar-Joseph G, *et al.*	65	18.7	Escalating Dose Epinephrine BRCT III Site 1
Bar-Joseph G, *et al.*	144	18.6	BRCT III Site 2
Bar-Joseph G, *et al.*	114	20.1	BRCT III Site 3
Bar-Joseph G, *et al.*	136	21.6	BRCT III Site 4
Bar-Joseph G, *et al.*	173	17.1	BRCT III Site 5
Bar-Joseph G, *et al.*	156	20.7	BRCT III Site 6
Bar-Joseph G, *et al.*	96	23.2	BRCT III Site 7
Bar-Joseph G, *et al.*	153	20.3	BRCT III Site 8
Bar-Joseph G, *et al.*	60	19.7	BRCT III Site 9
Bar-Joseph G, *et al.*	290	19.4	BRCT III Site 10
Bar-Joseph G, *et al.*	77	20.5	BRCT III Site 11
Bar-Joseph G, *et al.*	275	14.8	BRCT III Site 12
Bar-Joseph G, *et al.*	37	21.2	BRCT III Site 13
Bar-Joseph G, *et al.*	213	10.7	BRCT III Site 14
Bar-Joseph G, *et al.*	77	24.7	BRCT III Site 15
Bar-Joseph G, *et al.*	56	18.3	BRCT III Site 16

References

1. Stiell IG, Wells GA, Field B, et al. Advanced cardiac life support in out-of-hospital cardiac arrest. N Engl J Med 2004;351:647—56.
2. Fatovich DM, Prentice DA, Dobb GJ. Magnesium in cardiac arrest (the magic trial). Resuscitation 1997;35:237—41.
3. Wang HE, Min A, Hostler D, Chang CH, Callaway CW. Differential effects of out-of-hospital interventions on short- and long-term survival after cardiopulmonary arrest. Resuscitation 2005;67:69—74.
4. Niemann JT, Cairns CB, Sharma J, Lewis RJ. Treatment of prolonged ventricular fibrillation. Immediate countershock versus high-dose epinephrine and CPR preceding countershock. Circulation 1992;85:281—7.
5. Menegazzi JJ, Davis EA, Yealy DM, et al. An experimental algorithm versus standard advanced cardiac life support in a swine model of out-of-hospital cardiac arrest. Ann Emerg Med 1993;22:235—9.
6. Menegazzi JJ, Seaberg DC, Yealy DM, Davis EA, MacLeod BA. Combination pharmacotherapy with delayed countershock vs. standard advanced cardiac life support after prolonged ventricular fibrillation. Prehosp Emerg Care 2000;4: 31—47.
7. Prengel AW, Linstedt U, Zenz M, Wenzel V. Effects of combined administration of vasopressin, epinephrine, and norepinephrine during cardiopulmonary resuscitation in pigs. Crit Care Med 2005;33:2587—91.
8. Cammarata G, Weil MH, Sun S, Tang W, Wang J, Huang L. B1-adrenergic blockade during cardiopulmonary resuscitation improves survival. Crit Care Med 2004;32:S440—3.
9. Seaberg DC, Menegazzi JJ, Check B, MacLeod BA, Yealy DM. Use of a cardiocerebral-protective drug cocktail prior to countershock in a porcine model of prolonged ventricular fibrillation. Resuscitation 2001;51:301—8.
10. Prengel AW, Linder KH, Wenzel V, Tugtekin I, Anhaupl T. Splanchnic and renal blood flow after cardiopulmonary resuscitation with epinephrine and vasopressin in pigs. Resuscitation 1998;38:19—24.
11. Wenzel V, Lindner KH, Augenstein S, Prengel A, Strohmenger HU. Vasopressin combined with epinephrine decreases cerebral perfusion compared with vasopressin alone during cardiopulmonary resuscitation in pigs. Stroke 1998;29:1462—8.
12. Mulligan KA, McKnite SH, Lindner KH, Lindstrom PJ, Detloff B, Lurie KG. Synergistic effects of a vasopressin plus epinephrine during cardiopulmonary resuscitation. Resuscitation 1997;35:265—71.
13. Menegazzi JJ, Wang HE, Lightfoot CB, et al. Immediate defibrillation versus interventions first in a swine model of prolonged ventricular fibrillation. Resuscitation 2003;59:261—70.
14. Rittenberger JC, Bost JM, Menegazzi JJ. Time to give the first medication during resuscitation in out-of-hospital cardiac arrest. Resuscitation 2006;70:201—6.
15. Pititti DB. Meta Analysis, Decision Analysis, and Cost-Effectiveness Analysis. Oxford University Press; 1994.
16. Hunter JE, Schmidt FL. Methods of Meta-Analysis: Correcting Error and Bias in Research Findings. Newbury Park, CA: Sage; 1990. pp. 110—112.
17. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest. JAMA 2002;288:3035—8.
18. Menegazzi JJ, Callaway CW, Sherman LD, et al. Ventricular fibrillation scaling exponent can guide timing of defibrillation and other therapies. Circulation 2004;109: 926—31.
19. Wang HE, Menegazzi JJ, Lightfoot CB, et al. Effects of biphasic vs. monophasic defibrillation on the scaling exponent in a swine model of prolonged ventricular fibrillation. Acad Emerg Med 2001;8:771—80.
20. Beyersdorf F, Kirsch M, Buckberg GG, Allen BS. Warm glutamate/aspartate-enriched blood cardioplegic solution for perioperative sudden death. J Thorac Cardiovasc Surg 1992;104:1141—7.
21. Rittenberger JC, Menegazzi JJ, Callaway CW. Association of delay to first intervention with return of spontaneous circulation in a swine model of cardiac arrest. Resuscitation, in press.
22. International Liaison Committee on Resuscitation. Part 4. Advanced life support. Resuscitation 2005;67:213—47.
23. Persse DE, Key CB, Bradley RN, Miller CC, Dhingra A. Cardiac arrest survival as a function of ambulance deployment strategy in a large urban emergency medical services system. Resuscitation 2003;59:97—104.
24. Guyette FX, Rittenberger JC, Platt TE, Suffoletto BS, Hostler DP, Wang HE. Feasibility of basic emergency medical technicians to perform selected advanced life support interventions. Prehosp Emerg Care 2006;10(4):518—21.

25. Miller DD, Guimond G, Hostler DP, Platt T, Wang HE. Feasibility of sternal intraosseus access by emergency medical technician students. Prehosp Emerg Care 2005;9(1):73—8.
26. Callaham M, Madsen CD, Barton CW, Saunders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine vs. standard-dose epinephrine in prehospital cardiac arrest. JAMA 1992;268(19):2667—72.
27. Krieter H, Denz C, Janke C, et al. Hypertonic-hyperonocotic solutions reduce the release of cardiac troponin I and S-100 after successful cardiopulmonary resuscitation in pigs. Anesth Analg 2002;95:1031—6.
28. Loeckinger A, Kleinsasser A, Wenzel V, et al. Pulmonary gas exchange after cardiopulmonary resuscitation with either vasopressin or epinephrine. Crit Care Med 2002;30: 2059—62.
29. Krismer AC, Wenzel V, Voelckel WG, et al. Effects of vasopressin on adrenal gland regional perfusion during experimental cardiopulmonary resuscitation. Resuscitation 2003;56:223—8.
30. Little CM, Angelos MG, Paradis NA. Compared to angiotensin II, epinephrine is associated with high myocardial blood flow following return of spontaneous circulation after cardiac arrest. Resuscitation 2003;59:353—9.
31. Johansson J, Gedeborg R, Basu S, Rubertsson S. Increased cortical cerebral blood flow by continuous infusion of adrenaline (epinephrine) during experimental cardiopulmonary resuscitation. Resuscitaiton 2003;57:299—307.
32. Bahlmann L, Klaus S, Baumeier W, et al. Brain metabolism during cardiopulmonary resuscitation assessed with microdialysis. Resuscitation 2003;59:255—60.
33. Behringer W, Sterz F, Domanovits H, et al. Effects of manual high-impulse CPR on myocardial perfusion during cardiac arrest in pigs. Resuscitation 1997;34:271—9.
34. Voelckel WG, Lurie KG, McKnite S, et al. Effects of epinephrine and vasopressin in a piglet model of prolonged ventricular fibrillation and cardiopulmonary resuscitation. Crit Care Med 2002;30:957—62.
35. Holzer M, Behringer W, Sterz F, et al. Ventricular fibrillation median frequency may not be useful for monitoring during cardiac arrest treated with endothelin-1 or epinephrine. Anesth Anal 2004;99:1787—93.
36. Johansson J, Gedeborg R, Rubertsson S. Vasopressin versus continuous adrenaline during experimental cardiopulmonary resuscitation. Resuscitation 2004;62:61—9.
37. Amann A, Rheinberger K, Achleitner U, et al. The prediction of defibrillation outcome using a new combination of mean frequency and amplitude in porcine models of cardiac arrest. Anesth Analg 2002;95:716—22.
38. Adams JA, Bassuk J, Wu D, Kurlansky P. Survival and normal neurological outcome after CPR with periodic Gz acceleration and vasopressin. Resuscitation 2003;56:215—21.
39. Schwarz B, Mair P, Wagner-Berger H, et al. Neither vasopressin nor amiodarone improve CPR outcome in an animal model of hypothermic cardiac arrest. Acta Anaesth Scan 2003;47:1114—8.
40. Vukmir RB, Bircher NG, Radovsky A, Safar P. Sodium bicarbonate may improve outcome in dogs with brief or prolonged cardiac arrest. Crit Care Med 1995;23: 515—22.
41. Manning JE, Batson DN, Payne FB, et al. Selective aortic arch perfusion during cardiac arrest: enhanced resuscitation using oxygenated perflubron emulsion, with and without aortic arch epinephrine. Ann Emerg Med 1997;29:580—7.
42. Strohmenger HU, Lindner KH, Prengel AW, Pfenninger EG, Bothner U, Lurie KG. Effects of epinephrine and vasopressin on median fibrillation frequency and defibrillation success in a porcine model of cardiopulmonary resuscitation. Resuscitation 1996;31:65—73.
43. Ayoub IM, Kolarova J, Kantola RL, Sanders R, Gazmuri RJ. Cariporide minimizes adverse myocardial effects of epinephrine during resuscitation from ventricular fibrillation. Crit Care Med 2005;33:2599—605.
44. Stadlbauer KH, Wagner-Berger HG, Wenzel V, et al. Survival with full neurologic recover after prolonged cardiopulmonary resuscitation with a combination of vasopressin and epinephrine in pigs. Anesth Analg 2003;96:1743—9.
45. Mayr VD, Wenzel V, Voelckel WG, et al. Developing a vasopressor combination in a pig model of asphyxial cardiac arrest. Circulation 2001;104:1651—6.
46. Amann A, Achleitner U, Antretter H, et al. Analyzing ventricular fibrillation ECG-signals and predicting defibrillation success during cardiopulmonary resuscitation employing N(alpha)-histograms. Resuscitation 2001;50:77—85.
47. Hilwig RW, Kern KB, Berg RA, Sanders AB, Otto CW, Ewy GA. Catecholamines in cardiac arrest: role of alpha agonists, beta-adrenergic blockers and high-dose epinephrine. Resuscitation 2000;47:203—8.
48. Nozari A, Rubertsson S, Wiklund L. Intra-aortic administration of epinephrine above an aortic balloon occlusion during experimental CPR does not further improve cerebral blood flow and oxygenation. Resuscitation 2000;44: 119—27.
49. Prengel AW, Lindner KH, Wenzel V, Tugtekin I, Anhaupl T. Splanchnic and renal blood flow after cardiopulmonary resuscitation with epinephrine and vasopressin in pigs. Resuscitation 1998;38:19—24.
50. Wenzel V, Linder KH, Augenstein S, Prengel AW, Strohmenger HU. Vasopressin combined with epinephrine decreases cerebral perfusion compared with vasopressin alone during cardiopulmonary resuscitation in pigs. Stroke 1998;29:1462—7.
51. Wenzel V, Lindner KH, Mayer H, Lurie KG, Prengel AW. Vasopressin combined with nitroglycerin increases endocardial perfusion during cardiopulmonary resuscitation in pigs. Resuscitation 1998;38:13—7.
52. Lurie KG, Voelckel WG, Iskos DN, et al. Combination drug therapy with vasopressin, adrenaline (epinephrine) and nitroglycerin improves vital organ blood flow in a porcine model of ventricular fibrillation. Resuscitation 2002;54:187—94.
53. Berg RA, Hilwig RW, Kern KB, Ewy GA. Precountershock cardiopulmonary resuscitation improves ventricular fibrillation median frequency and myocardial readiness for successful defibrillation from prolonged ventricular fibrillation: a randomized, controlled swine study. Ann Emerg Med 2002;40:563—70.
54. Holzer M, Sterz F, Behringer W, et al. Endothelin-1 elevates regional cerebral perfusion during prolonged ventricular fibrillation cardiac arrest in pigs. Resuscitation 2002;55:317—27.
55. Prengel AW, Lindner KH, Anhaupl T, Vogt J, Lurie KG. Regulation of right atrial beta-adrenoreceptors after cardiopulmonary resuscitation in pigs. Resuscitation 1996;31:271—8.
56. Bleske BE, Warren EW, Rice TL, Shea MJ, Amidon G, Knight P. Comparison of intravenous and intranasal administration of epinephrine during CPR in a canine model. Ann Emerg Med 1992;21:1125—30.
57. Tang W, Weil MH, Schock RB, et al. Phased chest and abdominal compression-decompression. A new option for cardiopulmonary resuscitation. Circulation 1997;95:1335—40.
58. Lindner KH, Pfenninger EG, Lurie KG, Schurmann W, Lindner IM, Ahnfeld FW. Effects of active compression—

decompression resuscitation on myocardial and cerebral blood flow in pigs. Circulation 1993;88:1254—63.
59. Lindner KH, Prengel AW, Pfenninger EG, et al. Vasopressin improves vital organ blood flow during closed-chest cardiopulmonary resuscitation in pigs. Circulation 1995;91: 215—21.
60. Idris AH, Becker LB, Fuerst RS, et al. Effect of ventilation on resuscitation in an animal model of cardiac arrest. Circulation 1994;90:3063—9.
61. Bar-Joseph G, Weinberger T, Ben-Haim S. Response to repeated equal doses of epinephrine during cardiopulmonary resuscitation in dogs. Ann Emerg Med 2000;35: 3—10.
62. Paradis NA. Is a pressor necessary during aortic perfusion and oxygenation therapy of cardiac arrest? Ann Emerg Med 1999;34:697—702.
63. Bleske BE, Rice TL, Warren EW, et al. Effect of dose on the nasal absorption of epinephrine during cardiopulmonary resuscitation. Am J Emerg Med 1996;14:133—8.
64. Lindner KH, Ahnefeld FW, Bowdler IM. Comparison of different doses of epinephrine on myocardial perfusion and resuscitation success during cardiopulmonary resuscitation in a pig model. Am J Emerg Med 1991;9:27—31.
65. Wolf CF, Keck FS, Brinkmann A, Rigos D, Lindner KH, Grunert A. Unchanged 5′-deiodinating activity during the induction of a nonthyroidal illness. Horm Metab Res 1995;27:126—30.
66. Blecic S, Chaskis C, Vincent JL. Atropine administration in experimental electromechanical dissociation. Am J Emerg Med 1992;10:515—8.
67. Prengel AW, Lindner KH, Keller A, Lurie KG. Cardiovascilar function during the postressucitaiton phase after cardiac arrest in pigs: a comparison of epinephrine versus vasopressin. Crit Care Med 1996;24:2014—9.
68. Berg RA, Otto CW, Kern KB, et al. A randomized blinded trial of high-dose epinephrine versus standard-dose epinephrine in a swine model of pediatric asphyxial cardiac arrest. Crit Care Med 1996;24:1695—700.
69. Strohmenger HU, Lindner KH, Keller A, Lindner IM, Pfenninger E, Bothner U. Effects of graded doses of vasopressin on median fibrillation frequency in a porcine model of cardiopulmonary resuscitation: results of a prospective, randomized, controlled trial. Crit Care Med 1996;24:1360—5.
70. Bleske BE, Rice TL, Warren EW, De Las Alvas VR, Tait AR, Knight PR. The effect of sodium bicarbonate administration on the vasopressor effect of high-dose epinephrine during cardiopulmonary resuscitation in swine. Am J Emerg Med 1993;11:439—43.
71. Manning JE, Murphy CA, Batson DN, Perretta SG, Mueller RA, Norfleet EA. Aortic arch versus central venous epinephrine during CPR. Ann Emerg Med 1993;22: 703—8.
72. Wenzel V, Lindner KH, Prengel AW, et al. Vasopressin improves vital organ blood flow after prolonged cardiac arrest with postcountershock pulseless electrical activity in pigs. Crit Care Med 1999;27:486—92.
73. Mayr VD, Raedler C, Wenzel V, Lindner KH, Strohmenger HU. A comparison of epinephrine and vasopressin in a porcine model of cardiac arrest after rapid intravenous injection of bupivicaine. Anesth Analg 2004;98:1426—31.
74. Gervais HW, Schleien CL, Koehler RC, Berkowitz ID, Shaffner DH, Traystman RJ. Effect of adrenergic drugs on cerebral blood flow, metabolism, and evoked potentials after delayed cardiopulmonary resuscitation in dogs. Stroke 1991;22:1554—61.
75. Nejman GD, Griffith R, Van Ligten P, et al. Hemodynamic effects of 1-[3,4-dihydroxyphenyl]-1,2-diaminoethane versus norepinephrine during ventricular fibrillation and cardiopulmonary resuscitation. Resuscitation 1990;20: 243—52.
76. Achleitner U, Wenzel V, Strohmenger HU, et al. The effects of repeated doses of vasopressin or epinephrine on ventricular fibrillation in a porcine model of prolonged cardiopulmonary resuscitation. Anesth Analg 2000;90: 1067—75.
77. Voelckel WG, Lindner KH, Wenzel V, et al. Effect of small-dose dopamine on mesenteric blood flow and renal function in a pig model of cardiopulmonary resuscitation with vasopressin. Anesth Analg 1999;80:1430—6.
78. Lindner KH, Brinkmann A, Pfenninger EG, Lurie KG, Goertz A, Lindner IM. Effect of vasopressin in hemodynamic variables, organ blood flow, and acid—base status in a pig model of cardiopulmonary resuscitation. Anesth Analg 1993;77:427—35.
79. Gazmuri RJ, von Planta M, Weil MH, Rackow EC. Cardiac effects of carbon dioxide-consuming and carbon dioxide-generating buffers during cardiopulmonary resuscitation. J Am Coll Cardiol 1990;15:482—90.
80. Bleske BE, Rice TL, Warren EW, et al. Effect of vehicle on the nasal absorption of epinephrine during cardiopulmonary resuscitation. Pharmacotherapy 1996;16: 1039—45.
81. Jameson SJ, Mateer JR, DeBehnke DJ. Early volume expansion during cardiopulmonary resuscitation. Resuscitation 1993;26:243—50.
82. Wenzel V, Lindner KH, Prengel AW, Lurie KG, Strohmenger HU. Endobronchial vasopressine improves survival during cardiopulmonary resuscitation in pigs. Anesthesiology 1997;86:1375—81.
83. Lindner KH, Ahnefeld FW, Schuermann W, Bowdler IM. Epinephrine and norepinephrine in cardiopulmonary resuscitation. Effects on myocardial oxygen delivery and consumption. Chest 1990;97:1458—62.
84. Angelos MG, DeBehnke DJ, Leasure JE. Arterial blood gases during cardiac arrest: markers of blood flow in a canine model. Resuscitation 1992;23:101—11.
85. Prengel AW, Lindner KH, Keller A. Cerebral oxygenation during cardiopulmonary resuscitation with epinephrine and vasopressin in pigs. Stroke 1996;27:1241—8.
86. Littmann L, Ashline PT, Hayes WJ, et al. Aminophylline fails to improve the outcome of cardiopulmonary resuscitation from prolonged ventricular fibrillation: a placebo-controlled, randomized, blinded experimental study. J Am Coll Cardiol 1994;23:1708—14.
87. DeBehnke DJ, Angelos MG, Leasure JE. Use of cardiopulmonary bypass, high-dose epinephrine, and standard-dose epinephrine in resuscitation from post-countershock electromechanical dissociation. Ann Emerg Med 1992;21: 1051—7.
88. Manning JE, Murphy CA, Hertz CM, Perretta SG, Mueller RA, Norfleet EA. Selective aortic arch perfusion during cardiac arrest: a new resuscitation technique. Ann Emerg Med 1992;21:1058—65.
89. Schleien CL, Eberle B, Shaffner DH, Koehler RC, Traystman RJ. Reduced blood—brain barrier permeability after cardiac arrest by conjugated superoxide dismutase and catalase in piglets. Stroke 1994;25:1830—4.
90. Strohmenger HU, Wenzel V, Eberhard R, Guth BD, Lurie KG, Lindner KH. Effects of the specific bradycardic agent zatebradine on hemodynamic variables and myocardial blood flow during the early postresuscitation phase in pigs. Resuscitation 1999;42:211—20.
91. Lindberg L, Liao Q, Steen S. The effects of epinephrine/norepinephrine on end-tidal carbon dioxide concentration,

coronary perfusion pressure and pulmonary arterial blood flow during cardiopulmonary resuscitation. Resuscitation 2000;43:129—40.
92. Wenzel V, Lindner KH, Krismer AC, et al. Survival with full neurologic recovery and no cerebral pathology after prolonged cardiopulmonary resuscitation with vasopressin in pigs. J Am Coll Cardiol 2000;35:527—33.
93. Suddath WO, Deychak Y, Varghese PJ. Electrophysiologic basis by which epinephrine facilitates defibrillation after prolonged episodes of ventricular fibrillation. Ann Emerg Med 2001;38:201—6.
94. Nozari A, Rubertsson S, Wiklund L. Differences in the pharmacodynamics of epinephrine during and after experimental cardiopulmonary resuscitation. Resuscitation 2001;49: 59—72.
95. Krismer AC, Hogan QH, Wenzel V, et al. The efficacy of epinephrine or vasopressin for resuscitation during epidural anesthesia. Anesth Analg 2001;93:734—42, sdlkjf.
96. Idris AH, Wenzel V, Becker LB, Bannner MJ, Orban DJ. Does hypoxia or hypercarbia independently affect resuscitation from cardiac arrest? Chest 1995;108:522—8.
97. Barton C, Manning JE, Batson N. Effect of selective aortic arch perfusion on median frequency and peak amplitude of ventricular fibrillation in a canine model. Ann Emerg Med 1996;27:610—6.
98. Berg RA, Otto CW, Kern KB, et al. High-dose epinephrine results in greater early mortality after resuscitation from prolonged cardiac arrest in pigs: a prospective, randomized study. Crit Care Med 1994;22:282—90.
99. Killingsworth CR, Wei CC, Dell'Italia LJ, et al. Short-acting beta-adrenergic antagonist esmolol given at reperfusion improves survival after prolonged ventricular fibrillation. Circulation 2004;109:2469—74.
100. Cairns CB, Niemann JT. Hemodynamic effects of repeated doses of epinephrine after prolonged cardiac arrest and CPR: preliminary observations in an animal model. Resuscitation 1998;36:181—5.
101. Rubertsson S, Bircher NG, Smarik SD, Young MC, Alexander H, Grenvik A. Intra-aortic administration of epinephrine above aortic occlusion does not alter outcome of experimental cardiopulmonary resuscitation. Resuscitation 1999;42:57—63.
102. Wenzel V, Lindner KH, Augenstein S, et al. Intraosseous vasopressin improves coronary perfusion pressure rapidly during cardiopulmonary resuscitation in pigs. Crit Care Med 1999;27:1565—9.
103. Jasani MS, Nadkarni VM, Finkelstein MS, Mandell GA, Salzman SK, Norman ME. Effects of different techniques of endotracheal epinephrine administration in pediatric porcine hypoxic-hypercarbic cardiopulmonary arrest. Crit Care Med 1994;22:1174—80.
104. Rubertsson S, Grenvik A, Zemgulis V, Wiklund L. Systemic perfusion pressure and blood flow before and after administration of epinephrine during experimental cardiopulmonary resuscitation. Crit Care Med 1995;23: 1984—96.
105. Wenzel V, Lindner KH, Prengel AW, Strohmenger HU. Effect of phased chest and abdominal compression—decompression cardiopulmonary resuscitation on myocardial and cerebral blood flow in pigs. Crit Care Med 2000;28: 1107—12.
106. Wenzel V, Lindner KH, Baubin MA, Voelckel WG. Vasopressin decreases endogenous catecholamine plasma concentrations during cardiopulmonary resuscitation in pigs. Crit Care Med 2000;28:1096—100.
107. Voelckel WG, Lindner KH, Wenzel V, et al. Effects of vasopressin and epinephrine on splanchnic blood flow and renal function during and after cardiopulmonary resuscitation in pigs. Crit Care Med 2000;28:1083—8.
108. Hoekstra JW, Van Ligten P, Neumar R, Werman HA, Anderson J, Brown CG. Effect of high dose norepinephrine versus epinephrine on cerebral and myocardial blood flow during CPR. Resuscitation 1990;19:227—40.
109. Leong EC, Bendall JC, Boyd AC, Einstein R. Sodium bicarbonate improves the chance of resuscitation after 10 minutes of cardiac arrest in dogs. Resuscitation 2001;51: 309—15.
110. Kornberger E, Lindner KH, Mayr VD, et al. Effects of epinephrine in a pig model of hypothermic cardiac arrest and closed-chest cardiopulmonary resuscitation combined with active rewarming. Resuscitation 2001;50: 301—8.
111. Schwarz B, Mair P, Raedler C, Deckert D, Wenzel V, Lindner KH. Vasopressin improves survival in a pig model of hypothermic cardiopulmonary resuscitation. Crit Care Med 2002;30:1311—4.
112. Krismer AC, Wenzel V, Voelckel W, et al. Effect of the cardioselective ATP-sensitive potassium channel inhibitor HMR 1883 in a porcine model of cardiopulmonary resuscitation. Resuscitation 2002;53:299—306.
113. Nozari A, Rubertsson S, Wiklund L. Improved cerebral blood supply and oxygenation by aortic balloon occlusion combined with intra-aortic vasopressin administration during experimental cardiopulmonary resuscitation. Acta Anaesth Scand 2000;44:1209—19.
114. Voelckel WG, Lurie KG, McKnite S, et al. Comparison of epinephrine and vasopressin in a pediatric porcine model of asphyxial cardiac arrest. Crit Care Med 2000;28: 3777—83.
115. Roberts D, Landolfo K, Dobson K, Light RB. The effects of methoxamine and epinephrine on survival and regional distribution of cardiac output in dogs with prolonged ventricular fibrillation. Chest 1990;98:999—1005.
116. Brunette DD, Jameson SJ. Comparison of standard versus high-dose epinephrine in the resuscitation of cardiac arrest in dogs. Ann Emerg Med 1990;19:8—11.
117. Klouche K, Weil MH, Tang W, Povoas H, Kamohara T, Bisera J. A selective alpha(2)-adrenergic agonist for cardiac resuscitation. J Lab Clin Med 2002;140:27—34.
118. Hornchen U, Lussi C, Schuttler J. Potential risks of high-dose epinephrine for resuscitation from ventricular fibrillation in a porcine model. J Cardiothorac Vascular Anesth 1993;7:184—7.
119. Wenzel V, Lindner KH, Krismer AC, Miller EA, Voelckel WG, Lingnau W. Repeated administration of vasopressin but not epinephrine maintains coronary perfusion pressure after early and late administration during prolonged cardiopulmonary resuscitation in pigs. Circulation 1999;99:1379—84.
120. Bar-Joseph G, Weinberger T, Castel T, et al. Comparison of sodium bicarbonate, Carbicarb, and THAM during cardiopulmonary resuscitation in dogs. Crit Care Med 1998;26:1397—408.
121. Hoekstra JW, Rinnert K, Van Ligten P, Neumar R, Werman HA, Brown CG. The effectiveness of bystander CPR in an animal model. Ann Emerg Med 1990;19:881—6.
122. Angelos MG, Gaddis ML, Gaddis GM, Leasure JE. Improved survival and reduced myocardial necrosis with cardiopulmonary bypass reperfusion in a canine model of coronary occlusion and cardiac arrest. Ann Emerg Med 1990;19:1122—8.
123. Hilwig RW, Berg RA, Kern KB, Ewy GA. Endothelin-1 vasoconstriction during swine cardiopulmonary resuscitation improves coronary perfusion pressures but worsens postresuscitation outcome. Circulation 2000;101:2097—102.

124. DeBehnke DJ, Benson L. Effects of endothelin-1 on resuscitation rate during cardiac arrest. Resuscitation 2000;47:185—9.
125. Kornberger E, Prengel AW, Krismer A, et al. Vasopressin-mediated adrenocorticotropin release increases plasma cortisol concentrations during cardiopulmonary resuscitation. Crit Care Med 2000;28:3517—21.
126. Mulligan KA, McKnite SH, Lindner KH, Lindstrom PJ, Detloff B, Lurie KG. Synergistic effects of vasopressin plus epinephrine during cardiopulmonary resuscitation. Resuscitation 1997;35:265—71.
127. Gedeborg R, Rubertsson S, Wiklund L. Improved haemodynamics and restoration of spontaneous circulation with constant aortic occlusion during experimental cardiopulmonary resuscitation. Resuscitation 1999;40:171—80.
128. Babar SI, Berg RA, Hilwig RW, Kern KB, Ewy GA. Vasopressin versus epinephrine during cardiopulmonary resuscitation: a randomized swine outcome study. Resuscitation 1999;41:185—92.
129. Hornchen U, Lauven PM, Schuttler J, Dorer A, Stoeckel H. The pharmacokinetics of lidocaine in resuscitation conditions. Results of experimental studies on swine. Anaesthesist 1990;39:107—12.
130. Lindner KH, Prengel AW, Pfenninger EG, Lindner IM. Angiotensin II augments reflex activity of the sympathetic nervous system during cardiopulmonary resuscitation in pigs. Circulation 1995;92:1020—5.
131. Kern KB, Heidenreich JH, Higdon TA, et al. Effect of vasopressin on postresuscitation ventricular function: unknown consequences of the recent guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Crit Care Med 2004;32:S393—7.
132. Hornchen U, Schuttler J, Stoeckel H. Influence of the pulmonary circulation on adrenaline pharmacokinetics during cardiopulmonary resuscitation. Eur J Anesth 1992;9: 85—91.
133. Schindler I, Steltzer H, Weindlmayr-Goettel M, Steinbereithner K. Nimodipine after circulatory arrest: effects on oxygen delivery and consumption. J Crit Care 1994;9:18—24.
134. Hornchen U, Berg PW, Schuttler J. Potential risks of high-dose adrenaline for resuscitation following short-term heart arrest in animal experiments. Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie 1992;27:274—8.
135. Hornchen U, Lussi C, Thomas M, Schuttler J. The pulmonary first pass effect of noradrenaline following intravenous and endobronchial administration for resuscitation. Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie 1992;7:160—5.
136. Hornchen U, Lussi C, Schuttler J. New standards for catecholamine therapy in cardiopulmonary resuscitation? Results of a modified application in a resuscitation model. Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie 1992;7:225—9.
137. Liu XL, Nozari A, Basu S, Ronquist G, Ruertsson S, Wiklund L. Neurological outcome after experimental cardiopulmonary resuscitation: a result of delayed and potentially treatable neuronal injury? Acta Anaesth Scand 2002;46: 537—46.
138. Manning JE, Batson DN, Gansman TW, Murphy Jr CA, Perretta SG, Norfleet EA. Selective aortic arch perfusion using serial infusions of perflubron emulsion. Acad Emerg Med 1997;4:883—90.