Published in final edited form as:
Resuscitation. 2007 July ; 74(1): 13–26.

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

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Abstract

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 minutes. 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 minutes (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.

Keywords

cardiopulmonary resuscitation (CPR); cardiac arrest; resuscitation; drug therapy

1. 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.

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Conflict of Interest Statement
None.

[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 minutes (range 13.3–25.0; 95% CI around the mean 12.8, 25.9). [14, Appendix] Thus, clinically, these drugs are administered 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.

2. 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 & 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; and 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 vs. 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]

$weight_i = N_i$ Where N_i is the sample size for each study

And $\sum_{i=1}^{k} weight_j = N$ 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 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.

3. 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 unique data on time to first drug administration. There was 100% agreement between both reviewers on which studies to include in our analysis. The average time to first medication administration in these 2378 animals was 9.5 minutes (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 minutes; $p < 0.001$). 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).

4. Discussion

Drugs are administered approximately 10 minutes earlier in animal studies than in clinical trials. Specifically, animal studies administer drugs during the circulatory phase while clinical trials administer 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 0–4 minutes. During this initial phase, ventricular fibrillation responds well to countershock. The second phase, from 4–10 minutes, 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 minutes. 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 minutes, and an 83% probability of ROSC with drug administration at 9.5 minutes.

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 minutes. [23] A second method to improve drug delivery time is to provide first responders with the ability to establish intraosseus access and provide 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]

5. Conclusions

Time to first drug delivery in animal resuscitation studies occurs approximately 10 minutes earlier than in clinical trials. In animal trials, time to drug predicts ROSC. These data suggest that one reason for 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Drs. Rittenberger and 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.

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Appendix

Time to medication administration (minutes) 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

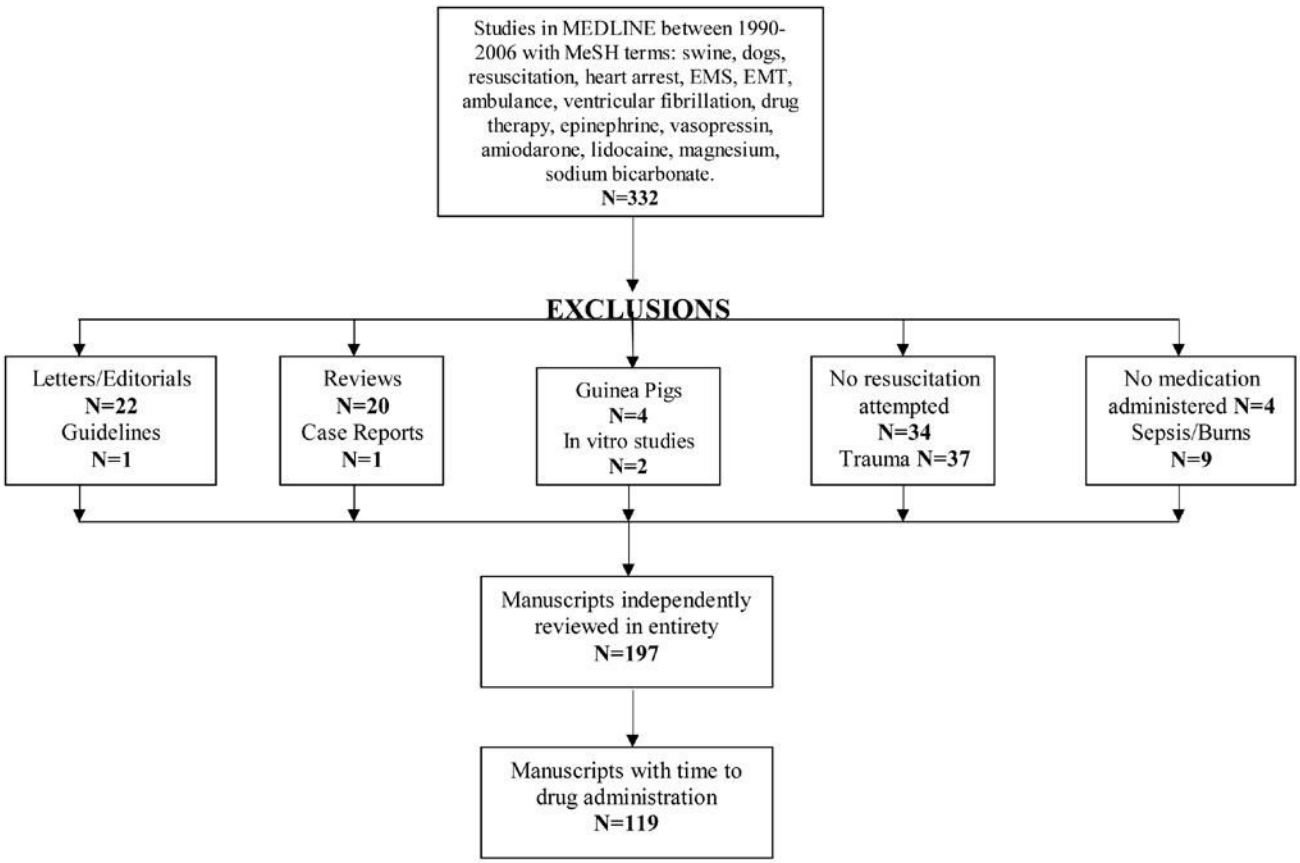

Figure 1.
Results of decision algorithm used.

Table 1

Time to drug administration (minutes) by study. Subject group given for studies comparing interventions.

Study	Number of subjects	Time to drug Administration	First Medication Received
Krieter H, *et al.* [27]	10	8	Epinephrine
Loeckinger A, *et al.* [28]	8	7	Vasopressin
	10	7	Epinephrine
Krismer AC, *et al.* [29]	7	7	Vasopressin
	6	7	Epinephrine
Little CM, *et al.* [30]	13	13	Angiotensin II
	11	13	Epinephrine
	13	13	Angiotensin II + epinephrine
Johansson J, *et al.* [31]	24	7	Epinephrine
Bahlmann L, *et al.* [32]	14	18	Vasopressin
Behringer W, *et al.* [33]	11	9	Epinephrine
Voelckel WG, *et al.* [34]	12	16	Vasopressin
	6	16	Vasopressin + epinephrine
Holzer M, *et al.* [35]	19	10	Endothelin-1
	6	10	Epinephrine
Johansson J, *et al.* [36]	12	7	Vasopressin
	12	7	Epinephrine
Prengel AW, *et al.* [37]	7	7	Epinephrine
	7	7	Vasopressin
	7	7	Vasopressin + epinephrine
Amann A, *et al.* [38]	16	7	Vasopressin
	9	7	Epinephrine
	11	7	Novel vasopressor
	12	4	Epinephrine
	11	4	Vasopressin
	2	10	Vasopressin
	3	10	Epinephrine
Adams JA, *et al.* [39]	12	18	Vasopressin
Schwarz B, *et al.* [40]	7	18	Vasopressin
	7	28	Amiodarone
Vukmir RB, *et al.* [41]	12	5	Epinephrine
	20	15	Epinephrine
Manning JE, *et al.* [42]	5	10.5	Epinephrine
	5	10.5	Aortic occlusion + epinephrine
	5	10.5	Aortic occlusion + Intraaortic epinephrine
Strohmenger HU, *et al.* [43]	7	7	Epinephrine
	7	7	Vasopressin
Ayoub IM, *et al.* [44]	8	10	Cariporide
	8	10	Epinephrine
	8	10	Cariporide + epinephrine
Stadlbauer KH, *et al.* [45]	6	7	Epinephrine
	6	7	Epinephrine + vasopressin
Mayr VD, *et al.* [46]	6	12	Epinephrine
	6	12	Vasopressin
	6	12	High-dose epinephrine + vasopressin
	6	12	Standard-dose epinephrine + vasopressin
Amann A, *et al.* [47]	11	7	Vasopressin
	5	7	Epinephrine
	5	12	Vasopressin
	4	12	Epinephrine
Hilwig RW, *et al.* [48]	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 A, *et al.* [49]	11	7	Aortic occlusion + epinephrine
	12	7	Epinephrine IV
Seaberg DC *et al.* [9]	7	9	Combination therapy including epinephrine + novel cardiocerebral-protective agent
	9	9	Magnesium
	8	10	Epinephrine
Menegazzi JJ, *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

Study	Number of subjects	Time to drug Administration	First Medication Received
	8	11	High-dose epinephrine
Prengel AW, *et al.* [50]	8	5	Epinephrine
	8	5	Vasopressin
Wenzel V, *et al.* [51]	8	18	Vasopressin
	8	18	Vasopressin + epinephrine
Wenzel V, *et al.* [52]	7	7	Vasopressin
	7	7	Vasopressin + nitroglycerin
Lurie KG, *et al.* [53]	12	8	Epinephrine + vasopressin
	12	8	Epinephrine
Berg RA, *et al.* [54]	12	11	Epinephrine
Holzer M, *et al.* [55]	21	10	Endothelin-1
	6	10	Epinephrine
Prengel AW, *et al.* [56]	6	6	Epinephrine
Bleske BE, *et al.* [57]	7	5	Intra-nasal epinephrine
	6	5	Epinephrine IV
Tang W, *et al.* [58]	10	9	Epinephrine
Lindner KH, *et al.* [59]	14	5.5	High-dose epinephrine
Lindner KH, *et al.* [60]	7	7	Epinephrine
	21	7	Vasopressin
Idris AH, *et al.* [61]	24	17	Epinephrine
Bar-Joseph G, *et al.* [62]	36	17	Epinephrine
Paradis NA, *et al.* [63]	13	8	Epinephrine
Bleske BE, *et al.* [64]	26	6	Epinephrine
Lindner KH, *et al.* [65]	28	8	Epinephrine
Wolf CF, *et al.* [66]	7	7	Epinephrine
	7	7	Norepinephrine
	7	7	Vasopressin
Blecic S, *et al.* [67]	6	9	Atropine
	6	9	Atropine
Prengel AW, *et al.* [68]	8	5	Epinephrine
	8	5	Vasopressin
Berg RA, *et al.* [69]	15	11	Standard-dose epinephrine
	15	11	High-dose epinephrine
Strohmenger HU, *et al.* [70]	21	7	Vasopressin
Bleske BE, *et al.* [71]	9	12	Bicarbonate
	9	13	Epinephrine
Menegazzi JJ, *et al.* [5]	9	8	Epinephrine
	9	9	Epinephrine
Manning JE, *et al.* [72]	16	12	Epinephrine
Wenzel V, *et al.* [73]	9	18	Epinephrine
	9	18	Vasopressin
Mayr VD, *et al.* [74]	7	3	Epinephrine
	7	3	Vasopressin
	7	3	Epinephrine + vasopressin
Gervais HW, *et al.* [75]	7	8	Epinephrine
	7	8	Phenylephrine
	7	8	Epinephrine + β blocker
Nejman GD, *et al.* [76]	6	13	Novel vasopressor
Achleitner U, *et al.* [77]	5	7	Vasopressin
	5	7	Epinephrine
	5	12	Vasopressin
	6	12	Epinephrine
Neimann JT, *et al.* [78]	14	8	Epinephrine
	14	7.5	Epinephrine
Voelckel WG, *et al.* [79]	12	7	Vasopressin
Lindner KH, *et al.* [80]	7	7	Epinephrine
	7	7	Vasopressin
Gazmuri RH, *et al.* [81]	8	8	Bicarbonate
	8	8	Carbicarb
Bleske BE, *et al.* [82]	7	6	Intra-nasal epinephrine
Jameson SJ, *et al.* [83]	19	18	Epinephrine
Wenzel V, *et al.* [84]	7	7	Vasopressin IV
	9	7	Endobronchial Vasopressin
Lindner KH, *et al.* [85]	7	5	Epinephrine
	7	5	Norepinephrine
Angelos MG, *et al.* [86]	8	15	Standard-dose epinephrine
	8	15	High-dose epinephrine
Prengel AW, *et al.* [87]	7	7	Vasopressin

Study	Number of subjects	Time to drug Administration	First Medication Received
	7	7	Epinephrine
Littmann L, *et al.* [88]	20	6.5	Epinephrine
	20	6	Epinephrine
DeBehnke DJ, *et al.* [89]	8	15	High-dose epinephrine
	8	15	Standard-dose epinephrine
Manning JE, *et al.* [90]	8	10	Epinephrine
Schleien CL, *et al.* [91]	16	8	Epinephrine
Strohmenger HU, *et al.* [92]	21	7	Epinephrine
Lindberg L, *et al.* [93]	6	6	Epinephrine
	6	6	Norepinephrine
Wenzel V, *et al.* [94]	6	7	Vasopressin
	6	7	Epinephrine
Menegazzi JJ, *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 WO, *et al.* [95]	10	10	Epinephrine
Nozari A, *et al.* [96]	11	13	Epinephrine
	11	13	Vasopressin
Krismer AC, *et al.* [97]	14	4	Epinephrine
	14	4	Vasopressin
Idris AH, *et al.* [98]	24	17	Epinephrine
Barton C, *et al.* [99]	4	12	Aortic occlusion + epinephrine
	4	12	Epinephrine
Berg RA, *et al.* [100]	15	16	High-dose epinephrine
	15	16	Standard-dose epinephrine
Killingsworth CR, *et al.* [101]	8	9	B blocker
Cairns CB, *et al.* [102]	14	8	Epinephrine
Rubertsson S, *et al.* [103]	8	11	Aortic occlusion + epinephrine
	8	11	Epinephrine IV
Wenzel V, *et al.* [104]	6	7	Vasopressin IV
	6	7	Intraosseous vasopressin
Jasani MS, *et al.* [105]	36	9	Epinephrine
Rubertsson S, *et al.* [106]	22	9	Epinephrine
Wenzel V, *et al.* [107]	12	7	Epinephrine
Wenzel V, *et al.* [108]	8	18	Vasopressin
Voelckel WG, *et al.* [109]	6	7	Vasopressin
	6	7	Epinephrine
Hoekstra JW, *et al.* [110]	7	13	Norepinephrine
	7	13	Epinephrine
Leong EC, *et al.* [111]	11	11	Epinephrine
	12	10	Epinephrine
Kornberger E, *et al.* [112]	6	7	Epinephrine
Schwarz B, *et al.* [113]	8	18	Vasopressin
Krismer AC, *et al.* [114]	6	9	Epinephrine
	6	9	Epinephrine + novel K^+ channel blocker
Nozari A, *et al.* [115]	10	7	Aortic occlusion + vasopressin
	10	7	Vasopressin
Voelckel WG, *et al.* [116]	6	16	Epinephrine
	6	16	Vasopressin
	6	16	Vasopressin + epinephrine
Roberts D, *et al.* [117]	6	3	Novel α_1-agonist
	6	3	Standard-dose epinephrine
	6	3	High-dose epinephrine
Prengel AW, *et al.* [118]	7	7	Epinephrine
	7	7	Vasopressin
Brunette DD, *et al.* [119]	10	15	Standard-dose epinephrine
	10	15	High-dose epinephrine
Klouche K, *et al.* [120]	7	9	Novel α_2-agonist
	7	9	Epinephrine
Hornchen U, *et al.* [121]	8	3	Standard-dose epinephrine
	8	3	High-dose epinephrine
Wenzel V, *et al.* [122]	6	7	Epinephrine
	6	7	Vasopressin

Study	Number of subjects	Time to drug Administration	First Medication Received
	6	12	Epinephrine
	6	12	Vasopressin
Bar-Joseph G, *et al.* [123]	38	17	Epinephrine
Hoekstra JW, *et al.* [124]	10	13	Epinephrine
Angelos MG, *et al.* [125]	8	10	Epinephrine
Hilwig RW, *et al.* [126]	10	8	Endothelin-1 + epinephrine
	17	8	Epinephrine
DeBehnke DJ, *et al.* [127]	5	13	Endothelin-1
	6	13	Epinephrine
Kornberger E, *et al.* [128]	7	7	Epinephrine
	7	7	Vasopressin
Mulligan KA, *et al.* [129]	11	8	Epinephrine
	7	8	Vasopressin
	11	8	Epinephrine + vasopressin
Gedeborg R, *et al.* [130]	13	10	Aortic occlusion + epinephrine
	13	10	Epinephrine
Babar SI, *et al.* [131]	17	8	Epinephrine
	18	8	Vasopressin
Hornchen U, *et al.* [132]	8	3	Epinephrine
	8	3	Endobronchial epinephrine
Lindner KH, *et al.* [133]	7	7	Angiotensin II
Kern KB, *et al.* [134]	16	12.5	Epinephrine
	16	12.5	Vasopressin
	16	12.5	Vasopressin
Hornchen, U, *et al.* [135]	8	3	Epinephrine IV
	8	3	Endobronchial epinephrine
Schindler I, *et al.* [136]	26	10	Epinephrine
Hornchen U, *et al.* [137]	16	3	Epinephrine
Hornchen U, *et al.* [138]	10	3	Norepinephrine IV
	10	3	Endotracheal norepinephrine
Hornchen U, *et al.* [139]	26	3	Epinephrine IV
	18	3	Endotracheal epinephrine
Liu XL, *et al.* [140]	10	10	Aortic occlusion + Vasopressin
	10	10	Aortic occlusion + epinephrine
	10	10	Epinephrine
Manning JE, *et al.* [141]	12	12	Epinephrine