

WORKSHEET for PROPOSED Evidence-Based GUIDELINE RECOMMENDATIONS

Worksheet Author: 	Taskforce/Subcommittee: __BLS __ACLS __PEDS __ID __PROAD <input checked="" type="checkbox"/> (NRP) Other:
Author's Home Resuscitation Council: <input checked="" type="checkbox"/> AHA __ANZCOR __CLAR __ERC __HSFC __HSFC __RCSA __IAHF __Other:	Date Submitted to Subcommittee: 5-28-04; revised 9-28-04 and 11-03-04

STEP 1: STATE THE PROPOSAL. State if this is a proposed new guideline; revision to current guideline; or deletion of current guideline.

Existing guideline, practice or training activity, or new guideline:

Existing Guideline

Epinephrine is indicated when the heart rate remains below 60 bpm after you have given 30 seconds of assisted ventilation and another 30 seconds of coordinated chest compressions and ventilation.

NRP

p. 6-7. The recommended dose in newborns is 0.1 to 0.3 mL/kg of a 1:10,000 solution (equal to 0.01 to 0.03 mg/kg) given rapidly. The recommended route is by endotracheal tube or intravenously. The endotracheal route may be associated with lower blood levels of the drug. Therefore, you might consider using the higher end of the dosage range when using this route. When giving epinephrine by endotracheal tube, be sure to give the drug directly into the tube, being careful not to leave it deposited in the endotracheal tube connector or adhered to the walls of the tube. Some people prefer to use a catheter to give the drug deeply into the tube. Whether the drug is given through an endotracheal tube or catheter, you may decide to flush the drug in with 0.5 to 1.0 mL of normal saline. You should follow the drug with several deep, positive-pressure breaths to distribute the drug throughout the lungs for absorption.

ILCOR

4.5.3.1. The recommended intravenous or endotracheal dose is 0.1-0.3 ml/kg of a 1:10,000 solution (0.01-0.03 mg/kg), repeated every 3-4 min as indicated.

Naloxone is indicated for a newborn if there is severe respiratory depression after positive-pressure ventilation has restored a normal heart rate and color AND there is a history of maternal narcotic administration within the past 4 hours

NRP

p. 7-3 The recommended dose is 0.1 mg/kg of 1.0 mg/ml solution via the preferred route of endotracheal or intravenous or acceptable routes of intramuscular or subcutaneous.

ILCOR

The recommended dose is 0.1 mg/kg of a 0.4 or 1.0 mg/ml solution given intravenously, endotracheally, or intramuscularly.

Step 1A: Refine the question; state the question as a positive (or negative) hypothesis. State proposed guideline recommendation as a specific, positive hypothesis. Use single sentence if possible. Include type of patients; setting (in-/out-of-hospital); specific interventions (dose, route); specific outcomes (ROSC vs. hospital discharge).

0.01 mg/kg of endotracheal epinephrine followed by 0.5-1cc NS flush is effective in establishing ROSC in newborns with HR < 60 beats per minute despite 30 seconds of assisted ventilation and another 30 seconds of coordinated chest compressions and ventilation.

And

0.1 mg/kg of endotracheal naloxone followed by 0.5-1cc NS flush is effective in reversal of respiratory depression for a newborn if there is severe respiratory depression after positive-pressure ventilation has restored a normal heart rate and color AND there is a history of maternal narcotic administration within the past 4 hours (**the # sign will be used to designate studies evaluating endotracheal naloxone**).

Step 1B: Gather the Evidence; define your search strategy. Describe search results; describe best sources for evidence.

List electronic databases searched (at least AHA EndNote 7 Master library [<http://ecc.heart.org/>], Cochrane database for systematic reviews and Central Register of Controlled Trials [<http://www.cochrane.org/>], MEDLINE

[<http://www.ncbi.nlm.nih.gov/PubMed/>], and Embase), and hand searches of journals, review articles, and books.

Medline (1966-2004), PubMed, Cochrane Database, and hand searches of journals and review articles

- State major criteria you used to limit your search; state inclusion or exclusion criteria (e.g., only human studies with control group? no animal studies? N subjects > minimal number? type of methodology? peer-reviewed manuscripts only? no abstract-only studies?)

Excluded non-English language

Search terms: newborn resuscitation, neonatal, newborn, epinephrine, adrenaline, naloxone, endotracheal, endobronchial, cardiopulmonary resuscitation

Search terms were combined in the following manner newborn resuscitation and epinephrine (n=103), newborn resuscitation and adrenaline (n=87), newborn resuscitation and naloxone (n=23), newborn resuscitation and endotracheal (n=333), neonatal and epinephrine (n=1719), neonatal and adrenaline (n=1602), neonatal and naloxone (n=350), neonatal and endotracheal (n=1236), neonatal and endobronchial (n=46), neonatal and cardiopulmonary resuscitation (n=506), newborn and epinephrine (n=2433), newborn and adrenaline (n=2299), newborn and naloxone (n=467), newborn and endotracheal (n=1246), newborn and endobronchial (n=51), newborn and cardiopulmonary resuscitation (n=2).

- Number of articles/sources meeting criteria for further review: Create a citation marker for each study (use the author initials and date or Arabic numeral, e.g., "Cummins-1"). If possible, please supply file of best references; EndNote 6+ required as reference manager using the ECC reference library.
52 articles reviewed

Best References: Barton-1998, Chernow-1984, Crespo-1991, DeBehenke-1994, Greenberg-1981, Greenberg-1982, Greenberg-1980, Greenberg 1984a, Greenberg-1984b, Greenberg-1988, Hasegawa-1986, Hornchen-1987, Jasani-1994, Jonmarker-1996, Johnston-1992, Kleinman-1999, Liebman-1997, Lindemann-1982, Lindemann-1984, Lucas-1994, Manisterski-2002, Marchant-1987, Mazkereth-1992, McCrerrick-1992, Mielke-1994, Mielke-1998, Mullet-1992, Niemann-1999, Niemann-2000, Niemann-2002, Naganobu-2000, Orłowski-1990, Paret-1997, Polin-1986, Quinton-1987, Raehl-1986, Ralston-1984, Ralston-1985, Raymondos-2000, Redding-1967, Roberts-1978, Roberts-1979a, Roberts-1979b, Schwab-1994, Tandberg-1982, Vaknin-2001, Weil-2000, Wyckoff-2001, Yang-1991, Zaritsky-1988, Zaritsky-1994, Ziino-2003

STEP 2: ASSESS THE QUALITY OF EACH STUDY

Step 2A: Determine the Level of Evidence. For each article/source from step 1, assign a level of evidence—based on study design and methodology.

Level of Evidence	Definitions (See manuscript for full details)
Level 1	Randomized clinical trials or meta-analyses of multiple clinical trials with substantial treatment effects
Level 2	Randomized clinical trials with smaller or less significant treatment effects
Level 3	<u>Prospective</u> , controlled, non-randomized, cohort studies
Level 4	<u>Historic</u> , non-randomized, cohort or case-control studies
Level 5	<u>Case series</u> : patients compiled in serial fashion, lacking a control group
Level 6	Animal studies or mechanical model studies
Level 7	Extrapolations from existing data collected for other purposes, theoretical analyses
Level 8	Rational conjecture (common sense); common practices accepted before evidence-based guidelines

Step 2B: Critically assess each article/source in terms of research design and methods.

Was the study well executed? Suggested criteria appear in the table below. Assess design and methods and provide an overall rating. Ratings apply within each Level; a Level 1 study can be excellent or poor as a clinical trial, just as a Level 6 study could be excellent or poor as an animal study. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study. For more detailed explanations please see attached assessment form.

Component of Study and	Excellent	Good	Fair	Poor	Unsatisfactory
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Rating					
Design & Methods	Highly appropriate sample or model, randomized, proper controls AND Outstanding accuracy, precision, and data collection in its class	Highly appropriate sample or model, randomized, proper controls OR Outstanding accuracy, precision, and data collection in its class	Adequate, design, but possibly biased OR Adequate under the circumstances	<i>Small or clearly biased population or model</i> OR <i>Weakly defensible in its class, limited data or measures</i>	<i>Anecdotal, no controls, off target end-points</i> OR <i>Not defensible in its class, insufficient data or measures</i>

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint

B = Survival of event D = Intact neurological survival

Step 2C: Determine the direction of the results and the statistics: supportive? neutral? opposed?

DIRECTION of study by results & statistics:	SUPPORT the proposal	NEUTRAL	OPPOSE the proposal
Results	Outcome of proposed guideline superior, to a clinically important degree, to current approaches	Outcome of proposed guideline no different from current approach	Outcome of proposed guideline inferior to current approach

Step 2D: Cross-tabulate assessed studies by a) level, b) quality and c) direction (ie, supporting or neutral/ opposing); **combine and summarize.** Exclude the *Poor* and *Unsatisfactory* studies. Sort the *Excellent*, *Good*, and *Fair* quality studies by both *Level and Quality of evidence*, and *Direction of support* in the summary grids below. Use citation marker (e.g. author/ date/source). In the *Neutral* or *Opposing* grid use bold font for *Opposing* studies to distinguish them from merely neutral studies. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study.

Supporting Evidence

0.01 mg/kg of endotracheal epinephrine followed by 0.5-1cc NS flush is effective in establishing ROSC in newborns with HR < 60 per minute despite 30 seconds of assisted ventilation and another 30 seconds of coordinated chest compressions and ventilation.

0.1 mg/kg of endotracheal naloxone followed by 0.5-1cc NS flush is effective in reversal of respiratory depression for a newborn if there is severe respiratory depression after positive-pressure ventilation has restored a normal heart rate and color AND there is a history of maternal narcotic administration within the past 4 hours

Quality of Evidence	Excellent								
	Good						*Jasani-1994 ^A		
	Fair			<i>*Schwab-1994</i>		<i>*Lindemann-1984^A</i>	*Chernow-1984 ^E Greenberg-1982 ^E *Hornchen-1987 ^{A&B} <i>Lucas-1994^E</i> *Mielke-1998 ^E Paret-1992 ^E *Ralston-1984 ^{A&E} *Ralston-1985 ^A *Redding-1967 ^E *Roberts-1978 ^E *Yang-1991 ^{B&E} # Greenberg-1980 ^E		
	1	2	3	4	5	6	7	8	
Level of Evidence									

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
B = Survival of event D = Intact neurological survival
Italics-denote neonatal subjects or model
*denotes used higher endotracheal dose than currently recommended
indicates study involving naloxone (adult model)

Neutral or Opposing Evidence

0.01 mg/kg of endotracheal epinephrine followed by 0.5-1cc NS flush is effective in establishing ROSC in newborns with HR < 60 per minute despite 30 seconds of assisted ventilation and another 30 seconds of coordinated chest compressions and ventilation.

0.1 mg/kg of endotracheal naloxone followed by 0.5-1cc NS flush is effective in reversal of respiratory depression for a newborn if there is severe respiratory depression after positive-pressure ventilation has restored a normal heart rate and color AND there is a history of maternal narcotic administration within the past 4 hours

Quality of Evidence	Excellent								
	Good						<i>Kleinman-1999^{A&E}</i>		
	Fair	<i>Ziino-2003^A</i>	<i>Jonmarker-1996^E</i> <i>*McCrirrick-1996^E</i> <i>Quinton-1987^{A,C,E}</i>	<i>Raymondos-2000^E</i>	<i>Niemann-2000^A</i> <i>Niemann-2002^{A&C}</i>	<i>*Crespo-1991^E</i> <i>Manisterski-2002^E</i> <i>Mazkereth-1992^E</i> <i>Naganobu-2000^E</i> <i>Orlowski-1990^E</i> <i>Roberts-1979a^E</i> <i>*Vaknin-1990^E</i>	<i>Mullet-1992^E</i>		

		1	2	3	4	5	6	7	8
Level of Evidence									

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint

B = Survival of event D = Intact neurological survival

Italics denotes neonatal subjects or model

*denotes used higher endotracheal dose than currently recommended

indicates study involving naloxone (adult model)

Bold print indicates opposing evidence (as opposed to neutral)

STEP 3. DETERMINE THE CLASS OF RECOMMENDATION. Select from these summary definitions.

CLASS	CLINICAL DEFINITION	REQUIRED LEVEL OF EVIDENCE
Class I <i>Definitely recommended.</i> Definitive, excellent evidence provides support.	<ul style="list-style-type: none"> • Always acceptable, safe • Definitely useful • Proven in both efficacy & effectiveness • Must be used in the intended manner for proper clinical indications. 	<ul style="list-style-type: none"> • One or more Level 1 studies are present (with rare exceptions) • Study results consistently positive and compelling
Class II: <i>Acceptable and useful</i>	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Not yet confirmed definitively 	<ul style="list-style-type: none"> • Most evidence is positive • Level 1 studies are absent, or inconsistent, or lack power • No evidence of harm
• Class IIa: <i>Acceptable and useful</i> Good evidence provides support	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered treatments of choice 	<ul style="list-style-type: none"> • Generally higher levels of evidence • Results are consistently positive
• Class IIb: <i>Acceptable and useful</i> Fair evidence provides support	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered optional or alternative treatments 	<ul style="list-style-type: none"> • Generally lower or intermediate levels of evidence • Generally, but not consistently, positive results
Class III: <i>Not acceptable, not useful, may be harmful</i>	<ul style="list-style-type: none"> • Unacceptable • Not useful clinically • May be harmful. 	<ul style="list-style-type: none"> • No positive high level data • Some studies suggest or confirm harm.
Indeterminate	<ul style="list-style-type: none"> • Research just getting started. • Continuing area of research • No recommendations until further research 	<ul style="list-style-type: none"> • Minimal evidence is available • Higher studies in progress • Results inconsistent, contradictory • Results not compelling

STEP 3: DETERMINE THE CLASS OF RECOMMENDATION. State a **Class of Recommendation** for the Guideline Proposal. State either **a) the intervention**, and then the conditions under which the intervention is either Class I, Class IIA, IIB, etc.; or **b) the condition**, and then whether the intervention is Class I, Class IIA, IIB, etc.

Indicate if this is a **Condition** or **Intervention: Final Class of recommendation:** **Class I-Definitely Recommended** **Class IIa-Acceptable & Useful; good evidence** **Class IIb-Acceptable & Useful; fair**

evidence Class III – Not Useful; may be harmful X Indeterminate-minimal evidence or inconsistent

Use 0.01 mg/kg epinephrine with 0.5-1.0 cc normal saline flush via the endotracheal route for heart rate < 60 bpm despite 30 seconds of effective ventilation and an additional 30 seconds of ventilation + cardiac compressions in the neonate

Use 0.1 mg/kg naloxone with 0.5-1.0 normal saline flush via the endotracheal route for opiate-induced respiratory depression in the neonate

REVIEWER'S PERSPECTIVE AND POTENTIAL CONFLICTS OF INTEREST: Briefly summarize your professional background, clinical specialty, research training, AHA experience, or other relevant personal background that define your perspective on the guideline proposal. List any potential conflicts of interest involving consulting, compensation, or equity positions related to drugs, devices, or entities impacted by the guideline proposal. Disclose any research funding from involved companies or interest groups. State any relevant philosophical, religious, or cultural beliefs or longstanding disagreements with an individual.

Assistant Professor of Pediatrics in the Division of Neonatology. In charge of resuscitation team at academic hospital with >16,000 deliveries annually, NRP instructor, research interests in newborn resuscitation

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK: Summarize your final evidence integration and the rationale for the class of recommendation. Describe any mismatches between the evidence and your final Class of Recommendation. "Mismatches" refer to selection of a class of recommendation that is heavily influenced by other factors than just the evidence. For example, the evidence is strong, but implementation is difficult or expensive; evidence weak, but future definitive evidence is unlikely to be obtained. Comment on contribution of animal or mechanical model studies to your final recommendation. Are results within animal studies homogeneous? Are animal results consistent with results from human studies? What is the frequency of adverse events? What is the possibility of harm? Describe any value or utility judgments you may have made, separate from the evidence. For example, you believe evidence-supported interventions should be limited to in-hospital use because you think proper use is too difficult for pre-hospital providers. Please include relevant key figures or tables to support your assessment.

The current recommendations regarding use of 0.01 mg/kg epinephrine with 0.5-1.0 cc normal saline flush via the endotracheal route for heart rate < 60 bpm despite 30 seconds of effective ventilation and an additional 30 seconds of ventilation + cardiac compressions in the neonate are **indeterminate** because there are no randomized trials using endotracheal epinephrine in neonates. The one neonatal reported cohort trial (Schwab-1994) and one neonatal case series (Lindemann-1984) that showed benefit used 10 times the currently recommended dose. In fact, almost every animal trial (most were adult cardiac arrest models) that showed any positive effect of endotracheal epinephrine used 5-10 times the currently recommended dose. The one neonatal model trial that used the currently recommended dose showed no benefit (Kleinman-1999).

The current recommendation of 0.5-1.0 cc normal saline as the diluent for endotracheal epinephrine is **indeterminate** because there are no trials in neonates or neonatal models examining the issue of volume or type of diluent. In adult models the evidence is conflicting with 2 trials reporting distilled water as advantageous compared to normal saline (Redding-1967, Naganobou-2000), one reporting normal saline as beneficial compared to distilled water (Greenberg-1982), and one reporting no difference between the two (Yang-1991).

The current recommendation regarding the dose of endotracheal naloxone is **indeterminate** as there are no human adult or neonatal trials examining the endotracheal naloxone use. The one small adult animal trial (Greenberg-1980) used the currently recommended dose and showed benefit.

Preliminary draft/outline/bullet points of Guidelines revision: Include points you think are important for inclusion by the person assigned to write this section. Use extra pages if necessary.

Attachments:

Bibliography in electronic form using the Endnote Master Library. It is recommended that the bibliography

be provided in annotated format. This will include the article abstract (if available) and any notes you would like to make providing specific comments on the quality, methodology and/or conclusions of the study.

Citation List

Citation Marker	Full Citation*
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Chernow – 1984	<p>Chernow, B., P. Holbrook, et al. (1984). "Epinephrine absorption after intratracheal administration." <i>Anesth Analg</i> 63(9): 829-32.</p> <p>Tracheal intubation during cardiopulmonary resuscitation often precedes establishment of an intravenous route for the administration of drugs. To determine the efficacy of intratracheal administration of drugs during cardiopulmonary resuscitation we measured plasma catecholamine levels and hemodynamic responses to intratracheal epinephrine (EPI) administration using a double-blind, randomized crossover design in 7 male baboons (<i>Papio anubis</i>), each studied twice, who received 5 ml of 1:10000 EPI on one day and 5 ml of 0.9% NaCl on another day. Arterial blood samples for measurement of plasma EPI and norepinephrine (NE) concentrations were collected, and heart rate (HR) and mean arterial blood pressure (MAP) were measured before and 1, 2, 4, 8, 16, and 30 min after intratracheal drug administration. Intratracheal EPI significantly (<i>P</i> less than 0.05) elevated HR to 120 +/- 6 from 105 +/- 6 beats/min, MAP to 120 +/- 4 from 112 +/- 5 mm Hg, and plasma EPI to 8882 +/- 2143 from 928 +/- 209 pg/ml within 1 min of administration, and these effects persisted for 30 min. Plasma NE levels did not change after intratracheal EPI administration. None of the four variables changed after intratracheal saline was given. We conclude that in subhuman primates, intratracheal EPI is rapidly absorbed and is an effective pressor agent when given by this route; and that these data lend support to the clinical practice of intratracheal EPI administration during cardiac arrest or in the treatment of shock.</p> <p><u>Critique</u></p> <p><i>Methodology: Double-blind, randomized cross-over design of 0.5 mg epinephrine compared to saline</i></p> <p><i>Participants: 7 male baboons; each studied twice</i></p> <p><i>Outcomes: plasma epinephrine levels, heart rate (HR), mean arterial pressure (MAP)</i></p> <p><i>Outcome designation: E</i></p> <p><i>Findings: endotracheal. epinephrine was rapidly absorbed (1 min) and increased the MAP and HR</i></p> <p><i>Comments: Not an arrest model, no weights given so actual dose per kg is unclear</i></p> <p><i>Level of Evidence: 6</i></p> <p><i>Quality: Fair</i></p>
Crespo-1991	<p>Crespo, S. G., J. M. Schoffstall, et al. (1991). "Comparison of two doses of endotracheal epinephrine in a cardiac arrest model." <i>Ann Emerg Med</i> 20(3): 230-4.</p> <p>STUDY OBJECTIVE: The objective of this study was to measure plasma catecholamine levels and the cardiovascular response before and after endotracheal administration of epinephrine in a swine cardiac arrest</p>

<p>Greenberg-1980</p>	<p>model. DESIGN: Prospective, controlled laboratory investigation. TYPE OF PARTICIPANTS: Twenty-one swine weighing 10 to 12 kg, anesthetized with ketamine and alpha-chloralose and ventilated with room air. INTERVENTIONS: Ventricular fibrillation was induced with 90 V of 60 Hz current delivered to the right ventricle by transvenous pacemaker. Blood samples for epinephrine were drawn before arrest and every two minutes thereafter. At five minutes, external mechanical cardiac compressions were initiated. Nine animals received no further therapy and served as controls. Two groups of six animals received either 0.01 mg/kg or 0.1 mg/kg of epinephrine through the endotracheal tube at ten and 20 minutes. Blood samples were assayed for epinephrine. MEASUREMENTS: Arterial blood pressure, lead II ECG, and plasma epinephrine. MAIN RESULTS: Swine receiving epinephrine 0.01 mg/kg had an increase in epinephrine levels after drug administration, but these were not significantly different from control levels. The 0.1-mg/kg dose group had a significant increase in plasma epinephrine levels compared with controls and the 0.01-mg/kg dose group after receiving epinephrine at ten and 20 minutes. These increases were from 14 +/- 3 to 215 +/- 40 ng/mL (+/- SEM) at 12 minutes after arrest and from 151 +/- 56 to 402 +/- 80 ng/mL at 22 minutes after arrest. CONCLUSION: These data suggest that standard dosing of epinephrine through the endotracheal tube during arrest does not produce significant increases in plasma catecholamines or blood pressure. Epinephrine 0.1 mg/kg produces a significant increase in plasma epinephrine levels, but it is not sufficient to produce a significant change in blood pressure.</p> <p><u>Critique</u></p> <p><i>Methodology: Non-randomized, unblinded animal trial of no drug versus 0.01 mg/kg versus 0.1 mg/kg of Epinephrine via endotracheal (ET) tube during CPR for 5 minutes of cardiac (V-fib) arrest. No sample size calculations.</i></p> <p><i>Participants: 10-12 kg piglets</i></p> <p><i>Outcomes: arterial blood pressure (BP) (mean and diastolic), lead II ECG, plasma epinephrine levels</i></p> <p><i>Outcome designation: E</i></p> <p><i>Findings: BP and epinephrine levels did not differ between the 0.01 mg/kg dose and no drug. 0.1 mg/kg dose caused increased drug levels but no sustained improvement in mean arterial blood pressure or diastolic BP.</i></p> <p><i>Comments:</i></p> <p><i>Level of Evidence: 6</i></p> <p><i>Quality: Fair</i></p> <p><i>Evidence: AGAINST Current dosing recommendation</i></p> <p>Greenberg, M. I., J. R. Roberts, et al. (1980). "Endotracheal naloxone reversal of morphine-induced respiratory depression in rabbits." <u>Ann Emerg Med</u> 9(6): 289-92.</p>
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<p>Greenberg-1982</p>	<p>In an emergency, intravenous access may be difficult to obtain rapidly. Alternate routes of administration for drugs are, therefore, desirable. Our study was performed to determine if naloxone could be efficacious in reversing morphine-induced respiratory depression in rabbits when administered using the endotracheal route. Our results indicate that naloxone administered in this fashion is effective in reversing morphine-induced respiratory depression in the rabbit. Mean minute ventilation was depressed to greater than half of resting baseline levels using morphine sulfate. Endotracheally administered naloxone reversed this respiratory depression and resulted in a greater than five-fold increase in mean minute ventilation above baseline levels. We concluded that endotracheal naloxone is efficacious in reversing morphine-induced respiratory depression in the rabbit. The endotracheal route may be an effective alternative for naloxone administration in man when rapid intravenous access is not obtainable.</p> <p><u>Critique</u> <i>Methodology: Case series of animals with opiate induced respiratory depression who received 0.1 mg/kg naloxone via an endotracheal tube.</i> <i>Participants: 4 adult rabbits</i> <i>Outcomes: Minute ventilation</i> <i>Outcome Designation: E</i> <i>Findings: All four had reversal of respiratory depression with endotracheal naloxone</i> <i>Comments: Adult animals, correct dose</i> <i>Level of evidence: 6</i> <i>Quality: poor/fair</i> <i>Evidence: Supports</i></p> <p>Greenberg, M. I., S. I. Baskin, et al. (1982). "Effects of endotracheally administered distilled water and normal saline on the arterial blood gases of dogs." <u>Ann Emerg Med</u> 11(11): 600-4.</p> <p>The effects of endotracheally (ET) administered distilled water (DW) and normal saline solution (NSS) on the arterial blood gases of dogs were compared. When distilled water was administered endotracheally, arterial pH was depressed to 99.36% of baseline values within 5 minutes. When compared to pH changes following ET administration of NSS the depression of pH following DW administration was significant (P less than .05). Following ET injection of DW, arterial PO₂ was depressed to 61% of baseline values and remained significantly depressed throughout the experiment. In comparison, following ET NSS administration, PO₂ was depressed substantially less, and remained at significantly higher levels for the entire experiment. In dogs, administration of NSS by the ET route produces less detrimental effects on arterial blood gases than does the ET administration of DW. This may have implications for the choice of diluent for human drug administration using the ET route.</p> <p><u>Critique</u></p>
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<p>Hornchen-1987</p>	<p><i>Methodology: Non-randomized cross-over design of 2 ml/kg of NS or sterile water via ET tube.</i></p> <p><i>Participants: 8 adult mongrel dogs (8-13 kg)</i></p> <p><i>Outcomes: pH, PaCO₂, PaO₂</i></p> <p><i>Outcome Designation: E</i></p> <p><i>Findings: normal saline via ET tube produced less detrimental effects on PaO₂ and pH than sterile water</i></p> <p><i>Comments: These are BIG volumes relative to what is used as diluent even in adults (16-26 cc). Unclear why they chose this volume rather than the 5-10 ml recommended in adult ACLS.</i></p> <p><i>Level of Evidence: 6</i></p> <p><i>Quality: Fair</i></p> <p><i>Evidence: Supports (NRP recommendation to use normal saline for diluent)</i></p>
<p>Jasani-1994</p>	<p>Hornchen, U., J. Schuttler, et al. (1987). "Endobronchial instillation of epinephrine during cardiopulmonary resuscitation." <u>Crit Care Med</u> 15(11): 1037-39.</p> <p>We used a standard animal CPR model to study the effectiveness and hemodynamic response of 100 micrograms/kg epinephrine administered endobronchially and to compare the findings after conventional iv administration. Results showed that the endobronchial and iv epinephrine medication improved the survival rate by 100% compared to that of a control group receiving no medication. Although the hemodynamic conditions during cardiac compression were not significantly different after both routes of drug administration, endobronchial instillation produced a prolonged drug action during the first hour of restored spontaneous circulation. A more extensive use of this type of drug administration, especially in out-of-hospital resuscitation, is suggested.</p> <p><u>Critique</u></p> <p><i>Methodology: Non-randomized, non-blinded, animal trial comparing 0.01 mg/kg i.v. to 0.1 mg/kg endobronchial</i></p> <p><i>Participants: 24 adolescent pigs (18-23 kg) in V-fib</i></p> <p><i>Outcomes: ROSC, survival of event</i></p> <p><i>Outcome Designation: A & B</i></p> <p><i>Findings: Endobronchial as effective as i.v and had more prolonged drug action</i></p> <p><i>Comments: Endobronchial rather than direct injection into ET tube, cardiac arrest model</i></p> <p><i>Level of Evidence: 6</i></p> <p><i>Quality: Fair</i></p> <p><i>Evidence: Supports use of ET route but dose is 10X that recommended by ILCOR</i></p> <p>Jasani, M. S., V. M. Nadkarni, et al. (1994). "Effects of different techniques of endotracheal epinephrine administration in pediatric</p>

<p>Jonmarker-1996</p>	<p>porcine hypoxic-hypercarbic cardiopulmonary arrest." <u>Crit Care Med</u> 22(7): 1174-80.</p> <p>OBJECTIVE: To compare three endotracheal epinephrine instillation techniques in a pediatric porcine hypoxic-hypercarbic cardiopulmonary arrest model. DESIGN: Prospective, randomized, laboratory comparison of three instillation techniques. SETTING: Large animal research facility at a children's hospital. SUBJECTS: Thirty-six preadolescent anesthetized and paralyzed Yucatan swine (mean weight 10.0 +/- 1.9 kg) with apnea-induced hypoxic and hypercarbic cardiopulmonary arrest. INTERVENTIONS: After 8 minutes of cardiopulmonary arrest and 1 minute of cardiopulmonary resuscitation (CPR), 500 micrograms (51 +/- 9 micrograms/kg) of radiolabeled endotracheal epinephrine was administered by direct injection (n = 17), injection via feeding catheter (n = 10), or via monitoring lumen built into the sidewall of the endotracheal tube (n = 9). CPR was resumed and continued for 5 minutes. If resuscitation occurred, monitoring was continued for 1 hr. Outcome variables included successful resuscitation, pulmonary distribution, heart rate, mean arterial pressure, plasma radiolabeled epinephrine counts, and total plasma epinephrine concentrations. Analysis by Fisher's exact test, one-way analysis of variance and Pearson's phi coefficient was performed. MEASUREMENTS AND MAIN RESULTS: Successful resuscitation occurred in 31% of all pigs with no difference between groups (p = .69). Bilateral distribution occurred in 39% with no difference between groups (p = .25). No correlation was noted between successful resuscitation and distribution (p = .65). HR, mean arterial pressure, plasma radiolabeled epinephrine counts, and total plasma epinephrine concentrations showed significant changes over time within groups, but no difference between groups at any time point. Adherence of the epinephrine dose to the endotracheal tube was < or = 1.5% in all cases. CONCLUSIONS: Instillation of 50 micrograms/kg of endotracheal epinephrine by three different techniques during pediatric porcine asphyxial arrest does not affect resuscitation rate, pulmonary distribution, hemodynamic response, or plasma exogenous and total epinephrine concentrations. No correlation was found between successful resuscitation and bilateral distribution. Therefore, currently recommended cumbersome endotracheal epinephrine instillation techniques may offer no resuscitation advantage over commonly used direct injection in this setting.</p> <p><u>Critique</u></p> <p><i>Methodology: Prospective, randomized lab comparison of 0.05mg/kg epinephrine directly injected into ET tube versus injection via a feeding catheter in the ET tube or via monitoring lumen built into the sidewall of ET tube</i></p> <p><i>Participants: Preadolescent Yucatan Swine</i></p> <p><i>Outcomes: ROSC (secondary outcomes HR, MAP, radiolabeled epinephrine counts and total plasma epinephrine concentrations</i></p>
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<p>Kleinman-1999</p>	<p><i>Outcome Designation: A</i> <i>Findings: No difference in ROSC between groups or other outcomes therefore recommend direct injection since it is the simplest</i> <i>Comments: Good model for neonates (hypoxic and hypercarbic)</i> <i>Level of Evidence: 6</i> <i>Quality: Good</i> <i>Evidence: Supports (although NRP currently recommends direct or via feeding tube)</i></p> <p>Jonmarker, C., A. K. Olsson, et al. (1996). "Hemodynamic effects of tracheal and intravenous adrenaline in infants with congenital heart anomalies." <i>Acta Anaesthesiol Scand</i> 40(8 Pt 1): 927-31.</p> <p>BACKGROUND: If intravenous access cannot be accomplished during cardiopulmonary resuscitation in children, tracheal administration of 100 micrograms/kg of adrenaline (ten times greater than the intravenous dose) is recommended. METHODS: In a randomized crossover study we recorded the hemodynamic effect of a low dose of intravenous adrenaline and a ten times greater tracheal dose. While anesthetized for open heart surgery, fourteen infants received one dose of adrenaline intravenously (0.3 microgram/kg) and the other tracheally (3 micrograms/kg). RESULTS: During the first 5 minutes after administration mean arterial pressure (MAP) and heart rate (HR) increased after both intravenous and tracheal administration (P < 0.001). The maximum increase in MAP was 28% (17-68%, median and range) after intravenous injection and 20% (6-69%, P < 0.05 when compared to intravenous injection) after tracheal instillation. In four infants, MAP increased less than 10% after tracheal instillation. The maximum increases in MAP and HR occurred 1 min (1-2 min) after intravenous injection and 3 min (2-4 min) after tracheal instillation (P < 0.001). CONCLUSION: Tracheal administration 3 micrograms/kg adrenaline increased mean arterial blood pressure in infants with congenital cardiac anomalies, but the increase occurred later and was less consistent than after 0.3 microgram/kg of adrenaline given intravenously.</p> <p><u><i>Critique</i></u> <i>Methodology: Randomized, cross-over study of epinephrine 0.3 µg/kg i.v. versus 3 µg/kg ET tube</i> <i>Participants: 14 infants intubated for open heart surgery</i> <i>Outcomes: Mean arterial pressure (MAP), heart rate</i> <i>Outcome designation: E</i> <i>Findings: The higher dose via ET tube increased MAP compared to baseline but it took longer and was less consistent</i> <i>Comments: Smaller doses than currently recommended. Non-arrest paradigm.</i> <i>Level of Evidence: 2</i> <i>Quality: Fair</i> <i>Evidence: AGAINST (Epinephrine was absorbed from the airways but</i></p>
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<p>Lindemann-1984</p>	<p><i>that absorption was unreliable).</i></p> <p>Kleinman, M. E., W. Oh, et al. (1999). "Comparison of intravenous and endotracheal epinephrine during cardiopulmonary resuscitation in newborn piglets." <i>Crit Care Med</i> 27(12): 2748-54.</p> <p>OBJECTIVE: To compare the efficacy of intravenous and endotracheal epinephrine administration, and intravenous administration above and below the diaphragm, during cardiopulmonary resuscitation in newborn piglets. DESIGN: Prospective, randomized, experimental laboratory protocol. SETTING: Perinatal cardiovascular research laboratory at a university school of medicine. SUBJECTS: Forty newborn piglets (<i>Sus domesticus</i>). INTERVENTIONS: After cardiac arrest by ventricular fibrillation, cardiopulmonary resuscitation was begun. Radiolabeled epinephrine or placebo (0.9% sodium chloride) was administered into the right atrium, femoral vein, or endotracheal tube. Chest compressions and ventilation were continued for 10 mins. MEASUREMENTS AND MAIN RESULTS: After epinephrine or placebo administration, samples were obtained from the systemic arterial circulation for measurement of radioisotope activity and plasma epinephrine concentrations. Mean carotid arterial blood pressure, right atrial, and inferior vena caval pressures were measured continuously. Epinephrine administration via the right atrium and femoral vein resulted in significant increases in plasma epinephrine concentration, percent of radioisotope recovery, and mean carotid arterial blood pressure, whereas endotracheal epinephrine administration did not. Placebo administered into the femoral vein resulted in a significant increase in percent radioisotope recovery, but not in plasma epinephrine concentration or carotid arterial blood pressure. Endotracheal administration of placebo did not result in significant increases in plasma epinephrine concentration, percent radioisotope recovery, or carotid arterial blood pressure. There were no significant differences between right atrial or inferior vena caval pressures among the groups. CONCLUSIONS: During cardiopulmonary resuscitation in newborn piglets, intravenous administration of epinephrine is more efficacious than endotracheal administration. Furthermore, efficacy is similar between femoral venous and right atrial administration.</p> <p><u>Critique</u></p> <p><i>Methodology: Prospective, randomized trial of 0.01 mg/kg in 2 ml NS [3H]-epinephrine or placebo in right atria, femoral vein or ET tube</i></p> <p><i>Participants: Newborn piglets with cardiac arrest via V-fib</i></p> <p><i>Outcomes: epinephrine concentrations, BP</i></p> <p><i>Outcome Designation: E (secondary outcome A)</i></p> <p><i>Findings: ET tube epinephrine did not result in significant increase in plasma epinephrine concentration, radioisotope recovery or increased in mean carotid arterial BP. Endotracheal epinephrine was not different from placebo for ROSC.</i></p> <p><i>Comments: Disappointing that they used a neonatal model yet induced</i></p>
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<p>Lucas-1994</p>	<p><i>arrest via V-fib rather than asphyxia. Did use currently recommended dose of endotracheal epinephrine.</i> <i>Level of Evidence: 6</i> <i>Quality: Good</i> <i>Evidence: AGAINST</i></p> <p>Lindemann, R. (1984). "Resuscitation of the newborn. Endotracheal administration of epinephrine." <i>Acta Paediatr Scand</i> 73(2): 210-2. During cardiopulmonary resuscitation, when an intravenous line is not present or easily obtainable, the intracardiac injection of drugs has been a traditional route of choice. However, the intracardiac administration may be associated with serious complications. We have given epinephrine endotracheally to ten newborn infants who all had bradycardia that did not respond to ventilation with 100% oxygen, to heart compression or to bicarbonate infusion. Epinephrine, 0.1 mg/ml was injected directly into the tracheal tube, and ventilation was immediately continued. A standardized procedure has been chosen by giving 0.25 ml to the infants weighing less than 1 500 g, 0.5 ml to those weighing between 1 500 and 2 500 g, and 1.0 ml to those greater than 2 500 g. All infants had a return to normal heart rhythm within seconds after installation of the epinephrine solution. The establishment of an intravenous line in small infants can be difficult, and the infants are usually intubated before the injection of epinephrine is considered. The endotracheal route should therefore be the first route of choice in the absence of a rapidly obtainable vascular access.</p> <p><u>Critique</u> <i>Methodology: Case Series of 10 newborns who all received 0.1 mg/kg Epinephrine directly into ET tube following lack of response to ventilation with 100% oxygen, CPR or bicarbonate (?they had an i.v.?)</i> <i>Participants: 7 asphyxiated newborns with low Apgar scores and 3 preemies in the NICU with cardiovascular collapse.</i> <i>Outcomes: Resolution of bradycardia, survival</i> <i>Outcome Designation: A</i> <i>Findings: All responded with increased heart rate within 5-10 s after the epinephrine.</i> <i>Comments: All other reports show 1-3 minutes before response to ET tube epinephrine so was it the epinephrine that they responded to or improved ventilation?</i> <i>Level of Evidence: 5</i> <i>Quality: Fair (ok for case series)</i> <i>Evidence: SUPPORTS</i></p> <p>Lucas, V. W., Jr., M. P. Preziosi, et al. (1994). "Epinephrine absorption following endotracheal administration: effects of hypoxia-induced low pulmonary blood flow." <i>Resuscitation</i> 27(1): 31-4. To investigate the effects of hypoxia-induced decreased pulmonary</p>
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<p>Manisterski-2002</p>	<p>blood flow on the trans-pulmonary absorption of epinephrine, we measured pulmonary blood flow and arterial plasma tritium counts per minute following endotracheal [³H]-epinephrine administration in six chronically instrumented newborn lambs. The lambs were ventilated alternately with room air and with a hypoxic gas mixture sufficient to decrease pulmonary blood flow to approximately 50% of baseline values. Using this model, we found that hypoxia-induced low pulmonary blood flow did not lead to lower concentrations of epinephrine following endotracheal administration, but rather higher concentrations (P < 0.03). In all six lambs, counts per minute of tritium were higher following administration during low pulmonary blood flow. There was a negative correlation between pulmonary blood flow and arterial plasma tritium counts per minute (r = -0.64, P < 0.03). We conclude that trans-pulmonary absorption of epinephrine is not decreased during times of hypoxia-induced low pulmonary blood flow. These data lend support to the clinical practice of intratracheal epinephrine administration during neonatal resuscitation.</p> <p><u>Critique</u> <i>Methodology: Each lamb served as own control for absorption of ET tube [³H]- epinephrine (0.3 µg/kg bolus with 2 cc NS flush) with and without hypoxia-induced low pulmonary blood flow. The order of treatment was randomly assigned. No blinding.</i> <i>Participants: 6 chronically instrumented newborn lambs</i> <i>Outcomes: epinephrine levels</i> <i>Outcome designation: E</i> <i>Findings: [³H]- Epinephrine absorption was higher with low pulmonary blood flow compared to normal pulmonary blood flow</i> <i>Comments: They used a very small dose. Model is hypoxia but would have been better to have asphyxia.</i> <i>Level of Evidence: 6</i> <i>Quality: Fair</i> <i>Evidence: SUPPORTS</i></p>
<p>Mazkereth-1992</p>	<p>Manisterski, Y., Z. Vaknin, et al. (2002). "Endotracheal epinephrine: a call for larger doses." <i>Anesth Analg</i> 95(4): 1037-41.</p> <p>Endotracheal administration of epinephrine 0.02 mg/kg (twice the IV dose) is recommended when IV access is unavailable during cardiopulmonary resuscitation. The standard IV dose has been considered too small for the endotracheal route by causing a detrimental decrease of arterial blood pressure (BP), presumably mediated by the beta-adrenergic receptor unopposed by alpha adrenergic vasoconstriction. We conducted a prospective, randomized, laboratory comparison of increasing doses of endotracheal epinephrine to ascertain the yet undetermined optimal dose of endotracheal epinephrine that would increase BP. After injecting normal saline (control), saline-diluted epinephrine (0.02, 0.035, 0.1, 0.2,</p>

and 0.3 mg/kg) was injected into the endotracheal tube of five anesthetized dogs at least 1 wk apart. Arterial blood samples for blood gases were collected before and at 14 time points up to 60 min after the drug administration. Heart rate and arterial BP were continuously monitored with a polygraph recorder. Only the 0.3 mg/kg dose successfully caused an increase in BP, observed 2 min after administration, and lasting for 10 min. An early decrease in BP was obviated only at a dose equivalent to 10-fold the currently recommended one. IMPLICATIONS: We conducted a prospective, randomized, laboratory comparison of increasing doses of endotracheal epinephrine to ascertain the yet undetermined optimal dose of endotracheal epinephrine that would increase arterial blood pressure (BP). A decrease in BP was obviated only at a dose equivalent to 10-fold the currently recommended one. Clinical studies using larger doses of endotracheal epinephrine and their use as first-line therapy in cardiac arrest are warranted.

Critique

Methodology: Prospective, randomized, lab trial of increasing doses of ET tube epinephrine

Participants: Adult Mongrel Dogs

Outcomes: Primary outcome of blood pressure (Secondary outcomes ABG, HR)

Outcome designation: E

Findings: Only the 0.3 mg/kg ET tube dose produced an elevation in BP

Comments: Healthy, non-arrest model

Level of Evidence: 6

Quality: Fair

Evidence: AGAINST current recommended dose

Mazkereth, R., G. Paret, et al. (1992). "Epinephrine blood concentrations after peripheral bronchial versus endotracheal administration of epinephrine in dogs." Crit Care Med **20**(11): 1582-7.

BACKGROUND AND METHODS: Emergency endotracheal drug administration has become an acceptable route for drug delivery during cardiopulmonary resuscitation. The purpose of the present study was to determine whether the site of endotracheal epinephrine injection is an important factor in its absorption. Epinephrine (1:1000), in a dose of 0.02 mg/kg diluted in 2 mL of saline, was given to ten anesthetized mongrel dogs. Each dog was studied twice: once when the epinephrine was injected into the endotracheal tube, and on another day, through the endotracheal tube via a flexible catheter wedged into a peripheral bronchus. Arterial blood samples for plasma epinephrine concentration determinations were collected, before and at 1, 2, 5, 10, 15, and 30 mins after each intratracheal drug administration. RESULTS: Both routes of epinephrine administration significantly increased plasma concentrations within 1 min of injection. Higher plasma epinephrine concentrations were achieved after peripheral bronchial epinephrine administration (maximal

McCirrick-
1992

Mielke-1998	<p>concentration 8.9 +/- 3.2 vs. 2.0 +/- 0.4 ng/mL), and the total dose absorbed was significantly (76.5 +/- 13.5 vs. 36.7 +/- 6.5 ng/min/mL, p < .05) higher. The time interval to reach maximal concentration was significantly shorter with the peripheral bronchial dosing than with the endotracheal route (1.3 +/- 0.2 vs. 2.7 +/- 0.5 min, p < .05). Neither group demonstrated a significant change in heart rate and both had similar, minor decreases in BP for > 2 to 5 mins. There were no significant differences between the arterial blood gases of the two groups at various stages of the experiment. CONCLUSIONS: In dogs, epinephrine administered via the peripheral bronchial route has a clear pharmacologic advantage over the endotracheal route. This advantage may be more important during cardiopulmonary resuscitation conditions and other low flow states, and may account for the failure observed with the endotracheal route in recently published clinical reports.</p> <p><u>Critique</u> <i>Methodology: No sample size calculation, Randomized cross-over lab study of 0.02 mg/kg in 2 ml of NS either direct injection into the ET tube or endobronchially via catheter inserted through ET tube</i> <i>Participants: 10 adult mongrel dogs each studied twice one week apart</i> <i>Outcomes: Epinephrine absorption, T_{max}, HR, BP, ABG</i> <i>Findings: Bronchial instillation had higher epinephrine concentrations with better absorption, shorter T_{max}. No difference in HR, BP or ABG parameters.</i> <i>Comments: Healthy, non-arrest model, used dose and diluent similar to what we use, no positive hemodynamic effects</i> <i>Level of Evidence: 6</i> <i>Quality: Fair</i> <i>Evidence: AGAINST direct injection compared to endobronchial, concerning that no hemodynamic effect at dose ILCOR recommends</i></p> <p>McCrirrick, A. and I. Kestin (1992). "Haemodynamic effects of tracheal compared with intravenous adrenaline." <u>Lancet</u> 340(8824): 868-70. If intravenous access is not available during cardiopulmonary resuscitation, tracheal administration of adrenaline 0.02 mg/kg, twice the intravenous dose, is recommended. In a randomised crossover study we investigated the haemodynamic effects of low doses of tracheal versus intravenous adrenaline. 12 anaesthetised patients having a hip replaced received one dose of adrenaline intravenously (0.1 microgram/kg) and the other tracheally (0.5 microgram/kg). There was a mean increase in systolic arterial pressure of 40.5 mm Hg (range 16-81) after the intravenous injection, with little effect on heart rate. Tracheal adrenaline had no effect on arterial pressure or heart rate. Thus low doses of tracheal adrenaline have no haemodynamic effects. We believe that the recommended tracheal dose of twice the intravenous dose is likely to be ineffective for the treatment of cardiac arrest. Animal studies suggest that a tracheal dose at least ten times the intravenous dose is required.</p>
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Mullet-1992	<p><u>Critique</u> <i>Methodology: Each patient received 2 doses of Epinephrine 0.1 µg/kg i.v. and 0.5 µg/kg via ETT. Randomization via coin toss as to which they received first. There was a power analysis but no blinding.</i> <i>Participants: Adult humans presenting for total hip replacement surgery</i> <i>Outcomes: arterial blood pressure and heart rate</i> <i>Findings: No change in BP or HR with ET tube epinephrine. Small increases in BP were seen with i.v. Epinephrine but no change in HR.</i> <i>Comments: Non-arrest situation. Extremely small doses-much lower than current recommendations.</i> <i>Level of Evidence: 2</i> <i>Quality: Fair</i> <i>Evidence: AGAINST</i> <i>Outcome Designation: E</i></p> <p>Mielke, L. L., C. Frank, et al. (1998). "Plasma catecholamine levels following tracheal and intravenous epinephrine administration in swine." <u>Resuscitation</u> 36(3): 187-92.</p> <p>We compared plasma epinephrine levels after three different tracheal epinephrine application techniques and intravenous injection in male and female anesthetized and paralyzed domestic pigs. Epinephrine was administered intravenously (10 µg/kg) (group i.v.) or tracheally (100 µg/kg) either by direct injection into the upper end of the tracheal tube (group Tube), via a suction tube placed into the bronchial system (group Catheter) or using an EDGAR tube (group EDGAR), each group: n = 8. Arterial plasma samples were drawn before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 10 min after epinephrine administration. Plasma concentrations of epinephrine were measured with high pressure liquid chromatography using electrochemical detection. Analysis was performed by regression analysis for correlated data. Total plasma epinephrine concentrations showed a significant increase within 0.5 min in all groups. However, peak plasma epinephrine levels in group i.v. were significantly higher than in tracheal groups, while no differences between tracheal groups over the time were found. We conclude that in swine with spontaneous circulation tracheal instillation techniques using special devices such as suction tubes or EDGAR tubes result in onset and peak plasma epinephrine levels equivalent to those after direct injection into the upper end of the tracheal tube.</p> <p><u>Critique</u> <i>Methodology: Randomized using random number table. Investigator determining primary outcome was blinded. No sample size calculations. 0.01 mg/kg i.v. versus 0.1 mg/kg (diluted in 5 ml NS) via ET tube versus suction cath in bronchus versus EDGAR endotracheal tubes, which enables direct injection into the bronchial system via a separate injection canal within the wall of the tube that terminates at the tip of the tube.</i> <i>Participants: Adult pigs in non-arrest</i></p>
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<p>Niemann-2000</p>	<p><i>Outcomes: Plasma epinephrine levels</i> <i>Outcome Designation: E</i> <i>Findings: Increased epinephrine levels within 30s for all groups. Peak epinephrine level higher in i.v. epinephrine group. No difference among different ET tube methods (peaks within 3 minutes)</i> <i>Comments: Well done study but in adult model of non-arrest and used higher dose than is recommended by ILCOR for neonates</i> <i>Level of Evidence: 6</i> <i>Quality: Fair (to answer our question)</i> <i>Evidence: FAVORS higher ET tube epinephrine dose. No disadvantage to direct injection of epinephrine compared to endobronchial.</i></p> <p>Mullett, C. J., J. Q. Kong, et al. (1992). "Age-related changes in pulmonary venous epinephrine concentration, and pulmonary vascular response after intratracheal epinephrine." <i>Pediatr Res</i> 31(5): 458-61.</p> <p>Using an isolated salt-perfused lung model in rabbits from 1 to 21 d of age, we measured the concentration of epinephrine in the pulmonary venous drainage and the pulmonary vascular response after a single dose of intratracheal epinephrine (0.1 microgram/g body weight). Lungs from 30 rabbits were isolated, ventilated, and perfused at one of four age groups (n = 7-8 per group). After ventilation/perfusion was judged to be stable, saline control was injected into the trachea, changes in pulmonary pressure were recorded, and perfusate was collected for 45 s. After restabilization, epinephrine was injected into the trachea, changes in pulmonary vascular pressure were recorded, and perfusate was collected for 45 s x two aliquots. Perfusate epinephrine concentrations were determined by HPLC. Little epinephrine was detected in the perfusate after control over all age groups, and little vascular response was noted. There was a significant age-related increase in perfusate epinephrine concentration as well as an age-related increase in vascular response (increased PAP), with the maximum epinephrine concentration and change in PAP noted at 14-21 d [group 4 = (1.72 +/- 0.42) x 10(4) pmol/L]. Also, in rabbits less than 6 d of age, deposition of epinephrine into the pulmonary venous drainage was delayed. In the rabbit model, the concentration of epinephrine reaching the heart via pulmonary circulation after intratracheal injection is, at birth, very low, and the pulmonary vascular response is diminished. Both increase as a function of age until 14-21 d of age. These findings may have clinical importance in human neonatal resuscitation endeavors.</p> <p><u>Critique</u> <i>Methodology: Lab model given endotracheal epinephrine</i> <i>Participants: rabbit lungs day 1-21</i> <i>Outcomes: epinephrine concentrations, vascular response</i> <i>Outcome designation: E</i> <i>Findings: Decreased concentrations of epinephrine reach the heart via the pulmonary circulation with decreasing age</i></p>
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<p>Niemann-2002</p>	<p><i>Level of Evidence: 7</i> <i>Quality: Fair</i> <i>Evidence: Against</i></p> <p>Niemann, J. T. and S. J. Stratton (2000). "Endotracheal versus intravenous epinephrine and atropine in out-of-hospital "primary" and postcountershock asystole." <u>Crit Care Med</u> 28(6): 1815-19.</p> <p>STUDY OBJECTIVE: Pulmonary blood flow during cardiac arrest and cardiopulmonary resuscitation (CPR) is <20% of normal, and transalveolar drug absorption is likely to be minimal. Animal and clinical CPR studies have not addressed the use of endotracheal (ET) epinephrine in doses currently recommended for adults (twice the intravenous dose). The purpose of this study was to compare the effects of ET and intravenous drugs on cardiac rhythm in the prehospital setting. DESIGN: A 3-yr (1995-1997) retrospective review of all cardiac arrests transported to a single, municipal teaching institution was performed. PATIENTS: Patients >18 yrs in atraumatic cardiac arrest whose first documented field rhythm was asystole with time-to-definitive care of ≤10 mins (primary asystole) and patients found in ventricular fibrillation who developed postcountershock asystole (secondary asystole) were included. Patients were grouped according to route of drug administration (IV, ET, or no drug therapy) as well as rhythm (primary or secondary asystole). A positive response to drug therapy was defined as any subsequent rhythm other than asystole during continued prehospital resuscitation. MEASUREMENTS AND MAIN RESULTS: A total of 136 patients met inclusion criteria. The following groups were defined: group 1, primary asystole/IV drugs (n = 39); group 2, postcountershock asystole/IV drugs (n = 39); group 3, primary asystole/ET drugs (n = 25); group 4, postcountershock asystole/ET drugs (n = 18); and group 5, primary or secondary asystole/no drug therapy (n = 15). Significant differences were not observed between groups with respect to age, gender, witnessed arrest, frequency of bystander CPR, or time-to-definitive care. The positive rhythm response rate was significantly greater in group 1 (64%) and group 2 (69%) (both p < .01) than in Group 3 (12%) or group 4 (11%). The response rate in the control group was 20% and not significantly different from either ET group. The intravenous groups also had a significantly greater rate of return of spontaneous circulation (17%) when compared with the ET groups (0%) (p = .005). CONCLUSION: We conclude that the currently recommended doses of epinephrine and atropine administered endotracheally are rarely effective in the setting of cardiac arrest and CPR.</p> <p><i>Critique</i> <i>Methodology: Retrospective cohort study of i.v. versus ET tube epinephrine versus control (no drug)</i> <i>Participants: >18 yrs adults in atraumatic cardiac arrest whose first documented field rhythm was asystole with time-to-definitive care of < or</i></p>
<p>Naganobu-2000</p>	<p><i>Participants: >18 yrs adults in atraumatic cardiac arrest whose first documented field rhythm was asystole with time-to-definitive care of < or</i></p>

=10 min (primary asystole) and patients found in ventricular fibrillation who developed postcountershock asystole (secondary asystole) were included

Outcomes: + rhythm change, ROSC

Outcomes designation: A

Findings: Currently recommended dose of ET tube epinephrine is rarely effective

Comments: Etiology of cardiac arrest may not apply to newborns

Level of Evidence: 4

Quality: Fair to Good

Evidence: AGAINST

Niemann, J. T., S. J. Stratton, et al. (2002). "Endotracheal drug administration during out-of-hospital resuscitation: where are the survivors?" *Resuscitation* **53**(2): 153-7.

BACKGROUND: Drugs administered endotracheally are effectively absorbed during normal spontaneous cardiac activity. However, animal cardiac arrest studies and limited clinical investigations do not support either the use of endotracheal (ET) drugs in doses currently recommended for adults or the method of direct endotracheal instillation. The purpose of this study was to compare the effect of intravenous (IV) and ET drug therapy on outcome from out-of-hospital cardiac arrest secondary to all cardiac arrest rhythms. DESIGN: Five and one-half year retrospective cohort study. SETTING: Municipal, university affiliated hospital. PATIENTS: Consecutive patients >18 years of age in nontraumatic, out-of-hospital cardiac arrest who received advanced cardiac life support (ACLS) medications by only the ET or IV route were included. INTERVENTIONS: None. RESULTS: Five hundred and ninety-six patients met inclusion criteria (IV drugs=495, ET drugs=101). There was no difference between groups in the rate of witnessed arrest and the frequency of bystander cardiopulmonary resuscitation (CPR). In the ET drug group, a significantly greater number of patients had an initial documented arrest rhythm of asystole compared to the IV drug group (56 vs 37%, P=0.01). The rate of return of spontaneous circulation (27 vs 15%, P=0.01) and survival to hospital admission rate (20 vs 9%, P=0.01) were significantly greater in the IV drug group. No patient who received ET drugs survived to hospital discharge compared to 5% of those receiving IV drugs (P=0.01). CONCLUSION: For our out-of-hospital advanced rescuer system, ET drugs at recommended doses (twice the IV dose) injected into an ET tube during cardiac arrest and CPR were of no benefit.

Critique

Methodology: Five and one-half year retrospective cohort study comparing i.v. to ET tube epinephrine

Participants: Adults >18 years of age in nontraumatic out-of-hospital cardiac arrest who received advanced cardiac life support (ACLS)

Orlowski-
1990

<p>Paret-1997</p>	<p><i>medications by only the ET or i.v. route</i></p> <p><i>Outcomes: Survival</i></p> <p><i>Outcome designation: A&C</i></p> <p><i>Findings: ET tube epinephrine of no benefit</i></p> <p><i>Comments:</i></p> <p><i>Level of Evidence: 4</i></p> <p><i>Quality: Fair</i></p> <p><i>Evidence: AGAINST</i></p> <p>Naganobu, K., Y. Hasebe, et al. (2000). "A comparison of distilled water and normal saline as diluents for endobronchial administration of epinephrine in the dog." <i>Anesth Analg</i> 91(2): 317-21.</p> <p>We compared the effects of distilled water and normal saline as diluents for the endobronchial administration of epinephrine in anesthetized dogs by using a cross-over design. Six dogs received 2 mL of either normal saline or distilled water into the bronchus, and the other solution was administered 1 wk later. Eight dogs received 0.02 mg/kg epinephrine diluted in either distilled water (E + water) or normal saline (E + saline) to a total volume of 2 mL into the bronchus, and the other solution was administered 1 wk later. Normal saline or distilled water without epinephrine did not affect the plasma epinephrine concentration, mean arterial pressure (MAP), and PaO₂. The peak plasma epinephrine concentration was significantly larger after treatment with E + water (26.5 +/- 7.9 ng/mL) than after E + saline (2.1 +/- 0.7 ng/mL). E + water caused an increase in MAP of 91 +/- 24 mm Hg, whereas E + saline did not affect MAP. The maximal decrease in PaO₂ after the administration of E + water (14 +/- 5 mm Hg) was significantly greater than after E + saline (7 +/- 2 mm Hg). In conclusion, distilled water as the diluent for endobronchially administered epinephrine to a total volume of 2 mL allowed better absorption of epinephrine compared with normal saline without a serious detrimental effect on PaO₂. Implications: Using a small volume of distilled water as the diluent for endobronchial epinephrine administration significantly increased epinephrine absorption and arterial pressure in comparison with normal saline, without having a serious detrimental effect on PaO₂, in an anesthetized, noncardiopulmonary, resuscitation dog model.</p> <p><u><i>Critique</i></u></p> <p><i>Methodology: Randomized, cross-over lab study. Experiment 1: 6 dogs received endobronchial 2cc of NS or distilled water with other solution administered 1 week later. 8 dogs received 0.02 mg/kg epinephrine in either 2 cc NS or distilled water with other treatment administered 1 week later.</i></p> <p><i>Participants: 14 health mongrel dogs (7.4-18.3 kg)</i></p> <p><i>Outcomes: Serial epinephrine levels, MAP and PaO₂</i></p> <p><i>Outcome Designation: E</i></p> <p><i>Findings: NS versus distilled water without epinephrine did not affect</i></p>
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<p>Quinton-1987</p>	<p><i>epinephrine concentration, MAP or PaO₂. Epinephrine with distilled water had higher peak plasma epinephrine concentration, higher MAP but higher drop in PaO₂ (still within normal PaO₂ range).</i></p> <p><i>Comments: Healthy, non-arrest model with endobronchial administration of drugs rather than direct ET tube injection as recommended by ILCOR. Did use dose and diluent volume similar to ILCOR recommendations.</i></p> <p><i>Level of Evidence: 6</i></p> <p><i>Quality: Fair</i></p> <p><i>Evidence: AGAINST current recommendation for NS as diluent</i></p> <p>Orlowski, J. P., J. M. Gallagher, et al. (1990). "Endotracheal epinephrine is unreliable." <u>Resuscitation</u> 19(2): 103-13.</p> <p>When intravenous access cannot be obtained in an emergency, the endotracheal route of emergency drug administration can be used for epinephrine, atropine, and lidocaine. Optimal drug dosages for endotracheal administration as well as the amount and type of diluent are presently unknown. We compared central intravenous, peripheral intravenous, intraosseous, and intratracheal administration of epinephrine 1:10,000 in both normotensive and hemorrhagic shock dogs. The shock model consisted of 50% blood volume depletion over 15 min. Epinephrine was administered in a dose of 0.01 mg/kg (0.1 cc/kg) by the intraosseous route, central, and peripheral intravenous routes followed by a 5 cc normal saline flush. Intratracheal administration consisted of epinephrine 0.01 and 0.02 mg/kg diluted 1:1 and 1:2 with normal saline or sterile water and administered deep into the tracheo-bronchial tree using a 30-cm catheter. The effect of epinephrine was assessed by the response of the arterial blood pressure. Epinephrine was equally effective by the intraosseous, central intravenous, and peripheral intravenous routes in terms of time to onset of action, time to peak effect, and magnitude of effect on systolic, diastolic, and mean arterial pressures in both the shock and non-shock animals. The duration of effect was significantly longer (P less than 0.02) for the intraosseous route of administration. The endotracheal route of administration was unreliable and not reproducible in either the normotensive or shock animals. In 8/12 episodes in normotensive animals, including 5 trials with double doses of 0.02 mg/kg and dilutions of 1:1 and 1:2, and in 4/9 studies with shock animals including three with double doses, there was no discernable response of systolic or diastolic blood pressure.</p> <p><u>Critique</u></p> <p><i>Methodology: Quasi-randomized order of treatment (ET tube always first) with each animal treated with all four routes (0.01 and 0.02mg/kg ET tube (deep endobronchial) versus 0.01 mg/kg i.o. versus central i.v. versus peripheral i.v.</i></p> <p><i>Participants: 10 adult dogs in both a normotensive and hemorrhagic shock paradigm.</i></p> <p><i>Outcomes: Arterial BP, time to effect, time to peak effect, magnitude of</i></p>
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<p>Ralston-1984</p>	<p><i>effect</i></p> <p><i>Outcome designation: E</i></p> <p><i>Findings: ET tube route unreliable for both normotensive and hemorrhagic shock paradigms</i></p> <p><i>Comments: Question whether correct statistics used-using paired t-test for 4 different comparisons per animal.</i></p> <p><i>Level of Evidence: 6</i></p> <p><i>Quality: Fair</i></p> <p><i>Evidence: AGAINST</i></p> <p>Paret, G., Z. Vaknin, et al. (1997). "Epinephrine pharmacokinetics and pharmaco-dynamics following endotracheal administration in dogs: the role of volume of diluent." <u>Resuscitation</u> 35(1): 77-82.</p> <p>OBJECTIVE: to define the optimal volume of dilution for endotracheal (ET) administration of epinephrine (EPI). DESIGN: prospective, randomized, laboratory comparison of four different volumes of dilution of endotracheal epinephrine (1, 2, 5, and 10 ml of normal saline). SETTING: large animal research facility of a university medical center. SUBJECTS AND INTERVENTIONS: epinephrine (0.02 mg/kg) diluted with four different volumes (1, 2, 5, and 10 ml) of normal saline was injected into the ET tube of five anesthetized dogs. Each dog served as its own control and received all four volumes in different sequences at least 1 week apart. Arterial blood samples for plasma epinephrine concentration and blood gases were collected before and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 10, 15, 20, 25, 30 and 60 min after drug administration. Heart rate and arterial blood pressure were continuously monitored with a polygraph recorder. MEASUREMENTS AND MAIN RESULTS: higher volumes of diluent (5 and 10 ml) caused a significant decrease of PaO₂, from 147 +/- 8 to 106 +/- 10 torr, compared with the lower volumes of diluent (1 and 2 ml), from 136 +/- 10 to 135 +/- 7 torr (P < 0.05). These effects persisted for over 30 min. Mean plasma epinephrine concentrations significantly increased within 15 s following administration for all the volumes of diluent. Mean plasma epinephrine concentrations, maximal epinephrine concentration (C_{max}) and the coefficient of absorption (K_a) were higher in the 5 and 10 ml groups. The time interval to reach maximal concentration (T_{max}) was shorter in the 5 and 10 ml groups. Yet these results were not significantly different. Heart rate, systolic and diastolic blood pressures did not differ significantly between the groups throughout the study. CONCLUSIONS: Dilution of endotracheal epinephrine into a 5 ml volume with saline optimizes drug uptake and delivery without adversely affecting oxygenation and ventilation.</p> <p><u>Critique</u></p> <p><i>Methodology: Prospective, randomized crossover trial of 0.02 mg/kg ET tube epinephrine in 1, 2, 5, or 10 ml NS (random order 1 week apart), not blinded, no sample size calculation</i></p>
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<p>Ralston-1985</p>	<p><i>Participants: 5 Adult, anesthetized dogs (9.5-15.5 kg)</i> <i>Outcomes: pharmacokinetic parameters C_{max} and T_{max} and rate of drug absorption K_a, pharmacodynamic parameters of HR, BP and oxygenation</i> <i>Outcome designation: E</i> <i>Findings: All had increased levels of Epinephrine within 15 seconds. Highest C_{max}, K_a and shortest T_{max} were with 5-10 ml dilutions but not significantly different. Biggest drop in PaO₂ was in 5-10 ml dilution groups (lasted 60 minutes). No difference in HR or BP</i> <i>Comments: Non-arrest model with normal pulmonary blood flow, concerning that there was no increase in BP with Epinephrine in any treatment group, don't show any baseline values prior to ET tube epinephrine</i> <i>Level of Evidence: 6</i> <i>Quality: Fair</i> <i>Evidence: SUPPORTIVE but they used a larger diluent volume than recommended by NRP; however, their model is larger than a newborn as well.</i></p>
<p>Raymondos-2000</p>	<p>Quinton, D. N., G. O'Byrne, et al. (1987). "Comparison of endotracheal and peripheral intravenous adrenaline in cardiac arrest. Is the endotracheal route reliable?" <i>Lancet</i> 1(8537): 828-9. Twelve patients presenting to an accident and emergency department in asystolic cardiac arrest were randomly allocated to treatment with endotracheal adrenaline (five patients) or peripheral intravenous adrenaline (seven patients). Femoral-artery blood samples were taken for assay of adrenaline and noradrenaline. After intravenous adrenaline there was a good clinical and biochemical response, but after endotracheal adrenaline there was no change in serum adrenaline and no measurable clinical response. The endotracheal route of adrenaline administration is not reliable in out-of-hospital cardiac arrest. <u>Critique</u> <i>Methodology: Randomized (method not described), not blinded, no sample size determination to i.v versus ET tube epinephrine (0.01 mg/kg).</i> <i>Participants: Adult patients presenting to emergency department in asystole or bradyarrhythmia</i> <i>Outcomes: ROSC, epinephrine levels</i> <i>Outcome designation: A, C, and E</i> <i>Findings: No clinical response to ET tube epinephrine</i> <i>Comments: Authors believed ET tube epinephrine to be potentially dangerous before starting their study</i> <i>Level of Evidence: 2</i> <i>Quality: Fair</i> <i>Evidence: AGAINST</i></p>

<p>Redding-1967</p>	<p>Ralston, S. H., W. D. Voorhees, et al. (1984). "Intrapulmonary epinephrine during prolonged cardiopulmonary resuscitation: improved regional blood flow and resuscitation in dogs." <u>Ann Emerg Med</u> 13(2): 79-86.</p> <p>Blood flow to vital organs was measured at five-minute intervals during 20 minutes of cardiopulmonary resuscitation (CPR) and ventricular fibrillation in two groups of anesthetized dogs (n = 15 per group). The relationship between organ blood flow and restoration of circulation after 20 minutes was assessed with no additional treatment in Group I and with intrapulmonary epinephrine in Group II. Cardiac output and organ blood flow did not vary significantly in Group I. In Group II, intrapulmonary epinephrine significantly improved blood flow to the myocardium, the brain, and the adrenals. A mean myocardial blood flow of less than 0.13 mL/min/g resulted in no survival, while a flow of greater than 0.16 mL/min/g resulted in survival. These studies show that a critical level of myocardial blood flow is required to restore ability of the heart to function as a pump after prolonged CPR, and that a drug that increases flow improves resuscitation efforts.</p> <p><u>Critique</u> <i>Methodology: Non-randomized, non-blinded, no sample-size calculations comparing no drug to intrapulmonary (via Swan-Ganz catheter) 0.1 mg/kg epinephrine in 10 ml saline</i> <i>Participants: 15 adult dogs in V-fib cardiac arrest in each group</i> <i>Outcomes: organ blood flow, ROSC</i> <i>Outcome designation: A & E</i> <i>Findings: No improvement in cardiac output but improved perfusion of the heart, brain, adrenals and decreased perfusion of the kidneys, no improvement in BP, they report doubling of ROSC however no stats done</i> <i>Comments: cardiac arrest model, is epinephrine via a Swan Ganz cath down the ET tube practical? When I run Fischer Exact Test on ROSC numbers although the intrapulmonary epinephrine is almost double, it is not statistically different (underpowered).</i> <i>Level of Evidence: 6</i> <i>Quality: Fair</i> <i>Evidence: SUPPORT</i></p> <p>Ralston, S.H., W.A. Tacker, et al. (1985). "Endotracheal versus intravenous epinephrine during electromechanical dissociation with CPR in dogs." <u>Ann Emerg Med</u> 14(11): 1044-8.</p> <p>The dose-response curves of epinephrine given either IV or endotracheally (ET) were compared during resuscitation from electromechanical dissociation (EMD). Ten anesthetized dogs were subjected to a two-minute period of electrically induced ventricular fibrillation (VF) followed by defibrillation without CPR to produce EMD. Mechanical CPR was followed by injection of either ET or IV epinephrine. Successful response was defined as a return of pulsatile</p>
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<p>Roberts-1978</p>	<p>blood pressure within two minutes of drug administration. Using log-dose increments of epinephrine, experimental trials were repeated in each animal. The IV and ET median effective doses were 14 and 130 micrograms/kg, respectively. When the trials were successful, the time between drug administration and either arterial blood pressure increases or return of spontaneous circulation did not differ significantly for the ET and IV groups. These results show that the dosage for epinephrine delivered ET must be higher than the IV dosage to achieve the same response during CPR.</p> <p><u>Critique</u> <i>Methodology: Alternated whether dogs received 0.01 mg/kg i.v or 0.1 mg/kg in 10 ml NS ET tube epinephrine first (not randomized), then doses increased or decreased depending on success or failure at ROSC.</i> <i>Participants: 10 mongrel adult dogs who received multiple dosing regimens with washout time in between</i> <i>Outcomes: ROSC</i> <i>Findings: ET tube epinephrine required doses 10X higher than i.v.</i> <i>Comments: CPR after only 2.5 minutes of cardiac arrest (not likely in neonates) and epinephrine levels were not measured. Outcomes for only 2 minutes.</i> <i>Level of Evidence: 6</i> <i>Quality: Fair</i> <i>Evidence: Supports use of ET tube epinephrine but suggests that a dose much larger than the dose recommended by NRP may be needed.</i></p>
<p>Roberts-1979a</p>	<p>Raymondos, K., B. Panning, et al. (2000). "Absorption and hemodynamic effects of airway administration of adrenaline in patients with severe cardiac disease." <u>Ann Intern Med</u> 132(10): 800-3.</p> <p>BACKGROUND: If intravenous access cannot be attained during resuscitation of adult patients, endotracheal application of at least 2 mg of adrenaline is recommended. However, the effects of this intervention have not yet been demonstrated in adults. OBJECTIVE: To demonstrate the effects of adrenaline administered through the airways. DESIGN: Prospective clinical trial. SETTING: Operating theater at university hospital. PATIENTS: 34 patients receiving implantable cardioverter defibrillators under general anesthesia. INTERVENTION: When mean arterial pressure decreased below 80 mm Hg, 100 times the effective central intravenous dose of adrenaline (mean +/- SD, 1.3+/-0.6 mg [range, 0.7 to 3 mg]) was administered over 5 seconds into the endotracheal tube or through a bronchial catheter. Ten forced ventilations followed. MEASUREMENTS: Hemodynamic variables were recorded with a polygraph recorder. Adrenaline levels were measured in 13 patients. RESULTS: Plasma levels and arterial pressure increased in all patients (P < 0.002). Higher plasma levels (P < 0.039) and greater arterial pressure (P < 0.001) were achieved with this method than with intravenous injection. The effects of adrenaline did not differ between the</p>

Schwab-1994	<p>two airway routes. Sustained ventricular arrhythmia did not occur. CONCLUSION: These substantial effects support the standard recommendation to consider the airways as an alternate route for at least 2 mg of adrenaline during resuscitation.</p> <p><u>Critique</u> <i>Methodology: Case Series</i> <i>Participants: Adult cardiac patients receiving implantable cardioverter defibrillators</i> <i>Outcomes: Adrenaline levels, hemodynamic parameters</i> <i>Outcome designation: E</i> <i>Findings: Administration of large (100X the i.v. dose) doses of epinephrine into the airways is hemodynamically effective</i> <i>Comments: non-arrest population</i> <i>Level of Evidence: 5</i> <i>Quality: Fair</i> <i>Evidence: NEUTRAL –ET tube epinephrine can cause hemodynamic effects but the dose used is much larger than the current dose recommended by ILCOR</i></p> <p>Redding J.S., Asuncion JS, Pearson JW. (1967). "Effective routes of drug administration during cardiac arrest." <i>Anesth Analg</i> 46(2): 253-8.</p> <p>No published abstract</p> <p><u>Critique</u> <i>Methodology: Non-randomized or blinded with no sample size calculations. Comparison of 1 mg epinephrine via i.v. versus ET tube in 1 cc NS, versus ET tube in 10 cc NS versus ET tube in 10 cc water.</i> <i>Participants: adult dogs (n=10 per group) in asphyxial arrest (5 minutes) followed by ventilation with oxygen, CPR and defibrillation if needed.</i> <i>Outcomes: ROSC, development of V-fib, time to ROSC</i> <i>Outcome Designation: A</i> <i>Findings:</i> <table border="1" style="display: inline-table; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;"><u>Route</u></th> <th style="text-align: left;"><u>ROSC</u></th> <th style="text-align: left;"><u>V-fib</u></th> <th style="text-align: left;"><u>Time to ROSC</u></th> </tr> </thead> <tbody> <tr> <td><i>i.v.</i></td> <td><i>10/10 ROSC</i></td> <td><i>2 V-fib</i></td> <td><i>127 s</i></td> </tr> <tr> <td><i>ETT 1mg in 1cc</i></td> <td><i>2/10 ROSC</i></td> <td><i>3 V-fib</i></td> <td><i>116 s</i></td> </tr> <tr> <td><i>ETT 1 mg in 10 cc NS</i></td> <td><i>8/10 ROSC</i></td> <td><i>2 V-fib</i></td> <td><i>217 s</i></td> </tr> <tr> <td><i>ETT 1 mg in 10 cc H₂O</i></td> <td><i>10/10 ROSC</i></td> <td><i>2 V-fib</i></td> <td><i>132 s</i></td> </tr> </tbody> </table></p> <p><i>Comments: Reports water is better absorbed into the lungs. Need the volume to wash the medication out of the ET tube Dosage was not standardized for weight (weights not reported)</i> <i>Level of Evidence: 6</i> <i>Quality: Fair</i> <i>Evidence: SUPPORTS</i></p> <p>Roberts, J. R., M. I. Greenburg, et al. (1978). "Comparison of the</p>	<u>Route</u>	<u>ROSC</u>	<u>V-fib</u>	<u>Time to ROSC</u>	<i>i.v.</i>	<i>10/10 ROSC</i>	<i>2 V-fib</i>	<i>127 s</i>	<i>ETT 1mg in 1cc</i>	<i>2/10 ROSC</i>	<i>3 V-fib</i>	<i>116 s</i>	<i>ETT 1 mg in 10 cc NS</i>	<i>8/10 ROSC</i>	<i>2 V-fib</i>	<i>217 s</i>	<i>ETT 1 mg in 10 cc H₂O</i>	<i>10/10 ROSC</i>	<i>2 V-fib</i>	<i>132 s</i>
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<p>Vaknin-2001</p>	<p>pharmacological effects of epinephrine administered by the intravenous and endotracheal routes." <u>Jacep</u> 7(7): 260-4.</p> <p>Epinephrine in various dosages was administered to anesthetized dogs by intravenous and endotracheal routes. Both methods produced measurable effects on heart rate, blood pressure, and respiration. Tachycardia occurred more rapidly after endotracheal administration than after intravenous administration. Respiration appeared to be supported more advantageously with the larger endotracheal dosages. The maximum blood pressure rise was delayed only 60 seconds by the endotracheal route. With an endotracheally administered dose of ten times the intravenous dose, equal responses in blood pressure were obtained. However, when equal doses are compared, there is only a two to three fold increase with the intravenous route. The endotracheal route may be less toxic at higher doses, affording greater safety when large amounts of epinephrine are used. It is concluded that endotracheally administered epinephrine produces significant pharmacologic effects in anesthetized dogs.</p> <p><u>Critique</u></p> <p><i>Methodology: 0.005, 0.03, 0.06, 0.09 mg/kg [³H]-epinephrine administered by ET tube on separate days then 1 week later 0.005, 0.03, 0.06, 0.09, 0.27 mg/kg [³H]-epinephrine in 5cc NS via ET tube on separate days. No randomization, blinding or sample size calculations, no statistical analysis mentioned</i></p> <p><i>Participants: 7 adult mongrel dogs</i></p> <p><i>Outcomes: Heart rate, blood pressure, respiratory rate</i></p> <p><i>Outcome designation: E</i></p> <p><i>Findings: ET epinephrine was absorbed and produced measurable pharmacologic effects. Maximal response in BP is delayed 60s for ET tube compared to i.v. but more sustained over time. ET tube dose needs to be 10 X the i.v. route to get similar rises in BP.</i></p> <p><i>Comments: Non-arrest anesthetized animals</i></p> <p><i>Level of Evidence: 6</i></p> <p><i>Quality: Fair</i></p> <p><i>Evidence: Supports (use of ET tube epinephrine but not the dose that is currently recommended by NRP)</i></p> <p>Roberts, J.R., M.I. Greenberg, et al. (1979). "Blood levels following intravenous and endotracheal epinephrine administration." <u>JACEP</u> 8(2): 53-6.</p> <p>The blood levels of epinephrine and its metabolites which were obtained when the drug was given by both the intravenous (IV) and endotracheal (ET) routes were compared. Anesthetized dogs were subjected to radioactive epinephrine in doses of 0.005, 0.03, 0.06, and 0.09 mg/kg administered both intravenously and endotracheally. Blood levels were obtained at 0.25, 0.75, 1.5, 3, 5, 10 and 30 minutes following injection and analyzed by thin layer chromatography. The maximum measured</p>
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<p>Yang-1991</p>	<p>concentration following IV injection was observed at 15 seconds. Epinephrine was rapidly metabolized with 20% of the original concentration detected at 5 minutes following IV injection. When the drug was given by the ET route, the maximum measured concentration was similarly observed at 15 seconds. Following ET installation, initial blood concentrations are sustained over a much longer period of time and 80% of the initial concentration was detected at 5 minutes. Maximum concentrations are approximately one-tenth of those achieved with an equal IV dosage. It is concluded that endotracheally and intravenously administered epinephrine rapidly reach maximum blood levels although there are differences in kinetics between the two routes.</p> <p><u>Critique</u> <i>Methodology: Non-randomized animal trial comparing serial drug dosages on epinephrine levels with i.v versus ET tube administration</i> <i>Participants: non-arrested adult dogs</i> <i>Outcomes: blood concentrations of epinephrine</i> <i>Findings: Need 10 times the dose endotracheally compared to i.v. to achieve the same levels</i> <i>Comments: Anesthetized animals but not in arrest</i> <i>Level of Evidence: 6</i> <i>Quality: Fair</i> <i>Evidence: Against currently recommended dose</i></p>
<p>Ziino-2003</p>	<p>Schwab, K. O. and H. B. von Stockhausen (1994). "Plasma catecholamines after endotracheal administration of adrenaline during postnatal resuscitation." <u>Arch Dis Child Fetal Neonatal Ed</u> 70(3): F213-7.</p> <p>To analyse the degradation of adrenaline after cardiopulmonary resuscitation of preterm neonates, free and sulphoconjugated adrenaline, noradrenaline, and dopamine were determined in 31 preterm neonates by a radioenzymatic method. Nine of the neonates received a high dose (250 micrograms/kg) of endotracheally administered adrenaline (1:1000); three of them had more than one dose of adrenaline. With the exception of sulphoconjugated dopamine, the free and sulphoconjugated catecholamine concentrations in preterm infants treated with adrenaline initially exceeded those in the untreated group. The concentrations decreased to the same range about two hours after birth. Free and sulphoconjugated adrenaline concentrations remained significantly increased in the adrenaline treated group, however, indicating a plateau effect. The correlation between free adrenaline and noradrenaline concentrations with their respective sulphoconjugated concentrations was highly significant. It is concluded that free catecholamines are rapidly degraded by sulphoconjugation in preterm neonates.</p> <p><u>Critique</u> <i>Methodology: Prospective non-randomized cohort study divided into those who received 0.25 mg/kg ET epinephrine versus none during resuscitation</i></p>

<p>Greenberg-1984a</p>	<p><i>Participants: 31 preterm infants who did not respond to ventilation, intubation and CPR in the DR</i></p> <p><i>Outcomes: Post resuscitation epinephrine and breakdown product levels</i></p> <p><i>Findings: Infants who received ET tube epinephrine had higher epinephrine levels up to 2 hours post resuscitation compared to control</i></p> <p><i>Comments: Main point was that preterm infants can rapidly metabolize epinephrine. However, this study showed that at least some of the ET tube epinephrine appears to be absorbed in preterm infants when using a much higher dose than is currently recommended</i></p> <p><i>Level of Evidence: 3</i></p> <p><i>Quality: Fair</i></p> <p><i>Evidence: SUPPORTS</i></p> <p>Vaknin, Z., Y. Manisterski, et al. (2001). "Is endotracheal adrenaline deleterious because of the beta adrenergic effect?" <i>Anesth Analg</i> 92(6): 1408-12.</p> <p>IV adrenaline increases coronary and cerebral perfusion pressures during cardiopulmonary resuscitation. We recently showed that endotracheal adrenaline can decrease blood pressure (BP), a detrimental effect presumably mediated by the beta 2-adrenergic receptor unopposed by alpha-adrenergic vasoconstriction. This prospective, randomized, laboratory comparison of endotracheal adrenaline (0.05 mg/kg diluted with normal saline to 10 mL total volume) with or without nonselective beta-blocker (propranolol) pretreatment was conducted in an attempt to clarify the mechanism of this BP decrease. Five mongrel dogs were given 0.05 mg/kg endotracheal adrenaline (diluted) or 0.05 mg/kg endotracheal adrenaline followed by an IV propranolol (0.1 mg/kg) pretreatment. Each dog served as its own control (10 mL of normal saline administered endotracheally) and received each regimen at least one week apart. Endotracheal adrenaline given after the propranolol pretreatment produced an increase in systolic, diastolic, and mean arterial BPs, from 165/110 mm Hg (mean 128 mm Hg) to 177.5/125 mm Hg (mean 142.5 mm Hg), respectively, as opposed to the hypotensive effect of isolated endotracheal adrenaline (P < 0.03). Thus, endotracheal adrenaline was associated with predominantly beta-adrenergic-mediated effects, causing hypotension via peripheral vasodilatation unopposed by alpha-adrenergic vasoconstriction. The search for the optimal dose of endotracheal adrenaline should be aimed at achieving the higher alpha-adrenergic vasoconstrictive threshold.</p> <p><u><i>Critique</i></u></p> <p><i>Methodology: Non-randomized animal trial</i></p> <p><i>Participants: Adult dogs</i></p> <p><i>Outcomes: HR, BP, ABG</i></p> <p><i>Outcomes Designation: E</i></p> <p><i>Findings: 0.05 mg/kg caused hypotension</i></p> <p><i>Comments: Non-arrest adult model</i></p>
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<p>Greenberg-1984b</p>	<p><i>Level of Evidence: 6</i> <i>Quality: Fair</i> <i>Evidence: AGAINST Currently recommended dose (needing larger dose to overcome beta-adrenergic effects of epinephrine)</i></p> <p>Yang, L.Y., C.Q. He, et al. (1991). "Endotracheal administration of epinephrine during cardiopulmonary resuscitation." <u>Chin Med J (Engl)</u> 104(12): 986-91.</p> <p>A hypoxia-induced canine cardiac model was used to study the effectiveness hemodynamic response, arterial blood gas and pulmonary pathologic changes after endotracheal (ET) epinephrine administration in comparison with those from intravenous (IV) administration. The results indicated that the survival rate was the same with the drug given by either route. The increase of hemodynamic indices was lower in the group after ET administration than that after IV administration. No significant influence was exerted on the drug effects whether the drug is diluted in normal saline or in distilled water and no serious detrimental effects occurred on the lung tissues following ET epinephrine administration.</p>
<p>Greenberg-1988</p>	<p><i>Critique</i></p> <p><i>Methodology: Randomized, non-blinded lab trial of ET tube 10 cc NS versus ET tube epinephrine (1 mg/10 cc NS) versus ET tube epinephrine (1 mg/10 cc distilled water) versus i.v. epinephrine (1 mg/10 cc NS). No sample size calculations.</i></p> <p><i>Participants: 24 (4 groups of 6) adult mongrel dogs (8-18 kg) with acute asphyxial arrest</i></p> <p><i>Outcomes: hemodynamic responses, ABG, pulmonary pathologic changes, survival rates</i></p> <p><i>Outcome designation: B, E</i></p> <p><i>Findings: No difference in very short term survival rate (20 min), increase in hemodynamic parameters less than with i.v., mild reversible pathologic changes in ET tube group.</i></p>
<p>Hasegawa-1986</p>	<p><i>Comments: Asphyxial arrest, used catheter beyond tip of ETT to administer drugs, underpowered to show any differences, no difference in time to onset of drug effect, ROSC, and duration of hypertension. No difference between diluents.</i></p> <p><i>Level of Evidence: 6</i> <i>Quality: Fair</i> <i>Evidence: Supports inclusion of ET tube epinephrine but using 10X dose recommended via NRP</i></p>
<p>Johnston-1992</p>	<p>Ziino, A. J., M. W. Davies, et al. (2003). "Epinephrine for the resuscitation of apparently stillborn or extremely bradycardic newborn infants." <u>Cochrane Database Syst Rev</u>(2): CD003849.</p>
<p>Mielke-1994</p>	<p>BACKGROUND: Epinephrine is a cardiac stimulant with complex effects on the heart and blood vessels. It has been used for decades in all age groups to treat cardiac arrest and bradycardia. Despite formal</p>

Polin-1986	<p>guidelines for the use of epinephrine in neonatal resuscitation, the evidence for these recommendations has not yet been rigorously scrutinised. While it is understood that this evidence is in large part derived from animal models and the adult human population, the contribution from work in the neonatal population remains unclear. In particular, it remains to be determined if any randomised studies in neonates have helped to establish if the administration of epinephrine in the context of apparent stillbirth or extreme bradycardia might influence mortality and morbidity. OBJECTIVES: Primary objective: To determine if the administration of epinephrine to apparently stillborn and extremely bradycardic newborns reduces mortality and morbidity Secondary objectives: To determine the effect of intravenous versus endotracheal administration on mortality and morbidity ; To determine the effect of high dose versus standard dose epinephrine on mortality and morbidity, where high dose is defined as any dose greater than the current recommended standard dose of 0.1 to 0.3ml/kg of a 1:10,000 solution of epinephrine; To determine whether the effect of epinephrine on mortality and morbidity varies with gestational age, i.e. term (greater than or equal to 37 weeks) versus pre-term (less than 37 weeks) SEARCH STRATEGY: Searches were made of Medline from 1966 to December 2002, CINAHL (from 1982), Current Contents (from 1988), EMBASE, and the Cochrane Controlled Trials Register (2002, issue 4). Bibliographies of conference proceedings were reviewed and unpublished studies were sought by hand searching the conference proceedings of the Society for Pediatric Research and the European Society for Pediatric Research from 1993 to 2002. SELECTION CRITERIA: Randomised and quasi-randomised controlled trials of newborns, both pre-term and term, receiving epinephrine for unexpected apparent stillbirth or extreme bradycardia. DATA COLLECTION AND ANALYSIS: No studies were found meeting the criteria for inclusion in this review MAIN RESULTS: No studies were found meeting the criteria for inclusion in this review. REVIEWER'S CONCLUSIONS: We found no randomised, controlled trials evaluating the administration of epinephrine to the apparently stillborn or extremely bradycardic newborn infant. Similarly, we found no randomised, controlled trials which addressed the issues of optimum dosage and route of administration of epinephrine. Current recommendations for the use of epinephrine in newborn infants are based only on evidence derived from animal models and the human adult literature. Randomised trials in neonates are urgently required to determine the role of epinephrine in this population.</p>
Raehl-1986	<p><i>Critique</i> <i>Methodology: Attempt at meta-analysis of RCT involving epinephrine use for resuscitation of neonates</i> <i>Participants: Neonates</i> <i>Outcomes: ROSC, Survival, Morbidity</i> <i>Findings: No RCT found on any topic of interest involving epinephrine</i></p>
Wyckoff-2001	<p><i>Critique</i> <i>Methodology: Attempt at meta-analysis of RCT involving epinephrine use for resuscitation of neonates</i> <i>Participants: Neonates</i> <i>Outcomes: ROSC, Survival, Morbidity</i> <i>Findings: No RCT found on any topic of interest involving epinephrine</i></p>

<p>Zaritsky-1988</p> <p>Barton-1998</p> <p>DeBehnke-1994</p> <p>Greenberg-1981</p> <p>Leibman-1997</p>	<p><i>and newborns</i></p> <p><i>Comments:</i></p> <p><i>Level of Evidence: 1</i></p> <p><i>Quality: Good search strategy but no trials to be found</i></p> <p><i>Evidence: NEUTRAL (There is no data for or against current recommendation)</i></p> <p style="text-align: center;">Papers Excluded</p> <p><u>Review Articles</u></p> <p>Greenberg, M. I. (1984). "Endotracheal drugs: state of the art." <u>Ann Emerg Med</u> 13(9 Pt 2): 789-90.</p> <p>Endotracheal drug administration has become an acceptable practice in a variety of clinical settings when an intravenous route is not available. Although accepted, its clinical utility in many situations is unproven. Some of the problems that result are presented.</p> <p>Greenberg, M. I. (1984). "The use of endotracheal medication in cardiac emergencies." <u>Resuscitation</u> 12(3): 155-65.</p> <p>The endotracheal route for drug administration provides a rapid means of accessing the systemic circulation when intravenous routes cannot be established in emergent situations. This route is relatively free of significant complications and has been documented as being successful numerous times in various clinical settings. Currently, the following drugs have been studied by this route: epinephrine, atropine, lidocaine, naloxone, bretylium, and diazepam. The paper reviews the current state of the art of endotracheal drug administration.</p> <p>Greenberg, M. I. (1988). "Emergency drug administration via the endotracheal route." <u>Mil Med</u> 153(10): 509-13.</p> <p>Hasegawa, E. A. (1986). "The endotracheal use of emergency drugs." <u>Heart Lung</u> 15(1): 60-3.</p> <p>The endotracheal route for medication is useful in emergency situations. Epinephrine, atropine, and naloxone have proved to be effective when administered by this route. Experience with lidocaine is largely anecdotal, but the available information and the drug's chemical properties indicate that endotracheal lidocaine may be considered if necessary. Drugs that should not be given by the endotracheal route include bretylium, diazepam, calcium salts, isoproterenol, norepinephrine, and sodium bicarbonate.</p> <p>Johnston, C. (1992). "Endotracheal drug delivery." <u>Pediatr Emerg Care</u> 8(2): 94-7.</p>
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Marchant-1987	<p>Mielke, L., E. Entholzner, et al. (1994). "[Drug administration via the endobronchial route. Possibilities of drug administration in emergency medicine]." <u>Fortschr Med</u> 112(27): 377-80.</p>
Roberts-1979b	<p>For cardiopulmonary resuscitation, the endobronchial route represents a good means of administering drugs with a systemic effect, such as adrenaline and atropine, even without a venous line. Via this route, however, higher doses are needed (2.5 times as much as those normally given intravenously). In order to produce a larger surface area within the bronchio-alveolar space and thus speed up absorption, the drugs are diluted in 5-10 ml solvent (isotonic saline solution or distilled water). For endobronchial administration of a drug, various techniques are employed, for example, simply injecting it into the upper end of the (endotracheal) tube, puncture of the tube the use of an application probe introduced into the endobronchial tube, aspiration or venacaval catheter, or the EDGAR tube with an injection needle incorporated within the tube wall. After injection, the diluted medication is distributed into the tiny branches of the bronchial tree by repeated hyperventilation. Despite the need for an adequate alternative to the venous route in the field of cardiopulmonary resuscitation, we still have very few reliable facts about the endobronchial application technique.</p>
Lindemann-1982	
Niemann-1999	<p>Polin, K., D. H. Brown, et al. (1986). "Endotracheal administration of epinephrine and atropine." <u>Pediatr Emerg Care</u> 2(3): 168-9.</p> <p>A case history of a seven-month-old girl arriving at the emergency department in cardiac arrest from an inhalation injury without venous access is described. The patient was resuscitated with endotracheal administration of epinephrine and atropine. A review of the literature of endotracheal administration of medications in pediatrics subsequently follows.</p>
Tandberg-1982	
	<p>Raehl, C. L. (1986). "Endotracheal drug therapy in cardiopulmonary resuscitation." <u>Clin Pharm</u> 5(7): 572-9.</p> <p>Use of endotracheal drug therapy during cardiopulmonary resuscitation (CPR) is reviewed. Endotracheal drug therapy--instillation of a drug solution directly into an endotracheal tube for absorption into the circulation via the alveoli--may be used during CPR when venous access is limited. Administration of drugs via a central vein is the most efficient route, but a central i.v. line may not be present and peripheral venous administration may not be possible because of vasoconstriction, trauma, other patient-related factors, or absence of personnel trained to insert i.v. catheters. An endotracheal tube is usually inserted during CPR; in most cases, this procedure can be performed outside the hospital by emergency medical personnel. Basic life-support measures are not interrupted during endotracheal administration as they are in intracardiac drug administration. Drugs that may be administered by the endotracheal route include epinephrine, atropine sulfate, lidocaine hydrochloride, naloxone</p>
Weil-2000	
Zaritsky-1994	

hydrochloride, and metaraminol bitartrate. Endotracheal delivery of calcium salts, sodium bicarbonate, and bretylium tosylate is not recommended. Pharmacokinetic data for drugs administered endotracheally are lacking; therefore, dosage recommendations are empirical. Usually, the same dose is administered endotracheally as by the i.v. route. Little is known about choice and volume of diluent and the best anatomic site of application. Endotracheal drug administration may replace intracardiac injection as the second-line alternative to intravenous drug injection during CPR.

Wyckoff, M. H., J. Perlman, et al. (2001). "Medications during resuscitation -- what is the evidence?" Semin Neonatol **6**(3): 251-9. Medication use during neonatal resuscitation is uncommon. The infrequent use of resuscitation medications has impeded rigorous investigations to determine the most effective agents and/or dosing regimens. The medications most commonly used during delivery room resuscitation include epinephrine, sodium bicarbonate, naloxone hydrochloride and volume expanders. The available evidence for each of these medications is reviewed in this article.

Zaritsky, A. (1988). "Selected concepts and controversies in pediatric cardiopulmonary resuscitation." Crit Care Clin **4**(4): 735-54. Although more than 80 years of research in cardiac resuscitation produced many important findings and greatly enhanced our understanding of the arrest state, outcome following pediatric cardiac arrest remains poor. Resuscitation guidelines have recently been published, but they may not reflect optimal therapy. Closed-chest compression-induced cardiac output may be higher in pediatric patients, particularly infants, than that previously reported in adults. To achieve higher cardiac outputs, direct cardiac compression is important; the recommended compression location has therefore been changed based on recent data. The optimal rate of compression, however, is uncertain, so further research is needed. Alternative vascular access sites, such as the endotracheal and intraosseous route for drug administration may permit more rapid drug delivery, but data suggest that a larger epinephrine dose than currently recommended should be used. It may also be helpful to dilute the drug in normal saline before endotracheal administration. Although experimental data suggest that a pure alpha-adrenergic agonist may be beneficial in a cardiac arrest, recent data show that epinephrine remains the drug of choice. Finally, the role of sodium bicarbonate in both the arrest and postarrest setting has become controversial. Recent data suggest that bicarbonate may be detrimental and that therapy of acidosis is best directed at improving perfusion, oxygenation, and ventilation. Alternative forms of therapy for acidosis, such as THAM and dichloroacetate may prove beneficial in the postarrest setting.

Letters, Case Reports, Commentaries

Barton, E. D. (1998). "Emergency medications via the endotracheal tube: when is this route preferred?" Acad Emerg Med **5**(9): 942-3.

Letter

DeBehnke, D. J. (1994). "Endotracheal epinephrine administration." Acad Emerg Med **1**(4): 326-7.

Letter/Commentary

Greenberg, M. I., J. R. Roberts, et al. (1981). "Use of endotracheally administered epinephrine in a pediatric patient." Am J Dis Child **135**(8): 767-8.

Case report

Leibman, J. B. (1997). "Should epinephrine be administered exclusively by the endotracheal route in respiratory arrest secondary to asthma?" Am J Emerg Med **15**(1): 106-7.

Letter/Case Report

Marchant, B. (1987). "Endotracheal adrenaline in cardiac arrest." Lancet **1**(8541): 1098.

Letter

Roberts, J. R., M. I. Greenberg, et al. (1979). "Endotracheal epinephrine in cardiorespiratory collapse." Jacep **8**(12): 515-9.

The endotracheal route for the administration of epinephrine has been studied extensively in dogs. There has been little in the medical literature to document the successful use of this technique in humans. The successful use of endotracheally administered epinephrine in two patients with cardiorespiratory collapse is reported. Specific points concerning endotracheal drugs are discussed and a set of guidelines for clinical use is offered.

Case report and review

Lindemann, R. (1982). "Endotracheal administration of epinephrine during cardiopulmonary resuscitation." Am J Dis Child **136**(8): 753-4.

Very small case series reported in letter

Niemann, J. T. (1999). "Endotracheal drugs during cardiac arrest and resuscitation: any port in a storm?" Crit Care Med **27**(12): 2839-40.

Commentary on Kleinman-1999

Tandberg, D. and D. Abercrombie (1982). "Treatment of heroin overdose with endotracheal naloxone." Ann Emerg Med **11**(8): 443-5.

A 24-year-old man with respiratory failure, severe bradycardia, and coma following heroin overdose was successfully resuscitated using endotracheally administered naloxone hydrochloride (Narcan). Post-treatment naloxone assays demonstrated the presence of large amounts of naloxone in the patient's blood and urine. Serial serum naloxone levels over the ensuing three hours showed pharmacokinetics which appear similar to those previously reported for intravenous naloxone.

Case Report

Weil, M. H. and W. Tang (2000). "Endotracheal administration of drugs during cardiopulmonary resuscitation." Crit Care Med **28**(6): 2144.

Commentary on Niemann-2000

Zaritsky, A. (1994). "Endotracheal epinephrine in cardiac arrest." Crit Care Med **22**(7): 1071-2.

Commentary on Jasani-1994

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