

EMS Research: Where do we go next?

What are the barriers to performing high-quality EMS research?

1. A paucity of highly skilled researchers.
2. Inadequate funding.
3. Failure of EMS professionals to understand the importance of conducting EMS research and translating the findings into clinical practice.
4. A lack of integrated information systems that provide for meaningful linkages with patient outcomes.
5. Logistical problems in obtaining informed consent.

What can we do about these problems?

1. A large cadre of career EMS investigators should be developed and supported in the initial stages of their careers. Highly structured training programs with content directed toward EMS research methodologies should be developed.
2. Centers of Excellence should be created to facilitate EMS research. These Centers will bring together experienced investigators, institutional expertise, and resources such as budgetary and information systems support. Centers will develop and maintain strong working relationships with local and regional EMS providers. As the focal point of these resources, Centers of Excellence will be the catalyst for collaboration between EMS systems and investigators. Such an environment will enable quality research to flourish.
3. Federal agencies that sponsor research should acknowledge their commitment to EMS research.
4. States, corporations, and charitable foundations should be encouraged to support EMS research.
5. The efforts of EMS professionals, delivery systems, academic centers and public policy makers should be organized to support and apply the results of research.
6. EMS professionals of all levels should hold themselves to higher standards of requiring evidence before implementing new procedures, devices or drugs.
7. There should be standardized data collection methods at local, regional, state and national levels. These data must be devoid of information that allows individual patient identification. All EMS provider agencies should adopt the Uniform Prehospital Data Elements for data collection.
8. The Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) should work with EMS research stakeholders to evaluate the current requirements for exception from informed consent in emergency situations and to identify those requirements that are serious impediments to conducting EMS research. The FDA, OHRP, and EMS research stakeholders should work together to develop and propose EMS-specific consent strategies as well as appropriate revisions to the existing regulations to reduce the impediments to research while continuing to adequately protect research subjects.

Sayre MR, White LJ, Brown LH, McHenry SD. The National EMS Research Agenda executive summary. Emergency Medical Services. Ann Emerg Med 2002; 40:636-43.

1. The example of rapid sequence intubation (RSI) for severe head injury patients: Does it help or hurt? How do we find out?

The evidence: Two recent publications, neither of which is a prospective, randomized, controlled trial:

1. Davis DP, Hoyt DB, Ochs M, et al. *The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. J Trauma 2003; 54: 444-453.* Setting: Eleven advanced life support agencies in San Diego County, CA, USA.

Methodology: Prospective enrollment of 209 consecutive trauma patients with GCS 3-8, head injury by mechanism or exam, transport time <10 min, inability to intubate without RSI. Each subject was hand-matched to three non-intubated historical controls (total 627).

Outcomes: Higher incidence of mortality and lower incidence of good outcome (discharge, sign out against medical advice, transferred to a rehabilitation facility, etc) in the intubated group. Hyperventilated ($PCO_2 < 33$ on arrival at the trauma center) RSI patients had higher mortality than non-hyperventilated RSI patients.

Conclusions: Paramedic RSI to facilitate field intubation of head-injured patients is associated with higher mortality and morbidity. The authors postulate transient hypoxia, inadvertent hyperventilation, and longer scene times as possible reasons.

“Ultimately, a randomized trial is warranted to further investigate the impact of prehospital RSI on outcome in head-injured patients.”

2. Bochicchio GV, Ilahi O, Joshi M, Bochicchio K, Scalea TM. *Endotracheal intubation in the field does not improve outcome in trauma patients who present without an acutely lethal traumatic brain injury. J Trauma 2003; 54: 307-311.*

Objective: “to prospectively evaluate whether prehospital intubation improved outcome in adult trauma patients with nonlethal (death within 48 hours) traumatic brain injury.”

Setting: R Adams Cowley Shock Trauma Center, Baltimore MD, USA

Methodology: Prospective enrollment of 191 consecutive patients with $GCS \leq 8$, head AIS ≥ 3 , intubated in field (78, 41%) or immediately upon arrival at the trauma center (113, 59%). Patients were not intubated in the field if either they were transported by a BLS unit that elected not to wait for a distant ALS unit, or the treating paramedic opted not to intubate.

Outcomes: Patients intubated in the field had a higher mortality rate, a higher rate of pneumonia, a higher number of ventilator days, longer ICU stays, and longer hospital stays.

Conclusions: Field intubation is associated with an increase in morbidity and mortality for patients with head injuries that are not acutely lethal.

“A randomized, prospective study is warranted to confirm these results.”

What we really need:

A prospective, randomized, controlled trial of RSI vs. bag-valve-mask airway management, adequately powered to detect a clinically meaningful difference in outcome.

2. The example of non-invasive ventilation (CPAP / BiPAP): Does it “work” in the out-of-hospital setting? How do we find out?

The evidence: Five publications, none of which are prospective, randomized, controlled trials:

1. *Hastings D, Monahan J, Gray C, Pavlakovich D, Bartram P. CPAP. A supportive adjunct for congestive heart failure in the prehospital setting. J Emerg Med Serv JEMS 1998; 23:58-65.*

Setting: Galveston, TX, USA: EMT-Bs, EMT-Is, and EMT-Ps trained for four hours.

Methodology: Six-month uncontrolled clinical trial (case series) of 32 patients.

Short term outcomes: “Most patients responded favorably,” a table lists reduced respiratory rate, reduced heart rate, increased SpO₂, and stabilized BP, with no numbers or statistics given; one patient was intubated in the field, none in the hospital.

Long term outcomes: None reported.

Conclusion: “The use of nasal CPAP...in the prehospital setting shows considerable promise.”

2. *Gardtman M, Waagstein L, Karlsson T, Herlitz J. Has an intensified treatment in the ambulance of patients with acute severe left heart failure improved the outcome? Eur J Emerg Med 2000; 7:15-24.*

Setting: Goteborg, Sweden: added sublingual nitroglycerin (4% before, 68% after), CPAP (<1% before, 91% after), and furosemide (13% before, 84% after) to mobile coronary care unit treatment options for “acute severe heart failure.”

Methodology: Before-and-after trial, with 158 patients in each group.

Short term outcomes: lower creatinine kinase-MB (median 13 before, 8 after, p=0.007) and lower incidence of pulmonary edema (76% before vs 93% after) on arrival at the hospital

Long term outcomes: no change in re-admission rates, or in one-year mortality (39.2% vs. 35.8%, p=0.64)

Conclusion: Some short-term benefit, no improvement in long-term mortality.

“This study suffers from the weakness of being an observational study and not a randomized trial.”

“We do not know which one of the three treatments was the most important.”

3. *Craven RA, Singletary N, Bosken L, Sewell E, Payne M, Lipsey R. Use of bilevel positive airway pressure in out-of-hospital patients. Acad Emerg Med 2000; 7:1065-8.*

Setting: Norfolk, VA: Paramedics and cardiac technicians trained for two hours; BiPAP units were placed on five of the city’s ten rescue units

Methodology: Pseudo-randomized clinical trial (five units with BiPAP, five without; no cross-over), with 62 patients enrolled (25 control, 37 BiPAP)

Short term outcomes: pulse oximetry: control 89% to 97%, BiPAP 82% to 95%;

intubations: control 28% vs BiPAP 11% (NS); admission: control 21/25 (12 ICU), BiPAP 32/37 (15 ICU); ED mortality: control 0, BiPAP 1; in-house mortality: control 2/24,

BiPAP 6/37; personnel felt BiPAP easy/very easy to use, safe/very safe to use, effective/very effective at reducing dyspnea and signs of respiratory distress.

Long term outcomes: None reported.

Conclusion: Personnel feel BiPAP is easy to use and is effective.

4. Kosowsky JM, Stephanides SL, Branson RD, Sayre MR. *Prehospital use of continuous positive airway pressure (CPAP) for presumed pulmonary edema: a preliminary case series. Prehosp Emerg Care 2001; 5:190-6.*

Setting: Cincinnati, OH: Four ALS ambulances were equipped with CPAP; paramedics were trained for at least four hours.

Methodology: Case series of 19 patients: 13 actually had cardiogenic pulmonary edema. (Others had COPD, pneumonia, intracranial hemorrhage.)

Short term outcomes: Respiratory rate did not change (34.0/min before CPAP to 33.3/min after CPAP); pulse oximetry increased (15 pts: means 83.3% to 95.4%).

Long term outcomes: None reported.

Conclusion: “pre-hospital use of CPAP is feasible and may avert the need for ETI”;

“Controlled clinical trials are needed to address the overall utility and cost-effectiveness of CPAP systems in the prehospital setting.”

5. Kallio T, Kuisma M, Alaspaa A, Rosenberg PH. *The use of prehospital continuous positive airway pressure treatment in presumed acute severe pulmonary edema. Prehosp Emerg Care 2003; 7:209-13.*

Setting: Helsinki, Finland: CPAP has been used routinely in the field for more than 10 years, but only by the one physician-staffed ambulance (not by the four paramedic-staffed ALS ambulances, or the seven BLS ambulances). Patients also receive an IV nitroglycerin drip, and IV morphine. (No furosemide is given until arrival at the hospital.)

Methodology: Two-year retrospective case series of 115 pts, 121 total transports.

Short term outcomes: significant increases in SpO₂ (means 77% to 90%) and significant reductions in RR, SBP, and HR were seen; 6 patients were intubated before arrival at hospital, 6 more patients intubated in the hospital. No comparison groups.

Long term outcomes: None reported.

Conclusions: Improvements in oxygenation, RR, HR, and SBP; nitroglycerine and morphine may have contributed; “...the benefit of prehospital CPAP needs to be verified in controlled, randomized studies.”

What we really need:

A prospective, randomized, controlled trial of non-invasive ventilation vs. “standard” treatment, adequately powered to detect a clinically meaningful difference in outcome.

Point to consider in designing the trial that is really needed:

1. It can't be “blinded,” except to the person judging outcome.
2. Experimental arm(s): CPAP, BiPAP, or both?
3. Presumably the study would allow (and would need to carefully track, to allow for comparison of groups) all other “standard” treatments (nitroglycerin, diuretics, morphine, oxygen, etc).
4. What outcome measures do we examine? And for each, what is a clinically meaningful difference?

Welsford M, Morrison LJ. Defining outcome measures for out-of-hospital trials in acute pulmonary edema. *Acad Emerg Med* 2002; 9: 983-988.

Respiratory distress was the #2 “priority condition” in adults in the EMSOP project, with alleviation of discomfort, impaired physiology, patient satisfaction, and survival as the primary outcome categories.

Methods: Identified outcome measures through a literature search focus group added several more, for a total of 21 possible measures. Half of the Ontario membership of CAEP was surveyed.

Results: respiratory rate, heart rate, out-of-hospital intubation rate, ED intubation rate, respiratory distress scale, subjective dyspnea scale, out-of-hospital mortality, and survival to discharge. (Should we examine long-term outcomes also?)

Regulatory issues in conducting out-of-hospital resuscitation research

What about the issue of informed consent in the hypothetical CPAP study being designed above? Craven et al. obtained informed consent in the field, with laminated cards – there is no discussion of how this was handled with critically ill patients.

A. The United States perspective

Summer 1993: Office for Protection from Research Risks: issues opinion calling for a strict interpretation of federal research regulations; requires prospective, informed consent for all NIH-funded research. FDA terminates two trials of active compression-decompression CPR. Federal moratorium on resuscitation research begins.

Oct 1994: Coalition of emergency physicians, critical care specialists, cardiologists, bioethicists, and others develop a consensus statement offering the development of federal regulations to address resuscitation research involving patients who are unable to provide consent. (Biros MH, Lewis RJ, Olson CM, Runge JW, Cummins RO, Fost N. Informed consent in emergency research. Consensus statement from the Coalition Conference of Acute Resuscitation and Critical Care Researchers. *JAMA* 1995; 273:1283-7.)

Oct 1996: FDA publishes its final rule (21 CFR 50.24) on “exceptions to informed consent in certain emergency research circumstances,” allowing for waiver of informed consent for certain types of research when informed consent cannot be obtained, if a number of conditions are met. Many of the coalition consensus recommendations are incorporated.

Sept 1998: FDA issues “Guidance for Institutional Review Boards and Clinical Investigators” with clarification of certain items (available at www.fda.gov/oc/ohrt/irbs/except.html)

Key requirements of 21 CFR 50.24:

1. “available treatments are unproven or unsatisfactory” – this is not strictly true in the case of CPAP, as it might be with hemorrhagic shock.
2. “there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation” – could do this with repeat patients.

3. "If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation."
4. "Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn"
5. "Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits"
6. "Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results"

U.S. studies that have been carried out or are underway using these provisions:

Sloan EP, Koenigsberg M, Gens D, et al. Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock: a randomized controlled efficacy trial. Jama 1999; 282:1857-64.

Ornato JP, McBurnie MA, Nichol G, et al. The Public Access Defibrillation (PAD) trial: study design and rationale. Resuscitation 2003; 56:135-47.

Kremers MS, Whisnant DR, Lowder LS, Gregg L. Initial experience using the Food and Drug administration guidelines for emergency research without consent. Ann Emerg Med 1999; 33:224-9.

Longstreth WT, Jr., Fahrenbruch CE, Olsufka M, Walsh TR, Copass MK, Cobb LA. Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest. Neurology 2002; 59:506-14.

Allredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001; 345:631-7.

At least two studies have failed due to inability to meet these provisions:

Kowey P, Ornato J. Resuscitation research and emergency waiver of informed consent. Resuscitation 2000; 47:307-10. (A study comparing lidocaine and amiodarone was cancelled due to difficulty getting FDA and IRB approval.)

Rozenberg A, Incagnoli P, Delpech P, et al. Prehospital use of minimally invasive direct cardiac massage (MID-CM): a pilot study. Resuscitation 2001; 50:257-62. (A multi-center EMS study of the MID-CM device was cancelled when the company's investors withdrew funding.)

Other commentary on this topic:

Biros MH. Development of the multiorganizational document regarding emergency research consent. Acad Emerg Med 1996; 3:101-5.

Lowenstein DH, Allredge BK, Allen F, et al. The prehospital treatment of status epilepticus (PHTSE) study: design and methodology. Control Clin Trials 2001; 22:290-309.

- Marwick C. *Research in emergency circumstances. Jama* 1995; 273:687-8.
- Olson CM. *The letter or the spirit. Consent for research in CPR. Jama* 1994; 271:1445-7.
- Levine RJ. *Research in emergency situations. The role of deferred consent. Jama* 1995; 273:1300-2.
- Sloan EP, Koenigsberg M, Houghton J, et al. *The informed consent process and the use of the exception to informed consent in the clinical trial of diaspirin cross-linked hemoglobin (DCLHb) in severe traumatic hemorrhagic shock. DCLHb Traumatic Hemorrhagic Shock study group. Acad Emerg Med* 1999; 6:1203-9.
- Sloan EP, Nagy K, Barrett J. *A proposed consent process in studies that use an exception to informed consent. Acad Emerg Med* 1999; 6:1283-91.
- Kremers MS, Whisnant DR, Lowder LS, Gregg L. *Initial experience using the Food and Drug administration guidelines for emergency research without consent. Ann Emerg Med* 1999; 33:224-9.
- Biros MH, Fish SS, Lewis RJ. *Implementing the Food and Drug Administration's final rule for waiver of informed consent in certain emergency research circumstances. Acad Emerg Med* 1999; 6:1272-82.

B. The European perspective (as viewed from the U.S.)

- Apr 2001: Directive 2001/20/EC of the European Parliament and of the Council.
 “persons incapable of giving their consent...in such cases the written consent of the patient’s legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.” Also mentions a “prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial”
- Jun 2002: Letter from resuscitation researchers from Austria, Germany, UK, Belgium, and Norway in *Resuscitation*: “The Directive makes no exception for emergency situations and therefore threatens to prevent all trials that have direct relevance to the management of victims of cardiac arrest.” *Sterz F, Singer EA, Bottiger B, et al. A serious threat to evidence based resuscitation within the European Union. Resuscitation* 2002; 53:237-8.
- Additional letters of support from Austria (2), Germany, Sweden, and the United States in the same issue of *Resuscitation*:
- “...unfortunate situation in the United States, where clinical research into resuscitation has been drastically reduced in recent years;” “We have to prevent politicians taking over research.” *Wenzel V. Optimising progress in resuscitation not optimising roadblocks. Resuscitation* 2002; 53:243-4.
- “I urge the EU ... not deprive patient in Europe of the possibility to be among the first to receive increasingly effective lifesaving measures” *Safar P. Clinical resuscitation research and informed consent. Resuscitation* 2002; 54:311-2.

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