# Improving Outcomes from Resuscitation: From H-H to TH to $H_2$

Tomas Drabek and Patrick M. Kochanek

*Circulation.* published online November 3, 2014;
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

DOI: 10.1161/CIRCULATIONAHA.114.013566

# Improving Outcomes from Resuscitation: From H-H to TH to $H_2$

**Running title:** *Drabek et al.; Improving outcomes from resuscitation*

Tomas Drabek, MD, PhD; Patrick M. Kochanek, MD, MCCM

University of Pittsburgh School of Medicine, Pittsburgh, PA



**Address for Correspondence:**
Tomas Drabek, MD, PhD
Safar Center for Resuscitation Research
University of Pittsburgh School of Medicine
3434 Fifth Ave
Pittsburgh, PA 15260
Tel/Fax: 412-383-1905
E-mail: drabekt@anes.upmc.edu

**Journal Subject Codes:** Basic science research:[130] Animal models of human disease, Heart failure:[11] Other heart failure

**Key words:** Editorial, cardiac arrest, resuscitation, hypothermia, brain ischemia

DOI: 10.1161/CIRCULATIONAHA.114.013566

Until the early 1950's there did not exist any effective treatment for airway obstruction or cardiac arrest for laypersons. In the late 50's isolated steps were described to establish a patent airway (A), provide mouth-to-mouth breathing (B) and restore circulation (C) with chest compressions. Tying those steps together into an A-B-C sequence became the basis of physiologically effective cardiopulmonary-cerebral resuscitation (CPCR), as the method was called originally.[1]

Although single steps proved to be effective, the outcomes of out-of-hospital CA treated by CPCR were not encouraging from the very start. The efforts provided by bystanders and medical personnel came often "too little too late",[2] and there was lack of specific therapies to treat the underlying causes or complications. The community-wide efforts of the public health organizations focused on the promotion of the "cardio-pulmonary resuscitation" (CPR), a newly coined term, now lacking the cerebral component.

It is thus not surprising that the mainstay of further medical research focused mainly on the heart. Restoration of cardiac rhythm became an essential centerpiece of resuscitation efforts. Significant improvements in survival of cardiac arrest victims were enabled by technological developments generally aimed to support the failing heart. The emergence of defibrillators in the 1960's, followed by percutaneous coronary interventions and mechanical devices supporting the failing heart granted the extra time to recover cardiac function in patients who would not have the same chance several years ago. The brain as the key and target organ seemed somewhat left behind, at least in these early years. Indeed, there was very little that medicine could offer to protect, or restore, the brain function.

Compared to the orchestrated full-front industry-sponsored research aimed at supporting the failing heart, only a few research centers remained interested in the brain. Negovsky's

Institute of Reanimatology in Moscow, Hossmann at the Max Planck Institute in Cologne and Peter Safar's Resuscitation Research Center in Pittsburgh were pioneers of brain-oriented resuscitation science that systematically explored the limits of restoring brain function, looking beyond the traditional horizons of the restoration of heart function. One of the areas of exploration in these investigations was the use of cerebral blood-flow promoting therapies includes hypertension and hemodilution ("H-H") designed to better support post-resuscitation brain metabolism.[3, 4]

Even if the most effective methods to preserve the circulation are employed, there are often insufficient reserves to combat evolving brain ischemia. These hemodynamic manipulations were complemented by contemporaneous explorations of the benefits of post-resuscitative therapeutic hypothermia ("TH"),[5, 6] previously well documented in cardiac surgery. The extensive work of Busto, Colbourne, and Corbett et al. documented the short and long-term benefits of hypothermia in small animal models of brain ischemia.[7] A major breakthrough in resuscitation science was achieved when two seminal papers showed that prolonged mild hypothermia improved survival and neurologic outcome in comatose survivors from cardiac arrest in a clinical setting.[8, 9] Therapeutic hypothermia has become an integral part of the resuscitation guidelines and despite recent challenges to specific details to its application,[10] targeted temperature management seems to have become an established paradigm of post-resuscitative care.

The use of pharmacologic adjuncts to prevent or ameliorate the deleterious effects of ischemia-reperfusion injury is a highly appealing concept. Different mechanistic strategies and cell signaling pathways were targeted, including delaying energy failure, protecting cell membrane integrity, preventing structural degradation, regulating protein synthesis, preventing

DOI: 10.1161/CIRCULATIONAHA.114.013566

re-oxygenation injury, and/or preserving mitochondria. Surprisingly, multiple established and promising novel drugs that seemed to have a potential to protect the brain in ischemia or restore post-resuscitation brain function have failed to deliver a breakthrough effect.[11] None of the drugs that may have yielded positive results in pre-clinical models has translated to successful clinical use.

In this issue of *Circulation*, Hayashida et al. report on a salutary effect of hydrogen ($H_2$) gas on outcome from experimental cardiac arrest in rats.[12] Inhalation of $H_2$ gas initiated upon resuscitation from six minutes of ventricular fibrillation cardiac arrest resulted in improved survival rate, neurologic outcome, and attenuation of histological damage. These results were comparable to the effects achieved with therapeutic hypothermia, while the best results were achieved when both techniques were combined.

These results are even more impressive when put into perspective with their previously published studies. The benefits of $H_2$ gas were documented in their prior work using a similar rat model of cardiac arrest resuscitated with 100% oxygen. Improvement of cardiac function with hydrogen inhalation was highlighted. The salutary impact of $H_2$ gas was at least partially attributed to its radical-scavenging effect.[13] However, prolonged administration of 100% oxygen in post-cardiac arrest victims could be deleterious in experimental setting and is not recommended in the clinical setting. In this study, the authors used resuscitation with “room air” to eliminate the potential harmful effects of post-resuscitative hyperoxia.[14] The benefits were sustained – moreover, the attenuation of CNS damage was now also documented. The authors should be applauded for their continuous efforts to explore the effects of $H_2$ on both the heart and the brain.

The average response time of urban EMS is around 7-10 minutes, and resuscitation

efforts lead to restoration of spontaneous circulation after ~ 25 min.[10] The rather short duration of the insult used in this experimental scenario – five or six minutes of ventricular fibrillation – with also rather short resuscitation efforts may not seem to be clinically relevant. These doubts are most likely unsubstantiated. Even as short experimental insults as these result in a significant post-resuscitative hemodynamic compromise and a substantial delayed neuronal degeneration in selectively vulnerable brain regions, as documented by multiple researchers worldwide.[15-17] Increased durations of the ischemic insult result in significant mortality, preventing systematic exploration of long-term outcome and complicating data interpretation with mortality bias. Thus, the paradigm used in this study is clinically relevant and well suited for testing promising therapeutic strategies.

The first report on the protective effects of $H_2$ [18] has been subsequently confirmed in various animal models, including limiting the infarct volume of brain[18] and heart[19] by reducing ischemia–reperfusion injury and providing protection against multiple-organ failure induced by sepsis.[20] These mechanisms could be shared with post-cardiac arrest syndrome which is often linked to sepsis-like state.[21, 22]

Several other studies explored the potential of $H_2$ therapy in different paradigms. Intraperitoneal administration of $H_2$ improved survival rate and neurological scores, reduced neuronal injury and inhibited neuronal apoptosis after ventricular fibrillation cardiac arrest in rabbits.[23] Intravenous treatment with hydrogen-enriched saline improved survival and neurological outcome after asphyxial cardiac arrest in rats, which were partially mediated by reducing oxidative stress, inflammation, and apoptosis.[24] The ostensibly subtle difference between the two types of cardiac arrests – ventricular fibrillation vs. asphyxial – could translate in significant differences in treatment strategies in the clinical setting. The field is beginning to

recognize the fact that “not all cardiac arrests are created equal”. Differences in underlying pathophysiological mechanisms[25-27] and outcomes between these two insults have been reported. Different regions of the brain show unique reaction even to the same insult, including different tissue oxygen levels[28] or neuroinflammation,[29] both purported targets of $H_2$ therapy. This is further underscored by the different efficacy of selected therapies in these respective insults, or even between cardiac arrest presenting with ventricular fibrillation vs. asystole.[30] It is thus reassuring that $H_2$was protective in multiple scenarios. The fact that $H_2$ was effective even in an intravenous formulation makes the drug even more potentially appealing.

The high dose of $H_2$ tested in this study was limited by administrative regulations. The dose-finding studies aimed at identifying the optimal therapeutical protocol were not yet completed. However, we are enthused that $H_2$ therapy – either inhalational or intravenous – exerts its benefits on both the heart and brain, providing a potential to put back the cerebral “C” into the CPCR concept. It is also important of paramount importance that the effects of $H_2$ are exerted independently of the effects of therapeutic hypothermia, and in fact the combined effects of these therapies appear to be synergistic. The exact underpinning mechanisms of these two therapies remain to be unveiled in future studies.

The exciting results with $H_2$ gas reported in the current study, put into perspective with multiple other reports, spark an enthusiasm for its future explorations in other experimental settings and potential translation into clinical settings. A clinical trial of hydrogen therapy in patients after cardiac arrest is currently underway.[31] We are eagerly awaiting the results.

**Conflict of Interest Disclosures:** Dr Drabek is funded by W81XWH-07-1-0682 from the US Army and from the Laerdal Foundation. Dr Kochanek is funded by NS087978 from NIH and W81XWH-10-1-0673 and W81XH-14-2-0018 from the U.S. Army. Dr Kochanek is a patent

holder on a hypothermia strategy “Emergency Preservation and Resuscitation” and a co-provisional patent holder on a Carnegie Mellon University Invention Disclosure 2012-081 “Validation of a Multiplex Biomarker Panel for Detection of Abusive Head Trauma in Well-Appearing Children”; and US Provisional Patent “Small Molecule Inhibitors of RNA Binding MOTIF (RBM) Proteins for the Treatment of Acute Cellular Injury.”

**References:**

1. Safar P, Bircher NG. *Cardiopulmonary cerebral resuscitation.* 3rd ed. London and Philadelphia: WB Saunders; 1988.

2. Eisenberg MS, Horwood BT, Cummins RO, Reynolds-Haertle R, Hearne TR. Cardiac arrest and resuscitation: a tale of 29 cities. *Ann Emerg Med*. 1990;19:179-186.

3. Leonov Y, Sterz F, Safar P, Johnson DW, Tisherman SA, Oku K. Hypertension with hemodilution prevents multifocal cerebral hypoperfusion after cardiac arrest in dogs. *Stroke*. 1992;23:45-53.

4. Sterz F, Leonov Y, Safar P, Radovsky A, Tisherman SA, Oku K. Hypertension with or without hemodilution after cardiac arrest in dogs. *Stroke*. 1990;21:1178-1184.

5. Leonov Y, Sterz F, Safar P, Radovsky A. Moderate hypothermia after cardiac arrest of 17 minutes in dogs. Effect on cerebral and cardiac outcome. *Stroke*. 1990;21:1600-1606.

6. Nozari A, Safar P, Stezoski SW, Wu X, Kostelnik S, Radovsky A, Tisherman S, Kochanek PM. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. *Circulation*. 2006;113:2690-2696.

7. Colbourne F, Corbett D. Delayed postischemic hypothermia: a six month survival study using behavioral and histological assessments of neuroprotection. *J Neurosci*. 1995;15:7250-7260.

8. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549-556.

9. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557-563.

10. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Aneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Kober L, Langorgen J, Lilja G, Moller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H, Investigators TTMT. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med*. 2013;369:2197-2206.

11. Tisherman SA. Suspended animation for resuscitation from exsanguinating hemorrhage. *Crit Care Med*. 2004;32:S46-50.

12. Hayashida K, Sano M, Kamimura N, Yokota T, Suzuki M, Ohta S, Fukuda K, Hori S. Hydrogen inhalation during normoxic resuscitation improves neurological outcome in a rat model of cardiac arrest, independent of targeted temperature management. *Circulation*. 2014;130:XX-XXX.

13. Hayashida K, Sano M, Kamimura N, Yokota T, Suzuki M, Maekawa Y, Kawamura A, Abe T, Ohta S, Fukuda K, Hori S. H(2) gas improves functional outcome after cardiac arrest to an extent comparable to therapeutic hypothermia in a rat model. *J Am Heart Assoc*. 2012;1:e003459.

14. Wang CH, Chang WT, Huang CH, Tsai MS, Yu PH, Wang AY, Chen NC, Chen WJ. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. *Resuscitation*. 2014;85:1142-1148.

15. Kwon WY, Suh GJ, Kim KS, Lee HJ, Jeong KY, Kwak YH, Kim K. Niacin suppresses the mitogen-activated protein kinase pathway and attenuates brain injury after cardiac arrest in rats. *Crit Care Med*. 2013;41:e223-232.

16. Janata A, Drabek T, Magnet IA, Stezoski JP, Janesko-Feldman K, Popp E, Garman RH, Tisherman SA, Kochanek PM. Extracorporeal versus conventional cardiopulmonary resuscitation after ventricular fibrillation cardiac arrest in rats: a feasibility trial. *Crit Care Med*. 2013;41:e211-222.

17. Popp E, Padosch SA, Vogel P, Schabitz WR, Schwab S, Bottiger BW. Effects of intracerebroventricular application of brain-derived neurotrophic factor on cerebral recovery after cardiac arrest in rats. *Crit Care Med*. 2004;32:S359-365.

18. Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, Katsura K, Katayama Y, Asoh S, Ohta S. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Nat Med*. 2007;13:688-694.

19. Hayashida K, Sano M, Ohsawa I, Shinmura K, Tamaki K, Kimura K, Endo J, Katayama T, Kawamura A, Kohsaka S, Makino S, Ohta S, Ogawa S, Fukuda K. Inhalation of hydrogen gas reduces infarct size in the rat model of myocardial ischemia-reperfusion injury. *Biochem Biophys Res Commun.* 2008;373:30-35.

20. Xie K, Liu L, Yu Y, Wang G. Hydrogen gas presents a promising therapeutic strategy for sepsis. *Biomed Res Int.* 2014;2014:807635.

21. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, Dhainaut JF, Cavaillon JM. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. *Circulation*. 2002;106:562-568.

22. Negovsky VA. Postresuscitation disease. *Crit Care Med*. 1988;16:942-946.

23. Huang G, Zhou J, Zhan W, Xiong Y, Hu C, Li X, Li X, Li Y, Liao X. The neuroprotective effects of intraperitoneal injection of hydrogen in rabbits with cardiac arrest. *Resuscitation*. 2013;84:690-695.

24. Huo TT, Zeng Y, Liu XN, Sun L, Han HZ, Chen HG, Lu ZH, Huang Y, Nie H, Dong HL, Xie KL, Xiong LZ. Hydrogen-rich saline improves survival and neurological outcome after cardiac arrest and cardiopulmonary resuscitation in rats. *Anesth Analg*. 2014;119:368-380.

25. Vaagenes P, Safar P, Moossy J, Rao G, Diven W, Ravi C, Arfors K. Asphyxiation versus ventricular fibrillation cardiac arrest in dogs. Differences in cerebral resuscitation effects--a preliminary study. *Resuscitation*. 1997;35:41-52.

26. Kamohara T, Weil MH, Tang W, Sun S, Yamaguchi H, Klouche K, Bisera J. A comparison of myocardial function after primary cardiac and primary asphyxial cardiac arrest. *Am J Respir Crit Care Med*. 2001;164:1221-1224.

27. Drabek T, Foley LM, Janata A, Stezoski J, Kevin Hitchens T, Manole MD, Kochanek PM. Global and regional differences in cerebral blood flow after asphyxial versus ventricular fibrillation cardiac arrest in rats using ASL-MRI. *Resuscitation*. 2014;85:964-971.

28. Manole MD, Kochanek PM, Bayir H, Alexander H, Dezfulian C, Fink EL, Bell MJ, Clark RS. Brain tissue oxygen monitoring identifies cortical hypoxia and thalamic hyperoxia after experimental cardiac arrest in rats. *Pediatr Res*. 2014;75:295-301.

29. Janata A, Magnet IA, Uray T, Stezoski JP, Janesko-Feldman K, Tisherman SA, Kochanek PM, Drabek T. Regional TNFalpha mapping in the brain reveals the striatum as a neuroinflammatory target after ventricular fibrillation cardiac arrest in rats. *Resuscitation*. 2014;85:694-701.

30. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-e292.

31. URL: http://www.umin.ac.jp/ctr/index.htm; Identifier: UMIN000012381. Accessed 10/29/2014.