Until the early 1950s, there did not exist any effective treatment for airway obstruction or cardiac arrest for laypersons. In the late 1950s, 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, as the method was called originally.1

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Although single steps proved to be effective, the outcomes of out-of-hospital cardiac arrest treated by cardiopulmonary-cerebral resuscitation 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 a 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 cardiopulmonary resuscitation, 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 the survival of patients who had had a cardiac arrest were enabled by technological developments generally aimed to support the failing heart. The emergence of defibrillators in the 1960s, 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 had 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.

In comparison with 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, which included hypertension and hemodilution, that were designed to better support postresuscitation brain metabolism.3,4

Even if the most effective methods to preserve the circulation are used, there are often insufficient reserves to combat evolving brain ischemia. These hemodynamic manipulations were complemented by contemporaneous explorations of the benefits of postresuscitative therapeutic hypothermia,5,6 previously well documented in cardiac surgery. The extensive work of Colbourne and Corbett7 documented the short- and long-term benefits of hypothermia in small animal models of brain ischemia. A major breakthrough in resuscitation science was achieved when 2 seminal articles showed that prolonged mild hypothermia improved survival and neurological 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 postresuscitative care.

The use of pharmacological 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 reoxygenation injury, and preserving mitochondria. Surprisingly, multiple established and promising novel drugs that seemed to have a potential to protect the brain in ischemia or restore postresuscitation brain function have failed to deliver a breakthrough effect.11 None of the drugs that may have yielded positive results in preclinical models has translated to successful clinical use.

In this issue of *Circulation*, Hayashida et al12 report on a salutary effect of hydrogen (H2) gas on the outcome from experimental cardiac arrest in rats. Inhalation of H2 gas initiated on resuscitation from 6 minutes of ventricular fibrillation cardiac arrest resulted in improved survival rate, neurological outcome, and attenuation of histological damage. These results were comparable to the effects achieved with therapeutic hypothermia, but 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 H2 gas were documented in their prior work by 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 H2 gas was at least...
partially attributed to its radical-scavenging effect. However, prolonged administration of 100% oxygen in patients after cardiac arrest could be deleterious in experimental settings and is not recommended in the clinical setting. In this study, the authors used resuscitation with room air to eliminate the potentially harmful effects of postresuscitative hyperoxia. The benefits were sustained – moreover, the attenuation of central nervous system damage was now also documented. The authors should be applauded for their continuous efforts to explore the effects of H₂ on both the heart and the brain.

The average response time of urban emergency medical services is ≈7 to 10 minutes, and resuscitation efforts lead to the restoration of spontaneous circulation after ≈25 minutes. The rather short duration of the insult used in this experimental scenario – 5 or 6 minutes of ventricular fibrillation – with also rather short resuscitation efforts may not seem to be clinically relevant. These doubts are most likely unsubstantiated. Even short experimental insults such as these result in a significant postresuscitative hemodynamic compromise and a substantial delayed neuronal degeneration in selectively vulnerable brain regions, as documented by multiple researchers worldwide. 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 H₂ has been subsequently confirmed in various animal models, including limiting the infarct volume of brain and heart by reducing ischemia-reperfusion injury and providing protection against multiple-organ failure induced by sepsis. These mechanisms could be shared with postcardiac arrest syndrome, which is often linked to a sepsislike state.

Several other studies explored the potential of H₂ therapy in different paradigms. Intraperitoneal administration of H₂ improved survival rate and neurological scores, reduced neuronal injury, and inhibited neuronal apoptosis after ventricular fibrillation cardiac arrest in rabbits. 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. The ostensibly subtle difference between the 2 types of cardiac arrests – ventricular fibrillation versus asphyxial – could translate into 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 and outcomes between these 2 insults have been reported. Different regions of the brain show a unique reaction even to the same insult, including different tissue oxygen levels or neuro-inflammation, both purported targets of H₂ 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 versus asystole. It is thus reassuring that H₂ was protective in multiple scenarios. The fact that H₂ was effective even in an intravenous formulation makes the drug even more potentially appealing.

The high dose of H₂ tested in this study was limited by administrative regulations. The dose-finding studies aimed at identifying the optimal therapeutic protocol were not yet completed. However, we are enthused that H₂ therapy – either inhalational or intravenous – exerts its benefits on both the heart and brain, providing a potential to put back the cerebral into the cardiopulmonary-cerebral resuscitation concept. It is also of paramount importance that the effects of H₂ 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 2 therapies remain to be unveiled in future studies.

The exciting results with H₂ 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. We are eagerly awaiting the results.

Disclosures
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References


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Improving Outcomes from Resuscitation: From Hypertension and Hemodilution to Therapeutic Hypothermia to H2
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