Application of cardiac surgery techniques to improve the results of cardiopulmonary resuscitation after cardiac arrest: Controlled automated reperfusion of the whole body

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Video clip is available online.

CARL components.

CENTRAL MESSAGE

The application of cardiac surgical techniques to reduce ischemia–reperfusion injury to the whole body can be used to improve the results of cardiopulmonary resuscitation after cardiac arrest.

See Commentary on page 53.

Until now, the overall results (survival and neurologic outcome) of cardiopulmonary resuscitation (CPR) after cardiac arrest (CA) have been quite dismal. They have improved when compared with the outcome over the past number of decades but are still far from ideal. This is true for both out-of-hospital cardiac arrest[1,2] and in-hospital cardiac arrest.[3] Survival after out-of-hospital cardiac arrest is reported to be in the range of 8% to 10%[2] with neurologic damage found in many of the survivors.[4] Nevertheless, all major efforts in the field of resuscitation (including CPR by laymen and professionals, improved alarm systems, and better medications) are more than valued and have resulted in some very favorable outcomes.

The pathophysiologic mechanism of injury after CA is ischemia reperfusion, not only in vital organs but also to the whole body (Figure 1). After ischemia induced by CA, low-flow reperfusion is usually established during the first phase by CPR (basic life support and advanced life support). CPR may result in the return of spontaneous circulation or (in selected cases) in the use of extracorporeal circulation. Even if return of spontaneous circulation could be established, intermittent phases of additional CA may occur.

Therefore, the reasons for the poor results of CPR after CA can be classified as:

- Critical underlying disease (eg, left ventricle rupture, free ruptured thoracic aortic aneurysms, and massive cerebral bleeding),
- Multimorbidities (eg, end-stage lung disease, chronic renal/liver failure, frailty, insulin-dependent diabetes, severe neurologic disorders, and end-stage cancer), and
- Acute multiorgan damage after ischemia–reperfusion injury.

To minimize this whole-body ischemia–reperfusion injury, we introduced the concept of controlled automated reperfusion of the whole body (CARL), which is based on cardiac surgical techniques, developed over the past 20 to 30 years (Figure 1, *C*). CARL was developed to reduce/avoid ischemia–reperfusion injury after CA but it has not been found to be successful in critical diseases or in multimorbid patients.

Intensive work in this field has resulted in previously unknown success in myocardial protection as well as organ protection in general.[5-7] Indeed, over the past decade a new

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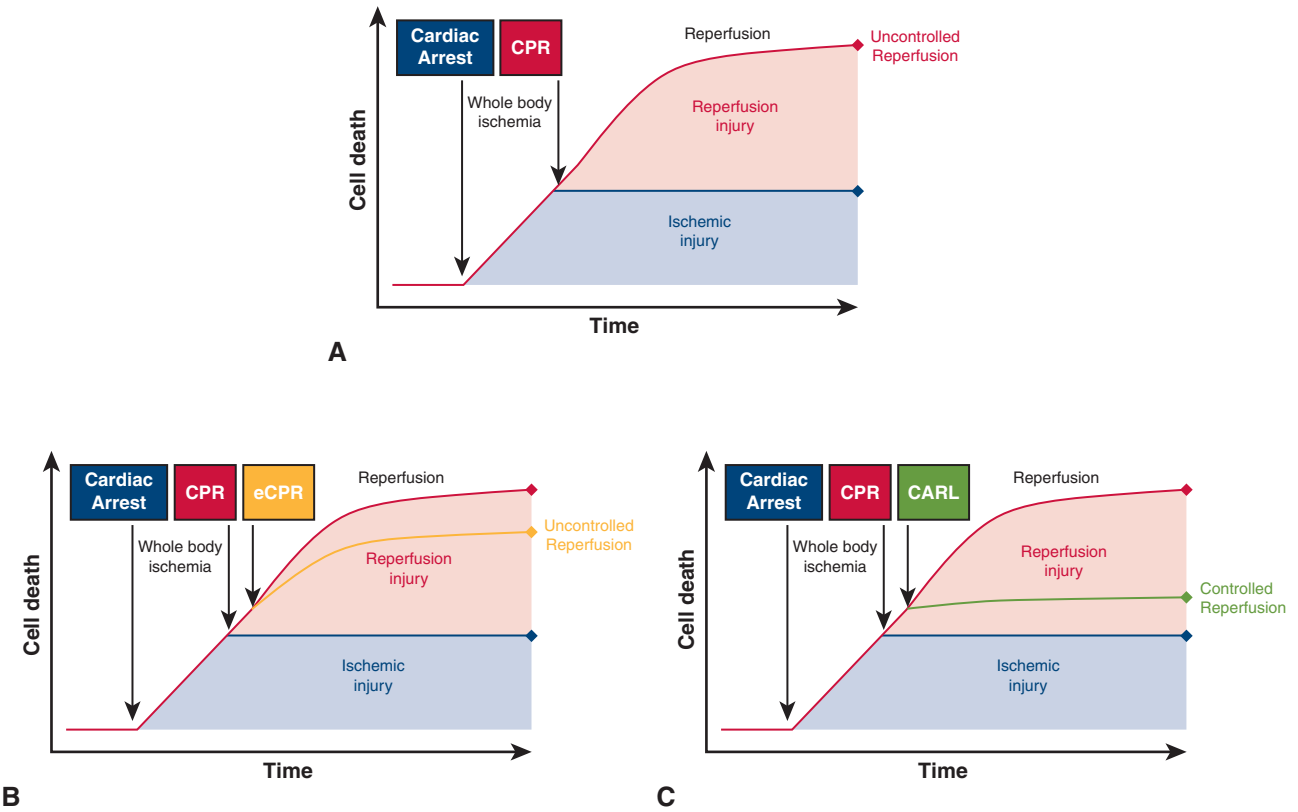

FIGURE 1. Development of ischemia reperfusion injury in treatments of cardiac arrest. Cardiac arrest results in whole body ischemia. A, Cardiopulmonary resuscitation (*CPR*) may restore minimal blood flow by chest compressions and few or no ventilation (minimal uncontrolled reperfusion; ie, unmodified blood, low flow, low pressure, minimal, or no oxygen). B, Extracorporeal CPR (*eCPR*) has shown beneficial effects but represents an undefined therapy approach. C, Controlled automated reperfusion of the whole body (*CARL*) reduces reperfusion injury by control and modification of more than 10 blood parameters and control and modification of specific reperfusion parameters (for details see Table 1).

field of research in applying innovative cardiac surgical techniques to the field of CA and CPR[8-14] has emerged.

The aim of this Invited Expert Opinion article is to review the pathophysiology of ischemia–reperfusion injury after CA, the scientific background and clinical development for CARL, and the latest experimental data. The CARL concept is also addressed in Video 1.

SCIENTIFIC BACKGROUND

Our group in Freiburg, in cooperation with our colleagues from Yale University and the Max-Planck-Institute in Cologne, Germany, has recently published a review in *Nature Reviews Neuroscience* describing the scientific background of the ischemia tolerance of the brain as the most ischemia-sensible organ and opportunities to treat ischemia reperfusion injury (IRI) by modifications and control of the initial reperfusion phase.[14] Previous reports have already shown that the ischemic tolerance, even of the brain, is substantially prolonged if appropriate reperfusion conditions are applied.[11,15,16]

After more than 15 to 20 years of research, our group has developed a technique called CARL (Figure 2), which enables users to clinically apply many of the important basic science principles recently outlined in detail.[14] The reperfusion parameters, which are controlled by our CARL technique, are summarized in Table 1.

In addition to the development of the scientific background for this new approach,[9-14] innovative

VIDEO 1. Professor Beyersdorf explains the rationale of controlled automated reperfusion of the whole body (CARL). Video available at: https://www.jtcvs.org/article/S2666-2736(21)00356-9/fulltext.

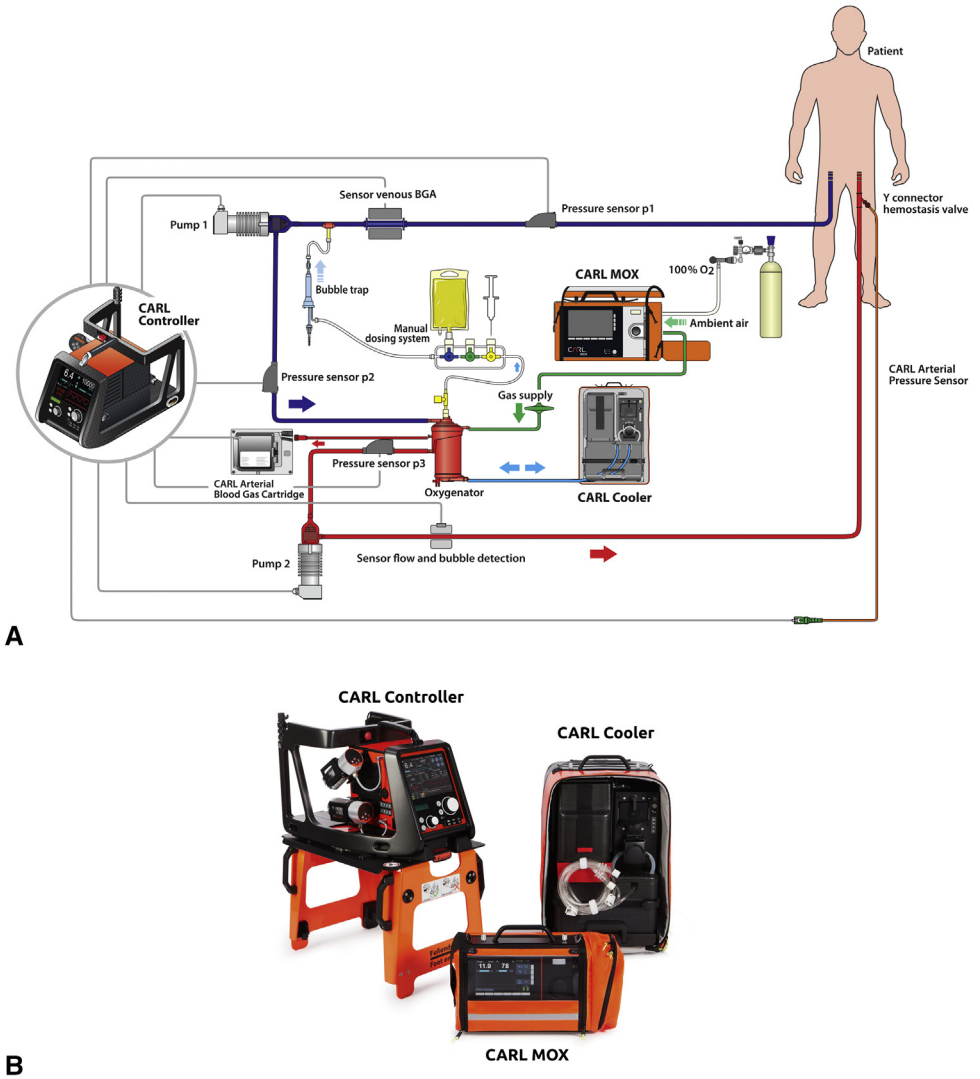

FIGURE 2. A, Schematic drawing of the controlled automated reperfusion of the whole body (*CARL*) set up. B, Picture of CARL controller, CARL oxygenation controller (*CARL MOX, Resuscitec GmbH, Freiburg, Germany*), and CARL cooler. *BGA*, Blood gas analysis.

technical developments have evolved and have resulted in a new, portable device (the CARL Controller, Resuscitec GmbH, Freiburg im Breisgau, Germany), which allows the principles of the CARL therapy to be applied (Table 1) in and out of the hospital, including controlled oxygenation (the CARL MOX) and immediate cooling of the patient (the CARL Cooler) (Figure 2). This technology can be used routinely inside the hospital, but is also intended to be used outside the hospital in selected cases. The out-of-hospital use is already being practiced in some centers in Germany.

To improve the results of CPR after CA, the use of extracorporeal circulation systems was introduced by several groups around the world.[50-53] Although its superiority over standard CPR techniques has not been established, there are several indications showing the beneficial effects in selected patients. Nevertheless, extracorporeal CPR does not address the consequences of ischemia–reperfusion injury directly (Figure 1). Therefore, based on the current pathophysiologic knowledge for brain viability after ischemia[14] the CARL therapy has been developed to control a number of different aspects of IRI, which are outlined in Tables 1 and 2.

PRELIMINARY CLINICAL DATA

The resulting clinical data of preliminary pilot studies using this new technique are very promising.[54-56] In the preliminary clinical study, 7 out of 14 surviving patients regained full consciousness, whereas 6 of these 7 were assigned to cerebral performance class 1.[55]

However, before any meaningful conclusions can be drawn, the ongoing multicenter, European clinical study (postmarket clinical follow-up) (DRKS00018967),

TABLE 1. Rationale for controlled automated reperfusion of the whole body (CARL)

Overall	Parameter	Rationale	Publications
Composition of reperfusate	Calcium	Lowering serum calcium to prevent cellular calcium uptake in first minutes of reperfusion to avoid additional cell damage	Refs[17-23]
	Sodium	Avoid excessive alterations of serum sodium levels with respect to cerebral volume displacements and subsequent cerebral edema	Refs[17,24,25]
	Potassium	Secondary cardioplegia; that is, convert ventricular flutter/fibrillation into asystole with subsequent minimized oxygen demand of the myocardium. Secondary cardioplegia using elevated potassium levels is only applicable when stable circulatory support is provided by extracorporeal circulation	Refs[26]
	Magnesium	Increase magnesium to support membrane stabilization	Ref[27]
	Viscosity	Lowering viscosity to improve perfusion by reducing the no-reflow-phenomenon	Refs[28]
	Hemodilution	Improving perfusion by reducing the no-reflow-phenomenon	Refs[28,29]
	Osmolality	Increase serum osmolality to limit cerebral edema and decrease vasopressor requirements	Refs[30,31]
	Colloid osmotic pressure	Increase colloid osmotic pressure to limit cerebral edema and decrease vasopressor requirements	Refs[30,31]
	Oxygen	Lowering oxygen to limit generation of oxygen free radicals	Refs[23,32]
	Carbon dioxide	Permission of temporary elevated carbon dioxide levels to support pH-stat strategy	Ref[33]
	pH	pH-stat strategy to lower cellular metabolism during first 30 min of reperfusion until substrates are replenished	Ref[33]
	Lidocaine	Addition of lidocaine for rhythm conversion or stabilization	Refs[27,34,35]
	Anticoagulation	Avoid clotting and improve microcirculatory perfusion	Ref[36]
	Free radical scavengers	Addition of free radical scavengers to limit reactive oxygen species	Refs[23,32,37-39]
Conditions of reperfusion	Flow	High Flow to enhance hemodynamic power to reopen capillary flow areas and counteract the no-reflow-phenomenon especially in the brain	Refs[40,41]
	Temperature	Immediate mild hypothermia to lower cellular oxygen demand	Refs[33,42-49]
	Pressure	High pressure to reduce the no-reflow-phenomenon	Refs[28,40,41]
	Pulsatility	Enhanced hemodynamic power to reopen capillary flow areas and counteract the no-reflow-phenomenon, especially in the brain	Ref[40]

Ref, Reference.

sponsored by a European Union grant (Horizon 2020) has to be finalized. The enrollment was unfortunately delayed by the COVID-19 pandemic and is now expected to be closed in the coming 12 to 18 months.

TABLE 2. Comparison of diagnostic and therapeutic options of cardiopulmonary resuscitation (*CPR*), extracorporeal CPR (*eCPR*), and controlled automated reperfusion of the whole body (*CARL*) after out-of-hospital cardiac arrest

Option	CPR	eCPR	CARL
Venoarterial perfusion and oxygenation	(✓)	✓	✓
High arterial perfusion pressure	–	–	✓
Pulsatile arterial blood flow	–	–	✓
High arterial blood flow	–	–	✓
Immediate hypothermia	–	–	✓
Continous BGA (venous and arterial)	–	–	✓
Controlled oxygenation	–	–	✓
Hypocalcemia	–	–	✓
Hyperkalemia	–	–	✓
Hyperosmolarity	–	–	✓

✓, Available/possible; (✓), partially available/possible; –, not available/not possible, *BGA*, blood gas analysis.

CONCLUSIONS

The application of cardiac surgical techniques and innovative approaches to reduce IRI after CA has shown superior outcomes in different experimental models. Extensive basic research has been performed to develop new treatment modalities and to improve results after CA. This knowledge has led to innovative technologies that enable the application of these novel therapeutic principles in clinical practice. Preliminary clinical data have shown very promising results.

Conflict of Interest Statement

Dr Beyersdorf is founder and shareholder of Resuscitec GmbH, a start-up company of the University Hospital Freiburg. Drs Trummer and Benk are part-time employees and shareholders of Resuscitec GmbH. Dr Pooth is a part-time employee of Resuscitec GmbH.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: ECMO, ECLS, controlled automated reperfusion of the whole body, CARL, ischemia reperfusion injury