Original Article

Controlled automated reperfusion of the whole body after cardiac arrest

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Background: Sudden circulatory arrest (CA) requiring cardiopulmonary resuscitation (CPR) has for decades been associated with high mortality and frequent neurological sequelae in the rarer survivors. The high mortality and morbidity are potentially related to a severe and global ischemia/reperfusion injury (IRI) of the whole body, especially the brain. Consequently, strategies to counteract this severe IRI may improve survival and neurological recovery of affected patients.

Methods: Based on the target to limit IRI in single organs, suitable parameters and methods were composed to form a global treatment concept, the CARL method (controlled automated reperfusion of the whole body). The concept centers on extracorporeal circulation, enhanced with readily available online monitoring. It allows for targeted adaption of different parameters (i.e., blood pressure and flow, temperature, oxygen content, electrolytes) during the reperfusion process, in the sense of a controlled reperfusion. Parameters and elements of the CARL method were extensively tested in a chronic animal model. An appropriate medical device, the system configuration "CIRD 1.0" (Controlled Integrated Resuscitation Device) is approved to be applied to patients.

Results: A set of parameters that support a limitation of a global IRI have been identified in over 250 animal experiments. Their specific targets and surveillance using adequate monitoring features are described. Using the CIRD in a single center, 14 patients with witnessed, but extremely prolonged CPR (51–120 minutes) have been treated with CARL. The outcome of these patients was favorable, with 7 of 14 patients regaining full consciousness and 6 of 7 allocated to Cerebral Performance Class (CPC) "1".

Conclusions: CA followed by CPR is associated with a very high mortality and frequent neurological sequelae. Limiting the occurring severe and global IRI may be a key to an improved survival and neurological recovery. Therefore, the therapeutic approach of CARL, which stands for a personalized, comprehensive therapy based on a readily available set of monitoring data and diagnostic findings, has been developed. First experience in patients indicates beneficial effects that call for further studies in the field of CARL.

Keywords: Cardiac arrest; cardiopulmonary resuscitation (CPR); controlled automated reperfusion of the whole body (CARL); ischemia reperfusion injury; advanced life support

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Introduction

The high incidence of acute circulatory arrest (CA), accompanied by high mortality and neurological sequelae in the few survivors, represents an ongoing challenge in healthcare (1). Regardless of the cause of CA, cardiopulmonary resuscitation (CPR) has been the treatment of choice for decades to counteract the life-threatening loss of circulation and respiratory function. However, during CPR, major challenges are arising, like (I) that the underlying cause of CA cannot be treated on site and (II) the absence of a reestablished spontaneous circulation, despite maximized efforts of emergency medical services. As a consequence of this dilemma and despite extensive effort in research and education of CPR in recent years, the outcome of affected patients in terms of survival and neurological recovery has been unsatisfactory over decades (1-3).

"Targeted CPR" (tCPR) is a relatively new concept, where during the resuscitative efforts specific hemodynamic, respiratory and metabolic targets are defined (4-7). Among others, compression depth of cardiac massage, arterial blood pressure, end-tidal CO_2 measurement and the titration of oxygen are core elements of tCPR (4,8). Although tCPR represents a logical step towards a rationale based and controlled therapeutic approach in CPR, due to a significant lack of available appropriate monitoring and related therapeutic interventions, the implementation of tCPR remains rudimentary (9).

At the same time, extracorporeal circulatory life support systems (ECLS) during CPR [extracorporeal CPR (eCPR)] have seen an increased use in recent years.

Here, similar limitations, as with tCPR, apply. Although blood circulation and respiratory function may quickly be replaced by ECLS, the lack in readily available monitoring leads to non-targeted treatment (10). Consequently, despite the additional time for the detection and therapy of treatable causes of CA, survival and neurological recovery of patients treated with eCPR has only improved to a limited extent (10-12). This framework of an insufficient therapeutic approach to a major healthcare problem promotes research and evolvement of new ideas in order to provide better survival and neurological recovery of affected patients. For this reason, the subsequently described concept of "controlled automated reperfusion of the whole body" (CARL) has been developed over the past 15 years.

Methods

Ischemia/reperfusion injury (IRI) has been a topic of a continued research for decades. At its core is the fact, that deprivation of blood flow (ischemia) causes a time-dependent cellular damage mainly related to a lack of required substrates (13). Reestablishing blood flow (reperfusion) to a former ischemic area primarily provides a new supply of nutrients for cellular metabolism. However, the extent of cellular damage is even increasing during the phase of reperfusion (*Figure 1*). This effect of continued cellular damage is related to a disparity of actual demand and supply of the damaged cells during reperfusion. Moreover, reperfusion injury is triggered within brief periods of seconds or minutes following the reinstitution of blood flow to the ischemic tissue, therefore adding the requirement of a timely intervention of counteractive measures. The comprehension of these mechanisms and the derived therapeutic options limiting IRI has become an established part of therapeutic regimen in cardiac surgery, solid organ transplantation and limb reperfusion (14-17).

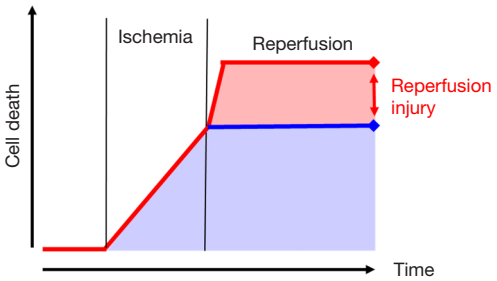

Figure 1 Ischemia reperfusion injury [modified from Garcia-Dorado *et al.*, Cardiovascular Research 2006 (13)]. Interruption of blood flow to the cells (ischemia) causes a time-dependent cellular damage. Reinstitution of blood flow with regular blood (reperfusion) does not prevent further damage (blue arrow), but is associated with continuation of cellular damage (reperfusion injury). In patients with sudden cardiac arrest, it is impossible to control ischemic damage. Therefore, the goal of the targeted algorithm of CARL is the reduction of the extent of reperfusion injury (red field) of the whole body and the brain immediately to a survivable and recoverable extent. CARL, controlled automated reperfusion of the whole body.

Core elements within the therapeutic approach to limit IRI are (I) gaining control over the physical conditions of reperfusion (i.e., blood pressure, blood flow, pulsatility, body temperature) and (II) the constitution of the reperfusion solution (recirculating blood), i.e., oxygen content, carbon dioxide level, pH, electrolyte content, osmolality (*Table 1*) (18-26). As mentioned above, readily

Table 1 Targets of controlled reperfusion of the whole body

Parameter	Target	Rationale
Arterial pO_2	100–200 mmHg	Limit generation of oxygen radicals
Arterial pCO_2	35–45 mmHg	Support pH-stat strategy
Arterial pH	≤7.25	pH-stat strategies in order to lower cellular metabolism during first 30 min of reperfusion until substrates are replenished
Potassium level in blood serum	>6 mmol/L	Convert ventricular flutter/fibrillation into asystole with subsequent minimized oxygen demand of the myocardium
		Secondary cardioplegia using elevated potassium levels are only applicable when stable circulatory support is provided by extracorporeal circulation
Sodium level in blood serum	136–146 mmol/L	Avoid excessive alterations of serum sodium levels with respect to cerebral volume displacements and subsequent cerebral edema
Calcium level in blood serum	≤0.5 mmol/L within the first 15 min of reperfusion	Prevention of cellular calcium uptake, thereby limiting cell edema
Pulsatile blood flow	60–80 mL/min/kg BW/min until pulsatile flow is generated by the patient	Enhanced hemodynamic power to reopen capillary flow areas and counteract no-reflow phenomenon especially in the brain
		Duration of pulsatile flow up to 60 min
Mean arterial blood pressure	80–120 mmHg	Enhance hemodynamic power to reopen capillary flow areas and counteract no-reflow phenomenon especially in the brain
Body hypothermia	32–33 ℃ core body temperature as fast as possible	Lowering cellular oxygen demand
Osmolality in blood serum	>320 mosmol/L	Limitation of cerebral edema
		Decrease vasopressor requirements

The target-oriented algorithm of CARL counteracts the global ischemia/reperfusion injury of the whole body and the brain during reperfusion after sudden cardiac arrest. Key parameters, their targeted range and the underlying rationale for adapting these values during the reperfusion period are displayed. CARL, controlled automated reperfusion of the whole body.

available and ample monitoring plays a key role in any therapeutic approach in these acute and critical sick patients. Therefore, extent and demand of suitable monitoring had been defined parallel to the conditions of reperfusion and the constitution of the recirculating blood within the CARL therapy. As a consequence of these demands, online and immediate blood gas analysis and arterial blood pressure monitoring have been implemented in the CARL setting, providing the treating team elementary information as baseline for a rationale-based targeted limitation of IRI, rather than an uncontrolled symptomatic therapy of CA.

Since the entity of CA is frequently associated with primarily myocardial pump failure, an extracorporeal circulation was chosen to take over basic circulatory and respiratory function within the therapeutic approach of CARL (*Table 2*). The treatment of IRI in different organs potentially requires different reperfusion conditions and solutions and may lead to contrary requirements. Exemplary for conflicting priorities in a setting of whole body reperfusion is the element "arterial blood pressure" in myocardial and cerebral reperfusion, with targeted gentle blood pressures during myocardial reperfusion and comparable high blood pressure demand in cerebral reperfusion (26,27). Based on this background and acknowledging such conflicting demands, the concept of CARL has been primarily drafted on established elements

Table 2 Availability of potential targets and therapeutic options of cardiopulmonary resuscitation, extracorporeal cardiopulmonary resuscitation and controlled reperfusion of the whole body during the initial stage of reperfusion following cardiac arrest

Potential targets and options	CARL	eCPR	CPR
Veno-arterial perfusion and oxygenation	✓	✓	(✓)
High arterial perfusion pressure	✓		
Pulsatile arterial blood-flow	✓		
High arterial blood-flow	✓		
Immediate Hypothermia	✓		
Online blood-gas analysis	✓		
Controlled oxygenation	✓		
Hypocalcemia	✓		
Hyperkalemia	✓		
Hyperosmolarity	✓		

Checked marks indicate the availability of potential targets and therapeutic options in the scenario of CPR, eCPR and CARL. Veno arterial perfusion and oxygenation may be provided by extracorporeal circulation and remains limited during CPR as indicated by brackets. CARL, controlled automated reperfusion of the whole body; CPR, cardiopulmonary resuscitation; eCPR, extracorporeal cardiopulmonary resuscitation.

of limiting IRI. Moreover, and apart from the focus of current CPR, the severe impact of a generalized IRI of the whole body and the specific demand of the not replaceable brain had been primarily addressed in the concept of CARL. Finally the global concept of CARL and its single elements were tested and further developed in numerous chronic animal experiments over the last 15 years (18-24,28).

The unique chronic animal model was established to investigate beneficial components in a setting of global reperfusion after severe ischemia with respect to the endpoints mortality and neurological recovery (21). The animals were exposed to periods of 15 and 20 minutes of unprotected warm ischemia, excluding any resuscitative attempts during this time (18,21,22). The following reperfusion period of 60 minutes was characterized by adapting the reperfusion conditions and the circulating blood according to the continuous and readily available monitoring (i.e., blood gas monitoring, arterial blood pressure, temperature measurement, mixed venous oxygen saturation etc.). Depending on the tested variable, up to 90% of the animals survived the experimental course with up to 90% of them indicating a complete neurological recovery (18,21-24).

In synopsis of the given publications in single organs and the results of the described animal experiments incorporating the global approach of CARL, a set of targets during the initial stage of reperfusion have been identified as beneficial. Continuous blood gas analysis is the starting point for a reasonable adaption of parameters like paO_2, PCO_2, pH, sodium, potassium and calcium. Beyond that, the presence of a continuous arterial blood pressure monitoring and blood flow allows a targeted adaption according to the individual needs of the patient up to the selection of approved infusion solutions supporting the global concept of CARL.

Medical device for the application of CARL

The described implementation of CARL required a suitable medical device in order to meet the aforementioned requirements of ample and readily available monitoring and a subsequent control of the conditions of reperfusion and the adaption of the recirculating blood. Since such a device was not available, a system configuration "Controlled Integrated Resuscitation Device" (CIRD 1.0; Resuscitec GmbH, Freiburg, Germany) was engineered and approved by the regulatory authorities. CIRD 1.0 is based on an ECLS and contains extended functionality, such as online blood gas monitoring, controlled oxygen supply, high and pulsatile blood flow and an appropriate cooling device for induction of hypothermia (*Figure 2*). This system configuration has been used to supply CARL therapy patients with acute CA und subsequent prolonged CPR.

Results

The aforementioned elements of a targeted and rationale-based management of extracorporeal circulation were summarized in a standard operating procedure (SOP) for hospital-based treatment. This document provides guidance for the team members during the highly interactive situation of continued CPR when the demand for extracorporeal support is arising.

The current expertise of patients treated with CARL comprises an uncontrolled and consecutive series of 14 patients with prolonged CPR following witnessed CA (unpublished data). In all cases, the interdisciplinary teams decided in an intention-to-treat situation on the

Figure 2 Controlled Integrated Resuscitation Device. Due to the absence of necessary monitoring and performance, conventional ECLS devices are not suitable for the implementation of CARL. In order to provide CARL, the system configuration "CIRD 1.0" was assembled by Resuscitec (Resuscitec GmbH, Freiburg, Germany) and approved by the regulatory authorities for patient treatment. CIRD 1.0 is based on an ECLS and contains extended functionality and performance like online blood-gas monitoring, controlled oxygen supply, high and pulsatile blood flow and an appropriate cooling device for induction of hypothermia. CARL, controlled automated reperfusion of the whole body; CIRD 1.0, Controlled Integrated Resuscitation Device; ECLS, extracorporeal life support system.

application of extracorporeal circulation using the CIRD 1.0 device. Therefore, all 14 patients received the monitored, rationale based and targeted therapeutic approach of CARL. The results of this approach were similar to those of the preclinical experiments. Despite the extremely prolonged preceding periods of CPR between 51 and 120 minutes, 7 of 14 surviving patients regained full consciousness while 6 of these 7 were assigned to Cerebral Performance Class (CPC) "1". This complete cerebral recovery also applied to one patient of this series with the most extended preceding period of 120 minutes CPR, who returned to her former work despite a remaining paresis of the legs due to an arteria spinalis anterior syndrome (29).

Conclusions

For decades, CA followed by CPR has been associated with very high mortality and frequent neurological sequelae in the few survivors. The current method of circulatory support in these situations dates back to the early 1960s, when external cardiac massage and defibrillation was invented. It presents a symptomatic therapy that aims towards a jump start of the just failing heart, so as to provide circulation. CPR supported by extracorporeal circulation (eCPR) has become more important and more widely accepted in recent years, as it might allow a better survival and neurological recovery by temporary takeover of circulation and gas exchange. However, the results of eCPR are still controversial. Limited improvements in survival and frequent neurological impairment of resuscitated patients are still reported.

Under these premises, there is growing evidence, that a severe and generalized IRI occurs during and after CPR and eCPR, causing severe harm in affected patients and leading to an unsatisfying morbidity and mortality (30-32). For this reason, 15 years back we focused our research onto the limitation of this generalized IRI of the whole body and the brain. The therapeutic CARL approach represents an evolved method that aims towards a limitation of a generalized IRI and follows the current highly demanded concept of tCPR (4,18,22,26). CARL allows for a rationale-based, personalized and comprehensive therapy based on a readily available set of monitoring data and diagnostic findings.

Our demand regarding a suitable medical device for the implementation of CARL was solved by assembling a system configuration, which allowed the application of CARL in 14 patients with prolonged CA. First experiences in these patients showed promising results with superior neurological recovery in the 50% survivors. Yet, these results can only contribute a little piece of evidence to the wide field of understanding and counteracting IRI following CA.

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Footnote

Conflicts of Interest: G Trummer, C Benk and F Beyersdorf are shareholder of Resuscitec GmbH. G Trummer and C Benk received salaries for part-time employment.

Ethical Statement: This study was approved by the Ethics Committee of Albert-Ludwig University Freiburg/ Germany, No. 86/14 (§23b MPG) on May 15th, 2014. Written informed consent was obtained from the patient for publication and any accompanying images.

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