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HERZZENTRUM

Controlled Integrated Resuscitation Device (CIRD) in the streets

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Conflict of Interest

Shareholder of ResuSciTec

(Start-up company of the University Freiburg, Germany)

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Tremendous developments in perfusion technology over the last decade: 1. Optimization of perfusion

- Extracorporeal circulation (heart-lung-machine)
- ECMO
- ECLS
- Ante- and retrograd cerebral perfusion
- Myocardial protection

Next evolutionary step in extracorporeal circulation: 2. Treatment during perfusion

Maintain physiologic perfusion of normal tissue

↓

Provide treatment with extracorporeal perfusion for diseased tissue.

- Isolated organ perfusion for transplantation (OCS)
  - Lung
  - Heart

Recent innovations in extracorporeal perfusion – Treatment of damaged tissue by ischemia

- Myocardium (Beyersdorf et al., 1992; Buckberg 1986)
- Skeletal muscle (Beyersdorf et al.,1991)
- Lung (Halldorsson et al., 1998)
- Kidney (Haab et al.,1996)
- Liver (Hong et al., 2012)

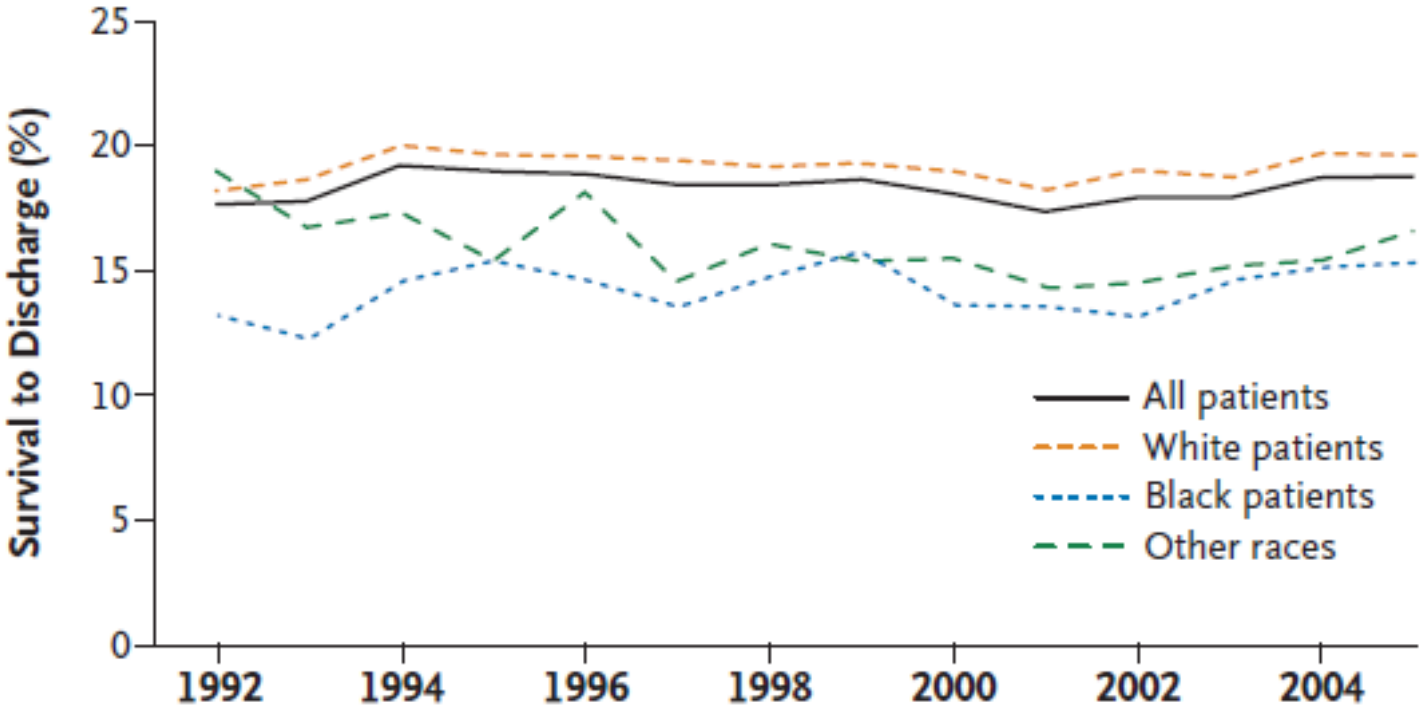


Figure 1. Survival to Hospital Discharge after In-Hospital CPR, According to Year and Race.

Survival is poorer for black and other nonwhite patients ($P<0.001$). There is no significant change in overall survival from 1992 to 2005 ($P=0.57$ with the use of the likelihood-ratio test).

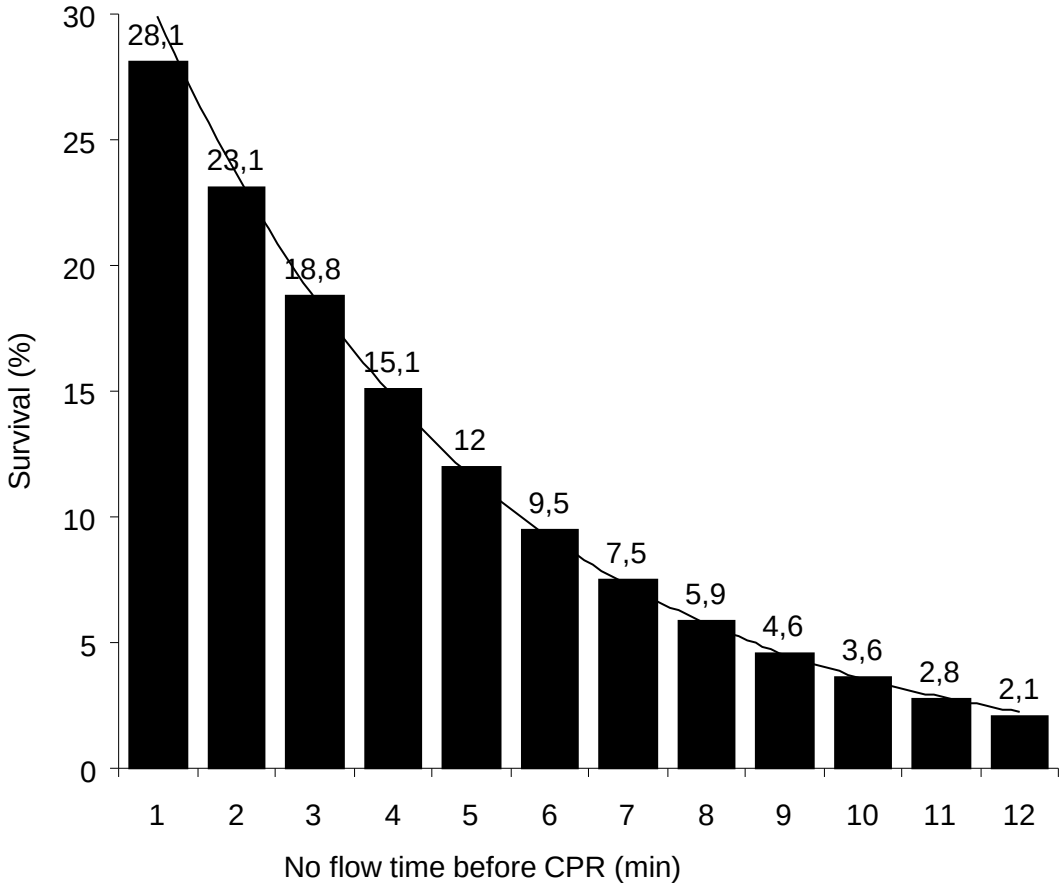
(Ehlenbach WJ et al. NEJM 2009; 361: 22-31)

Survival out-of-hospital-CPR

Survival 1-5 %

Neurologic intact survival < 1.5 %

(El-Menyar AA Chest 2005; 128: 2835-46)

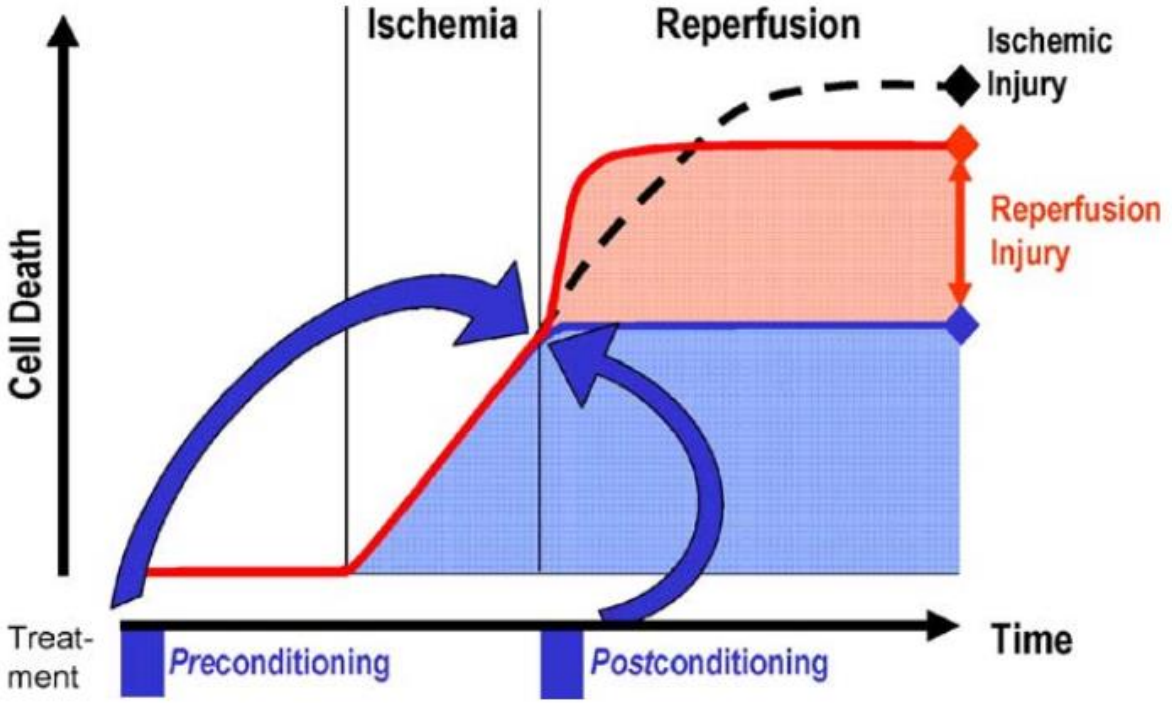


Dissertation Breuninger, Freiburg, 2012

Pathophysiology of inadequate hemodynamics during CPR

- ischemic insult after cardiac arrest
- low flow state
  - coronary perfusion
  - cerebral perfusion
- post-resuscitation syndrome
  - early inflammatory response („sepsis like“)
  - myocardial dysfunction
  - neurologic dysfunction

Ischemic-Reperfusion Injury



Garcia-Dorado et al, Cardiovasc Res. 2006

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Main reasons for poor prognosis in cardiac arrest patients

- ischemia / reperfusion injury during cardiac arrest and CPR
- lack of return of spontaneous circulation (ROSC)
- re-arrest from hemodynamic instability after ROSC
- Multi-organ dysfunction
- Post-resuscitation syndrome

Results after extracorporeal CPR using ECLS (eCPR)

Neurologic intact survival

12.3 %

Inverse relationship between survival and Collapse-to-ECLS interval

(Nagao et al. Circ J 2010; 74: 77-85)
(Morimura et al. Resuscitation 2011; 82: 10-14)

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New Approach to CPR: Controlled automated reperfusion of the whole body (CARL)

- Control of the conditions of reperfusion after cardiac arrest
- Control of the compositions of the initial reperfusate after cardiac arrest
- Automation of analysis of blood parameters to determine individual constituents of the reperfusate

Control of the conditions of reperfusion after cardiac arrest

Control of the conditions of reperfusion

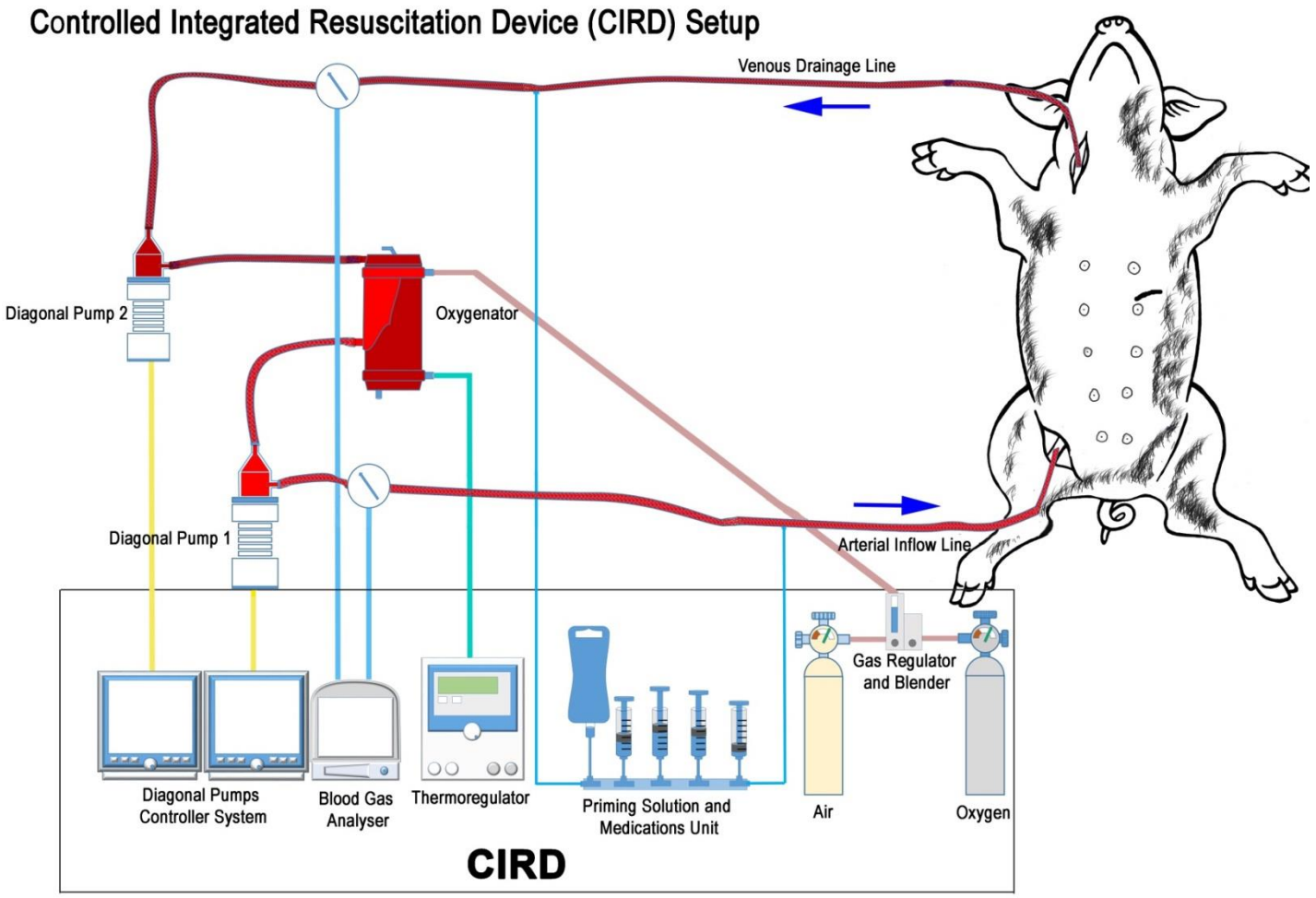
- High perfusion pressure (> 80 mmHg)
- Pulsatile perfusion
- High Flow
- Immediate hypothermia
- Avoid inotropes

Control of the composition of the reperfusate after cardiac arrest

Control of the composition of the reperfusate

- Pharmacologic defibrillation by potassium (secondary cardioplegia)
- Immediate heparinization to counteract hypercoagulation after cardiac arrest
- Hyperosmolarity
- Control initial oxygen content
- Blood pH
- Prevention of cellular calcium overload
- Free radical inhibition

Automation of analysis of blood parameters to determine individual constituents of the reperfusate



Taunyane, Beyersdorf et al.

Experimental evaluation of the concept of Controlled Automated Reperfusion of the whole body (CARL)

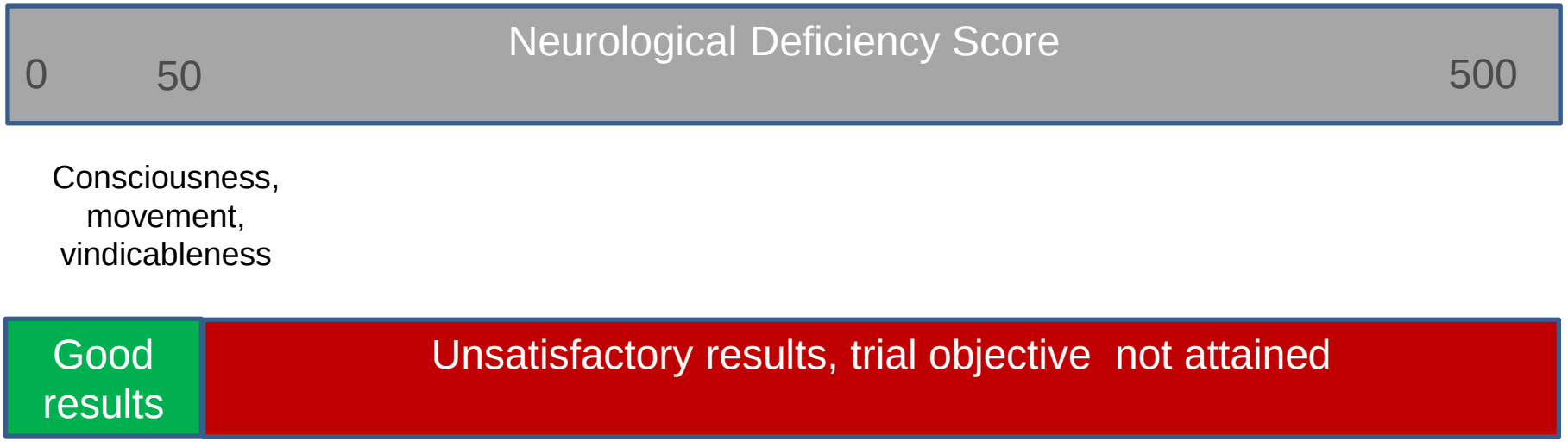
2005 – 2016

n > 200 pig experiments with a follow-up period of 7 days

Parameters

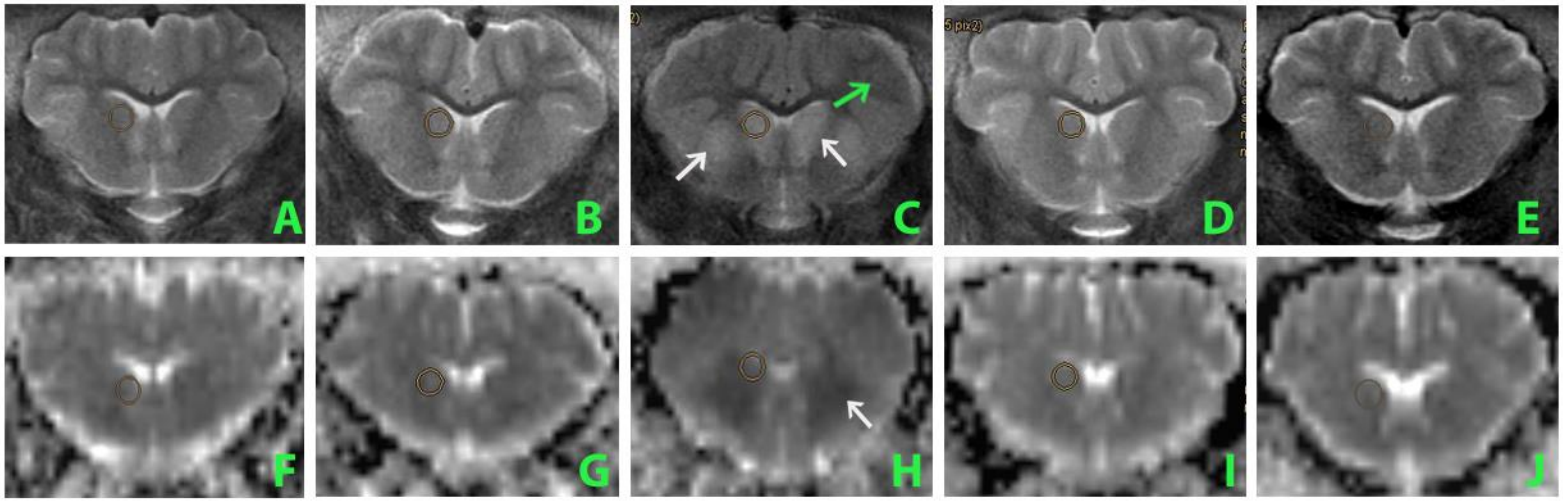
- Mortality
- Hemodynamics and perfusion parameters
- Cellular injury markers (AST, ALT, CK, NSE)
- Laboratory data (blood serum)
- Neurologic assessment
  - Neurologic deficit score
  - MRI
  - Glial fibrillary acidic protein (GFAP) immunohistochemistry

Evaluation basis of the animal experiments



Mortality and neurological recovery during an observation period of 7 days

Forbess et al, Ann Thorac Surg. 1995

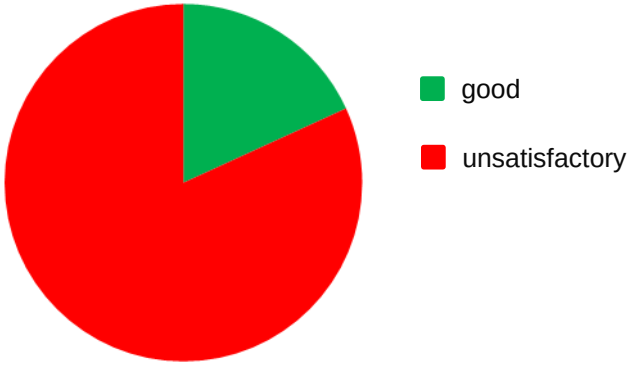


Taunyane, Beyersdorf et al. in press

Animal experiments 20 minutes I

Investigated parameter
Normothermia

N=11
2/11 good
9/11 unsatisfactory



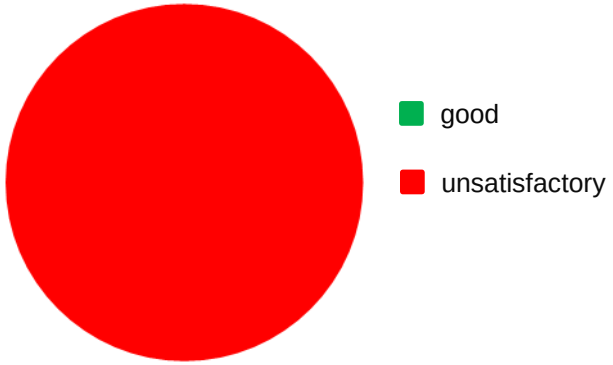
Interpretation
Normothermia in the reperfusion phase has adverse effects

Consequence
Hypothermia should be part of the controlled reperfusion

Animal experiments 20 minutes II

Investigated parameter
100 % Oxygen application with CIRD

N=8
0/8 good
8/8 unsatisfactory



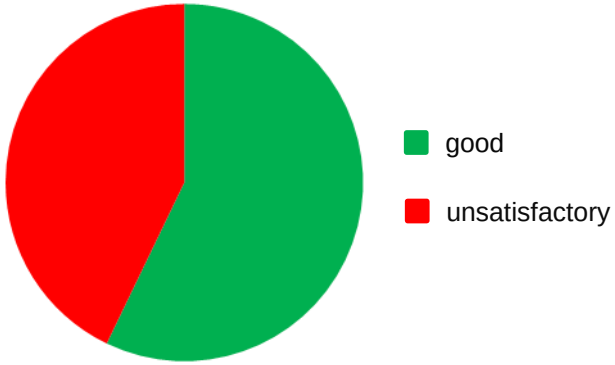
Interpretation
The application of 100% oxygen in the reperfusion phase is unfavorable

Consequence
Oxygen should be applied cautiously and controlled

Animal experiments 20 minutes III

Gruppe: 214

Investigated parameter
Compensation of hyponatremia



N=7
4/7 good
3/7 unsatisfactory

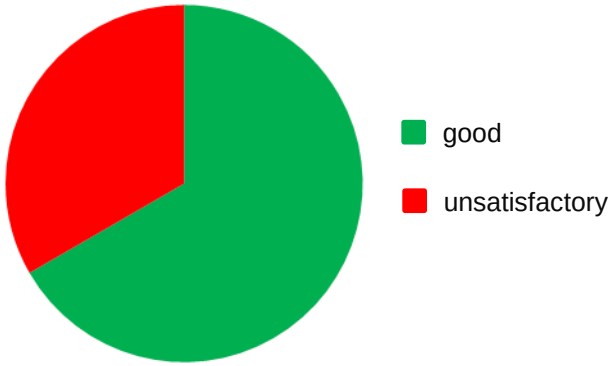
Interpretation
A correction of the sodium level during the reperfusion could have a favorable effect

Consequence
Sodium application should be considered using a dosing system

Animal experiments 20 minutes IV

Group: 215

Investigated parameter
Laminar blood flow



N=6
4/6 good
2/6 unsatisfactory

Interpretation
In the animal model (60 kg bw) satisfactory results could be achieved with a laminar blood flow. The power limit of the blood pump was however not attained.

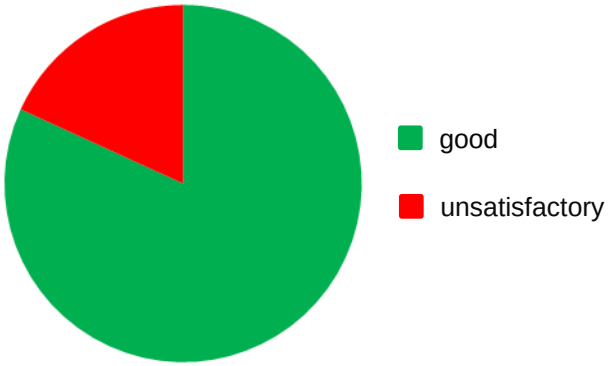
Consequence
A sufficient blood flow must be achieved for animals with higher body weight

Animal experiments 20 minutes V

Group: 211

„CIRD“

N=11
9/11 good
2/11 unsatisfactory



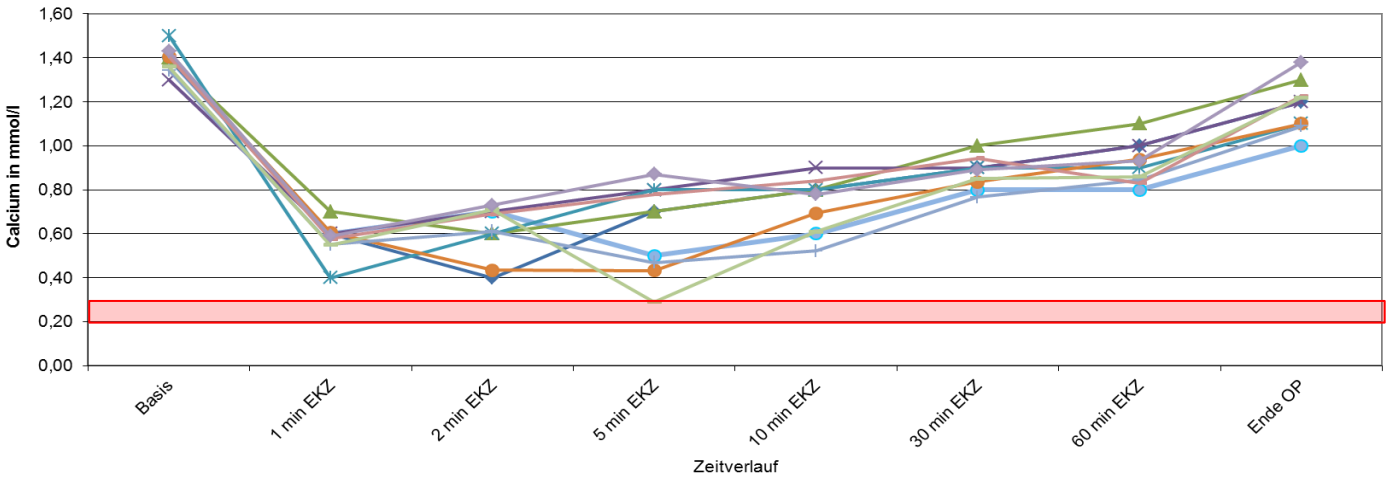
Interpretation
Obtaining and establishing a systematic reperfusion technique with very good results with an ischemic time of 20 minutes

Consequence
The implementation of all the individual elements in CIRD is useful

Optimization of Ca++ control

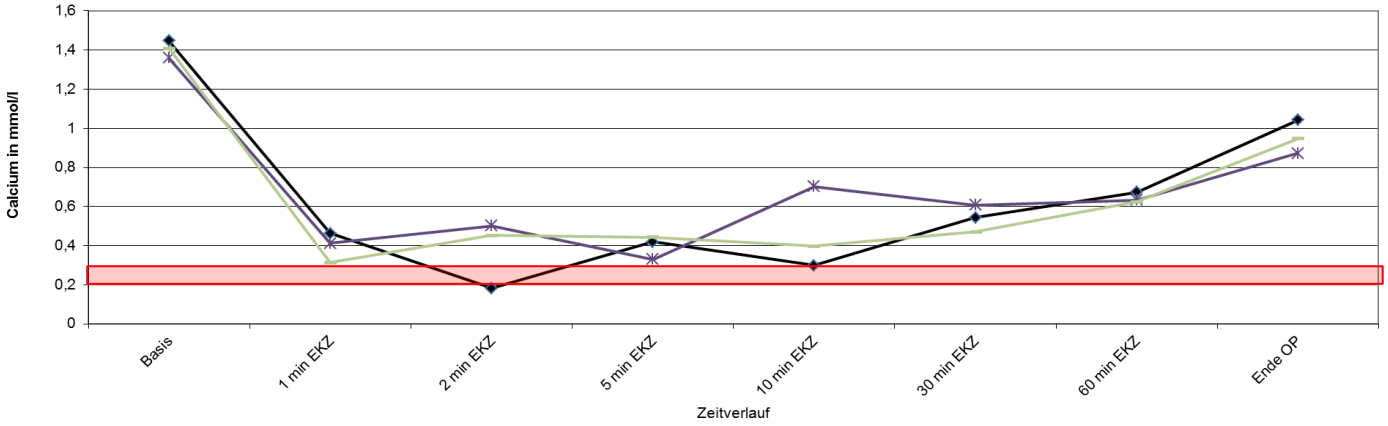
Ca++ Absenkung:

Priming



Ca++ Absenkung:

Priming + Reperfusions phase



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Controlled Integrated Resuscitation Device (CIRD) (ResuSciTec)

CIRD 1.0

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CIRD 1.0 “First in Man” at 10-01-2014

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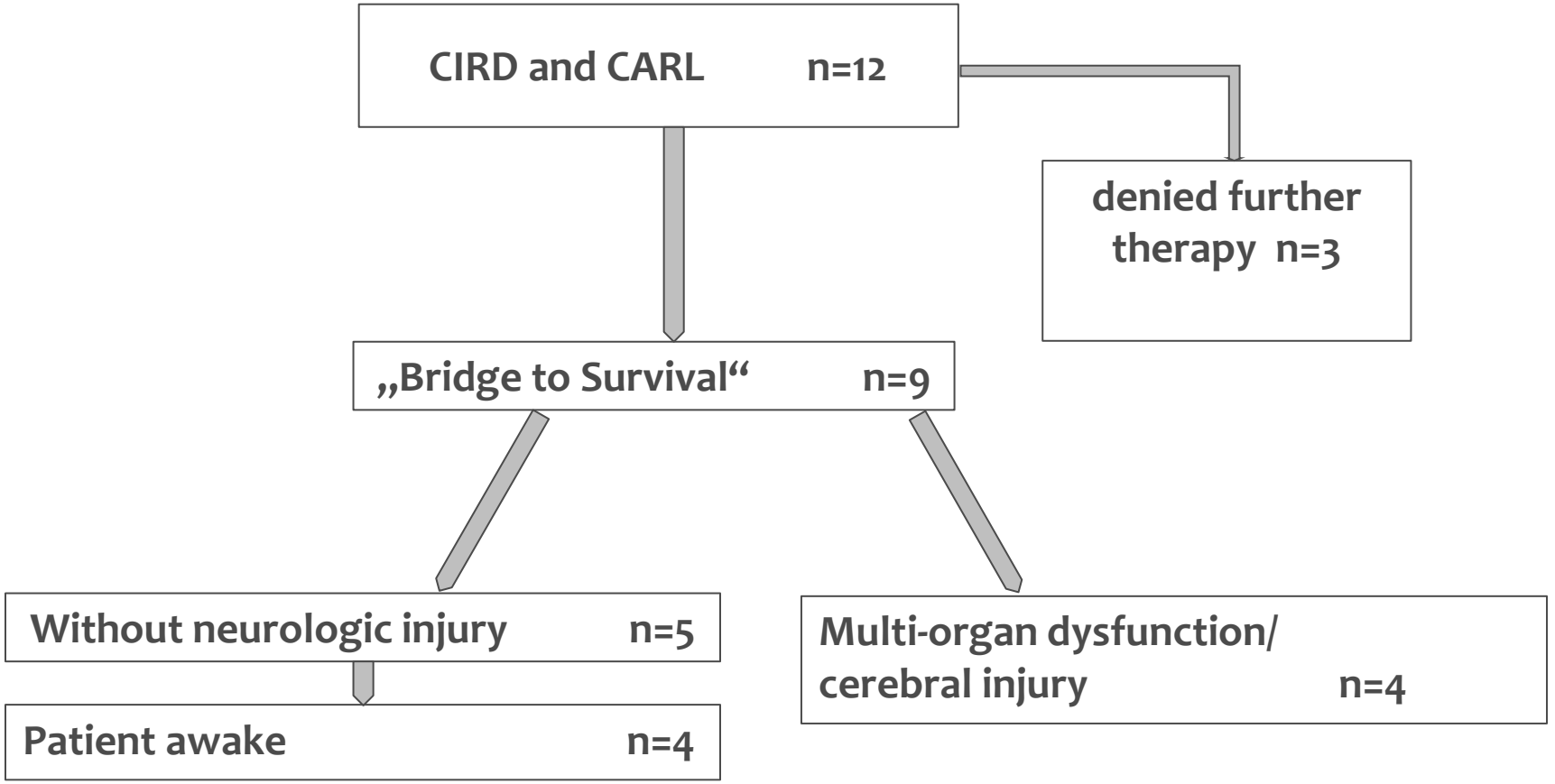
First clinical results using CARL in out-of-hospital cardiac arrest



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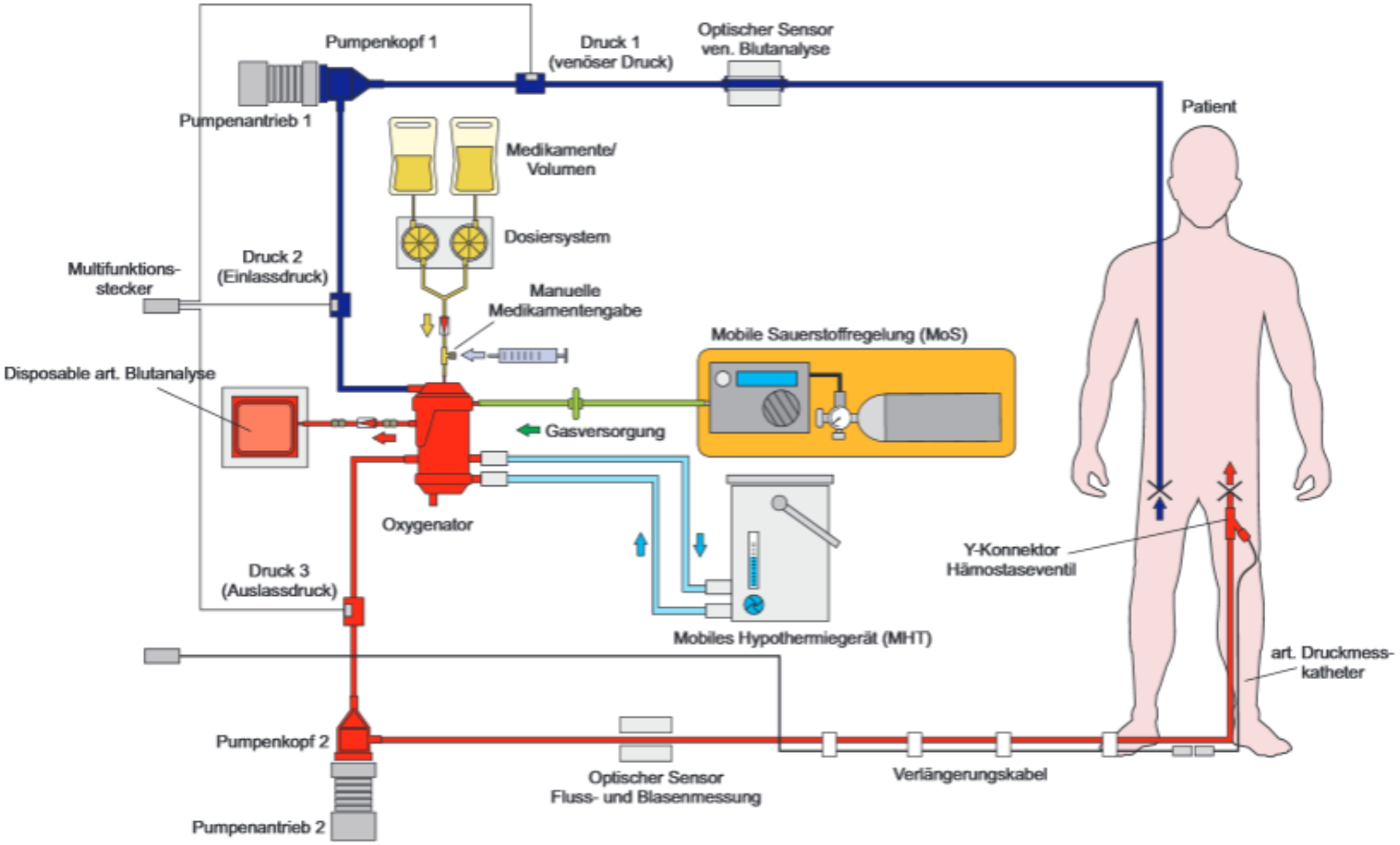
Schematic realization of Controlled Integrated Resuscitation Device (CIRD)



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Conclusions

- Currently, neurologic intact survival after in- and out-of-hospital cardiac arrest is extremely poor.
- Controlled automated reperfusion of the whole body (CARL) is a promising new strategy after cardiac arrest.
- Clinical studies using controlled automated reperfusion of the whole body (CARL) have started.