Chapter 10

Strategies of Neuroprotection after Successful Resuscitation

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Additional information is available at the end of the chapter

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Abstract

Post-cardiac arrest syndrome (PCAS) incorporates post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion syndrome and the precipitating pathology. Brain injury remains the leading cause of death in the post-cardiac arrest period. One of our main goals during post-resuscitation care is to guide a proper neuroprotective strategy. We are going to summarize the tools of neuroprotection in post-cardiac arrest therapy. The role of normoxia/normocapnia, normoglycemia, seizure control, sedation and pharmacologic strategies will be discussed in brief. The handling of temperature management and the management of hemodynamic variables to secure satisfactory cerebral perfusion will be worked out in details. Targeted temperature management is the main tool of neuroprotection in post-cardiac arrest therapy. We are going to conclude the principles of temperature control after successful resuscitation pointing out its beneficial effects. This method has also several complications that are going to be discussed highlighting its hemodynamic impacts. There is no evidence about target hemodynamic parameters during post-cardiac arrest syndrome to maintain cerebral perfusion neither about the most effective hemodynamic monitoring system. We are presenting preliminary data of our study where we investigate the effect of PiCCO™ (Pulse index Continous Cardiac Output) monitoring on the outcome in this patient group.

Keywords: post-cardiac arrest syndrome, post-cardiac arrest brain injury, post-resuscitation therapy, targeted temperature management, hemodynamic parameters

1. Introduction

Sudden cardiac arrest is one of the leading causes of death in Europe [1]. The outcome is still very poor: the hospital discharge varies between 7 and 10% after out-of-hospital cardiac arrest (OHCA) and it is approximately 25% after in-hospital cardiac arrest (IHCA) [1]. The chain of

survival describes links that lead to a successful resuscitation [2]. The fourth element covers proper post-resuscitation care to restore quality of life. It is well known that the management of post-resuscitation cardiac arrest syndrome affects outcome and it is an important part of the resuscitation process. Pointing out the growing importance of post-resuscitation therapy, the European Resuscitation Council (ERC) introduced a separate chapter about post-resuscitation care in the 2015 guidelines [3]. One of the key elements to improve survival rate after sudden cardiac arrest may be the enhancement of post-resuscitation therapy.

The post-cardiac arrest brain injury remains the main cause of mortality in the post-cardiac arrest period, being as high as 68% after OHCA and 25% after IHCA [4]. These data show that one of our leading goals during post-resuscitation therapy is to prevent secondary brain damage and guide a proper neuroprotective therapy.

We are going to point out the importance and process of recent neuroprotective strategies in this chapter. The role of normoxia, normocapnia, normoglycemia, seizure control, sedation and pharmacotherapy will be discussed in brief and we will work out in more details the place of control of hemodynamic parameters and targeted temperature management (TTM) in post-cardiac arrest condition.

2. Post-cardiac arrest syndrome

The post-resuscitation disease, later called post-cardiac arrest syndrome (PCAS) was first described in 1972 by Vladimir Negovsky as the unnatural pathophysiological state created by successful cardiopulmonary resuscitation (CPR) once resumption of spontaneous circulation has been achieved after whole body ischemia [5].

Post-cardiac arrest syndrome is the unique and complex combination of pathophysiological processes, including post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia-reperfusion response and the unresolved pathological process causing cardiac arrest [6]. The contribution of each of these components in an individual patient depends on several factors including comorbidities, duration of the ischemic insult and the cause of cardiac arrest itself.

2.1. Systemic ischemia-reperfusion response

The pathophysiology of PCAS is very complex and contains processes that are still not completely understood. It is dominated by ischemia and reperfusion followed by systemic inflammatory response syndrome (SIRS). The reduced oxygen supply during ischemia or the so-called "no-flow phase" brings a decrease in adenosine-triphosphate synthesis and leads to cell membrane depolarization and opens the voltage-dependent calcium channels. Intracytoplasmic calcium level increases as a consequence that is responsible for cell damage. During reperfusion or the "low-flow phase", blood flow restores but oxygen radical species are formed. The hydroxyl radical is cytotoxic and causes cell death [7]. The plasma of patients after OHCA was analyzed and an acute pro-oxidant state within the cells was

showed [8]. Cytokine production, activation of complements and expression of leukocyte adhesion molecules stimulate the activation of polymorphonuclear neutrophils and lead to systemic inflammation and multiorgan failure. Inflammatory response syndrome is associated with changes of hemostasis effecting secondary damage in endothelium that is followed by thrombus formation and increased capillary permeability [9]. It is important to point out that the worsening of visceral lesions occurs during reperfusion and is extended over the first hours, explaining the potential efficacy of delayed TTM. The clinical manifestation of PCAS-induced inflammatory response reaction shows a lot of similarities with sepsis [9]. The clinical picture is dominated by hemodynamic instability in the first hours and days. It leads to organ hypoperfusion if untreated and a consecutive multiorgan failure. The hypoperfusion of brain, caused by these hemodynamic changes, may lead to secondary brain damage and worse neurological outcome in this patient group.

2.2. Post-cardiac arrest brain injury

The anoxic-ischemic neurological damages remain the leading cause of death occurring in patients resuscitated from cardiac arrest [4]. Its clinical manifestation is very widespread: coma, seizures, myoclonus, varying degrees of neurocognitive dysfunction and brain death may occur [10].

The neurological damage is initiated during "no-flow phase", but is accelerated during the "low-flow period". The triggers of brain injury after cardiac arrest and a successful resuscitation are: excitotoxicity, disrupted calcium homeostasis, formation of free radicals, activation of protease cascades and apoptosis signaling pathways [11, 12]. Most of these pathways activate over hours to days after the return of spontaneous circulation (ROSC). If cardiac arrest is prolonged, failure of microcirculatory reperfusion may appear despite adequate cerebral perfusion pressure (CPP) leading to micro-infarctions. On the other hand, in the first minutes immediately after ROSC, a macroscopic hyperemia may occur that is caused by elevated CPP and impaired autoregulation [13]. As a consequence brain edema and reperfusion injury will exacerbate. Mullner et al. showed that a higher mean arterial pressure (MAP) did not improve the neurological outcome in the first 5 minutes after ROSC but if they were kept at a higher MAP in the first 2 hours after ROSC, the neurological outcome improved [14]. There are growing data to show that overload of oxygen during the initial phase after ROSC may be also harmful and can exacerbate cerebral damage through mitochondrial injury and free radical production [15].

Secondary brain injury may be evoked by a number of insults caused mainly by inappropriate post-cardiac arrest treatment in the first hours and days after cardiac arrest: hypo/hyperoxia, hypo/hypercapnia, hypotension, hypo/hyperglycemia, pyrexia, impaired cerebral autoregulation and brain edema.

One of the consequences of the primary brain damage is the impairment in cerebral autoregulation, however human data are limited [13]. It results that the cerebral perfusion varies with CPP in the acute and subacute phase of the disease. Experimental and clinical studies show that cerebral blood flow (CBF) and metabolic rate of cerebral oxygen consumption is decreased in the first 24–48 hours after ROSC due to increased cerebral vascular resistance [16].

Specific brain regions appear to be most commonly affected with events causing poor systemic circulation [17]. These regions are insulted because they lie in watershed vascular areas or their neurons are located at areas with a higher metabolic rate and oxygen/glucose demand more vulnerable to ischemia.

The neurological syndromes that occur in cardiac arrest survivors can be partially explained by the focal areas of brain injury [17]. The CA1 pyramidal neurons of the hippocampus are commonly damaged with prolonged ischemia, resulting impairment in memory functioning. Cerebellar Purkinje cell injury may result in ataxia, commonly manifesting as a gait disturbance from axial instability. Other commonly affected neurons include thalamic reticular neurons, the medium-sized striatal neurons and the pyramidal neurons in the layers 3, 5 and 6 of neocortex. With more prolonged periods of ischemia, arterial border zone regions can be appreciated macroscopically on neuroimaging. Patients with prolonged period of hypoxia followed by a global ischemic event appears to be susceptible to preferential injury to the subcortical white matter, in what appears to be a primary myelinolytic process. It is postulated that injury occurs preferentially in the subcortical matter in situations in which there is a significant period of alveolar hypoventilation, progressive acidosis and severe metabolic disturbances in the peri-arrest period.

2.3. Post-cardiac arrest myocardial dysfunction

Post-cardiac arrest myocardial dysfunction also contributes to the low survival rate after OHCA and IHCA [4]. However, this phenomenon is responsive to therapy and is reversible. Heart rate and blood pressure may be extremely variable immediately after ROSC caused by the transient increase in serum catecholamine concentration of endogenous and exogenous origin. When post-cardiac arrest myocardial dysfunction occurs, it can be detected within minutes of ROSC by appropriate monitoring. During the period with significant dysfunction, coronary blood flow is not reduced, indicating a true stunning phenomenon rather than permanent injury or infarction. This global dysfunction is transient and full recovery can occur, usually between 24 and 48 hours after the cardiac arrest. The responsiveness of post-cardiac arrest global myocardial dysfunction to inotropic drugs is well documented in animal studies [18]. In swines, dobutamine infusions dramatically improve systolic (left ventricular ejection fraction) and diastolic (isovolumetric relaxation of left ventricle) dysfunction after cardiac arrest [19].

2.4. Persistent precipitating pathology

The pathophysiology of post-cardiac arrest syndrome is commonly complicated by persisting acute pathology that caused or contributed to the cardiac arrest itself. On the other hand differential diagnosis and management of the precipitating pathology can be made more difficult by the symptoms and pathophysiologic changes caused by post-cardiac arrest syndrome. Some of the most frequent conditions leading to cardiac arrest are the followings: acute coronary syndrome, acute aortic syndromes, pulmonary embolism, pulmonary diseases (COPD, asthma bronchiale, pneumothorax), hypovolemia due to hemorrhage or dehydration, sepsis, central nervous system diseases and various toxidromes. The potential treatments are interventions specific for each disease guided by the patient's condition.

3. Tools of neuroprotection in post-resuscitation care

3.1. Normoxia and normocapnia

Arterial oxygen could be a modifiable component of patient care after cardiac arrest in order to deliver better neurological outcomes.

In the search for modifiable ROSC factors, the role of supplemental oxygen, which is often administered in high concentrations to patients after cardiac arrest, has come into controversy. Early oxygen administration can influence oxidative metabolism, respiratory markers, vasoconstrictive status and blood flow, and may thus be an important predictor of outcome [20]. Although it is intuitive that insufficient oxygen delivery can exacerbate cerebral anoxia, excessive oxygen delivery can also be harmful by increasing the amount of oxygen free radicals and subsequent reperfusion injury. Pure oxygen therapy after cardiac arrest has previously been shown to worsen neurological outcome in animal models and exposure to hypocapnia and hypercapnia after ROSC has been associated with poor neurological function at hospital discharge [20].

Oxygen creates a paradox when delivered to the damaged brain. If there is too little oxygen then potential anoxic injury may occur, while too much oxygen may increase the production of oxygen free radicals, leading to cellular injury and apoptosis [21].

In clinically relevant experimental models of cardiac arrest, hyperoxia has been shown to worsen the severity of oxidative stress, causing a greater loss of pyruvate dehydrogenase complex, impairment of oxidative energy metabolism and higher oxidation of brain lipids, culminating in more severe brain histopathologic changes and worse neurological deficits [21].

Kilgannon et al. reported data from adult intensive care units (ICU) of 120 US hospitals incorporated in a large administrative database named "Project IMPACT" and it included 6326 patients divided into three groups (hyperoxia, normoxia and hypoxia) according to the first partial pressure of oxygen in arterial blood (PaO_2) obtained within 24 hours following ICU arrival [22]. Arterial hyperoxia and hypoxia were defined as a PaO_2 higher than 300 mmHg and a PaO_2 lower than 60 mmHg, respectively. The authors found that in-hospital mortality was significantly higher in the hyperoxia group as compared with both the normoxia and the hypoxia group (63 vs. 45 and 57%, respectively).

In addition, among hospital survivors, patients with hyperoxia had a significantly lower likelihood of independent functional status at hospital discharge as compared with patients with normoxia (29 vs. 38%, respectively).

A secondary analysis showed a dose-dependent association between supranormal PaO_2 and risk of in-hospital death [23]. In particular, 25 mmHg increase in PaO_2 was associated with 6% increase in relative risk of death. Given that the median post-resuscitation PaO_2 in this sample was 231 mmHg, it appears that a high proportion of adult patients resuscitated from cardiac arrest have exposure to supranormal oxygen tension. Considering the linear increase in risk of death associated with PaO_2, these results suggest a need for clinical trials of a controlled oxygen therapy after resuscitation from cardiac arrest.

The ERC guidelines for post-resuscitation care recommend the avoidance of unnecessary arterial hyperoxia and a controlled reoxygenation strategy targeting an arterial oxygen saturation of 94–96% [3].

Carbon-dioxide (CO_2) may have neuroprotective properties, as it is thought that mild increase in its level improves cerebral perfusion and it has anticonvulsant, anti-inflammatory and antioxidants properties [24]. On the other hand, its decrease has been associated with neuronal injury in animal models and after traumatic brain injury.

Schneider et al. published an observational cohort study to observe the relationship between arterial CO_2 partial pressure ($PaCO_2$) and outcome in 16,542 patients admitted to the ICU after cardiac arrest [24]. This study was the first to report the relationship between $PaCO_2$ and mortality and an alternative marker of likely neurological outcome.

Within 24 hours of admission, about one in five patients had at least one episode of hypercapnia. Such abnormal values most often occurred within the first 2 hours of ICU admission and that hypercapnia may have been associated with non-ventricular fibrillation (VF) cardiac arrest and underlying respiratory disease. Compared with normocapnia, hypocapnia was associated with a greater risk of death and a lower likelihood of being discharged home among survivors.

On the other hand, hypercapnia was associated with similar mortality or outcome rates to normocapnia but with a higher chance of being discharged home among survivors.

Cerebral autoregulation is impaired after ROSC, but cerebrovascular reactivity to CO_2 is preserved. A decrease in $PaCO_2$ determines cerebral vasoconstriction with a consequent reduction of cerebral blood flow (CBF) whereas the opposite occurs when $PaCO_2$ is increased. There is evidence that CBF could be decreased in the post-resuscitation phase due to an imbalance between local vasodilators and vasoconstrictors but CO_2-mediated vasodilatation might reverse these abnormalities.

The ERC guidelines suggest adjusting ventilation to achieve normocapnia and monitoring the $ETCO_2$ (end tidal carbon dioxide level) and arterial blood gas values during post-resuscitation therapy [3].

3.2. Glucose control

Any stressful systemic injury, such as cardiac arrest, evokes a complex response involving glucoregulatory hormones such as catecholamines, glucagon and glucocorticoids. The increase of these hormones may result in glucose intolerance and hyperglycemia, as they can mobilize glucose and other energy substrates from storage pools. Glucose metabolism via anaerobic glycolysis is the only brain energy pathway that can sustain energy metabolism for any significant period of time (minutes) during an ischemic episode.

Unfortunately, it is common following CPR that the transport of glucose to brain tissues may become inadequate to satisfy cerebral metabolism [25]. Consequently, when cerebral perfusion is compromised, moderate hyperglycemia may facilitate glucose transport through the elevated blood glucose diffusion gradient that maximizes cellular glucose uptake.

On one hand, there are various studies that have shown that high blood glucose levels after ROSC are associated with increased mortality and poor neurological outcome for patients who experience OHCA. For IHCA patients, Beiser et al. reported that for patients without diabetes mellitus, both hypoglycemia and hyperglycemia were associated with decreased survival odds. However, for patients with diabetes mellitus, there was little association between blood glucose level and survival, except with extreme hyperglycemia [26].

On the other hand, there are several studies that have found out that normalization of blood glucose levels in critically ill patients with brain injury may be associated with greater risk of critical reductions in brain glucose levels and energy crises [27]. Therefore, acute stress hyperglycemia noted during the early post-ROSC phase might be a physiologic, rather than a pathologic response and attempts at interfering with this complex adaptive response may be harmful rather than protective.

It is proven that hypoglycemia needs to be avoided in critically ill patients. In a study by Arabi et al., mortality in patients with hypoglycemia was multipled compared to patients with conventional therapy [28]. Unrecognized episodes of hypoglycaemia are more harmful than the benefit of strict normoglycemia, especially in patients with brain damage [29].

The American Heart Association (AHA) guidelines do not recommend a target blood glucose range for post-ROSC patients [30]. The ERC guidelines suggest that blood glucose level should be maintained below 180 mg/dl (10 mmol/L) in these patients and that hypoglycemia should be strictly avoided [3].

3.3. Seizures control

Many of patients who remain comatose after successful resuscitation, will suffer from seizures. The appearance of seizures may be variable, from single focal onset through myoclonus to generalized tonic-clonic fit.

Acute post-hypoxic myoclonus (PHM) occurs in about 18–25% of these patients, typically within the first 24 hours after CPR [31]. Commonly, the myoclonus appears days or weeks after the hypoxic episode when consciousness is regained. Myoclonus is a hyperkinetic movement disorder characterized as a sudden, jerky, shock-like movement. It can involve different body parts individually (focal), contiguously (segmental) or asynchronously (multifocal). When repetitive, the jerks may be regular or irregular, sometimes mimicking tremor.

There are several EEG findings in acute PHM: burst suppression (56%), spike-wave activity (37%), myoclonic status epilepticus (31%), diffuse slow background and waves (21%) and alpha coma (7%). These severe diffuse EEG abnormalities are consistent with marked diffuse cerebral dysfunction.

The exact neuronal damage and pathophysiology that gives origin to acute PHM is not clear. [32] Treatment is indeed challenging and no published guidelines exist as the hypoxic injury may lead to mixed and varying clinical findings of this myoclonus. Moreover, a drug treatment for one type may not work well in another or may even induce worsening [33].

3.4. Sedation

Sedative agents play a vital role in the management of patients with an acute brain damage. However, there is no evidence to support the defined duration of sedation neither the agent that should be used after cardiac arrest. Sedation acts to protect the brain against the extension of primary acute brain injury and secondary cerebral insults [34]. It has always been used in association with cooling methods, since the first non-randomized trials investigating targeted temperature management or therapeutic hypothermia (TH) effects on outcome. In this setting sedatives were often co-administered with muscle relaxants.

The main goals to use sedation during targeted temperature management are the reduction of oxygen consumption, control of shivering, the reduction of agitation and ventilator dyssynchrony, which may be detrimental for neurological recovery [34]. Clinically detectable shivering can increase systemic metabolic rate with 24–160% above baseline resting energy expenditure and increase inflammatory markers. The use of neuromuscular blocking agents to avoid shivering is controversial and we think it should be the agent of an ultimate case because it may mask seizures and its prolonged use (more than 1 day) may lead to muscle weakness, prolonged ventilation and ICU stay.

There are no data about the influence of outcome of sedatives used after cardiac arrest. A combination of hypnotics and opioids is used in the most of cases [35]. Short-acting drugs are preferred, for example, remifentanil, alfentanil and propofol.

3.5. Pharmacologic strategies

There is still lack of proved pharmacological interventions providing neuroprotection for patients after successful resuscitation. However, there are some promising drugs that may have some beneficial effect on neurological recovery in this patient group. Most of these agents have been studied in experimental research and only a few clinical data are achievable.

Xenon is one of the most commonly investigated pharmacologic treatments in post-resuscitation therapy. Pre-clinical studies have shown that it can prevent the development of ischemic-reperfusion brain injury [36]. A randomized single blind trial investigated the cerebroprotective effect of xenon in 110 comatose patients after OHCA [37]. One half of patients received xenon combined with therapeutic hypothermia and the other half was treated only with hypothermic therapy. They did not find any difference in survival and neurologic outcome after 6 months but there was less white matter damage controlled with magnetic resonance imaging (MRI) in the xenon-treated group. On the basis of these findings the efficacy of xenon must be investigated in further clinical trials at this patient group. Also we need to point out its disadvantages: it is still quite expensive and its storage needs special circumstances.

The impact of early high-dose erythropoietin was also investigated in patients after OHCA in a single blind randomized trial but neither mortality, neither Cerebral Performance Category (CPC) scale improved after this treatment, only rate of thrombotic complications increased [38].

Rosuvastatin was shown to improve survival, myocardial function and neurologic recovery in a rat model after successful resuscitation [39]. A combination of three drugs (lovastatin, minocycline and lamotrigine) was also studied in a mouse model after brain ischemia provoked by

artery carotid occlusion [40]. As a result a decreased neurological deficit was reached suggesting a potential beneficial effect of this treatment in post-cardiac arrest therapy.

One of the promising, easily achievable and affordable drugs that may have potential benefit in neuroprotection after cardiac arrest is thiamine. It is a type of B vitamins that is essential for the proper functioning of nervous system. It modulates the activity of pyruvate dehydrogenase that is a main enzyme in Krebs cycle. It has been shown that mitochondrial dysfunction and impaired aerobic metabolism may be a cause of cerebral damage after cardiac arrest [41]. This led to the idea to investigate the effect of thiamine in mice after successful resuscitation [42]. Mice treated with thiamine after cardiac arrest had a better 10-day survival and improved neurological outcome than control individuals. The histology also showed an ameliorated brain injury after thiamine treatment. The investigators also checked the activity of pyruvate dehydrogenase in human blood in patients after successful resuscitation and found that it was significantly lowered compared to control healthy volunteers. We think thiamine may be a pharmacological pathway in treating post-cardiac arrest brain injury but its clinical effect and proper dosage need to be investigated in clinical trials.

3.6. Targeted temperature management

3.6.1. Principles and guidelines

Two trials published by the New England Journal of Medicine in 2002, involving patients who remained unconscious after resuscitation from cardiac arrest, compared therapeutic hypothermia (32–34°C for 12–24 hours) with standard treatment [43, 44]. These trials showed a significant improvement in neurologic function and survival with therapeutic hypothermia. This treatment method was incorporated into the resuscitation guidelines in 2005. For more than a decade, mild-induced hypothermia (32–34°C) was the standard of care for patients remaining comatose after resuscitation from OHCA with an initial shockable rhythm, and this has been extrapolated to survivors with initially non-shockable rhythms and to patients with IHCA.

Traditionally, therapeutic hypothermia (TH) refers to deliberate reduction of the core body temperature to a range of 32–34°C in patients who do not regain consciousness after ROSC.

Since the 2015 ERC guidelines, term targeted temperature management (TTM) is suggested to use instead of therapeutic hypothermia and the new recommendation is to keep patients' core temperature between 32 and 36°C [3]. However, this expression is not always unique and many use phrase therapeutic hypothermia for goal temperature 32–34°C and term TTM for goal temperature 36°C.

There are still several unanswered questions regarding targeted temperature management after cardiac arrest. We still do not exactly know which patients benefit from lower and which from a higher level of temperature. Only the detrimental effect of fever is proven of the effects of temperature in post-cardiac arrest syndrome. Further questions are when exactly to start cooling and how long to keep cooling, which still need more clinical trials to be answered.

The 2016 guidelines of American Academy of Neurology (AAN) on reducing brain injury following cardiac arrest try to give a more precise direction how to handle temperature management in this patient group [45].

Because patients with initial rhythm of ventricular fibrillation/ventricular tachycardia (VF/VT) or pulseless electrical activity (PEA)/asystole differ in causes of cardiac arrest and outcome, the guideline deals separately with these patient groups. It recommends the use of therapeutic hypothermia (32–34°C for 24 hours) if the initial rhythm was VF/VT and patients remain comatose after successful resuscitation. It also says that for patients with an initial rhythm of VF/VT or PEA/asystole TTM (36°C for 24 hours followed by 8 hours of rewarming to 37°C and temperature maintenance below 37.5°C until 72 hours) is likely as effective as TH and may be a good alternative. If the initial rhythm is PEA/asystole, than the use of TH possibly improves outcome over non-hypothermia treatment.

In 2013 a trial to investigate the benefits and harms of two targeted temperature regimens was conducted, called the Targeted Temperature Management (TTM) trial [46].

In the TTM trial, 950 all-rhythm OHCA patients from 36 ICUs in Europe and Australia were randomized for 36 hours of temperature control (comprising 28 hours at the target temperature followed by slow rewarm) at either 33°C or 36°C. Temperature was managed with intravascular or surface cooling devices for 36 hours, while the patients were sedated and mechanically ventilated. TTM at 33°C was associated with decreased heart rate, elevated serum lactate level, the need for increased vasopressor support and a higher extended cardiovascular SOFA score compared with TTM at 36°C. However, it is important to point out the higher proportion of bystander witnessed cardiac arrest (90%) and of bystander CPR (73%). Moreover, the time to start basic life support (BLS) was shorter in both groups, among 1 minute. These facts by themselves would provide an improvement in the outcome of patients regardless the hypothermia. Nevertheless, the median time of ROSC was 25 minutes in both groups.

The TTM trial has also been criticized because the temperature was tightly controlled and it took a short time to reach 33°C, but also because the whole trial cohort was less ill than in previous trials. It should be taken into account that the previous studies were performed several years ago, and that during the last decade the intensive care therapy has improved a lot itself [47].

It is also a very important fact that in TTM trial there was no fever during the therapy. When comparing the TTM trial and the previous trial temperature results, we can appreciate that the temperature after re-warming was lower in the TTM trial [43, 44, 46].

Kaneko et al. conducted an observational study between January 2005 and March 2013 called the J-Pulse-Hypo Japanese prospective cohort. The objective of the study was to identify subgroups of patients who might be suitable candidates for lower targeted temperature during TTM after ROSC [48].

Participants were divided into lower (32–33.5°C) or moderate (34–35°C) temperature groups. In this study a favorable primary outcome was defined as CPC (Cerebral Performance Category) 1–2 on day 30. The subgroups of patients were divided and analyzed in the following way: age ≤60 vs. >60 years and resuscitation interval of ≤30 vs. >30 minutes.

The results demonstrated that the lower temperature group significantly improved the proportion of patients with favorable neurological outcomes in the subgroup of patients with a

resuscitation interval of ≤30 minutes. There were some differences between this study and the TTM Trial, including shorter time to reach the targeted temperature (180 minutes), longer time at the targeted temperature (34 hours), and longer re-warming period (3 days).

When to start cooling is also an interesting and still unanswered question regarding TTM. It was shown in preclinical studies that initiating cooling as soon as possible after resuscitation improves neurologic outcome [49]. Clinical studies investigating the beneficial effects of cooling initiated in pre-hospital setting did not show positive outcome. A Cochrane review studied 7 trials (2369 patients) investigating the effect of pre-hospital cooling on survival, cerebral injury, side effects, quality of life and length of hospital stay [50]. There was no difference in survival between pre-hospital and intra-hospital cooling groups, neither in neurologic outcome. The rate of re-arrests was higher among patients who received pre-hospital cooling in four of the investigated trials.

The guidelines of AAN do not suggest the use of pre-hospital cooling while it is ineffective in improving neurological outcome and survival [45]. One of the explanations for this phenomenon may be the fact, which has been already mentioned, that there are some complex mechanisms leading to post-cardiac arrest brain injury appearing some hours after ROSC. On the other hand high volumes of cold infusions are used to initiate TTM during pre-hospital cooling leading to pulmonary edema and complications causing more harm than benefit. We also need to mention the heterogeneity of studied cooling methods in pre-hospital setting. To prove its efficacy or inefficiency further studies are needed.

3.6.2. Beneficial effects in post-cardiac arrest syndrome

Hypothermia provides significant cardiac and neurological protective effects through different pathways. Hypothermic mechanisms providing myocardial protection include improved energy production during ischemia, increased calcium sensitivity of myocytes, regulation of mitochondrial oxidative phosphorylation and preserved myocardial vascular autoregulation. All of these protective mechanisms would result in increased myocardial contractility.

After a post-anoxic injury, hypothermia may also protect cerebral function through decreasing apoptosis, reducing the release of excitatory (glutamate and dopamine) neurotransmitters, attenuating the reactive oxygen species production, preserving the blood-brain barrier, providing protection of cerebral microcirculation and decreasing intracranial pressure. Hypothermia decreases the cerebral metabolic rate of oxygen by about 6% for each 1°C reduction in core temperature and this may reduce the release of excitatory amino acids and free radicals.

Shivering will increase metabolic and heat production, thus reducing cooling rates. The occurrence of shivering in cardiac arrest survivors who undergo mild induced hypothermia is associated with a good neurological outcome. Occurrence of shivering was similar at a target temperature of 33 and 36°C.

Mild induced hypothermia increases systemic vascular resistance and causes arrhythmias (usually bradycardia). However, the bradycardia caused by mild induced hypothermia may be beneficial: it reduces diastolic dysfunction and its occurrence has been associated with good neurological outcome.

3.6.3. Side effects

Therapeutic hypothermia is an effective tool in neuroprotection after cardiac arrest, however it may cause several side effects that need to be monitored and declined during its use. Polyuria and electrolyte abnormalities such as hypophosphatemia, hypokalemia, hypomagnesemia and hypocalcemia may appear.

Insulin sensitivity and insulin secretion are decreased, that lead to hyperglycemia. Moreover, coagulation system can get impaired and bleeding risk is increased.

Hypothermia can impair immune system and extend infection rates. It is associated with an increased incidence of pneumonia, although the use of prophylactic antibiotics may prevent it to emerge.

The clearance of sedative drugs and neuromuscular blockers is reduced by up to 30% at a core temperature of 34°C. Clearance of sedative and other drugs will be closer to normal at a temperature of 37°C.

3.6.4. Practice of cooling

Whenever the indication is established the hypothermic treatment should be started as soon as possible. The trial performed in 2002 had the induction within 6–26 hours, with a median of 8 hours [43].

Hypothermic treatment and TTM has three phases such as induction of cooling, maintenance and rewarming.

Cooling may be delivered via external, internal and combined cooling methods. External cooling is carried out by traditional icepacks placed on the groin, axilla and sides of neck; surface temperature changer devices with thermo-feedback function such as blankets or self-adhesive plastic fluid-containers or cooling helmets over the head of the patient.

Internal cooling means intrabody cooling as intravascular, intrabladder or intragastrical method. It may be delivered via infusion of 30 ml/kg of 4°C saline, which decreases core temperature by 1.5°C. Intravascular cooling enables more precise control than external methods. The most precise temperature control with the fastest induction, reaction to temperature changes and rewarming is achievable via endovascular heat-exchange catheter. This latter is the most expensive method on the field.

3.6.5. Practice of TTM and post-cardiac arrest therapy in Semmelweis University Heart and Vascular Center

- Protocolisation: our cardiac ICU has a prospective protocol of care to anticipate, monitor, and treat each of the impaired organ functions by optimizing systemic perfusion, restoring metabolic homeostasis and support organ system function to increase the likelihood of survival with potentially good neurological outcome.
- Technical background: our cardiac ICU has 11 monitored beds, with central monitoring system as well. Seven invasive mechanical ventilators, two non-invasive mechanical ventilators

and four intraaortic balloon pumps are available. For patients who need mechanical circulatory support extracorporeal membrane oxygenator (ECMO)/ventricular assist device (VAD) background is available by the cardiac surgeons and cardiac surgical ICU.

- TTM target temperature: 33°C. The target time to achieve target temperature is usually 3–6 hours using thermo-feedback blanket device (**Figure 1**) and 1–2 hours using intravascular cooling catheters. Latter is rarely used due to the price of the catheter. The maintenance duration of target temperature is 24 hours. Rewarming duration is set to 0.25°C/hour that means approximately 16 hours. Invasive hemodynamic monitoring during TTM is also used but only upon the attending physician's preference and the equipment availability.
- Intubation and mechanical ventilation is always obligatory during TTM since sedation and if needed neuromuscular blockade is also used in these patients. Midazolam is the choice of sedation if the patient is hemodynamically unstable and propofol, if the patient is stable. Opioids are administered to decrease the cerebral metabolic rate additionally.
- Tight monitoring of invasive blood pressure, rhythm, ECG morphology, diuresis, core temperature and hemodynamic variables is obligatory.
- Prevention is also started at admission: the post-cardiac arrest patients with circulatory impairment are at higher risk of decubitus, stress ulcer and infections.
- Sampling from trachea, pharynx, nose, groins for cultures are done at admission and empiric intravenous antibiotic therapy is initiated. Infection risk is 7–17% by the literature, but no significant effect on mortality was shown.
- We plan to establish a continuous EEG monitoring during sedation and TTM but it is available only in limited fashion at the moment.

3.7. Cerebral perfusion

Patients with post-cardiac arrest syndrome experience on-going oxidant damage, profound systemic inflammation with vasodilation, myocardial stunning and adrenal axis suppression, which commonly result in major hemodynamic instability. Targeted temperature management with a lower core body temperature affects circulatory variables also negatively. As we previously mentioned the injured brain commonly has a dysfunctional autoregulation. This leads to the fact that blood pressure alterations in the post-cardiac arrest period may influence on-going cerebral injury and eventual neurologic outcome [51]. With disruption of normal cerebrovascular autoregulation, CBF may become directly related to cerebral perfusion pressure, which is dependent on MAP.

Hypotension may lead to persistent tissue hypoperfusion after ROSC, which may produce secondary cellular injury after the initial insult.

Kilgannon et al. studied the time-weighted average mean arterial pressure (TWA-MAP) for the first 6 hours after ROSC [51]. It was found that arterial hypotension was common while relatively fewer patients had an intrinsic hypertensive surge. It was determined that TWA-MAP was associated with neurologic outcome. This association appears to be driven by the strong association between hypotension and poor neurologic outcome, as opposed to an association

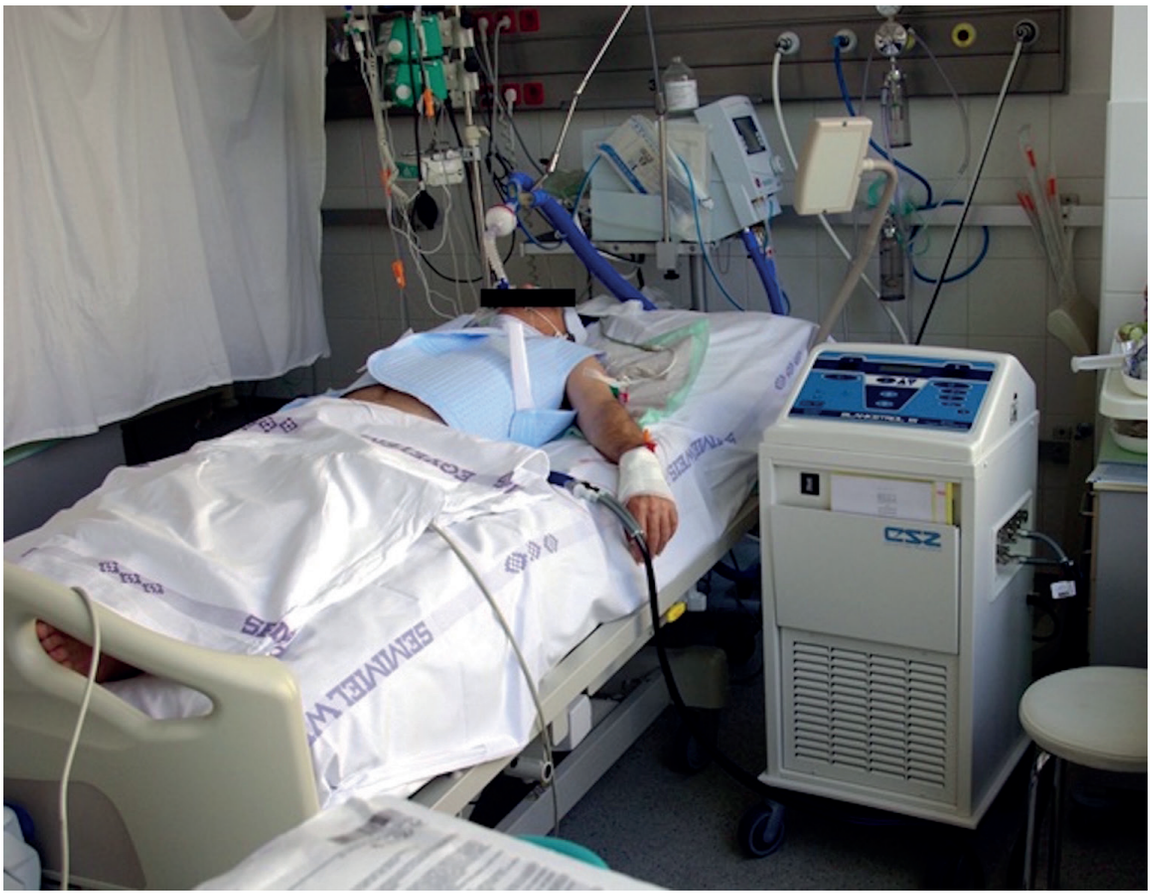

Figure 1. Thermo-feedback device used for external cooling in our practice.

between intrinsic hypertension and better neurologic outcome. In the analysis, there was a threshold effect with a TWA-MAP greater than 70 mmHg having the greatest association with good neurologic function, and they did not find higher MAP thresholds to be associated with favorable outcome.

The frequency and significance of post-ROSC arterial hypotension among cardiac arrest victims was measured at the time of ICU admission in a large, multicenter cohort study performed by Trzeciak et al. [52]. It was found that 47% of patients who survive cardiac arrest have post-ROSC hypotension, and two-thirds of these patients do not survive to hospital discharge. The presence of post-ROSC hypotension at the time of ICU admission is associated with an approximate two-fold risk of in-hospital mortality. It was identified that the post-ROSC condition is characterized by patchy microcirculatory cerebral hypoperfusion, and arterial pressure in the post-cardiac arrest period is a major determinant of the degree of cerebral perfusion impairment.

In spite of the studies that have tried to determine the appropriate blood pressure target after ROSC for a better neurological outcome, the results have not been conclusive. A recent study showed inverse effect between arterial pressure and survival [53]. In the absence of definitive data, the ERC guidelines recommend a target blood pressure that secures a satisfactory urine output (1 ml/kg/h) and a decreasing/normalizing lactate level taking into consideration the patient's normal blood pressure [3].

As a conclusion we can state that there are no clear data about the target blood pressure in post-cardiac arrest patients neither in shock patients [54]. There is lack of studies investigating the optimal target blood pressure in cardiogenic shock. However, it is showed that a target MAP of 65 mmHg may be satisfactory in septic shock patients, we need to point out that it is associated with a higher risk of acute kidney injury if the patient has a history of hypertension [55]. The main message of these findings is that the target blood pressure should be individualized to secure a proper perfusion of organs and an adequate perfusion of brain to prevent further secondary cerebral damage.

3.8. Hemodynamic monitoring during post-cardiac arrest syndrome and the hemodynamic effects of therapeutic hypothermia: a case control study (preliminary data)

We think that an expanded hemodynamic monitoring may be a more precise and useful tool to guide the hemodynamic management of post-cardiac arrest patients than observing only blood pressure. As we mentioned previously, there are several components leading to hemodynamic instability in this patient group and we need to mention also the complexity of the precipitating pathology causing cardiac arrest. To monitor cardiac output and its components (preload, afterload and contractility) gives a more synthetic picture about the condition of the patient's circulation and consecutive organ perfusion.

The most ideal method should be the least invasive providing the most information about the patient's circulatory condition with a simple usability. Echocardiography is a method that helps in characterizing the hemodynamic disorders, selecting the most optimal therapeutic intervention and assessing the response to it [54]. On the other hand it should be mentioned as a limitation that it is not a continuous technique for hemodynamic monitoring and it needs a lot of time of practice to reach an adequate level of usage.

Pulmonary artery catheter (PAC) provides important information about hemodynamic variables and tissue perfusion but it is one of the most invasive tools and there is no evidence about its superiority over other monitoring methods [56]. It is not the most useful system in determining preload because it measures only static parameters (central venous pressure and pulmonary occlusion pressure) instead of dynamic variables. The 2015 European Society of Intensive Care Medicine (ESICM) consensus on hemodynamic monitoring does not recommend its routine use in shock only in refractory shock with right ventricular dysfunction [54].

Transpulmonary thermodilution devices like PiCCO™ (Pulse index Contour Cardiac Output) are less invasive than PAC and they still provide enough precise information to be used in critically ill patients. Its additive advantage is the possibility to measure dynamic variables in fluid management. Tagami et al. validated this method in post-cardiac arrest patients even if therapeutic hypothermia (32–34°C) was used [57].

Recently developed non-invasive methods using pulse contour analysis and volume clamp technique to measure cardiac output should be limited to perioperative use because its value during shock, vasopressor therapy or targeted temperature management is questionable [54].

There is no evidence if the use of these methods affects patients' outcome in critical care not even in post-resuscitation therapy. Taking the above mentioned findings altogether we think

PiCCO™ monitoring system may be a suitable tool in post-cardiac arrest patients hemodynamic monitoring. There is still lack of evidence which hemodynamic variables should be monitored and which parameters should be targeted.

The aim of our study was to investigate if the use of PiCCO™ monitoring and the PiCCO™-guided hemodynamic assessment of post-cardiac arrest patients affect the survival, length of ventilation, length of ICU stay and the application of catecholamines. We also investigated the changes of hemodynamic variables during therapeutic hypothermia and were interested in how the most important tool of neuroprotection in post-cardiac arrest syndrome affects hemodynamics.

3.8.1. Patients and methods

We enrolled comatose patients after successful resuscitation who received therapeutic hypothermia and were treated in Semmelweis University Heart and Vascular Center between 2008 January and 2012 July. Inclusion and exclusion criteria are specified in **Figure 2**. We excluded patients who were given hypothermic therapy with physical cooling and ice packs, because the target temperature was not reached in most of the cases.

The post-resuscitation therapy and therapeutic hypothermia was initiated as soon as possible after the admission following the ERC guideline. The goal temperature was 32–34°C according to the even actual protocol (that is the reason we use term "therapeutic hypothermia" instead of "targeted temperature management"). The hypothermic treatment contained three phases: induction, maintenance and rewarming. The patients received 30 ml/kg cold (4°C) crystalloids in

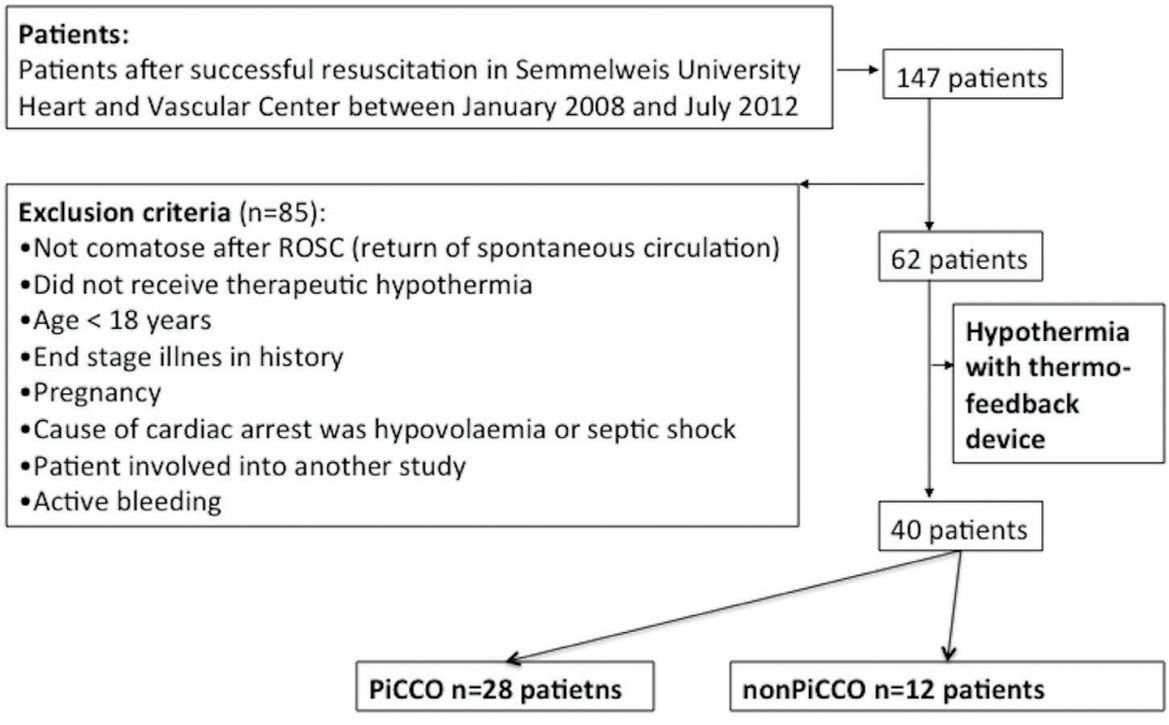

Figure 2. Inclusion and exclusion criteria.

the induction phase and were further cooled with Blanketrol III™ (Cincinatti SubZero) thermofeedback device. The same device was used during the maintenance phase. The rewarming was a passive process where we tried to keep the 0.25°C/h rewarming speed. The patients' temperature was measured with an esophageal thermometer and they were sedated with benzodiazepine and opioids given intravenously. If it was indicated, we performed coronarography and percutanous coronary intervention before initiating hypothermia.

Patients were divided into two groups on the basis of what type of hemodynamic monitoring has been administered. We monitored by the members of nonPiCCO group oxygen saturation, ECG, invasive arterial blood pressure, central venous pressure, diuresis, blood gas parameters and serum lactate level. The patients' vasopressor, inotrope and fluid therapy was guided on the basis of these variables.

The previously mentioned monitoring and interventions were augmented with PiCCO™ (Pulsion Medical System) thermodilution device in PiCCO group. We accomplished a measurement at the initiation of hypothermia and performed it every 6 hours in the first 48 hours of treatment. The following variables were controlled: cardiac index (CI: l/min/m^2), systemic vascular resistance index (SVRI: dyn sec/cm^5), global end-diastolic volume index (GEDI: l/m^2), extravascular lung water index (ELWI: ml/kg/m^2).

The allocation of patients was directed by the access of the thermodilution device. Mortality, circumstances of CPR, length of ventilation and ICU stay and the usage of catecholamine therapy were recorded in both groups and compared. In PiCCO group, the hemodynamic variables (CI, SVRI, GEDI, ELWI) were controlled at the initiation of hypothermia, in the 12th, 24th and 48th hour of hypothermia and after rewarming. The statistical analysis was performed with two-tailed t-test and Mann-Whitney test when we compared the two groups. We used Wilcoxon test and Bonferroni correction in analyzing the PiCCO measurements. Significance of p value was set at <0.05. The Semmelweis University Regional and Institutional Committee of Science and Research Ethics accepted our study.

3.8.2. Results

We treated 147 successfully resuscitated patients in Semmelweis University Heart and Vascular Center between 2008 January and 2012 July. On the basis of our inclusion and exclusion criteria 40 patients were enrolled into our study: 28 in PiCCO group and 12 in nonPiCCO group. There was no significant difference in demographic data and the circumstances of CPR between the two groups (**Table 1**).

The survival (**Figure 3**), length of ventilation and length of ICU stay were also similar in both groups (**Table 1**). Length of ventilation was 5 ± 3 days in PiCCO and 6 ± 5 days in nonPiCCO group, respectively ($p = 0.57$). The patients in PiCCO group spent 7 ± 4 days at ICU and the members of nonPiCCO group 8 ± 5 days ($p = 1.00$).

In the usage of catecholamines we found that patients in nonPiCCO group received less vasopressors and inotropes than patients in PiCCO group (PiCCO: 71% of patients vs. nonPiCCO: 58% of patients), however the difference was not significant **(Table 2)**.

	PiCCO (n = 28)	nonPiCCO (n = 12)	p
Age (years)	62 ± 10	69 ± 8	**0.095**
Male	82%	67%	**0.25**
Female	18%	33%	
OHCA	64%	46%	**0.22**
IHCA	36%	54%	
Time until ROSC (minutes)	13 ± 6	17 ± 4	**0.059**
Initial rhythm			
VF/pnVT	63%	58%	**0.4**
PEA/Asy	37%	42%	
Bystander CPR			
Performed	72%	90%	**0.07**
Did not performed	18%	10%	
Length of mechanical ventilation (days)	7 ± 4	8 ± 5	**0.57**
Length of ICU stay (days)	5 ± 3	6 ± 5	**1**

OHCA: out-of-hospital cardiac arrest; IHCA: in-hospital cardiac arrest; ROSC: return of spontaneous circulation; VF: ventricular fibrillation; VT: ventricular tachycadria; PEA: pulseless electrical activity.

Table 1. The comparison of demographic data, circumstances of CPR, length of mechanical ventilation and length of ICU stay between PiCCO and nonPiCCO groups. Significance of p value was set at <0.05.

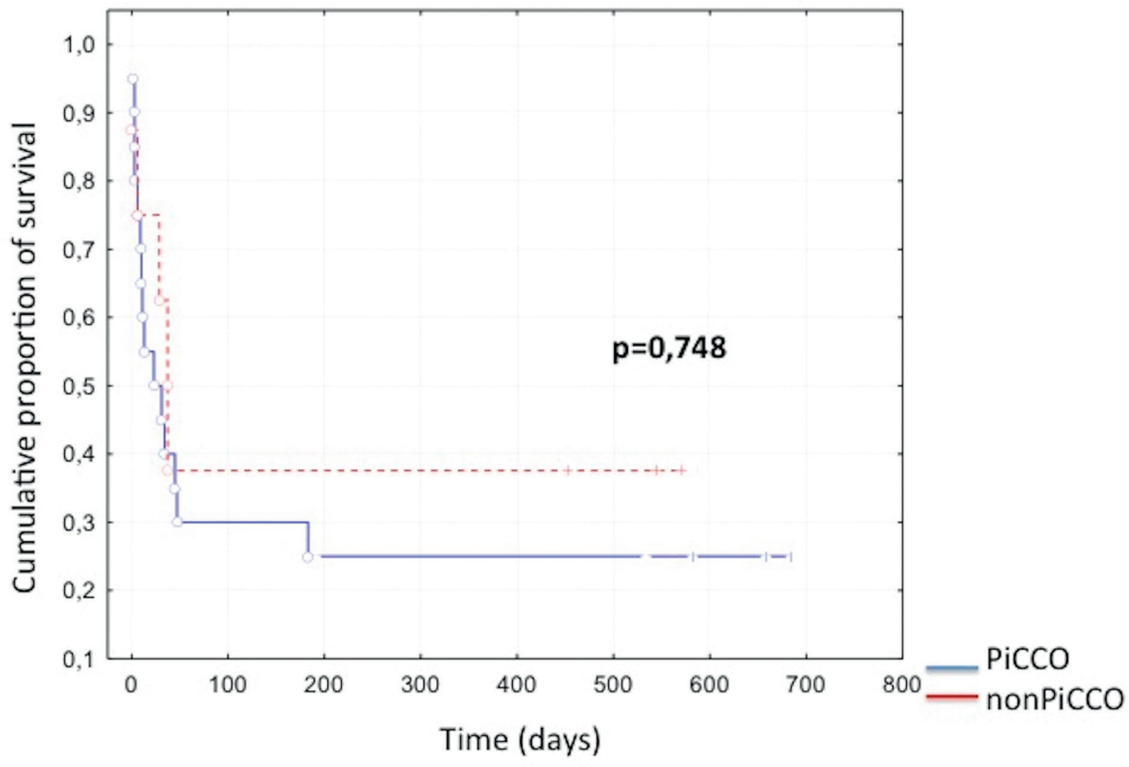

Figure 3. The comparison of survival between PiCCO and nonPiCCO group.

Combination of catecholamines	PiCCO (n = 28) (%)	nonPiCCO (n = 12) (%)
0	29	42
1	36	25
2	21	8
3	14	25

Table 2. The comparison of catecholamine administration between PiCCO and nonPiCCO group.

In the course of the measurement of hemodynamic variables during therapeutic hypothermia there was significant difference in cardiac index and systemic vascular resistance index between the values in the 12th hour of hypothermia and after rewarming (CI: 1.8 ± 0.5 l/min/m^2 vs. 2.9 ± 0.9 l/min/m^2, $p < 0.001$; SVRI: 3686 ± 1264 dyn sec/cm^5 vs. 1627 ± 414 dyn sec/cm^5, $p < 0.001$) (**Figure 4**). Cardiac index decreased in the first 12–24 hours and showed improvement after this period. Systemic vascular resistance index changed parallel with cardiac index but the opposite way. The changes in ELWI and GEDI did not show significant difference during the examined interval.

3.8.3. Discussion

Post-resuscitation therapy as the fourth link of chain of survival is one of the mortality determining factors among post-cardiac arrest patients. One of the most important parts of

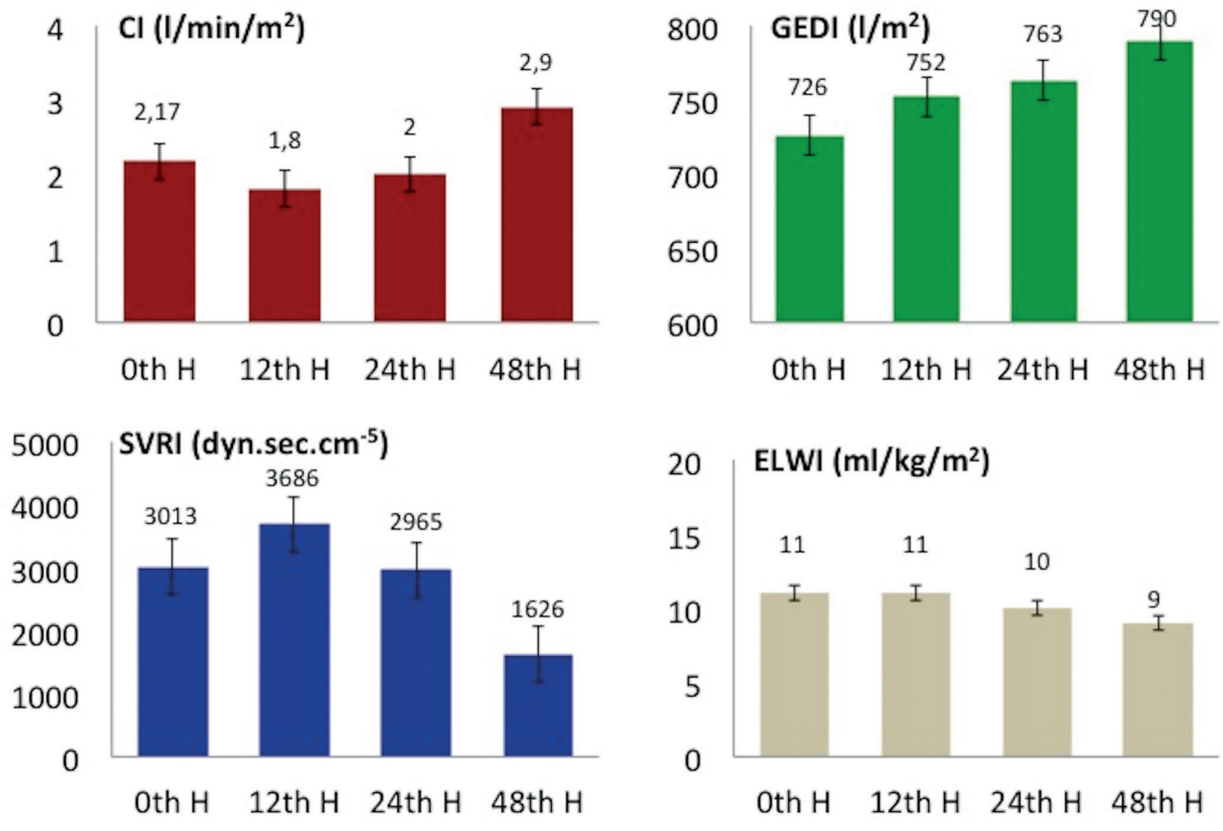

Figure 4. The changes of hemodynamic variables during therapeutic hypothermia (CI: cardiac index; SVRI: systemic vascular resistance index; GEDI: global end-diastolic volume index; ELWI: extravascular lung water index; H: hour).

post-resuscitation therapy is the proper attendance of cardiovascular disorders and an adequate guidance of hemodynamic management. The main goal is to secure a satisfactory organ perfusion and to prevent secondary brain damage by providing a sufficient cerebral blood flow despite the impaired cerebral autoregulation.

As we mentioned previously, there are several components leading to hemodynamic instability in patients after successful resuscitation [6]. There is pronounced vasodilatation due to systemic inflammatory response syndrome (SIRS) following an ischemia-reperfusion episode. The precipitating pathology itself resulted that cardiac arrest is a cardiovascular disease in most of cases. Cardiac stunning may develop after ROSC as a consequence of SIRS.

Targeted temperature management and therapeutic hypothermia may also affect hemodynamic variables of post-cardiac arrest patients in a negative manner: bradycardia, decrease in cardiac output and increase in systemic vascular resistance can evolve [58, 59]. As a consequence of lower temperature primarily during induction phase polyuria may occur resulting in hypovolemia [60]. Systolic and diastolic dysfunction was provoked in pigs while they were treated with hypothermia [61]. On the other hand these effects may be advantageous in this patient group because it has been shown that post-cardiac arrest patients with bradycardia had better outcome than patients whose heart rate was higher [62]. The increase of systemic vascular resistance is also a beneficial effect and may compensate the vasodilatory consequence of SIRS.

Bernard et al. used PAC as a hemodynamic monitoring in post-cardiac arrest patients and found that cardiac index was in tendency lower and systemic vascular resistance index was significantly higher in hypothermic group compared to normothermic patients [44]. It was also shown that cardiac index was in 66% of patients below 1.5 l/min/m^2 in the first 12 hours after ROSC in OHCA patients who were treated with therapeutic hypothermia. [63] They also used PAC to monitor hemodynamic variables.

As we mentioned it previously, we chose PiCCO™ monitoring system because it is less invasive than PAC and it was earlier validated in PCAS and therapeutic hypothermia [57]. We found during our measurements that cardiac index had the lowest value in the 12th hour of hypothermic treatment and it was significantly higher after rewarming. Investigating peripheral vascular resistance we measured the highest value of SVRI in the 12th hour of therapeutic hypothermia and a significantly lower value after rewarming. Our findings are similar to the measurements that have been performed with PAC.

On the basis of our results we think that there is a deteriorating hemodynamic instability during the first 24 hours after ROSC as a part of post-resuscitation syndrome. We also need to point out that treatment with lower temperature may also affect hemodynamic parameters. Our opinion is that taking these facts into consideration it is important to use a higher level of hemodynamic monitoring in this patient group to guide our hemodynamic therapy mainly if the patients are treated with targeted temperature management.

It is a different question if hemodynamic monitoring affects patients' outcome and mortality. There is no evidence which non-invasive, semi-invasive or invasive tool for hemodynamic monitoring should be used in critically ill patients. We think the answer is not simple and

depends on patient, disease, patient's condition and the staff's practical knowledge. There is no evidence neither which parameters should we monitor and target during our therapy. To get closer to the answer more studies and randomized controlled trials are needed.

We were investigating in our study weather PiCCO™-guided therapy affects outcome in patients after successful resuscitation. There was no significant difference in demographic data and the circumstances of CPR between the two groups, so they were comparable. There was no difference in mortality, neither in the length of ventilation nor ICU stay between the groups. We found the same what was previously published in international literature. We found that in tendency more vasopressors and inotropes were used during the PiCCO™-guided therapy. It is very important to use these agents for the shortest time and in the lowest dose as possible to avoid side effects. PiCCO™-guided therapy, as it is shown in our study, may be a helpful equipment to fulfill this role.

The limitation of our study is the low number of study participants. We are planning to expand the investigation and we hope that with the increased number of patients enrolled we are getting a clearer result.

3.8.4. Conclusion

As a conclusion of our study, we can say that PiCCO™-guided therapy did not improve mortality, length of ventilation and ICU stay among our post-cardiac arrest patients. On the other hand we need to point out that it may play a role in conducting the vasoactive and inotrope therapy more adequately in this patient group. We proved that the decrease of cardiac index and increase of systemic vascular resistance index is observable also with PiCCO™ monitoring in the first 24 hours after successful resuscitation, during targeted temperature management.

4. Summary

A strong chain of survival can increase the chances of survival and recovery for victims of cardiac arrest. We summarized our recent knowledge about neuroprotective strategies after successful resuscitation in this chapter, that is, one of the most important parts of post-resuscitation therapy.

Normoxia, normocapnia, normoglycemia and a proper level of sedation must be maintained in order to avoid secondary brain damage. The use of pharmacologic strategies is questionable but thiamine may be a promising agent in improving neurological outcome. Its efficiency needs further clinical investigations.

Targeted temperature management is the most effective tool in our hand today. It has positive effect in the neurological recovery by decreasing fever, providing myocardial protection, slowing the brain metabolism and decreasing the inflammatory response. However, there are still many questionable topics in its implementation, like the targeted temperature, method, timing, duration of the therapy and the rewarming rate.

The proper management of hemodynamics in this patient group is also essential to secure a satisfactory brain perfusion, but the way of hemodynamic monitoring and the targets of hemodynamic variables are also subjects of further investigations. We think that PiCCO™-guided therapy can be a good direction to tailor vasopressor, inotrope and fluid therapy after cardiac arrest and during TTM.

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