INVESTIGATION OF KEY FACTORS AFFECTING CARDIAC ARREST OUTCOME: FROM BASIC LIFE SUPPORT TO POST-CARDIAC ARREST THERAPY

PhD thesis

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List of abbreviations

AED	Automated External Defibrillator
ALS	Advanced Life Support
AUC	Area Under Curve
BLR	Binary Logistic Regression
BLS	Basic Life Support
BP	Blood Pressure
CC	Chest Compression
CCRV	Chest Compression Release Velocity
CI	Cardiac Index
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
CS	Cardiogenic Shock
DNR	Do Not Resuscitate
EMS	Emergency Medical Service
ELWI	Extravascular Lung Water Index
ERC	European Resuscitation Council
ESICM	European Society of Intensive Care Medicine
GEDI	Global End Diastolic Index
GEF	Global Ejection Fraction
HIBI	Hypoxic-Ischaemic Brain Injury
IABP	Intra-Aortic Balloon Pump
ICU	Intensive Care Unit
IHCA	In-Hospital Cardiac Arrest
IQR	Inter-Quartile Range
MAP	Mean Arterial Pressure
mTHT	Mild Therapeutic Hypothermia
MV	Mechanical Ventilation
N	Number of all patients
n	Number of patients in a particular subgroup
NSTEMI	Non-ST segment Elevation Myocardial Infarction
O	Older patient group
OHCA	Out-of-Hospital Cardiac Arrest
PAC	Pulmonary Artery Catheter
PCI	Percutaneous Coronary Intervention
PiCCO®	Pulse index Continuous Cardiac Output
PCAS	Post-Cardiac Arrest Syndrome
plVT	Pulseless Ventricular Tachycardia

Publ	Publication
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
ROSC	Return of Spontaneous Circulation
SCA	Sudden Cardiac Arrest
SRA	Skill Retention Assessment
STEMI	ST-segment Elevation Myocardial Infarction
SVRI	Systemic Vascular Resistance Index
TTM	Target Temperature Management
VF	Ventricular Fibrillation
VO	Very Old patient group
Y	Younger patient group

1. Introduction

1.1 Epidemiology of cardiac arrest

Sudden cardiac arrest (SCA) leads to significant number of deaths in Europe, where it is the third leading cause of mortality (1, 2).

The epidemiological characteristics of European out-of-hospital cardiac arrests (OHCA) are described by the EuReCa trials (1, 3). Twenty-eight countries (including Hungary) were involved in the EuReCa TWO prospective, multicenter study in the year 2017 covering a population of 178,879,118 (1). Data were collected with Utstein-style over a three-month period. The average OHCA incidence ranged from 67 to 170 per 100,000 inhabitants annually with an expressed variation among the countries. The main reasons explaining this variation include the variability of Emergency Medical Service (EMS) systems, differences in education and data reporting quality among the participating countries (4, 5). These results show that the incidence of OHCA in Europe is not clearly known, however, it can be well estimated based on these data.

In addition, the EuReCa TWO trial investigated the incidence of factors influencing the success of cardiopulmonary resuscitation (CPR). It was shown that the rate of bystander CPR varies between the European countries, as well as the use of automated external defibrillators (AED). The latter is infrequently applied overall the continent (1).

Furthermore, the trial explored the average survival rate at hospital discharge, which was 8% with a variation from 0 to 18% (1). Aspects influencing survival and leading to the heterogeneity of survival variation among the European countries are the following: cause of SCA, initial rhythm, gender, comorbidities, ethnicity, socioeconomic deprivation, the location of SCA and the organisation of EMS and health system (6-12).

The Hungarian data of the EuReCa TWO trial confirmed 3430 OHCAs during the investigation period and showed an annual OHCA incidence of 140 per 100,000 inhabitants (1). Additionally, the incidence of initiated CPR was 81 per 100,000 inhabitants with a 4.5% mean survival rate. A subgroup analysis investigated the survival rate for patients having SCA witnessed by a bystander and an initial shockable rhythm. The results of the Hungarian population showed 11% mean survival rate for this group.

The incidence of in-hospital cardiac arrest (IHCA) is even more difficult to specify. Most research investigating the characteristics of IHCA performed single-center studies. Moreover, differences in Do Not Resuscitate (DNR) policies and difficulties in the reporting of IHCAs lead to significant variation of IHCA rates among the countries (13, 14). The IHCA frequency per 1,000 hospital admissions has been recorded as 1.8 in Denmark, 1.7 in Sweden, 1.8 in the United Kingdom and 2.8 in Poland (15-17). There are no accurate data published regarding the Hungarian IHCA situation.

1.2 Chain of survival

The approach of the chain of survival was first introduced in 1985 in Germany and its current format was published in the 2005 European Resuscitation Council (ERC) guidelines in order to establish a visualization of the interconnecting steps needed for successful resuscitation (18). Performing appropriate chain links leads to a better outcome of SCA (Figure 1) (19). It needs to be emphasized, that the chain is as strong, as its weakest link.

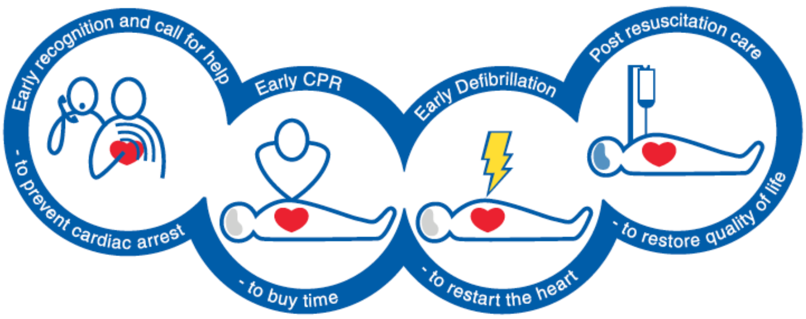


Figure 1. Chain of survival: *The chain of survival summarizes the most important steps of CPR required to achieve the return of spontaneous circulation and good quality of life. Reprinted from Resuscitation, 95, Perkins, GD et al, European Resuscitation Council Guidelines for Resuscitation 2015: Section 2. Adult basic life support and automated external defibrillation, 81-99, 2015, with permission from Elsevier (19).*

1.2.1 Early recognition and call for help

The role of early recognition and call for help is to prevent SCA and activate EMS. This first link highlights the importance of identifying patients with the risk of SCA and applying appropriate steps to avoid it, as well as recognizing if SCA occurred. Lay people play an important role in recognizing conditions leading to SCA in the field (chest pain, anaphylaxis, stroke etc.) (20). In addition, early warning systems help health-care personnel to notice patients with the risk of SCA in hospitals (21). To initiate chain of survival, there is a need for a proper and quick diagnosis of peri-arrest condition or SCA, which has the following criteria: unresponsiveness and lack of normal breathing. The examination of carotid pulse during basic life support (BLS) has not been recommended since 2015 (19).

1.2.2 Early CPR

The goal or early CPR is to slow down the degree of brain and heart damage, and to win time until the defibrillator and advanced help arrive. The SCA survival may be doubled or even tripled if CPR is initiated immediately (22-24). The appropriate training of lay people and suitable medical dispatcher assistance during the emergency calls can improve this link.

1.2.3 Early defibrillation

Early defibrillation aims to restore normal heart rhythm. The survival rate can be as high as 50-70% if a defibrillator is applied in the first 3-5 minutes right after the appearance of SCA in the case of shockable rhythm. In addition, every minute of delay decreases the chances of survival to discharge by 10-12% (25, 26). A widespread training of lay people and public-access defibrillator programs can bring large progress in the implementation of this step (27).

1.2.4 Adequate post-resuscitation therapy

The goal of early advanced life support (ALS) and adequate post-resuscitation therapy is to recover brain function and restore life quality. ALS covers higher-level airway management, use of manual defibrillator, securing intravenous or intraosseous line, applying medication, as well as recognition and correction of reversible causes of SCA. It needs to be highlighted, that ALS has not given benefit compared to optimized BLS with rapid defibrillation (28). However, an early ALS administration showed improved survival to hospital discharge in a prospective study investigating 35,000 patients (29). Proper post-resuscitation therapy contains complex intensive therapeutic measures to protect organs and mainly brain from secondary damage and it has great importance in providing a good quality of life (30).

The above-mentioned steps play a crucial role in the survival of SCA; however, they are not the only determining factors. Validity and quality of the current guidelines representing science, the efficient caregiver education symbolizing education and a well-functioning local chain of survival referring to the proper guideline implementation compose the formula of survival (Figure 2), which influences survival rate in significant extent (31). It should also be noted that the current product arithmetical of the survival formula has still not reached the ideal value (Figure 2). Science is not only an element of this formula but also harmonizes education and practical implementation. It should be noted that it is difficult to provide large randomized controlled trials in the field of resuscitation and we are frequently forced to make conclusions based on observational studies.

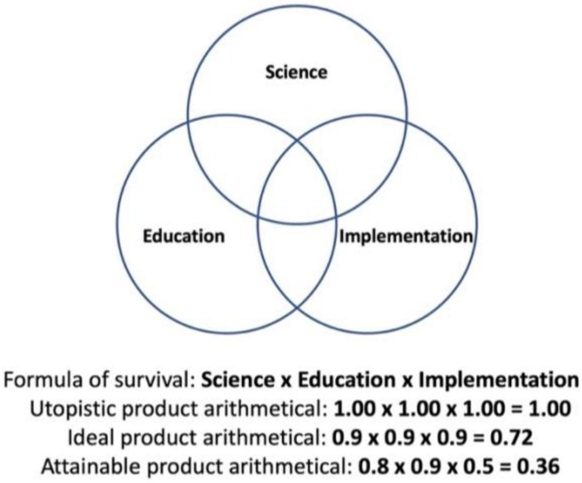


Figure 2. The formula of survival (31)

1.3 Factors affecting the outcome of cardiopulmonary resuscitation

The chain and formula of survival compile the most important elements affecting the survival and outcome of SCA, as mentioned previously. The quality of BLS, early defibrillation and proper post-resuscitation therapy form the bases of guideline creation and implementation. In addition, proper education of both lay people and health-care workers is needed to achieve success in CPR and advance in SCA outcome. The most important knowledge and evidence concerning these tools and determinants affecting survival after SCA are detailed below.

1.3.1 The quality of basic life support

OHCA victims receiving bystander CPR are four times more likely to survive than victims without bystander CPR (32). This finding shows, that BLS initiated by lay people in the field has a positive effect on the SCA outcome and is more advantageous than no action. Furthermore, an additional increase in survival rate may be reached by improving BLS quality, which can be attained in several ways.

As a first step, it is essential to recognize SCA (33, 34). The current evidence shows that patient's unresponsiveness and the lack of normal breathing compose the criteria for starting BLS (35). Carotid artery palpation is unreliable in a stressful emergency situation not only for lay people, but medical professionals, as well (36, 37).

The next step highlights the importance of alerting the EMS and of advanced professional help. Current guidelines suggest the "call first" approach in the case of lone bystanders instead of the "CPR first" strategy (33-35). There is lack of clear evidence to recommend the "CPR first" method, however, an observational study investigating 5446 OHCAs and their outcome found similar survival rates between the two approaches (38). In addition, higher survival was found with "CPR first" strategy in special subgroups. However, the study reported several limitations, and it does not present enough evidence to change the current recommendations.

Dispatchers play an important role in SCA recognition and assisting BLS through phone call (39). They can increase bystander CPR initiation rate and quality, if they provide appropriate help to lay people until the arrival of EMS. The creation of national protocols and adequate dispatcher education are key elements to reach progress in this area.

Correctly performed chest compressions (Figure 3) compose the most crucial element of CPR. They replace the work of the malfunctioned heart and provide vital organ perfusion until the return of spontaneous circulation (ROSC). The criteria of high-quality chest compression are the following (33-35):

- correct hand position
- adequate compression depth (5-6 cm)
- appropriate compression rate (100-120/minutes)
- proper degree of chest wall recoil
- minimized pause duration in chest compressions

Based on our recent knowledge, the optimal hand position is in the lower part of the sternum and should be taught to lay people delivering chest compressions in the "middle of the chest". There are no data reporting different survival rate or outcome with varying hand positions (35). Studies relying on imaging techniques investigating the effect of hand position and anatomy on the outcome are difficult to interpret, because there are important anatomical differences between the victims depending on age, pregnancy, obesity or the presence of congenital heart disease (40, 41).

Figure 3. Chest compressions during BLS: *High-quality chest compressions are carried out in the middle of the chest with the following characteristics: depth of 5-6 cm, frequency of 100-120/min, proper degree of chest wall recoil.*

The current ERC guidelines recommend keeping chest compressions 5-6 cm's deep with a rate of 100-120/min (35). The evidence supporting this is based mostly on prospective observational study results and only on a few randomized controlled trials (42-53). Table 1 shows the summary of investigations examining the association between chest compression depth or rate and outcome published in the last ten years. On one hand, it was shown that survival rate improved with the increase of chest compression depth (42-44). On the other hand, chest compressions deeper than 6 cm were associated with more organ damage and complications (45). Despite this, the most effective depth is still unknown and further investigation is needed for its determination.

Chest compression frequency of 125/min was associated with higher ROSC rate, however, the influence of chest compression frequency on survival is still not clear (48, 49).

Chest compressions need to be interrupted during rescue breaths, defibrillation shocks or rhythm analysis. A better survival was found if the pauses in chest compressions were shorter than 10 seconds (54).

In addition, correct chest wall recoil plays an important role in achieving high-quality chest compressions. A complete chest recoil leads to better venous return and more effective CPR (55, 56).

30:2 compression to ventilation ratio is suggested by the current guidelines (35). This recommendation is based on the findings, which showed better neurological outcome if 30:2 ratio was applied instead of 15:2 (57). In specific situations – mainly in lay rescuer setting - chest compression-only CPR is acceptable. However, in the lack of clear evidence, bystanders trained in CPR and without any other contraindications should keep 30:2 compression-ventilation ratio (35).

Table 1. Studies examining the association between chest compression depth or rate and outcome. *BP: blood pressure, CC: chest compression, CCRV: chest compression release velocity (the maximum velocity of chest release in the posterior and anterior direction), IHCA: in-hospital cardiac arrest, N: number of patients, OHCA: out-of-hospital cardiac arrest, Publ: publication, ROSC: return of spontaneous circulation.*

Author	Publ year	Type of the study	Study year	N of patients	Subject of investigation	Conclusion
Idris AH et al. (48)	2012	prospectively acquired, restrospectively analyzed	2005-2007	3098	Association between CC rate and outcome.	ROSC rate peaked at CC rate 125/min. CC rate was not associated with survival.
Stiell IG et al. (43)	2012	prospective cohort	2006-2009	1029	CC depth and survival	There is a strong association between survival and increased CC depth. The most effective depth is unknown.
Hellevuo H et al. (45)	2013	prospective observational	2009-2011	170	CC depth and complications	CC deeper than 6 cm was associated with more injuries and complications.
Stiell IG et al. (42)	2014	prospective observational	2007-2010	9136	CC depth and survival or ROSC rate	Survival is associated with CC depth. Maximum survival was achieved in the CC interval of 40.3 - 55.3 mm.
Vadeboncoeur T et al. (44)	2014	prospective observational	2008-2011	593	CC depth and survival	Deeper CC was associated with better survival and functional outcome.
Sainio M et al. (46)	2015	prospective observational	2008-2011	39	Association between CC depth, rate and blood pressure during CC	Deeper CC does not equal higher BP in every patient.

Idris AH et al. (47)	2015	prospective observational	2007-2009	10371	Association between CC rate and survival.	CC rate between 100-120/min was associated with the highest survival after adjustment for CC depth and fraction.
Kovacs A et al. (53)	2015	prospective observational	2008-2013	981	CCRV	CCRV was independently associated with improved survival and favorable neurological outcome.
Cheskes S et al. (52)	2015	retrospective observational	2012-2014	1137	CCRV	When adjusted for Utstein variables and CPR quality metrics, CCRV was not associated with OHCA outcome.
Hwang SO et al. (49)	2016	RCT	2011-2012	292	CC rate with 100/min vs 120/min	No difference was found in the OHCA-outcome between 100 CC and 120 CC groups.
Kilgannon JH et al. (50)	2017	prospective observational	2013-2015	222	CC rate effect on ROSC among IHCA patients	CC rate of 121-140/min had the highest probability of ROSC.
Sutton RM et al. (51)	2018	observational	2013-2016	164	Association between CC rate and survival among paediatric IHCA victims	Higher rate categories were associated with lower systolic BP during CC. Lower CC rate resulted higher rate of survival to hospital.

1.3.2 Early defibrillation

Survival can be increased significantly with early defibrillation (58). AEDs may help lay people treat shockable rhythms quickly, safely and effectively before the arrival of EMS, without prior healthcare skills and knowledge. The probability of ROSC success is reduced by 3-5% for each delayed minute without defibrillation in the case of shockable rhythm. Defibrillators must be set up quickly, however, guidelines recommend a short period of CPR until the defibrillator is prepared to analyze rhythm (35). To our recent knowledge, the right parasternal-apical position of AED electrodes is effective during CPR, and there is no evidence showing advantage of other electrode positions (59). Public access defibrillator programs and appropriate education play a significant role in disseminating and implementing the use of AEDs.

1.3.3 The quality of post-resuscitation treatment

The fourth link of chain of survival incorporates proper post-resuscitation treatment. We need to emphasize that the chain is as strong, as its weakest element. This finding leads to the fact that the fourth chain link is as important as the other three components, even if it does not directly include elements of CPR. In addition, adequately guided post-resuscitation therapy is crucial in securing good quality of life after recovery (30).

To highlight the priority of post-resuscitation management, ERC Guidelines introduced a new, separate section in 2015 to conclude the newest evidence and recommendations regarding post-cardiac arrest treatment (60).

Post-resuscitation therapy is initiated immediately after ROSC in the field, ambulance or hospital, depending on the location of cardiac arrest. Patients after successful CPR require proper monitoring, diagnostic and therapeutic steps to prevent the recurrence of cardiac arrest and to maintain adequate organ perfusion. In addition, these patients should be admitted to the intensive care unit (ICU) or at least high dependency units as soon as possible (30).

There are several areas of post-resuscitation treatment, which can be improved to provide high-quality patient care and influence patients' outcome in a positive way. Post-cardiac arrest therapy includes several interventions to protect organs – especially brain and myocardium – damaged during the no-flow and low-flow period from further, secondary injuries. The principles of post-cardiac arrest syndrome and main steps of post-cardiac arrest therapy will be explained in chapter 1.4 in details.

1.3.4 The role of education in improving the outcome of cardiopulmonary resuscitation

As the formula of survival summarized earlier, proper education of CPR skills among both lay people and healthcare professionals plays an important role in improving the outcome of patients suffering SCA (31). ERC Guidelines created a separate chapter in 2015 and 2021 to give suggestions and recommendations regarding CPR education (61, 62).

The main roles and key points of bystanders' CPR education are the followings: strengthening the willingness to perform CPR, reinforcing the chain of survival and distributing CPR trainings in a wide range. Healthcare professionals need to be taught not only high-quality CPR, but proper ALS and non-technical skills as well (62).

It was shown that BLS skills deteriorate in 3 to even 12 months after training, if not used (63-65). This finding leads to educational interventions aimed at prolonging skill retention and enhance the effectiveness of BLS trainings. The goal of BLS education is to teach high-quality chest compressions and the application of AED, regardless of the rescuers' healthcare qualification (62).

There are numerous methods to teach and learn CPR skills and to improve skill retention. However, there is no didactic approach, which is better than the others based on our current knowledge. Performing CPR skills needs not only theoretical knowledge but also a development in psychomotor abilities, which requires practical training. Two main factors play an important role in providing high-quality education and successful CPR training: the instructor's commitment and the extent of a proper feedback on accomplishment (66).

Several studies have investigated BLS skill retention of medical students and junior doctors, which have revealed serious gaps in their BLS knowledge (67-69). It also has been shown that these skills declined mostly in the first month after the course and stayed constant after one year (70, 71). One of the most important factors influencing BLS skill retention among medical students is previous clinical experience in BLS or ALS (72).

Various studies have investigated the factors affecting skill retention. As CPR skills decay with time (depending on the qualification of rescuers), it is suggested to repeat CPR trainings and to organize refresher courses (73, 74). The exact optimal time of refresher trainings is unknown. However, ERC recommends a so-called Life-Long-Learning strategy with recertification modules every 6-12 months (62).

Other ways of skill retention enhancement were also examined and combining these methods with refresher courses may be an effective long-term procedure to prolong CPR skill retention: the use of audio-visual tools and feedback devices, the application of virtual patients, or CPR education during childhood (75-77). The latter method is used during the Kids Save Lives program, which directs to deliver CPR knowledge to as many children as possible worldwide (78).

In addition, it was shown that testing skills at the end of CPR courses can increase the effectiveness of learning. Medical students taking practical exam at the end of CPR courses have improved skill retention controlled two weeks after the training compared to students using the same time period for practicing (79). Moreover, skill retention after such testing may last six months (80). A randomized non-inferiority trial showed the advantage of repetitive sessions of formative self-testing to update CPR skills (81). These findings have been explained with testing effect. Testing effect refers to the fact that repeated retrieval of memories during testing augments knowledge retention better than repeated studying (82). It also needs to be highlighted that testing effect appears even in the lack of feedback after the exam (83). However, there are only a few studies investigating the testing effect respect to CPR skill retention and further investigation is needed to clarify its role.

1.3.5 The role of patient's age in the outcome of cardiopulmonary resuscitation

The role of patient's age is an important and ambiguous factor in predicting and determining the outcome of SCA. It is known that the population is aging rapidly with increasing life expectancy and decreasing fertility. In addition, the number of people above 90 years will possibly reach 30 million by 2030 (84). The increased number of the aging population leads to a rising ratio of old and very old patients suffering SCA and requiring treatment in the ICUs after ROSC (85).

Some evidence highlights the fact that older age may result in worse outcome after OHCA (86-94). However, this relationship is influenced by various factors and therefore exposes many questions regarding the nature of this finding. In addition, frailty, pathophysiologic changes related to older age and comorbidities influence the outcome of post-resuscitation treatment. However, current guidelines still do not differentiate between the therapeutic recommendations of younger and older patients (30). There are only a few studies describing the quality and outcome of CPR, post-resuscitation therapy and post-cardiac arrest target temperature management (TTM) in the elderly (95-101).

It is a crucial point to clear the exact function and influence of patient age in the prognostication during CPR and post-resuscitation treatment to avoid wrong decisions and therapeutic approaches.

1.4 Post-cardiac arrest syndrome

Post-cardiac arrest syndrome (PCAS) was first described in 1972 by Vladimir Negovsky as an abnormal condition following whole body ischemia resulting from no- or low-perfusion during SCA and reperfusion after successful CPR (102).

1.4.1 Elements of post-cardiac arrest syndrome

PCAS has four elements based on a combination of complex pathophysiological mechanisms: post-cardiac arrest hypoxic-ischemic brain injury (HIBI), post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response and the unresolved pathological process causing SCA (103, 104). The extent of these components and the severity of the patient's condition depends on a number of factors, such as the cause of SCA, ischemia duration and the patient's comorbidities.

PCAS can be divided into five phases based on elapsed time (defined by the International Liaison Committee on Resuscitation), which include the immediate phase (first 20 minutes after ROSC), the early phase (from 20 minutes to 6-12 hours after ROSC), the intermediate period (from 6-12 hours to 72 hours after ROSC), the recovery period (3 days after ROSC) and finally the rehabilitation phase (105).

1.4.1.1 Post-cardiac arrest hypoxic-ischemic brain injury

Post-cardiac arrest HIBI is one of the leading causes of death during the post-cardiac arrest period in the ICU (106). It needs to be highlighted that cardiovascular origin of death is more frequent in the first three days of ICU treatment, but neurological cause dominates in the later phases. Death is a result of treatment withdrawal due to neurological reason in 66% of OHCA patients and 25% of IHCA patients (107, 108).

The clinical manifestations of HIBI vary widely, from neurocognitive disorders, myoclonus or seizures to coma and brain death (109).

HIBI begins during the so-called no-flow phase and is advanced during the low-flow period. The no-flow phase describes the period between the onset of SCA and the initiation of chest compressions, while the low-flow phase refers to the period spent with chest compressions. It should be emphasized that approximately 30% of normal cardiac output can be achieved in the low-flow phase, even when high-quality BLS and chest compression are applied. Pathophysiological factors triggering HIBI include excitotoxicity, free radical formation, activation of protease cascades and apoptotic pathways, as well as calcium homeostasis disorders (110, 111). It needs to be highlighted, that most of these processes are activated over hours to days even after ROSC. The full restoration of brain microcirculation requires some time during reperfusion after ROSC, particularly if CPR was prolonged. Moreover, a macroscopic brain hyperemia is present in the first minutes of ROSC leading to edema formation and reperfusion brain injury (112). These facts may explain some findings regarding the value of mean arterial pressure (MAP) right after ROSC. Higher MAP in the first five minutes immediately after ROSC did not improve neurological outcome, however, constantly higher MAP achieved during the first two hours after ROSC led to better neurological results (113). Additionally, oxygen oversupply after ROSC may impair cerebral function leading to free radical production and mitochondrial injury (114).

In addition to primary brain damage mentioned previously, secondary cerebral injury is also a concern during the treatment of PCAS, as it may be exacerbated by improper post-cardiac arrest therapy. Provoking factors leading to secondary brain damage include hypo-/hyperoxia, hypo-/hypercapnia, pyrexia and prolonged low MAP.

As cerebral autoregulation is impaired due to the primary cerebral injury, it is crucial to achieve a constant and adequate MAP, because cerebral blood flow depends on cerebral perfusion pressure during the first 24-48 hours after ROSC (112). Current data show, that cerebral vascular resistance is also increased during this period, leading to impaired cerebral perfusion and brain tissue hypoxia (115). However, the responsiveness of cerebral perfusion to carbon dioxide level is still preserved in these cases.

1.4.1.2 Post-cardiac arrest myocardial injury

Post-cardiac arrest myocardial dysfunction occurring during PCAS may also lead to higher mortality of this patient group (106). However, it needs to be highlighted that this type of myocardial injury is reversible and responds well to adequate therapy (116).

There is an increase in blood catecholamine concentration immediately after ROSC leading to variable heart rate and blood pressure during this period. The signs of myocardial dysfunction can be identified in the first phase of PCAS, if appropriate monitoring is applied.

Coronary perfusion is retained during post-cardiac arrest myocardial injury showing that the predominant reason of this dysfunction is stunning, which resolves between 24-48 hours after ROSC in most of the cases (117). Animal studies have shown that post-cardiac arrest myocardial dysfunction has a good response to catecholamines. Dobutamine administration adequately improved left ventricular ejection fraction and isovolumetric relaxation after cardiac arrest in porcine models (118).

1.4.1.3 Systemic ischemia/reperfusion syndrome

Systemic ischemia followed by generalized reperfusion and systemic inflammatory response syndrome form crucial elements of pathophysiological changes occurring after SCA and ROSC (105). The severity of ischemia/reperfusion syndrome depends primarily on the length of the no-flow and low-flow phases. Calcium homeostasis disturbances, oxygen radical formation, cytokine production, complement activation and expression of leukocyte adhesion molecules lead to systemic inflammation and - if this condition is not recognized and treated in time - a consistent multiorgan failure may appear. Disturbances of homeostasis leading to endothelial damage, vasodilation, thrombus formation and increased capillary permeability explain clinical manifestations of ischemia/reperfusion syndrome, which shows several similarities with sepsis (119). Hemodynamic changes dominate in the first phases of post-cardiac arrest period leading to organ hypoperfusion with the danger of secondary brain damage without adequate treatment.

1.4.1.4 The unresolved precipitating pathology

Pathophysiological changes resulting from the unresolved and persistent precipitating pathology, which caused SCA, will combine with pathophysiological changes originating from systemic or localized damages mentioned above. It is crucial to diagnose and treat the reversible causes of SCA as soon as possible, as this is the key moment to reach therapeutic success during the management of patients suffering SCA.

Ample etiologies may lead to SCA, however research in the last few years mainly focused on cardiac origin and little is known about non-cardiac causes of SCA (30). Early diagnosis has a great importance in guiding proper patient management and to secure transport of patients to appropriate centers for further treatment.

1.4.2 Post-cardiac arrest therapy

Post-cardiac arrest therapy has two main goals: it provides supportive therapy and in parallel it aims to diagnose and treat the cause of SCA. In addition, supportive therapy aids patient stabilization to win time until causative therapy is accomplished, as well as provide organ protection from secondary damages. Neuroprotection is a central question during post-cardiac arrest treatment (104). Although the following paragraphs describe the most important elements of neuroprotection, but it needs to be stressed that these components are not only vital for cerebral protection, but the protection of other organs as well.

1.4.2.1 Oxygenation and ventilation

Current guidelines recommend avoiding not only hypoxemia, but hyperoxia as well after ROSC (30). These suggestions are based on the results of seven randomized controlled trials and 36 observational studies.

Hypoxia and insufficient oxygen supply can lead to cerebral anoxia and worse neurological outcome. However, an oxygen oversupply may also be harmful and can exacerbate secondary organ damages (especially in the brain and heart) by increasing the concentration of free oxygen radicals, leading to consequential reperfusion injury (120).

Data originating from a multicenter cohort study including 6326 ICU patients and 120 US hospitals showed that in-hospital mortality was significantly higher in the presence of hyperoxia (defined as $PaO2 > 300$ mmHg in the study) compared to normoxia ($PaO2 > 60$ mmHg and < 300 mmHg) or hypoxia ($PaO2 <60$ mmHg) measured during the first 24 hours following ICU admission (121). The subgroup analysis of survivors found better functional neurological outcome in the normoxia group compared to the hyperoxia group.

In addition, a dose-dependent relationship was detected between supernormal arterial oxygen tension and in-hospital death risk during a secondary analysis (122).

Different oxygenation targets applied for varying durations in the first 48 hours after ROSC have been compared in six randomized controlled trials, but none of them could provide an exact answer and clear evidence on what arterial oxygen value should be targeted during the early post-resuscitation period (123-128).

A number of observational studies investigated the effect of carbon dioxide level on neurological outcome during post-resuscitation care. Some of them found that mild hypercapnia may be beneficial during post-resuscitation therapy, however, some other studies found the opposite (129-131). We also need to express that patients are prone to hypocapnia if target temperature management (TTM) is applied pointing to the usefulness of frequent carbon-dioxide level monitoring in this patient group (132).

1.4.2.2 Hemodynamic optimization

Significant vasodilation induced by systemic ischemia/reperfusion injury, myocardial stunning, cardiac dysfunction caused by acute myocardial infarction (as a cause of SCA), as well as consequences of adrenal axis suppression can occur during the post-resuscitation period leading to severe hemodynamic instability (116, 133). In addition, TTM with a target temperature of 32-36 °C is applied during the first 24 hours after ROSC, which may negatively influence hemodynamic parameters resulting in bradycardia, arrhythmias, hypovolemia, increased systemic vascular resistance, and their main consequence, decreased cardiac output (134).

Cerebral autoregulation is impaired in the case of brain injury, which means that hemodynamic changes and blood pressure alterations (especially MAP) during the post-resuscitation period has a direct influence on cerebral perfusion, and hence secondary cerebral damage and neurological outcome.

A study investigating the effect of time-weighted average mean arterial pressure during the first six hours after ROSC found that hypotension was common, and it was associated with poor neurological outcome (135). Moreover, they showed that time-weighted average MAP greater than 70 mmHg had the best association with good neurological function.

A multi-center cohort study investigated the frequency of hypotension at the time of ICU admission among patients after successful CPR (136). Half of the patients had hypotension during ICU admission, and two thirds of hypotensive patients died during hospitalization. This finding may be explained by the fact that post-cardiac arrest period is characterized by patchy microcirculatory cerebral hypoperfusion, which may be compensated with adequate arterial pressure. However, the results of studies trying to determine the adequate blood pressure target during post-cardiac arrest period are inconclusive, as there are data that have shown an inverse effect between arterial pressure and mortality (137).

Current guidelines suggest hemodynamic goals (MAP, systolic blood pressure etc.) to be monitored carefully during post-resuscitation interventions (30). However, there is lack of evidence to recommend specific hemodynamic goals, or to advise specific hemodynamic monitoring tools. Hemodynamic goals should be considered based on individual patient needs.

There are some data showing that bradycardia is associated with better outcome during post-resuscitation therapy and this effect does not depend on the use of TTM (138). Based on these findings, bradycardia should not be treated as long as there are no signs of hypoperfusion (30).

Cardiac output monitoring is suggested in the case of persistent hemodynamic instability, however, there is no evidence on which hemodynamic parameters should be monitored and which monitoring method should be used (30). Cardiac output can be measured with echocardiography, thermodilution methods or non-invasive pulse contour analysis. The application of the latter should be limited to perioperative use, because its validity during TTM, vasopressor therapy or shock is questionable (139).

Echocardiography is non-invasive and precise in characterizing patients' hemodynamic conditions; however, it is not a continuous method, requires proper practice and has a wide range of inter-observer variability.

Thermodilution methods used and investigated most frequently include pulmonary artery catheter (PAC) or Pulse index Continuous Cardiac Output (PiCCO®) monitoring system. PAC is the gold standard of cardiac output measurement, which provides important information about hemodynamic variables and tissue perfusion. Nevertheless, this procedure is especially invasive, and no evidence proves its superiority over other monitoring techniques (140). The 2015 European Society of Intensive Care Medicine (ESICM) consensus on hemodynamic monitoring recommends the application of PAC only in refractory shock with right ventricular dysfunction (139).

The PiCCO® monitoring system is less invasive than the above-mentioned PAC. It uses transpulmonary thermodilution and pulse contour analysis to specify hemodynamic parameters. Transpulmonary thermodilution is performed as follows: a cold liquid bolus is applied via central venous catheter passing through various thoracic compartments, and a peripheral arterial thermodilution catheter (mostly inserted into the femoral superficial artery) detects the temperature curve, calculating cardiac output with the modified Stewart-Hamilton equation (141). In addition, a continuous cardiac output monitoring by recording the pulse pressure wave can also be used. Cardiac output is directly measured with PiCCO®, however this monitoring system also measures and/or calculates other parameters, which provide additional information about the circulatory system: cardiac index (CI) is related to the performance of the heart and the size of the individual, systemic vascular resistance index (SVRI) represents afterload, global end diastolic index (GEDI) – which is the volume of blood contained in the four chambers of the heart related to the body surface area – reflects preload, global ejection fraction (GEF) gives information about cardiac systolic function, and extravascular lung water index (ELWI) informs about the presence of pulmonary edema.

PiCCO®-guided therapy showed better outcome in critically ill patients suffering from sepsis or necrotizing pancreatitis, as well as during cardiac surgery (142-144). Its adequacy was also assessed in post-cardiac arrest conditions when therapeutic hypothermia (32-34 °C) was applied (145). The results of this investigation verified the applicability of PiCCO® during post-resuscitation treatment even in the presence of mild hypothermia. In a previous study, we showed that hemodynamic optimization guided by PiCCO® may influence catecholamine administration during post-resuscitation TTM (146). However, it has a great importance to clarify whether PiCCO® monitoring guided therapy affects outcome and mortality in this patient group.

There is little evidence regarding the use of various vasoactive and positive inotropic agents in post-resuscitation treatment. Noradrenaline was found to be the most frequently used vasopressor to achieve adequate MAP levels and dobutamine was the most common inotropic medication. Some data suggest that noradrenaline was well-tolerated among post-cardiac arrest patients (147). Furthermore, it was shown that dobutamine increased cardiac index, however its application did not affect neurological outcome (147).

1.4.2.3 Glucose control

Glucoregulatory hormones, such as catecholamines, glucagon and glucocorticoids are increased during the post-cardiac arrest period resulting in hyperglycemia. We also need to highlight, that the brain's only energy source and pathway, which is able to sustain metabolism during an ischemic episode, is the anaerobic glycolysis utilizing glucose. Adequate serum glucose management is a crucial question during post-resuscitation therapy.

Moderate hyperglycemia may be beneficial in the early phases after ROSC to facilitate glucose transport and cerebral glucose intake – when cerebral perfusion is compromised (148). However, there are some studies reporting the association between high blood glucose levels in the early post-cardiac arrest period after OHCA and higher mortality or worse neurological outcome (149). It was also shown, that both hypo- and hyperglycemia impaired survival in IHCA patients (150). Nevertheless, diabetic patients' mortality was not influenced by blood glucose levels, except when extreme hyperglycemia was present.

A number of studies found that normalization of hyperglycemia can lead to brain glucose reduction and energy crisis among critically ill patients with cerebral damage (151). Unrecognized hypoglycemic episodes may be more harmful and can lead to increased mortality.

Based on the above-mentioned data, ERC guidelines recommend to strictly avoid hypoglycemia and to maintain blood glucose level below 10 mmol/l (30).

1.4.2.4 Seizure control and sedation

The frequency of seizures occurring during the post-resuscitation period is approximately 20-30% (152). Seizures are usually associated with HIBI and may be diagnosed by direct observation of the convulsion itself or by the recognition of typical activity signs in the EEG.

Myoclonus is the most common convulsion type after SCA. It develops during the first days of post-cardiac arrest period and it can be present during the first days or even first weeks (153). It is associated with poor outcome in most of the cases, however, there are some patients who can survive with good outcome despite myoclonus (154).

The appearance of seizures suggests the presence of HIBI. In addition, seizures may enhance secondary brain injury and worsen the pre-existing brain damage. Therefore, aggressive and rapid seizure control is required in the post-cardiac arrest period. However, there is no evidence to support prophylactic medication against convulsions (155). Moreover, there is lack of evidence to confirm which antiepileptics should be applied during post-resuscitation therapy. Valproate or levetiracetam suppress electrical EEG activity in this patient group (156). Phenytoin is effective as well, however its negative hemodynamic consequences need to be taken into consideration. Sedatives have some seizure inhibiting effects, of which propofol or benzodiazepines are routinely used in the first 24-48 hours of treatment.

Appropriately guided sedation strategy has an important role in high-quality post-resuscitation treatment. Sedation prevents the propagation of primary brain injury and the development of secondary brain injury through many pathways. It reduces oxygen consumption, agitation, ventilator desynchrony and provides shivering control during TTM (157). However, there are no data on which sedative agent is the most optimal during post-cardiac arrest treatment, what the optimal duration is, or what the most ideal depth of sedation is. As a clinical practice, hypnotics and opioids are used frequently with the combination of muscle relaxants. The application of the latter should be minimized because of its severe and long-lasting side-effects: it can mask convulsions, lead to muscle weakness and prolong the duration of mechanical ventilation (158). Additionally, cerebral monitoring (electroencephalography, bispectral index or entropy monitor) is mandatory when administering a muscle relaxant because muscle relaxation may mask seizure activity.

1.4.2.5 Pharmacologic strategies

There are some promising experimental results regarding the use of neuroprotective drugs, however, no clinical studies proved their efficacy in post-resuscitation therapy.

Erythropoetin, cyclosporine, or exenatide were investigated among post-cardiac arrest patients, but no positive neurological effects were found regarding these agents (159-161). Volatile anesthetics have influenced cardiac and cerebral recovery positively in experimental settings, however, there are no clinical data to support these findings (162).

Xenon is one of the most investigated agents today, which also showed benefit in animal experiments, but it is still under clinical evaluation (163, 164). It needs to be pointed out, that xenon is expensive and requires special storage circumstances and dosing devices.

Thiamine is an easily attenable and affordable drug and its efficacy in post-cardiac arrest treatment was shown during experimental studies. It was also demonstrated that the activity of pyruvate dehydrogenase was significantly decreased in humans after successful CPR and may be a target of thiamine in this patient group (165).

1.4.2.6 Targeted temperature management

Current guidelines recommend the application of TTM among patients who remain comatose after ROSC (30). TTM means to aim constant target temperature between 32-36 °C for 24 hours. It is still an important and unresolved question, which patient populations benefit from the lower and which groups from the higher temperature, and further investigations are required to find the right answer. What is clearly known, that fever should be strictly controlled and avoided in the first 72 hours of treatment (166).

Two studies were published in the New England Journal of Medicine in 2002, which investigated the effect of mild therapeutic hypothermia (mTHT) applied for 24 hours after ROSC in comatose patients. The target temperature in these studies was 32-34 °C. They found better neurological outcome in the cooled patient group compared to patients, who did not undergo hypothermic treatment (167, 168). We need to highlight that fever was not uncommon in the control groups, where patients did not receive mTHT. Based on these data, mTHT (32-34 °C) was introduced to post-cardiac arrest guidelines in 2005 and still remains a cornerstone in post-cardiac arrest neuroprotection (169). The term TTM was suggested instead of mTHT by the 2015 ERC guidelines, because target temperature was modified to 32-36 °C based on the results of the Targeted Temperature Management (TTM) trial (60). The TTM trial investigated the benefits and side-effects of two targeted temperature regimens: a deeper hypothermia regimen targeting 33 °C and a milder regimen targeting 36 °C (170). 36 ICUs in Europe and Australia took a part in this randomized controlled trial and included 950 OHCA patients. Patients were cooled to 33 or 36 °C for 36 hours (the last 8 hours contained the period of slow rewarming) with surface or intravascular cooling method. The primary outcome was all-cause mortality at the end of the study, which was 50% in the 33 °C group and 48% in the 36 °C group. The lower temperature range was associated with elevated lactate level, increased vasopressor requirement, decreased heart rate and higher extended cardiovascular SOFA score. The results showed that targeting higher temperature range did not worsen the outcome. It needs to be highlighted, that the proportion of bystander CPR was above the average (73%) and time between collapse and the initiation of CPR was short (approx. 1 minute) in this study. In addition, patients in the TTM trial were less ill and had no fever during the therapy in contrast to population of previous studies (167, 168, 170).

Despite the fact that TTM is one of the most investigated topics in post-resuscitation therapy, there are still several unanswered questions regarding this treatment option. The exact target temperature, the optimal initiation time, duration or the most optimal cooling method are still unknown.

The Pulse-Hypo Japanese prospective cohort study investigated the differences between patients cooled to 32-33.5 °C and patients treated with 34-35 °C (171). The primary outcome was cerebral performance category (CPC) on day 30 after ROSC. The analysis found better neurological outcome in the lower temperature group, if CPR interval was shorter than 30 minutes. Time to reach target temperature was shorter, duration of TTM and re-warming period were longer, than in the TTM trial.

Some preclinical studies have shown that cooling started after ROSC as fast as possible can improve neurological outcome (172). However, clinical studies did not find any benefit from prehospital cooling, in fact, re-arrest occurred more frequently among patients who received TTM in the prehospital setting (173). The possible explanation of these findings is complex and have multiple causes. There are some mechanisms leading to brain injury mentioned earlier, which appear some hours later after the ischemic insult (110). Additionally, a big amount of intravenous fluid given to initiate TTM may lead to pulmonary edema and cardiac complications. It is difficult to clear the exact etiology of SCA in some cases during the prehospital treatment, which may lead to inappropriate administration of TTM in the field.

The pathophysiological principles of TTM’s beneficial cardio- and neuroprotective effects are reached by different pathways. The following hypothermic mechanisms are responsible for cardiac protection and increased myocardial contractility: energy production improvement during ischemia, increase in myocyte calcium sensitivity, regulation of mitochondrial oxidative phosphorylation and preservation of myocardial autoregulation (134, 174). Hypothermia influences not only cardiac function, but the whole circulatory system as well. It results in bradycardia, which is a beneficial side-effect, as it was associated with better outcome in post-cardiac arrest patients (138). Additionally, lower temperature can lead to arrhythmias, reduced cardiac output and increased systemic vascular resistance.

Cerebral protective effect of hypothermia is achieved by decreasing the apoptosis rate, reducing the levels of excitatory neurotransmitters, attenuating the reactive oxygen species production, improving brain autoregulation and reducing intracranial pressure (175). In addition, hypothermia reduces oxygen metabolic rate by approximately 6% for each 1 °C reduction in core temperature.

Lower core temperature can cause shivering, which was observed at 33 °C and at 36 °C similarly. On one hand, it needs to be treated effectively, because shivering increases metabolic side effects, oxygen demand and heat production, which counteract cooling therapy. On the other hand, its occurrence was associated with favorable neurological outcome among post-cardiac arrest patients treated with mTHT (176).

There are some side effects and complications of TTM, which need to be considered during this therapeutic option and patients should be strictly monitored to recognize their signs early (174, 177). Polyuria induced by TTM can result in severe hypovolemia combined with electrolyte abnormalities, such as hypokalemia, hypomagnesemia, hypophosphatemia or hypocalcemia (178). Hyperglycemia is also frequently observed during lower core temperature due to decreased insulin sensitivity and secretion. In addition, coagulopathies, impaired immune system function and reduced clearance of sedatives and other drugs may be present. Body temperature is reduced only mildly during TTM, therefore it has only limited contraindications. In the case of severe systemic infections, preexisting coagulopathy (except fibrinolytic treatment) or severe hemodynamic instability the upper temperature level (36 °C) should be targeted (60).

If TTM is indicated, it should be initiated by trained and experienced personnel as soon as possible (177). This therapeutic method has three phases: induction, maintenance and rewarming. There are several types of cooling techniques, which may be used based on the availability of the equipment at a given institute (60, 104). External cooling can be performed by traditional ice packs placed above large vessels in the groin, axilla and neck, or so-called surface temperature changer devices can be applied. The latter use thermo-feedback systems and self-adhesive blankets and/or helmets to provide more precise and comfortable form of TTM (179).

Internal cooling methods include intravascular, intrabladder and intragastric techniques (179). The easiest way of intravascular cooling is the application of 4 ºC crystalloid infusions, which is frequently used during the induction phase. However, it is difficult to control precise temperature changes during this method. Intravascular temperature management systems apply an intravascular catheter (placed into the femoral or jugular vein) with a closed circuit for circulating cold crystalloids to cool the blood. Endovascular temperature management is the most effective and fast way of TTM, however, the method's superiority over other forms of TTM could not be proved regarding the patients' outcome (30).

2. Objectives

Ample studies have investigated the effectiveness of CPR and post-resuscitation treatment practice, resulting in well-designed and detailed guidelines to provide recommendations on how to improve the management of patients suffering SCA. Despite this, overall survival rate of SCA remains still very low and there are several unanswered questions in resuscitation science. Several aspects of both the chain of survival and the formula of survival require further examination in order to clarify uncertainties, improve efficiency and achieve better neurological outcome as well as higher overall survival rate. Additionally, only a few studies examined the Hungarian implementation of the chain and formula of survival (180-182).

The aim of this thesis is to identify and uncover currently unknown key factors that may strengthen the chain of survival. In addition, I aimed to evaluate current Hungarian practice of CPR education and post-resuscitation treatment in order to reveal possible points of improvement. To achieve these goals, I investigated the efficacy of resuscitation from the following aspects:

- As an assessment of the first three links of the chain of survival, I evaluated the influence of skill exams on skill retention during BLS education among medical students.
- With a goal to enhance the fourth link of the chain of survival and provide higher quality of life for survivors, I investigated the role of hemodynamic management and advanced hemodynamic monitoring during post-cardiac arrest treatment.
- To clear the exact function of older patient age during resuscitation, I examined the association between age and outcome of post-resuscitation therapy.

The objectives of my thesis are explained in more details in the following chapters.

2.1 Influence of examination timing on skill retention after BLS training

Based on the current literature, testing effect and taking skill exams after BLS training could prolong BLS skill retention. However, only a few studies investigated the testing effect in respect to BLS skill retention. To our knowledge, no studies have investigated the influence of test timing on learning outcome. Therefore, the aim of our first study was to investigate the influence of testing and the timing of the examination on BLS skill retention among fifth year medical students at Semmelweis University (183).

2.2 Hemodynamic management during post-cardiac arrest therapy and TTM

It has been previously shown that TTM has an influence on hemodynamics during post-cardiac arrest treatment. There is a requirement of proper hemodynamic management during post-resuscitation care. However, there is no evidence which parameters should be monitored and which monitoring tool should be applied.

The objective of our second study was to evaluate the effects of PiCCO®-guided hemodynamic management on mortality in comatose patients treated with TTM after ROSC (184). Moreover, we focused on disentangling the relationship between PiCCO®-monitoring, patients' condition, and mortality by analyzing interaction effects.

2.3 The role of patient's age in post-cardiac arrest therapy in an elderly patient population

The aim of our third study was to investigate the characteristics and outcome of post-cardiac arrest treatment and effect of age on post-cardiac arrest therapy outcomes in an elderly population. Additionally, we examined hemodynamic changes during TTM and their differences between the different age groups, as an extension of the previous research. To accomplish our objectives, the study included two parts: we performed a retrospective cohort study based on the local database of Semmelweis University Heart and Vascular Center, and a systemic review of the current literature (185).

3. Methods

3.1 Influence of examination timing on skill retention after BLS training

3.1.1 Study design and participants

This was a post-test only, partial coverage, prospective quasi-experimental study designed to evaluate a BLS training course among 464 fifth year medical students at Semmelweis University in the first semester of 2013/2014. Students participated in the compulsory Emergency Medicine course, which contained thirteen 70-minute long lectures (a lecture session covered several topics) and five 90-minute long practice sessions during the study period (BLS training formed a part of this course). Participants were presumed to have had no organized BLS training prior to the course, with the exception of some basic first aid training that was part of their driving license course or an element of their curriculum in the first year of their medical studies.

The Semmelweis University Regional and Institutional Committee of Science and Research Ethics approved our study (approval number: 160/2014). The informed consent was waived due to the nature of the study based on our national regulations. Participation in the study and study results did not affect students' grades since the results were processed anonymously according to the protocol of the ethical committee.

3.1.2 Group assignment

Groups were systematically but non-randomly assigned to either a control group or one of two experimental groups based on consecutive sampling according to their date of participation in the BLS practice sessions: the first 12 groups (n=179 students) were assigned into the NoExam control group, the second 12 groups (n=165 students) were assigned into the EndExam experimental group, and the third 9 groups (n=120 participants) were assigned into the 3mExam experimental group (Figure 4). Participation in the groups was blinded in the sense that participants had no knowledge of an exam at the beginning of the course and those assigned to the study groups learned of their scheduled exam at the time of their training session.

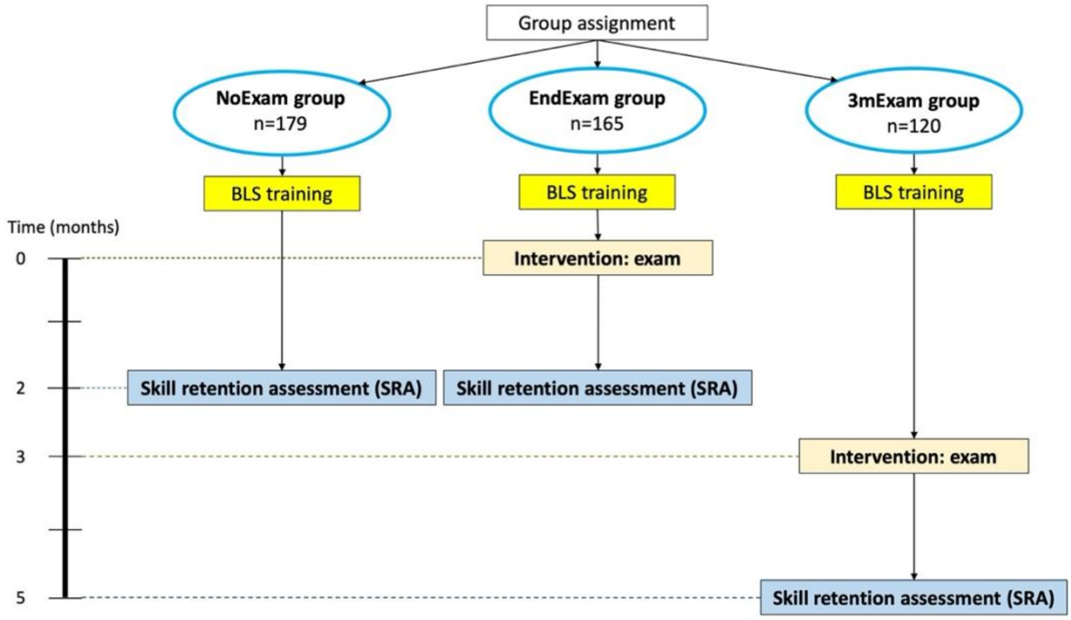


Figure 4. Group assignment and the diagram of the BLS study design (183).

3.1.3 BLS training

As part of this study, participants received a 45-minute BLS lecture and a 90-minute BLS training session according to the 2010 ERC Guidelines, which were appropriate at the time of the study (186). Working in pairs, the students had to solve simple BLS scenarios after a four-step presentation; one student performed BLS, and the other assisted them. Everyone performed at least one complete BLS algorithm. Each student received the same education and was presented with the same scenario.

Peyton's Four-step Approach (187) - also preferred by the ERC - was used as the teaching method during the training sessions, which contains four steps:

- Step 1: Real-time demonstration on the manikin - the instructor shows the process of BLS without any comments.
- Step 2: Repeated demonstration on the manikin with explanation – the instructor displays the process again slowly and explains it in detail.

- Step 3: Demonstration lead by a student on the manikin – the instructor shows the process of BLS again based on the instructions of a selected student.
- Step 4: Demonstration performed by a student on the manikin – the student who gave the instructions in the previous step performs BLS under the inspection of the instructor.

The teacher to student ratio during the training sessions was 1:7. Ambu Man C Torso® (Ambu A/S, Copenhagen, Denmark) manikins were used during the BLS simulation training and exams. Students were observed and corrected by continuous assessment and finished the training only when they have presented satisfactory BLS skills.

3.1.4 Intervention – practical exam

As it can be seen in Figure 4, the NoExam group had no practical exam after the training. Students in the EndExam group took a practical exam immediately following their BLS course, and students in the 3mExam group took the practical exam three months after the BLS course. The three-month period for the exam for the third group was chosen because it mirrors the official end-semester examination period. As a note, students in the 3mExam group had no organized opportunity to practice BLS between their course and their exam and were specifically asked not to train during these three months.

3.1.5 Evaluation – skill retention assessment (SRA)

The evaluation consisted of a skill retention assessment (SRA), which was identical in nature with the exam, meaning that participants knew that they were being assessed and they were assessed using identical criteria, but during the exam they were told that their assessments were scored, while during the SRA they were not told that their assessments were scored.

As part of the evaluation, students had to enact and resolve a BLS scenario, supervised by independent ERC instructors who had not been involved in the training. The following ten BLS steps were assessed: 1. shouting for help, 2. verifying consciousness, 3. testing for vital signs, 4. call for ALS team, 5. position of hands on the chest, 6. depth of chest compressions, 7. rate of chest compressions, 8. consistency of chest compressions, 9. maintaining a 30:2 compression to ventilation ratio, and 10. duty cycle.

A checklist of steps being correctly vs. incorrectly performed was used for evaluation. Chest compression depth was measured by the built-in sensor in the Ambu Man Torso®, and chest compression frequency was determined using a stopwatch. A BLS step was considered correct if it met the ERC guidelines described above, and if it was performed correctly at least 75% of the time during the assessment (186). Correctly and incorrectly performed events were recorded. The students received a score of 1 for a properly implemented step and a score of 0 for an incorrect performance, which was recorded in the evaluation sheet.

As Figure 4 shows, the SRA took place two months after the BLS training for the NoExam and EndExam groups and five months after the BLS training (i.e., two months after the practical exam) for the 3mExam group. The two-month period for the follow-up assessment (SRA) was chosen because it was the longest time period in which all three groups were able to complete the evaluation of the course within the academic year.

3.1.6 Statistical analysis

A summary score was calculated by adding up the individual BLS scores in the SRA. The distribution of the average scores for each BLS step and for the total score was compared across the three groups using the Kruskal-Wallis test overall and the Dunn's post-hoc test among groups. The level of significance was set at $p<0.05$. Statistical analysis was performed using SPSS v13.0 (SPSS Inc., Chicago, IL). Figures were created using GraphPad Prism version 8.1.1. (GraphPad Software, La Jolla, CA).

3.2 Hemodynamic management during post-cardiac arrest therapy and TTM

3.2.1 Study design

This was a quasi-feasibility retrospective longitudinal chart review analysis of PiCCO® use among a small real-world patient population. Study participants were all patients (N=254) who successfully underwent CPR after either OHCA or IHCA between January 2008 and January 2015 at Semmelweis University Heart and Vascular Center.

Patient assignment to PiCCO® monitoring followed a real-world systematic consecutive treatment allocation protocol, as follows. The Center has only one PiCCO® system for 10 beds altogether, and if it was available, then it was assigned to the first admitted patient. Any consecutive patient received treatment without PiCCO® until PiCCO® was available again. At that point, the next consecutive patient received PiCCO® monitoring and guidance to treatment.

Institutional medical records and charts were reviewed to estimate the in-hospital management in the first 72 hours after admission. Information related to pre-hospital emergency care by OHCA patients was obtained from the records of emergency medical service and Utstein reports.

The Semmelweis University Regional and Institutional Committee of Science and Research Ethics approved our study (approval number: 19/2019). The written informed consent requirement was waived due to the retrospective nature of the study.

3.2.2 Patients and initial therapy

We included in our analysis those comatose patients who were cooled to 32-34 °C for 24 hours after ROSC on the basis of the even actual ERC guidelines (188), were older than 18 years, had no end stage illness in history, were not pregnant, had no active bleeding, whose cause of cardiac arrest had a probable cardiac origin, and were not involved in a clinical trial. In addition, only patients cooled with Blanketrol III® (Cincinatti SubZero Products, Cincinatti, USA) thermo-feedback device were enrolled into the study – those patients whose temperature management was applied with ice packs and/or physical cooling were excluded, because target temperatures could not be reached in most of these cases. Twenty-three patients were excluded from the study due to lack of data. After the sampling process depicted in Figure 5, the final study sample included 63 patients (33 who were applied and 30 who were not applied PiCCO® monitoring).

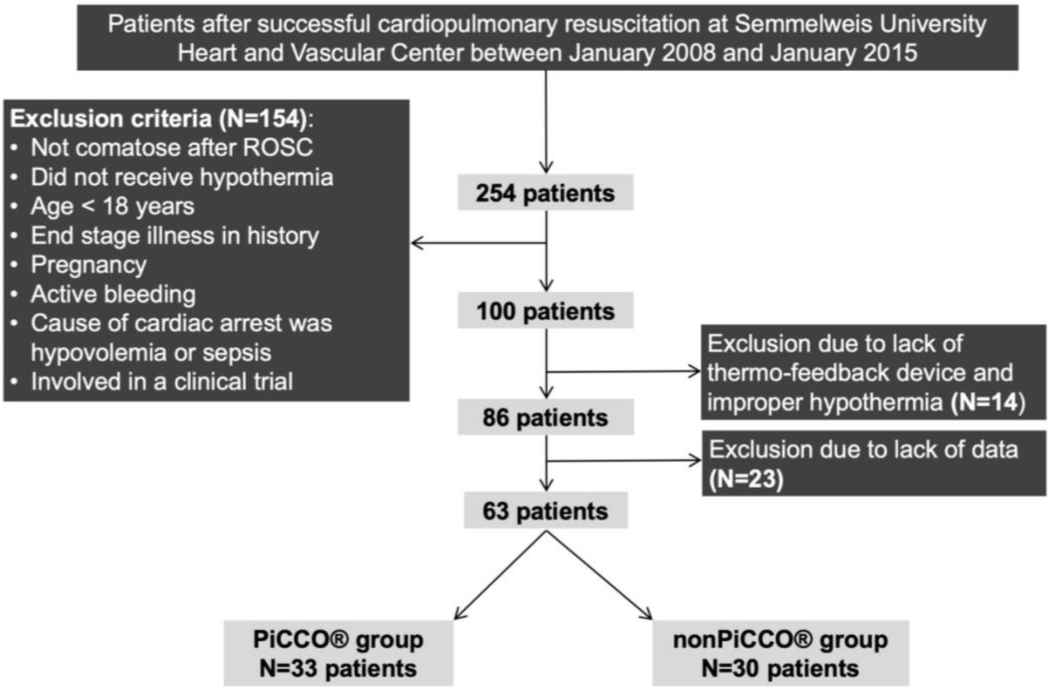


Figure 5. Patient groups of the hemodynamic monitoring assessment study with inclusion and exclusion criteria (184). *254 patients after successful cardiopulmonary resuscitation were screened and 63 were included into the study. N: number of patients; PiCCO®: Pulse index Contour Cardiac Output.*

Post-resuscitation therapy and TTM were initiated as soon as possible after the admission of OHCA-patients and after ROSC of IHCA-patients. All patients received standardized critical care according to our institutional protocol. An acute coronarography was performed in each case, which was followed by percutanous coronary intervention (PCI) and/or intra-aortic balloon pump (IABP) insertion, if indicated. All patients were treated in the ICU at the acute phase of the assessment. We upheld mechanical ventilation until the patients fulfilled extubation criteria.

Oxygen saturation, electrocardiogram, invasive arterial blood pressure, central venous pressure, diuresis, blood gas parameters and serum lactate level were monitored for all patients. An echocardiography was performed after the admission to the ICU to assess the heart function. If it was available, the basic hemodynamic monitoring was augmented with PiCCO® monitor (Pulsion Medical System, Munich, Germany); thermodilution measurements were applied at least every 12 hours during the first 48 hours after the initiation of cooling. We measured the following variables: cardiac index (CI: L/min/m^2), systemic vascular resistance index (SVRI: dyn.sec.cm^{-5}), global end-diastolic volume index (GEDI: mL/m^2), extravascular lung water index (ELWI: mL/kg/m^2) and global ejection fraction (GEF: %). If patients had IABP their device was paused for the time of thermodilution measurement.

Fluid, vasopressor, and inotrope therapy were accomplished by monitoring heart rate, MAP, central venous pressure, diuresis and lactate levels for patients without PiCCO®. We used the goal parameters given by the actual ERC guidelines (188). Dopamine at vasopressor dose or noradrenaline were administered as vasopressors after fluid challenge if MAP was still lower than 65 mmHg or diuresis fell below 1 mL/kg/hour (Figure 6). Fluid challenge was administered even in the case of elevated lactate level referring to low perfusion of the peripheral tissues. Dobutamine was used if positive inotropic agent was required based on the echocardiography at admission. The hemodynamic management was guided by PiCCO® parameters and the principles of therapy decision tree of Pulsion Medical System were applied for PiCCO® patients (189). Figures 7A and 7B show the detailed hemodynamic management of PiCCO® monitored patients.

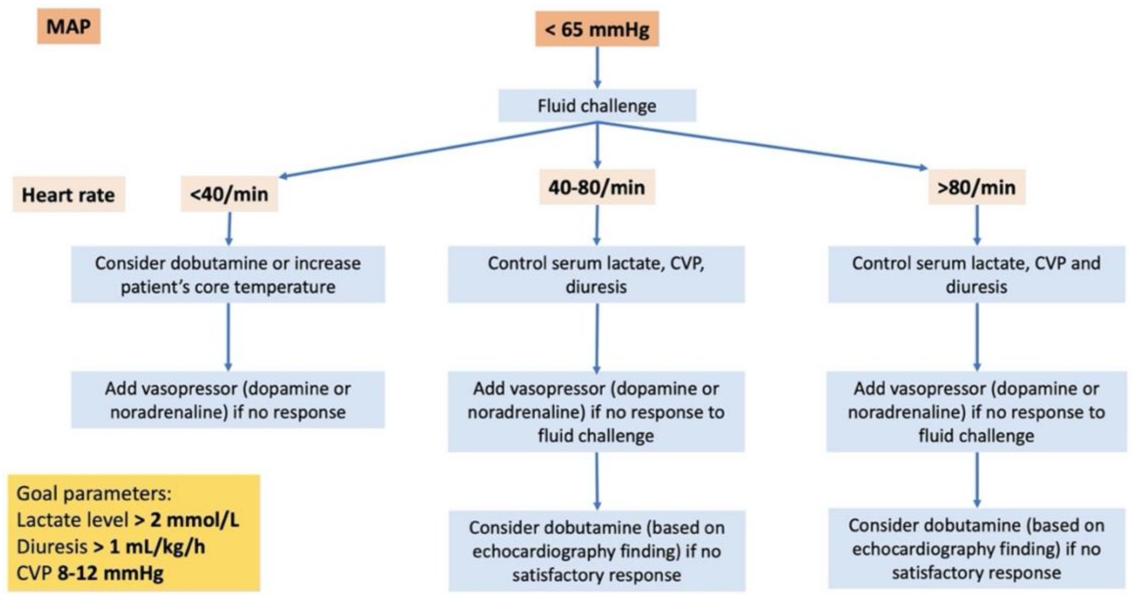


Figure 6. Hemodynamic management of patients in nonPiCCO® group. *CVP: central venous pressure, MAP: mean arterial pressure.*

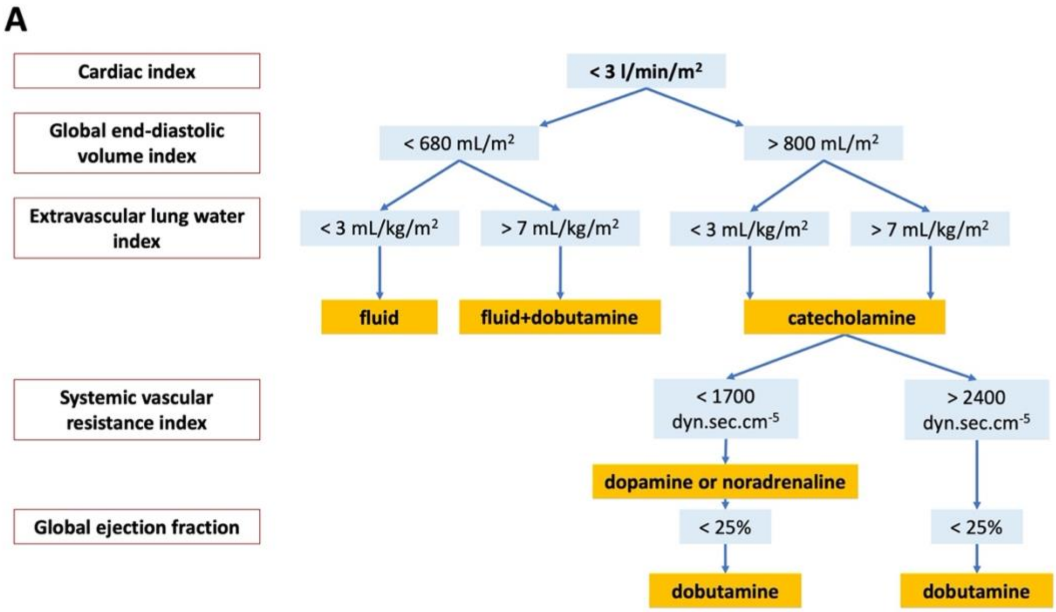


Figure 7A. Hemodynamic management of patients in PiCCO® group in the case of low (<3 L/min/m²) cardiac index (184).

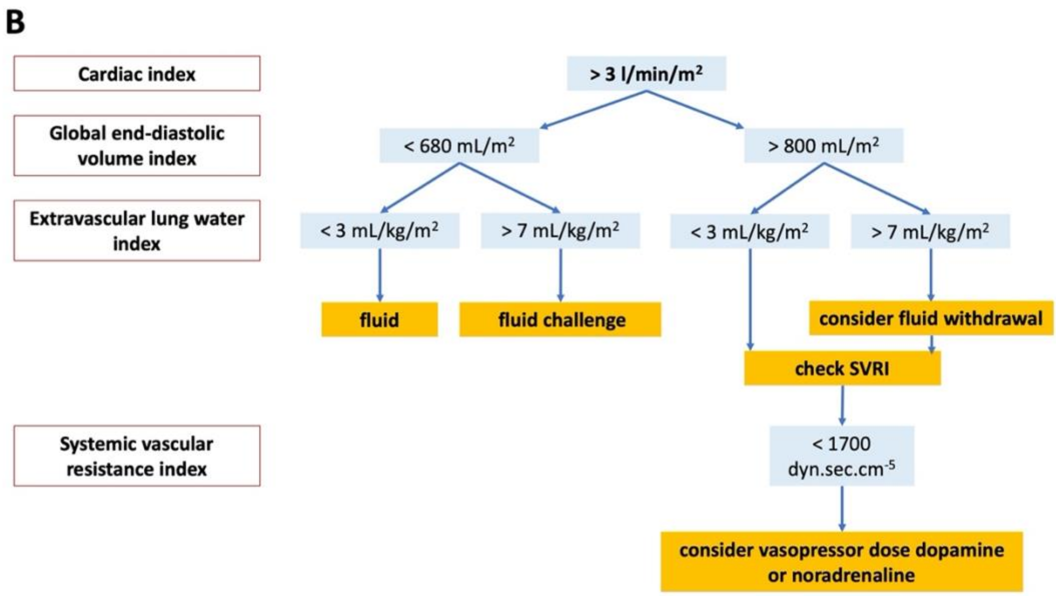


Figure 7B. Hemodynamic management of patients in PiCCO® group in the case of normal or high (>3 L/min/m²) cardiac index (184). *SVRI: systemic vascular resistance index.*

A combination of catecholamines was applied in the case of therapy resistant hemodynamic instability in both groups. As an alternative inotrope levosimendan was administered beside vasopressor treatment based on clinical judgement of the treating physician if long standing critical low cardiac performance was present.

TTM was divided into three phases: induction of cooling, maintenance phase, and rewarming. During the induction of TTM 30 ml/kg crystalloids were given to the patients, and the previously mentioned thermo-feedback device was used. The temperature in maintenance phase was upheld with the same device. After 24 hours of hypothermia, rewarming was achieved by passively trying to keep a 0.25˚C/hour rewarming speed until normothermia was reached. Prevention and control of fever still played an important role in the first 72 hours of the assessment. Patients received a combination of intravenous benzodiazepine and opioid as sedation during hypothermia. Their core temperature was measured with an esophageal thermometer.

Additionally, patient data extracted included the patients' age, gender, previous health conditions affecting cardiovascular system (diabetes, hypertension, stroke, hyperlipidemia, and acute myocardial infarction), circumstances of CPR (time between collapse and ROSC, if the patient was on monitor at the time of collapse, if basic life support was performed, and initial rhythm) and important steps of therapy after ROSC (presence of cardiogenic shock (CS), ST segment elevation and non-ST segment elevation myocardial infarction (STEMI and NSTEMI), frequency of acute PCI, frequency of IABP insertion, ejection fraction after ROSC, and necessity of levosimendan administration after ROSC).

To express the adequacy of PiCCO®-guided therapy, we analyzed patients' changes in temperature during TTM, hemodynamic parameters, and catecholamine dosing.

3.2.3 Outcome

Primary patient outcome was defined as mortality after 30 days. Secondary patient outcome was defined as mortality after one year. All patient follow-up and mortality data were obtained at least up till one year after admission based on the health insurance records of the National Health Insurance Fund of Hungary, which contains accurate and valid information on the vital records of the entire population of Hungary. Patients' death as a hard end point was defined as passivation of the healthcare ID in the national records. Patient outcomes were obtained by means of the patients' unique healthcare ID. Once patient data were matched with the vital records, patient IDs were anonymized for further data management and analysis.

3.2.3 Statistical analysis

First, three sets of bivariate statistical tests were performed: we assessed differences between 1. the PiCCO® and non-PiCCO® groups (yes vs. no), 2. mortality after 30 days (yes vs. no) and 3. mortality after one year (yes vs. no). Mann-Whitney's U tests was used for continuous variables and Chi-square test or (in case of small sample sizes) Fisher's exact test was applied for categorical variables. Additionally, Kaplan-Meyer curves and Log-rank tests for significance were used as longitudinal data to assess differences in mortality between PiCCO® and non-PiCCO® groups and for those variables where mortality was at least marginally significant using the categorical Chi-square analysis. Given the significant or marginally significant differences between the study groups including the patients' severity and other characteristics, it is difficult to assess how the hemodynamic management guided by PiCCO® could affect outcome of the cardiac arrest patients. Therefore, interaction effects were explored (candidate variable vs. PiCCO® use vs. mortality) using the same statistical methods as in the bivariate analysis for those variables that had at least marginal associations with both PiCCO® use and mortality. Additionally, logistic regression analysis was performed using the interaction terms as dummy variables. If there were zero cell sizes, then dummy categories were combined with non-zero cells. In a first set of logistic regression models, all interaction dummy variables were included, and in a second set of models only statistically significant dummies stayed.

Continuous variables are described with median values and their corresponding interquartile range, and categorical data are described as percentages. Not more than 10% of the data were missing; we performed multiple imputation using the k-nearest neighbor algorithm to replace variables with missing values.

The changes of hemodynamic parameters and catecholamine administration during TTM were assessed with Friedman test.

We identified $p<0.05$ for statistical significance and $p<0.2$ and $p\geq0.05$ for marginal significance. Data management and statistical analysis was performed using TIBCO

STATISTICA v13.4 (Tibco Software Inc., Palo Alto, CA), and figures were created using GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA).

3.3 The role of age in post-cardiac arrest therapy in an elderly patient population

3.3.1 Study design of the local investigation

We screened 254 patients who underwent a successful CPR after OHCA or IHCA and were admitted to the intensive care unit of Semmelweis University Heart and Vascular Centre due to a suspected cardiac origin between January 2008 and January 2015. Only comatose patients treated with a thermo-feedback cooling device who were older than 18 years and had no end-stage illness in their medical history, were included into our analysis. Patients, whose suspected cause of cardiac arrest was active bleeding, hypovolemia or sepsis, were excluded from the investigation. Altogether 25 patients were excluded due to insufficient documentation and lack of data. In total, 61 patients were included in our study. Medical charts were reviewed retrospectively to obtain demographic data, previous medical history, circumstances of CPR, management in the first 48 hours after ROSC, hemodynamic parameters (heart rate, MAP, CI, SVRI and serum lactate level) during the different phases of TTM, length of ICU stay, length of mechanical ventilation, CPC and survival. Patients were categorized into three groups based on their age: 1. Younger (Y) group (patients aged 65 years or younger), 2. Older (O) group (patients between 66-75 years), 3. Very Old (VO) group (patients older than 75 years). As the oldest patient was 84 years old, no older age groups were created.

The Semmelweis University Regional and Institutional Committee of Science and Research Ethics approved our study (approval Nr.: 19/2019). No informed consent was acquired according to our national regulations due to the retrospective nature of the study.

3.3.2 Patient management

Standardized post-resuscitation therapy and TTM based on our institutional protocol were initiated as soon as possible after the admission of the patients to the ICU. The goal parameters given by ERC guidelines were utilized to guide our post-resuscitation management (186). Beside the standard monitoring of ICU patients (oxygen saturation, electrocardiogram, invasive arterial blood pressure, diuresis, blood gas and serum lactate level analysis, and echocardiography), an advanced hemodynamic monitoring with PiCCO® (Pulsion Medical System, Feldkirchen, Germany) was applied, if it was available. Measurements with thermodilution were performed every 12 hours during the first 48 hours after the initiation of TTM. An acute coronarography was performed with PCI and/or IABP insertion, if indicated. Catecholamines were applied in mono- or combination therapy to support the cardiovascular system, if clinically indicated. In the case of severe cardiac impairment, levosimendan treatment was initiated.

Patients were cooled to 32-34 °C according to the actual ERC guidelines (186). TTM consisted of three phases: induction, maintenance, and rewarming. Patients received 30 ml/kg crystalloid infusion and Blanketrol III™ (Cincinatti SubZero Products, Cincinatti, USA) thermo-feedback device was used during the induction phase. The target temperature was ensured with the same device during the maintenance phase. After 24 hours, rewarming was performed passively until normothermia was reached. Esophageal temperature probe was used for temperature assessment. Sedation was maintained with intravenous opioids and benzodiazepines, and intravenous muscle relaxant was administered in the case of severe shivering during TTM.

3.3.3 Outcome of the retrospective cohort study

Primary outcomes were 30-day and one-year survival and neurologic outcome. Neurologic outcome was assessed with the CPC categorization (table 2).

Secondary outcomes were hemodynamic changes and catecholamine administration during TTM.

Table 2. Cerebral performance categories (190). *CPC: cerebral performance category.*

CPC scale	Symptoms
CPC 1 Good neurologic performance	conscious, alert, able to work
CPC 2 Moderate cerebral disability	conscious, independent activities of daily life
CPC 3 Severe cerebral disability	conscious, dependent on others for daily life support
CPC 4 Coma or vegetative state	any degree of coma without the presence of brain death
CPC 5 Brain death	apnea, areflexia, silent electroencephalogram

3.3.4 Statistical analysis of the retrospective cohort study

Demographic data (age, gender), circumstances of CPR (location, BLS performed, monitor used at the time of cardiac arrest, initial rhythm), past history (hypertension, hyperlipidemia, myocardial infarction, diabetes, stroke), cause of cardiac arrest (STEMI, NSTEMI, other), therapeutic steps and associated parameters in the first 48 hours after ROSC (acute PCI, levosimendan treatment, ejection fraction at the admission of ICU, IABP insertion, PiCCO® application, catecholamine therapy, serum lactate level, MAP, heart rate, CI and SVRI), as well as length of ICU stay, length of mechanical ventilation, and CPC were compared between the three groups.

Categorical variables were presented as numbers and percentages. Continuous variables were described with median and interquartile range. No more than 5% of values were missing and were replaced with median value. Chi-square test or Fischer's exact test were applied for categorical variables with Bonferroni correction for proportion comparison. Kruskal-Wallis test with Dunn's post hoc analysis was used for continuous variables.

Kaplan-Meier curve and Log-rank test were performed to present and compare 30-day and 1-year survival between the three groups.

Binary logistic regression and receiver operating characteristic (ROC) curve analysis were conducted. CPC, 30-day survival and one-year survival represented the dependent variable and age composed the independent variable. The level of significance was set at $p<0.05$.

Statistical analysis was performed using SPSS v25.0 (SPSS Inc., Chicago, IL). Figures were created using GraphPad Prism version 8.1.1. (GraphPad Software, La Jolla, CA).

3.3.5 Systemic review of the literature

A literature search was conducted through the PubMed/Medline database in December 2019 using the keywords („cardiopulmonary resuscitation" OR „post-resuscitation*" OR „post-cardiac arrest*" OR „therapeutic hypothermia" OR „target temperature management") AND (elderly OR age*). Inclusion criteria were original, full text articles investigating the outcome of old (age>65 years) patients undergoing successful CPR and receiving post-cardiac arrest therapy. Articles older than five years, articles written not in English, case reports, case series, reviews, publications without full text, studies investigating extracorporeal cardiopulmonary resuscitation and papers not elaborating on the aspects of post-cardiac arrest therapy were excluded. Titles and abstracts found during the literature search were screened to select appropriate papers for final evaluation.

4. Results

4.1 Influence of examination timing on skill retention after BLS training

The gender distribution of groups did not differ significantly (p=0.228) (NoExam: 61%, EndExam: 52%, 3mExam: 58% females – data not shown in table or figure). As can be seen in Table 3, the SRA two months after the training in the NoExam, two months after the training and the exam in the EndExam, and two months after the exam in the 3mExam group showed significantly different scores across the groups regarding shouting for help, testing vital signs, position of hands, rate of chest compression, consistency of chest compression, 30:2 ratio, duty cycle, and total score. There was no significant difference in examining consciousness, calling for ALS team, and depth of chest compression.

Table 3. A comparison of BLS step mean scores and total score by group using Kruskal-Wallis test (183). *Scoring based on 0=incorrect and 1=correct. The total score is a sum of the individual BLS scores. ALS: advanced life support, BLS: basic life support, n: number of students, p: level of significance, SD: standard deviation. Significant p-values (p<0.05) are indicated in italic.*

	NoExam n=179	**EndExam** n=165	**3mExam** n=120	
BLS step	Mean score±SD			p
Shouting for help	0.5±0.5	0.5±0.5	0.8±0.4	*<0.001*
Examining consciousness	0.9±0.2	0.9±0.3	1.0±0.2	0.143
Testing vital signs	0.6±0.5	0.5±0.5	1.0±0.0	*<0.001*
Call for ALS team	0.9±0.2	1.0±0.1	1.0±0.1	0.063
Position of hands	0.6±0.5	0.5±0.5	0.9±0.4	*<0.001*
Depth of chest compression	0.7±0.4	0.8±0.4	0.8±0.4	0.812
Rate of chest compression	0.7±0.4	0.6±0.5	0.8±0.4	*<0.001*
Consistency of chest compression	0.8±0.4	0.7±0.5	1.0±0.2	*<0.001*
30:2 ratio	0.9±0.2	0.9±0.3	1.0±0.1	*0.046*
Duty cycle	0.8±0.4	0.9±0.3	1.0±0.2	*<0.001*
Total score (0-10)	7.6±1.6	7.3±1.8	9.1±0.8	*<0.001*

Furthermore, as can be seen in Figure 8 showing the post-hoc differences across groups, students in the 3mExam group performed significantly better than students in either the NoExam or the EndExam groups in shouting for help, testing vital signs, positioning of hands, and consistency of chest compression. In addition, the 3mExam group had a significantly better performance in rate of chest compression compared to the EndExam group (which had significantly lower scores for this step than the NoExam group), as well as in keeping the 30:2 ratio. Duty cycle was retained significantly better in the 3mExam group compared to the NoExam group. The NoExam group had a higher mean score in rate and consistency of chest compressions than the EndExam group, however the EndExam group's skill retention was significantly better in duty cycle compared to the NoExam group. Overall, the NoExam and the EndExam groups showed similar scores in skill retention.

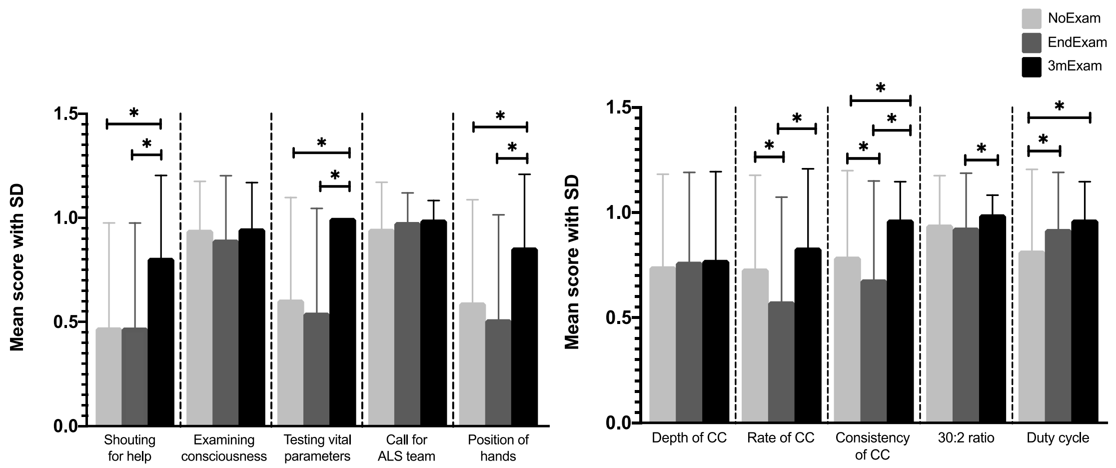


Figure 8. A comparison of BLS step mean scores by group using Kruskal-Wallis test and post-hoc analysis (183). *Students in 3mExam group showed the best skill retention during the final evaluation. NoExam and EndExam groups' performance was similar, except rate and consistency of chest compression, and duty cycle. Scoring based on 0=incorrect and 1=correct. Significant differences (p<0.05) and the results of post-hoc analysis are marked with asterix. ALS: advanced life support, CC: chest compression, SD: standard deviation.*

The mean total score of students was significantly higher in the 3mExam group compared to both the NoExam and the EndExam groups, and there was no difference in the total score of the latter two groups (Figure 9). Moreover, the 3mExam group had less variability in total scores (and many of the sub-scores) than the other two groups, and the minimum total score for the 3mExam group was only 1 point lower than the average of the other two groups.

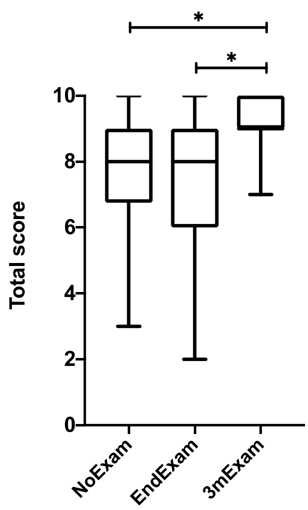


Figure 9. A comparison of total scores by group using Kruskal-Wallis test and post-hoc analysis (183). *3mExam group's total score was significantly higher than the total score reached by NoExam or EndExam groups. The total score is a sum of the individual BLS scores. Significant differences (p<0.05) and the results of post-hoc analysis are marked with asterix. Box-and-whisker plot: the box extends from the 25 to 75 percentile and interprets the mean value, while the whiskers show minimum and maximum values.*

4.2 Hemodynamic management during post-cardiac arrest therapy and TTM

4.2.1 Characterisctics of patients, PiCCO® use, 30-day and 1-year mortality

Patient characteristics are shown in Table 4. Altogether, 52% of the patients received PiCCO®, 38% died after 30 days, and 57% died after one year.

Table 4. Patient characteristics of the study investigating the effectiveness of PiCCO® monitor (184). *AMI: acute myocardial infarction, BLS: basic life support, CPR: cardiopulmonary resuscitation, EF: ejection fraction, IABP: intra-aortic balloon pump, IHCA: in-hospital cardiac arrest, IQR: interquartile range, MI: myocardial infarction, n: number of patients, Misc: miscellaneous, NSTEMI: non-ST–elevation myocardial infarction, PCI: percutaneous coronary intervention, PEA: pulseless electrical activity, ROSC: return of spontaneous circulation, STEMI: ST-elevation myocardial infarction, VF: ventricular fibrillation, VT: ventricular tachycardia.*

	Total n (%) or Median (IQR)
Total	63 (100%)
Age	64 (56, 69)
Gender (female in %)	19 (30%)
IHCA	11 (17 %)
Prior history:	
Hypertension	45 (71%)
Diabetes	18 (29%)
Hyperlipidemia	30 (48%)
AMI	15 (24%)
Stroke	6 (10%)
Circumstances of CPR:	
Patient on monitor when collapsed	9 (14%)
BLS performed by bystanders	49 (78%)
Time to ROSC (minutes)	20 (15, 30)
Initial rhythm:	
VF	42 (67%)
VT	2 (3%)
PEA	10 (16%)
Asystole	9 (14%)
Cause of cardiac arrest	
STEMI	38 (60%)
NSTEMI	8 (13%)
Misc	17 (27%)
Cardiac condition after ROSC	
Cardiogenic shock (clinical signs)	14 (22%)
EF after ROSC (%)	36 (29, 48)
Therapy after ROSC:	
Catecholamine therapy	39 (62%)
Acute PCI	51 (81%)
Levosimendan	7 (11%)
IABP use	16 (25%)
Time to reach target temperature (hours)	3,8 (2.0, 5.1)
PiCCO™ application rate	33 (52%)
Died at 30 days	24 (38%)
Died at 1 year	36 (57%)

Patients with PiCCO® application were significantly more likely to die after 30 days, and marginally more likely to die after one year than non-PiCCO® patients (Figure 10).

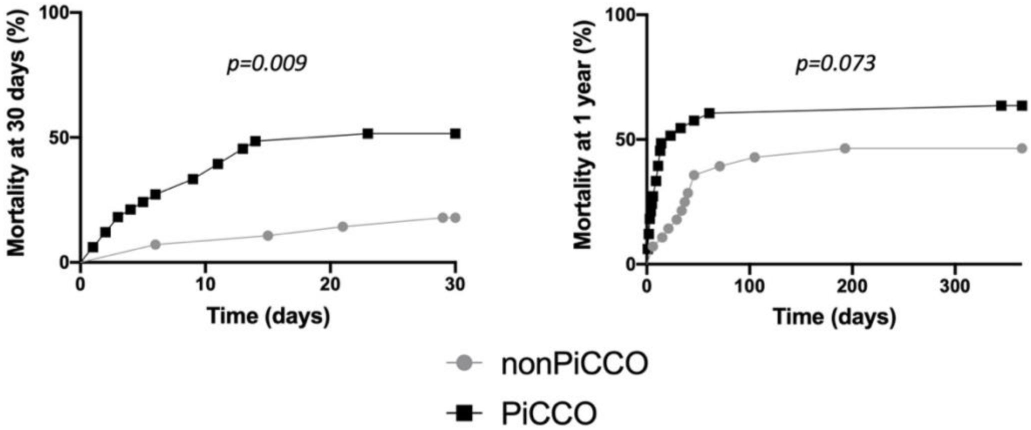


Figure 10. Cumulative incidence of 30-day and one-year mortality by PiCCO® status (184). *Kaplan-Meyer curves and Log-rank tests were performed. p: level of significance; PiCCO: Pulse index Contour Cardiac Output. Significant p-values (p<0.05) or marginally significant p-values (p<0.2) are indicated in italic.*

As Figure 11 shows, at least marginal difference for both PiCCO® application and either 30-day or one-year mortality was found among patients with hyperlipidemia; prior history of stroke; STEMI as a cause of cardiac arrest; PCI, CS, IABP, and catecholamine treatment after ROSC.

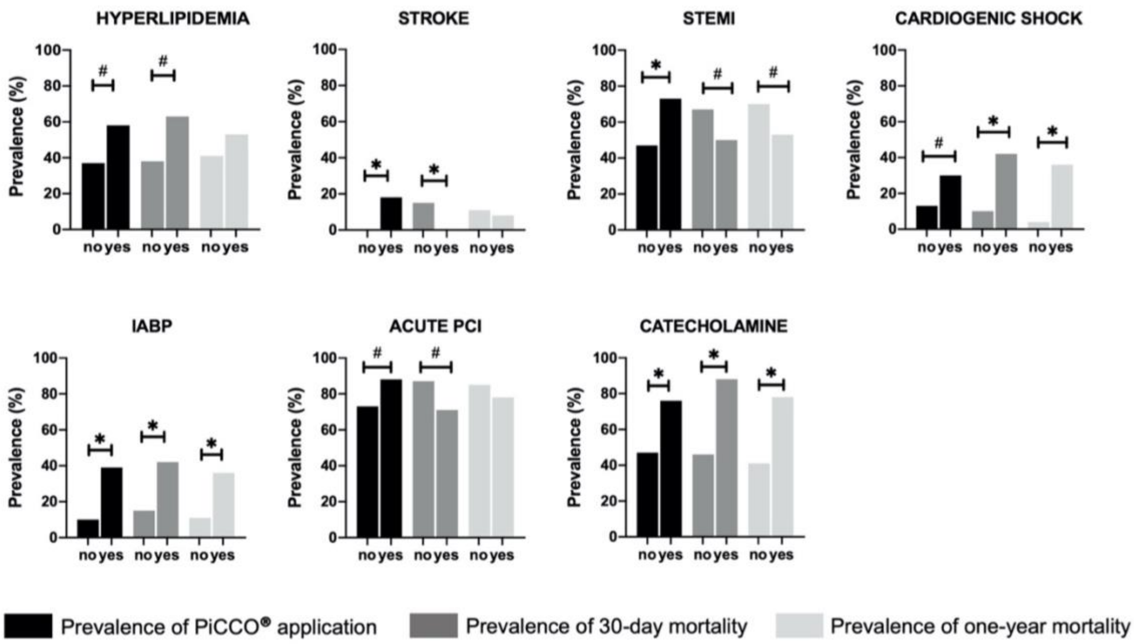


Figure 11. Comparison of PiCCO® use, 30-day mortality, and one-year mortality by patient condition characteristics in the study investigating the effect of PiCCO® monitoring (184). *Chi-square test was performed. ∗: p<0.05; #: p<0.2; PiCCO: Pulse index Contour Cardiac Output, IABP: intra-aortic balloon pump, PCI: percutaneous coronary intervention, STEMI: ST-elevation myocardial infarction.*

4.2.2. Interaction effects between 30-day mortality, PiCCO® use and patient characteristics

Figure 12 visualizes the multivariate interaction effects between 30-day mortality, PiCCO® use, and patient characteristics, statistically controlled for the effects of the subgroups. Accordingly, patients with either PiCCO® or hyperlipidemia were marginally and patients with both PiCCO® and hyperlipidemia were significantly more likely to die at day 30 than patients with neither PiCCO® nor hyperlipidemia. Moreover, patients with PiCCO® but no STEMI were significantly more likely to die than patients with no PiCCO® or patients with both PiCCO® and STEMI. Additionally, patients with cardiogenic shock regardless of PiCCO® were significantly much more likely and patients with PiCCO® but not cardiogenic shock were significantly more likely to die than patients with neither cardiogenic shock nor PiCCO®. Furthermore, patients with PiCCO® but no IABP were marginally and patients with IABP regardless of PiCCO®

were significantly more likely to die than patients with neither IABP nor PiCCO®. In addition, patients receiving catecholamine treatment after ROSC but no PiCCO® were marginally more likely and patients with both catecholamine and PiCCO® were significantly more likely to die than patients with no catecholamine. Moreover, patients with no stroke but with PiCCO® application were significantly more likely to die than patients with neither stroke nor PiCCO® or patients with both stroke and PiCCO®. Furthermore, lower mortality was seen in patients with PCI but without PiCCO® compared to patients without PCI regardless of PiCCO® or patients with both PCI and PiCCO®.

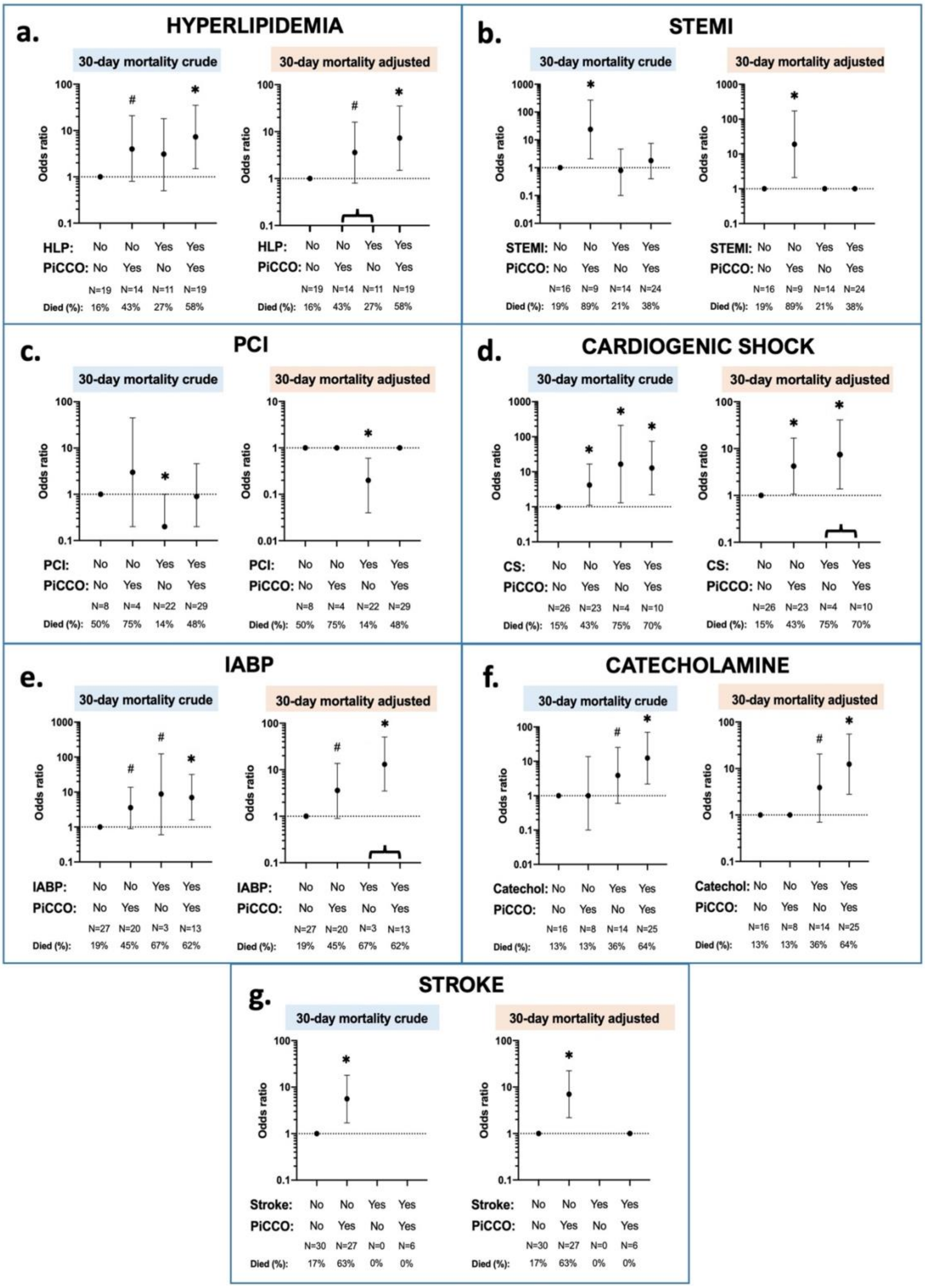


Figure 12. Interaction effects between PiCCO®-application, 30-day mortality and patient condition characteristics (184). *Crude and adjusted logistic regressions were performed. In the crude models, all the interaction term dummy variables were*

included as separate variables. In the adjusted models, non-significant dummies were combined. ∗: p<0.05; #: p<0.2; catechol: catecholamine, CS: cardiogenic shock, HLP: hyperlipidemia, IABP: intra-aortic balloon pump, N: number of patients, PCI: percutaneous coronary intervention, PiCCO: Pulse index Contour Cardiac Output, STEMI: ST-elevation myocardial infarction.

4.2.3. Interaction effects between one-year mortality, PiCCO® use and patient characteristics

Multivariate interaction effects between one-year mortality, PiCCO® use and patient characteristics, statistically controlled for the effects of the subgroups, are shown in Figure 13. Patients with PiCCO® but no STEMI were marginally more likely to die than patients without PiCCO® regardless of STEMI or patients with both PiCCO® and STEMI. Additionally, patients receiving catecholamines after ROSC regardless of PiCCO® were significantly more likely to die than patients who did not receive catecholamine treatment. Moreover, patients with PiCCO® application but without stroke in past history were marginally more likely to die than patients with both stroke and PiCCO® or patients with neither stroke nor PiCCO®. Additionally, although no interaction was found for CS, PiCCO® and one-year mortality, neither for IABP, PiCCO® and one-year mortality, CS and IABP were independent predictors of mortality. Finally, once controlled for subgroups, the interactions between hyperlipidemia, PiCCO® and one-year mortality, as well as between PCI, PiCCO® and one-year mortality were no longer statistically significant.

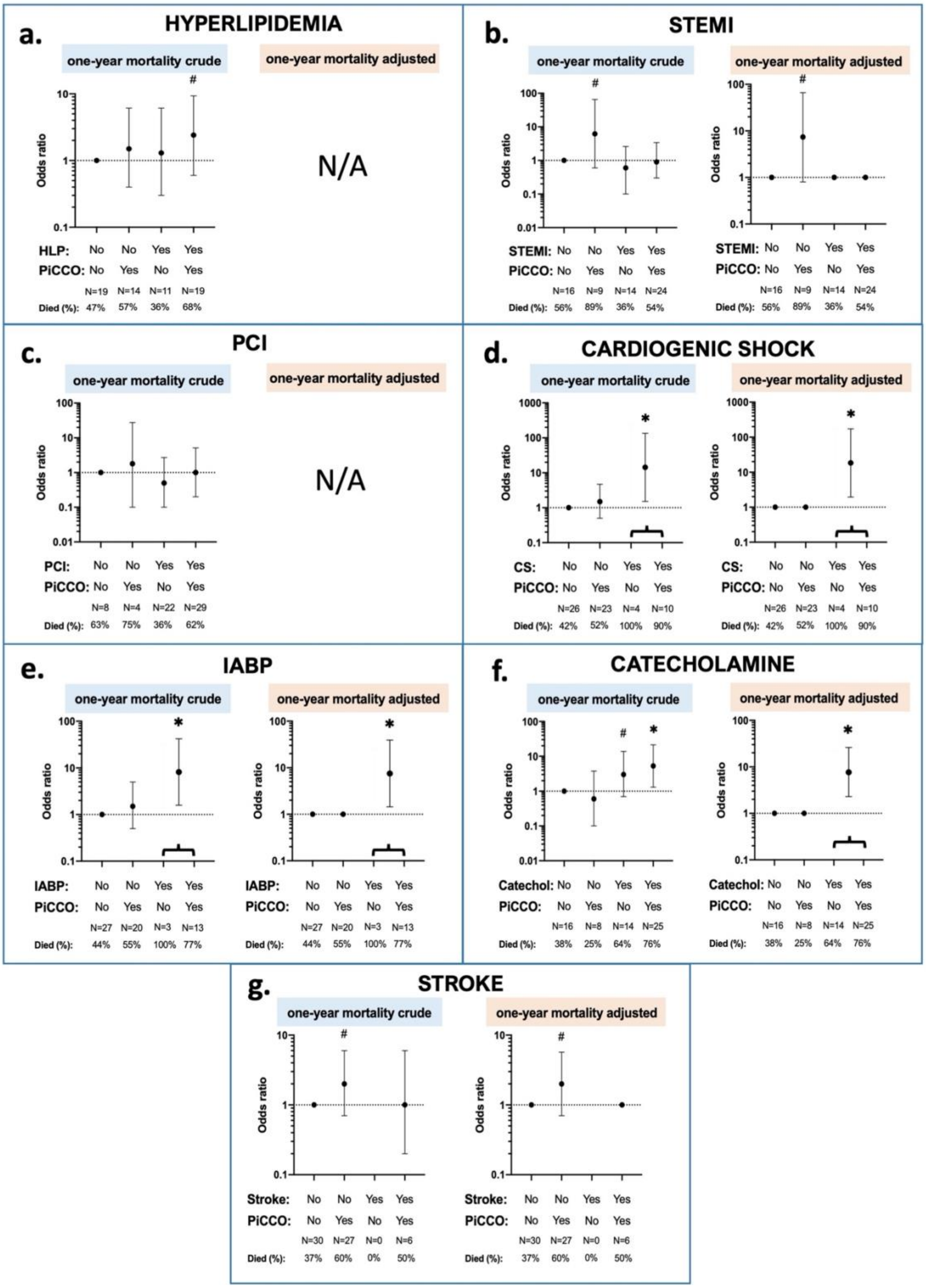


Figure 13. Interaction effects between PiCCO®-application, one-year mortality, and patient condition characteristics (184). *Crude and adjusted logistic regressions were performed. In the crude models, all the interaction term dummy variables were*

included as separate variables. In the adjusted models, non-significant dummies were combined. ∗: p<0.05; #: p<0.2; catechol: catecholamine, CS: cardiogenic shock, HLP: hyperlipidemia, IABP: intra-aortic balloon pump, N: number of patients, PCI: percutaneous coronary intervention, PiCCO: Pulse index Contour Cardiac Output, STEMI: ST-elevation myocardial infarction.

4.2.4. Hemodynamic changes during TTM and adequacy of PiCCO®-guided hemodynamic management

Temperature changes during TTM can be seen in Figure 14.

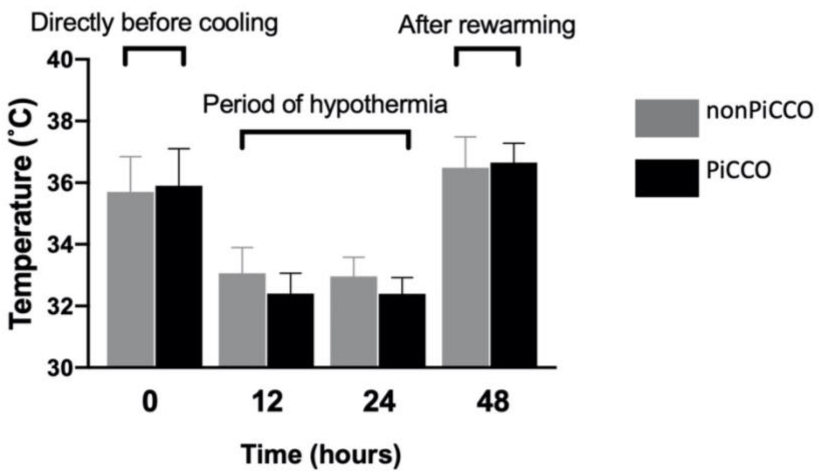


Figure 14. Changes of temperature during target temperature management (TTM) in the study investigating the effect of PiCCO® monitor (184). *PiCCO® and nonPiCCO® groups are compared. 0: initiation of TTM; 12 and 24: TTM (32-34 ºC); 48: measurement after rewarming. Values are presented as median with interquartile range.*

Heart rate decreased significantly during hypothermia compared to normothermic phases of TTM in both groups without any significant difference between the groups (Figure 15). In contrast, MAP showed only marginally different changes during TTM (Figure 15).

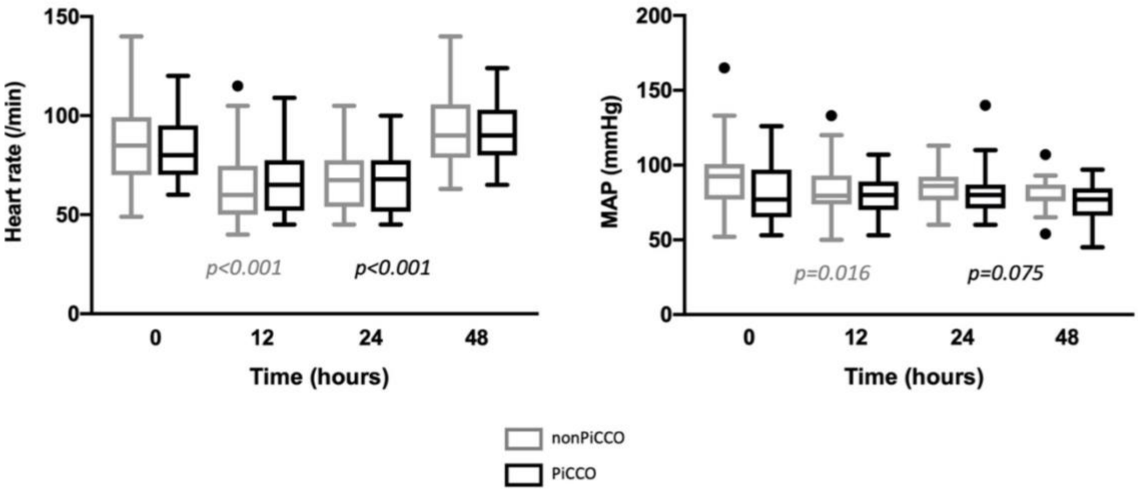


Figure 15. Changes of heart rate and mean arterial pressure (MAP) during target temperature management (TTM) in PiCCO® and nonPiCCO® groups (184). *0: initiation of TTM; 12 and 24: TTM (32-34 ºC); 48: measurement after rewarming. P values show the results of Friedman-test analyzing the changes of heart rate and MAP during TTM within nonPiCCO® and PiCCO® groups (grey color refers to nonPiCCO® and black color refers to PiCCO® group, respectively). Significant p-values (p<0.05) or marginally significant p-values (p<0.2) are indicated in italic. Heart rate decreased during low temperature in both groups, however, MAP remained constant. Mann-Whitney test was performed to compare PiCCO® and nonPiCCO® groups. Box-Whisker plot: Values are presented as Box-Whisker plot by Tukey method.*

Figure 16 shows the results of PiCCO® measurements during the different phases of TTM and after rewarming. Our findings suggest that CI, SVRI, GEF and ELWI are significantly influenced by lower temperature. The adequacy of hemodynamic management can be seen in Figure 17, which shows catecholamine dosage during TTM in both groups. The administration of catecholamines follows the changes of MAP in the nonPiCCO® group, and the parameter changes measured by PiCCO® in the PiCCO® group. In addition, the PiCCO® group required a higher dose of noradrenaline after rewarming than nonPiCCO® group.

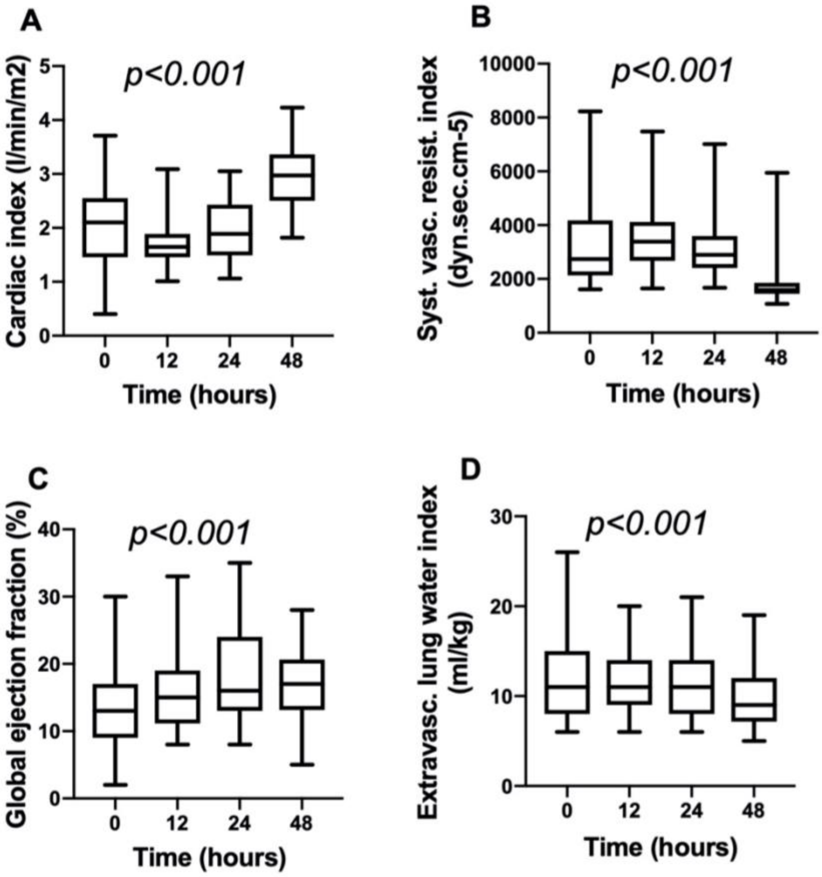


Figure 16. Changes of cardiac index, systemic vascular resistance index, global ejection fraction and extravascular lung water index during target temperature management (TTM) in PiCCO® group (184). *0: initiation of TTM; 12 and 24: TTM (32-34 ºC); 48: measurement after rewarming. P values show the results of Friedman-test analyzing the changes of hemodynamic parameters during the different phases of TTM. Significant p-values ($p<0.05$) or marginally significant p-values ($p<0.2$) are indicated in italic. Box-Whisker plot: the box extends from the 25 to 75 percentile and interprets median, while the whiskers show minimum and maximum values.*

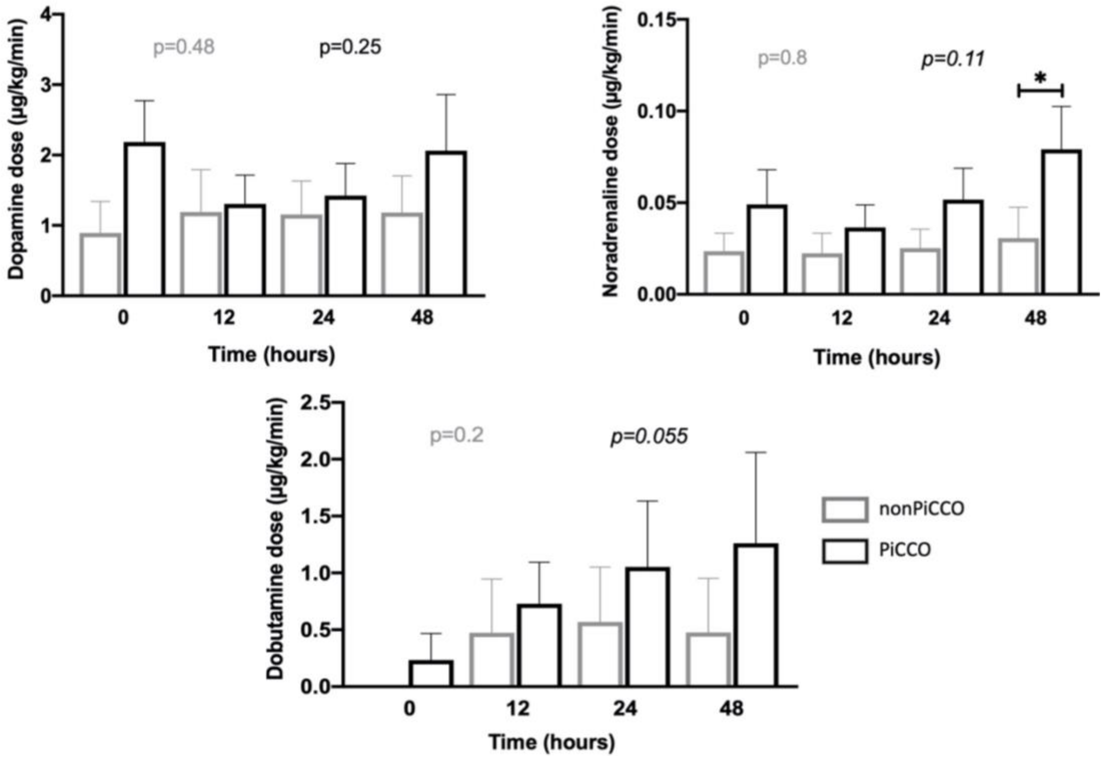


Figure 17. Changes of dopamine, noradrenaline and dobutamine dosage during target temperature management (TTM) in PiCCO® and nonPiCCO® groups (184). *0: initiation of TTM; 12 and 24: TTM (32-34 ºC); 48: measurement after rewarming. P values show the results of Friedman-test analyzing the changes of catecholamine dosage during TTM within nonPiCCO® and PiCCO® group (grey color refers to nonPiCCO® and black color refers to PiCCO® group, respectively). Significant p-values (p<0.05) or marginally significant p-values (p<0.2) are indicated in italic. Values are presented as mean and standard error of mean. Noradrenaline and dobutamine dosage showed marginally significant changes in PiCCO® group during TTM. Mann-Whitney test was performed to compare PiCCO® and nonPiCCO® groups. Significant differences (p<0.05) are marked with asterix. Significantly more noradrenaline was administered in PiCCO® group after rewarming compared to nonPiCCO® group.*

4.3 The role of patient's age in post-cardiac arrest therapy in an elderly patient population

4.3.1 Patient characteristics

Table 5 and 6 show basic characteristics of patients, circumstances of CPR, main steps in the first 48 hours of post-resuscitation therapy and neurologic outcome. Age was significantly associated with having a monitored cardiac arrest and a history of hypertension: with younger patients having significantly lower probability of these conditions than older or very old patients. Older and very old patients had a tendency of longer ICU stay, but this difference was not significant. The length of mechanical ventilation was similar in all age groups.

No other differences were found between the age groups in the other assessed variables, including PiCCO® administration.

Table 5. Basic characteristics and circumstances of CPR among patients included in the study investigating the influence of age on post-cardiac arrest therapy outcome (185). *Kruskal-Wallis and Chi-square tests were applied, p<0.05 is in italic. Age≤65y: Y group; age 66-75y: O group; age>75y: VO group. BLS: basic life support; CPR: cardiopulmonary resuscitation; N/n: number of patients; NSTEMI: non-ST segment elevation myocardial infarction; OHCA: out-of-hospital cardiac arrest; STEMI: ST segment elevation myocardial infarction.*

	Total N (%) or Median (25%,75%)	**age <65 y** n (%) or Median (25%,75%)	**age 65-75 y** n (%) or Median (25%,75%)	**age >75 y** n (%) or Median (25%,75%)	**p**
Total	61 (100%)	31 (100%)	23 (100%)	7 (100%)	
Age (years)	64 (56,69)	56 (48,62)	69 (67,71)	79 (78,81)	*<0.001*
Gender (male)	42 (69%)	22 (71%)	16 (70%)	4 (57%)	0.772
Circumstances of CPR					
OHCA	50 (82%)	27 (87%)	19 (83%)	4 (57%)	0.176
BLS performed	49 (80%)	23 (74%)	20 (83%)	7 (100%)	0.282
Patient on monitor	8 (13%)	0 (0%)	5 (22%)	3 (43%)	*0.003*
Shockable rhythm	42 (69%)	23 (74%)	13 (57%)	6 (86%)	0.226
Past history					
Hypertension	43 (70%)	17 (55%)	19 (83%)	7 (100%)	*0.017*
Hyperlipidemia	29 (48%)	11 (35%)	13 (57%)	5 (71%)	0.125
Diabetes	17 (28%)	6 (19%)	7 (30%)	4 (57%)	0.124
Myocardial infarction	15 (25%)	4 (13%)	8 (35%)	3 (43%)	0.089
Stroke	6 (10%)	2 (6%)	3 (13%)	1 (14%)	0.663
Origin of cardiac arrest					
STEMI	37 (61%)	19 (61%)	16 (70%)	2 (29%)	0.150
NSTEMI	8 (13%)	3 (10%)	3 (13%)	2 (29%)	0.409
Other	16 (26%)	9 (29%)	4 (17%)	3 (42%)	0.358

Table 6. Aspects of post-cardiac arrest therapy in the first 48 hours after ROSC among patients included in the study investigating the influence of age on post-cardiac arrest therapy outcome (185). *Kruskal-Wallis and Chi-square tests were applied. Age≤65y: Y group; age 66-75y: O group; age>75y: VO group. CPC: cerebral performance category; EF: ejection fraction at admission to the ICU; h: hours; IABP: intra-aortic balloon pump; ICU: intensive care unit; MV: mechanical ventilation; N/n: number of patients; PCI: percutaneous coronary intervention; PiCCO: Pulse index Contour Cardiac Output; T0: temperature at admission; T12: temperature 12 hours after admission; T24: temperature 24 hours after admission; T48: temperature 48 hours after admission; TT: target temperature. Serum lactate levels after 0, 12, 24 and 48 hours after admission are given in mmol/l. Length of IABP use, ICU stay and MV are given in days and time to reach TT is given in hours.*

	Total N (%) or Median (25%,75%)	**age <65 y** n (%) or Median (25%,75%)	**age 65-75 y** n (%) or Median (25%,75%)	**age >75 y** n (%) or Median (25%,75%)	**p**
Total	61 (100%)	31 (100%)	23 (100%)	7 (100%)	
Therapy in the first 48 hours after ROSC					
Acute PCI	49 (80%)	25 (81%)	19 (83%)	5 (71%)	0.807
Levosimendan	6 (10%)	1 (3%)	3 (13%)	2 (29%)	0.102
EF (%)	37.0 (29.0,48.0)	40.0 (30.0,50.0)	36.0 (25.0,44.0)	31.0 (23.0,37.0)	0.204
IABP	15 (25%)	4 (13%)	9 (39%)	2 (29%)	0.084
Length of IABP use	0 (0,0)	0 (0,0)	0 (0,2.5)	0 (0,2)	0.089
PiCCO®	31 (51%)	15 (48%)	12 (52%)	4 (57%)	0.904
Serum lactate 0 h	4.4 (3.0,6.1)	4.4 (3.2,5.7)	4.0 (2.2,7.5)	5.0 (3.1,7.8)	0.531
Serum lactate 12 h	2.1 (1.4,3.2)	2.6 (1.4,3.2)	2.1 (1.4,4.5)	2.0 (1.4,2.7)	0.925
Serum lactate 24 h	1.8 (1.2,3.2)	1.8 (1.2,3.2)	1.7 (1.2,3.2)	2.6 (1.7,3.3)	0.527
Serum lactate 48 h	1.7 (1.3,2.5)	1.6 (1.2,2.2)	2.0 (1.3,2.5)	3.1 (1.0,6.2)	0.326
Length of ICU stay	7 (4.0,8.0)	5.0 (3.3,7.0)	7.0 (4.0,10.0)	10 (5.0,11.0)	0.081
Length of MV	5.0 (3.5,7.0)	5.0 (3.0,7.0)	6.0 (4.0,7.0)	5.0 (5.0,8.0)	0.220
Temperature changes in the first 48 hours after ROSC					
T0 (°C)	36.0 (35.3,36.4)	35.7 (35.3,36.5)	36.1 (35.2,36.3)	36.2 (34.4,36.4)	0.833
T12 (°C)	32.7 (32.2,33.1)	32.7 (32.0,33.0)	32.6 (32.1,33.1)	33.0 (32.3,33.5)	0.570
T24 (°C)	32.7 (32.1,33.0)	32.7 (32.1,33.1)	32.4 (32.1,33.0)	32.9 (32.3,33.0)	0.778
T48 (°C)	36.6 (36.2,37.0)	36.6 (36.1,37.0)	36.6 (36.2,36.8)	36.7 (36.0,37.0)	0.775
Time to reach TT	3.8 (2.0,5.1)	3.0 (2.0,5.0)	4.0 (2.0,6.0)	3.8 (2.5,6.0)	0.676
Outcome					
CPC 1,2 at ICU discharge	18 (30%)	8 (26%)	7 (30%)	3 (43%)	0.666

4.3.2 Survival and neurological outcome

30-day and one-year survival (Figure 18), as well as neurological outcome (Table 6) did not differ across the age groups. Age was useless as a predictor of 30-day survival, one-year survival and neurological outcome after successful CPR in our study population (Figures 19-21).

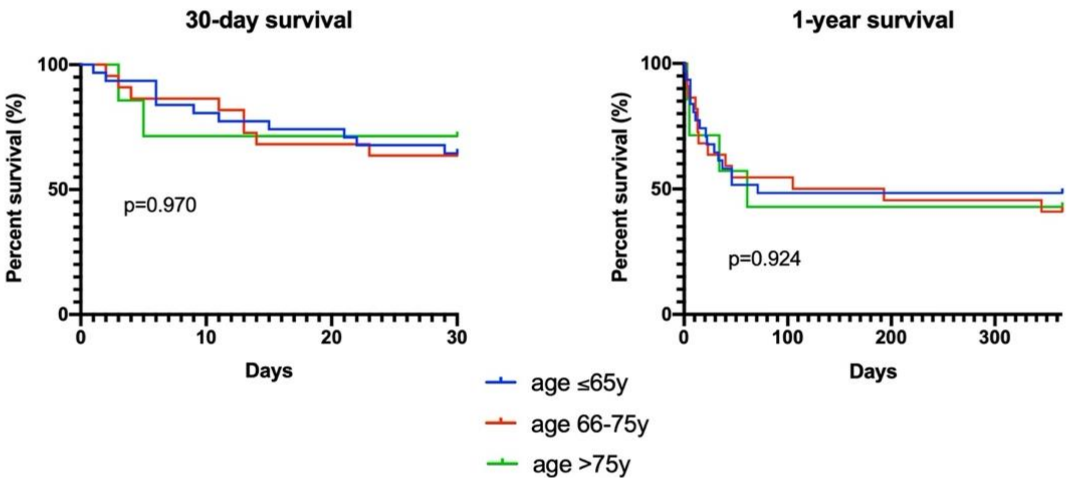
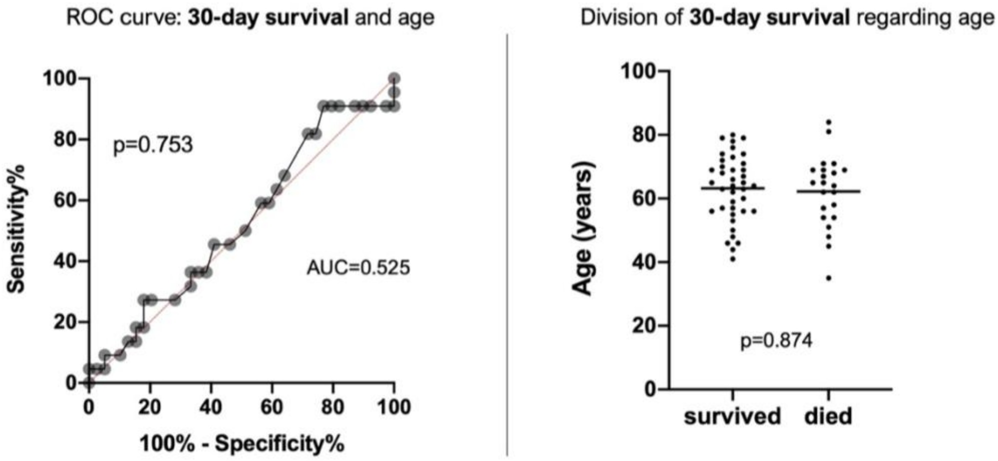
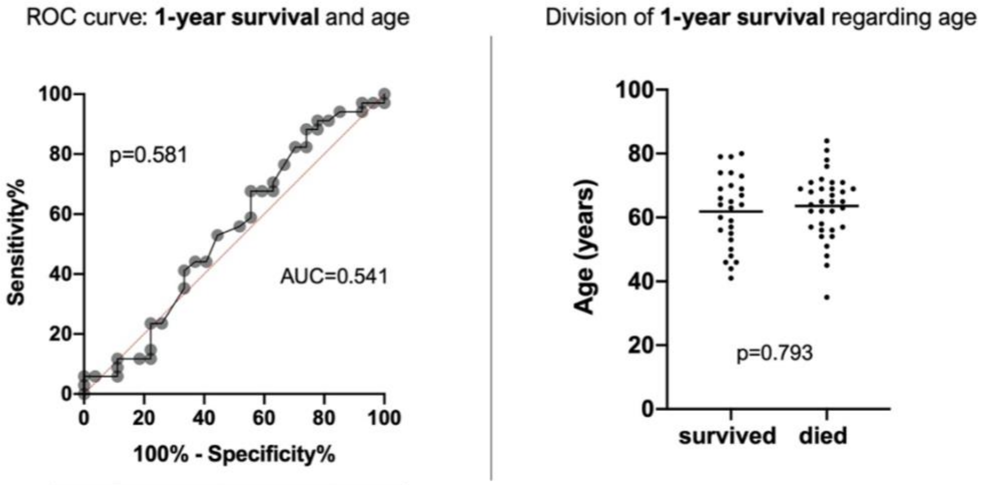


Figure 18. Comparison of 30-day and one-year survival between age groups in the study investigating the influence of age on post-cardiac arrest therapy outcome (185). *Kaplan-Meier curves and Log-rank test were performed; Age≤65y: Y group; age 66-75y: O group; age>75y: VO group.*



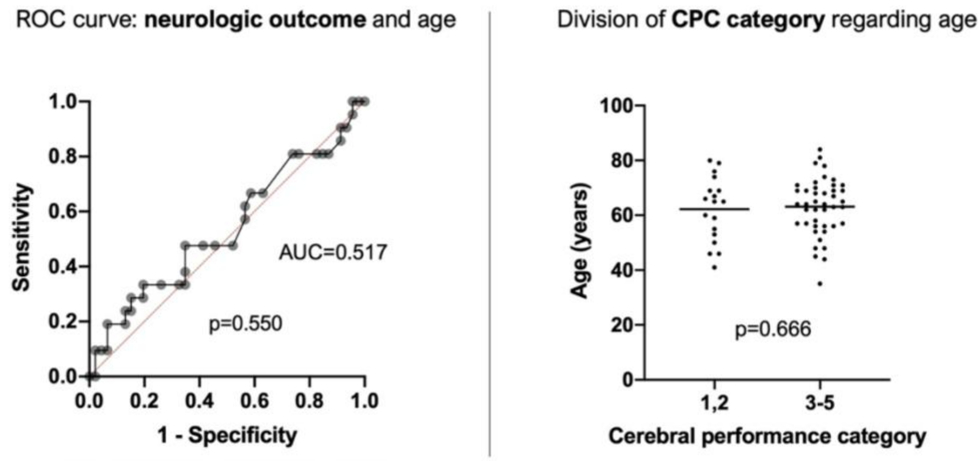
	Odds ratio	CI 95%	p
BLR	0.99	0.94-1.04	0.737

Figure 19. ROC (receiver operating characteristic) curve describing the relationship between age and 30-day survival in the study investigating the influence of age on post-cardiac arrest therapy outcome (185). *AUC: area under curve. Binary logistic regression was (BLR) performed. Scatter plot with median is shown on the right with the results of Chi-square test.*



	Odds ratio	CI 95%	p
BLR	1.02	0.97-1.06	0.535

Figure 20. ROC (receiver operating characteristic) curve describing the relationship between age and one-year survival in the study investigating the influence of age on post-cardiac arrest therapy outcome (185). *AUC: area under curve. Binary logistic regression was (BLR) performed. Scatter plot with median is shown on the right with the results of Chi-square test.*



	Odds ratio	CI 95%	p
BLR	0.99	0.94-1.04	0.771

Figure 21. ROC (receiver operating characteristic) curve describing the relationship between age and neurologic outcome in the study investigating the influence of age on post-cardiac arrest therapy outcome (185). *AUC: area under curve. CPC: cerebral performance category. Binary logistic regression was performed (BLR). Scatter plot with median is shown on the right with the results of Chi-square test.*

4.3.3 Hemodynamic management

Figure 22 shows heart rate, MAP and the rate of catecholamine administration during the different phases of TTM in the groups. Very old patients had significantly lower MAP during low temperature and after rewarming than younger patients (MAP 12 hours after initiation of TTM*: p=0.019*; MAP 24 hours after initiation of TTM*: p=0.003*; MAP after rewarming: *p=0.032*). Additionally, older patients had a lower MAP 24 hours after the initiation of TTM than younger patients (*p=0.020*). Furthermore, older and very old patients were more likely to receive catecholamines at initiation of TTM (*p<0.001*) and during low temperature (12 hours after initiation of TTM: *p=0.002*; 24 hours after initiation of TTM: *p=0.004*) than younger patients.

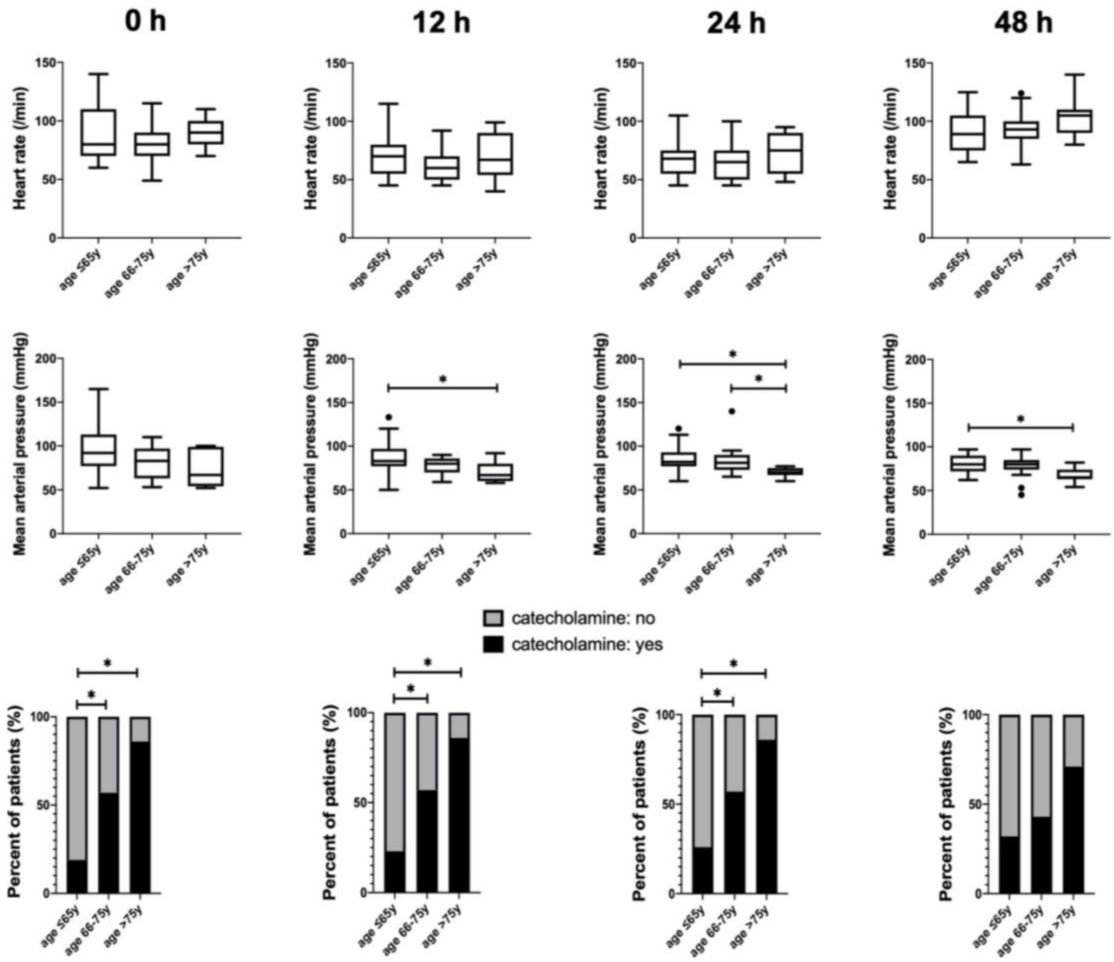


Figure 22. Comparison of heart rate, MAP and catecholamine requirement during the first 48 hours after ROSC between the groups in the study investigating the influence of age on post-cardiac arrest therapy outcome (185). *0h: initiation of TTM; 12h and 24h: TTM (32-34 ºC); 48h: measurement after rewarming. Age≤65y: Y group; age 66-75y: O group; age>75y: VO group. Kruskal-Wallis and Dunn's post hoc test were performed for continuous, and Chi-square test with Bonferroni correction for categorical variables. Star: p<0.05. Box-and-whiskers plot are interpreted with Tukey method.*

Of those 31 patients who received PiCCO®, CI and SVRI measured during the different phases of cooling were similar in all age categories (Figure 21).

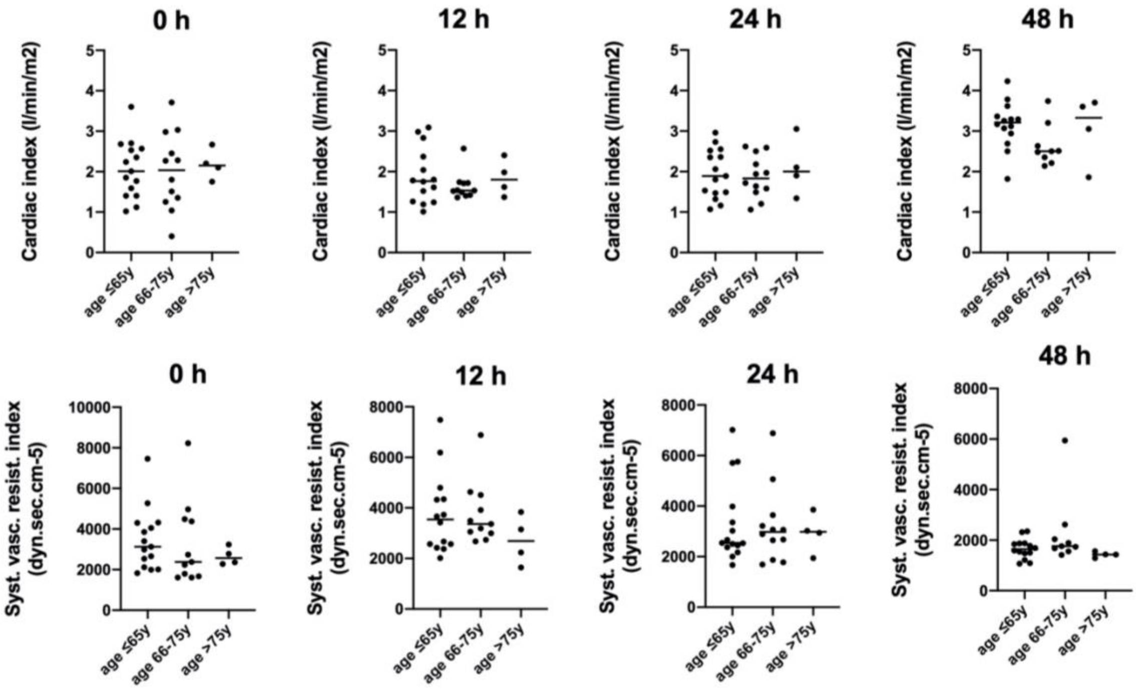


Figure 23. Comparison of CI and SVRI during the first 48 hours after ROSC between the age groups (among the subgroups treated with PiCCO®) in the study investigating the influence of age on post-cardiac arrest therapy outcome (185). *0h: initiation of TTM; 12h and 24h: TTM (32-34 ºC); 48h: measurement after rewarming. Age≤65y: Y group; age 66-75y: O group; age>75y: VO group. Kruskal-Wallis and Dunn's post hoc test were performed.*

4.3.4 Systemic review of the literature

3419 articles were identified and screened during the literature search and finally seven were included into the review (Figure 22). Tables 7 and 8 summarize the characteristics and results of the incorporated articles.

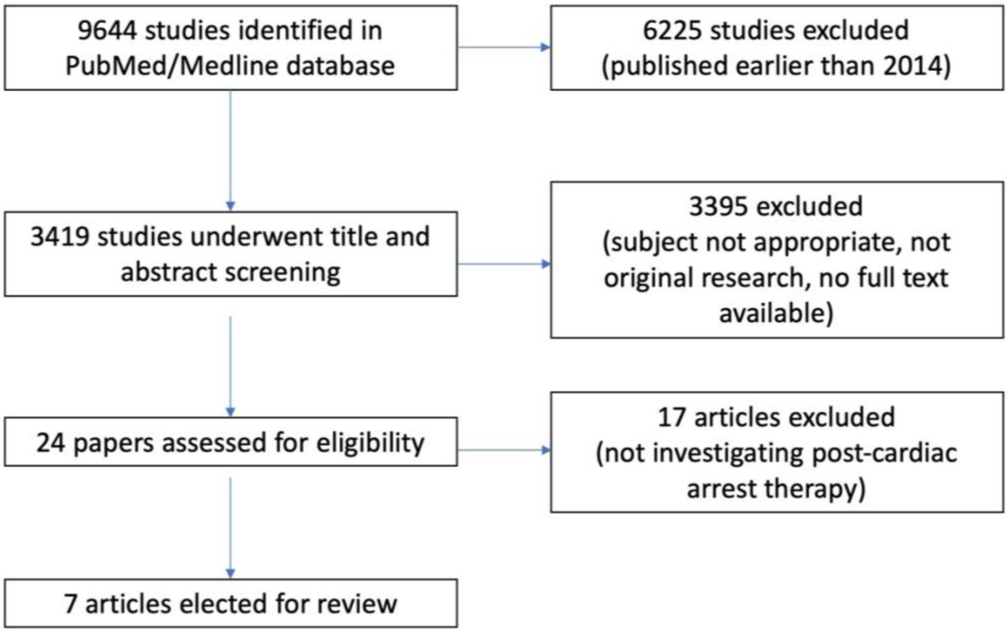


Figure 24. Process of literature search regarding the association of age and post-cardiac arrest therapy outcome in PubMed/Medline database (185).

Six papers applied a retrospective analysis and only one article used prospectively collected data to investigate characteristics and outcome of elderly patients receiving CPR and post-cardiac arrest therapy (95-101). Most of the studies were multicenter or nationwide evaluations. The outcome of IHCA patients was investigated in only one paper (98). Neither age grouping, nor the investigated outcome were homogenous in the studies. Additionally, the rate of TTM was also variable among the papers. The effect of TTM on mortality of the elderly was investigated in only one study, which could not show an association between the application of TTM and survival (95). Furthermore, the effect of TTM on neurological outcome was determined in two papers: Winther-Jensen et al. reported an increase in poor neurological outcome with advanced age, but it was not modified by the level (33 vs 36 °C) of TTM (101). Wallmüller et al. showed an association between TTM and good neurological outcome only in patients younger than 65 years (99). None of the studies examined the hemodynamic effects of TTM in the older patient group. The rate of acute PCI was analyzed in five studies: three of them showed a decline in the number of performed PCI with the increase of age (96, 100, 101). In addition, Aissaoui et al. described a benefit of PCI on outcome in patients up to 75 years (95). One article reported the rate of administration of catecholamines: 92% of nonagenarians received catecholamine during post-resuscitation therapy (98). Three studies described the rate of acute therapy termination, which was higher among older patients (98, 100, 101). Five papers assessed the independent predictors of mortality, and three articles described the independent predictors of favorable neurological outcome (95-97, 99, 100) (Table 9).

All studies reported worse survival rate in older compared to younger patients. Neurological outcome among survivors also deteriorated with increasing age, but this tendency was more moderate and old patients survived with a favorable neurological outcome in most of the studies. Moreover, all the studies point out that older age should not be basis for consideration to withdraw intensive post-cardiac arrest therapy since age has no significant predictive value on mortality (Tables 7 and 8).

Table 7. Characteristics of studies included in the systemic literature review regarding the association of age and post-cardiac arrest therapy outcome (185). *CPC: cerebral performance category; CPR: cardiopulmonary resuscitation; ICU: intensive care unit; IHCA: in-hospital cardiac arrest; N: number of patients included into the study; OHCA: out-of-hospital cardiac arrest; SCA: sudden cardiac arrest; TTM: target temperature management; y: year; * 30-day survival; $ survival at hospital discharge; ❑6 -month survival; & CPC1,2 at 180 days; # CPC 1,2 at hospital discharge; ☼ CPC 1,2 at ICU discharge; ✕ CPC 1,2 after 6 months.*

Author	Study period	Study design	Location of SCA	N	Age classification	Outcome	Survival	Good neurologic outcome among survivors
Winther-Jensen et al.	2010-2013	multicenter, post-hoc analysis of TTM-trial	OHCA	950	<65,66-70,71-75, 76-80, >80y	survival and neurologic outcome (CPC and Rankin scale)	* **<65y**: 70%, **66-70y**: 55%, **71-75y**: 55%, **76-80y**: 38%, **>80y**: 28%	& **<65y**: 62%, **66-70y**: 39%, **71-75y**: 42%, **76-80y**: 30%, **>80y**: 18%
Winther-Jensen et al.	2007-2011	multicenter, prospective	OHCA	2509	<80 and >80y	successful CPR, 30-day survival, neurologic outcome (CPC)	* **<80y**: 45%; **>80y**: 20%	# **<80y**: 84%; **>80y**: 79%
Aissaoui et al.	2011-2015	retrospective	OHCA	1502	<65, 65-75, >75y	neurologic outcome and survival at hospital discharge	$ **<65y**: 44%, **65-75y**: 42%, **>75y**: 28%	☼ **<65y**: 42%%, **65-75y**: 38%, **>75y**: 24%
Roedl at el.	2008-2016	retrospective	OHCA, IHCA	48	>90y	evaluation of patient charecteristics, ICU- and neurologic outcome	6-month: 29%; 1-year: 23%	6-month: 92%; 1-year: 55%
Hiemstra et al.	2001-2010	retrospective	OHCA	810	<75 and >75y	survival	$ **<75y**: 57%%, **>75y**: 33%	# **<75y**: 97%, **>75y**: 92%
Wallmüller at al.	1992-2015	retrospective	OHCA	1885	<50, 50-64, 65-74, >75y	comparison of patients with TTM and without (neurologic outcome)	❑ **<50y**: 59%, **50-64y**: 52%, **65-74y**: 35%, **>75y**: 27%	✕ **<50y**: 51% , **50-64y**: 48%, **65-74y**: 34%, **>75y**: 30%
Pätz et al.	2001-2012	multicenter, retrospective	OHCA	902	<65, 65-74, 75-84, >85y	28-day and 180-day survival, favorable neurologic outcome (CPC 1,2)	1-month: **<65y**: 70% **65-74y**: 49%, **75-84y**: 34% , **>85y**: 35% 6-month: **<65y**: 63% **65-74y**: 39%, **75-84y**: 24% , **>85y**: 27%	1-month: **<65y**: 80% **65-74y**: 80%, **75-84y**: 68% , **>85y**: 70% 6-month: **<65y**: 85% **65-74y**: 90%, **75-84y**: 75% , **>85y**: 63%

Table 8. Results of the studies included in the systemic literature review regarding the association of age and post-cardiac arrest therapy outcome (185). *CAG: coronary angiography; CCI: Charleson's Comorbidity Index; CPR: cardiopulmonary resuscitation; EMS: emergency medical system; GCS: Glasgow Coma Scale; PCI: percutaneous coronary intervention; NA: non-applicable (not analysed in the referred study); ROSC: return of spontaneous circulation; TTM: target temperature management; y: year; * 33 or 36 ℃; ● 32-34 ℃; ◦ level of TTM not defined*

Author	TTM	Acute PCI	Catecholamine therapy	Active therapy terminated	Independent predictors of mortality	Independent predictors of favorable neurologic outcome
Winther-Jensen et al.	* all patients received TTM	**<65y**: 49%, **66-70y**: 38%, **71-75y**: 40%, **76-79y**: 36%, **>80y**: 15%	NA	**<65y**:12%, **66-70y**: 20%, **71-75y**: 14%, **76-79y**: 23%, **>80y**:13%	NA	NA
Winther-Jensen et al.	◦ **<80y**: 52%, **>80y**: 32%	**<80y**: 27%, **>80y**: 10%	NA	**<80y**: 10%, **>80y**: 19%	age>80, CCI>2, non-shockable rhythm, lack of bystander CPR, non-public arrest, longer time to ROSC, lack of TTM	NA
Aissaoui et al.	◦ **<65y**: 64%, **65-75y**: 66%, **>75y**: 62%	**<65y**: 56%, **65-75y**: 46%, **>75y**: 50%	NA	NA	arrest at home, no-flow period > 3 min, low-flow period > 20 min, lack of CAG	CAG, TTM, bystander CPR, arrest at public region, no-flow period shorter than 3 min, low-flow period shorter than 20 min
Roedl at el.	◦ **>90y**: 13%	NA	**>90y**: 92%	**>90y**: 25%	NA	NA
Hiemstra et al.	● **<75y**: 38%, **>75y**: 32%	**<75y**: 43%, **>75y**: 25%	NA	NA	older age, GCS at admission (at older patients)	NA
Wallmüller at al.	● **<50y**: 47%, **50-64y**: 47%, **65-74y**: 53% , **>75y**: 50%	NA	NA	NA	increasing age	younger age
Pätz et al.	● all patients received TTM	No difference by age categories (p=0.201; Fisher's exact test)	NA	NA	increasing age, time to ROSC, lack of bystander CPR, non-cardiac origin of cardiac arrest	bystander CPR, time of hypoxia, defibrillation performed by EMS

5. Discussion

The chain of survival includes four main elements, including recognizing SCA and call for help, high-quality chest compressions, early defibrillation and proper post-resuscitation therapy (19). Additionally, the formula of survival highlights the importance of adequate guideline formation, education of CPR skills and appropriate implementation of resuscitation steps in increasing the success rate of CPR and SCA survival (31). Despite the well-designed resuscitation research and guidelines updated every five years, the overall survival of SCA is still poor (1). There are several aspects of the resuscitation process that need more exploration and clarification.

This thesis aimed to investigate and conclude some key factors, which might play a role in the improvement of patients' outcome during and after SCA. Factors from several steps of the chain of survival and formula of survival were examined during our studies, because the chain is only as strong, as its weakest link. It leads to the fact, that it is crucial to provide proper performance in all of the links to reach success and improved survival after CPR.

In our first study, we identified how we could improve skill retention with appropriate practical exams after BLS trainings (183). This study covers the first three links of the chain of survival and the education part from the formula of survival.

The second and third investigations covered the fourth link, investigating the efficacy of post-resuscitation therapy.

The results of our second study showed that while there was an interaction effect between PiCCO®-guided therapy, patients condition and mortality during post-cardiac arrest treatment, after 30 days for most conditions and after one year we saw either no effect of PiCCO®-guided hemodynamic management on survival or a worsening of survival among patients who had no underlying conditions and received PiCCO® (184). In addition, we found that catecholamine administration also influences survival in this patient group. The third research describes the usefulness and efficacy of post-resuscitation therapy and hemodynamic management in the elderly. Significant differences were found in MAP and catecholamine dosage between the investigated age groups during the first 48 hours after ROSC and during TTM (185). We also described that there is no evidence to support the limitation of post-cardiac arrest treatment based only on older age (185).

5.1 Prolonging BLS skill retention with practical exam

5.1.1 Influence of examination timing on skill retention after BLS training

Improving skill retention in BLS education is an important issue because it might lead to a higher success rate of CPR and improve outcome (191, 192). Quality of chest compressions is one of the most important factors that determines the outcome of a cardiac arrest patient (35). It has been shown that formal certified courses and their periodic renewal improve the outcome of CPR (193). However, a significant degree of skill impairment can occur within 3 to 12 months after training (63-65). Several methods have been investigated as a tool to prolong skill retention (73-77). Our goal was to find an effective skill retention method that is simple, time- and cost-effective. We used simulation training during our courses and exams, because it is of great benefit for the students and a proper teaching tool of BLS skills (194).

Our results demonstrate that testing and the timing of testing after BLS training do influence BLS skill retention among higher grade medical students. We found that students who took an exam three months after their BLS training had significantly better overall skill retention assessed during the SRA two months after the exam than students who either took no exam or had the exam immediately after the training.

One may wonder why we chose three months after training as the time point for administering the BLS skills exam to students in the third group. The timing means that for students in the 3mExam group, five months have elapsed between the end of their BLS training and the skill retention assessment, compared with two months for the other two groups. We chose this time point because it mirrors the official end-semester examination period. In addition, for each group, we assessed BLS skill retention two months after the last educational intervention, as the exam was considered as an intervention due to the “testing effect”.

During the exams and the SRA, we evaluated ten essential BLS components, which may contribute to the detection of cardiac arrest and a successful CPR and therefore influence patient outcome. These steps are important in recognizing cardiac arrest (examining consciousness, testing vital parameters), calling for help, and performing correct chest compressions (position of hands, depth, frequency and consistency of chest compressions, maintaining 30:2 compression to ventilation ratio, and duty cycle). It is well known that early recognition and immediate CPR may double or triple the likelihood of survival of IHCA and OHCA with ventricular fibrillation (195, 196). There is also evidence that the proper rate and depth of chest compressions increase the rate of ROSC (197, 198).

It has already been shown that testing skills after BLS training improves skill retention more than spending the same duration with additional training at the end of a course (79). This finding may be the result of the "testing effect", a phenomenon based on the fact that retrieval of memories during a test is more effective in creating long-term memory than additional study and training time (79, 80, 199). From a psychological point of view, the stress response might play an important role in improving skill retention, and remembrance during testing acts as a stress factor. One of the neuronal changes that occurs in response to stress plays an important role in creating memories (200). It has also been shown that prior knowledge of testing improves sensorimotor learning (201). Students in the EndExam group became aware of testing only at the beginning of the training, which might have influenced their performance negatively in some sensorimotor skills. Students in the 3mExam group had more time to prepare psychologically for their exam and therefore had a longer exposure to the stress effect. However, they did not get organized re-trainings to practice BLS skills before their exam. We also need to consider that testing three months after training may have a more complex educational impact and it should not be taken as a single testing step.

Surprisingly we found no significant difference between NoExam and EndExam groups, which contradicts formerly published data (79, 80, 202). As we mentioned previously, this may be the result of the complexity of the stress response. These results highlight the fact that further investigations are needed to understand the effectiveness of testing and timing of testing after BLS training.

5.1.2 Limitations of the study

Some limitations of our study need to be considered. Although our instructors received the same training in teaching BLS and performed the same quality teaching based on the standard ERC instructors' guidelines, it would have been preferable if the same instructor had taught all of the students. The exams were also administered by multiple instructors. Although we tried to evaluate the students' performances using standard guidelines, we cannot rule out teacher-related differences (203). We also need to highlight the lack of information about the preparation of the 3mExam group for their exam. They did not have an organized opportunity to practice after the course, but we cannot rule out that some might have practiced their skills in some other training format.

5.2 Hemodynamic management during post-cardiac arrest therapy and TTM

5.2.1 Interaction effects between mortality, PiCCO® use and patient characteristics

To our knowledge, there are no published studies regarding the association between PiCCO® guided therapy and survival in post-cardiac arrest treatment. We found five interaction patterns between patients' condition and being monitored with PiCCO® with regard to mortality after 30 days, which distilled down to three interaction patterns by the end of the first year. As such, our analysis presents a valuable insight into the nuances of advanced hemodynamic monitoring and hemodynamic management during post-cardiac arrest therapy.

The uniqueness of our study is that we disentangled the interaction effects between PiCCO® application, mortality and patients' condition in order to elucidate the potential cause of decayed survival rate in PiCCO® monitored patients. We found that there was a complex interaction between the use of PiCCO® and both 30-day and 1-year mortality, depending on the medical condition of the patient.

We identified *five groups regarding 30-day mortality*. In the *first group* having a condition and receiving PiCCO® meant increased risk compared to either not having the condition or not receiving PiCCO®, as in the case of hyperlipidemia. Specifically, 30-day mortality in patients who both had hyperlipidemia and also received PiCCO® was higher than among those who either had no hyperlipidemia or received no PiCCO®.

In the *second group* not having the condition but receiving PiCCO® meant increased risk compared to either not having the condition or having the condition regardless of PiCCO®, as in the case of STEMI and stroke. Specifically, 30-day mortality in patients without STEMI (without stroke, respectively) who also received PiCCO® was higher than among those who either had no STEMI (no stroke, respectively) and received no PiCCO®, or had STEMI (stroke, respectively) regardless of PiCCO®.

In the *third group* having the condition or receiving PiCCO® meant increased risk compared to not having the condition and not receiving PiCCO®, as in the case of CS and IABP. Specifically, 30-day mortality in patients who had either CS (IABP, respectively) or received PiCCO® was higher than among those who neither had CS (IABP, respectively) nor received PiCCO®.

In the *fourth group* not having the condition or receiving PiCCO® meant increased risk compared to having the condition and not receiving PiCCO®, as in the case of PCI. Specifically, 30-day mortality in patients who had either no PCI or received PiCCO® was higher than among those who had PCI and did not receive PiCCO®.

In the *fifth group* having the condition regardless of PiCCO® meant increased risk compared to not having the condition, as in the case of receiving catecholamine. Specifically, 30-day mortality in patients who received catecholamine was higher than among those who did not receive catecholamine, regardless of PiCCO®.

Furthermore, we identified *three groups regarding one-year mortality*. In the *first group,* there was no difference in one-year mortality either regarding PiCCO® application or regarding the presence of the condition, as in the case of hyperlipidemia in prior history or treatment with PCI after ROSC.

In the *second group*, having the condition regardless of PiCCO® meant increased risk compared to not having the condition, as in the case of IABP, CS and catecholamine administration. Specifically, the one-year mortality was higher in patients treated with IABP (having CS, receiving catecholamine, respectively) than among patients without these conditions regardless of PiCCO®.

In the *third group,* not having the condition but receiving PiCCO® meant increased risk compared to either not having the condition or having the condition regardless of PiCCO®, as in the case of STEMI and stroke. Specifically, one-year mortality in patients without STEMI (without stroke, respectively) who also received PiCCO® was higher than among those who either had no STEMI (no stroke, respectively) and received no PiCCO®, or had STEMI (stroke, respectively) regardless of PiCCO®.

Adequate hemodynamic management is one of the key elements in post-cardiac arrest therapy. Patients after successful CPR may experience a global ischemic-reperfusion injury and myocardial depression, as parts of post-cardiac arrest syndrome, leading to hemodynamic instability after ROSC (204, 205). Furthermore, the precipitating cause of cardiac arrest itself may result in a deterioration of hemodynamic parameters. It is also well-known that TTM has an influence on hemodynamics by several pathways. A decrease in heart rate and cardiac output, an increase in systemic vascular resistance, as well as hypovolaemia caused by raised diuresis may be present as consequences of lower body temperature (206-209). As the path leading to hemodynamic instability in post-cardiac arrest syndrome is multifactorial, there is a requirement of proper monitoring tools and proper hemodynamic goal parameters to guide the therapy of these patients.

Despite the complexity of the circulatory effects in post-cardiac arrest period, there is no clear evidence and therefore guidelines about exactly which parameters should be monitored, which goal parameters should be kept during patients' management, and which monitoring tools should be used to guide the treatment (135, 209-212). The current ERC guidelines recommend to target a mean arterial pressure to achieve a satisfactory urine output (1 ml/kg/h) and a decreasing or normal serum lactate level, considering the patient's habitual blood pressure, the cause of cardiac arrest, and the severity of probable cardiac dysfunction (30). Moreover, the guidelines suggest that additional cardiac output monitoring may help to guide therapy in hemodynamically unstable patients (30). However, there is no evidence that cardiac output measuring affects outcome in this patient group.

Transpulmonary thermodilution and pulse contour analysis are applied during PiCCO® monitoring, which allow intermittent and continuous measurements of cardiac output. Furthermore, several additional measured and calculated parameters can be estimated beside cardiac output reflecting preload, cardiac function and the vascular tone (213, 214). However, pulmonary artery catheter is the gold standard of thermodilution based cardiac output measurement (215). PiCCO® is less invasive, it is less influenced by respiratory fluctuations, and has a longer dwell time (216, 217). The European Society of Intensive Care Medicine suggests the application of artery pulmonary catheter only in refractory shock with concomitant right ventricular failure (139). PiCCO® was found to be effective in the evaluation of hemodynamic situations in critically ill patients, leading to a faster decision making (218, 219). The PiCCO®-guided hemodynamic management shortened the duration of vasoactive therapy, mechanical ventilation and ICU stay among elderly patients with cardiogenic shock after acute myocardial infarction (220). However, there is a lack of evidence regarding the effect of PiCCO® monitoring system and PiCCO® guided therapy on mortality in post-cardiac arrest treatment – and this is why our study findings are unique and much needed.

The results of the interaction effect analysis between PiCCO® application, mortality, and patients' characteristics show that more severe patient condition *per se* was not the cause of higher mortality rate in the PiCCO® group. Moreover, patients in better health conditions (without STEMI, without cardiogenic shock, without the need of IABP support or without stroke in prior history) had worse outcomes against PiCCO®-guided therapy. Our finding supports the literature, as the European Society of Intensive Care Medicine recommends the use of cardiac output monitoring and the application of transpulmonary thermodilution in patients with severe shock not responding to initial therapy (139).

In addition, significantly more catecholamines were administered overall in the PiCCO® group tailored by the results of the cardiac performance and resistance measurements. Furthermore, a tendency of higher doses of dopamine, dobutamine and noradrenaline could be observed during TTM in PiCCO® monitored patients with a significant difference in noradrenaline dosing after rewarming. It is well-known that long-term catecholamine administration itself may worsen the outcome (221, 222). The casual relationship raises further questions: does the advanced hemodynamic monitoring provide benefit in patients who do not have severe shock or are they overtreated based on the PiCCO® measurements? It was shown that noradrenaline improves tissue perfusion and cardiac output in severely hypotensive patients; however, in the lack of hypotension it may impair microvascular perfusion (223, 224).

Furthermore, we need to point out that the injured brain after successful CPR frequently has an impaired autoregulation resulting the MAP dependence of cerebral blood flow (112, 135). This fact raises the question if the monitoring of cardiac output and advanced hemodynamic parameters is the proper way to guide post-cardiac arrest therapy or the much simpler standard MAP measurement and the clinical judgement of tissue perfusion give enough information.

It should be emphasized that the application of PAC in various patient groups, which is still the gold standard of cardiac output measurement, was not associated with decreased mortality (225, 226). Moreover, there are some data suggesting increased mortality of PAC use due to its invasiveness (227, 228). This explains why it is recommended only in special circumstances as a hemodynamic monitoring tool. Some experts highlight that the primary goal of PAC application is not to affect survival but to refine hemodynamic management, especially in patients with severe comorbidities (229). Based on this, we can hypothesize that the effect of PiCCO®-guided hemodynamic therapy on mortality is also complex, and its exact effect, which should be investigated, remains to be elucidated.

We suggest applying PiCCO® in post-cardiac arrest therapy in selected cases based on our results. Moreover, further prospective studies are needed to clarify which patient groups benefit from cardiac output monitoring and thermodilution methods after successful CPR.

5.2.2 Catecholamine administration and mortality

Another important finding of our study was that catecholamine administration worsened both 30-day and one-year mortality in this patient group. It is important to clear the causality of worse survival regarding catecholamine dosage: is the catecholamine itself worsening outcome, or are the people receiving catecholamine sicker? On one hand, the side-effects of catecholamine usage (arrhythmias, increased cardiac oxygen consumption, splanchnic hypoperfusion etc.) may worsen outcome and only the least necessary amount of catecholamine if any should be administered (221). On the other hand, a delay in catecholamine therapy or an improper hemodynamic stabilization may lead to tissue hypoperfusion and deterioration in patients' condition (230). Further investigation is required to explain the effects and characteristics of catecholamine treatment in post-cardiac arrest therapy.

5.2.3 Limitations of the study

Our study has a number of limitations, most of which are related to its retrospective nature and small sample size. Patients were enrolled into the study non-randomly, and the analysis was based on retrospectively collected data. The grouping of patients was assigned based on the availability of a PiCCO® monitor. Although the baseline characteristics of the groups have been proven to be well-balanced, statistically only one interaction effect analysis was available between the three variable groups. The lack of possibility to adjust for other factors may have left some confounding elements that should be addressed in a bigger study population.

The improper evaluation of PiCCO® measurements should represent an additional limitation of our study. However, the trends of catecholamine and vasoactive dosage followed the changes of specific hemodynamic parameters, showing the adequacy of therapy. In addition, serum lactate levels decreased in parallel during and after TTM in both the PiCCO® and non-PiCCO® groups. Although a local protocol was available regarding hemodynamic management at our ICU, we cannot rule out some therapy-related and treating physician-preference based differences, since treatment in the ICU cannot always be standardized.

Another limitation may be that many factors including cause of cardiac arrest, arrest time and duration of cardiopulmonary resuscitation may be different between IHCA and OHCA, and therefore patients and their outcomes may be different. We performed a statistical analysis comparing IHCA and OHCA patients and found no significant differences, which may be due to the very small number of patients in the IHCA group. Therefore, we consider that there was no statistical necessity to control for this variable in the analysis.

5.3 The role of age in post-cardiac arrest therapy in an elderly patient population

We aimed to give an overview of the management and outcome of elderly patients after successful cardiopulmonary resuscitation and post-resuscitation therapy in our retrospective cohort study and systemic literature review.

5.3.1 The association between age and CPR outcome

There are several questions, challenges and ethical dilemmas in the post-cardiac arrest treatment of the aging population. Data from previously published studies demonstrate the association between age and outcome in this patient group (86-94). However, this relationship is influenced by various factors and therefore raises many questions regarding the nature of this finding.

We could not show any association between age, 30-day or one-year survival and neurological outcome at discharge among patients treated after ROSC at our ICU. This finding fully contradicts formerly published data. All papers included in our literature review found a decrease in survival with increasing age, and four of them reported advanced age as one of the independent predictors of mortality (95-101). On the other hand, the association between age and neurological outcome was not so obvious, as four studies noticed favorable neurological outcome among old survivors (96, 98-100). There was a tendency of better neurological outcome among very old patients in our investigation, but this difference was not statistically significant. We would like to highlight that the design, age categorization and measured outcomes were heterogenous in the studies as were the interventions during post-resuscitation therapy.

In addition, our literature review showed that the rate of therapy termination during post-cardiac arrest therapy was higher in the older population, nonetheless the exact conditions and criteria of this step in the treatment were not specified. Additionally, it has been previously described that the rate of CPR initiated by EMS was lower and duration of CPR was shorter in elderly patients (93).

The population is aging rapidly, and life expectancy is becoming higher. In parallel, there is an increasing number of ICU admissions of patients older than 75 years and of cardiac arrests (231). Furthermore, elderly people’s health conditions are better than before as is the quality of post-resuscitation therapy (232). Individual patient factors, premorbid status and the circumstances of CPR and post-cardiac arrest therapy play an important role in the management of elderly patients after ROSC and in the decision of therapeutic strategies.

5.3.2 The association between age and post-cardiac arrest therapy outcome

We also evaluated the differences in post-cardiac arrest treatment between the age groups. The rate of acute PCI was similar among the investigated groups. However, our literature review revealed contradicting information, as some studies showed the same result, but others found the opposite (95-97, 100, 101). TTM was applied in all cases in our retrospective cohort. Additionally, there was no difference in TTM use among younger and older patients in the studies included in our literature review except for two, where older patients were less likely to receive TTM (95-99, 101). Furthermore, the question of TTM efficacy and its influence on neurological outcome in the elderly was raised only in two investigations with contradicting results. The post-hoc analysis of TTM-trial showed that age had no impact on the effectiveness of TTM (101). On the other hand, a retrospective cohort study found a marked effect of mild therapeutic hypothermia on neurological outcome only among patients below 65 years (99).

5.3.3 Hemodynamic changes during TTM among elderly patients

The management of hemodynamic changes during post-cardiac arrest therapy and TTM also play an important role in the post-resuscitation period. Nonetheless we found no evidence in the literature published in the last five years assessing the hemodynamic management of the elderly after a successful CPR. The changes of heart rate, MAP, CI and SVRI during TTM were described in our study. We found a significantly lower MAP in old patients during low temperature and after rewarming, but SVRI and CI did not differ between the age groups. The decreased MAP in the older patients may be explained by the lower vasoconstrictive response to hypothermia in the elderly, as well as the increased usage of antihypertensive agents due to hypertension in this patient group. In addition, we showed an increase in catecholamine consumption with increasing age. The need for catecholamines was interpreted only in one paper in our literature review. Roedl at al. found that catecholamines were applied in 92% of patients older than 90 years to maintain sufficient MAP during post-resuscitation therapy (98). These findings highlight the relevance of hemodynamic management in older patients and the requirement of further studies focusing on this aspect.

There are several pathophysiologic changes explaining the differences in hemodynamic parameters and catecholamine consumption between the age groups. It has been previously shown that the condition of cardiovascular system changes with age. Both experimental and clinical studies showed that aging promotes generalized endothelial dysfunction leading to functional alterations in peripheral vasculature (233). Moreover, macrovascular endothelial function impairment and increased endothelial stiffness were found among patients older than 65 years, however endothelial dysfunction may be regulated with weight-loss in this patient group (234, 235). NrF2 (nuclear factor-erythroid-2-related factor 2) dysfunction is one of the key elements in promoting cell senescence leading to age-related vascular diseases, as its impaired function results in a lower antioxidant response (236-238). Furthermore, chronically increased sympathetic nervous system activity plays also an important role in several cardiovascular changes in advanced age resulting hypertension, diastolic dysfunction, increase in ventricular and aortic wall thickness (239).

The long-standing shear stress during aging with or without hypertension continuously effects the vascular endothelial cell integrity and therefore the vasodilatative responsiveness. Both the NO pathway that is responsible for vasodilation, and the alfa-adrenergic receptorial vasopressor regulation are aggravated. Nevertheless, the latter may be the reason of higher noradrenaline need for maintaining an optimal MAP. Our results concerning the lower blood pressure characteristics in older patients suggest a lower vasoreactivity of the elderly under hypothermic conditions where a physiologic systemic vascular resistance increase is expected. Hypertension may also affect cerebral synopses through increased microvascular oxidative stress and inflammation, promoting a more rapid cerebral aging (240).

There is a requirement of comparable, randomized controlled trials to clarify the issues raised in the management of the elderly after CPR. Neither the data found in the literature, nor the results of our retrospective analysis support the withholding of CPR and post-resuscitation therapy based on age only.

5.3.4 Limitations of the study

Our retrospective analysis has several limitations/drawbacks, most of which are related to its retrospective manner and small size of the investigated population.

The limitations of literature review are associated with the design and methodology of data collection of included original papers. Most of them performed a retrospective analysis based on a nation-wide registry. There were no unified age classifications, investigated treatment options and outcomes. We included articles published only in the last five years, but not prior to that. The reason for that was the improvement and dynamic changes of the assessment of post-cardiac arrest patients and exponentially growing data on post-cardiac arrest treatment during the past decade.

Despite these limitations our study gives a broad overview of all currently available data regarding the management of post-cardiac elderly patients.

6. Conclusion

The chain of survival and formula of survival determine the most important factors of patients' outcome after SCA. The chain of survival contains the elements of BLS and post-resuscitation therapy, while formula of survival summarizes the effects of guideline creation, implementation and education on survival. Despite having well-designed and regularly updated guidelines, overall survival rate of SCA is still very poor. There are several aspects of CPR and post-resuscitation therapy, which require improvement and can lead to more effective patient management.

We investigated three aspects regarding the improvement of management and survival after SCA. All of the studies were performed in Hungary reflecting the quality of Hungarian education and patient' s care.

As the first aspect, we focused on the enhancement of BLS teaching efficacy. It is well-known, that properly taught BLS skills deteriorate in 3 to 12 months, if these skills are not used. There are several methods to improve BLS skill retention, one of which may be testing these skills after the BLS training. However, the exact method and proper timing of testing is still unknown. We examined in our prospective quasi-experimental study the effect of practical exam and timing of the examination on BLS skill retention after BLS course among fifth year medical students. Our results showed that the timing of testing affects skill retention after BLS training. We provided evidence that testing BLS skills three months after BLS session may be more effective than either testing immediately at the end of the course or not testing at all. In addition, we found no difference in the skill retention of the latter two groups in our study population, which contradicts formerly published data.

The second and third aspects of our resuscitation research include elements of post-resuscitation therapy.

Post-cardiac arrest syndrome may lead to hemodynamic instability caused by multiplex factors, including the effects of TTM. Proper hemodynamic monitoring and management of hemodynamic parameters is indispensable in this patient group. The accuracy of the PiCCO® monitoring system was confirmed in the lower temperature environment of post-cardiac arrest therapy. However, little is known about the effectiveness of PiCCO®-guided hemodynamic management regarding mortality outcomes in post-cardiac arrest patients. Our analysis pointed out that 30-day mortality was significantly, and one-year mortality was marginally higher among PiCCO® patients compared to the lack of PiCCO® monitoring. We found a complex interaction effect between the application of PiCCO®, mortality and patients' condition. More severe condition per se was not the cause of higher mortality rate in the PiCCO® group. Patients in better health conditions (without STEMI, without CS, without IABP or without stroke in prior history) had worse outcome with PiCCO®-guided therapy. In addition, we found that catecholamine administration worsened both 30-day and one-year mortality among all patients during post-resuscitation treatment.

The population is aging and life expectancy increases, which leads to the increase of the proportion of old people suffering SCA. Older age is associated with several physiologic and pathophysiologic changes that can influence their management. However, there are no different treatment recommendations regarding older and younger patients in the current guidelines. We investigated the effect of age on post-cardiac arrest therapy outcome in an elderly population based on our local database and a systemic review of the literature. We could not find any association between age and survival or neurological outcome in our own patient population. Studies included into our systemic review reported worse survival in the elderly, although old survivors showed favorable neurological outcome in most of the cases. Additionally, we demonstrated that MAP and catecholamine requirement differed significantly between the specific age groups during TTM with the highest catecholamine administration among very old patients. Based on our results there is a lack of evidence to support the limitation of post-cardiac arrest treatment in the aging population. Further prospective studies are needed to support the results we obtained.

7. Summary

Sudden cardiac arrest is one of the leading causes of death in Europe and Hungary. The survival rate remains still very low, ranging between 0-18% in Europe and approximately 4.5% in Hungary. The chain of survival and formula of survival summarize the key factors affecting outcome and survival of patients with SCA.

Our research aimed to find some specific factors regarding BLS education and post-resuscitation therapy, which might enhance the efficacy of the chain and formula of survival.

We investigated the effectiveness of BLS education, and we assessed methods, which can help in prolonging skill retention after BLS training. Properly performed BLS is crucial in improving the outcome of SCA. We found that testing BLS skills three months after the training may be more effective in skill retention enhancement than not testing these skills or testing them immediately at the end of the course.

Proper hemodynamic management during the early phases of the post-cardiac arrest period is a key element in increasing the rate of favorable neurological outcome and survival. Complex hemodynamic changes can appear after ROSC with multifactorial etiologies and consequences. However, there is still a lack of evidence which hemodynamic monitoring system should be applied, and which hemodynamic goals should be targeted during PCAS and TTM. We showed that PiCCO®-guided therapy affects both 30-day and one-year mortality. Moreover, there was a complex interaction relationship between PiCCO®-guided treatment, patients' condition and mortality for most conditions.

The proportion of old post-cardiac arrest patients is rising, which raises several questions from professional and ethical point of view. We did not find a clear association between older age and worse long-term outcome in this patient population. We suggest avoiding limitations of further treatment based only on age. In addition, hemodynamic management of very old patients requires special attention, as these patients had lower MAP and needed more catecholamines during TTM than younger patients in our study.

8. Összefoglalás

A hirtelen szívhalál jelenleg az egyik vezető halálok Európában és Magyarországon. A túlélési lánc és az ún. túlélési képlet foglalják össze azokat a tényezőket, melyek ismereteink szerint meghatározzák a hirtelen szívhalált szenvedő betegek kimenetelét és túlélési esélyeit. Vizsgálataink során arra kerestük a választ, hogy a hirtelen szívhalál és újraélesztés kimenetelét, túlélését milyen további tényezők segítségével javíthatjuk.

A megfelelően kivitelezett alapszintű újraélesztés (BLS) nélkülözhetetlen a sikeres újraélesztési folyamathoz. Tézisem egyik fontos kérdése, hogy a BLS oktatásának eredményessége hogyan növelhető, illetve a BLS készségmegőrzés milyen módszerekkel fokozható. Az erre irányuló vizsgálatunk során arra a megállapításra jutottunk, hogy a BLS készségmegőrzés hatékonyabb, ha az orvostanhallgatók három hónappal a BLS tanfolyam után gyakorlati vizsgát tesznek, ahhoz képest, hogy egyáltalán nem tesznek gyakorlati vizsgát, vagy közvetlenül a tanfolyam után vizsgáznak.

Az adekvát hemodinamikai ellátás a poszt-reszuszcitációs terápia egy nélkülözhetetlen eleme, mely a betegek neurológiai kimenetelét és túlélését is jelentősen befolyásolja. A keringés visszatérését követően különféle, összetett folyamatoknak köszönhetően számos hemodinamikai változás léphet fel. Ezért is fontos, hogy a poszt-reszuszcitációs terápia során adekvát hemodinamikai monitorozást és ellátást végezzünk. Egyelőre nincs kellő bizonyíték arra vonatkozóan, hogy melyik monitorizáló eszköz a legelőnyösebb ebben a betegcsoportban. Vizsgálataink során azt találtuk, hogy a PiCCO® monitorozás által vezérelt hemodinamikai terápia negatívan befolyásolta mind a 30 napos, mind az egy éves túlélést. Ezenfelül komplex összefüggést mutattunk ki a PiCCO® monitorozás alkalmazása, a betegek állapota, valamint túlélése közt.

A poszt-reszuszcitációs betegek körében is egyre nő az idősek aránya. Tézisem harmadik fő kérdése az volt, hogy a kor befolyásolja-e a poszt-reszuszcitációs ellátás kimenetelét és a túlélést. Eredményeink nem mutattak egyértelmű összefüggést az idős kor és a rosszabb kimenetel közt, ezért nem javasoljuk, hogy az idős kor önmagában a poszt-reszuszcitációs terápia kontraindikációját jelentse. Vizsgálatunk eredményei emellett rámutattak arra is, hogy az idős betegek hemodinamikai ellátása külön figyelmet igényel, mivel a nagyon idős betegek hemodinamikailag instabilabbak és több katekolamint igényeltek, mint a fiatalabbak.

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10. List of publications

10.1 Publications included in the thesis

Kovács E, Gyarmathy VA, Pilecky D, Fekete-Győr A, Szakál-Tóth Zs, Gellér L, Hauser B, Gál J, Merkely B, Zima E. (2021) An interaction effect analysis of thermodilution-guided hemodynamic optimization, patient condition and mortality after successful cardiopulmonary resuscitation. Int J Environ Res Public Health, 18: 5223.
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∑ IF = 7.311 + 0.497

10.2 Other publications by the author

Kiss B, Fekete-Győr A, Szakál-Tóth Zs, Párkányi A, Jenei Zs, Nyéki P, Becker D, Molnár L, Ruzsa Z, Dér G, **Kovács E**, Pilecky D, Gellér L, Veli-Pekka H, Merkely B, Zima E. (2021) Pilot analysis of the usefulness of mortality risk score systems at resuscitated patients. Orv Hetil, 162(2): 52-60.
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