A CRITICAL REVIEW ABOUT THE CURRENT ERC-GUIDELINES (2021) FOR POST-RESUSCITATION CARE IN ADULT PATIENTS

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Thesis mentor: Prof. Vlatka Sotošek, MD, PhD

The graduation thesis was graded on in_____, before the Committee composed of the following members:

1. Prof. Alan Šustić, MD, PhD (Committee Head)
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The graduation thesis contains_____pages, ____ figures,_____tables,_____references.

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List of abbreviations and acronyms

ACNS – American clinical neurophysiology society

ADC – Apparent diffusion coefficient

AEP – Auditory evoked potentials

AKI – Acute kidney injury

ALS – Advanced Life Support

ARDS – Acute respiratory distress syndrome

BLS – Basic Life Support

CBF – Cerebral blood flow

CO – Cardiac output

DVT – Deep vein thrombosis

DWI – Diffusion weighted imaging

ERC - European Resuscitation Council

ESE - Electrographic status epilepticus

GCS – Glasgow coma score

GFAP - Glial fibrillary acidic protein

IABP – Intra- aortic balloon pump

ICU – Intensive care unit

IHCA – In-hospital cardiac arrest

LBBB – Left bundle branch block

MAP – Mean arterial pressure

Nfl - Serum neurofilament light chain

NPi – Neurological pupillary index

NSE - Neuron-specific enolase

NSTEMI – Non-ST-elevation myocardial infarction

OHCA – Out of hospital cardiac arrest

PCI - Percutaneous coronary intervention

ROSC – Return of spontaneous circulation

SSEP - Somatosensory evoked potentials

STEMI – ST-elevation myocardial infarction

TTM - Targeted Temperature Management

VEP – Visual evoked potentials

Introduction

In the 21st century, “sudden cardiac arrest” is among the top mortality factors in Europe (1). It is defined by the American Heart Association as an “abrupt loss of heart function in a person who may or may not have been diagnosed with heart disease” (2). Europe exhibits a lower incidence of cardiac arrest compared to other regions globally, with “out-of-hospital cardiac arrest (OHCA)” occurring at a rate of 67 to 170 cases per 100,000 inhabitants over a twelve-month period. Additionally, the annual incidence of cardiac arrest among hospitalized patients is estimated to be 1.5 to 2.8 cases per 1,000 individuals (1).

Immediate intervention such as basic life support (BLS) has been promoted among the population and belongs already to basic educational skills. Nevertheless, in only 50-60% of “out-of-hospital cardiac arrest (OHCA)” (5) cases, qualified workforce begins or carries on cardiopulmonary resuscitation (1). Even though most European countries provide resuscitation assistance via phone, help seekers are not calling the emergency number due to various reasons (1,3).

An early start of CPR coupled with early defibrillation is essential for the survival of cardiac arrest patients and may highly increase their survival (3). Fortunately, nowadays the presence of automated defibrillators (AED) at public places gains increasing attention. An early defibrillation of a shockable cardiac rhythm in the first five minutes after collapse may increase the survival rate up to 70%. Moreover, the early start of advanced life support (ALS), which is a standard practice all over the world, improves survival upon hospital discharge (3).

Since the resuscitation procedures are following strict algorithms, the treatment should not end with re-achieving a spontaneous circulation (ROSC) (4). Therefore, the European Resuscitation Council (ERC) published their first combined resuscitation guidelines in 2015 (5). These guidelines correspond to the consensus of different organizations from Europe, Canada, Australia, New Zealand, South Africa, America, and Asia, providing treatment recommendations based on their evidence. The main focus of the discussion encompasses various aspects, such as: “oxygenation control, hemodynamic targets, coronary perfusion, targeted temperature management (TTM), seizure control, prognostication, rehabilitation, and long-term outcome” (5). Additionally, a significant portion of the discussion revolves around preventing post-cardiac arrest syndrome (5). Each person experiencing cardiac arrest requires immediate intensive care treatment after ROSC, which should follow evidence based recommendations (5).

The European Resuscitation Council is a society founded in 1989, setting standard guidelines for resuscitation and training among Europe and globally. As an association of over 30 National Resuscitation Councils, its main function is providing scientific evidence for the published guidelines and raise awareness for resuscitation and cardiac arrest prior to it. As part of the "International Liaison Committee On Resuscitation"(5), ERC experts participate in the worldwide "Consensus On Science and Treatment Recommendations" (5). Based on that activity, the ERC has been publishing new guidelines in their official journal "Resuscitation" regularly (6).

Basic and Advanced live support

To provide detailed instructions about cardiopulmonary resuscitation, the ERC publishes guidelines for the performance of BLS and ALS to laypeople and professionals respectively. Both guidelines will be described briefly since a successful reestablishment of spontaneous circulation is the most important prerequisite to proceed to the post-resuscitation care.

The BLS guidelines are intended to encourage everybody to provide first-aid if a person collapses.

As a first step, caregivers should make sure that the scene is being secured for victims, bystanders, and themselves and should ask for help (4). Caregivers should address the victim and check for their response. In case of an unresponsive victim, airway opening maneuvers, such as moving the head backwards and putting up the chin, should be performed. Following that, the caregiver should check for any abnormal breathing patterns via the "look, listen, feel" approach for approximately 10 seconds (4). If the breathing is considered as unregular, including infrequent, heavy, or noisy breathing, the emergency hotline should be dialed immediately. The universal emergency number to reach the emergency medical services or firefighters in the European Union is 112. A further important part in the current BLS guidelines encounters early defibrillation with an AED. If there are any bystanders at the scene, somebody should get an AED as long as chest-compressions are still executed. Upon suspecting a cardiac arrest, chest compressions should be initiated promptly (4). To provide adequate chest compressions the caregiver should kneel at the side of the victim, placing the hands above each other on the lower part of the sternum. The optimal position for chest compressions is a 90-degree angle above the chest with straight arms. Each compression should go approximately 5-6cm deep at a frequency of 100-120/min. Trained caregivers may perform two rescue breaths, following every 30 chest compressions.

If the caregivers are not skilled enough or unable to give rescue breaths, CPR should be continued (4). As soon as an AED arrives it should be implemented in the resuscitation process, by turning it on and following the instructions of the device. CPR should be continued, until further instructions of healthcare professionals or the victim showing definite signs of recovery just like: eye-opening, spontaneous breathing, or moving (4). Upon arrival of the emergency medical team, the patient status should be reassessed by checking the breathing and central pulses of the patient. If cardiac arrest is still suspected, chest compressions should be continued as well as connecting defibrillator electrodes inferior to the right clavicle of the patient and in the left midaxillary line, where usually the V6 ECG-electrode is placed (7). Cardiac rhythms associated with cardiac arrest can be categorized into shockable and non-shockable rhythms. Non-shockable rhythms encompass pulseless electrical activity and asystole. In such cases, it is recommended to continue with 30 chest compressions followed by two rescue breaths for an additional two minutes before reassessing the cardiac rhythm (7). “Shockable rhythms” (5) are defined as ventricular fibrillation and pulseless ventricular tachycardia. In this rhythms, biphasic defibrillation should be provided with 150-200 Joules in the first cycle, followed by 150-360 Joules in subsequent cycles (7). Special attention needs to be driven to the secure position of all people surrounding the patient during defibrillation. Immediately after shock delivery, chest compressions need to be continued without rechecking the pulse or rhythm for two further minutes. During that time, a patent airway should be secured via endotracheal intubation or supraglottic devices. After establishing a secure airway, the chest compressions need to be executed with a frequency of 100-120/min without interrupting the compressions for ventilation. The patient should be ventilated at a respiratory frequency of 10/min from that point on. Waveform capnography can offer additional insights into the effectiveness of cardiopulmonary resuscitation (CPR) and serve as a predictive tool throughout the resuscitation process (7). Furthermore, an intravenous or intraosseous access should be established in that cycle. This access allows the resuscitation team to apply certain medications at a given point. For non-shockable rhythms, it is advised to administer 1mg of adrenaline as early as possible and repeat the dose every 3-5 minutes. Conversely, in the case of shockable rhythms, 1mg of adrenaline should be given after the third shock and subsequently repeated every 3-5 minutes (7). Moreover, Amiodarone should be considered in shockable rhythms also after the third shock, with 300mg as a first dose and 150mg in subsequent application. While treating cardiac arrest, it is crucial to assess and address any reversible factors that could have led to the arrest, implementing appropriate interventions to correct them.

The reversible causes of cardiac arrest are classified as “4Hs and 4Ts” (8), including: “hypoxia, hypovolemia, hyper-/hypokalemia and metabolic disorders, hypothermia, tension pneumothorax, tamponade, thrombosis, and toxic agents” (7). In an optimal scenario the patient will re-establish spontaneous circulation and post-resuscitation care should be started, as discussed further in this graduation thesis.

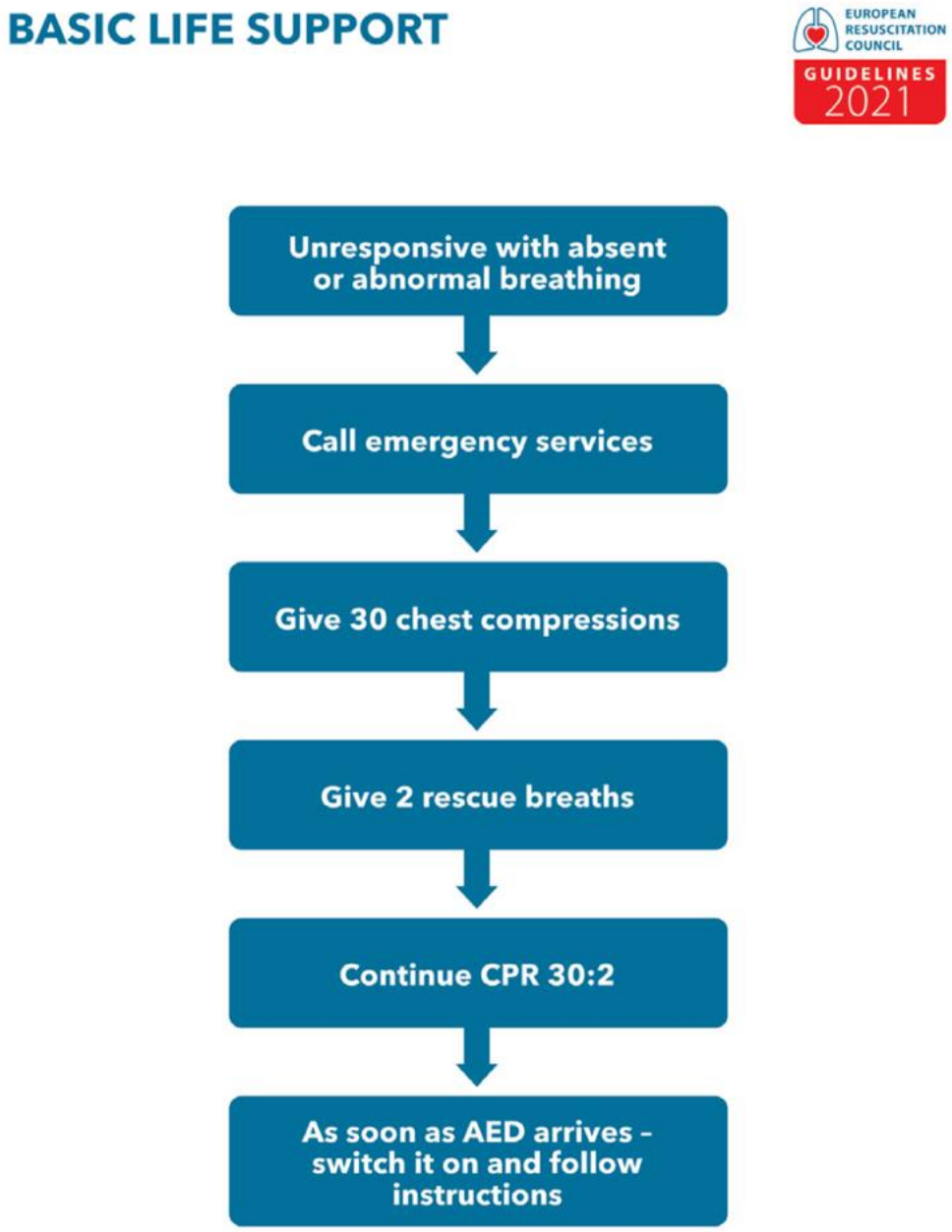

Figure 1: “Basic life support algorithm” (Source: Olasveengen TM, Semeraro F, Ristagno G, Castren M, Handley A, Kuzovlev A, et al. European Resuscitation Council Guidelines 2021: Basic Life Support. Resuscitation. 2021 Apr;161:98–114)

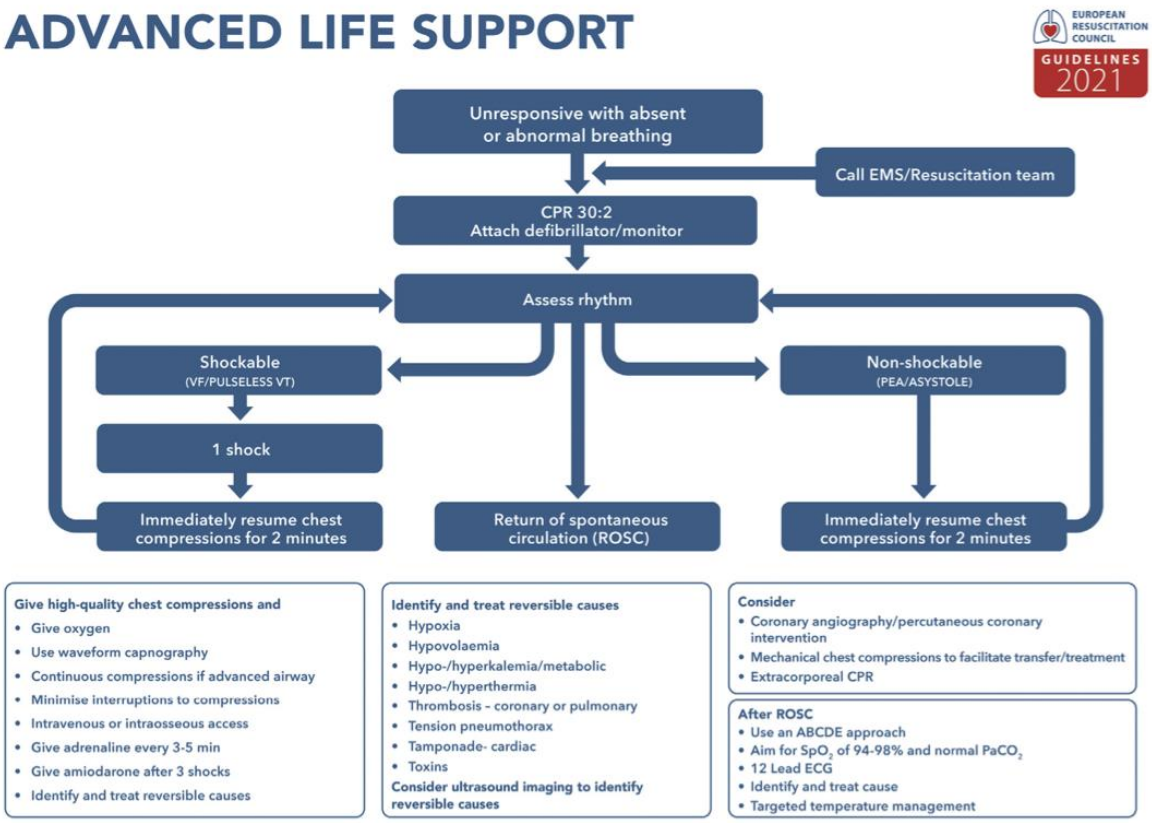

Figure 2: "Adult advanced life support algorithm" (Source: Soar J, Böttiger BW, Carli P, Couper K, Deakin CD, Djärv T, et al. European Resuscitation Council Guidelines 2021: Adult advanced life support. Resuscitation. 2021 Apr;161:115–51.)

Aims and objectives

This thesis aims to summarize and analyze the current ERC post resuscitation care guidelines (2021) as well as its implication in clinical practice. In addition, this literature review is intended to present useful recommendations, based on current guidelines, regarding the treatment and support of cardiac arrest survivors.

Literature review: "European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care"

The term "post-cardiac arrest syndrome" (5) describes: "hypoxic ischemic brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and the persistent precipitating pathology" (5). Each component contributes to a certain degree, dependent on the factor causing of cardiac arrest, extend of ischemia, and prearrest comorbidities (9). The severity of the syndrome is influenced by the "duration and cause of cardiac arrest" (5). For example, in 66.6% of "out-of-hospital cardiac arrest (OHCA)" (5) cases and 25% of "in-hospital cardiac arrest (IHCA)" (5) cases, patients who survive the transfer to an "intensive care unit (ICU)" (5) have life-sustaining measures discontinued due to negative outcomes (10). Usually, the main mortality factor is of cardiovascular origin within the first five days. Later than that, the main cause of death includes the "withdrawal of life-sustaining therapy (WLST)" (5) after prognostication of "hypoxic-ischemic brain injury" (5,10,11). "Hypoxic-ischemic brain injury" (5) typically presents with hypotension, hypoxemia or hyperoxemia, pyrexia, hyperglycemia or hypoglycemia, and seizures (5). Myocardial dysfunction is another prevalent characteristic observed in post-cardiac arrest syndrome, which usually recovers after 2-3 days (12,13). After successful resuscitation, immune and coagulation pathways get activated due to "ischemia-reperfusion injury" (5). This activation increases the risk of infection and may lead to multi-organ failure (14–17). In many cases, post-cardiac arrest syndrome may mimic sepsis. This "sepsis-like" presentation may manifest as hypovolemia, vasodilation, endothelial injuries, or abnormal microcirculation (5). All patients require immediate post-resuscitation care after ROSC (5). This includes, in the first place A-B-C approach, as well as diagnosing the cause of cardiac arrest. Hereby, the causes might be differentiated in cardiac and non-cardiac origin. It is essential to establish a diagnosis as soon as possible to establish a further treatment plan, including transport to a specialized ICU or a cardiac arrest center (5).

Airway

The ERC guidelines for post-resuscitation care state that patients require continuous airway and ventilation support. If the duration of cardiac arrest was short, with an instant return of adequate cerebral function, endotracheal intubation is not necessary (5). In that case, the airway is considered open and secure.

If the patient presents with an arterial blood oxygenation <94%, in a non-intubated patient, an O_2-face mask may be required to ensure further oxygenation (5).
On the other hand, in comatose or sedated patients, endotracheal intubation may be needed to ensure a patent airway for controlled ventilation and prevent aspiration of stomach contents, if it was not previously applied during resuscitation intervention (5). Endotracheal intubation should just be performed by skilled personnel, and the correct placement needs to be confirmed by waveform capnography (18). Hemodynamically unstable patients may require drug assisted intubation with an analgesic, a low dose sedative, and a rapid onset neuromuscular blockage (19). Alternatives for opening the airway include basic manual measures or supraglottic devices (5).

Breathing: Ventilation and oxygenation

After establishing a secure airway, proper oxygenation needs to be ensured. In the period after ROSC, until there are reliable measures of blood oxygenation, 100% oxygen should be applied. Reliable measures for blood oxygenation include pulse oximetry, however, arterial blood gas analysis (ABG) is preferred (20). In the process of the disease the contribution of blood oxygenation remains to be clarified (5). A negative outcome is often associated with cerebral ischemia following cardiac arrest (21), which may lead to the fallacy that more oxygen increases brain oxygenation (5). This is considered true to a certain degree, as a higher oxygen saturation also increases the amount of free oxygen radicals, which may be harmful (22). Taking into account this evidence, the ERC recommends to avoid hypoxemia (PaO_2 <8 kPa or 60mmHg) but also hypoxemia due to the previously mentioned reasons (5). Once an "arterial blood gas analysis" (5) is possible, oxygen should be titrated to a 94-98% saturation, respectively PaO_2 10-13 kPa or 70-100 mmHg (20). It is important to mention that the results of the arterial blood gas analysis may differ according to different body temperatures. Therefore, the guidelines recommend to constantly "use either a temperature or non-temperature-corrected approach"(5) during ABG analysis. Several studies have investigated the optimal level of blood oxygenation, but all of them failed to show precise results regarding the better outcome or biomarkers indicating neurological injury (5). Besides the airway and oxygenation, control of ventilation should not be neglected. After ROSC, the patient normally presents with an increased partial pressure of CO_2 due to intra-arrest hypoventilation (23). Hypercapnia results in vasodilation, increased cerebral blood flow, as well as heightened cerebral blood volume, intracranial pressure (5).

On the other hand, hypocapnia fosters vasoconstriction and may cause cerebral ischemia (24). The ERC defined the target values for CO_2 as $PaCO_2$ 4.5-6.0 kPa or 35-45 mmHg, according to several studies which showed mixed results (5).
Observational data from the UK showed an even worse outcome if hypoxia and hypocapnia were present in the initial 24h after "cardiac arrest" (5). Lung protective ventilation should be provided with a "tidal volume of 6-8mL/kg ideal body weight" (5,25). Within the framework of ventilation several factors were associated with a poor outcome. "Acute respiratory distress syndrome (ARDS)" (5) is very common in mechanically ventilated patients and associated with an unfortunate post cardiac arrest outcome (26,27). Furthermore, the guidelines state that: "low lung compliance predicts poor functional outcome in OHCA patients" (5,28).

Circulation

After managing the airway, oxygenation and ventilation, circulatory support is the next step. One main part is the coronary reperfusion. After ROSC, an immediate cardiac catheterization evaluation and intervention should be performed, if a cardiac source of the arrest is suspected. A typical sign therefore may be a "ST-elevation (STE) or left bundle branch block (LBBB) on the post- ROSC ECG" (5). Evidently, these patients have an acute coronary lesion in approximately 80% of the cases (29). Patients with a STEMI on ECG, show a significantly decreasing mortality with an emergency percutaneous coronary intervention (PCI) (30).
Besides that, cardiac catheterization laboratory evaluation and PCI may also be an option for NSTEMI patients. Observational studies have indicated that the absence of ST-elevation on an electrocardiogram does not rule out a coronary artery occlusion (31). The decision whether performing an evaluation via cardiac catheterization or not should be based on the hemodynamic or electrical instability of the helpseeker. Furthermore, taking into account the history, symptoms before cardiac arrest, the initial cardiac rhythm, and echocardiographic results (32). It is widely discussed if NSTEMI patients benefit from early PCI rather than from initiation standard ICU care. In 2020, the European Society of Cardiology recommended delayed angiography in "hemodynamically stable patients, without ST-elevation, who were successfully resuscitated after OHCA" (33). Special caution belongs to patients suffering from hypoxic-ischemic brain injury. If they display signs of irreversible hypoxic-ischemic brain injury, the benefit of PCI is arguable (34).

Moreover, circulatory support includes hemodynamic monitoring and management. This comprehends monitoring with continuous invasive blood pressure measurement, which is also reasonable for cardiac output (CO) in hemodynamically instable patients (5).

Approximately 60% of cardiac arrest patients show a low cardiac index and myocardial dysfunction after ROSC (35). Further cardiac assessment should include an urgent echocardiography, especially for patients with a known or suspected cardiac pathology. Echocardiography helps to assess: "cardiac pathology, quantify the degree of myocardial dysfunction and helps to guide the hemodynamic management" (5). A low CO is not necessarily associated with a poor treatment result, as long as the lactate clearance is maintained (36). Although a low CO is not always connected to a negative outcome, hypotension is (37). Consequently, the ERC recommends avoiding hypotension "below 65 mmHg of mean arterial pressure (MAP)" (5). This threshold is necessary to provide "adequate urine output (> 0.5 ml/kg/h) and normal to decreasing lactate values" (5). Additionally, the MAP is directly related to the "cerebral blood flow (CBF)" (5,38). In many post resuscitation patients the CBF autoregulation remains impaired (39). A retrospective study showed that the ideal MAP for patients with preserved autoregulation is at 85 mmHg, whereas for patients with impaired autoregulation the optimal MAP is even higher (at 100 mmHg) (5,39).

In case of hypotension, perfusion should be maintained with fluids, as well as vasopressors and inotropes (5). During the first 24h after ROSC, appliance of 4-5L crystalloid solution is correspondent to a reduced incidence of acute kidney injuries (AKI) (40). Regarding perfusion maintenance provided by vasopressors and inotropes in hypotensive shock, a Cochrane review including 28 RCTs did not find any mortality benefit in any drug (41). Noradrenaline is preferred over adrenaline, since adrenaline may cause a refractive shock (42). Inotropic support should be given by dobutamine (43).

Concerning the heart rate, one retrospective study presented that tachycardia may be an indicator of poor outcome (44). Whereas bradycardia has shown favorable outcomes, and should be left untreated, if an adequate perfusion with normal lactate and oxygenation levels is given (45). Especially for TTM patients, bradycardia is a good prognostic factor (45). TTM will be emphasized later in this review paper.

Further cardiac arrhythmias may be caused by impaired electrolyte levels, especially altered potassium levels. The ERC recommends to achieve normal potassium values between 4.0 and 4.5 mmol/L (5). Hypokalemia was related to ventricular arrhythmias, while hyperkalemia has revealed fatal results (46).

In persistent cardiogenic shock and treatment failure with vasoactive drugs and inotropes, mechanical circulatory support may be considered (47). Mechanical circulatory support may be necessary for approximately 10-15% of "out-of-hospital cardiac arrest (OHCA)" (5) patients experiencing persistent "cardiogenic shock" (5,48). Comparisons of different possibilities of mechanical circulatory support showed that IMPELLA appears to be superior to IABP (49).
A preventive measurement for mechanical circulatory support includes implanted cardioverter defibrillators, which are indicated as primary prevention in patients with chronic heart disease or secondary after a life-endangering arrhythmic event (50,51).

Disability

The point disability focuses mainly on the neurological impact of the post cardiac arrest patient. For these patients convulsions are described in around 20-30% of cases admitted to an ICU, which is a sign of severe hypoxic- ischemic brain injury (5). Electro-encephalography (EEG) is widely used for diagnosis of seizures and monitoring the subsequent treatment effects, with questionable cost-effectiveness in some settings (5). Epileptiform patterns in EEG occur equally often like clinical convulsions (52). The dominant type of seizure in "post-cardiac arrest patients" (5), is myoclonus, which is defined as sudden involuntary muscle contractions (53,54). Myoclonus may be divided into generalized, focal and multifocal forms, which usually develop all along the first two days after cardiac arrest (55). In general, myoclonus is often linked to an unfavorable prognosis, although there are instances where cardiac arrest survivors have a positive outcome (56). In EEG myoclonus manifests as "synchronous time-locked discharges or burst suppression" (5,57), which confirms its cortical origin (58).
A certain type of myoclonus is Lance-Adams Syndrome, which can be observed in patients which regained consciousness (59,60). Lance-Adams syndrome usually impacts the limbs and is induced by sensory or motor stimulations (60), which also may become chronic (56). Early signs of this syndrome may include generalized myoclonus in unconscious patients (5). Lance-Adams syndrome is normally linked to a good outcome for post cardiac arrest patients (57,59).
In post resuscitation care, EEG is not just a diagnostic and monitoring tool, but also used for prognostication, which will be emphasized more deeply later in this review. Bad prognostic signs in EEG include suppression patterns or suppressed background without reactivity (57,61). Furthermore, a bad prognostic sign may be an early onset (< 24h) of electrographic seizures, before a continuous background activity has been recovered.

In these patients, drugs may affect the seizures and further diagnostics like somatosensory evoked potentials (SSEP), serum NSE and neuroradiology may be required (5).

The 2021 ERC post-resuscitation care guidelines do not recommend a routine seizure prophylaxis (5). First line treatment in symptomatic, post cardiac arrest patients include Levetiracetam or Sodium Valproate in combination to sedative drugs, although there is limited evidence (62). The usage of Propofol and Benzodiazepines during mechanical ventilation and TTM is pervasive in ICU treatment around the world. These medications may, depending on their dosage, suppress myoclonus and epileptiform activity in EEG. As a result, seizures may be masked by sedation, and therefore manifest just as the sedation stops (5). Furthermore, antiepileptics and sedative drugs may delay the recovery of cardiac arrest survivors and prolong their hospitalization (63). Phenytoin is not suitable for treatment of status epilepticus due to its negative inotropic and vasodilative effect (64), whereas Thiopental and Phenobarbital are suitable just for selected patients (5).

Besides seizure control, temperature control or TTM plays a major role under the point disability, which is frequently discussed. "Targeted temperature management (TTM)" (5) is suggested for patients who remain unconscious after ROSC. The ERC recommends that TTM should be introduced immediately to a degree of 32ºC-36ºC for at least 24h, regardless the initial heart rhythm (5,65). Mild induced hypothermia is considered as neuroprotective, although the precise mechanisms behind these effects remain unclear (66,67). A study from 2014 investigating the cytokine response in TTM performed on OHCA patients, did not show any difference regarding inflammatory cytokine levels in patients treated or not treated with TTM (68). Other studies suggest that the faster the onset of TTM, the better the outcome considering the 90-day survival (5,69). However, pre-hospital onset of TTM has not shown any significant effect on the outcome, quite the contrary. The usage of pre-hospital cold fluids may cause hypothermia which is associated with re-arrest (5,70).

The optimal temperature for TTM is an assumption based on the variety of today's study results (5). Temperature levels lower than 33ºC were associated with bradycardia, elevated lactate levels and higher cardiovascular SOFA scores (71,72). Cognitive function, neurological outcome and brain injury bio markers do not seem to be related to the temperature levels in TTM (5). The optimal duration of TTM remains to be discussed, and is assumed to be at approximately 24h, taking into account possible adverse effects of hypothermia (5).

Randomized trials showed no difference between longer (72h) and shorter (24h) durations of TTM in terms of the patient's outcome (73). Fortunately, there are few contraindications for TTM. Contraindications include just severe cardiovascular impairment, which therefore leads to a higher temperature target during TTM (71).

A general recommendation of the ERC in the temperature control of a post cardiac arrest patient includes avoidance of fever (> 37.7ºC) for at least 72h for patients who stay unconscious after ROSC (5). Fever mostly appears in the first three days after successful cardiopulmonary resuscitation, but is connected to an unfavorable neurological outcome (74). Furthermore, rebound hyperthermia after TTM is correlated with worse consequences in patients surviving cardiac arrest (75).

Other therapies, to improve neurological aftereffect following cardiac arrest, have been investigated in experimental settings. Animal models have demonstrated that volatile anesthetic drugs contribute to enhanced cardiac and cerebral recovery. (76). Additionally, specific extracorporeal life support concepts have shown good neurological survival after cardiac arrest in humans, and are undergoing additional clinical assessment (77–79).

General intensive care management

The usual length of hospitalization is highly individual and depends on the time of awakening from coma. This period may last from a few days, up to several months. Most post cardiac arrest patients need extensive pain management and sedation. Therefore, it is endorsed to use "short acting sedatives and opioids" (5). In a study from 2012, the combination of Propofol and Fentanyl was compared with Midazolam and Fentanyl, with a mixed result. Propofol and Remifentanil showed a briefer time of awakening, but on contrary had an increased need of noradrenaline, in the context of therapeutic hypothermia (80). Especially in TTM, since shivering is a common side effect, sedation and pain management may be required. Even though shivering is a common side effect, neuromuscular relaxation is not routinely recommended during TTM, and should just be considered in patients with severe shivering or ARDS (81,82). Patients require to be treated in a 30º head-up position during their ICU stay. This position can help to reduce "intracranial pressure"(5) and lower the risk of aspiration or ventilator-associated pneumonia (5,83). Despite the fact that ICU patients are vulnerable to developing pneumonia, it is not recommended to use antibiotics on a routine basis (5).

Indeed, antibiotics may decrease the frequency of ventilator associated pneumonia, but there are no additional benefits of routinely antibiotic use (84). Therefore, antibiotics are just indicated during ICU treatment if the patients show suspicious pulmonary infiltrates (5).

During ICU stay, patients are at risk to develop stress ulcers (5). Since there is a significant number of cases under anticoagulation and antiplatelet medication, it is reasonable to "provide stress ulcer prophylaxis routinely" (5), in order to prevent gastrointestinal bleeding (15,85,86). Anyhow, routine stress ulcer prophylaxis does not decrease the mortality in ICU patients (87,88).

Moreover, it is recommended to provide a routine deep vein thrombosis (DVT) prophylaxis in ICU patients (89,90). The guidelines claim that: "antiplatelet drugs do not prevent DVTs" (5,91). Patients who receive therapeutic hypothermia treatment after "out-of-hospital cardiac arrest (OHCA)" (5) are particularly susceptible to the development of deep vein thromboses (DVTs) (92). Therefore, an individual treatment approach for the prevention of DVTs in ICU patients is crucial, and should follow the general ICU recommendations (89).

Another important point under the perspective of general intensive care management is the target blood glucose level. According to the given guidelines, blood glucose levels should be sustained in the range of 7.8-10 mmol/L or 140-180 mg/dL (5). Hyperglycemia is common after OHCA, and may be treated with insulin infusion if required (5,46). On the other hand, it is important to avoid hypoglycemia <4mmol/L or <70 mg/dL (93). Since hypoglycemia is harmful for critical ill patients, it should be treated with glucose containing solutions (94). However, for patients suffering from brain injury, glucose containing solutions are not routinely indicated (95). Enteral nutrition is recommended for ICU patients. For a person treated with TTM it is recommended to start nutrition via a nasogastric tube, beginning with low rates and increasing them as the body temperature increases (5,96).

Prognostication

Most patients suffer from hypoxic ischemic brain injury after OHCA. Nevertheless, most of these patients do not die from brain death, but from withdrawal of life-sustaining therapy during their ICU stay (5). Prognostication is a predominant part of post resuscitation treatment in comatose patients. This approach includes the evaluation of the patient via "clinical examination, electrophysiology, biomarkers, and imaging" (5).

It is crucial to emphasize that no single predictor is completely accurate, highlighting the necessity of a multimodal neuro-prognostication approach (5). During this multimodal approach it is particularly important to keep an eye on several factors. One problem may occur as self-fulfilling prophecy bias could lead to premature conclusion on the patients outcome due to falsely optimistic or pessimistic predictions (5,97,98). This is may be the case especially in TTM patients before rewarming (5). Since a too early assessment may proof wrong later on during the clinical course (99), the minimal time period for assessment of neurological prognostication is 30 days (100). Reassessment should be considered three or six months after the incident (101).

According to Nolan et al. cardiovascular instability "is the second most common cause of in hospital cardiac death" (5,11). A phenomenon which may be observed in roughly 16% of cardiac arrest patients is the "death after awakening". Patients who regain consciousness following cardiac arrest may succumb to non-neurological causes of death thereafter (5). This phenomenon is more common in IHCA than in OHCA and occurs approximately 3-18 days after regaining consciousness (102).

The process of prognostication starts with a detailed clinical examination. Major parts of the clinical examination are based on the pupillary light reflexes, corneal reflexes, and assessment of myoclonus. Benefits of the clinical examination include that they are cheap and require minimal equipment. On the contrary, they are prone to subjectivity and may be interfered by sedatives, opioids or relaxants (5). Poor outcome predictors during clinical examination include bilateral absence of pupillary reflex, "bilateral absence of corneal reflex, […] presence of myoclonus" (5), and a lack of motor response. The "bilateral absence of pupillary reflexes" (5) has a rather low specificity at 20-25% in the first hours, which constantly rises up to 100% after 96h (103). An advantage is that the assessment is very inexpensive, but to the detriment of objectivity (104). Since this assessment is very subjective, analysis of the pupillary reflexes should be assessed via quantitative pupillometry. Quantitative pupillometry assesses the reduction of the pupillary size in percent, and consequently provides a quantitative and objective measurement of pupillary response (105). From this percentage reduction obtained, as well as from pupillary size and constriction/dilation velocity, the neurological pupillary index (NPi) may be calculated. Nolan et al. state that: "the NPi can predict unfavorable outcome with no false positive results from < 24h up to 72h after ROSC" (5), where NPi > 3 is defined as normal. Major limitations include that the threshold level is variable and it is very cost expensive (103).

Additionally, another poor prognostic factor is the bilateral absence of corneal reflexes. This absence shows 100% specificity but only 25-40% sensitivity at 72h after ROSC (103). During this examination, additional attention should be raised on the medications of the patients, since the corneal reflex is "prone to interference from sedatives, opioids or muscle relaxants" (5,106).

Furthermore, the occurrence of myoclonus within 96h after arrest, particularly status myoclonus within 72h after ROSC is a poor prognostic sign which should be further investigated via EEG (103,106). Moreover, the absence of extensor motor response showed a lower potential of complete rehabilitation (103). The motor response is evaluated via the Glasgow coma score (GCS). Considering the motor part, $M \leq 3$ may be used as a criterion to perform further prognostication after cardiac arrest. Special awareness should be raised by the possible interference with muscle relaxants (107).

An essential part of prognostication in "post cardiac arrest patients" (5) is the neurophysiological assessment. Performing an electroencephalogram (EEG) assessment is recommended for patients who remain unconscious after the "return of spontaneous circulation (ROSC)" (5). Under the aspect of EEG, prognostication is mainly based on the background activity, which is categorized in continuous, discontinuous, burst suppression, and suppression (108). Continuous background activity is considered as self-explaining and will not be further discussed. Discontinuous background activity is defined as > 10% suppression periods, but is thought to have low to inconsistent performance after ROSC (109). Burst suppression is characterized as the alternation between suppression and bursts, accounting for 50-99% of the recording (110). In that case, so called "identical bursts" show a poor prognosis (111). As in some other prognostic factors, burst suppressions may also be interfered with sedative drugs, which should raise special awareness in the EEG assessment (5). Suppression is defined as a background activity < 10µV, which is usual throughout the first 24h after the incident. If the background activity remains below 10µV for more than 24 hours after the "return of spontaneous circulation (ROSC)" (5), it is regarded as a reliable indicator of a poor prognosis (5). This conclusion is drawn from only one study, which reported false positive results (5,112). EEG reactivity is defined as "a measurable change in amplitude upon external stimulation" (5), but has a discussable prognostic significance since its performance varies between studies (5,103). Following cardiac arrest and the "return of spontaneous circulation (ROSC)" (5), the electroencephalogram (EEG) typically exhibits suppression initially but recovers to a "continuous normal voltage pattern" (98) within 24 hours (5).

Therefore, the restitution time correlates to the outcome (5,108). To guarantee an accurate prognostication, TTM and sedation of the patient must be contemplated as well (5).

In summary, malignant EEG patterns and poor prognostic factors considering the neurophysiology include the following:

According to the guidelines, the presence of a "suppressed background, with or without periodic discharges and burst suppression" (5), indicates a negative prognosis (5). Furthermore, unequivocal seizures in the first 72h after ROSC, and absence of background activity may lead to the assumption of a poor prognosis. Under the point of absent background activity it needs to be mentioned, that this pattern has a high sensitivity but low specificity in the first 24h after ROSC, which increases in time respectively.

Moreover, Nolan et al. state that "bilateral absence of somatosensory evoked cortical N20-potentials" (5) are considered as a poor prognostic sign, but have to be assessed in the scope of other clinical examination results as well as in the use of neuromuscular relaxants (5). Additionally, some superimposed patterns on EEG may show poor prognosis, whereas "Stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs)" have no proven prognostic significance (5,113). In this case, superimposed patterns here include "periodic discharges, sporadic epileptiform discharges, electrographic seizures and electrographic status epilepticus" (5).

Periodic discharges refer to waveform patterns that occur in a repetitive manner, with measurable intervals between each discharge (110). When accompanied by a "continuous and reactive EEG-background pattern" (5), periodic discharges should not be seen as indicative of negative results (57).

"Sporadic epileptiform discharges" (5) are described as "sharp waves or spikes resembling those seen in patients with epilepsy, but without the regularity of a periodic pattern" (5). There is a lack of data to support the notion that sporadic epileptiform discharges reliably indicate a poor neurological prognosis (97).

Electrographic seizures are usually unequivocal seizures , which are defined by the "American clinical neurophysiology society (ACNS)" (5) as "generalized rhythmic spike-and wave discharges with a frequency of > 3Hz or clearly evolving discharges of any type > 4Hz" (5,110). Generally speaking, seizures have a high specificity for a unfavorable outcome at any time post ROSC (114). "Electrographic status epilepticus (ESE)" (5) is officially characterized by the ACNS as "an electrographic seizure for > 10 continuous minutes or for a total duration of > 20% of any 60-minute period of recording" (5).

Following cardiac arrest, in most cases, the presence of epileptiform status epilepticus (ESE) is connected to an unfavorable prognosis. Taking into account, that some studies also showed results with good outcome after ESE, awareness should be risen to the fact that in these studies the definition of ESE was not equal (5,61,115,116). Due to this specific reason, the European Resuscitation Council (ERC) guidelines are advising against using the term "status epilepticus". Instead, they recommend assessing the electroencephalogram (EEG) for the presence of superimposed discharges or clear-cut seizures, following the standardized ACNS terminology (5).

Another part of the neuro-prognostication is the assessment of evoked potentials, which are frequently classified as “somatosensory evoked potentials (SSEP)” (5), “visual evoked potentials (VEP)” (5) and “auditory evoked potentials (AEP)” (5). VEP and AEP showed no evidence-based results until this point, for that reason they are not suitable as a prognostic tool. SSEPs are usually triggered by median nerve stimulation, and signals get recorded at “peripheral brachial plexus, cervical level, subcortical level and at the level of sensory cortex” (5). At any given time, the “bilateral absence of short latency N20 potentials” (5) is regarded as an unfavorable prognostic indicator (5). The measurement of SSEPs show very little limitations, since the only known drug depressing it are barbiturates (117).

As part of the multi-modal prognostic approach, also specific biomarkers may be considered. The main advantage of biomarkers is that they deliver prognostic values with no regard whether the patient is sedated or not. Limitations include mainly their availability and the lack of laboratory references, since there have been just insufficient study populations, or the results lack external validation. As part of sequential measurements, one commonly employed biomarker is neuron-specific enolase (NSE) (5). NSE is contained in erythrocytes, which provides the probability of false positive results in case of hemolysis. Since NSE has a longer elimination half-life than hemoglobin, levels of NSE may be increased longer than hemolysis actually persists (118). After 24h the NSE levels usually decrease in patients with a suspected good outcome. Instead, increasing values between 24h and 48h or 72h, when combined with elevated levels subsequent to 48h and 72h are associated with a poor prognosis (5). Other biomarkers have also been taken into consideration, just as: “S100B, glial fibrillary acidic protein (GFAP), serum tau protein or serum neurofilament light chain (Nfl)” (5). S100B did not show any significant value, and showed no connection to elevating or decreasing NSE values (119). A previous observational study has shown, that GFAP displays poor prognostic values after 48h +/- 12h with 100% specificity but just 21.3% sensitivity (120).

Additionally, elevated serum tau protein levels have been associated with unfavorable neurological outcomes after six months, exhibiting 100% specificity but varying sensitivity rates up to 42% (121). Conversely, the evaluation of neurofilament light chain (Nfl) has not yielded consistent evidence across multiple studies (122). Given the above-mentioned facts, there is no recommendation of neither S100B, nor GFAP, serum tau protein nor Nfl assessment in the 2021 ERC post-resuscitation care guidelines (5).

Additionally, one main part of the multimodal neuro-prognostication approach is the assessment via imaging methods, particularly "computed tomography (CT)" (5) and "magnetic resonance imaging (MRI) of the brain" (5). The 2021 ERC post-resuscitation care guidelines suggest that prognostic imaging should just be performed in experienced centers, since its major limitation, besides the fact that it is no bedside technique, is the lack of standardization. Therefore, as with other prognostic tools, it is recommended that also imaging should be considered as a part of the prognostic entity, and prognostication should not be based exclusively on imaging methods (5). An unfavorable outcome may be assumed, in the case of signs of generalized brain edema in CT. Generalized brain edema may manifest as a "reduction of the grey matter/white matter ratio" (5) 72h after ROSC, which may occur early in patients with "hypoxic- ischemic brain injury" (5,123). There has been evidence from one study, which confirmed 100% specificity already 1h after ROSC, nevertheless, the threshold levels are varying from study to study (103).

As a counter part to the CT, MRI may also show reasonable testimony for a negative outcome. Significantly, the identification of "extensive diffusion restriction on diffusion-weighted brain MRI (DWI)"(5) performed 2-7 days after the "return of spontaneous circulation (ROSC)" (5) is highly specific for an unfavorable prognosis (124). For better standardization and semiquantitative analysis of DWI changes the apparent diffusion coefficient (ADC) has been established, but its prognostic significance varies between studies (103).

Prognostic strategy

It is recommended to start the process of prognostication with a detailed clinical examination, to confirm or rule out hypoxic ischemic brain injury or even subsequent brain death (125). The patient is considered brain death if certain criteria are met, such as: external stimuli do not cause awareness or arousal, nonreactive to light stimulus fixed or dilated pupils, ocular and corneal reflexes may not be seen, and gag reflex, cough reflex and facial movements are absent to respective stimuli.

Moreover, there are no peripheral movements of the limbs after noxious stimulation, and during apnea test there are no spontaneous respirations at the targets of pH < 7.30 and $PaCO_2$ > 60 mmHg (5). The clinical evaluation to confirm brain death can be impeded by "[…] sedation, hypothermia, severe hypotension, […] and metabolic or respiratory abnormalities" (126). Consequently, it is advisable to postpone the assessment until these factors can be ruled out (127).

As above mentioned, a weak motor response has a high sensitivity for a poor outcome, as well as, bilaterally absent N20 SSEP or absent pupillary light reflex (5,128,129). In order to avoid falsely pessimistic prognostication, signs of good outcome should be actively assessed, taking into account a benign EEG within 24h after ROSC, or low respectively decreasing NSE after 24h, 48h and 72h (5,107,109). It is important to mention, that these positive prognostic signs may mislead prognostication, since they may coexist with bad prognostic signs (130).

Withdrawal of life-sustaining therapy

In a population of "cardiac arrest patients" (5), after ROSC the primary origin of mortality is secondary in the ICU due to withdrawal of life-sustaining therapy (131). For decision making, in terms of WLST, the decision is primarily grounded on the assumption of an unfavorable neurological prognosis (5). Besides the predicted neurological outcome several other factors should be considered as well, such as: age of the patient, general health of the patient, including co-morbidities and organ function in general. Furthermore, the preferences of the patient have to be respected (5). To prevent falsely pessimistic conclusions, prognosis should be postponed pending a minimum of 72h after ROSC (132). It is crucial to involve the relatives of the patient into the current status, since the decision of WLST is always fatal for the patient (5).

Long-term outcome after cardiac arrest

Generally speaking, patients who remain unconscious after one month rarely recover and therefore have a poor prognosis (133,134). A great part of cardiac arrest survivors suffers from long term cognitive impairments. Even though, during the first three months most cognitive recovery occurs. Before discharge, both physical and non-physical impairments should be evaluated, and their progress should be monitored three months after (5). This evaluation should encompass cognitive screening, assessment of emotional issues and fatigue, and offer information and support to both the survivor and their family members (135).

Organ donation

If the legal and ethical obligations of the local institution are fulfilled, organ donation should be contemplated for patients who have been diagnosed with brain death after the “return of spontaneous circulation” (5,136,137). If the neurological criteria are not met, organ donation should still be taken into account in ventilated patients before WLST or just after cardiac arrest occurs (5).

Discussion

The post resuscitation care guidelines provide guidance through an extremely important and particularly difficult part of critical care. The ERC consists of a broad committee of experts from all over the world, who are always providing the current expert opinion in the guidelines. Since false or inconsequent decisions in that period may end fatal for the patient, new versions of the guidelines require confirmation or new findings in other studies. Overall, the ERC's post-resuscitation guidelines are evidence-based, and provide a useful framework for managing patients who suffered from cardiac arrest. However, there are some areas where the guidelines could be improved or further developed.

One area where the guidelines could be upgraded is in the use of advanced hemodynamic monitoring tools as for example cardiac output monitors or transpulmonary thermodilution devices. While the guidelines mention the importance of monitoring hemodynamic parameters, they do not provide clear guidance on when or how to use these more advanced tools.

Another area where the guidelines could be further developed is in the treatment of patients with severe “hypoxic-ischemic brain injury” (5). While the guidelines recommend targeted temperature management and seizure prophylaxis for these patients, there is limited guidance on other aspects of care such as nutrition, pain management, and psychological support. Under the aspect of TTM, the current ERC post-resuscitation guidelines made significant improvements compared to the previous guidelines in suggesting a specific target temperature range and moreover, providing suggestions for enteral nutrition during TTM which was not further described in previous guidelines. Furthermore, the process of neuroprognostication got significantly improved by suggesting the usage of EEG. This may help especially in treating seizures whilst avoiding routine seizure prophylaxis. Although there is some improvement in apparated diagnostic tools, the 2021 ERC post resuscitation care guidelines emphasize once more the importance of a multimodal neuroprognostication approach, including clinical examination, electrophysiology, biomarkers, and imaging.

A further improvement is the suggestion for using short acting opioids and sedatives, which showed better outcomes and shorter periods of need for intensive care.

Overall, the ERC's post-resuscitation guidelines provide a solid foundation for managing patients after cardiac arrest, but there is room for further development and refinement in certain areas. Healthcare providers should consistently stay updated with the latest guidelines and adapt their practices accordingly to deliver optimal care to critically ill patients.

Conclusion

To conclude all previously discussed recommendations in the 2021 post-resuscitation care guidelines, there is to point out that post-resuscitation care should be started for all patients immediately after ROSC using the ABCDE approach (5).

A patent airway needs to be established in every patient after ROSC, if not established during the process of resuscitation. Airway management may be provided by endotracheal intubation or supraglottic devices from skilled personnel. Correct tube placement needs to be confirmed via "waveform capnography" (5).

In the absence of blood oxygenation measurement, it is recommended to administer 100% oxygen and adjust it to achieve a saturation level of 94-98% or a PaO_2 between 10-13 kPa or 75-100 mmHg based on "arterial blood gas analysis" (5) after it is available. Hypoxemia needs to be avoided (5). Mechanically ventilated patients should be treated with a "lung protective ventilation strategy" (5) with a "tidal volume of 6-8 mL/kg ideal bodyweight" (5). Normocapnia should be targeted following ROSC to $PaCO_2$ values of 4.5-6.0 kPa or 35-45mmHg, adjusted to the patient's body temperature respectively, especially in TTM (5).

Emergent cardiac catheterization laboratory evaluation needs to be performed in all STEMI patients, but also without ST-elevation if other causes are very unlikely (5).

To prevent hypotension ("mean arterial pressure < 65 mmHg" (5)), attain sufficient urine output (> 0.5 mL/kg/h), and reduce lactate levels, it is essential to provide hemodynamic monitoring through an arterial line for all patients (5). Perfusion should be maintained with "fluids, noradrenaline and/or dobutamine" (5). During TTM, bradycardia may be left untreated if adequate perfusion is provided. Steroids are not routinely recommended, whereas it is suggested to avoid hypokalemia.

Furthermore, it is favored to perform echocardiography as soon as possible to assess the cardiac function and cardiac pathologies. In persistent cardiogenic shock, mechanical circulatory support may be considered (5).

To diagnose seizures and monitor treatment effects EEG should be used. The ERC suggests against routine seizure prophylaxis, but to treat seizures with levetiracetam or sodium valproate in combination with sedative drugs as a first-line measure (5).

For any unconscious patient following cardiac arrest, "targeted temperature management" (5) is recommended, with a suggested temperature range therefore is 32ºC-36ºC for at least 24h. The goal is to avoid fever > 37.7 ºC for at least 72h. The initiation of hypothermia using pre-hospital intravenous cold fluids is not recommended (5).

Moreover, the recommendations suggest using short acting sedatives and opioids, and avoiding routine use of neuromuscular blocking during TTM. Stress ulcer prophylaxis, as well as deep venous thrombosis prophylaxis should be provided, and blood glucose levels should be targeted at a level of 7.8-10 mmol/L or 140-180 mg/dL. During TTM enteral feeding should be started at low rates and be continuously increased as the body temperature rises. It is not recommended to routinely use antibiotic prophylaxis (5).

Neurological prognostication plays a major role in post-resuscitation care, and should include "clinical examination, electrophysiology, biomarkers, and imaging" (5). Nolan et al. emphasizes that "no single predictor is 100% accurate" (5), every result has to be evaluated in a greater context to avoid falsely negative or positive expectations for relatives and professionals (5).

Clinical examination may be interfered by sedatives, opioids, or muscle relaxants, which must always be considered. Poor outcome predictors include: The "bilateral absence of pupillary and corneal reflexes" (5), along with myoclonus occurring within the initial 96h after the "return of spontaneous circulation (ROSC)" (5), or status myoclonus within 72h, should be noted (5).

For neurophysiologic assessment it is endorsed to perform an EEG in unresponsive patients. Highly malignant EEG patterns are characterized by a suppressed background activity, accompanied by periodic discharges or burst-suppression (5). Unequivocal seizures within 72h, absence of background reactivity and "bilateral absence of somatosensory evoked cortical N20-potentials" (5) indicate a poor prognosis (5).

The most reliable biomarker for predicting neurological outcome is NSE, and poor prognosis may be predicted in increasing values after 24h, 48h or 72h. Poor outcome predictors from imaging methods include generalized brain edema in CT or extensive diffusion restriction in MRI (5).

After assessing the neurological outcome predictions, if a poor prediction is made, a potential "withdrawal of life-sustaining therapy" (5) should be discussed. The decision should not rely exclusively on the objective degree of brain injury but should reflect the patient's overall situation, including preferences, age, and comorbidities. Communication between professionals and relatives is crucial in making treatment decisions.(5).

Organ donation may be considered in patients who fulfil the brain-death criteria, or in mechanically ventilated patients after the decision of therapy withdrawal, following the local ethical and legal requirements (5).

The guidelines recommend considering organ donation in patients who meet brain-death criteria or who have life-sustaining therapy withdrawn.

In patients with a good neurological outcome, physical and cognitive assessment should be performed before discharge and at a follow-up three months after discharge (5).

As a prospective for the future, more data must be gathered regarding all parts of this paper, to provide more evidence for the recommendations presented. This hopefully increases the survival rate among the population after cardiac arrest. Since nowadays and probably also in the near future the most efficient treatment for cardiac-arrest patients is to prevent cardiac arrest in the first place.

Summary

Every patient should receive post-resuscitation care, starting immediately after ROSC. Optimally in a specialized cardiac arrest center (5). Following ROSC, ABC approach should be used to stabilize the patient. This includes insertion of an advanced airway, oxygen titration to 94-98%, proper ventilation to achieve normocapnia, and establishment of a reliable intravenous or intraosseous access to restore normovolemia and avoid hypotension (5).

Patients showing ST-elevation on the post-“return of spontaneous circulation (ROSC)” (5) “electrocardiogram (ECG)” (5) and those with suspected cardiac origin but without ST-elevation should undergo prompt evaluation and intervention in the cardiac catheterization laboratory (5). Patients who remain comatose after the “return of spontaneous circulation (ROSC)” (5), irrespective of the initial rhythm or the location of the cardiac arrest, should receive targeted temperature management (5).

Multimodal neurological prognostication including “clinical examination, electrophysiology, biomarkers, and imaging” (5) may help in making further treatment plans.

Before discharge, physical and non-physical impairments should be assessed, for further rehabilitation. Every patient should be followed up after three months, reassessing possible impairments (5).

Keywords: Cardiac Arrest, Intensive Care, Multimodal Neuroprognostication, Targeted Temperature Management, Seizure Prophylaxis, Hemodynamic Monitoring, Follow-Up Assessment

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Table of figures

Curriculum Vitae

This graduation thesis was written by Lucas Frederic Schlagenhauf, born on 03.09.1998 in Tübingen, Germany. In 2016 he graduated from Gymnasium Balingen (high school) with A-levels in Physical Education and Physics. Following high school, he visited a school for emergency medical staff of the German Red Cross (DRK Landesschule Pfalzgrafenweiler and Akademie Diemed), which he finished with outstanding success. Until September 2017, he volunteered for the emergency medical services of the German Red Cross in his hometown Balingen, Germany. After one year of full-time volunteering, Lucas Frederic started his medical studies at the University of Rijeka, Faculty of Medicine, in 2017. Since 2017, Lucas Frederic Schlagenhauf has completed every year of his study in the standard period with excellent grades. During his studies, he gained practical experience during internships at Kantonsspital Frauenfeld and Flurystiftung Spital Schiers (Switzerland) in the departments of Surgery and Anesthesiology. Until this day, he is still volunteering at the emergency medical services in his hometown. After his graduation in summer 2023, he will start his residency at the Department of Anesthesiology at Klinikum Stuttgart.