Translational Research: An Ongoing Challenge in Cardiac Arrest

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…time is necessary for teachers to teach, for learners to learn, and…for the education process to be long enough for major educational objectives to be met.

M. H. Weil (1927–2011).

23.1 Background

Cardiovascular disease is the first cause of mortality in developed countries. The heart responds to many pathological conditions with hypertrophic growth by enlarging individual myocytes to augment the cardiac pump function and to decrease ventricular wall tension. Initially, such cardiac elements are often compensatory, but as time progresses these changes evidence subclinical and/or symptomatic grading of dysfunction. Cardiac remodeling and hypertrophy are the major predictors leading to heart failure and dangerous arrhythmias, ultimately determining a condition of sudden cardiac death (SCA) [1].

Advances in medicine emerge from molecular and genetic studies of cardiovascular disease in experimental models and in patients at risk. In the last 20 years selected therapeutic targets have emerged and have a tangible translational potential given the available pharmacologic agents that could be readily evaluated in human observations and in clinical trials [2]. Indeed, there is growing evidence of the importance of translational science and medicine, according to the bench-bedside concept, in the improvement of patient outcome, even though the definitions of translational science, translational medicine, and clinical medicine need to be further clarified. In other words, clinical and translational medicine are expected to include scientific and regulatory investigations to translate preclinical research to clinical application with a specific emphasis on new biotechnologies, biomaterials, bioengineering, disease-specific biomarkers, cellular and molecular

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medicine, 'omics science, bioinformatics, applied immunology, molecular imaging, drug discovery and development, and health policy regulation.

Translational medicine should meet the increasing demand for expanding the biomedical workforce and education programs that attract and retain young people to the translational biomedical science. In the present perspective we selected a series of contributions, a sort of decalogue about clinical and translational medicine, to support the efforts of scientists and clinicians to understand better the mechanisms of biological and cellular disorders in animal models, in human being studies, and in the clinical randomized controlled trials. This dynamic concept is maintained and supported by continuing education and training programs to save lives. The central pillar to implement guidelines and ultimately the clinical outcome is based on the importance of translation research to guide future directions and perspectives in the field of resuscitation science.

23.2 Sudden Cardiac Arrest

Cardiac arrest is a dramatic condition leading to sudden death if two determinant interventions, basic life support, and early defibrillation, cannot be performed on time. In coincidence with the decreased mortality from coronary artery disease, there is evidence pointing toward a decrease in rates of SCA in the United States during the second half of the twentieth century. However, the alarming rise in prevalence of obesity and diabetes in the first decade of the new millennium both in the United States and worldwide, would indicate that this favorable trend is unlikely to persist [3]. SCA is a complex phenotype, and determinants are likely to be multifactorial. More recently, an additional significant genetic component has been considered in the context of multiple cardiac conditions, comorbidities, as well as epidemiologic and environmental factors [4].

In real life, the critical time intervals, in part based on the Utstein templates for documenting the sequence of interventions [5], begins with the call for emergency assistance, documents arrival time of rescuers including bystander, the interventions performed by the emergency medical responders at the site of the victim, and the sequences of interventions that follow. In the instance of ventricular fibrillation (VF), automated external defibrillation (AED) has enfranchised non professional rescuers to reverse VF. Current evidence supports the value of a well-organized program of bystanders initiated CPR and, in some settings, public access defibrillation [6]. Within the past year, the Chain of Survival has been amended to include an additional link, namely post-resuscitation management [7]. The therapeutic management of patients that recover spontaneous circulation, based on life support measures and a series of actions based on "clinical judgment," might not be the best way to treat patients with post-cardiac arrest syndrome. The use of the goal-guided protocols to manage these patients including therapeutic measures of proven efficacy, such as mild therapeutic hypothermia and early revascularization, when indicated, can improve the prognosis considerably in these patients [8].

In this sense, the term cardiopulmonary and cerebral resuscitation proposed by scientists and practitioners might be more appropriate.

An alternative approach to improve survival from SCA is to use the continuous quality improvement (CQI) approach, a process often used to address public health problems. CQI advocates that one obtains baseline survival rate for his/her field of action and uses this baseline data to achieve improvements under a continuous re-evaluation process. Using CQI, significant improvement in survival of patients with out-of-hospital cardiac arrest has been achieved. For example, Drs. Ewy and Sanders from Arizona recommended that all emergency medical systems determined their baseline survival rates from cardiac arrest and considered implementing the CQI approach if the community did not obtain a neurologically intact survival rate of at least 30 % [9].

The translation of basic science into everyday clinical practice may be difficult and it still remains a major issue in contemporary medicine. For this purpose, a new discipline has been created, the translational research, which has been trying to assess the discrepancies between research and clinical field. Translational research is a continuum of research in which basic science discovering is integrated into clinical applications and clinical observations are used to generate scientific topics of basic science [10]. Research to advance cardiac arrest knowledge is a difficult task. Experts set up a series of guidelines that represent a keystone for educational needs and evolving technology.

23.3 Decalogue of Translation Research

The official definition of translational research as stated by the National Institute of Health (NIH) is as follows: "Translational research transforms scientific discoveries arising from laboratory, clinical or population studies into new clinical tools and applications that improve human health by reducing disease incidence, morbidity and mortality" (modified from "Transforming Translation—Harnessing Discovery for Patient and Public Benefit"—Report of the Translational Research Working Group of the National Cancer Advisory Board, US NIH, 2007).

Translational research moves in a bidirectional manner from one type of research to another—from basic research to patient-oriented research, to population-based research, and back—and involves collaboration among scientists from multiple disciplines. Research in resuscitation training should be considered an example of translational science, where rigorous studies of skill acquisition with outcome measures serve to transfer the results to the clinical environment for analysis of their impact upon patient care [11]. Medicine moves basic biological discoveries from the research bench to the patient-care setting and uses clinical observations to inform basic biology. It focuses on patient care, including the creation of new diagnostics, prognostics, prevention strategies, and therapies based on biological discoveries. Bioinformatics involves algorithms to represent, store, and analyze basic biological data, including DNA sequence, RNA expression, and

Table 23.1 Decalogue of translation research

Pharmacology, regenerative medicine, and tissue engineering
Inflammation during resuscitation
Oxygenation during and after cardiopulmonary resuscitation
Cardioprotection
Vasopressor agents for cardiopulmonary resuscitation
Amplitude Spectrum Area (AMSA)
Na^+/H^+ channelpathies and pharmacological defibrillation
Brain ischemia/reperfusion
Therapeutic hypothermia
Kynurenine pathway

protein and small-molecule abundance within cells. Translational bioinformatics spans these two fields; it involves the development of algorithms to analyze basic molecular and cellular data with an explicit goal of affecting clinical care. In this section of the book the authors summarize some experimental and clinical aspects of translation research in the field of resuscitation (Table 23.1).

23.3.1 Pharmacology, Regenerative Medicine, and Tissue Engineering

Regenerative medicine is a rapidly evolving multidisciplinary, translational research field whose explicit purpose is to advance technologies for the repair and replacement of damaged cells, tissues, and organs [12]. Scientific progress in the field has been steady and expectations for its robust clinical application continue to rise. Indeed, in 2007, the phrase "regenerative pharmacology" was coined to describe the enormous possibilities that could occur at the interface between pharmacology, regenerative medicine, and tissue engineering. The operational definition of regenerative pharmacology is "the application of pharmacological sciences to accelerate, optimize, and characterize (either in vitro or in vivo) the development, maturation, and function of bioengineered and regenerating tissues." Thus, regenerative pharmacology seeks to cure disease through restoration of tissue/organ function. This strategy is distinct from standard pharmacotherapy, which is often limited to the amelioration of symptoms. The goal here is to get pharmacologists more involved in this field of research by exposing them to the tools, opportunities, challenges, and interdisciplinary expertise that will be required to ensure awareness and galvanize involvement. Christ and coworkers reported that science can drive future innovations in regenerative medicine and tissue engineering and thus help to revolutionize the discovery of curative

therapeutics [13]. In the setting of cardiac arrest, Dr. Wang and colleagues have reported that administration of allogeneic bone marrow mesenchymal stem cells improved myocardial function and survival after cardiopulmonary resuscitation in myocardial infarcted rats [14].

23.3.2 Inflammation During Resuscitation

Proinflammatory mediators such as tumor necrosis factor-alpha (TNFα) have been implicated in the pathophysiology of a number of acute disease states. TNFα can contribute to cell death, apoptosis, and organ dysfunction. It can be generated during sepsis or ischemia-reperfusion by activation of cell mitogen-activated protein kinases and nuclear factor kappa B. A number of strategies to modulate TNF have been recently explored, including factors directed toward mitogen-activated protein kinases, TNFα transcription, anti-inflammatory ligands, heat shock proteins, and TNF-binding proteins. However, TNFα may also play an important role in the adaptive response to injury and inflammation. Control of the deleterious effects of TNFα and other proinflammatory cytokines represents a realistic goal for clinical emergency medicine [15]. Indeed, an important inflammatory response, similar to a sepsis-like syndrome, occurs after resuscitation from cardiac arrest [16]. Interactions among pleiotropic mediators, coagulation abnormalities, activation of the inflammatory cytokine cascade, chemokine upregulation, and ultimately recruitment of inflammatory leukocytes and reactive astrogliosis have been reported after cardiac arrest and are major players in the final outcome [16, 17]. Several translational approaches have been investigated in animal models of cardiac arrest and proposed to the clinical scenario such to mitigate the post-resuscitation inflammation, i.e., hypothermia and/or therapeutic gases [18, 19].

23.3.3 Oxygenation During and After Cardiopulmonary Resuscitation

Reversal of tissue hypoxia, particularly in the heart and brain, is a fundamental goal of cardiopulmonary resuscitation. However, a growing body of evidence suggests that hyperoxia, especially after return of spontaneous circulation, may worsen outcome. Therefore, the concept of controlled oxygenation during and after cardiac arrest has become determinant [20, 21].

Animal studies over the last two decades have built a compelling case that arterial hyperoxemia during the first hours after resuscitation causes increased oxidative damage, increased neuronal death, and worse neurological function. In a meta-analysis of animal studies, treatment with 100 % oxygen resulted in a significantly worse neurological deficit score than oxygen administered at lower concentrations, with a standardized mean difference of −0.64 (95 % CI −1.06 to

−0.22). In four of five studies, histological evidence of increased neuronal damage was present in animals that received 100 % oxygen therapy. The administration of 100 % oxygen therapy was therefore associated with worse neurological outcome than lower oxygen concentrations in animal models of cardiac arrest [21].

However, human data are limited [22–24]. There are conflicting findings from observational studies regarding the nature of the association between hyperoxia and risk of mortality in patients admitted to intensive care following cardiac arrest. The only prospective randomized clinical trial comparing different inspired oxygen concentrations in post-cardiac arrest patients was underpowered to detect a difference in survival or neurologic outcome. More recently, a retrospective analysis of data from a multicenter registry found that initial arterial hyperoxemia ($paO2 \geq 300$ mmHg) was associated with increased mortality and worse functional outcome in patients admitted to the intensive unit care after cardiac arrest. The existing evidence, though limited, has contributed to new guidelines for oxygen therapy in patients resuscitated from cardiac arrest. The benefit of supplemental oxygen during cardiopulmonary resuscitation remains uncertain. However, in patients who achieve resuscitation after cardiac arrest, available evidence supports adjusting inspired oxygen content to avoid arterial hyperoxemia while providing adequate arterial oxyhemoglobin saturation. This strategy is likely to be most effective when initiated as soon as possible and appears to be most important during the first hours after resuscitation. Definitive clinical trials are needed to determine the ultimate impact on outcome.

23.3.4 Cardioprotection

The National Heart, Lung, and Blood Institute convened a Workshop on September 20–21, 2010, called "New Horizons in Cardioprotection," to identify future research directions for cardioprotection against ischemia and reperfusion injury. Since the early 1970s, there has been evidence that the size of a myocardial infarction (MI) could be altered by various interventions. Early coronary artery reperfusion has been an intervention that consistently reduces myocardial infarct size in animal models as well as in humans. Pharmacological adjunctive therapies have failed to either reduce infarct size or improve clinical outcome. However, some adjunctive therapies have shown promise in data subanalyses or subpopulations of clinical trials (adenosine, therapeutic hypothermia, and hyperoxemic reperfusion) or in small clinical trials (atrial natriuretic peptide, ischemic postconditioning, and cyclosporine, the mitochondrial permeability transition pore inhibitor) [25]. Indeed, over the past 30 years, hundreds of experimental interventions (both pharmacological and nonpharmacological) have been reported to protect the ischemic myocardium in experimental animals; however, with the exception of early reperfusion, none of them has been translated succesfully into the clinical practice.

The National Heart, Lung, and Blood Institute convened a working group to discuss the reasons for the failure to translate potential therapies for protecting the heart from ischemia and reperfusion and to recommend new approaches to accomplish this goal. The Working Group concluded that cardioprotection in the setting of acute myocardial infarction, cardiac surgery, and cardiac arrest was at a crossroad. Present basic research approaches to identify cardioprotective therapies are inefficient and counterproductive. For three decades, significant resources have been invested in single-center studies that have often yielded inconclusive results. A new paradigm is needed to obviate many of the difficulties associated with translation of basic science findings. The Working Group urged a new focus on translational research that emphasizes efficacy and clinically relevant outcomes, and recommended the establishment of a system for rigorous preclinical testing of promising cardioprotective agents with clinical trial-like approaches (i.e., blinded, randomized, multicenter, and adequately powered studies using standardized methods). Accordingly, a national preclinical research consortium would enable rational translation of important basic science findings into clinical use [26].

23.3.5 Vasopressor Agents for Cardiopulmonary Resuscitation

The primary goal of cardiopulmonary resuscitation is to reestablish blood flow to vital organs until spontaneous circulation is restored. Adrenergic vasopressor agents produce systemic vasoconstriction. This increases aortic diastolic pressure, and consequently, coronary and cerebral perfusion pressures. The pharmacologic responses to the adrenergic agents are mediated by a group of receptors that are classified as alpha (alpha), including alpha1 and alpha2, and beta (beta), including beta1 and beta2. Epinephrine, which has each of these adrenergic actions, has been the preferred adrenergic agent for the management of cardiac arrest for almost 40 years. Its primary efficacy is due to its alpha-adrenergic vasopressor effects. This contrasts with its beta-adrenergic actions, which are inotropic, chronotropic, and vasodilator. Accordingly, beta-adrenergic actions prompt increases in myocardial oxygen consumption, ectopic ventricular arrhythmias, and transient hypoxemia due to pulmonary arteriovenous shunting. This may account for the failure to demonstrate that epinephrine improves ultimate outcome in human victims of cardiac arrest. Accordingly, epinephrine, the primary pharmacological intervention in the treatment of cardiac arrest, improves only the immediate outcome [27]. Major interest has more recently been focused on selective alpha-adrenergic agonists [28]. Both alpha1-agonists and alpha2-agonists are peripheral vasopressors. However, rapid desensitization of alpha1-adrenergic receptors occurs during cardiopulmonary resuscitation. Moreover, alpha1-adrenergic receptors are present in the myocardium, and beta1-agonists, like beta-adrenergic agonists, increase myocardial oxygen consumption. If they cross the blood–brain barrier, alpha2-adrenoceptor agonists also have centrally acting vasodilator effects. In the absence of central nervous system access, alpha2-adrenergic agonists have selective

peripheral vasoconstrictor effects. Experimentally, these selective alpha2-agonists have been reported to be as effective as epinephrine for initial cardiac resuscitation and have the additional advantage of minimizing myocardial oxygen consumption during the global myocardial ischemia of cardiac arrest. The effects of selective alpha[2]-adrenergic agonist alpha-methylnorepinephrine (alpha-MNE) on the initial success of resuscitation and post-resuscitation myocardial function were compared with nonselective alpha- and beta-adrenergic epinephrine in a swine model of cardiac arrest. Ejection fraction was reduced by 35 % and 14 % by epinephrine and alpha-MNE, respectively, after resuscitation. Epinephrine and alpha-MNE increased post-resuscitation heart rate by 38 % and 15 %, respectively. Accordingly, significantly less post-resuscitation impairment followed the administration of alpha-MNE [29]. The combination of epinephrine and vasopressin may be effective, but has been incompletely studied. Clinical trials of vasopressor agents, which minimize direct myocardial effects are needed [30].

23.3.6 Na^+/H^+ Channelpathies and Pharmacological Defibrillation

Voltage-gated Na(+) channels are essential for the amplitude and upstroke velocity of the cardiac action potential, which are important determinants for impulse propagation and impulse conduction velocity throughout the working myocardium. Mutations in the major cardiac Na(+) channel gene SCN5A have been implicated in rare, familial forms of cardiac arrhythmias, namely LQT3, Brugada syndrome, progressive cardiac conduction disorder, and sudden infant death syndrome. Indeed, it is now recognized that mutations that increase Na^+ current (INa) delay cardiac repolarization, prolong action potential duration, and cause long QT syndrome, while mutations that reduce INa decrease cardiac excitability, reduce electrical conduction velocity, and induce Brugada syndrome, progressive cardiac conduction disease, sick sinus syndrome, or combinations thereof. Recently, mutation-induced INa dysfunction was also linked to dilated cardiomyopathy, atrial fibrillation, and sudden infant death syndrome. It is increasingly recognized that such mutations, apart from changing channel gating characteristics, may also be related to changes in channel protein trafficking and expression. Regulation of ion channel protein expression depends on a fine-tuned balance among various processes, such as gene transcription, RNA processing, protein synthesis, assembly and post-translational modification, the transport to the cell surface, the anchoring to the cytoskeleton, and regulation of endocytosis and controlled degradation of the protein [31]. While clinical and genetic studies have laid the foundation for our understanding of cardiac sodium channelopathies by establishing links between arrhythmogenic diseases and mutations in genes that encode various subunits of the cardiac sodium channel, biophysical studies (particularly in heterologous expression systems and transgenic mouse models) have provided insights into the mechanisms by which INa dysfunction causes disease in such channelopathies.

Amin and coworkers described the structure and function of the cardiac sodium channel and its various subunits, summarizing major cardiac sodium channelopathies and the current knowledge concerning their genetic background and underlying molecular mechanisms, and discussing recent advances in the discovery of mutation-specific therapies in the management of these channelopathies [32, 33]. Indeed, the concept of Na^+-H^+ exchange (NHE) involvement in cardiac pathology has been exposed for decades and supported by a plethora of experimental studies demonstrating salutary effects of NHE inhibition in protecting the myocardium against ischemic and reperfusion injury as well as attenuating myocardial remodeling and heart failure. NHE is actually a family of sodium and proton transporting proteins of which 10 isoforms have been identified. Myocardial NHE is represented primarily by the ubiquitous NHE-1 subtype which is expressed in most tissues. The robust positive results seen with NHE-1 inhibitors in experimental studies have led to a relatively rapid development of these pharmacological agents for clinical assessment, especially as potential cardioprotective therapies. Episodes of VF and myocardial dysfunction commonly occur after cardiac resuscitation compromising the return of stable circulation. Gazmuri and coworkers investigated in a pig model of VF whether limiting Na(+)-induced cytosolic Ca(2 +) overload using the sarcolemmal (NHE-1) inhibitor cariporide. Cariporide administered at the start of chest compression helped to restore electrically and mechanically stable circulation after resuscitation from cardiac arrest [34].

The EXPEDITION study addressed the efficacy and safety of inhibiting the NHE-1 by cariporide in the prevention of death or MI in patients undergoing coronary artery bypass graft surgery. The premise was that inhibition of NHE-1 limits intracellcular Na^+ accumulation and thereby limits Na/Ca-exchanger-mediated calcium overload to reduce infarct size. Surprisingly, the incidence of death or MI was reduced from 20.3 % in the placebo group to 16.6 % in the treatment group ($p = 0.0002$). Paradoxically, MI alone declined from 18.9 % in the placebo group to 14.4 % in the treatment group ($p = 0.000005$), while mortality alone increased from 1.5 % in the placebo group to 2.2 % with cariporide ($p = 0.02$). The increase in mortality was associated with an increase in cerebrovascular events. Unlike the salutary effects that were maintained at 6 months, the difference in mortality at 6 months was not significant. As a result of the increased mortality associated with an increase in cerebrovascular events, it was considered unlikely that cariporide would have been used clinically [35].

23.3.7 Amplitude Spectrum Area

High quality cardiopulmonary resuscitation and prompt defibrillation when appropriate (i.e., in VF and pulseless ventricular tachycardia) are currently the best early treatment for cardiac arrest. In cases of prolonged cardiac arrest due to shockable rhythms, it is reasonable to presume that a period of CPR before

defibrillation could partially revert the metabolic and hemodynamic deteriorations imposed on the heart by the no flow state, thus increasing the chances of successful defibrillation. Despite supporting early evidences in cardiac arrest cases in which Emergency Medical System response time was longer than 5 min, recent studies have failed to confirm a survival benefit of routine CPR before defibrillation. These data have imposed a change in guidelines from 2005 to 2010. Taking into account all the variables encountered when treating cardiac arrest (heart condition before cardiac arrest, time elapsed, metabolic and hemodynamic changes, efficacy of CPR, responsiveness to defibrillation attempt), it would be helpful to have a real-time and noninvasive tool able to predict the chances of defibrillation success [36].

In a recent study by Ristagno and coworkers the efficacy of an electrocardiographic parameter, "amplitude spectrum area" (AMSA), to predict the likelihood that any one electrical shock would restore a perfusing rhythm was investigated during cardiopulmonary resuscitation in human victims of out-of-hospital cardiac arrest [37]. AMSA analysis is not invalidated by artifacts produced by chest compression and thus it can be performed during CPR, avoiding detrimental interruptions of chest compression and ventilation. Analysis was performed on a database of electrocardiographic records, representing lead 2 equivalent recordings from AEDs including 210 defibrillation attempts from 90 victims of out-of-hospital cardiac arrest. AMSA values were significantly greater in successful defibrillation (restoration of a perfusing rhythm), compared to unsuccessful defibrillation ($P < 0.0001$). An AMSA value of 12 mV Hz was able to predict the success of each defibrillation attempt with high sensitivity and specificity. AMSA, indeed, represents a clinically applicable method, which provides a real-time prediction of the success of defibrillation attempts. AMSA may minimize the delivery of futile and detrimental electrical shocks, reducing thereby post-resuscitation myocardial injury. Recent evidences have suggested that ECG waveform analysis of VF, such as the derived Amplitude Spectrum Area, can fit the purpose of monitoring the CPR effectiveness and predicting the responsiveness to defibrillation. While awaiting clinical studies confirming this promising approach, CPR performed according to high quality standard and with minimal interruptions together with early defibrillation are the best immediate ways to achieve resuscitation [38].

23.3.8 Brain Ischemia and Reperfusion

Brain damage accompanying cardiac arrest and resuscitation is frequent and devastating. Neurons in the hippocampal CA1 and CA4 zones and cortical layers III and V are selectively vulnerable to death after an ischemia and reperfusion injury. Ultrastructural evidence indicates that most of the structural damage is associated with reperfusion, during which the vulnerable neurons develop disaggregation of polyribosomes, peroxidative damage to unsaturated fatty acids in the

plasma membrane, and prominent alterations in the structure of the Golgi apparatus that is responsible for membrane assembly. Reperfusion is also associated with prominent production of messenger RNAs for stress proteins and for the proteins of the activator protein-1 complex, but vulnerable neurons fail to efficiently translate these messages into the proteins. The inhibition of protein synthesis during reperfusion involves alteration of translation initiation factors, specifically serine phosphorylation of the alpha-subunit of eukaryotic initiation factor-2 (elF-2 alpha). Growth factors—in particular, insulin—have the potential to reverse phosphorylation of elF-2 alpha, promote effective translation of the mRNA transcripts generated in response to ischemia and reperfusion, enhance neuronal defenses against radicals, and stimulate lipid synthesis and membrane repair. There is now substantial evidence that the insulin-class growth factors have neuron-sparing effects against damage by radicals and ischemia and reperfusion. This new knowledge may provide a fundamental basis for a rational approach to "cerebral resuscitation" that will allow substantial amelioration of the often dismal neurologic outcome now associated with resuscitation from cardiac arrest [39].

Recommendations represent the most extensive and rigorous systematic review of the resuscitation literature to date. Current guideline recommendations include the induction of mild therapeutic hypothermia for comatose cardiac arrest survivors. Accordingly, constituent national member associations of International Liaison Committee on Resuscitation (ILCOR), including the American Heart Association, incorporated the recommendation for therapeutic hypothermia into their respective guidelines. Despite these endorsements there is a concern that therapeutic hypothermia is not being used consistently in the clinical practice. Data from a number of surveys in Europe and the United States suggest that rates of use of hypotermia may be as low as 30–40 % of instances. Despite the cost and effort associated with the production of guidelines and the potential impact on patient care, current efforts in implementing the guideline have not achieved widespread success [40].

23.3.9 Therapeutic Hypothermia

The estimated number of out-of-hospital care arrest cases is about 300,000 per year in the United States. Two landmark studies published in 2002 demonstrated that the use of therapeutic hypothermia after cardiac arrest decreased mortality and improved neurologic outcome. Based on these studies, the ILCOR and the American Heart Association recommended the use of therapeutic hypothermia after cardiac arrest. Therapeutic hypothermia is defined as a controlled lowering of core body temperature to 32–34 °C. This temperature goal represents the optimal balance between clinical effect and cardiovascular toxicity. Therapeutic hypothermia does require resources to be implemented, including device, close nursing care, and monitoring. It is important to select patients who have potential for

benefit from this technique which is a limited resource and carries potential complications.

Good neurologic outcome after cardiac arrest is hard to achieve. Interventions during the resuscitation phase and treatment within the first hours after the event are critical. Therapeutic hypothermia following return of spontaneous circulation has been advocated for decades prior to its clinical acceptance [41]. More than a decade ago it has been reported that young and healthy people underwent accidental deep hypothermia with cardiac arrest were able to survive with no or minimal cerebral impairment even after prolonged cardiac arrest. The concept of hypothermia for reducing either or both ischemic and reperfusion injury of the brain represents a pioneering contribution of the late Professor Peter Safar and the persistence of his efforts through his students, and especially Professor Fritz Sterz [42–44]. In 1996, Professor Safar induced hypothermia by instilling Ringer's solution maintained at a temperature of 4 °C into the abdominal cavity of dogs after resuscitation from cardiac arrest. Cooling was maintained for 12 h. Functional recovery was associated with minimal histological brain damage [41]. More recent investigations provided evidence that even better neurological and cardiac outcomes may be achieved if hypothermia is begun during CPR. Rapid and selective head cooling has been specifically investigated by our group. Head cooling reduced jugular venous temperature by 3.7 °C over an interval of 5 min during experimental CPR and significantly increased the likelihood of resuscitation, minimized post-resuscitation neurological deficit and myocardial dysfunction, and resulted in significantly greater 96 h functional survival [44].

More recently, a collaborative team approach involving physicians and nurses is critical for successful development and implementation of therapeutic hypothermia. In 2004, the "Advanced Cardiac Admission Program" was launched at the St. Luke's Roosevelt Hospital Center of Columbia University in New York. The program consisted of a series of projects, which have been developed to bridge the gap between published guidelines and implementation during "real world" patient care. The pathway was divided into three steps: Step I, from the field through the emergency department into the cardiac catherization laboratory and to the critical care unit; Step II, induced invasive hypothermia protocol in the critical care unit (this step was divided into three phases: 1, invasive cooling for the first 24 h; 2, rewarming; 3, maintenance); Step III, management post the rewarming phase, including the recommendation for out-of-hospital therapy and the ethical decision to define goal of care [45].

Arrich and coworkers performed a systematic review and meta-analysis to assess the effectiveness of therapeutic hypothermia in patients after cardiac arrest. The authors searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2007 Issue 1); MEDLINE (1971 to January 2007); EMBASE (1987 to January 2007); CINAHL (1988 to January 2007); PASCAL (2000 to January 2007); and BIOSIS (1989 to January 2007). The authors included all randomized controlled trials assessing the effectiveness of the therapeutic hypothermia in patients after cardiac arrest without language restrictions. Studies were restricted to adult populations cooled with any

cooling method applied within 6 h of cardiac arrest. Overall, four trials and one abstract reporting on 481 patients were included in the systematic review. Quality of the included studies was good in three out of five included studies. For the three comparable studies on conventional cooling methods all authors provided individual patient data. With conventional cooling methods patients in the hypothermia group were more likely to reach a best cerebral performance categories score of one or two (CPC, five-point scale; 1 = good cerebral performance, to 5 = brain death) during hospital stay (individual patient data; RR, 1.55; 95 % CI 1.22–1.96) and were more likely to survive to hospital discharge (individual patient data; RR, 1.35; 95 % CI 1.10–1.65) compared to standard post-resuscitation care. Across all studies there was no significant difference in reported adverse events between hypothermia and control. The authors concluded that conventional cooling methods to induce mild therapeutic hypothermia seemed to improve survival and neurologic outcome after cardiac arrest. The review supported the current best medical practice as recommended by the International Resuscitation Guidelines [46].

23.3.10 Kynurenine Pathway

Post-stroke inflammation may induce upregulation of the kynurenine (KYN) pathway for tryptophan (TRP) oxidation, resulting in neuroprotective (kynurenic acid, KA) and neurotoxic metabolites (3-hydroxyanthranillic acid, 3-HAA). Brouns and coworkers investigated whether activity of the kynurenine pathway in acute ischemic stroke was related to initial stroke severity, long-term stroke outcome, and the ischemia-induced inflammatory response. Plasma concentrations of TRP and its metabolites were measured in 149 stroke patients at admission, at 24 h, at 72 h, and at day 7 after stroke onset. Indeed, the activity of the kynurenine pathway for TRP degradation in acute ischemic stroke correlated with stroke severity and long-term stroke outcome. Accordingly, TRP oxidation was related to the stroke-induced inflammatory response [47].

More recently, Ristagno and coworkers measured TRP and KYN metabolites concentrations in plasma from rats, pigs, and humans after cardiac arrest in order to assess KYN pathway activation and its potential role in post-resuscitation outcome [48]. KYN pathway was activated after cardiac arrest in rats, pigs, and humans. Decreases in TRP occurred during the post-resuscitation period and were accompanied by significant increases in its major metabolites, 3-hydroxyanthranilic acid (3-HAA) and kynurenic acid in each species, that persisted up to 3–5 days post-cardiac arrest ($p < 0.01$). In rats, changes in KYN metabolites reflected changes in post-resuscitation myocardial function. In pigs, changes in TRP and increases in 3-HAA were significanlty related to the severity of cerebral histopathogical injuries. In humans, KYN pathway activation was observed, together with systemic inflammation. Post-cardiac arrest increases in 3-HAA were greater in patients that did not survive. In this fully translational investigation, the

authors concluded that the KYN pathway was activated early following resuscitation from cardiac in rats, pigs, and humans, and might have contributed to post-resuscitation outcome.

23.4 Future Direction and Perspectives

The quality of education and frequency of training retraining are critical factors in improving the effectiveness of resuscitation. Resuscitation programs should systematically monitor cardiac arrests, the quality of resuscitation care provided, and the outcome. This information is necessary to optimize resuscitation care and improve the resuscitation performance [49].

Teaching strategies should be evaluated and compared on the basis of how well learners achieve predefined teaching outcomes. Unfortunately, there is not a single method suitable for all circumstances. CPR consists of cognitive as well as team and psychomotor skills. Hence, it might be beneficial to learn and train the different aspects of CPR in different modes and at different times.

Moreover, health education specialists have the training and the experience to engage in and facilitate translational research, as well as the opportunity to learn from the translational efforts of other professions and enhance research, practice, and community partnerships through translational efforts [50].

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