Complex cardiovascular centre General University Hospital in Prague and Prague Emergency Service

A clinical trial protocol

Title: Hyperinvasive approach to out-of hospital cardiac arrest using mechanical chest compression device, prehospital intraarrest cooling, extracorporeal life support and early invasive assessment compared to standard of care. A randomized parallel groups comparative study proposal. “Prague OHCA study"

Aim: to test hyperinvasive vs. standard approach in out-of hospital cardiac arrest

Protocol supported: grant support will be asked for

Study phase: IV.

To be approved by the Ethical board of the General University Hospital and 1st Medical School Charles University in Prague.

Responsible investigator: Jan Bělohlávek, MD.

Hyperinvasive approach to out-of hospital cardiac arrest using mechanical chest compression device, prehospital intraarrest cooling, extracorporeal life support and early invasive assessment compared to standard of care. A randomized parallel groups comparative study proposal. “Prague OHCA study"

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Abstract:

Background: Out of hospital cardiac arrest (OHCA) has a poor outcome. Recent non-randomized studies of ECLS (extracorporeal life support) in OHCA provided promising results and suggested further prospective multicenter studies to define population with OHCA that would benefit from ECLS.

Aim: to perform a prospective randomized multicenter clinical study comparing use of prehospital intraarrest hypothermia, mechanical chest compression device, ECLS and early invasive investigation and treatment (coronary angiography/percutaneous coronary intervention [PCI]; pulmonary angiography/percutaneous embolectomy) in all patients with OHCA of presumed cardiac origin compared to a standard of care.

Methods: this paper describes methodology and design of the proposed trial.

Planned intervention: patients with wittnessed OHCA without ROSC (return of spontaneous circulation) after a minimum of 5 minutes of ACLS by emergency medical service (EMS) team and after performance of all necessary initial procedures (defibrillation, airway securence, intravenous access establishment) will be randomized in a 1:1 design to standard vs. hyperinvasive arm. In hyperinvasive arm, mechanical compression device together with intranasal evaporative cooling will be immediately instituted and patients will be transferred directly to cardiac center cathlab under ongoing CPR. After admission to cathlab, overall status, ROSC and ECLS inclusion/exclusion criteria will be evaluated and in case of no contraindications to ECLS and no ROSC or ROSC with shock, veno-arterial ECLS will be started as soon as possible. After ECLS institution, mild hypothermia will be continued by means of ECLS cooling and immediate invasive investigation will be performed in all patients. Standard postresuscitation care will follow. Patients in standard arm will be managed on scene. When ROSC achieved, they will be transferred to cardiac center and further treated as per recent guidelines including mild hypothermia.

Primary outcome: 6 months survival with good neurological outcome (Cerebral Performance Category 1-2). Secondary outcomes will include 30 day neurological and cardic recovery.

Discussion: authors offer a protocol of a proposed randomized study comparing a combined „hyperinvasive“ approach to a standard of care in refractory OHCA. Initial time of cardiac arrest before randomization to above arms is expected to be 15-20 minutes. The protocol is

opened for sharing by other cardiac centers with available ECLS and cathlab teams trained to admit patients with refractory cardiac arrest under ongoing CPR. A prove of concept study will be started soon. The aim of the authors is to establish a net of centers for a multicenter trial initiation.

Ethics and registration: the protocol has been approved by an Institutional Review Board and registered under ClinicalTrials.gov identifier: NCT01511666.

Keywords: cardiac arrest; hypothermia; extracorporeal life support; mechanical compression device;

Introduction

Cardiac arrest is a significant socio-economic burden (1, 2). The aim of the care for patients suffering from cardiac arrest is a neurologically intact survival, ie. avoidance of irreversible organ damage, mainly the brain hypoxic-reperfusion injury. However, neurologically favourable survival in patients resuscitated worldwide by emergency services is only 5-15 %, eventually 8-40 % in patients with initially shockable rhythms (3). In Prague, in 2008, 493 patients were resuscitated by Prague Emergency medical service (EMS) for OHCA (out of hospital cardiac arrest). ROSC (return of spontaneous circulation) was reached in 56 % of cases, 43 % survived the episode, 15 % were discharged home with favourable neurological outcome, however, back to the fully active life including job attendance returned only 7 % of the original cohort (4). A key prerequisite for a succesful outcome is minimalization of time delays, resuscitation quality, complex intensive care and treatment of cardiac arrest cause (5-7). So far, the only proven method for increased survival with good neurological outcome is early inititation of mild hypothermia and probably also the rapidly reached target temperature (3, 8). However, the use of hypothermia affects individual estimation of prognosis (9, 10) and the whole topic of hypothermia needs further evaluations and studies including potentially beneficial intraarrest cooling (11-15). Recent systematic review on intraarrest hypothermia confirmed its beneficial effect in terms of survival and neurological outcome in an experimental setting, however, clinical data on the efficacy of intraarrest cooling are still limited (16-20**)**.

Similarly, chest compression devices are being increasingly used in OHCA, despite the fact that their role is still controversial (21-25). They provide uninterrupted continuous compressions even during the transport, decrease the demands on Emergency Medical Service (EMS) crew and provide a bridge to other methods like PCI (percutaneous coronary intervention) or ECLS (extracorporeal life support)/ECMO (extracorporeal membrane oxygenation) initiation (26). Current European Resusctitation Council (ERC) guidelines (27**)** consider mechanical compression devices, ie. LUCAS (Lund University Cardiac Arrest System; Physio-Control Inc./Jolife AB, Lund, Sweden) and Autopulse (LDB - load distributing band; ZOLL, Chelmsford, MA, U.S.A.) to be potentially beneficial, however, with not yet evidently proven beneficial impact on patients survival and recommend further randomized studies.

Accordingly, the indication of mechanical support devices during cardiopulmonary resuscitation (CPR), i.e. the ECLS/ECMO is controversial in cardiac arrest patients and no definitive role has been determined. Encouraging results of E-CPR (extracorporeal CPR) for

cardiac arrest of cardiac origin in adults were shown recently both for IHCA and OHCA (inhospital -, out of hospital cardiac arrest) (28-33), in inhospital pediatric CA (34-36) and recently has been even proposed for out of hospital „on scene“ refractory CA (37-39). However, the results are still not satisfactory yielding wide survival rate range from 4 % (32) to 48% (33). This may be related to different definitions of refractory cardiac arrest, ie. from 10 (31) to 30 minutes (33) before ECLS initiation is considered. For in hospital cardiac arrest the survival with good neurological outcome has been observed in up to 20 to 30% of cases (26, 28, 30, 40, 41). Therefore, ECLS has been assigned a low-grade recommendation in recent guidelines for inhospital cardiac arrest (42). However, the good results obtained in IHCA cardiac arrests can not be automatically extrapolated to OHCA patients because of longer transport times and possible delay in ECLS initiation (43).

Therefore, we designed a randomized trial of „hyperinvasive“ approach encompassing all above mentioned sofisticated methods and hypothesized, that improved logistics of prehospital OHCA management and immediate on-admission ECLS institution might bring beneficial impact on patient survival (44).

Assuming, that refractory cardiac arrest may be caused by a treatable condition, all mentioned interventions are approached as only temporizing techniques to allow for further diagnostics and therapy, mainly the coronary angiography ± PCI (percutaneous coronary intervention), eventually other investigations (i.e. pulmonary angiography, aortography or brain CT).

The aim of this comparative study is to collect prospective, randomized data on prehospital use of a chest compression device combined with intraarrest evaporative cooling as a bridge to in hospital emergency ECLS implantation followed by immediate invasive diagnostics and treatment in cases of witnessed out-of-hospital refractory cardiac arrest (OHCA) of predominantly cardiac origin to assess an impact of this combined „hyperinvasive“ approach on 6 months survival with favourable neurological outcome (primary endpoint), 30 day neurological and cardiac recovery (secondary outcomes), quality of life, safety and cost-effectiveness (tertiary outcomes).

Hypotheses

We hypothesize, that combination of above methods will provide increased occurence of primary and secondary outcomes and will offer a reasonable quality of life for survivors (assessed by SF-36 questionaire). We further suppose, that the combination of above methods

will be cost-effective as assessed by QALY (quality adjusted life year) determination. We also expect same occurence of complications by using mechanical chest compression device in comparison to manual massage and increased rate of bleeding complications in ECLS, however, compensated by survival benefit in otherwise futile conditions.

Proposed study protocol

Until stated otherwise, study will be realized only during working hours, ie. 8 AM to 4 PM, to facilitate inhospital logistics and assure presence of key cathlab and ECMO team members. After the official initiation of the study, study coordinator in cardiac center will be notified by a SMS (Short Message Service) alert on every occassion when Prague EMS dispatch center will activate Rapid Response Vehicle (RRV) for wittnessed collapse suspected from cardiac arrest or cardiac arrest witnessed by EMS personell. Coordinator will check for intensive care bed and ECLS capacity and via the dispatch center will notify the EMS team. See the outline of the study (**figure 1)** and study phases summarized in **table 1**.

On arrival to the scene, patients will be evaluated by an EMS physician to confirm OHCA and standard ACLS (advanced cardiac life support) will be initiated. After a minimum of 5 minutes of ACLS guided by emergency physician and performance of all necessary initial procedures according to recent guidelines and as per physician decision on the scene (ie. defibrillations, airway management, intravenous access establishment) and while the patient is being resuscitated by other EMS team members for continuing cardiac arrest (i.e. no ROSC occurence) screening for study eligibility will be performed, see **table 2** for inclusion and exclusion criteria. After the emergency physician on scene evaluates the eligibility criteria and identifies a possibly eligible patient, he directly contacts the cardiac center coordinator by a mobile phone and when consensus on eligibility is established including the bed capacity and ECLS team availability, **(Decision point 1 in the project outline)**, randomization procedure will be performed by a cardiac center coordinator on-line using a computer web based randomization system. Study number will be assigned to the patient and the treatment arm assignment will be notified to the emergency physician on hold. Patients will be randomized in a 1:1 design to hyperinvasive or standard arm.

In **hyperinvasive arm** a mechanical chest compression device (LUCAS) will be immediately instituted on scene. Tympanic temperature will be measured, NIRS (near infrared spectroscopy) monitoring and cooling by RhinoChill device will be initiated as soon as possible, realistically immediately after delivering the patient to the ambulance car.

Thereafter, patients will be transferred directly to cardiac center cathlab under continuous CPR to fulfil the timeline of reaching ECLS team within 60 minutes after collapse. The use of drugs, further defibrillations or other interventions during transport are on a discretion of the emergency physician. On admission to cathlab, overall status, ROSC presence and ECLS inclusion/exclusion criteria will be evaluated **(Decision point 2 in the project outline, figure 1)**. **ECLS eligibility (table 3)**: no ROSC or ROSC with ongoing shock state (defined as sustained hypotension below 90 mmHg of systolic pressure or need for moderate to high doses of vasopressors), admission to cathlab not later than 60 minutes after the collapse/initial call to EMS, no signs of death or irreversible organ damage and no contraindications to ECLS institution (known bleeding diathesis, inadequate arterial and venous access for femoro-femoral veno-arterial ECLS). If the ECLS team members reach consensus on ECLS eligibility, it will be started as soon as possible by a standard percutaneous femoro-femoral approach. After ECLS institution, mild hypothermia will be continued by means of extracorporeal circuit cooling and immediate coronary angiography +/- PCI (eventually pulmonary angiography, aortography or head CT if cause of arrest still not obvious) will be performed in all patients. If the patient randomized to hyperinvasive arm reaches ROSC during the transport or after admission to cathlab before ECLS institution, he will undergo initial clinical assessment, ECG, urgent echocardiography and will continue with invasive investigations as mentioned above.

Patients randomized to a **standard arm** will be managed as per recent ERC guidelines, ie. continued ACLS. The use of drugs and further defibrillations are on a discretion of the emergency physician. If ROSC is achieved, patients will be transferred to the same hospital to one of intensive care units, coronary angiography/PCI will be performed only if indicated according to routine practice (ie. in STEMI/high risk nonSTEMI). Mild therapeutic hypothermia will be started as soon as possible after ROSC (including prehospital cooling on a discretion of the emergency physician), intraarrest cooling will not be allowed in standard arm.

Randomization process:

The online randomization process during the ongoing CPR has been selected to overcome selection bias in cluster randomizations, because study arm assignment before starting CPR can influence the decision making (24). Accordingly, chest compression device, i.e. LUCAS

has to be carried to all putative OHCA victims and will be used only when randomization to hyperinvasive arm occurs. This is somewhat inconvinient to EMS crew, however, necessary to avoid unintentional bias. In contrary to this, intranasal cooling will be started in the ambulance vehicle, because carrying another device to the scene would be too demanding and time delay for transporting a patient from the scene to an ambulance car will be negligible. The randomization phone call between the emergency physician and coordinating cardiologist/intensivist at the cardiac center is a crucial activity to properly enroll the patients and fullfil the inclusion/exclusion criteria. These phonecalls have been already trained during the seminars and investigator meetings and should not last more than 60 sec. At the time of the phone call, all the vital procedures performed by the EMS physician are already done, and at least 3 other rescue persons are on the scene. Thus, the physician can safely make this phone call, while others are continuing the CPR. The web based randomization system has been chosen, to maximally shorten the necessary time. Only following information will be requested after logging into the system: patient estimated age and gender and confirmation of I/E criteria. Immediately therafter the patient number and treatment assignment will be generated. For the case of web randomization system failure, envelopes with treatment arm assignment will be prepared in the coordinating center, just next to the computer used for randomization.

All patients admitted to hospital in both arms will have immediate biochemical evaluation, continuing neurological monitoring by near-infrared spectroscopy and brief urgent echocardiography. Nasal cooling in hyperinvasive arm will continue until transition to systemic cooling either by ECLS or by intravascular cooling catheter or standard surface cooling combined with rapid intravenous administration of cold normal saline. EMS and hospital personnel will not be blinded during the treatment. Neurological assessment will be performed before discharge and will be provided by a neurologist blinded to the treatment assignment.

Since the official initiation of the study, all patients resuscitated by Prague EMS not fullfilling elegibility criteria for this study will also be followed for outcome assessment and will constitute the third comparative group, „Prague OHCA study registry“ patients (**see the outline of the study**).

Devices used:

LUCAS (Lund University Cardiac Arrest System, Physio-Control Inc./Jolife AB, Lund, Sweden) device for mechanical chest compressions, http://www.physio-control.com/LUCAS.

RhinoChill device (BeneChill, Inc., San Diego, Calif, USA) device for intraarrest intranasal evaporative cooling, http://www.benechill.com/wp/rhinochill-trade/rhinochill-device.

For ECLS, MAQUET PLS console (MAQUET Cardiopulmonary AG, Hirrlingen, Germany) or alternatively Medtronic 550 Bio-Console (Medtronic Perfusion Systems, Brooklyn Park, MN, USA) with adapter, and Rotaflow RF 32 centrifugal pump with Quadrox PLS hollow fibre BIOLINE® coated membrane oxygenator (MAQUET Cardiopulmonary AG, Hirrlingen, Germany), MAQUET PLS tubing set and a mechanical gas blender (Sechrist, Anaheim, CA, USA) will be used. Edwards cannulae (Fem-Flex Cannulae, Edwards Lifesciences Research Medical Inc., Midvale, UT, USA) will be used for femoro-femoral cannulation.

An INVOS device (INVOS Cerebral/Somatic Oximeter, Covidien, Boulder, CO, USA) will be used for near infrared spectroscopy **neuromonitoring** during both prehospital and inhospital phase.

Ethics, safety and registration:

The study has been approved by the Institutional Review Board of the General Teaching Hospital and 1st Medical School, Charles University in Prague. Ethical considerations for treating subjects without their expressed consent are in accordance with the Helsinki Declaration of 1964, revised in 2008. The subject's legal representative will be informed of the subject's study participation as soon as practical, and patients who regain normal neurological function will be asked to provide their consent for use of the data. The study has been registered under ClinicalTrials.gov identifier: NCT01511666. The study will be supported by a research grant of the Internal Grant Agency of the Ministry of Health, Czech Republic, **NT13225-4/2012.**

Data safety monitoring board (DSMB)

An independent DSMB consisting of experts in the field of cardiac arrest will follow the overall study progression and integrity. DSMB will meet after inclusion of every 30 patients or every 6 months, whatever comes first, to evaluate the progress in the study and review all adverse events. Study data will be monitored by a professional contracted CRO (contract research organization).

Outcomes:

Primary outcome

Composite endpoint of 6 months survival with good neurological outcome (CPC 1-2).

Secondary outcomes

1/ 30 day neurological recovery - defined as no or minimal neurological impairment (CPC 1 or 2) at any timepoint within first 30 days after initial cardiac arrest.

2/ 30 day cardiac recovery - will be assessed by the clinical status of hemodynamic stability defined as no need for pharmacological or mechanical cardiac support. Systolic function will be measured by echocardiography .

Tertiary outcomes

Early outcome will also be monitored by means of ROSC achievement, defined as a palpable puls and measurable blood pressure without ECLS and ROSB (return of spontaneous beating) on ECLS, defined as palpable pulse or pulsatile flow on arterial invasive blood pressure curve. All patients will be followed untill discharge home or to a longterm care or rehabilitation center and in an Outpatient Heart Failure Clinic of the coordinating center. Quality of life will be assessed using SF-36 questionnaire on discharge and during the 6 months visit. Safety of the invasive methods will be monitored by adverse events occurence in survivors and organ damage will be assessed on autopsies in nonsurvivors. Cost-effectiveness will be evaluated by determination of QALY (Quality Adjusted Life Year).

Timeline: During the initial months of **2012** we expect a development of web based randomization and database system including CRF (case report form). EMS personell has been trained in all necessary procedures and methods (i.e. LUCAS and RhinoChill device) during 2011 (3 seminars per 4 hours) and routinely uses LUCAS device in cardiac arrest setting. A simulation study is planned for the first half of 2012, i.e. 3-5 patients will be „randomized“ to hyperinvasive arm, to be sure, that the protocol is feasible, all procedures are well trained and ECLS team is able to meet quickly and connect the patient to ECLS as per scheduled outline. Only therafter and following DSMB recommendation a real randomized study phase will be initiated. We expect approximatelly 40 patients to be enrolled yearly untill planned number of patients according to power analysis, or DSMB stops the study.

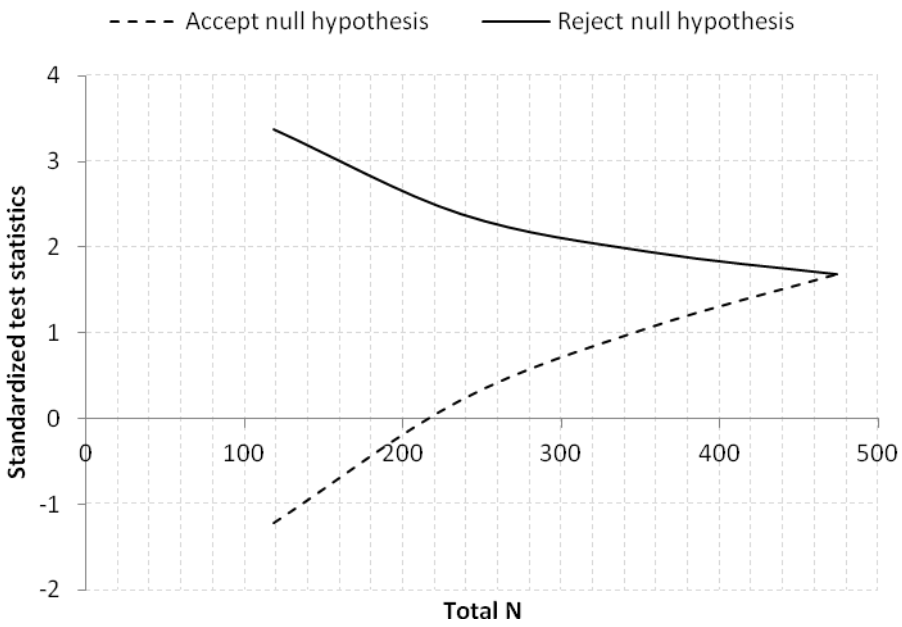
Statistical considerations

Initial statistical analysis was performed taking into account three proposed groups of patients. First, patients who will not be randomized, i.e. Prague OHCA study registry patients (see study outline on **Figure 1**). These patients will not fulfil inclusion/exclusion criteria mainly by means of not having "refractory" cardiac arrest, ie. succesfull ROSC will be reached withing 5-10 minutes of ACLS provided by EMS physician staffed team. According to Prague EMS study assessing overall outcome of all CPRs in Prague in 2008 (4) with 15 % overall short term survival with favourable neurological outcome (discharged home), we expect better, approximately 20-30 % of "primary outcome" occurence in this comparative group of patients. The other two groups in randomized part of the study will yield standard and hyperinvasive arm patients with rather worse outcomes. We expect 90 % mortality in standard arm, that is 10 % six-month survival with favourable neurological outcome.

The power analysis of the study

The power analysis was computed for superiority of hyperinvasive approach over standard approach, i.e. using one tailed test with the alpha=0.05 and desired power 0.9. In the standard arm 10% six-month survival with favourable neurological outcome (primary outcome) is assumed and 15 % increase in primary outcome occurence (6 month survival with favourable neurological outcome) is considered as clinically relevant. Three scenarios with 10%, 15% and 20% increase of primary outcome were computed. The analysis was computed using ADDPLAN BASE version 6.0, Aptiv Solutions, Cologne, Germany.

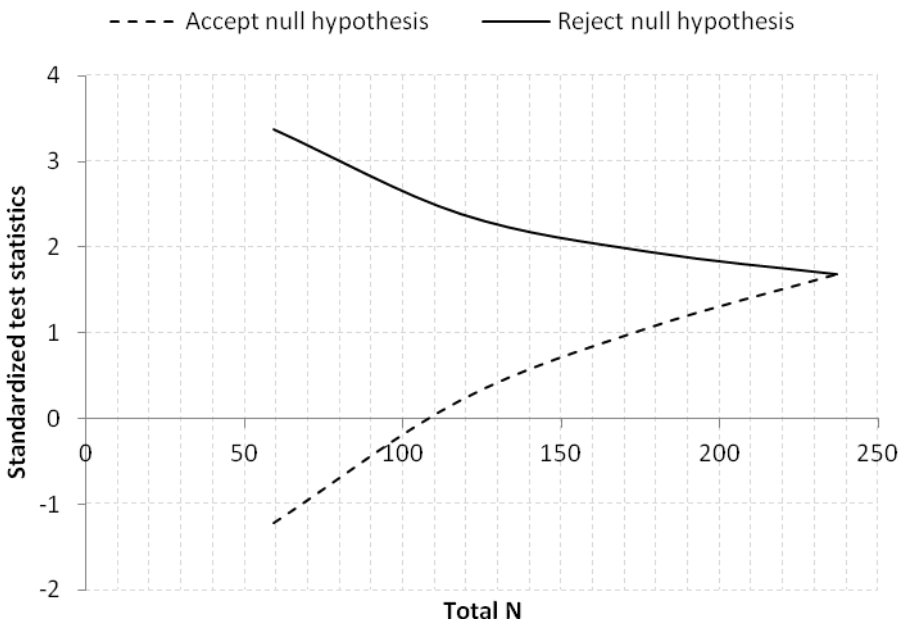
Scenario 1: standard (10%) vs. hyperinvase (20%) groups with allocation ratio 1; one tailed test with alpha=0.05 and power=0.9.
A design with a maximum of K = 4 stages was chosen. The critical values and the test characteristics of the group sequential test design were calculated for a Pampallona and Tsiatis design with boundary shape parameter Delta0 = 0.00 to reject H0, and boundary shape parameter Delta1 = 0.00 to reject H1. This yields a total of 236.9 + 236.9 = 473.9 observations. For comparison, the sample size in a fixed sample size design is n1 = 216.5, n2 = 216.5. The expected (average) total sample size under the alternative hypothesis is 319.0, under a value midway between H0 and H1 it is 353.7, and under the null hypothesis it is 284.0.



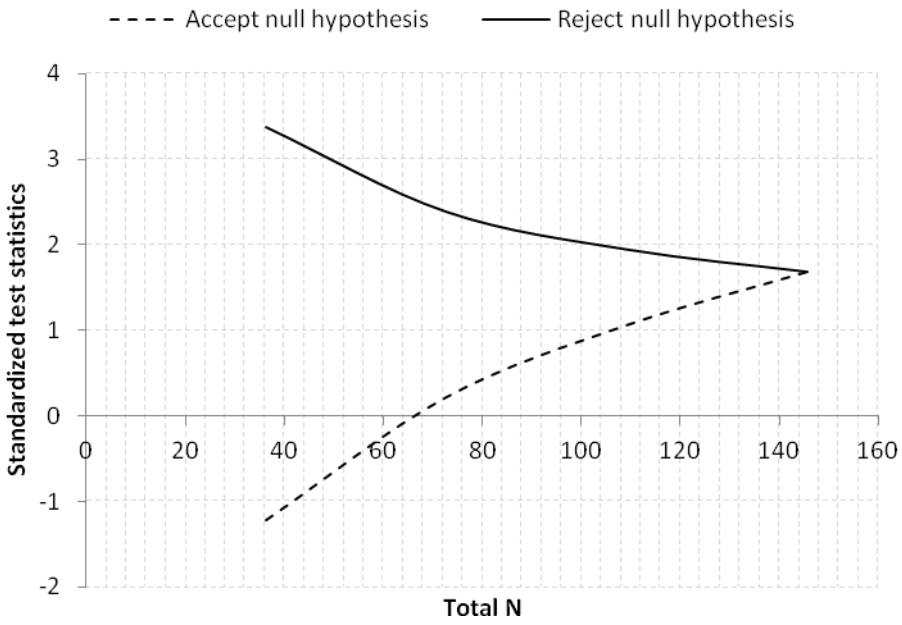
Scenario 2: standard (10%) vs. hyperinvase (25%) groups with allocation ratio 1; one tailed test with alpha=0.05 and power=0.9.

A design with a maximum of K = 4 stages was chosen. The critical values and the test characteristics of the group sequential test design were calculated for a Pampallona and Tsiatis design with boundary shape parameter Delta0 = 0.00 to reject H0, and boundary shape parameter Delta1 = 0.00 to reject H1.

This yields a total of 118.2 + 118.2 = 236.4 observations. For comparison, the sample size in a fixed sample size design is n1 = 108.0, n2 = 108.0. The expected (average) total sample size under the alternative hypothesis is 159.2, under a value midway between H0 and H1 it is 176.5, and under the null hypothesis it is 141.7.


Accept null hypothesis
Reject null hypothesis
Standardized test statistics
4
3
2
1
0
-1
-2
0
50
100
150
200
250
Total N

Scenario 3: standard (10%) vs. hyperinvase (30%) groups with allocation ratio 1; one tailed test with alpha=0.05 and power=0.9.
A design with a maximum of K = 4 stages was chosen. The critical values and the test characteristics of the group sequential test design were calculated for a Pampallona and Tsiatis design with boundary shape parameter Delta0 = 0.00 to reject H0, and boundary shape parameter Delta1 = 0.00 to reject H1.
This yields a total of 72.9 + 72.9 = 145.8 observations. For comparison, the sample size in a fixed sample size design is n1 = 66.6, n2 = 66.6. The expected (average) total sample size under the alternative hypothesis is 98.2, under a value midway between H0 and H1 it is 108.8, and under the null hypothesis it is 87.4.



Cooperation

The project will be executed in a close cooperation of Complex Cardiac Center of General Teaching Hospital with Prague Emergency Medical Service. Both institutions cooperate on a day by day basis during the routine care for cardiac arrest patients including admissions during ongoing CPR. In these occasions the cardiac center is alerted early and the catheterization and ECLS team is prepared at the cathlab. The decision on ECLS initiation is always reached consensually within the ECMO team members (**Belohlavek-JCardiovascSurg**).

Readinnes of cooperating institutions

Complex Cardiac Center of General Teaching Hospital, Charles University in Prague admits approximatelly 100 patients after cardiac arrest yearly. Approximately 20 patients per year is treated by ECLS under ECMO team guidance, coordinated by principal investigator of this project (JB). Untill now, 65 patients have been treated by ECMO and some of these results and experiences have been published (**Belohlavek 2x, Kunstyr, Rohn**). Cardiac center is located in the center of the city.

Prague EMS provides a prehospital urgent care within the capitol Prague by a randez-vous system with rapid response vehicles (RRV) staffed by emergency physicians and ambulance cars staffed by paramedics and intensive care nurses. Necessary devices, i.e. LUCAS for mechanical masage and RhinoChill for intranasal evaporative cooling are currently available for all RRVs. An INVOS device (INVOS Cerebral/Somatic Oximeter, Covidien, Boulder, CO, USA) for near infrared spectroscopy monitoring is also available, however only for one inspector car. This car is alerted routinely in every resuscitated OHCA in Prague for CPR assistance, however, inclusion into the study is possible without INVOS availability. An analysis of cardiac arrest occurence in Prague in 2007-2010 confirms a frequent occurence in the center of the city, which is a favourable precondition to reach short transport times to cardiac center (personal communication with OF – data not published).

Planned substudies

1/ Genetic substudy will be performed to examine genetic polymorphisms associated with cardiac arrest, mainly the polymorphism deemed to be responsible for primary ventricular fibrillation during AMI.

2/ Autoptic substudy will evaluate causes of death in refractory cardiac arrest and also the injuries caused by devices used during CPR.

3/ Angiography substudy with evaluation of coronary flow during ECMO will assess the adequacy of coronary flow generated by ECMO. This substudy aims to prove, whether after initial stabilisation of a post CPR patient with ECMO and after performance of all diagnostic investigations and therapeutical interventions, the coronary flow generated by ECMO is adequate. Coronary flow will be measured in proximal parts of coronary artery (presumably LAD) by means of Doppler flow wire measurument by using ComboMap Pressure & Flow Measurement System (Volcano Corporation, Rancho Cordova, CA, USA). A blood flow Doppler signal will be obtained and analyzed in real-time, blood flow velocity will be

measured in cm/sec as an average peak value (APV) obtained from 5 consecutive instantaneous peak velocity (IPV) measurements. A mean APV during the last minute of 5 minute stabilization period will be used for evaluation. Values will be stored for further off-line analysis and APV will be considered as a surrogate marker of coronary artery blood flow [**Doucette, Olivecrona, Belohlavek -Critical Care**]. Absolute coronary flow will also be determined using offline coronary artery diameter measurement by QCA (quantitative coronary angiography). For comparison, we will use the data from patients in whom CFR/FFR examination will be performed based on routine clinical indication.

Discussion: This complex and logistically demanding project has been designed to collect a clear result stating whether the combination of modern sophisticated methods improves or not the unfavourable prognosis of cardiac arrest patients. The project differs from other already performed studies by randomizing the patients to a combination of potentially beneficial methods used in cardiac arrest. Such a combination or „hyperinvasive" approach has not been performed so far, as per our knowledge. The underlying „all in one" concept is to maximize the beneficial effect on outcome of cardiac arrest patients, i.e. to keep the end-organ perfusion by mechanical chest compression, to avoid neurological damage by early intraarrest intranasal evaporative cooling and to bridge to ECLS with further invasive evaluation to identify and immediately treat the cause of refractory arrest by means of percutaneous techniques, if cause is identified. Of course, we may also expect untreatable causes of sudden refractory arrest like aortic aneurysmal rupture, intracranial bleeding with occipital conus, unidentified trauma with severe inner organ damage, initially unrecognizable poisoning etc. However, we also expect a significant proportion of potentially treatable causes, mainly the ongoing ischemia due to acute coronary obstuction and massive pulmonary embolism with severe right ventricle failure. As per available data (**Nolan-80%**) and our own experience (**Smid, Belohlavek - data in submission**), in 80% of OHCA wictims, cardiac etiology can be identified with diagnostic accuracy in prehospital phase of approximately 75 % (**Pokorna M - Resuscitation).** Two thirds of these patients suffer either acute coronary syndrome or pulmonary embolism. In remaining one third of patients, complications of chronic heart failure is the most frequent cause.

A key prerequisite for succesful result is strict compliance with proposed timeline (see the outline of the study on **figure 1**.) and adequate use of all devices. Therefore, study preparation

phase lasted almost one year long. All RRV crews had to become perfectly familiar with LUCAS device and were repeatedly trained in application of this device. The same applies for prehospital RhinoChill device use and also for an acute implantantion of ECLS by ECMO team in cathlab. All study investigators, cathlab and ICUpersonnel have also been repeatedly trained in study protocol. Moreover, initially we plan at least 3-5 patients to be „randomized" to hyperinvasive approach (simulation phase) before real randomized study starts, to prove the concept and feasibility of the protocol. This allows us to recognize potential logistic barriers or any other misconceptions. Further on, the pilot phase of the study will be performd only within working hours, ie. 8 AM to 4 PM and only when principal investigator is present, to optimize for personal and organizational demands. Based on initial result and feasibility of the whole concept, after randomization of 30 patients, DSMB will decide whether to continue the study or not.

We also seriously considered the definition of „refractory" cardiac arrest, as this definition varies in available studies (**Ying, Guen**). We expect the average time to randomization in our proposed study to be around 20 minutes, considering following time intervals: 9 minutes is an average response time for a RRV to reach the patient with OHCA in Prague (**Franek**); a minimum of 5 minutes of ACLS by the EMS team on scene including performance of all necessary procedures (defibrillation or defibrillations, airway securence, intravenous access establishment), we actually expect this interval to last longer, ie. approximately 10 minutes and 1-2 minutes of randomization phone call with cardiac center coordinator.

Contribution of the project and clinical consequences: Potential contribution is crucial taking into account the socio-economic consequencies of cardiac arrest. Cardiac arrest often affects relatively young fully active persons, has high mortality and survivors often suffer severe neurological damage, which causes both personal tragedies to patients and to their relatives and increases in health care costs. If the beneficial effect of proposed combination of therapeutical methods were proved, it might have a profound influence on logistics of emergency care for cardiac arrest patients, mainly in cities and urban agglomerations similar to Prague, i.e. in cities with well organized prehospital care, short arrival times and within city center located cardiac center with emergently available ECLS and cathlab team capacity.

Conclusion: Authors offer a protocol of a proposed randomized study enrolling patients with wittnessed OHCA presumably of cardiac origin planned to be initiated in Prague in 2012. Study will compare hyperinvasive approach encompassing prehospital cooling, mechanical

chest compression device, VA ECLS and immediate invasive diagnostics in all patients compared to a standard of care. The protocol is opened for sharing by other cardiac centers with readily available ECLS and cathlab teams used to cooperate with emergency medical services to admit patients with refractory cardiac arrest under ongoing CPR to establish a net of centers for a multicenter trial realization.

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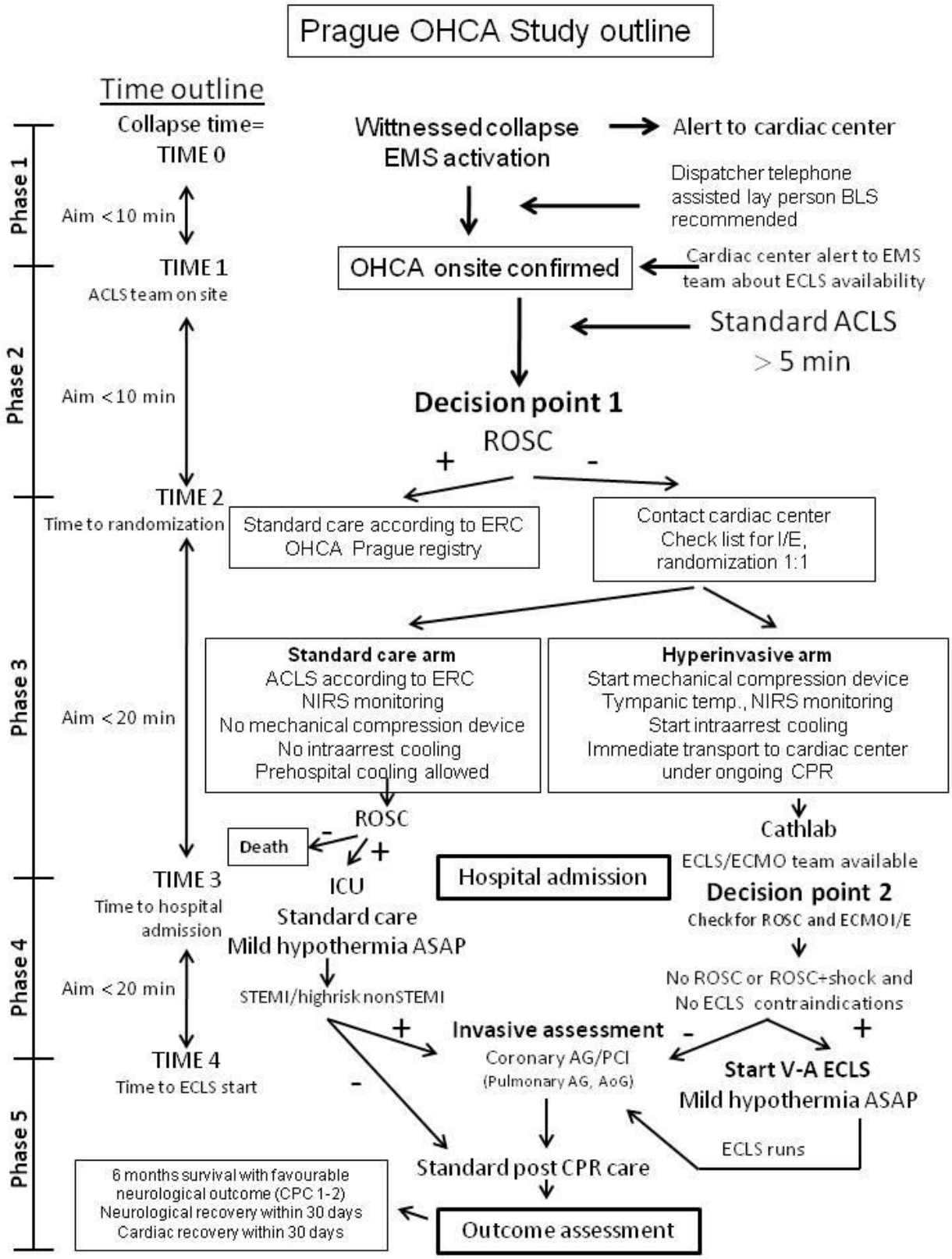
Authors contribution:

JB is a main author, cencepted and designed the study and prepared the manuscript. JJ and VK prepared the statistical power analysis. KK, OF, MP, JD, RS, JV and ZS substantially contributed to conception and design and will be responsible for acquisition, verification and interpretation of prehospital data. OS, JH, MB and AL participated on conception and design and will be responsible for acquisition, verification and interpretation of inhospital data. VM and AL obtained research funding and AL has also given a final approval of the version to be published.

Figure 1. Prague OHCA study outline.



TRIAL PROTOCOL and summary of changes

Hyperinvasive approach to out of hospital cardiac arrest using mechanical chest compression device, intraarrest cooling, ECLS (extracorporeal life support) and early coronary angiography/PCI in all patients compared to standard of care.

A randomized, parallel groups comparative clinical trial

Short title: **Hyperinvasive approach in Cardiac Arrest**

Acronym: **Prague OHCA study**

PROTOCOL REGISTRATION NUMBER: ClinicalTrials.gov: NCT01511666

Protocol	Version	Date	Summary of changes
Czech initial protocol for IRB approval and grant application	Version 1	1-Feb-2011	-
English protocol	Version 1	1-Feb-2011	No change
Czech protocol after IRB approval, registration and grant received	Version 2	19-Jul-2012	No change
Czech amended protocol	Version 2, amendment 1	5-Apr-2013	1/extracorporeal circuit will be filled with 4°C saline for earlier hypothermia achievement 2/genetic substudy 3/autoptic substudy 4/ angiography substudy 5/microcirculatory substudy
English amended protocol	Version 2, amendment 1	5-Apr-2013	1/extracorporeal circuit will be filled with 4°C saline for earlier hypothermia achievement 2/genetic substudy 3/autoptic substudy 4/ angiography substudy 5/microcirculatory substudy
Czech amended protocol	Version 2, amendment 2	10-Jan-2014	1/ crossover rules defined 2/ TTM to 36°C allowed 3/mechanical CPR allowed in both arms
Czech amended protocol	Version 2, amendment 3	2-Jul-2016	Rhinochill device used only when available

Jan Bělohlávek, Prague, May 25, 2021