JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment on Functional Neurologic Outcome in Refractory Out-of-Hospital Cardiac Arrest
A Randomized Clinical Trial

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IMPORTANCE Out-of-hospital cardiac arrest (OHCA) has poor outcome. Whether intra-arrest transport, extracorporeal cardiopulmonary resuscitation (ECPR), and immediate invasive assessment and treatment (invasive strategy) is beneficial in this setting remains uncertain.

OBJECTIVE To determine whether an early invasive approach in adults with refractory OHCA improves neurologically favorable survival.

DESIGN, SETTING, AND PARTICIPANTS Single-center, randomized clinical trial in Prague, Czech Republic, of adults with a witnessed OHCA of presumed cardiac origin without return of spontaneous circulation. A total of 256 participants, of a planned sample size of 285, were enrolled between March 2013 and October 2020. Patients were observed until death or day 180 (last patient follow-up ended on March 30, 2021).

INTERVENTIONS In the invasive strategy group (n = 124), mechanical compression was initiated, followed by intra-arrest transport to a cardiac center for ECPR and immediate invasive assessment and treatment. Regular advanced cardiac life support was continued on-site in the standard strategy group (n = 132).

MAIN OUTCOMES AND MEASURES The primary outcome was survival with a good neurologic outcome (defined as Cerebral Performance Category [CPC] 1-2) at 180 days after randomization. Secondary outcomes included neurologic recovery at 30 days (defined as CPC 1-2 at any time within the first 30 days) and cardiac recovery at 30 days (defined as no need for pharmacological or mechanical cardiac support for at least 24 hours).

RESULTS The trial was stopped at the recommendation of the data and safety monitoring board when prespecified criteria for futility were met. Among 256 patients (median age, 58 years; 44 [17%] women), 256 (100%) completed the trial. In the main analysis, 39 patients (31.5%) in the invasive strategy group and 29 (22.0%) in the standard strategy group survived to 180 days with good neurologic outcome (odds ratio [OR], 1.63 [95% CI, 0.93 to 2.85]; difference, 9.5% [95% CI, −1.3% to 20.1%]; $P = .09$). At 30 days, neurologic recovery had occurred in 38 patients (30.6%) in the invasive strategy group and in 24 (18.2%) in the standard strategy group (OR, 1.99 [95% CI, 1.11 to 3.57]; difference, 12.4% [95% CI, 1.9% to 22.7%]; $P = .02$), and cardiac recovery had occurred in 54 (43.5%) and 45 (34.1%) patients, respectively (OR, 1.49 [95% CI, 0.91 to 2.47]; difference, 9.4% [95% CI, −2.5% to 21%]; $P = .12$). Bleeding occurred more frequently in the invasive strategy vs standard strategy group (31% vs 15%, respectively).

CONCLUSIONS AND RELEVANCE Among patients with refractory out-of-hospital cardiac arrest, the bundle of early intra-arrest transport, ECPR, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcome at 180 days compared with standard resuscitation. However, the trial was possibly underpowered to detect a clinically relevant difference.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01511666

JAMA. 2022;327(8):737-747. doi:10.1001/jama.2022.1025

Visual Abstract

Supplemental content

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Section Editor: Christopher Seymour, MD, Associate Editor, *JAMA* (christopher.seymour@jamanetwork.org).

Out-of-hospital cardiac arrest (OHCA) is a significant socioeconomic burden to society.[1] In a large trial, 50% of patients who attained stable return of spontaneous circulation (ROSC) during initial resuscitation and were transferred to the hospital for postresuscitation care achieved neurologically favorable survival.[2] However, refractory cardiac arrest (ie, prolonged cardiac arrest and cardiac arrest without ROSC in the field) is associated with poor clinical outcomes.[3] In patients without ROSC, the odds of survival are low when transport to the hospital occurs during ongoing cardiopulmonary resuscitation (CPR), usually less than 4%.[4,5]

Temporary replacement of a failing circulation by extracorporeal life support (ECLS), a method called extracorporeal cardiopulmonary resuscitation (ECPR), has been recognized as a potential approach to refractory cardiac arrest.[6-8] Despite encouraging results of nonrandomized studies, a meta-analysis,[9] and 1 recently published small randomized trial,[10] the benefit of ECPR in refractory OHCA remains uncertain.[11,12] Recent European Resuscitation Guidelines[13] provide a weak recommendation for ECPR, which may be considered as a rescue method when conventional CPR is failing, with very low certainty of evidence.

The purpose of this randomized clinical trial was to compare the bundle of early intra-arrest transport to the hospital using mechanical CPR, ECPR, and immediate invasive assessment and treatment vs standard treatment in refractory OHCA for achieving survival with good neurologic outcome at 180 days.

Key Points

Question In patients with witnessed refractory out-of-hospital cardiac arrest, does early intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and invasive assessment and treatment improve outcomes compared with standard resuscitation?

Findings In this randomized clinical trial that included 256 patients, survival with neurologically favorable outcome (Cerebral Performance Category 1-2) at 180 days occurred in 31.5% in the invasive strategy group and 22.0% in the standard resuscitation group, a difference that was not statistically significant.

Meaning Among patients with refractory out-of-hospital cardiac arrest, the bundle of early intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcome at 180 days compared with standard resuscitation, although the trial was possibly underpowered to detect a clinically relevant difference.

Methods

Study Design

This randomized clinical trial was conducted at a single center in Prague, Czech Republic, from March 1, 2013, to October 25, 2020 (with final follow-up on March 30, 2021). The study protocol, including statistical analysis plan (Supplement 1), was published in detail prior to study initiation,[14] and the study was approved by the institutional review board of the General University Hospital and First Faculty of Medicine, Charles University in Prague (192/11S-IV).

Each participant's legal representative was informed of the participant's study enrollment and was asked for written informed consent as soon as possible. All patients who regained normal neurologic function were asked to provide their written consent regarding the use of their data. Consent requirements were waived for patients who died at the scene and never reached the hospital and for participants without known legal representatives. As specified in the protocol, a data and safety monitoring board reviewed the data on patient outcome and complications every 6 months or after every 30 patients enrolled, whichever came first. An independent contract research organization verified and monitored the study data.

Participants

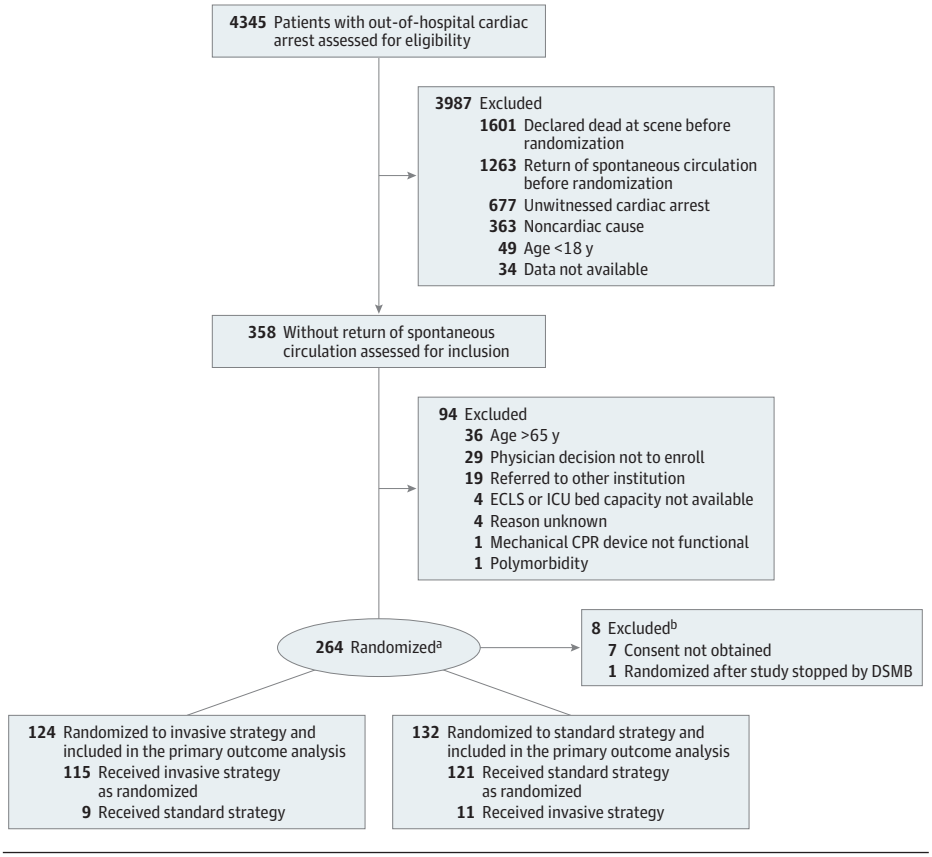
Adults aged 18 to 65 years receiving ongoing resuscitation for witnessed OHCA of presumed cardiac etiology were eligible for enrollment in the trial, given that they had received a minimum of 5 minutes of advanced cardiac life support without ROSC and when the ECPR team was available at the cardiac center. Patients who had unwitnessed cardiac arrest or presumed noncardiac cause, had suspected or confirmed pregnancy, attained ROSC within 5 minutes during initial resuscitation, regained consciousness, had obvious life-limiting comorbidities, bleeding diathesis, known do-not-resuscitate order, or known prearrest Cerebral Performance Category (CPC)[15] 3 or greater were excluded (**Figure 1**; eTable 1 in Supplement 2).

Enrollment and Randomization

Enrollment was conducted with the close cooperation of the Prague Emergency Medical Service dispatch center. The study coordinator in the cardiac center was notified by an automatic Short Message Service alert on every occasion when the dispatch center initiated telephone-assisted bystander chest compressions and activated a rapid response vehicle for a witnessed collapse suspected to be cardiac arrest of presumed cardiac cause. A telephone connection was subsequently established during the ongoing chest compressions between the cardiac center coordinator and the physician or paramedic on scene (randomization call). The coordinator logged into a web-based secured randomization system that was available 24 hours per day and maintained by the Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno. An assigned patient number and intervention group, ie, invasive group or standard group, was recorded. The log-in link was accessible from all computers within the cardiac center and from the smartphone of the coordinator.

For randomization, the patient's estimated age and sex as well as confirmation of the inclusion/exclusion criteria were recorded (eTable 1 in Supplement 2). Randomization into the standard strategy or invasive strategy group was based on 4 strata (men ≤45 years, men >45 years, women ≤45 years,

Figure 1. Prehospital Flow of Participants in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest



DSMB indicates data and safety monitoring board; ECLS, extracorporeal life support; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

[a] Randomization into standard strategy and invasive strategy groups was based on 4 strata (men ≤45 years, men >45 years, women ≤45 years, women >45 years), with block size of 8.

[b] Seven patients were excluded after randomization because consent was refused and information was not available as to how many were randomized to each group for analysis.

women >45 years), with block size of 8. The block size was not disclosed to research personnel.

Intervention

Patients randomized to the standard strategy group received continued advanced cardiac life support on site. The use of drugs, further defibrillations, or other interventions followed recommended guidelines.[16,17] If ROSC was achieved (defined as a cardiac electrical activity with palpable pulse), transport to the hospital was initiated and an early invasive strategy (ie, coronary angiography) was encouraged.

A mechanical chest compression device (LUCAS, Lund University Cardiac Arrest System; Physio-Control Inc/Jolife AB, Lund, Sweden) was originally reserved for the invasive strategy group only; however, following the publication of a major trial on mechanical chest compression,[18] the attachment of a mechanical chest compression device was left to the discretion of the emergency physician and was allowed for use at any point during CPR.

In the invasive strategy group, intra-arrest intranasal evaporative cooling via a RhinoChill device (BeneChill Inc) was initiated if feasible (this device became unavailable during the course of the study in 2016) and the patient was immediately transferred directly to the cardiac center catheterization laboratory during ongoing CPR with the intention of proceeding with ECPR if ROSC was not achieved en route or on admission. The use of drugs, further defibrillations en route, or other interventions during transport followed European Resuscitation Council guidelines.[16,17] The team, including study coordinator, intensivist, perfusionist (a specialist responsible for an ECLS), interventional cardiologist, study data manager, and interventional and intensive care unit nurses simultaneously prepared all the necessary equipment. A dry-primed extracorporeal life support machine was ready to be used in the catheterization laboratory when needed.

On admission, the overall status, ROSC presence, and ECLS implantation inclusion/exclusion criteria (eTable 1 in Supplement 2) were evaluated. The ECLS cannulation was performed on the catheterization table during ongoing mechanical CPR using a femoro-femoral approach. After commencement of ECLS and following the completion of the invasive diagnostic and therapeutic procedures (ie, coronary, and eventually pulmonary or aortic angiography and percutaneous coronary intervention, if appropriate), an antegrade perfusion cannula was implanted in the cannulated limb under ultrasound guidance. Patients receiving ECLS were continuously anticoagulated with heparin unless contraindicated, with a target activated partial thromboplastin time of 50 to 70 seconds.

Postresuscitation care was standardized in both study groups. All patients admitted to the hospital had an immediate biochemical evaluation, an urgent bedside echocardiogram, and whole-body computed tomography if feasible and clinically indicated. In-hospital target temperature management to 33 °C was initiated as soon as possible either via ECLS heat exchanger or other routine measures (intravascular or surface feedback device cooling). Following the publication of a target temperature management trial,[19] in cases with early awakening or complications of hypothermia, a strict temperature management to 36 °C was allowed instead of 33 °C. All other postarrest critical care management, including withdrawal of life-sustaining therapy, complied with European Resuscitation Council guidelines and other generally accepted approaches.[16-18,20]

A crossover from the standard strategy group to the invasive strategy group (and vice versa) was allowed in selected patients. In the standard to invasive strategy group, the decision was made based on the request of an emergency physician. At least 2 additional unsuccessful defibrillations were required after randomization before a crossover was accepted by the cardiac center coordinator. The crossover from invasive strategy to standard strategy was accepted when continuing care with invasive measures was deemed to be futile. The termination of resuscitation efforts followed the European Resuscitation Council guidelines,[16,17] although the final decision was based on the discretion of the emergency physician or cardiac intensivist in charge.

Outcomes

Primary Outcome

Primary outcome was 180-day survival with favorable neurologic status defined as no or minimal neurologic impairment (CPC 1 or 2). The CPC schema ranges from 1 (defined as conscious, alert, able to work), 2 (conscious, sufficient cerebral function for independent activities of daily life, able to work in sheltered environment), 3 (conscious, dependent on others for daily support), 4 (comatous, vegetative state) to 5 (brain death).

Neurologic outcome was assessed by a neurologist in a blinded fashion.

Secondary Outcomes

Secondary outcomes included 30-day survival with cardiac recovery (no need for pharmacological or mechanical cardiac support for 24 hours) and neurologic recovery (CPC 1 or 2) at any point within the first 30 days after cardiac arrest.

Exploratory Analyses

Survival to 180 days was assessed as a post hoc outcome. Post hoc subgroup analyses for the primary outcome were performed in the following subgroups: older than 65 years vs 65 years or younger, sex, place of cardiac arrest, initial rhythm, pH below median value vs above, lactate level below median value vs above, and cause of cardiac arrest.

Complications

Bleeding complications were assessed based on Thrombolysis in Myocardial Infarction classification[21] under "major" category, defined as any intracranial hemorrhage (excluding microhemorrhages <10 mm), fatal bleeding directly resulting in death within 7 days, or overt bleeding associated with a decrease in hemoglobin concentration of 5 g/dL or a 15% absolute decrease in hematocrit. Organ lacerations were assessed both by morphological examinations (mainly computed tomography) and during autopsies. Technical complications related to ECLS were gathered and reported by perfusionists.

Power Analysis and Sample Size Calculation

Sample size determination was computed for the statistical superiority of invasive strategy over standard strategy using a 2-tailed test with $\alpha = .05$ and 90% power. A 10% 6-month survival with favorable neurologic outcome in the standard strategy group was expected. Three scenarios were suggested: 10% increase of primary outcome, with 571 patients expected to be enrolled; 15% increase, with 285 patients; and 20% increase, with 176 patients.[14]

Statistical Analysis

A complete case analysis, with no assumptions made for missing data, was performed for primary and secondary outcomes. In the main analysis, patient data were analyzed according to randomization group, and data from patients who crossed over were analyzed by original group assignment. A post hoc analysis pooled all patients treated with ECPR (both those allocated to the invasive strategy group and receiving ECPR and those allocated to the standard strategy group and receiving ECPR after crossover to the invasive strategy group).

Continuous data were evaluated for a normal distribution by Shapiro-Wilk test. Numeric variables are expressed as medians and IQRs. The 2-sided Mann-Whitney test was used to compare cardiac arrest times and laboratory values. Categorical values were compared using the 2-sided Fisher exact test (for 2 × 2 table) or χ^2 test. The primary and secondary outcomes are reported by odds ratios and absolute differences with 95% confidence intervals.

The survival analysis was performed by the Kaplan-Meier analysis and log-rank test and considered patients alive at day 180 regardless of their neurologic status. A subgroup analysis was computed using logistic regression and analysis of interaction between given stratification and study group. Because of the potential for type I error due to multiple comparisons, findings for secondary outcomes and subgroup analyses should be interpreted as exploratory.

A 2-sided $P < .05$ was considered statistically significant. Statistical analyses were performed with MedCalc version 19.7 (MedCalc Software Ltd) and SPSS version 26.0.0.0 (IBM Corp).

Results

The study was terminated on October 25, 2020, at the recommendation of the data and safety monitoring board (Supplement 3) because the standardized test statistics for results of primary end point in the study intersected a prespecified stopping rule for futility at n = 256 (eFigure 1 in Supplement 2).

Table 1. Baseline Demographics and Prehospital Resuscitation Characteristics of Included Patients in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

Characteristics	No. (%)	
	Invasive strategy (n = 124)	Standard strategy (n = 132)
Age, median (IQR), y	59 (48-66)	57 (47-65)
Sex		
Men	102 (82)	110 (83)
Women	22 (18)	22 (17)
Medical history, No./total (%)[a]		
Hypertension	47/108 (44)	42/83 (51)
Diabetes	19/104 (18)	17/83 (21)
Coronary artery disease	17/104 (16)	17/83 (21)
Chronic heart failure	11/106 (10)	5/79 (6)
COPD	8/105 (8)	2/79 (3)
Chronic kidney disease	3/104 (3)	2/79 (3)
Implanted ICD	3/121 (3)	0/89
Location of cardiac arrest		
Public place	44 (36)	54 (41)
Home	42 (34)	34 (26)
EMS	19 (15)	17 (13)
Car	8 (7)	7 (5)
Workplace	5 (4)	14 (11)
Hotel	4 (3)	6 (5)
Health facility	2 (2)	0
Initial rhythm[b]		
Ventricular fibrillation	72 (58)	84 (64)
Asystole	31 (25)	24 (18)
Pulseless electrical activity	21 (17)	24 (18)
Bystander CPR[c]	123 (99)	129 (98)
Telephone-assisted bystander CPR	96 (77)	107 (81)
Time from collapse to EMS arrival, median (IQR), min	8 (7-11)	9 (7-11)
Time from collapse to ACLS, median (IQR), min	10 (7-13)	11 (8-14)
Time to telephone-assisted CPR, median (IQR), min	3 (2-5)	2 (1-4)
Time from collapse to randomization, median (IQR), min	24 (21-30)	26 (19-31)
No. of prehospital epinephrine doses, median (IQR), mg	4 (2-5)	5 (3-7)
No. of prehospital defibrillation attempts, median (IQR)	4 (2-6)	4 (2-7)
Mechanical CPR[d]	114 (92)	104 (79)
Intermittent ROSC[e]	41 (33)	45 (34)
Hypothermia initiated in field[f]	21 (17)	12 (9)

Abbreviations: ACLS, advanced cardiac life support; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ICD, implantable cardioverter-defibrillator; ROSC, return of spontaneous circulation.

[a] The information for several categories was obtained later during patient care from EMS, caregivers, relatives, and chart reviews and might not have been available to caregivers during initial treatment.

[b] As determined by EMS.

[c] High rate of bystander CPR consistent with generally high rate in Prague (>80%) as reported in a Eureca 2 study.[27]

[d] Use of LUCAS device (Lund University Cardiac Arrest System; Physio-Control Inc/Jolife AB).

[e] Defined as an unsustained palpable pulse with organized ECG rhythm.

[f] Prehospital hypothermia provided by means of intranasal evaporative cooling was used in the invasive strategy group and those patients in the standard strategy group who crossed over to the invasive approach. This method became unavailable during the course of the study in 2016; therefore, the percentage of use is low.

During the study enrollment period from March 1, 2013, to October 25, 2020, 4345 attended cardiac arrests occurred within the Prague region. After exclusion of those without presumed cardiac cause, those that lacked a witness, patients who achieved ROSC, or patients who died without consideration for study enrollment, 358 patients with arrest refractory to initial resuscitation efforts remained. Of these, 264 were eligible for the study enrollment and randomized. Later, 8 patients were withdrawn; for 7, consent was not obtained from the relatives, and 1 patient was erroneously randomized after the study was already stopped.

In total, 256 patients were analyzed, 124 allocated to the invasive strategy group and 132 to the standard strategy group. Overall, in 20 patients (7.6%), a crossover was accepted. There were 11 crossovers from the standard strategy group to the invasive strategy group (all except 1 involved patients with refractory ventricular fibrillation) and 9 crossovers from the invasive strategy group to the standard strategy group (Figure 1).

Patient and Cardiac Arrest Characteristics

Table 1 reports the main demographics of the study population. The median age was 59 years (IQR, 48-66) for the invasive strategy group and 57 years (IQR, 47-65) for the standard strategy group, and 44 of the 256 patients (17%) were women. Hypertension, diabetes, and coronary artery disease

Table 2. Primary and Secondary Outcomes in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

	No. (%)			
	Invasive strategy (n = 124)	Standard strategy (n = 132)	Absolute difference, % (95% CI)	*P* value
Primary outcome				
Survival with minimal or no neurologic impairment at 180 d[a]	39 (31.5)	29 (22.0)	9.5 (−1.3 to 20.1)	.09
Secondary outcomes				
Survival with minimal or no neurologic impairment at 30 d[a]	38 (30.6)	24 (18.2)	12.4 (1.9 to 22.7)	.02
Cardiac recovery at 30 d[b]	54 (43.5)	45 (34.1)	9.4 (−2.5 to 21)	.12

[a] Defined as Cerebral Performance Category 1 or 2. The Cerebral Performance Category schema ranges from 1 (defined as conscious, alert, able to work), 2 (conscious, sufficient cerebral function for independent activities of daily life, able to work in sheltered environment), 3 (conscious, dependent on others for daily support), 4 (comatous, vegetative state) to 5 (defined as brain death). All patients observed to death or 180 days.

[b] Defined as absence of both pharmacological and mechanical cardiac support for at least 24 hours.

were prevailing comorbidities. The most frequent cause of cardiac arrest was acute coronary syndrome in both the invasive strategy group (64/124 [52%]) and the standard strategy group (63/132 [48%]).

Cardiac arrest occurred most commonly in a public place (44/124 patients [36%] in invasive strategy group, 54/132 [41%] in the standard strategy group). Ventricular fibrillation was the most common initial rhythm (72/124 patients [58%] in the invasive strategy group and 84/132 [64%] in the standard strategy group). Bystander CPR was performed in 123 of 124 cases (99%) in the invasive strategy group and in 129 of 132 (98%) in the standard strategy group, as well as telephone-assisted dispatch center CPR in 96 of 124 (77%) and 107 of 132 (81%), initiated within median of 3 (IQR, 2-5) and 2 (IQR, 1-4) minutes after the collapse in the respective groups. Patients were randomized within a median of 24 (IQR, 21-30) and 26 (IQR, 19-31) minutes after collapse for the invasive strategy and standard strategy groups, respectively.

Primary Outcome

Survival with favorable neurologic outcome at 180 days occurred in 39 of 124 patients (31.5%) in the invasive strategy group and 29 of 132 patients (22%) in the standard strategy group, a difference that was not statistically significant (odds ratio, 1.63 [95% CI, 0.93 to 2.85]; absolute difference, 9.5% [95% CI, −1.3% to 20.1%]; *P* = .09) (**Table 2**). There were no missing data for the primary outcome analysis.

Secondary Outcomes

Neurologic recovery at 30 days occurred in 38 of 124 patients (30.6%) in the invasive strategy group and 24 of 132 (18.2%) in the standard strategy group (odds ratio, 1.99 [95% CI, 1.11 to 3.57]; absolute difference, 12.4% [95% CI, 1.9% to 22.7%]; *P* = .02).

Cardiac recovery at 30 days occurred in 54 of 124 patients (43.5%) in the invasive strategy group and 45 of 132 (34.1%) in the standard strategy group (odds ratio, 1.49 [95% CI, 0.91 to 2.47]; absolute difference, 9.4% [95% CI, −2.5 to 21%]; *P* = .12).

Resuscitation and Hospitalization Procedures and Outcomes

In the invasive strategy group, a median of 4 (IQR, 2-5) epinephrine doses were used, compared with 5 (IQR, 3-7) in the standard strategy group (*P* = .002), while the number of prehospital defibrillations was median of 4 (IQR, 2-6) in the invasive strategy group vs 4 (IQR, 2-7) in the standard strategy group. Intermittent ROSC was identified in 41 of 124 patients (33%) in the invasive strategy group and 45 of 132 (34%) in the standard strategy group.

As **Table 3** describes in detail, more patients in the invasive strategy group were admitted to the hospital after a shorter time of transport from the scene. The overall CPR time was longer in the invasive strategy group (median, 58 [IQR, 43-70] vs 46 [IQR, 33-68] minutes, *P* = .04), as every effort was made to bring the patient to the hospital catheterization laboratory for ECPR.

Among patients admitted to the hospital, target temperature management was used in 117 of 123 patients (95%) in the invasive strategy group and 61 of 87 (70%) in the standard strategy group (*P* < .001). Those who did not receive temperature control (6 in the invasive strategy group and 26 in the standard strategy group) either had contraindications (mainly advanced hemodynamic instability) or died early, before reaching the intensive care unit (eTable 2 in Supplement 2).

An invasive assessment with diagnostic angiography was performed in 120 of 123 admitted patients (98%) in the invasive strategy group and 67 of 87 (77%) in the standard strategy group (*P* < .001), corresponding mainly to coronary angiography. Immediate PCI was performed successfully in 56 of 62 patients (90%) in the invasive strategy group and 24 of 30 (80%) in the standard strategy group (*P* = .20). Of note, in 3 patients, emergency balloon aortic valvuloplasty was performed. On admission, patients in invasive strategy vs standard strategy group had lower pH (median, 6.93 [IQR, 6.8-7.1] vs 7.03 [IQR, 6.9-7.2]; *P* = .001) and higher serum lactate levels (median, 12.5 [IQR, 9.2-16] mmol/L vs 10.4 [IQR, 7.5-13.5] mmol/L; *P* = .01).

Table 3. Additional Outcomes Related to Transport, Hospitalization, and Intervention in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

Prehospital and early hospital events	No. (%)	
	Invasive strategy (n = 124)	Standard strategy (n = 132)
Arrived to hospital	123 (99)	87 (66)
Time from collapse to hospital arrival, median (IQR), min	49 (44-60)	60 (50-69)
Transport time - time from randomization to admission, median (IQR), min	26 (19-33)	33 (25-42)
Prehospital declaration of death	1 (1)	45 (34)
Declaration of death within 1 h of hospital admission	10 (8)	19 (14)
Time of CPR (time to death/ROSC or ECLS), median (IQR), min	58 (43-70)	46 (33-68)
Duration of CPR, min		
<30	14 (11)	26 (20)
≥30 and <45	19 (15)	33 (25)
≥45	91 (73)	73 (55)
Sustained ROSC on admission[a]	34 (27)	58 (44)
Hospitalization events		
Target temperature management used, No./total (%)[b]	117/123 (95)	61/87 (70)
Extracorporeal life support		
ECLS implanted	82 (66)	10 (8)
Time to ECLS, median (IQR), min	61 (55-70) [n = 81]	62 (51-73) [n = 10]
Time of implantation (door to ECLS), median (IQR), min	12 (9-15) [n = 80]	16 (11-17) [n = 10]
Invasive assessment, No./total (%)		
Diagnostic angiography	120/123 (98)	67/87 (77)
Coronary angiography	115/120 (96)	66/67 (99)
Aortography	28/120 (24)	13/67 (19)
Left ventricle angiography	26/120 (22)	21/67 (31)
Pulmonary angiography	22/120 (18)	5/67 (8)
Emergency invasive interventions, No./total (%)		
PCI (both for ACS and CAD)[c]		
Successful	56/62 (90)	24/30 (80)
Unsuccessful	6/62 (10)	6/30 (20)
Balloon valvuloplasty	0/120	3 (4)
Laboratory values on admission		
pH [reference, 7.36-7.44], median (IQR)	6.93 (6.8-7.1)	7.03 (6.9-7.2)
Lactate [reference, 0.5-2.0], median (IQR), mmol/L	12.5 (9.2-16)	10.4 (7.5-13.5)
Cause of cardiac arrest (including autopsy findings)		
Acute coronary syndrome	64 (52)	63 (48)
Coronary artery disease-chronic	14 (11)	18 (14)
Pulmonary embolism	12 (10)	12 (9)
Chronic heart failure	8 (7)	6 (5)
Myocarditis	6 (5)	2 (2)
Accidental hypothermia	3 (2)	1 (1)
Bleeding-other	3 (2)	0
Cardiomyopathy	3 (2)	6 (5)
Unknown	3 (2)	12 (9)
Aortic stenosis	2 (2)	6 (5)
Aortic dissection type A	2 (2)	2 (2)
Pulmonary hypertension	2 (2)	0
Intracranial hemorrhage	1 (1)	2 (2)
Other	1 (1)	1 (1)
Sepsis	0	1 (1)
Cause of death		
No.	84	101
Multiple organ failure	35 (42)	17 (17)
Brain death	21 (25)	9 (9)
Refractory arrest	13 (16)	67 (66)
Cardiogenic shock	10 (12)	4 (4)
Bleeding	4 (5)	0
Unknown	1 (1)	4 (4)
Withdrawal of life-sustaining therapy	21 (17)	14 (11)
Evaluated for organ donation[d]	21 (17)	3 (2)
Accepted for organ donation	13 (11)	2 (2)
Complications/other events, No./total (%)		
Bleeding—any[e]	36/116 (31)	10/69 (15)
Overt	24/36 (67)	8/10 (80)
Intracranial hemorrhage	8/36 (22)	2/10 (20)
Fatal	4/36 (11)	0/10
Organ lacerations	4/114 (4)	3/103 (3)
Technical[f]	3/124 (2)	0/132

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ECLS, extracorporeal life support; MOF, multiple organ failure syndrome; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation.

[a] Defined as a palpable pulse with organized ECG rhythm for at least 20 minutes.

[b] Target temperature management indicates all cooling categories, including intravascular and surface feedback device cooling and ECLS heat exchanger cooling.

[c] PCI was deemed successful if resulting in residual stenosis of less than 50% with Thrombolysis in Myocardial Infarction grade 2 or 3 flow.

[d] Evaluation by the transplant center as a potential donor.

[e] Bleeding complications were assessed based on Thrombolysis in Myocardial Infarction classification[21] under "major" category, defined as any intracranial hemorrhage (excluding microhemorrhages <10 mm), fatal bleeding directly resulting in death within 7 days, or overt bleeding associated with a decrease in hemoglobin concentration of 5 g/dL or or a 15% absolute decrease in hematocrit.

[f] Any device failures during periresuscitation care, mainly focused on extracorporeal life support components.

Cause of death was different between the groups, with multiple organ failure syndrome being the most frequent cause in the invasive strategy group (35/84 [42%]) and refractory arrest in the standard strategy group (67/101 [66%]).

Withdrawal of life-sustaining therapies occurred in 21 of 124 patients (17%) in the invasive strategy group and 14 of 132 (11%) in the standard strategy group. Organ donation, both considered and accepted, was more frequent in the invasive strategy group (Table 3).

In the invasive strategy group, 11 of 124 patients (9%) were declared dead on scene or during transport or died within 1 hour after admission, compared with 64 of 132 (49%) in the standard strategy group ($P < .001$). Thirty-four of 124 patients (27%) in the invasive strategy group and 58 of 132 (44%) in the standard strategy group achieved sustained ROSC ($P = .01$). For details of resuscitation outcomes, see Table 3 and eFigure 2 in Supplement 2.

Complications

In the invasive strategy group, more major bleeding events were observed (31% vs 15%), including fatal, intracranial, and overt bleeds (Table 3). By contrast, organ lacerations caused by CPR occurred in 4 patients (3.5%) in the invasive strategy group and 3 (2.9%) in the standard strategy group, and technical complications occurred in 3 patients (2.4%) in the invasive strategy group and 0 patients in the standard strategy group (eTables 3 and 4 in Supplement 2). Protocol deviations are described in eTable 5 in Supplement 2.

Additional Analyses

ECPR Outcomes and Crossover Groups

ECPR for ongoing refractory cardiac arrest at admission to the hospital was implemented in 10 patients in the standard strategy group, exclusively in those crossed over to the invasive strategy (10 of 11 crossovers; 1 reached sustained ROSC en route), and in 82 of 124 patients (66%) randomized to the invasive strategy group. Three patients in the invasive strategy group implanted with ECLS died within 1 hour after admission. Among those who ultimately received ECPR, survival with a favorable neurologic outcome at 180 days occurred in 4 of 10 (40%) of those crossed over from the standard strategy group to the invasive strategy group and in 16 of 82 (20%) who were randomized to the invasive group and received ECPR, corresponding to overall neurologically favorable outcome at 180 days of 22% (20/92 patients) when patients who received ECPR from both groups are pooled. All other patients in the standard strategy group who did not obtain stable ROSC and were not crossed over died.

While 5 of 11 patients (45%) who were randomized to the standard strategy and crossed over to the invasive approach had favorable neurologic outcome at 180 days, no patient who was randomized to the invasive strategy group and crossed over to standard resuscitation survived (n = 9).

Survival to 180 Days

Of the 256 participants, 68 (27%) survived to 180 days with favorable neurologic outcome. Comparison of 180-day Kaplan-Meier survival analysis in the entire invasive strategy and standard strategy groups is shown in eFigure 3 in Supplement 2.

Subgroup Analysis

Post hoc subgroup analysis is provided in **Figure 2**. Details of number of patients in different times of CPR subgroups with favorable neurologic outcome are reported in eFigure 4 in Supplement 2.

Discussion

In this single-center randomized clinical trial, an invasive strategy encompassing the bundle of early intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and invasive assessment in refractory out-of-hospital cardiac arrest of presumed cardiac origin did not significantly improve 180-day survival with favorable neurologic outcome compared with standard care. The study was terminated after enrolling 256 patients by the decision of the data and safety monitoring board, while reaching a stopping rule within prespecified scenarios. However, considering wide confidence intervals in the between-group difference for the primary outcome, the study may have been underpowered to detect a clinically important difference in favor of the invasive strategy group.

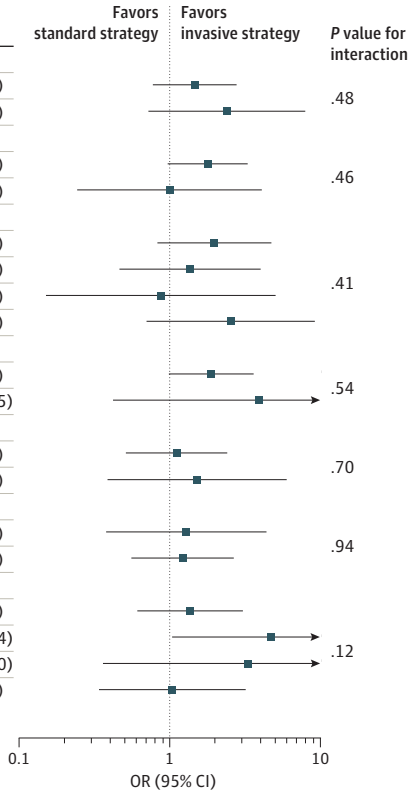
In the predefined secondary outcome analysis, a significantly improved 30-day neurologic recovery defined as CPC 1 or 2 was shown in favor of invasive strategy, in contrast to cardiac recovery, which was not statistically different between the groups. Invasive approach was associated with an increased risk of bleeding complications, an inherent complication of ECPR.[23]

Prague Emergency Medical Service is a single emergency service that covers the area of Prague, serving 1.25 million individuals, and operates with 1 dispatch center using a rapid response vehicle system with an emergency physician. Approximately 500 to 600 resuscitated cardiac arrests occur in Prague each year,[24] and patients with presumed cardiac etiology who achieve ROSC are distributed to several cardiac centers. During the study period, randomized patients constituted 6% of all persons who experienced cardiac arrest and received CPR (Figure 1). This is comparable to the proportions in Vienna and other studies that have suggested 4% to 6% of OHCAs to be suitable for an intra-arrest transport approach.[25,26] However, in these studies, potential candidates were evaluated retrospectively, whereas in this study, patients were evaluated during ongoing on-scene CPR. More than 90% of bystander CPR in this study affirms previously reported generally high percentage of bystander CPR in Prague,[27] in line with more than 77% of patients receiving concurrently telephone-assisted CPR. Patients were randomized after a median of 24 (IQR, 21-30) and 26 (IQR, 19-31) minutes of ongoing cardiac arrest, thus including approximately 15 minutes of advanced cardiac life support. This is a reasonable time to consider rescue interventions such as ECPR followed by immediate coronary reperfusion.[22,28] Patients experienced true refractory OHCAs, with many being resuscitated for more than 45 minutes in both groups while a still substantial proportion of patients ultimately achieved sustained ROSC.

Until now, to our knowledge, only 1 small, randomized study (ARREST) in refractory OHCA has been published.[10] The study was prematurely stopped after 30 randomized patients based on a recommendation of the data and safety

Figure 2. Post Hoc Analysis, Primary Outcome According to Subgroups in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

	Survival with minimal or no neurologic impairment at 180 d, No./total No. (%)			
	Invasive strategy	Standard strategy	Difference, % (95% CI)	OR (95% CI)
Age, y				
<65	29/89 (32.6)	24/97 (24.7)	7.8 (-5.1 to 20.8)	1.47 (0.78-2.79)
≥65	10/35 (28.6)	5/35 (14.3)	14.3 (-4.6 to 33.2)	2.40 (0.72-7.95)
Sex				
Men	34/102 (33.3)	24/110 (21.8)	11.5 (-0.5 to 23.5)	1.79 (0.97-3.30)
Women	5/22 (22.7%)	5/22 (22.7)	0.0 (-24.8 to 24.8)	1.00 (0.24-4.10)
Place of cardiac arrest				
Public	17/44 (38.6)	13/54 (24.1)	14.6 (-3.8 to 32.9)	1.99 (0.83-4.74)
Home	11/42 (26.2)	7/34 (20.6)	5.6 (-13.4 to 24.6)	1.37 (0.47-4.03)
EMS	3/19 (15.8)	3/17 (17.6)	-1.9 (-26.3 to 22.6)	0.88 (0.15-5.05)
Other	8/19 (42.1)	6/27 (22.2)	19.9 (-7.3 to 47.1)	2.55 (0.70-9.21)
Initial rhythm				
Shockable	35/72 (48.6)	28/84 (33.3)	15.3 (0.0 to 30.6)	1.89 (0.99-3.62)
Nonshockable	4/52 (7.7)	1/48 (2.1)	5.6 (-2.7 to 13.9)	3.92 (0.42-36.35)
pH[a]				
≥6.95	29/54 (53.7)	25/49 (51.0)	2.7 (-16.6 to 22.0)	1.11 (0.51-2.42)
<6.95	10/69 (14.5)	3/30 (10.0)	4.5 (-9.1 to 18.1)	1.53 (0.39-5.99)
Lactate[a]				
≥11.6 mmol/L	12/70 (17.1)	4/29 (13.8)	3.3 (-12.0 to 18.7)	1.29 (0.38-4.40)
<11.6 mmol/L	27/52 (51.9)	23/49 (46.9)	5.0 (-14.5 to 24.5)	1.22 (0.56-2.67)
Cardiac arrest cause				
ACS	18/64 (28.1)	14/63 (22.2)	5.9 (-9.2 to 21.0)	1.37 (0.61-3.07)
CAD	9/14 (64.3)	5/18 (27.8)	36.5 (4.0 to 69.0)	4.68 (1.04-21.04)
CHF	5/8 (62.5)	2/6 (33.3)	29.2 (-21.3 to 79.6)	3.33 (0.36-30.70)
Other	7/38 (18.4)	8/45 (17.8)	0.6 (-16.0 to 17.3)	1.04 (0.34-3.20)



ACS indicates acute coronary syndrome; CAD, coronary artery disease; CHF, chronic heart failure; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; OR, odds ratio; ROSC, return of spontaneous circulation.

[a] For pH and lactate level, the first values after admission are used.

monitoring board because of superiority of early extracorporeal membrane oxygenation (ECMO)-facilitated resuscitation vs standard advanced cardiac life support treatment. The ARREST trial showed that ECMO-facilitated resuscitation for patients with OHCA and refractory ventricular fibrillation significantly improved survival to hospital discharge and functional status compared with patients receiving standard advanced cardiac life support (6/14 patients [43%] vs 1/15 [7%]; risk difference, 36.2% [95% CI, 3.7% to 59.2%]; posterior probability of ECMO superiority, 0.9861). Cumulative 6-month survival was also significantly better in the early ECMO group.[10] The ARREST study differed from the present study mainly in 2 aspects: only patients presenting with shockable rhythms were considered, and patients were randomized after being transferred to the hospital, ie, after approximately 50 minutes of CPR. In contrast, the present study randomized patients during on-scene ongoing CPR, thus comparing different treatment scenarios to consider at the point of impending refractoriness, rather than ultimate rescue option after 50 minutes of unsuccessful CPR, when a standard approach has negligible chance for success.[3,28,29]

An ongoing question related to intra-arrest transport and early invasive treatment for refractory OHCA is the timing of when such an approach should be considered. In this study, the timeline that was adhered to matched the timeline as planned in the protocol and probably represents a realistic timeline in semicrowded urban areas using in-hospital ECPR for OHCA. Patients were admitted within a median of 49 (IQR, 44-60) minutes of collapse in the invasive strategy group, representing approximately 26 minutes of retrieval and transport from the scene to the hospital. The initial decision process to randomize patients after adequate time allowing to achieve ROSC prehospitally thus well correlates with the proposed 16 minutes of professional on-scene CPR[22] and may be considered a satisfactory approach to select truly refractory cases, given that 64% of patients in this study experienced cardiac arrest longer than 45 minutes.

Still, converting on-scene CPR into intra-arrest transport eventually followed by ECPR may not improve outcome.[3,26] Questions remain as to whether it is possible to identify patients early during CPR who may ultimately benefit from such an approach. Several studies have assessed the relationship between the length of cardiac arrest and ECPR treatment.[28-30]

To our knowledge, there have been no other studies in a cardiac arrest population that randomized patients online via a web-based randomization process during ongoing

on-scene CPR. The overall pooled neurologically favorable survival at 180 days of 27% (31.5% in the invasive strategy group, 22% in the standard strategy group, 22% in the pooled ECPR group) is comparable to that in other nonrandomized studies evaluating ECPR (29%[31] and 33%[32]).

If an early invasive approach is to be considered, it should be provided in a well-functioning prehospital system linked to a cooperating ECPR cardiac arrest center.[33]

Studies of refractory OHCA treated by ECPR inherently address potential organ donation[34,35]; potential donors were frequently considered, and organ donations occurred.

Limitations

This study has several limitations. First, the study had a single-center design and limited enrollment. Second, a priori scenarios of expected benefit provided by invasive approach were not reached, presumably because of higher-than-expected survival in the standard strategy group. Third, the study may have thus been underpowered to detect a statistically significant difference for the primary outcome. Fourth, the study design allowed crossover. The trial was designed to represent routine clinical care, and EMS crews thus decided to transport some patients receiving ongoing CPR for ECPR despite being originally randomized to the standard strategy group. For crossover from invasive to standard intervention, patients were apparently deemed not to be candidates for advanced therapies, but such determinations may contain a degree of subjectivity that could influence outcomes. Nonetheless, the rate of crossover was low (7.5%) compared with other studies.[36,37]

Conclusions

Among patients with refractory out-of-hospital cardiac arrest, the bundle of early intra-arrest transport, ECPR, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcome at 180 days compared with standard resuscitation. However, the trial was possibly underpowered to detect a clinically relevant difference.

ARTICLE INFORMATION

Accepted for Publication: January 20, 2022.

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Author Contributions: Dr Belohlavek had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Conflict of Interest Disclosures: Dr Belohlavek reported receiving lecture honoraria from Maquet Company. No other authors reported disclosures.

Funding/Support: This study was supported by a research grant from the Internal Grant Agency Ministry of Health, Czech Republic (NT 13225-4/2012), by Progres Q38/LF1 and Cooperatio/INCA institutional support. BeneChill Inc provided 8 Rhinochill devices and, for the purpose of this study, provided the application sets and evaporative liquid at a reduced cost. Physio-Control, a division of Medtronic, provided 8 LUCAS devices for the purpose of this study. Maquet provided the MAQUET PLS device for ECLS.

Role of the Funder/Sponsor: The Internal Grant Agency Ministry of Health, BeneChill, Physio-Control, and Maquet had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: A list of the Prague OHCA Study Group members is available in Supplement 4.

Data Sharing Statement: See Supplement 5.

Additional Contributions: We thank the Prague Emergency Medical Service teams and the coronary care unit and the catheterization laboratory teams of the 2nd Department of Internal Medicine, Cardiovascular Medicine, General University Hospital in Prague, for their efforts in providing quality care.

REFERENCES

1. Perkins GD, Graesner JT, Semeraro F, et al; European Resuscitation Council Guideline Collaborators. European Resuscitation Council Guidelines 2021: executive summary. *Resuscitation*. 2021;161:1-60. doi:10.1016/j.resuscitation.2021.02.003

2. Dankiewicz J, Cronberg T, Lilja G, et al; TTM2 Trial Investigators. Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med*. 2021;384(24):2283-2294. doi:10.1056/NEJMoa2100591

3. Grunau B, Kime N, Leroux B, et al. Association of intra-arrest transport vs continued on-scene resuscitation with survival to hospital discharge among patients with out-of-hospital cardiac arrest. *JAMA*. 2020;324(11):1058-1067. doi:10.1001/jama.2020.14185

4. Drennan IR, Lin S, Sidalak DE, Morrison LJ. Survival rates in out-of-hospital cardiac arrest patients transported without prehospital return of spontaneous circulation: an observational cohort study. *Resuscitation*. 2014;85(11):1488-1493. doi:10.1016/j.resuscitation.2014.07.011

5. de Graaf C, Beesems SG, Koster RW. Time of on-scene resuscitation in out of-hospital cardiac arrest patients transported without return of spontaneous circulation. *Resuscitation*. 2019;138:235-242. doi:10.1016/j.resuscitation.2019.03.030

6. Schober A, Sterz F, Herkner H, et al. Emergency extracorporeal life support and ongoing resuscitation: a retrospective comparison for refractory out-of-hospital cardiac arrest. *Emerg Med J*. 2017;34(5):277-281. doi:10.1136/emermed-2015-205232

7. Ortega-Deballon I, Hornby L, Shemie SD, Bhanji F, Guadagno E. Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: a systematic review of international practices and outcomes. *Resuscitation*. 2016;101:12-20. doi:10.1016/j.resuscitation.2016.01.018

8. Haas NL, Coute RA, Hsu CH, Cranford JA, Neumar RW. Descriptive analysis of extracorporeal cardiopulmonary resuscitation following out-of-hospital cardiac arrest—an ELSO registry study. *Resuscitation*. 2017;119:56-62. doi:10.1016/j.resuscitation.2017.08.003

9. Holmberg MJ, Geri G, Wiberg S, et al; International Liaison Committee on Resuscitation's (ILCOR) Advanced Life Support and Pediatric Task Forces. Extracorporeal cardiopulmonary resuscitation for cardiac arrest: a systematic review. *Resuscitation*. 2018;131:91-100. doi:10.1016/j.resuscitation.2018.07.029

10. Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet*. 2020;396(10265):1807-1816. doi:10.1016/S0140-6736(20)32338-2

11. Dennis M, Lal S, Forrest P, et al. In-depth extracorporeal cardiopulmonary resuscitation in adult out-of-hospital cardiac arrest. *J Am Heart Assoc*. 2020;9(10):e016521. doi:10.1161/JAHA.120.016521

12. Bougouin W, Dumas F, Lamhaut L, et al; Sudden Death Expertise Center investigators. Extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest: a registry study. *Eur Heart J*. 2020;41(21):1961-1971. doi:10.1093/eurheartj/ehz753

13. Lott C, Truhlář A, Alfonzo A, et al; ERC Special Circumstances Writing Group Collaborators. European Resuscitation Council Guidelines 2021: cardiac arrest in special circumstances. *Resuscitation*. 2021;161:152-219. doi:10.1016/j.resuscitation.2021.02.011

14. Belohlavek J, Kucera K, Jarkovsky J, et al. 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. *J Transl Med*. 2012;10:163. doi:10.1186/1479-5876-10-163

15. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1(7905):480-484. doi:10.1016/S0140-6736(75)92830-5

16. Nolan JP, Soar J, Zideman DA, et al; ERC Guidelines Writing Group. European Resuscitation Council Guidelines for Resuscitation 2010: section 1: executive summary. *Resuscitation*. 2010;81(10):1219-1276. doi:10.1016/j.resuscitation.2010.08.021

17. Monsieurs KG, Nolan JP, Bossaert LL, et al; ERC Guidelines 2015 Writing Group. European Resuscitation Council Guidelines for Resuscitation 2015: section 1: executive summary. *Resuscitation*. 2015;95:1-80. doi:10.1016/j.resuscitation.2015.07.038

18. Rubertsson S, Lindgren E, Smekal D, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. *JAMA*. 2014;311(1):53-61. doi:10.1001/jama.2013.282538

19. Nielsen N, Wetterslev J, Cronberg T, et al; TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*. 2013;369(23):2197-2206. doi:10.1056/NEJMoa1310519

20. Gaieski DF, Band RA, Abella BS, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Resuscitation*. 2009;80(4):418-424. doi:10.1016/j.resuscitation.2008.12.015

21. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) phase II trial. *Ann Intern Med*. 1991;115(4):256-265. doi:10.7326/0003-4819-115-4-256

22. Grunau B, Reynolds J, Scheuermeyer F, et al. Relationship between time-to-ROSC and survival in out-of-hospital cardiac arrest ECPR candidates: when is the best time to consider transport to hospital? *Prehosp Emerg Care*. 2016;20(5):615-622. doi:10.3109/10903127.2016.1149652

23. Thomas J, Kostousov V, Teruya J. Bleeding and thrombotic complications in the use of extracorporeal membrane oxygenation. *Semin Thromb Hemost*. 2018;44(1):20-29. doi:10.1055/s-0037-1606179

24. Franěk O, Pokorná M, Sukupová P. Pre-hospital cardiac arrest in Prague, Czech Republic—the Utstein-style report. *Resuscitation*. 2010;81(7):831-835. doi:10.1016/j.resuscitation.2010.03.005

25. Poppe M, Weiser C, Holzer M, et al. The incidence of "load&go" out-of-hospital cardiac arrest candidates for emergency department utilization of emergency extracorporeal life support: a one-year review. *Resuscitation*. 2015;91:131-136. doi:10.1016/j.resuscitation.2015.03.003

26. Alm-Kruse K, Sørensen G, Osbakk SA, et al. Outcome in refractory out-of-hospital cardiac arrest before and after implementation of an ECPR protocol. *Resuscitation*. 2021;162:35-42. doi:10.1016/j.resuscitation.2021.01.038

27. Gräsner JT, Wnent J, Herlitz J, et al. Survival after out-of-hospital cardiac arrest in Europe: results of the EuReCa TWO study. *Resuscitation*. 2020;148:218-226. doi:10.1016/j.resuscitation.2019.12.042

28. Wengenmayer T, Rombach S, Ramshorn F, et al. Influence of low-flow time on survival after extracorporeal cardiopulmonary resuscitation (eCPR). *Crit Care*. 2017;21(1):157. doi:10.1186/s13054-017-1744-8

29. Bartos JA, Carlson K, Carlson C, et al. Surviving refractory out-of-hospital ventricular fibrillation cardiac arrest: critical care and extracorporeal membrane oxygenation management. *Resuscitation*. 2018;132:47-55. doi:10.1016/j.resuscitation.2018.08.030

30. Leick J, Liebetrau C, Szardien S, et al. Door-to-implantation time of extracorporeal life support systems predicts mortality in patients with out-of-hospital cardiac arrest. *Clin Res Cardiol*. 2013;102(9):661-669. doi:10.1007/s00392-013-0580-3

31. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. *Crit Care Med*. 2013;41(5):1186-1196. doi:10.1097/CCM.0b013e31827ca4c8

32. Bartos JA, Grunau B, Carlson C, et al. Improved survival with extracorporeal cardiopulmonary resuscitation despite progressive metabolic derangement associated with prolonged resuscitation. *Circulation*. 2020;141(11):877-886. doi:10.1161/CIRCULATIONAHA.119.042173

33. Sinning C, Ahrens I, Cariou A, et al. The cardiac arrest centre for the treatment of sudden cardiac arrest due to presumed cardiac cause—aims, function and structure: position paper of the Association for Acute CardioVascular Care of the European Society of Cardiology (AVCV), European Association of Percutaneous Coronary Interventions (EAPCI), European Heart Rhythm Association (EHRA), European Resuscitation Council (ERC), European Society for Emergency Medicine (EUSEM) and European Society of Intensive Care Medicine (ESICM). *Eur Heart J Acute Cardiovasc Care*. 2020;9(4 suppl):S193-S202. doi:10.1177/2048872620963492

34. Ortega-Deballon I, De La Plaza-Horche E. A comprehensive approach to refractory cardiac arrest: saving more lives one way or another. *Heart Lung Vessel*. 2014;6(3):149-151.

35. Ortega-Deballon I, Hornby L, Shemie SD. Protocols for uncontrolled donation after circulatory death: a systematic review of international guidelines, practices and transplant outcomes. *Crit Care*. 2015;19:268. doi:10.1186/s13054-015-0985-7

36. Thiele H, Akin I, Sandri M, et al; CULPRIT-SHOCK Investigators. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med*. 2017;377(25):2419-2432. doi:10.1056/NEJMoa1710261

37. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378(21):1965-1975. doi:10.1056/NEJMoa1800385

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.

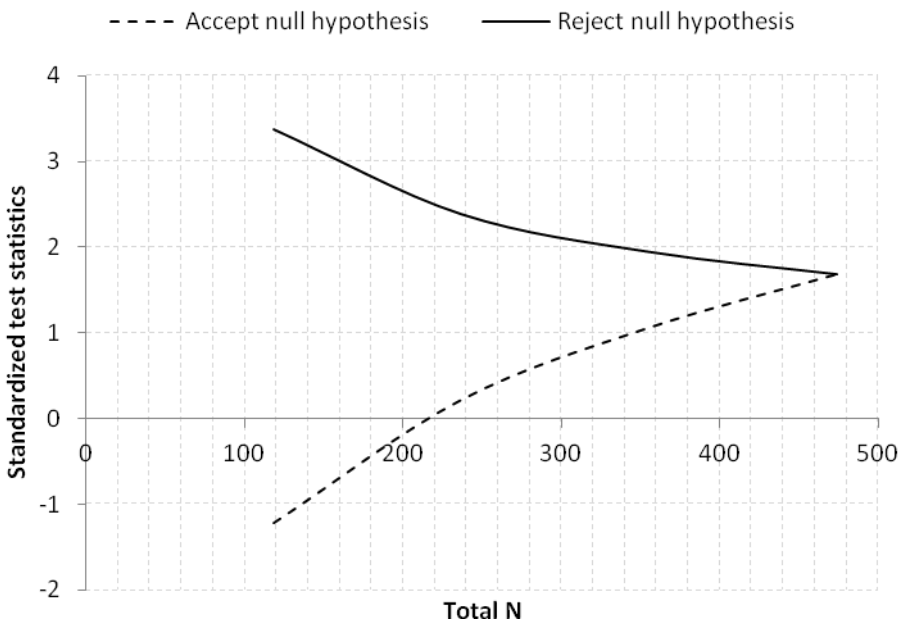
Statistical considerations

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.

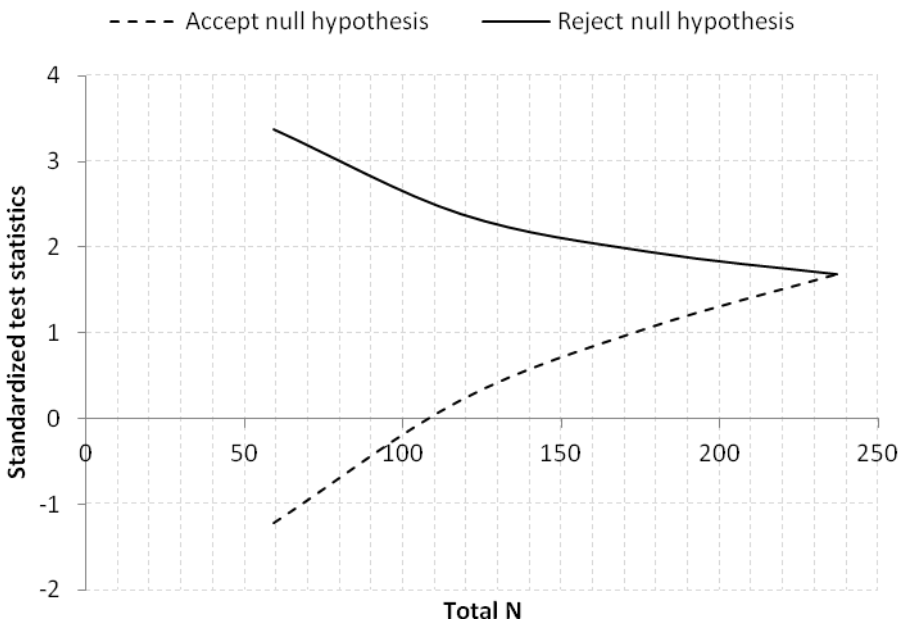
Scenario 1: standard (10%) vs. hyperinvase (20%) groups with allocation ratio 1; one tailed test with alpha=0.05 and power=0.9.
A design with a maximum of K = 4 stages was chosen. The critical values and the test characteristics of the group sequential test design were calculated for a Pampallona and 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.

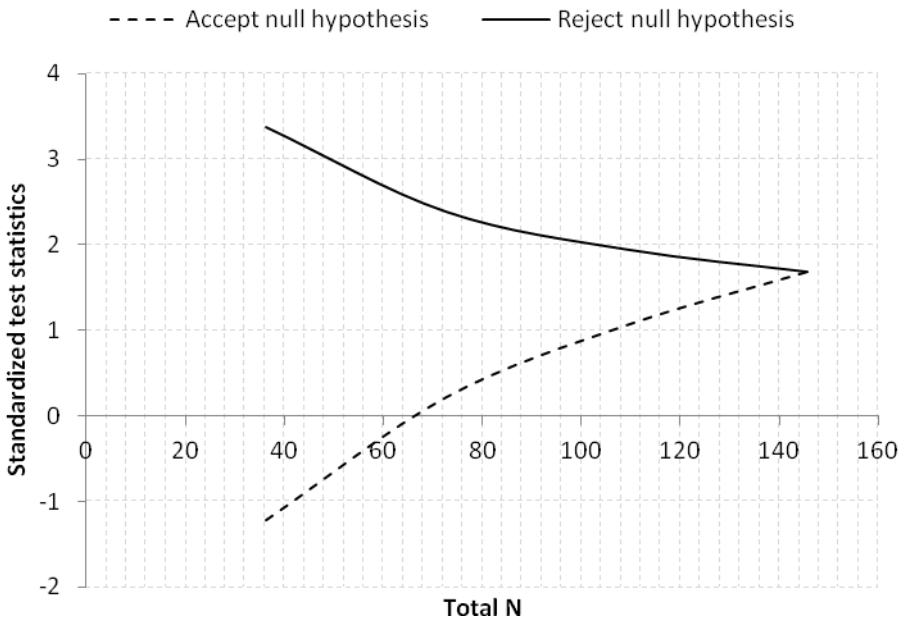
This yields a total of 118.2 + 118.2 = 236.4 observations. For comparison, the sample size in a fixed sample size design is n1 = 108.0, n2 = 108.0. The expected (average) total sample size under the alternative hypothesis is 159.2, under a value midway between H0 and H1 it is 176.5, and under the null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

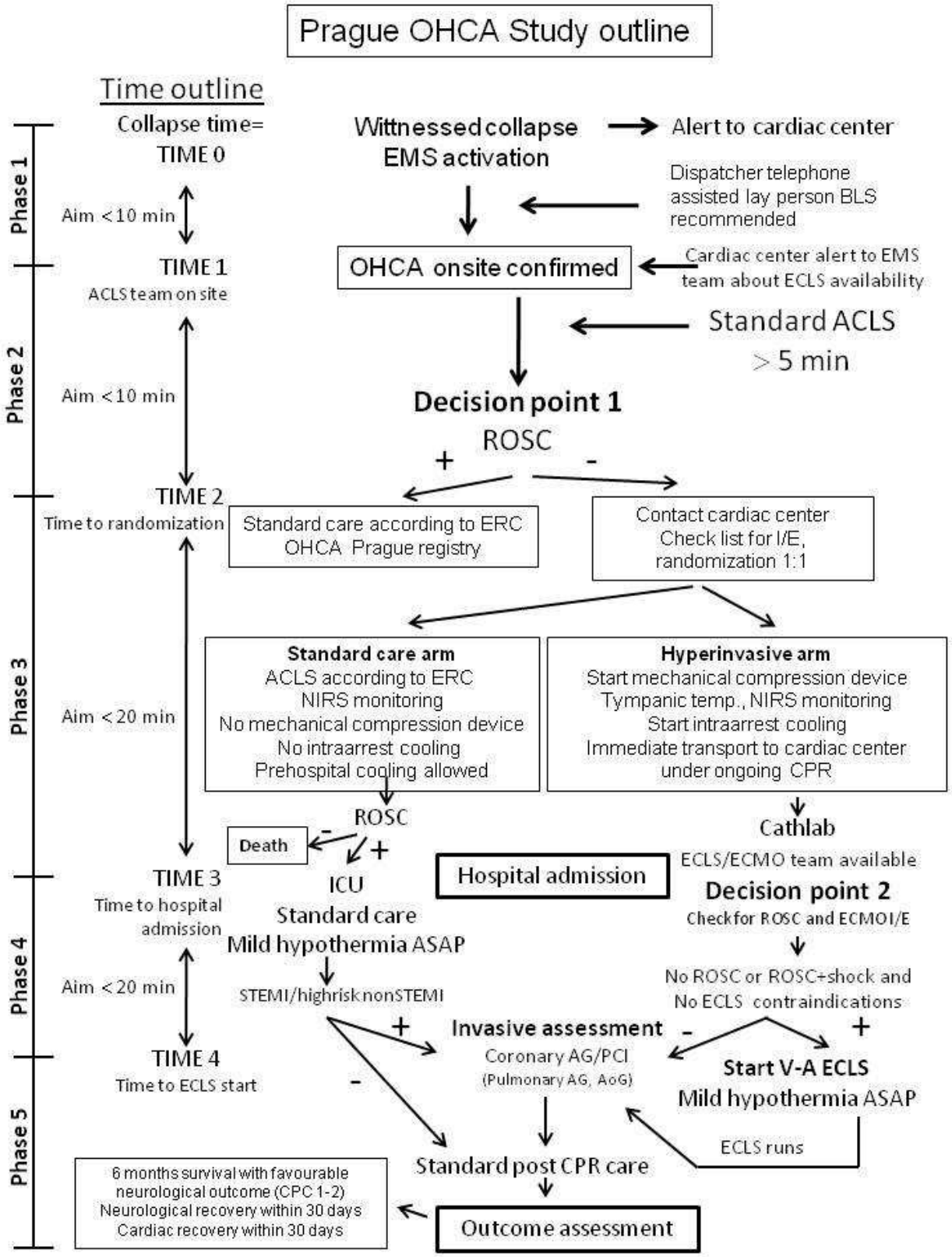
chest compression device, VA ECLS and immediate invasive diagnostics in all patients compared to a standard of care. The protocol is opened for sharing by other cardiac centers with readily available ECLS and cathlab teams used to cooperate with emergency medical services to admit patients with refractory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

Acknowledgements: A Puroklima a.s. company, a distributor for Czech Republic for Medtronic (LUCAS) and Benechill (RhinoChill) devices provided eight LUCAS and Rhinochill devices to Prague EMS to equip all RRVs and for the purpose of the study will also provide the application sets and evaporative liquid per substantially reduced cost. Maquet company provided the MAQUET PLS device for ECMO. Covidien company provided the INVOS device for NIRS measurement and tympanic for prehospital and on-arrival temperature determination.

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

Supplementary Online Content

Belohlavek J, Smalcova J, Rob D, et al; . Effect of intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and immediate invasive assessment and treatment on functional neurologic outcome in refractory out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2022.1025

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Study inclusion and exclusion criteria[18] in a Study of Intra-arrestTransport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

Panel A. Entry criteria for enrollment into the study.

Inclusion criteria	**Exclusion criteria**
Age ≥18 and ≤ 65 years	Out of hospital cardiac arrest of presumed non-cardiac cause
Witnessed out of hospital cardiac arrest of presumed cardiac cause	Unwitnessed collapse
Minimum of 5 minutes of advanced cardiac life support performed by emergency medical service team without sustained return of spontaneous circulation	Suspected or confirmed pregnancy
Unconsciousness (Glasgow Coma Score <8)	Return of spontaneous circulation within 5 minutes of advanced cardiac life support performed by emergency medical service team
Extracorporeal life support team and intensive care unit bed capacity in cardiac center available	Conscious patient
	Known bleeding diathesis or suspected or confirmed acute or recent intracranial bleeding
	Suspected or confirmed acute stroke
	Known severe chronic organ dysfunction or other limitations in therapy
	"Do not resuscitate" order or other circumstances making 180 day survival unlikely
	Known pre-arrest cerebral performance category ≥ 3

Panel B. Criteria for initiation of extracorporeal life support (ECLS).

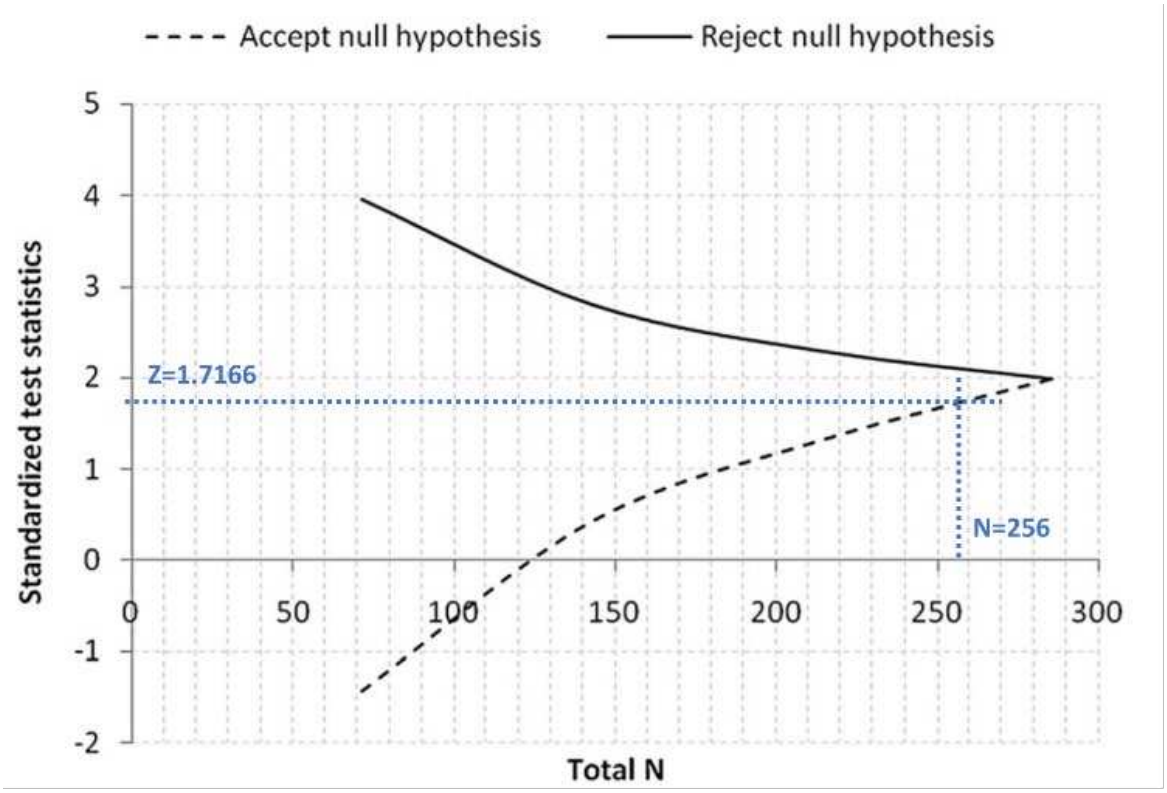
Footnote: *if collapse time was not exactly known, initial call to emergency medical service was considered

Abbreviations: ACLS: advanced cardiac life support; CPC: cerebral performance category; ECLS: extracorporeal life support; ICU: intensive care unit; OHCA: out-of hospital cardiac arrest; ROSC: return of spontaneous circulation; EMS: emergency medical service.

Inclusion criteria	**Exclusion criteria**
No return of spontaneous circulation or return of spontaneous circulation with ongoing shock (defined as sustained hypotension below 90 mmHg of systolic pressure or need for moderate to high doses of vasopressors)	Signs of death or irreversible organ damage
Admission to cathlab not later than 60 minutes after the collapse/initial call to emergency medical service*	Known bleeding diathesis
Consensus of cardiac center team members on extracorporeal life support initiation	Inadequate arterial and/or venous access for femoro-femoral cannulation

eFigure 1. Stopping rule in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

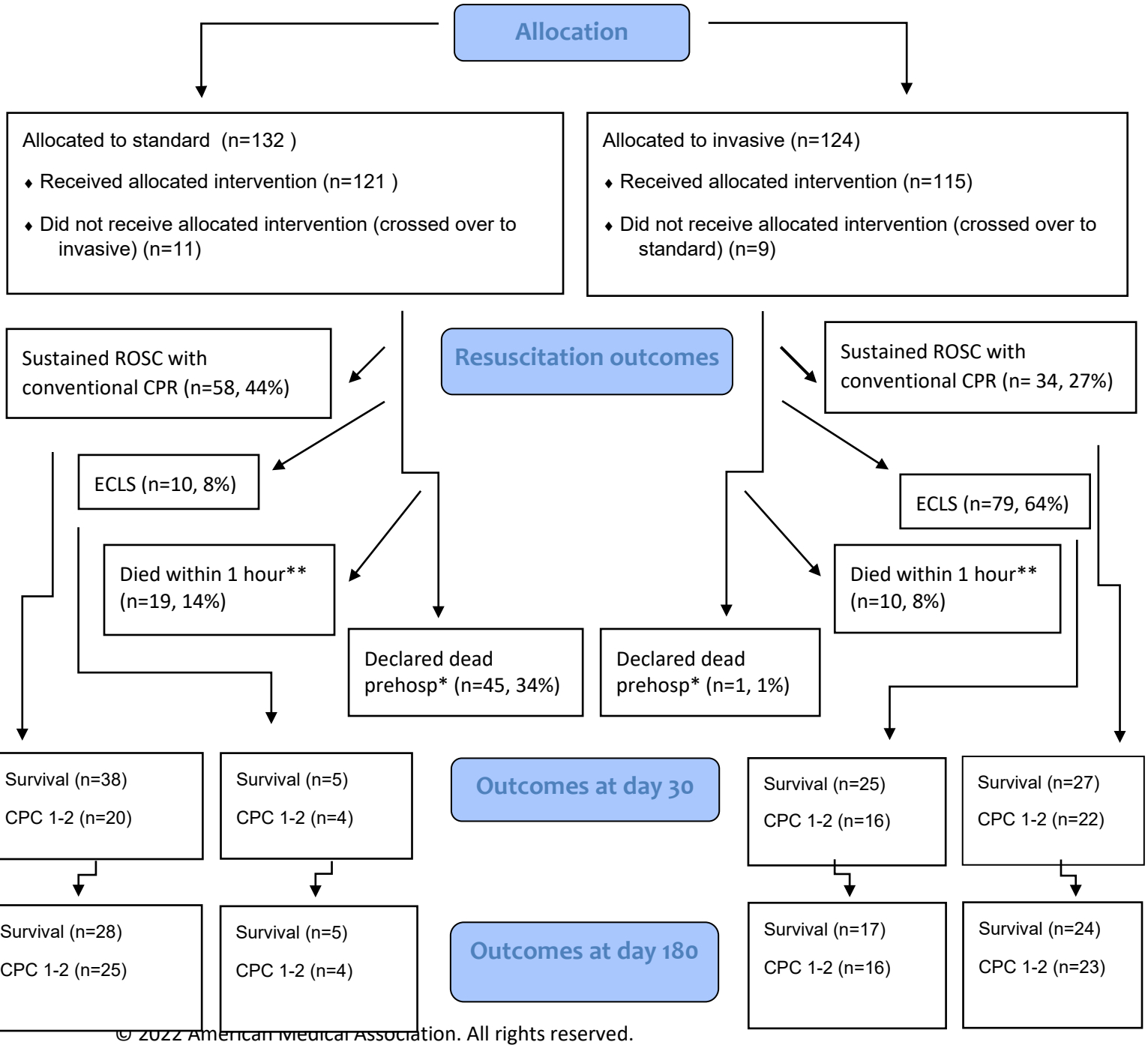
Footnote: Graphical delineation for scenario 2, estimated 15% increase of primary outcome in invasive (25%) vs. standard (10%) groups.



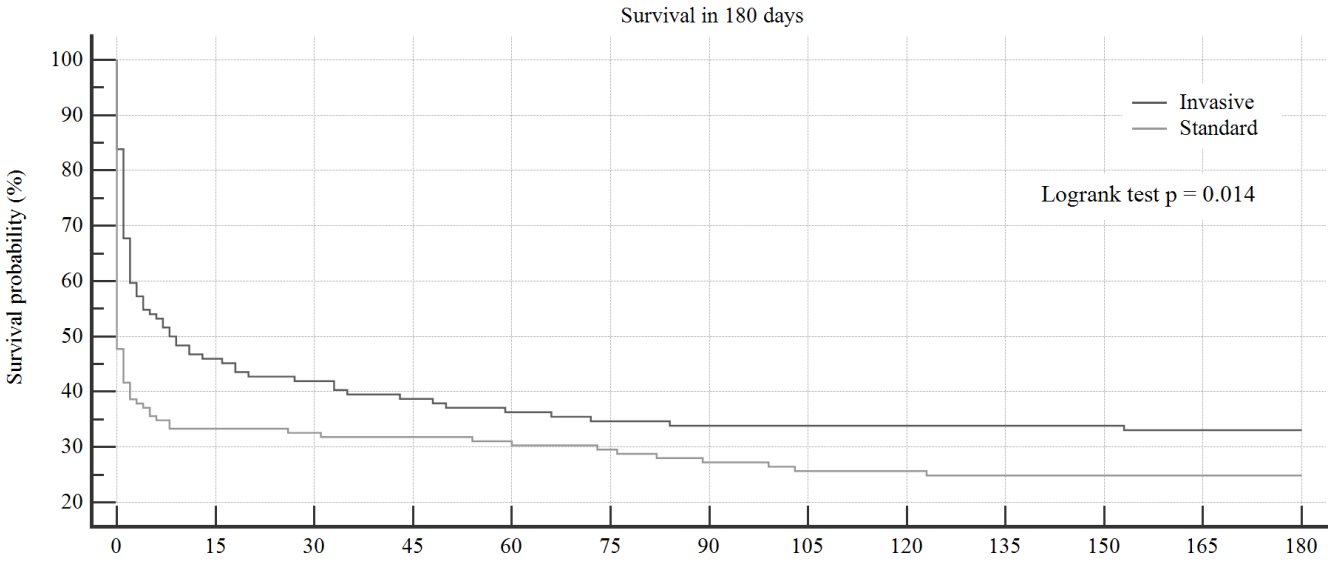
eFigure 2. Allocation and resuscitation outcomes flow chart in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

Footnotes: *Declared dead prehosp – declared dead prehospitally or on admission. **Died within 1 hour – pronounced dead within one hour after admission.
Three patients allocated to invasive group and implanted with ECLS died within 1 hour after admission, therefore number of ECLS patients 79.

Abbreviations: CPC: cerebral performance category; ECLS: extracorporeal life support; ICU: intensive care unit; OHCA: out-of hospital cardiac arrest; ROSC: return of spontaneous circulation; EMS: emergency medical service.



eFigure 3. Kaplan-Meier survival analysis in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest



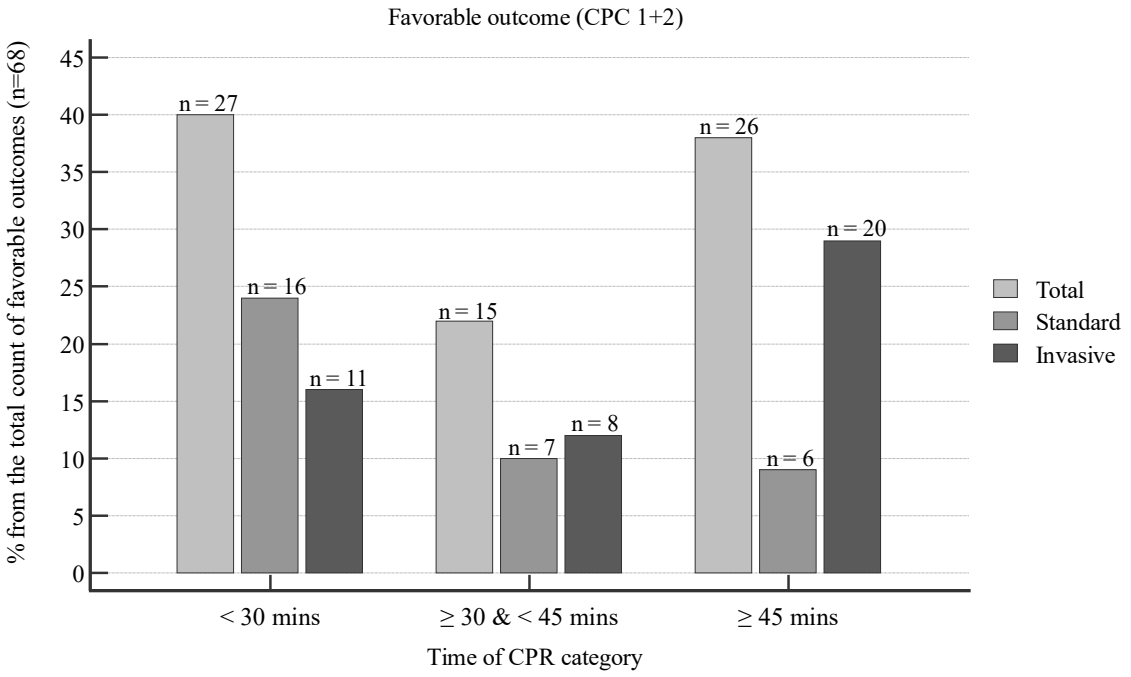
Number at risk

Group: Invasive												
124	57	52	48	45	43	42	42	41	41	41	40	39
Group: Standard												
132	44	43	42	40	39	35	33	32	31	31	31	31

eFigure 4. Favorable neurological outcome after 180 days in time of CPR subgroups in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

Footnote: Numbers above the bars represent number of patients in respective groups. Six patients surviving with a favorable neurological outcome in ≥45 mins standard group include 4 patients crossed over from standard to invasive group.

Abbreviations: CPC: cerebral performance category; CPR: cardiopulmonary resuscitation.



eTable 2. Causes of target temperature management exclusion in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

Patient number	Cause of target temperature management exclusion
4	early death, instability, time to death since admission 26min
15	early death, instability, time to death since admission 17min
24	bleeding
31	instability, time to death since admission 6h 49min
40	early death, instability, time to death since admission 62min
57	early death, instability, time to death since admission 50min
98	instability, time to death since admission 3h 9min
104	early death, instability, time to death since admission 15min
110	early death, instability, time to death since admission 18min
123	early death, instability, time to death since admission 17min
125	early death, instability, time to death since admission 65min
129	bleeding
132	early death, instability, time to death since admission 22min
133	early death, instability, time to death since admission 20min
138	early death, instability, time to death since admission 47min
141	early death, instability, time to death since admission 32min
146	early death, instability, time to death since admission 18min
152	instability, time to death since admission 5h 39min
157	early death, instability, time to death since admission 33min
160	bleeding
169	early death, instability, time to death since admission 40min
179	early death, instability, time to death since admission 17min
180	early death, instability, time to death since admission 1min
193	early death, instability, time to death since admission 51min
209	early death, instability, time to death since admission 22min
222	early death, instability, time to death since admission 36min
227	bleeding
236	early death, instability, time to death since admission 26min
237	early death, instability, time to death since admission 30min
248	early death, instability, time to death since admission 64min
255	early death, instability, time to death since admission 23min
261	early death, instability, time to death since admission 28min

eTable 3. Organ lacerations in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

Pt. Number 90	right lung perforation by broken ribs, ipsilateral hemothorax
Pt. Number 94	right atrium tear by sharp piece of broken rib, hemopericardium
Pt. Number 106	liver tear, hemoperitoneum
Pt. Number 139	liver tear, omental bleed
Pt. Number 155	liver tear, hemoperitoneum
Pt. Number 160	liver tear, hemoperitoneum
Pt. Number 248	liver tear, hemoperitoneum

eTable 4. Technical complications in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

Pt. Number: 99 – oxygenator failure	A patient on inotropic and vasopressor therapy, an episode of hypotension and hypoxia for less than 5 mins observed, attributed to oxygenator failure, corrected by perfusionist intervention.
Pt. Number 148 – cathlab angiography failure	Patient admitted to the cathlab, uncomplicated ECMO cannulation, later angiography device failure, change of the cathlab room needed, 15 mins delay in coronary angiography which revelead nonsignificant CAD.
Pt. Number 240 – ventilator failure	During coronary angiography suddenly hypoxia attributed to ventilator failure, switched to bag ventilation, changed ventilator.

eTable 5. Summary of all protocol deviations in a Study of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment in Refractory Out-of-Hospital Cardiac Arrest

Footnotes:

Age: 63 enrolled patients were older than 65 years due to a poor estimate during the initial resuscitation on the scene. All patients remained in the analysis, this fact became obvious later on during the admission to hospital.

Other institution referral: Three patients were transported to other institution based on a decision of treating emergency physician. All patients remained in the analysis and the data were retrieved.

Crossovers: Crossovers were allowed both from standard to invasive arm and from invasive to standard arm, see the methods section. Overall, 20 patients were crossed, 11 from standard to invasive and 9 from invasive to standard arm.

Transport to hospital in standard arm despite no return of spontaneous circulation (ROSC): In standard arm, 15 patients have been transported to hospital by emergency crews without sustained ROSC and without approval for crossover to invasive arm. After admission, standard advanced cardiac life support was continued according to guidelines.

ECLS time: In invasive arm, 11 patients were implanted with ECLS despite the fact of being admitted to hospital after 60 mins of cardiac arrest. All patients remained in the analysis.

Witnessed arrest: All cardiac arrest cases enrolled in the study were witnessed with the exception of 4 patients, see below, all patients remained in the analysis, because this fact became obvious later on during the admission to hospital.

No target temperature management (TTM): No TTM was provided in 32 patients due to below reasons, see supplementary table 2.

Normothermia in the invasive arm: In 57 patients in invasive arm, normothermia of 36°C was used instead of hypothermia and this was allowed after the publication of TTM trial.[19] This occurred in early awaking patients or in patients with complications of hypothermia.

Eplanation for the table abbreviations: **age:** age over 65 years; **other institution:** transported to other cardiac center, a decision of a treating emergency physician; **cross:** crossovers in both arms; **noROSC transport in S arm:** patients being transported to hospital without sustained return of spontaneous circulation and without approval for a crossover; **noTTM:** all admitted to hospital not receiving target temperature management; **ecmo-time:** patients in invasive arm who received ECMO despite being admitted after 60 mins of cardiac arrest; **NW:** not witnessed cardiac arrest; normo-i: normothermia in invasive arm.

OHCA study	Protocol deviations					
Patient number	**Age criteria**	**Crossover/noROSC transport**	**noTTM**	**normo-i**	**ecmo-time**	**NW**
1	age					
2	age					
4		cross	noTTM			
5	age					
10		cross				
12		cross				
13		cross				
15	age	noROSC transport in S arm	noTTM			
16				normo-i		
17	age			normo-i		
20		cross				
21		cross				
22				normo-i		
23				normo-i		
24	other institution		noTTM			
26		cross				
27				normo-i		
28					ecmo-time	
29		cross				
30				normo-i		
31	age		noTTM			
33	age			normo-i	ecmo-time	
34				normo-i		
35		cross				
37				normo-i		
38				normo-i		
40	other institution	noROSC transport in S arm	noTTM			NW
43				normo-i		
44		cross				
45	age			normo-i		
46		cross				
47				normo-i		
48				normo-i		
52		cross				
53	age					
54		cross				
56	age					
57		cross	noTTM			
62					ecmo-time	
63				normo-i		
68				normo-i		
72				normo-i		
73	age	cross				
76	age					
77				normo-i	ecmo-time	

78				normo-i		
80	age					
81	age					
89		cross				
90	age			normo-i		
93	age					
94	age					
96					ecmo-time	
98			noTTM			
99	age			normo-i		
100	age					
103	age			normo-i		
104		noROSC transport in S arm	noTTM			
105	age					
106				normo-i		
107					ecmo-time	
108					ecmo-time	
109	age					
110			noTTM			
114				normo-i		
117	age					
121	age			normo-i		
122				normo-i		
123	age	cross	noTTM			
124	age					
125	other institution	noROSC transport in S arm	noTTM			
126	age			normo-i		
127	age					
129			noTTM			
130	age			normo-i		
132		noROSC transport in S arm	noTTM			
133		noROSC transport in S arm	noTTM			
134	age					
136	age			normo-i		
138			noTTM			
139	age			normo-i		
140	age			normo-i		
141	age	noROSC transport in S arm	noTTM			
142				normo-i		
143	age					
146			noTTM			
147	age			normo-i		
148					ecmo-time	

149				normo-i		
151	age					
152			noTTM			
153					ecmo-time	
155				normo-i		
156				normo-i		
157			noTTM			
159				normo-i		
160			noTTM			
163						
164		cross				NW
165	age					
167	age					
169	age		noTTM			
171				normo-i		
173	age					
176	age					
178	age					
179		noROSC transport in S arm	noTTM			
180	age	noROSC transport in S arm	noTTM			
181				normo-i		
185				normo-i		
186	age					
187	age					
188	age					
190	age					
193		noROSC transport in S arm	noTTM			
194	age					
196	age					
197	age					
199				normo-i		
200	age					
201	age					
203				normo-i		
204					ecmo-time	
206				normo-i		
208				normo-i	ecmo-time	
209			noTTM			
210	age			normo-i		
211				normo-i		
213	age					
218	age			normo-i		
221				normo-i		

222		noROSC transport in S arm	noTTM			
224	age					
225				normo-i		
226						NW
227			noTTM			
228				normo-i		
229	age					
230				normo-i		NW
233				normo-i		
236		cross	noTTM			
237			noTTM			
238	age					
239						
240	age					
241		noROSC transport in S arm				
242				normo-i		
245	age					
248		noROSC transport in S arm	noTTM			
251	age					
252		cross				
254				normo-i		
255		noROSC transport in S arm	noTTM			
256				normo-i		
257				normo-i		
258				normo-i		
261	age	noROSC transport in S arm	noTTM			

DSMB recommendation

TRIAL PROTOCOL

Title: Hyperinvasive Approach in Refractory Out-of-Hospital Cardiac Arrest.

Prague OHCA study

PROTOCOL REGISTRATION NUMBER: ClinicalTrials.gov: NCT01511666

To whom it may concern:

Based on report from 19-Oct-2020 DSMB recommends to stop the study.

Rationale: Sample size reached scenario 2 model in the protocol, statistically significant difference in primary outcome was not met. Other study results report improved 30 days neurological recovery (secondary outcome), 180 days survival, survival in a subgroup of patients resuscitated more than 45 mins – all in favor of hyperinvasive approach. Survival reported in patients crossed over from standard to hyperinvasive arm is 45% (5 of 11).

Prague, Oct 25, 2020

Petr Ošťádal, MD, PhD. .....

Anatolij Truhlář, MD, PhD. .....

Zdravotnická záchranná služba
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Supplemental Online Content: Nonauthor Collaborators

*Indicates required information. Only first name, last name, and suffix will appear in PubMed.

***Group Name(s): Prague OHCA Study Group**							
***First Name and Middle Initial(s)**	***Last Name**	***Suffix (eg, Jr, III)**	Academic Degrees	Institution	Location (city, state/province, country)	Role or Contribution, eg, chair, principal investigator	Group (if more than 1 Group listed in the byline) and/or Subgroup (eg, Steering Committee)
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Belohlavek J, Smalcova J, Rob D, et al; . Effect of intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and immediate invasive assessment and treatment on functional neurologic outcome in refractory out-of-hospital cardiac arrest: a randomized clinical trial. JAMA. doi:10.1001/jama.2022.1025

Data Sharing Statement

Data
Data available: Yes
Data types: Deidentified participant data
How to access data: jan.belohlavek@vfn.cz
When available: beginning date: 08-01-2022

Supporting Documents
Document types: Informed consent form
How to access documents: jan.belohlavek@vfn.cz
When available: beginning date: 08-01-2022

Additional Information
Who can access the data: Researchers who provide a methodologically sound proposal.
Types of analyses: To achieve aims in the approved proposal.
Mechanisms of data availability: After approval of a proposal.