ORIGINAL ARTICLE

Results of targeted temperature management of patients after sudden out-of-hospital cardiac arrest: a comparison between intensive general and cardiac care units

Robert J. Kowalik[1], Anna Fojt[1], Krzysztof Ozierański[1], Michał Peller[1], Paweł Andruszkiewicz[2], Marek Banaszewski[3], Marek Gierlotka[4,5], Elżbieta Kremis[6], Janina Stępińska[3], Beata Średniawa[6,7], Barbara Zawiślak[8], Łukasz Kołtowski[1], Marcin Grabowski[1], Grzegorz Opolski[1]

1 1st Department of Cardiology, Medical University of Warsaw, Warsaw, Poland
2 2nd Department of Anesthesiology and Intensive Care, Central Teaching Hospital, Medical University of Warsaw, Warsaw, Poland
3 Intensive Cardiac Therapy Clinic, Institute of Cardiology, Warsaw, Poland
4 Department of Cardiology, University Hospital, Institute of Medicine, Faculty of Natural Sciences and Technology, University of Opole, Poland
5 3rd Department of Cardiology, Silesian Centre for Heart Diseases, Zabrze, Poland
6 Department of Cardiology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Katowice, Poland
7 Silesian Center for Heart Diseases, Zabrze, Poland
8 2nd Department of Clinical Cardiology and Cardiovascular Interventions, The University Hospital in Krakow, Kraków, Poland

EDITORIAL
by Grand et al, see p. 4

ABSTRACT

BACKGROUND Targeted temperature management (TTM) is used to treat patients after sudden out-of-hospital cardiac arrest (OHCA).

AIMS The aim of the study was to compare the results of TTM between intensive general and cardiac care units (ICCUs).

METHODS The Polish Registry of Therapeutic Hypothermia obtained data on 377 patients with OHCA from 26 centers (257 and 120 patients treated at the ICCU and intensive care unit [ICU], respectively). Eligibility for TTM was based on the current inclusion criteria for therapy. Medical history as well as data on TTM and additional treatment were analyzed. The main outcomes included in-hospital survival and complications as well as neurologic assessment using the Glasgow Coma Scale (GCS) and Rankin scale.

RESULTS Both ICU and ICCU patients were mostly male (mean age, 60 years). There were no significant differences regarding the medical history, mechanism of arrhythmia responsible for OHCA, GCS score on admission, time of cardiopulmonary resuscitation activities, and the time to target temperature (33°C). Coronary angiography and the use of dual antiplatelet therapy, intra-aortic balloon pump, intravascular hypothermia, dopamine, and dobutamine were more common in ICCU patients, while ICU patients more often received norepinephrine. Pneumonia and acute renal failure were more frequent in the ICCU group. Death occurred in 17% and 20% of ICU and ICCU patients, respectively ($P = 0.57$). The Rankin class after 48 hours since discontinuation of sedation and at discharge was comparable between groups.

CONCLUSIONS The ICCU has become a considerable alternative to the ICU to treat OHCA patients with TTM.

Correspondence to:
Krzysztof Ozierański, MD, PhD, 1st Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02-097 Warszawa, Poland, phone: +48 22 599 19 58, email: krzysztof.ozieranski@gmail.com
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INTRODUCTION Targeted temperature management (TTM) has been used to treat patients after sudden out-of-hospital cardiac arrest (OHCA) for more than 15 years. As demonstrated by numerous clinical studies and meta-analyses, this is the only known effective neuroprotection method used to improve the neurologic status of patients and reduce mortality.[1,2] Most studies

WHAT'S NEW?

The study assessed real-world data from the Polish Registry of Therapeutic Hypothermia on targeted temperature management (TTM), a procedure used to treat patients after sudden out-of-hospital cardiac arrest (OHCA). Cardiac intensive care units were shown to offer a feasible alternative to intensive care units in terms of the use of TTM for the treatment of OHCA patients. Both units presented similar survival rates and a high percentage of good neurologic outcome. The TTM was characterized by a good safety profile and a low rate of adverse events.

KEY WORDS
intensive cardiac care unit, intensive care unit, neurologic outcomes, sudden cardiac arrest, targeted temperature management

on TTM were conducted at typical intensive care units (ICUs), with access to mechanical ventilation and personnel with extensive knowledge on the treatment of postcardiac arrest syndrome.

Based on data from the Polish Registry of Therapeutic Hypothermia, since 2012, patients with OHCA have been increasingly treated not only at the ICU, but a large proportion have been managed also at intensive cardiac care units (ICCUs). This can be explained by the fact that, according to current guidelines, every patient with OHCA, especially with a cardiac rhythm requring defibrillation (ventricular fibrillation or ventricular tachycardia), should first undergo coronary angiography to rule out a coronary cause of cardiac arrest.[3] Moreover, abnormalities typical for acute coronary syndrome are often registered in the first electrocardiogram recordings, which requires an urgent coronary angiography and invasive treatment of coronary artery disease. This approach provides a wider range of therapeutic options for patients with postcardiac arrest syndrome by inclusion of typical cardiac procedures and pharmacotherapy, such as those used in the treatment of myocardial infarction, heart failure, cardiogenic shock, or arrhythmias. Current standards specifying requirements as to the equipment and qualifications of medical personnel have resulted in the ICCU gradually taking over the full care of patients with OHCA.[4]

To date, there have been no studies directly comparing treatment outcomes between patients with OHCA treated at the ICU and ICCU. The Polish Registry of Therapeutic Hypothermia provides such an opportunity. It was started to assess the need for TTM on a national scale as well as to develop a policy for the reimbursement of this medical procedure.[5] The aim of the current analysis was specifically to compare the outcomes of the TTM between the ICCU and ICU.

METHODS

Study population The Polish Registry of Therapeutic Hypothermia obtained data on 377 patients with OHCA from 26 centers (16 ICCUs and 10 ICUs). Most patients (n = 257) were treated at the ICCU, while 120 patients, at the ICU. Each patient with OHCA completed a protocol for the TTM approved in Poland. The data on the patient was then registered in an electronic case report form (eCRF).

Study design Patients were considered eligible for the TTM based on the current inclusion criteria for therapy. Each patient had to meet all the criteria, and no contraindications could be present (TABLE 1).

Anonymous data included, among others, demographic characteristics, medical history, place and circumstances of an OHCA episode, presence of witnesses, confirmed information on whether cardiopulmonary resuscitation (CPR) was performed, baseline heart rhythm, delayed time to CPR, duration of CPR until return of spontaneous circulation (ROSC), and evaluation of neurologic status on admission. The additional part of the eCRF contained data on the initial

TABLE 1 Inclusion and exclusion criteria for targeted temperature management

Inclusion criteria	Exclusion criteria
Presence of OHCA	The patient responds to the instructions (GCS >8)
Age at least 18 years	More than 4 hours since OHCA
Cardiac cause of OHCA	Life-threatening bleeding or infection
Any type of initial cardiac arrhythmia (VF, VT, PEA, asystole)	Coagulopathy[a]
Lack of consciousness (GCS score ≤8)	Recent (<14 days) major surgery
Stable ROSC	Suspected intracranial pathology
	Severe hemodynamic instability on catecholamines
	End-stage diseases
	Pregnancy

a Defined as congenital coagulation disorders in history.

Abbreviations: GCS, Glasgow Coma Scale; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia diagnosis and reason for OHCA treatment, in particular data on coronary angiography and the type of a coronary intervention. A separate section included data on the procedure itself: the initial temperature, confirmed administration of cold saline infusion, type of a cooling method, initial pharmacotherapy, target temperature (all centers assumed 33°C for the target cooling temperature), and duration of treatment, including the slow heating phase until the physiological temperature was reached. An important part of the eCRF concerned information on in-hospital complications and side effects of the TTM as well as all-cause death. Hemorrhagic complications were assessed using a scale from the REPLACE-2 trial (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events).[6]

Shock without specifying its cause was diagnosed in the case of persistent hypotension defined as one of the following: a systolic blood pressure of less than 90 mm Hg, mean blood pressure of less than 65 mm Hg, or decrease in systolic blood pressure by more than 40 mm Hg in relation to the baseline value. The neurologic status was evaluated 48 hours after the infusion of sedatives was completed, and then at discharge. The neurologic assessment was performed using the Glasgow Coma Scale (GCS) and 6-point Rankin scale,[7] assuming that classes 1 and 2 (a small degree of disability) and classes 5 and 6 (a very severe degree of disability) on the Rankin scale corresponded to good and poor neurologic outcome, respectively.

Statistical analysis The distribution of continuous variables was assessed with the Shapiro–Wilk test. All continuous variables showed a nonnormal distribution. Continuous and categorical variables were presented as median (interquartile range) and number (percentage), respectively. Differences between continuous variables were assessed with the Mann–Whitney test. For the analysis of categorical variables, the Fisher exact test was used. To determine the risk factors of mortality and neurologic outcome, a logistic regression analysis was used. A P value of less than 0.05 was considered significant for all tests. The statistical analysis was performed using the SAS® software, version 9.4 (SAS Institute, Cary, North Carolina, United States).

RESULTS

Patients in the ICU and ICCU groups were mostly male, with a mean age of 60 years. There were no significant differences in the medical history, mechanism of arrhythmia responsible for OHCA, time of CPR activities, or the time of ROSC. In the ICU group, OHCA occurred more frequently at home ($P = 0.047$), while the ICCU group was more likely to have been diagnosed with ST-segment elevation myocardial infarction ($P = 0.002$). The groups did not differ significantly in terms of the initial GCS score or the time from the start of cooling to achieving the target temperature (33°C). However, in the ICCU group, the period of primary cooling was significantly longer (TABLE 2).

Coronary angiography and angioplasty were more frequently performed in ICCU patients; therefore, they more often received dual antiplatelet therapy. Intra-aortic balloon pump (IABP) or devices for intravascular hypothermia were also more common in the ICCU group, while the use of sedatives was more frequent in patients treated at the ICU. The most common catecholamine used in the ICU was norepinephrine, while in the ICCU, dopamine and dobutamine. A prophylactic use of antibiotics was similar in both units (TABLE 2).

Complications such as pneumonia and acute renal failure were more commonly observed in the ICCU than in the ICU group ($P = 0.01$ and $P = 0.05$, respectively). During treatment, death occurred in 17% and 20% of ICU and ICCU patients, respectively ($P = 0.57$). The most important risk factors for death in each group were identified using the univariable logistic regression analysis (TABLE 3).

The neurologic status of patients was assessed after 48 hours from the discontinuation of sedation and at discharge. The first neurologic assessment revealed that most patients in the ICCU and ICU were in class 3 and 4, respectively, on the Rankin scale. The Rankin score at discharge was comparable between groups: 33% and 27% of ICCU and ICU patients, respectively, obtained a good Rankin score (class 1 or 2), while a very severe degree of disability (class 5 or 6) was reported in 19.8% and 15.5% of ICCU and ICU patients, respectively. The remaining patients were classified as class 3 (FIGURES 1 and 2).

In the univariable analysis, independent clinical factors that had the most significant impact on the neurologic outcome of patients were identified (TABLE 4).

DISCUSSION

Treatment of patients with OHCA is challenging and requires an appropriate organization of departments, access to specialized equipment for TTM, as well as highly skilled and knowledgeable staff members. Based on data from the Polish Registry of Therapeutic Hypothermia, cardiologists are increasingly using this treatment method. An additional advantage of the ICCU is the access to coronary angiography, IABP, and electrotherapy.[8] The registry provides the opportunity to compare the results of treatment between the ICCU and ICU. To our knowledge, this is the first such analysis in the literature.

In our study, we did not show any significant differences in the final neurologic outcome and

TABLE 2 Baseline characteristics of the study groups

Variable	ICU (n = 120)	ICCU (n = 257)	*P* value
Demographic data and comorbidities			
Age, y	60 (51–67)	60 (52–67)	0.8
Male sex	96 (80)	206 (80)	1
Myocardial infarction	25 (21)	51 (20)	0.89
Stroke	2 (1.7)	10 (3.9)	0.35
Diabetes	20 (17)	44 (17)	1
Arterial hypertension	48 (40)	1178 (46)	0.32
Chronic kidney disease	9 (7.6)	13 (5.1)	0.35
Anemia	3 (2.5)	6 (2.2)	1
Circumstances of OHCA			
First cardiac rhythm VF or VT	91 (76)	208 (81)	0.33
Witness of CPR	64 (53)	134 (52)	0.91
OHCA at home	70 (58)	117 (46)	0.047
OHCA in a public place	38 (32)	108 (42)	0.07
Witness of OHCA	97 (81)	195 (76)	0.41
STEMI on admission	42 (35)	136 (53)	0.002
NSTEMI on admission	26 (22)	72 (28)	0.24
Shock on admission	23 (19)	57 (22)	0.68
Baseline temperatures and time parameters of TTM			
Prehospital temperature, °C	36.4 (36–36.7)	36.6 (36–36.6)	0.56
Temperature on admission, °C	36.4 (36–36.6)	36.5 (36–36.6)	0.56
Time from ROSC to cold saline infusion	175 (80–230)	83 (35–125)	<0.001

Data are presented as number (percentage) or median (interquartile range).

Abbreviations: CPR, cardiopulmonary resuscitation; ICU, intensive care unit; ICCU, intensive cardiac care unit; NSTEMI, non–ST-
-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TTM, targeted temperature management; others, see TABLE 1

TABLE 3 Predictors of all-cause death in the study groups

Variable	ICU		ICCU	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.49 (0.99–2.24)	0.06	1.59 (1.19–2.13)	0.002
GCS score after ROSC	0.61 (0.39–0.96)	0.03	0.78 (0.58–1.03)	0.08
Rankin class after 48 hours	8.85 (3.09–25.32)	<0.0001	2.20 (1.36–3.57)	0.001
Diabetes	3.56 (1.20–10.58)	0.02	0.38 (0.18–0.83)	0.01
Chronic kidney disease	4.70 (1.14–19.4)	0.03	0.39 (0.19–0.8)	0.01
First cardiac rhythm VF or VT	0.29 (0.11–0.81)	0.02	2.05 (1.03–4.1)	0.04
Shock on admission	8.86 (3.05–25.78)	<0.0001	2.25 (1.2–4.23)	0.01
Use of catecholamines	4.89 (1.72–13.89)	0.003	2.54 (1.34–4.81)	0.004
Use of noradrenaline	6.10 (1.34–27.759)	0.02	2.25 (1.19–4.24)	0.01
Use of dopamine	2.70 (0.10–7.33)	0.05	–	–

Abbreviations: OR, odds ratio; others, see TABLES 1 and 2

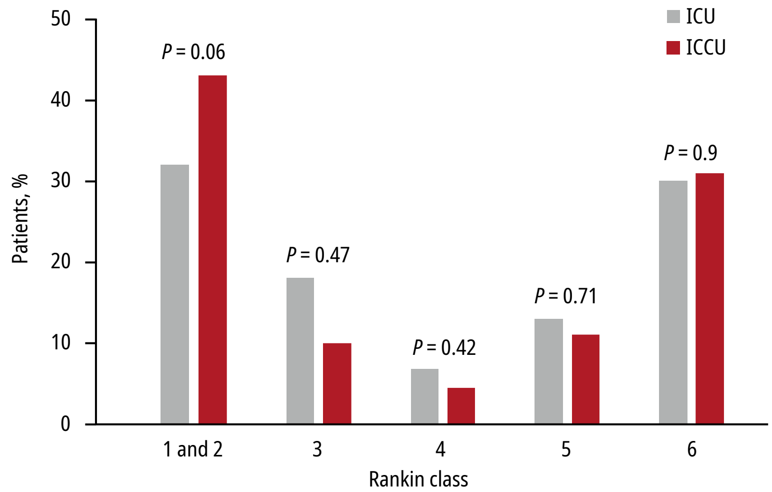

FIGURE 1 Neurologic outcome of the study groups according to the Rankin class after 48-hour treatment

Abbreviations: see TABLE 2

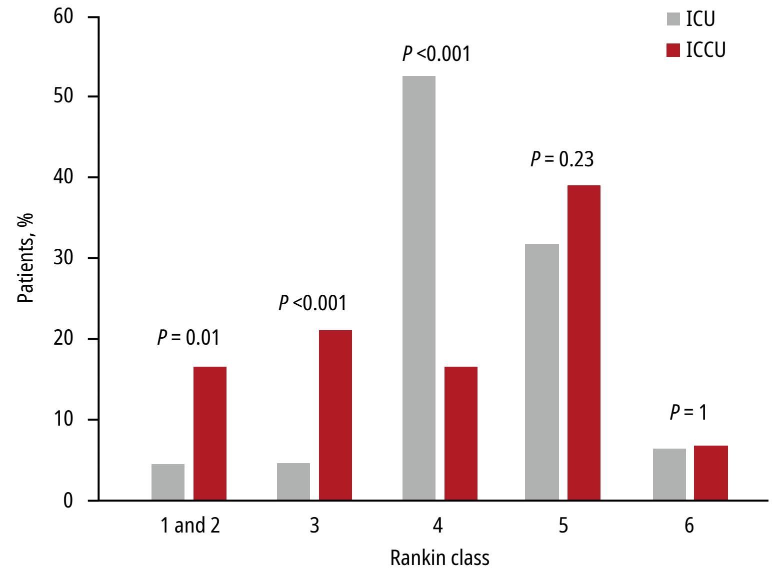

FIGURE 2 Neurologic outcome of the study groups according to the Rankin class at hospital discharge

Abbreviations: see TABLE 2

the death rate between patients treated at the ICCU and ICU. However, some important differences regarding the treatment of patients with OHCA should be noted. After ROSC, patients at the ICCU received an infusion of cold saline significantly faster and were more quickly connected to a cooling device than those at the ICU, but the total time to reach the target temperature (33°C) was similar in both groups. As shown in previous studies on hypothermia, the time from the start of CPR to ROSC or the time from ROSC to achieving hypothermia and target temperature does not predict the prognosis,[9] and it appears that in our study these factors also did not affect the neurologic outcome. We observed that important predictors of death in both groups were typical clinical factors, such as patient age, GCS score after CPR, the first recorded rhythm requiring defibrillation, and shock on hospital admission. In addition, in the ICCU group, the presence of a witness during OHCA was associated with lower mortality. Similar risk factors were also reported by Kozinski et al[10] in a series of TTM studies.

In the current study, a significant advantage of using intravascular TTM was observed in the ICCU group. Gillies et al[11] proved that both methods, external and endovascular, provide the same treatment results with the same safety profile. Therefore, it can be assumed that the differences in the applied cooling methods in our study were unlikely to affect the final results.

We also observed that a considerable proportion of patients were treated with catecholamine infusions (about 30% in each group). However, the groups differed in terms of the type of medication. De Backer et al[12] showed that neither norepinephrine nor dopamine had an advantage in the treatment of shock, although side effects were more frequent in patients treated with dopamine. Moreover, in the current European Society of Cardiology guidelines for the treatment of acute heart failure, the use of norepinephrine is preferred over dopamine or dobutamine in patients with shock.[13]

Importantly, we observed a high percentage of IABP use. While it was used only in 3.4% of patients at the ICU (most likely due to the limited availability of the device), in the ICCU, it was applied in over 13% of patients. This result is not supported by any available evidence. Moreover, the current recommendations have even recognized IABP as ineffective and potentially harmful.[13]

As for the analysis of complications, 2 findings are particularly interesting. First, there were no reported cases of acute renal failure in the ICU (0% vs 3.5% in the ICCU). This discrepancy might have been caused by acute renal failure due to contrast-induced nephropathy as a complication of coronary angiography, which was more commonly performed in the ICCU group. Unfortunately, the registry does not provide separate data on the cause of acute renal failure. Second, pneumonia was more common in ICCU patients. As the use of antibiotic prophylaxis was similar in both groups (about 80%), the difference might have been caused by the more frequent use of bronchoscopy in the ICU than in the ICCU. However, the occurrence of pneumonia did not affect the risk of death or the final neurologic outcome. This is in line with a study by Mongardon et al,[14] who reported that pneumonia was not associated with death and neurologic outcome, but only with the length of hospitalization. In the current analysis, the frequency

TABLE 4 Predictors of good neurologic outcome in the study groups

Variable	OR (95% CI)	*P* value
ICU		
Age	0.68 (0.51–0.92)	0.01
Rankin class after 48 hours	0.07 (0.02–0.29)	<0.001
Antipyretic drugs	0.16 (0.04–0.74)	0.02
Hypotension (SBP <90 mm Hg) treated with fluid infusion	0.20 (0.06–0.74)	0.02
ICCU		
Age	0.52 (0.39–0.68)	<0.001
GCS after ROSC	1.64 (1.30–2.06)	<0.001
GCS score on admission	1.72 (1.37–2.16)	<0.001
Rankin class after 48 hours	0.15 (0.08–0.28)	<0.001
First cardiac rhythm VF or VT	6.57 (2.42–17.8)	<0.001
Shock on admission	0.62 (0.30–1.27)	0.19
Witness of CPR	2.18 (1.15–4.14)	0.02
Witness of OHCA	5.21 (1.72–15.8)	0.004

Abbreviations: SBP, systolic blood pressure; others, see TABLES 1 and 2

of other complications did not differ significantly between groups and was in line with previous results on TTM.[15]

In our study, we compared neurologic outcomes and mortality between patients treated at the ICU and ICCU. During the treatment, death was reported in 17% and 20% of ICU and ICCU patients, respectively, which is lower than in previous studies on TTM. For example, Nilsen et al[16] reported a mortality rate of 50%. Perhaps this is due to the fact that the authors conducted an early assessment of prognosis (after 72 hours), on the basis of which intensive therapy was discontinued in patients considered to have severe or irreversible neurologic damage. Previous studies showed clear neurologic benefits in patients with OHCA treated with TTM compared with a control group.[1,17] Meanwhile, we showed that a large percentage of patients who were initially (after sedation had been stopped) classified as Rankin class 4 or 5 obtained good neurologic outcome after further treatment. Moreover, it may be highlighted that there were more patients with Rankin class 1, 2, or 3 in the ICCU than in the ICU group.

Good neurologic outcome observed in 32% to 43% of patients appears to be a satisfactory result, and is in line with the results of a previous study on TTM.[18] A direct comparison of the overall results of treatment between our registry and a European registry provided interesting findings.[19] The survival rate in Poland was higher than that in the European registry (69.2% vs 56%). However, while there was a similar rate of good neurologic outcome (39.4% vs 44%), Polish patients were more likely to have poor neurologic status (29.8% vs 12%). It would also be interesting to investigate what proportion of patients discharged with a significant neurologic deficit were then referred to a rehabilitation program, as well as to assess a long-term neurologic outcome and mortality rate of the study population.

The main limitation of our study is the lack of randomization. Various factors might have influenced the quality of data, such as no certainty as to the accuracy of the reported times during the prehospital treatment and the lack of information on the cause of death or acute renal failure.

The strength of the study is its observational design and the fact that data were obtained from both academic and nonacademic centers. Therefore, the study presents real-life data on the treatment of patients with OHCA. Despite the described limitations, our study is the first to compare treatment outcomes between patients with OHCA treated at the ICU and ICCU.

In conclusion, the ICCU has become a valuable alternative to the ICU to provide treatment for patients with OHCA. In our study, similar survival rates and neurologic outcome, with a high percentage of good results and an acceptable level of poor outcomes, were observed both for the ICCU and ICU. The TTM was characterized by a good safety profile and a low number of adverse events. However, well-designed randomized trials are needed to further compare treatment outcomes between these patient populations.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT All authors contributed to the concept and design of the study, as well as to the acquisition, analysis, and interpretation of data. RJK, AF, KO, MP, and ŁK performed statistical analysis. RJK, AF, KO, and MP drafted the manuscript. All authors critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the study, ensuring its integrity and accuracy.

CONFLICT OF INTEREST None declared.

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