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Is Hypothermia After Cardiac Arrest Effective in Both Shockable and Nonshockable Patients?

Insights From a Large Registry

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Background—Although the level of evidence of improvement is significant in cardiac arrest patients resuscitated from a shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia [VF/VT]), the use of therapeutic mild hypothermia (TMH) is more controversial in nonshockable patients (pulseless electric activity or asystole [PEA/asystole]). We therefore assessed the prognostic value of hypothermia for neurological outcome at hospital discharge according to first-recorded cardiac rhythm in a large cohort.

Methods and Results—Between January 2000 and December 2009, data from 1145 consecutive out-of-hospital cardiac arrest patients in whom a successful resuscitation had been achieved were prospectively collected. The association of TMH with a good neurological outcome at hospital discharge (cerebral performance categories level 1 or 2) was quantified by logistic regression analysis. TMH was induced in 457/708 patients (65%) in VF/VT and in 261/437 patients (60%) in PEA/asystole. Overall, 342/1145 patients (30%) reached a favorable outcome (cerebral performance categories level 1 or 2) at hospital discharge, respectively 274/708 (39%) in VF/VT and 68/437 (16%) in PEA/asystole ($P<0.001$). After adjustment, in VF/VT patients, TMH was associated with increased odds of good neurological outcome (adjusted odds ratio, 1.90; 95% confidence interval, 1.18 to 3.06) whereas in PEA/asystole patients, TMH was not significantly associated with good neurological outcome (adjusted odds ratio, 0.71; 95% confidence interval, 0.37 to 1.36).

Conclusions—In this large cohort of cardiac arrest patients, hypothermia was independently associated with an improved outcome at hospital discharge in patients presenting with VF/VT. By contrast, TMH was not associated with good outcome in nonshockable patients. Further investigations are needed to clarify this lack of efficiency in PEA/asystole. **(*Circulation*. 2011;123:877-886.)**

Key Words: cardiac arrest ■ hypothermia ■ resuscitation ■ outcome assessment

Each year, at least 225 000 new out-of-hospital cardiac arrests (OHCA) occur in Europe and in the US.[1,2] Even after a successful resuscitation and transportation procedure, survival rates to hospital discharge of these patients remain low, ranging from 21% to 33%.[3–5] The poor prognosis of these patients in whom the return of spontaneous circulation (ROSC) has been initially achieved is attributed to postcardiac arrest syndrome, which is the combination of postcardiac brain injury, circulatory dysfunction, and systemic ischemia/reperfusion response.[6]

Clinical Perspective on p 886

Animal studies[7–9] have demonstrated that hypothermia is able to decrease the consequences of the anoxo-ischemic neurological injury that follows the cerebral reperfusion. In the last decade, 2 randomized clinical trials[10,11] and a meta-analysis[12] have confirmed the benefit in OHCA comatose survivors cooled within the minutes or hours after initial resuscitation from an out-of-hospital ventricular fibrillation (VF). As a consequence, the most recent guidelines[13] include the routine practice of therapeutic hypothermia in the management of comatose survivors of OHCA, particularly if VF was the initial rhythm, and suggest its use as a class I recommendation. Although the proportion of OHCA patients presenting a nonshockable rhythm (pulseless electric activity [PEA] or asystole) has recently increased,[14] recommendations are narrowly given for the use of hypothermia in these

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patients. Available clinical studies that focused on therapeutic hypothermia in nonshockable patients were often of small sample size and yielded conflicting results.[15–18] Finally, recent guidelines asserted that the benefit of induced hypothermia in nonshockable patients was possible but still questionable and emphasized that further studies would be required on this issue.[6,13]

As a tertiary care center, our multidisciplinary team specializes in the management of post-OHCA patients recruited in a large urban area (Paris, France). Over the last 10 years, we progressively included induced hypothermia in our local procedures, regardless of the first presenting rhythm (shockable or not). Using our prospective data registry, the influence of therapeutic hypothermia on hospital outcome was assessed in OHCA patients, separately in those with VF/TV and in those with PEA/asystole as initial presenting rhythm.

Methods

Study Setting

Management of OHCA in Paris, France, involves mobile emergency units and fire departments that immediately provide both basic and advanced life support. After a call from a witness and in suspected cases of cardiac arrest, the closest emergency unit is dispatched to the scene. Out-of-hospital resuscitation is performed by an emergency team that includes at least 1 physician trained in emergency medicine according to international guidelines.[19] Patients in whom the resuscitation process fails are not transported to hospital. Most patients in whom ROSC is achieved are then referred to the intensive care unit (ICU) of our tertiary care center. At ICU admission, patients are treated and explored according to standard resuscitative guidelines including TMH. In cases without obvious extracardiac cause, the ambulance brings the patients directly to the catheterization laboratory and secondarily to the ICU where they are then cooled. In cases with obvious extracardiac cause, patients are immediately admitted to ICU and can benefit from hypothermia treatment promptly.

Data Collection

All nontraumatic OHCA patients admitted consecutively from January 2000 to June 2009 after a successful resuscitation with ROSC were included. Patient data were prospectively collected according to Utstein recommendations.[20] Baseline characteristics such as age, gender, cardiovascular risk factors (hypertension, diabetes mellitus, and current smoking), location of cardiac arrest and initial cardiac rhythm recorded by the automated defibrillator (VF/ventricular tachycardia [VT] or PEA/asystole) were included in the database. Using data from the emergency medical service, the delays between the onset of OHCA and basic life support (BLS) and between BLS and ROSC were measured. The total epinephrine dose that was provided during the prehospital resuscitation and the use of TMH during the postcardiac arrest period were noticed. Blood lactate (mmol/L), creatinine (μmol/L) and troponin (μg/L) levels were measured at hospital admission. Postresuscitation shock was defined as the occurrence or the persistence of an arterial hypotension (mean arterial pressure <60 mm Hg or systolic blood pressure <90 mm Hg) sustained for >60 minutes after ROSC in spite of adequate fluid resuscitation and requiring norepinephrine or epinephrine infusion.[21] The definitive cause of the cardiac arrest was confirmed at hospital discharge through consideration of all available data obtained during hospital stay. Acute coronary syndromes and/or primary ventricular arrhythmia were considered cardiac causes. All other causes were considered extracardiac causes.

Therapeutic Hypothermia

When employed, TMH was started immediately at ICU admission using external cooling by forced cold air during the first 24 hours in order to obtain a target temperature between 32°C and 34°C.[22] In the absence of shock or complications, sedation was interrupted at the end of the hypothermia period. Normothermia between 37°C and 37.5°C was then achieved using passive rewarming (0.3°C/h) and maintained during the next 24 hours. Patients were extubated as soon as their neurological and respiratory status allowed it. Temperature was collected by a bladder probe during ICU stay. Adverse events such as arrhythmias, cardiac arrest recurrences, infectious complications, and cardiogenic shock and/or pulmonary edema were also collected.

Hypothermia was progressively implemented over the study period. To appreciate the potential influence of time, the study period was subdivided according to 3 time intervals. The first interval, which took place between 2000 and 2003, corresponds to the "prehypothermia era": during this period, systematic and active hypothermia was not recommended after resuscitation from cardiac arrest.[23] The second interval, which took place between 2004 and 2006, corresponds to the hypothermia implementation phase, consecutive to the publication and dissemination of international guidelines.[24] The third interval, from 2007 to 2009, includes a period during which hypothermia became routinely used during the management of OHCA.

Table 1. Cerebral Performance Category Scale

Good outcome	
1	Conscious and alert with normal function or only slight disability.
2	Conscious and alert with moderate disability.
Bad outcome	
3	Conscious with severe disability.
4	Comatose or persistent vegetative state.
5	Brain dead or death from other causes.

Outcome Assessment

The primary outcome was defined by the level reached on the cerebral performance categories scale (CPC) at hospital discharge.[25] Good outcome includes patients with a good cerebral performance (CPC1) or a moderate cerebral disability (CPC2). Unfavorable outcome was defined by a severe cerebral disability (CPC3), a coma or a vegetative state (CPC4), or death (CPC5) (Table 1). The CPC level was prospectively assessed by a first physician at hospital discharge and was controlled by a second and independent physician blinded for hypothermia treatment. Each case of disagreement was resolved by a consensus. Our local ethics committee approved the study protocol.

Statistical Analysis

The cohort was dichotomized according to the first recorded cardiac rhythm on the field, and analysis was conducted separately in patients with a shockable rhythm (ie, VF/VT) and in those with a nonshockable rhythm (ie, PEA/asystole). Inside each group, comparisons were performed between hypothermia-treated patients and nonhypothermia patients. Comparisons between groups used χ^2 test for categorical variables and Student t test for continuous variables. Potential confounding factors in the association between TMH and good neurological outcome were identified using a P value <0.15. The association of TMH with good neurological outcome was thereafter adjusted for these identified confounding factors in a single multivariable logistic regression analysis, allowing estimating odds ratios (ORs) and their 95% confidence intervals (CIs). At this stage, $P<0.05$ was considered statistically significant. The identification of the confounders in patients with VF/VT and in patients with PEA/asystole was also made using 2 alternative methods. In the first, confounders were those that modified the univariate OR of TMH for good neurological outcome by $>10\%$ when covariating with TMH on a 1-at-a-time basis. The latter and TMH were thereafter included in a same multivariate logistic regression model. In the second, all

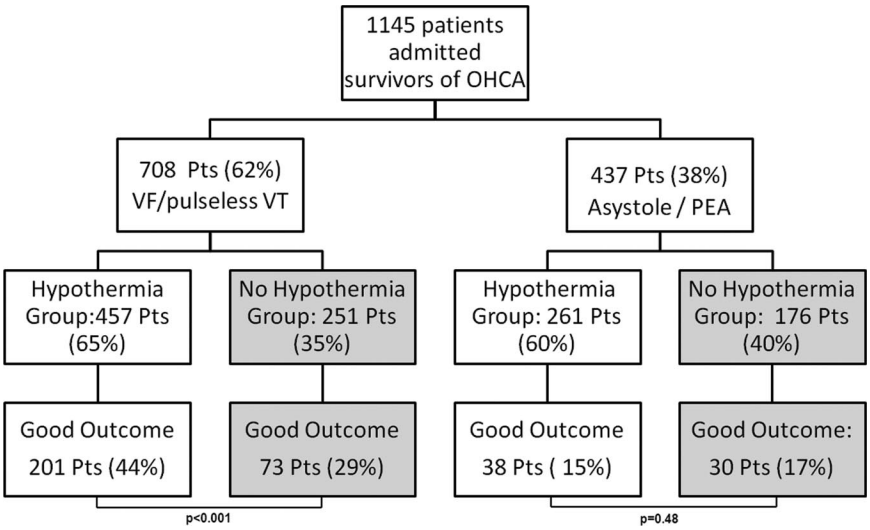

Figure 1. Outcome of admitted survivors of OHCA according to performance of TMH. Pts indicates patients.

potential confounders were selected on an a priori basis and were included in a single multivariable logistic regression model together with TMH. Because OR estimates for TMH were comparable with either 3 methods, only the first described method was used in the present article. Moreover, 2-by-2 interaction terms between TMH and each retained confounder were tested 1 at a time in the fully adjusted models and the Wald test was used to assess whether or not interaction was statistically significant ($P<0.10$). All analyses were 2 sided, and calculations were performed using STATA/SE 11.0 software (College Station, TX).

Results

From January 2000 to June 2009, 1145 nontraumatic OHCA patients have been transported to hospital after a successful resuscitation and directly admitted to our ICU. As shown in Figure 1, 708 (62%) presented with VF/VT as their initial rhythm (shockable rhythm). For the remaining 437 patients (38%) with nonshockable rhythm, asystole was found in 351/437 patients (80%) and PEA in 86/437 patients (20%). During the whole study period, therapeutic hypothermia was induced in 457/708 patients (65%) with VF/VT and in 261/437 patients (60%) with nonshockable rhythm ($P=0.10$).

Baseline Characteristics

In the overall cohort, the men-to-women ratio was 3:1 and the median age was 59 years (interquartile range, 49 to 71). Cardiac arrest occurred most frequently at home (42%) and was witnessed in 87% of cases. The prehospital team delivered an initial defibrillation in 708/1145 (62%) patients. The median delays between collapse and BLS (no flow) and between BLS and ROSC (low flow) were respectively 4 (interquartile range, 0 to 10) and 15 (interquartile range, 8 to 25) minutes. Cardiac cause of arrest was found in 437/1145 patients (38%).

Table 2 compares the baseline characteristics and the usual severity criteria of patients who did and did not receive hypothermia, separately in patients in VF/VT and in PEA/asystole. In shockable patients, baseline characteristics were similar in both subgroups except for hypertension and age. In nonshockable patients, only hypertension was significantly more frequent in hypothermia-treated patients. In addition, hypothermia treatment was displayed similarly regardless of the cardiac arrest cause in both subgroups.

Temperature Assessment

Detailed description of cooling is depicted in Table 3. At ICU admission, temperature did not differ between cooled and noncooled patients, both in shockable and in nonshockable patients (respectively, $P=0.41$ and $P=0.35$). In hypothermia-treated patients, delay to reach the targeted temperature (<34°C) was longer in patients with a shockable initial rhythm (612±296.4 minutes versus 522±348.6 minutes, $P=0.001$), but the duration of cooling was similar between the 2 presenting-rhythm subgroups (1139±462.2 minutes versus 1103±529.8 minutes, $P=0.34$). Therefore, temperatures were lower in the hypothermia group and stayed under the target temperature (<34°C) at the first and second day, reaching respectively 33.12°C (±1.32) and 33.30°C (±1.39) for the VF/VT group and 32.84°C (±1.57) and 33.22°C (±1.39) for the PEA/asystole group. On the third day, hypothermia-treated and non–hypothermia-treated patients reached normal temperature values both in patients with VF/VT and PEA/asystole.

Adverse events are detailed in online-only Data Supplement Table I. The occurrence of cardiogenic shock and/or pulmonary edema was similar across the different subgroups. Arrhythmias and cardiac arrest recurrences were more frequent in non–hypothermia-treated patients in both shockable and nonshockable groups. On the other hand, infectious complications were more frequent in hypothermia-treated patients, regardless of the initial rhythm.

Outcome Assessment

Overall, a good neurological outcome (CPC 1 to 2) was observed at hospital discharge in 342/1145 patients (30%). Among them, 223 patients (65%) reached CPC1 and 119 (35%) reached CPC2. In patients with VF/VT as initial rhythm, 274/708 had a good outcome (39%), with 176/274 patients reaching CPC1 (64%) and 98/274 patients reaching CPC2 (36%). In patients with PEA/asystole as initial rhythm, 68 (16%) had a good outcome, with 47/68 (69%) reaching CPC1 and 21/68

Table 2. Baseline Characteristics

	VF/VT				PEA/Asystole			
	Overall (n=708)	TMH	No TMH	*P**	Overall (n=437)	TMH	No TMH	*P**
Hypertension	218 (35)	155 (38)	63 (29)	0.02	148 (38)	101 (42)	47 (31)	0.03
Diabetes mellitus	77 (12)	53 (13)	24 (11)	0.42	76 (19)	52 (22)	24 (16)	0.16
Smoker	261 (48)	168 (47)	93 (48)	0.80	124 (38)	85 (42)	39 (31)	0.06
Men	562 (79)	359 (79)	203 (81)	0.47	275 (63)	164 (63)	111 (63)	0.96
Age, y†								
<49	188 (27)	111 (24)	77 (31)	0.05	105 (24)	59 (23)	46 (26)	0.68
49-59	201 (28)	124 (27)	77 (31)		95 (22)	55 (21)	40 (23)	
59-71	163 (23)	109 (24)	54 (21)		111 (25)	71 (27)	40 (23)	
>71	156 (22)	113 (25)	43 (17)		126 (29)	76 (29)	50 (28)	
Cardiac arrest cause								
Cardiac cause	386 (55)	247 (54)	139 (55)	0.73	51 (12)	28 (11)	23 (13)	0.46
Extracardiac cause	322 (45)	210 (46)	112 (45)		386 (88)	233 (89)	153 (87)	
Location								
Public area	171 (24)	105 (23)	66 (27)	0.25	113 (26)	60 (23)	53 (30)	0.23
Home	251 (36)	158 (35)	93 (37)		233 (53)	146 (56)	87 (49)	
Other	284 (40)	194 (42)	90 (36)		91 (21)	55 (21)	36 (21)	
Time from collapse to BLS‡								
<4 minutes	333 (50)	219 (51)	114 (50)	0.89	193 (49)	110 (46)	83 (55)	0.07
Time from BLS to ROSC‡								
≤15 min	297 (44)	192 (43)	105 (48)	0.23	188 (47)	110 (44)	78 (55)	0.051

All data are expressed as n(%) taking into account missing data.

**P* values for comparison between TMH group and no TMH group obtained from a χ^2 test.

†Age was classified according to interquartiles.

‡Time from collapse to BLS and time from BLS to ROSC were classified according to their respective median values.

(31%) CPC2. In patients with bad outcome (n=803), 23 patients (3%) were survivors at their hospital discharge but with severe neurological sequelae (CPC3 or CPC4).

As shown in Figure 1, therapeutic hypothermia was associated with a significant better outcome in patients with a VF/VT (44% versus 29%, $P<0.001$) but not in patients with PEA/asystole (15% versus 17%, $P=0.48$). These rates correspond to a nonadjusted OR of hypothermia for good outcome of 1.91 (95% CI, 1.38 to 2.66) and 0.83 (95% CI, 0.49 to 1.40) in patients with VF/VT and PEA/asystole, respectively.

Table 4 displays the results of univariate analysis according to initial rhythm subgroups. Resuscitation delays, total dose of epinephrine given during the prehospital care phase, location of cardiac arrest, blood lactate level, and the occurrence of postresuscitation shock were significantly associated with the outcome in both subgroups. Additionally, in the VF/VT group, diabetes mellitus, smoking, age, the use of

Table 3. Assessment of TMH

	VF/VT (n=708)			PEA/Asystole (n=437)		
	TMH (n=457)	No TMH (n=251)	*P**	TMH (n=261)	No TMH (n=176)	*P**
Temperature at ICU admission, °C, mean (SD)	35.56 (1.56)	35.68 (2.14)	0.40	35.11 (1.72)	34.92 (2.34)	0.35
Time from collapse to reach temperature <34°C, min, mean (SD)†	612.6 (296.4)			522.6 (348.6)		
Lowest temperature, °C, mean (SD)						
Day 1	33.12 (1.32)	35.49 (1.75)	<0.001	32.84 (1.57)	34.70 (2.11)	<0.001
Day 2	33.30 (1.39)	36.79 (1.50)	<0.001	33.22 (1.39)	36.60 (1.29)	<0.001
Day 3	36.93 (1.14)	37.33 (0.84)	<0.001	36.65 (1.17)	37.06 (0.95)	0.007
Duration of cooling, min, mean (SD)‡	1139.4 (469.2)			1103.4 (529.8)		

**P* values for comparison between TMH group and no TMH group obtained from Student *t* test; comparison between VF/VT group and PEA/asystole group based on Student *t* test were for †$P=0.001$ and ‡$P=0.34$.

Table 4. Factors Associated With Outcome According to Initial Cardiac Rhythm

	VF/VT			PEA/Asystole		
	Good Outcome (N=274), n (%)	Bad Outcome (N=434), n (%)	*P**	Good Outcome (N=68), n (%)	Bad Outcome (N=369), n (%)	*P**
Hypertension	82 (33)	136 (36)	0.39	28 (44)	120 (37)	0.24
Diabetes mellitus	19 (8)	58 (15)	0.003	10 (16)	66 (20)	0.44
Smoker	118 (52)	143 (44)	0.06	23 (39)	101 (37)	0.81
Men	219 (80)	343 (79)	0.77	44 (65)	231 (61)	0.74
Age, y†						
<49	94 (34)	94 (22)	<0.001	13 (19)	92 (25)	0.75
49–59	81 (30)	120 (28)		15 (22)	80 (22)	
59–71	52 (19)	111 (26)		18 (26)	93 (25)	
>71	47 (17)	109 (24)		22 (33)	104 (28)	
Witnessed location	246 (95)	357 (89)	0.005	59 (89)	279 (79)	0.055
Public Area	133 (49)	151 (35)	<0.001	18 (27)	73 (20)	0.024
Home	65 (24)	186 (43)		26 (38)	207 (56)	
Other	76 (27)	93 (22)		24 (35)	89 (24)	
Time from collapse to BLS‡						
<4 minutes	172 (65)	161 (37)	<0.001	43 (68)	150 (46)	0.001
Time from BLS to ROSC‡						
≤15 minutes	171 (66)	126 (31)	<0.001	54 (83)	134 (40)	<0.001
Epinephrine, total dose in mg‡						
<3	36 (14)	215 (52)	<0.001	19 (28)	182 (51)	0.001
TMH	201 (73)	256 (59)	<0.001	38 (56)	223 (60)	0.48
Troponin, μg/L†						
<0.5	47 (21)	45 (15)	0.002	21 (47)	119 (47)	0.96
0.5–2.3	49 (22)	50 (16)		13 (28)	43 (28)	
2.3–10.4	72 (32)	86 (28)		8 (17)	43 (17)	
>10.4	56 (25)	125 (41)		5 (11)	22 (11)	
Creatinine, μmol/L†						
<43	60 (22)	104 (27)	<0.001	16 (24)	86 (26)	0.12
43–93	110 (41)	67 (17)		21 (32)	65 (19)	
93–137	64 (24)	103 (27)		16 (24)	86 (16)	
>137	33 (12)	116 (29)		13 (20)	97 (39)	
Blood lactate, mmol/L†						
>2.2	115 (45)	75 (20)	<0.001	19 (29)	45 (14)	<0.001
2.2–4.5	80 (31)	96 (25)		22 (33)	63 (20)	
4.5–8.5	42 (16)	100 (27)		14 (21)	96 (30)	
>8.5	20 (8)	107 (28)		11 (17)	117 (36)	
Postresuscitation circulatory shock	71 (26)	166 (38)	0.001	19 (28)	166 (45)	0.009

All data are expressed in n (%) taking into account missing data.

*P values for comparison between outcomes obtained from a χ^2 test.

†Age, troponin, lactate, and creatinine blood levels were classified according to interquartiles.

‡Time from collapse to BLS, time from BLS to ROSC, and total dose of epinephrine were classified according to their respective median.

therapeutic hypothermia, and blood levels of troponin and creatinine were also related to the outcome.

Multivariable Analysis

In the VF/VT subgroup, longer delay between collapse and BLS and between BLS and ROSC, higher initial administered dose of epinephrine, the occurrence of postresuscitation shock, increase in blood lactate, and older age were inversely associated with a better neurological outcome. In contrast, the use of TMH (adjusted OR 1.90, 95% CI, 1.18 to 3.06) was positively associated with a better neurological outcome (Figure 2A).

In the PEA/asystole subgroup (Figure 2B), longer resuscitation delays, increase in blood lactate, and postresuscitation shock were inversely related to a good outcome. Likewise, TMH tended to be inversely associated with good outcome although the adjusted OR did not reach statistical significance (adjusted OR, 0.71; 95% CI, 0.37 to 1.36).

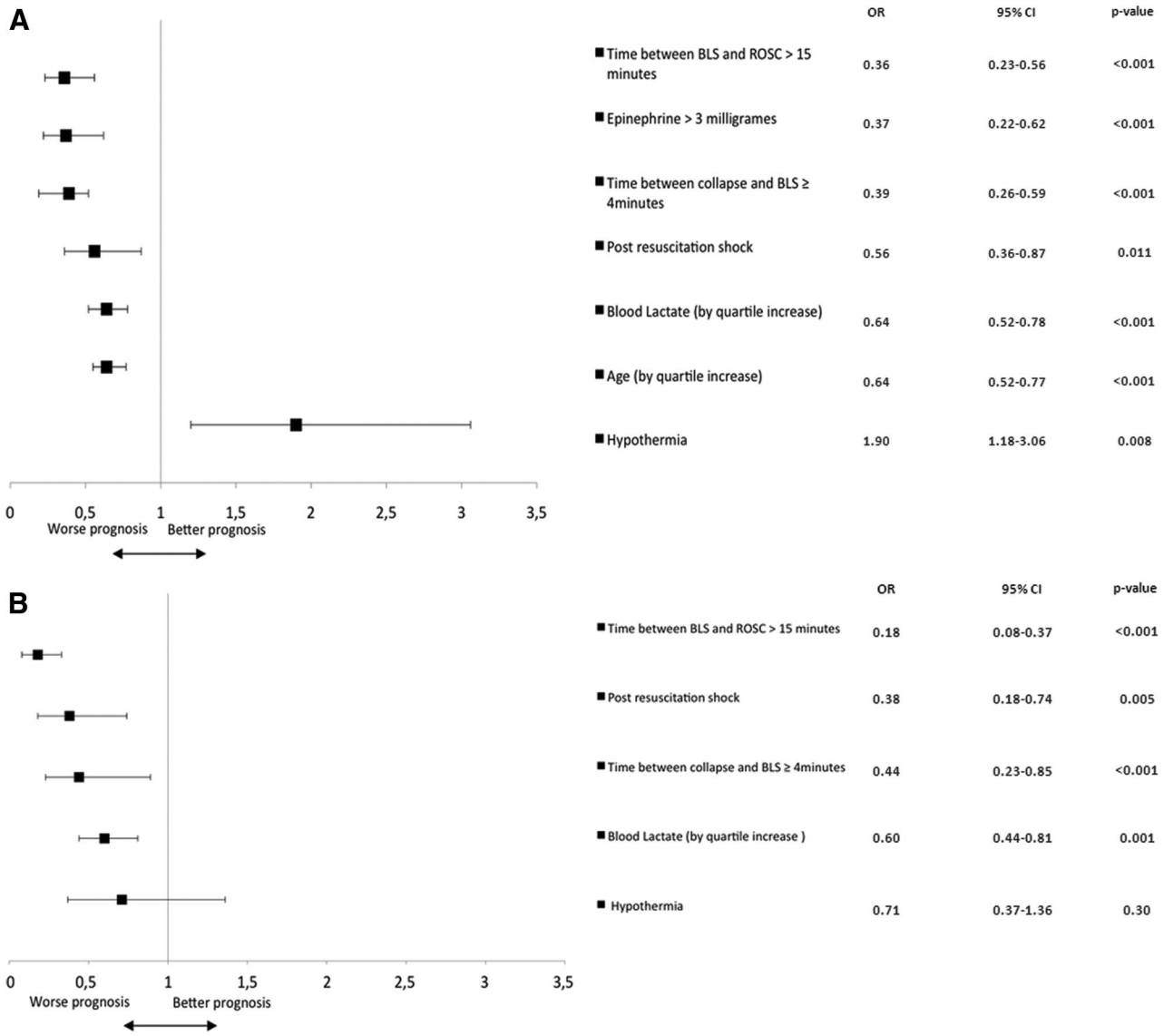

Figure 2. Predictive factors associated with outcome after multivariate analysis. A, VF/VT group; B, PEA/asystole group.

On the basis of the fully adjusted model, there was no significant interaction between any confounder and TMH in patients with VF/VT and in those with PEA/asystole (all *P* values for interaction >0.10; not shown).

Separate analysis focusing on different subsets inside the VF/VT group demonstrated a higher benefit of TMH for men (OR, 2.26; 95% CI, 1.34 to 3.82; $P=0.002$), for patients in whom a cardiac cause of the cardiac arrest was finally identified (OR, 2.15; 95% CI, 1.25 to 3.69; $P=0.005$), when the delay between collapse and BLS was <4 minutes (OR, 2.20; 95% CI, 1.18 to 4.10; $P=0.01$), and when the delay between BLS and ROSC was >15 minutes (OR, 2.08; 95% CI, 1.03 to 4.21; $P=0.04$).

As expected, the rate of TMH use increased across the 3 time intervals from 36% between 2000 to 2003 in VF/VT and in PEA/asystole patients to 86% in VF/VT and 73% in PEA/asystole patients, respectively (Figure 3). Through these 3 periods and for each subgroup of initial rhythm, the proportion of early coronary angiogram (averaging 78% in VF/VT patients and 30% in PEA/asystole patients) and the proportion of cardiac cause (determined at hospital discharge from clinical and biological features and coronary angiogram results; 77% (543/708) for VF/VT patients and 18% (78/435) for PEA/asystole patients) remained stable. Focusing on patients admitted during the 2004 to 2009 period, we found that baseline characteristics were similar between cooled and uncooled patients in each subgroup. Only time interval between BLS and ROSC was proportionally shorter in uncooled patients for the nonshockable subgroup ($P=0.03$). However, the rates of good neurological outcome associated with TMH in VF/VT and in PEA/asystole patients did not vary significantly within each time interval (Figure 4).

Discussion

In this large cohort of 1145 consecutive OHCA patients admitted alive to a tertiary center in Paris, France, TMH nearly doubled the probability of being discharged with a favorable neurological outcome in patients resuscitated from

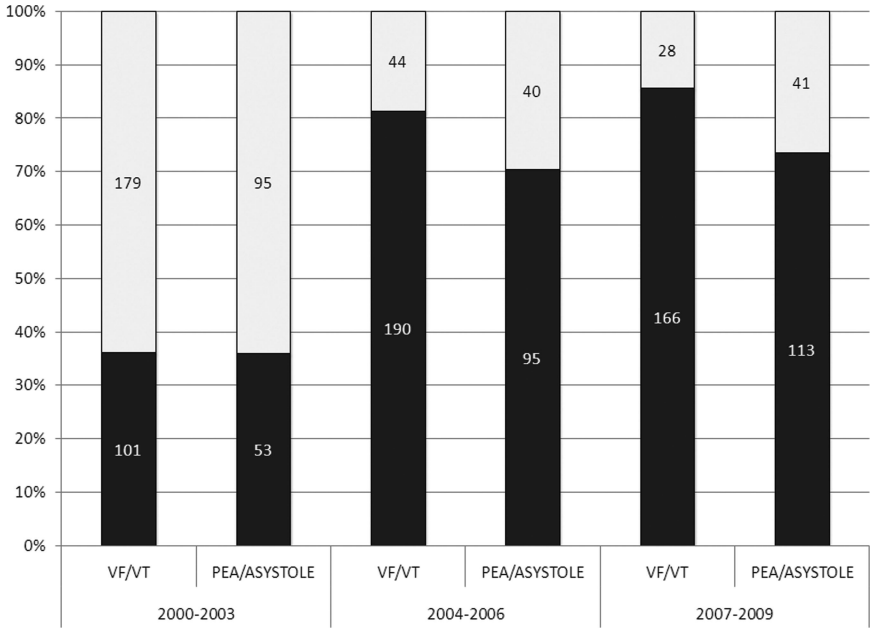

Figure 3. Implementation of TMH over study periods. In each bar, the proportion of patients who received TMH appears in black and the proportion of patients who did not receive TMH appears in gray.

a shockable (VF/VT) cardiac arrest, independently from others pre- and intrahospital risk factors. By contrast, in patients resuscitated from a nonshockable cardiac arrest (PEA/asystole), TMH tended to worsen the prognosis although the association was not statistically significant.

TMH has been shown to be of clinical benefit in VF/VT cardiac arrest in 2 randomized controlled trials[10,11] and has been recommended since 2003 in these patients.[13] In most recent observational studies, TMH in VF/VT patients was also found to be associated with a better prognosis.[26] The observational study of Arrich[16]confirmed the benefit of TMH in VF patients even if analyses did not take into account the effect of several confounding factors such as prehospital care characteristics. A small randomized controlled trial[15] also showed a favorable effect of TMH on the outcome although the benefit was not statistically significant. More recently,

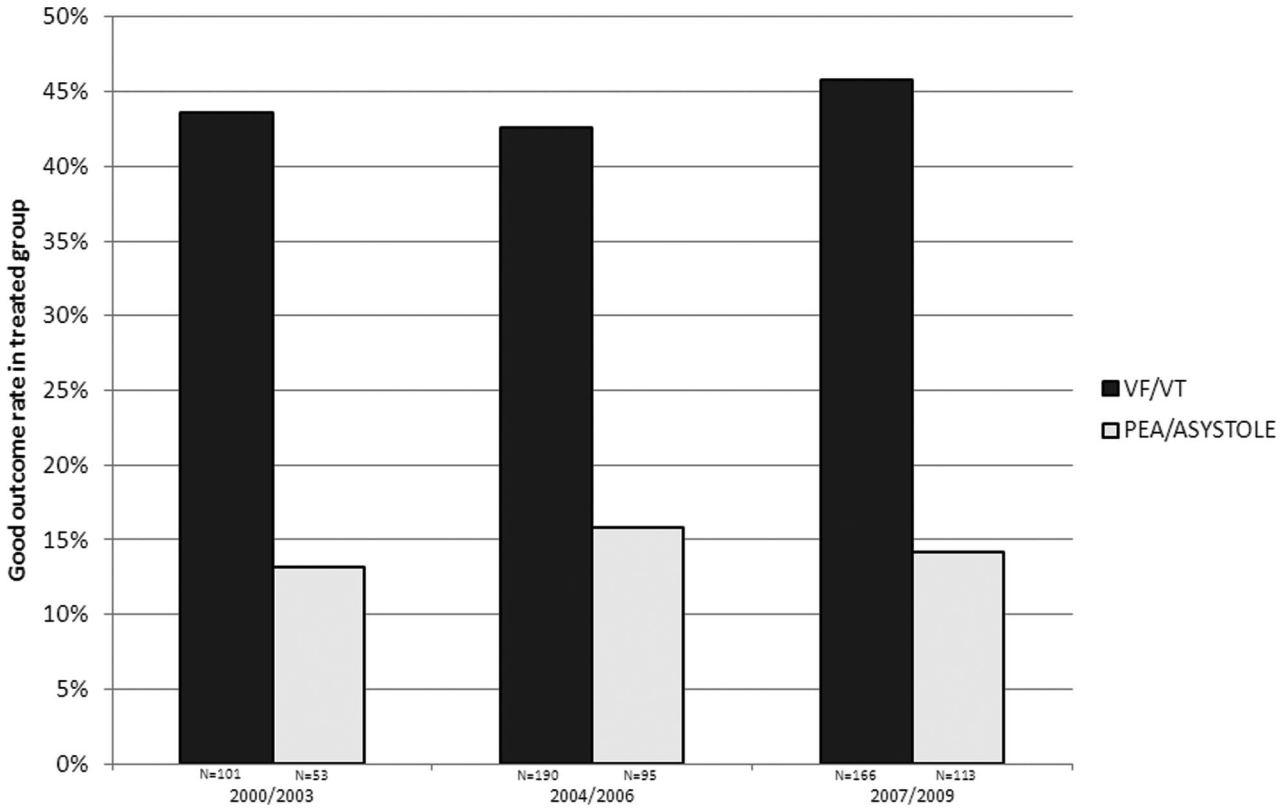

Figure 4. Good outcome rates in TMH patients over study periods, according to initial rhythm. These rates are calculated in patients who did receive TMH.

Oddo et al[18] showed better survival and improved neurological outcome rates in cooled post–cardiac arrest patients. However, the authors failed to show any independent benefit of TMH once usual OHCA prognostic factors were adjusted. The present study extends the findings of these previous confirmatory studies with a much larger sample size, and it also adjusts analysis for known pre- and intrahospital prognostic factors. Our results reinforce the strength of international recommendations on the use of therapeutic hypothermia in shockable patients and encourage its generalization in that setting.

Our second critical result is the apparent absence of benefit from induced hypothermia in patients presenting with a nonshockable rhythm. Moreover, we observed a trend toward a detrimental effect on prognosis in this subgroup of patients. Only a few studies have looked at the potential benefit of induced hypothermia in nonshockable OHCA patients, and these have provided conflicting results. In a small randomized controlled trial of 30 patients, induced hypothermia demonstrated a beneficial effect in nonshockable patients[27] whereas in a more recent trial, induced hypothermia was related to a trend toward a harmful effect.[15] In observational studies, mixed results have been also reported. In the study by Arrich,[16] hypothermia was positively associated with OHCA survival rate but without significant association. In a multivariable analysis, Oddo et al[28] have also found a positive but not significant association between hypothermia and outcome in a small subset of patients. Reasons for this lack of association are not clear even if a different hypothesis can be made. This nonshockable subgroup presented a longer resuscitation process compared to the shockable subgroup, leading to a higher rate of postresuscitation circulatory shock, as previously shown by Laurent et al.[21] Given the importance of these parameters for post–cardiac arrest brain damage occurrence, the "dose" of hypothermia (relative to duration and/or level) that was employed in our treatment proceeding could have been inadequate and/or not sufficient. Furthermore, there is a well known link between cardiac arrest cause and the first cardiac rhythm because shockable OHCAs, as observed in our population, are more often related to primary cardiac causes. The pathophysiological consequences of a circulatory arrest that occurred in an organism that was not previously oxygen deprived are probably not similar to those that can be observed after anoxo-ischemia, with the consequence that brain damage observed in this latter situation is usually more severe.[29,30] It can be supposed that the risk–benefit ratio of induced hypothermia, which is clearly favorable in shockable patients, is altered in nonshockable patients. Altogether, although the proportion of OHCA survivors with a nonshockable initial cardiac rhythm has been increasing, recommendations are still uncertain,[13] and studies on that specific topic are warranted.[6] To date, the benefit of the actually recommended scheme of hypothermia treatment is debatable in nonshockable patients. It does not mean that hypothermia should not be employed in nonshockable patients. Further prospective clinical studies testing different schemes of hypothermia treatment should be encouraged in these patients.

The present study also puts forward the impressive implementation of TMH over the last 10 years. Whereas previous studies highlighted the underuse of hypothermia,[31,32] cooling has been performed in recent years in a proportion that reaches nearly 80%. Nevertheless, some additional advances could be implemented. Animal studies suggest the benefit of a very early cooling in the first 2 hours after ROSC.[7,33] Our delays to obtain the target temperature seem quite long at 612.6 minutes for VF/VT and 522.6 minutes for PEA/asystole, respectively, even if they are similar to previously reported delays.[11] The external cooling technique that was used in these patients is known to be slower in reducing core temperature than internal cooling.[24] The rate of adverse events reported is similar to that coming from other studies even if the quality of collected data and disparities between cooling techniques prevent any comparison.[34] Therefore, targeted temperature between 32 and 34°C was obtained in the treated group, substantiating the feasibility and the effectiveness of this technique. In addition, the exclusive use of this procedure in our study guarantees the homogeneity of patient care.

Several limitations must be acknowledged. The observational design of our study precluded any inferences on a causal link between hypothermia and prognosis. However, even if patients were not randomized to receive or not receive TMH, we found very similar baseline and severity criteria between cooled and not-cooled patients. This similarity suggests that physician choice to provide or not provide TMH was not influenced by these factors but was mainly due to progressive implementation of this treatment over time. However, our findings may not be generalizable to other nonspecialized centers. Indeed, this study was performed in Paris where prehospital management of OHCA is performed by both fire departments and medical teams according to predefined standard protocols, which could explain the high rate of shockable patients. Patients were managed in a tertiary center by a multidisciplinary team that was highly experienced in the care of cardiac arrest. In particular, TMH was performed in a high proportion of patients in recent years, reflecting the high level of guidelines implementation. The follow-up duration that was limited to the hospital stay represents another limitation. However, several studies have demonstrated stable long-term good outcome rates after discharge in survivors of OHCA.[35,36] Finally, external cooling technique starting only at ICU admission could be less efficient compared to other procedures.[37]

In conclusion, the present study conducted in a large OHCA survivors cohort highlights the independent association between induced hypothermia and better neurological outcome at discharge in shockable patients. Therefore, our findings support and encourage unconditionally its routine practice in agreement with international guidelines. However, we also show that the benefit of hypothermia in nonshockable OHCA patients is still not demonstrated. Our results emphasize the need for further clinical investigations testing new and different schemes of hypothermia in these patients, with the aim to reinforce its potential efficiency.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Neurological outcome in out-of hospital cardiac arrest remains poor, even for patients in whom a successful return of spontaneous circulation has been obtained. Therapeutic mild hypothermia could improve neurological outcome, particularly in patients with shockable initial rhythm (ie, ventricular fibrillation or pulseless tachycardia). However, its benefit is not well established in patients with nonshockable rhythms. In a tertiary center in Paris, France, therapeutic mild hypothermia has been progressively implemented over the last decade, regardless of the presented rhythm, in 457 of 708 shockable patients (65%) and in 261 of 437 nonshockable patients (60%). Overall, 342 of 1145 patients (30%) achieved a favorable outcome at hospital discharge, 274 of 708 shockable patients (39%) and 68 of 437 nonshockable patients (16%), respectively. Therapeutic mild hypothermia was associated with a nearly 2-fold improvement in favorable neurological outcome in shockable patients (adjusted odds ratio, 1.90; 95% confidence interval, 1.18 to 3.06) whereas no significant association was found in nonshockable patients (adjusted odds ratio, 0.71; 95% confidence interval, 0.37 to 1.36). Therefore, these findings support and strongly encourage the routine practice of therapeutic mild hypothermia in agreement with international guidelines in patients with ventricular fibrillation/ventricular tachycardia as initial rhythm. However, the benefit of hypothermia in nonshockable patients is still debatable. Further clinical investigations such as randomized trials are warranted to test new and different schemes of hypothermia in the most severely brain damaged patients, with the aim to reinforce its potential efficiency.

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SUPPLEMENT MATERIAL

Supplement Table

	VT/VF				ASYSTOLE/PEA			
	Overall N=708	**Hypothermia group N=457**	**No hypothermia group N=251**	**p value***	**Overall N=437**	**Hypothermia group N=261**	**No hypothermia group N=176**	**p value***
Cardiac arrest recurrence	121 (17)	65 (14)	56 (22)	0.006	71 (16)	20 (8)	51 (29)	<0.001
Cardiogenic shock and/or pulmonary oedema	188 (27)	116 (25)	72 (29)	0.34	82 (19)	48 (18)	34 (19)	0.81
Infectious complication	386 (55)	275 (60)	111(44)	<0.001	218 (50)	149 (57)	69 (39)	<0.001