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Fabrice Daviaud
Florence Dumas
Nadège Demars
Guillaume Geri
Adrien Bouglé
Tristan Morichau-Beauchant
Yên-Lan Nguyen
Wulfran Bougouin
Frédéric Pène
Julien Charpentier
Alain Cariou

Blood glucose level and outcome after cardiac arrest: insights from a large registry in the hypothermia era

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Take-home message: The role of glycemia during the post-resuscitation period in cardiac arrest patients is unknown. In this study we found that a high level of glycemia during the first 48 h following a cardiac arrest was associated with a poor outcome.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-014-3269-9) contains supplementary material, which is available to authorized users.

F. Daviaud · N. Demars · G. Geri · A. Bouglé · T. Morichau-Beauchant · Y.-L. Nguyen · W. Bougouin · F. Pène · J. Charpentier · A. Cariou (✉)
Medical Intensive Care Unit, Cochin University Hospital, Assistance Publique-Hôpitaux de Paris, 27 rue du Faubourg Saint Jacques, 75014 Paris, France
e-mail: alain.cariou@cch.aphp.fr
Tel.: +33-1-58412501
Fax: +33-1-58412505

F. Daviaud
e-mail: daviaudfabrice@gmail.com

F. Dumas
Emergency Department, Cochin University Hospital, Assistance Publique-Hôpitaux de Paris, 27 rue du Faubourg Saint Jacques, 75014 Paris, France

F. Daviaud · F. Dumas · G. Geri · A. Bouglé · T. Morichau-Beauchant · Y.-L. Nguyen · W. Bougouin · F. Pène · J. Charpentier · A. Cariou
Paris Descartes University, Paris, France

F. Dumas · A. Cariou
INSERM U970 (Team 4), 56 rue Leblanc, 75015 Paris, France

Abstract *Introduction:* The influence of blood glucose (BG) level during the post-resuscitation period after out-of-hospital cardiac arrest (OHCA) is still debated. To evaluate the relationship between blood glucose level and outcome, we included the median glycemia and its maximal amplitude over the first 48 h following ICU admission in an analysis of outcome predictors. *Methods:* We conducted a database study in a cardiac arrest center in Paris, France. Between 2006 and 2010, we included 381 patients who were all resuscitated from an OHCA. A moderate glycemic control was applied in all patients. The median glycemia and the largest change over the first 48 h were included in a multivariate analysis that was performed to determine parameters associated with a favorable outcome. *Results:* Of the 381 patients, 136 (36 %) had a favorable outcome (CPC 1–2). Median BG level was 7.6 mmol/L (6.3–9.8) in patients with a favorable outcome compared to 9.0 mmol/L (IQR 7.1–10.6) for patients with an unfavorable outcome ($p < 0.01$). Median BG level variation was 7.1 (4.2–11) and 9.6 (5.9–13.6) mmol/L in patients with and without a favorable outcome, respectively ($p < 0.01$). In multivariate analysis, an increased median BG level over the first 48 h was found to be an independent predictor of poor issue [OR = 0.43; 95 % CI (0.24–0.78), $p = 0.006$]. Finally a progressive increase in median BG level was associated with a progressive increase in the proportion of patients with a poor outcome. *Conclusion:* We observed a relationship between high blood glucose level and outcome after cardiac arrest. These results suggest the need to test a strategy combining both control of glycemia and minimization of glycemic variations for its ability to improve post-resuscitation care.

Keywords Cardiac arrest · Neurologic outcome · Blood glucose · Glycemic variations · Caloric input · Insulin intake

Introduction

The poor prognosis of post-cardiac arrest patients, in whom a return of spontaneous circulation (ROSC) has been initially achieved, is mainly attributed to post-cardiac arrest syndrome, which can be viewed as the combination of post-cardiac brain injury, circulatory dysfunction, and systemic ischemia/reperfusion response [1]. The aggravation of tissue damage that occurs during this period can be measured by the loss of homeostasis control. In this way, experimental data showed a negative influence of hyperglycemia on secondary neurological lesions during the ischemic period but also during the reperfusion period [2–4]. A link between hyperglycemia and poor neurologic prognosis was also suspected in different clinical acute settings [4–6], but is not firmly established. Furthermore previous studies that investigated the relationship between glycemic control and post-cardiac arrest prognosis were mostly conducted before the therapeutic hypothermia era. Lowering of the core temperature is now widely performed in this population but may unfortunately further impair glucose homeostasis [7, 8]. By examining a registry database study, Nielsen et al. [9] identified hyperglycemia as an independent mortality risk factor in cooled patients. Nurmi et al. [10] also identified changes of glycemia that occurred during pre-hospital care as being a prognosis factor. In contrast, Cueni-Villoz et al. [11] reported that the mean BG level was not an independent predictor of in-hospital mortality in this population. On the whole, the link between BG level and prognosis is unknown in post-cardiac arrest patients. As highlighted by current guidelines, it is difficult to recommend a strict glycemic control in this population because the risk of hyperglycemia is not sufficiently established [12].

To provide further information and improve post-resuscitation care, we aimed to analyze the relationship between BG level and outcome in a large ICU registry. In addition to BG level, we also investigated the amplitude of BG changes during the first 48 h following resuscitation. Preliminary results were presented during the 2013 ESICM Congress [13].

Materials and methods

Study design

As a tertiary center, our multidisciplinary team is specialized in the management of post out-of-hospital cardiac arrest (OHCA) patients recruited in a large urban area (Paris, France). All data obtained during the post-resuscitation period were collected in an electronic prospective database. We thus performed a retrospective analysis of these prospectively acquired data.

Outcome assessment

The primary outcome was defined as the level reached on the cerebral performance categories scale (CPC) at hospital discharge [14, 15]. Favorable outcome included patients with a good cerebral performance (CPC 1) or a moderate cerebral disability (CPC 2). Unfavorable outcome was defined by a severe cerebral disability (CPC 3), a coma or a vegetative state (CPC 4), or death (CPC 5). The CPC level was prospectively assessed by a first physician at hospital discharge and was controlled by a second and independent physician blinded to post-resuscitation treatments. Each case of disagreement was resolved by consensus. When it was necessary, treatment withdrawal was done according to a specific procedure (see electronic supplementary material, ESM).

Setting and patients

All consecutive OHCA patients admitted consecutively from November 2006 to January 2010 after a successful resuscitation with ROSC were included in the analysis if they were still alive at the end of the first 48 h and if the cause of cardiac arrest was not a brain lesion (i.e., brain traumatic injury, stroke etc.). Patients' data were prospectively collected according to Utstein recommendations [16]. Our local ethics committee approved the data collection and study protocol.

Data collection

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/VT or PEA/asystole) were included in the database. Using data from the emergency medical service (EMS), the delays between the onset of OHCA and basic life support (BLS) and between BLS and ROSC were measured. Post-CA shock was defined as the need for continuous vasopressor infusion to maintain a mean arterial pressure above 60 mmHg for more than 6 h following restoration of spontaneous circulation (ROSC), despite adequate fluid loading.

Therapeutic hypothermia

When employed, hypothermia was started immediately at intensive care unit (ICU) admission using external cooling by forced cold air cooling during the first 24 h in order to obtain a target temperature between 32 and 34 °C [17]. In the absence of shock or complications, sedation was interrupted at the end of the hypothermia period.

Normothermia between 37 and 37.5 °C was then achieved using passive rewarming (0.3 °C/h) and maintained during the next 24 h. Patients were extubated as soon as their neurological and respiratory status allowed it.

Blood glucose parameters

Capillary blood glucose (BG) measurements were performed every 3 h after ICU admission. BG parameters that were analyzed were BG level at admission, median BG level over the first 48 h, and median variation of BG level over this period calculated as the largest difference between minimal and maximal values during the first 48 h after CA.

Glycemic control

All patients were treated according to the same protocol that was not modified during the study period. Most of it was inspired by AHA guidelines about cardiopulmonary resuscitation [12]. During the first 48 h, only isotonic saline solution was administered. Enteral nutrition was usually started during the first 48 h in the absence of contraindication. BG was measured every 3 h, mainly through blood capillary samples. A nurse-driven adjustment of insulin infusion rate was done depending on values of BG according to a written algorithm, aiming to maintain glycemia between 5.1 and 7.7 mmol/L (see ESM).

Parameters linked to BG level were evaluated such as previous diabetes, hypoglycemia episodes, amount of insulin given to the patient during the first 48 h, and caloric intake during the same period. Moderate and severe hypoglycemias were defined by BG values below 3.3 and 2.2 mmol/L, respectively.

Statistical analysis

Descriptive statistics are reported as medians (with interquartile range) and as counts and percentages for continuous and categorical variables, respectively. Characteristics between OHCA patients with and without favorable neurologic outcome were compared using Student or Mann–Whitney–Wilcoxon's rank sum test, and Pearson Chi-square test or the Fisher's exact test, as appropriate, for continuous and categorical variables, respectively.

Univariate logistic regression analysis was carried out to identify variables significantly associated with the outcome ($p < 0.20$). Secondarily we have included these factors, pre-existing diabetes, and median BG level during the first 48 h in a multivariate logistic regression, using a backward stepwise analysis, to determine significant predictors for good outcome ($p < 0.05$). Finally we also performed a sensitivity analysis in the group of patients who received therapeutic hypothermia (TH).

All statistical tests were two-sided using statistical significance defined as p value less than 0.05. Analyses were performed using Stata/SE 11.2 software (Stata, College Station, TX, USA).

Results

From November 2006 to January 2010, 498 patients were admitted to our ICU after OHCA. Among them, 117 patients were not included in the analysis (14 had a cardiac arrest due to an acute cerebral pathology and 103 patients died during the first 48 h following initial event). Finally, 381 patients were studied, of whom 36 % had a good outcome (CPC 1 or 2) at discharge (see ESM).

Baseline characteristics

The median age was 60 (51; 73) with a majority of men (71 %). Patients with a poor outcome were significantly older, but there was no other significant difference regarding baseline characteristics between the two groups (Table 1). By comparison with patients with a good outcome, OHCA occurred more frequently at home in patients with an unfavorable outcome (37 vs. 17 %, $p < 0.01$). Median "no-flow" and "low-flow" durations were also significantly longer in those patients ($p < 0.01$ for both). The median amount of epinephrine administered during resuscitation (>2 vs. <2 mg; $p < 0.01$) and admission blood lactate level (7 vs. 3.2 mmol/L; $p < 0.01$) were higher in patients with unfavorable compared to those with favorable outcome. An initial shockable rhythm was more frequently observed in patients with a favorable outcome (51 vs. 34 %, $p < 0.01$). TH was similarly performed in the two groups. The proportion of patients with a post-CA shock was similar between the two groups (Table 1).

Glycemic control during the first 48 h

At admission, the median BG level was 7.6 (6.3, 9.8) mmol/L in patients with a favorable outcome compared to 9.0 (7.1, 10.6) mmol/L for patients with an unfavorable outcome ($p < 0.01$) (Fig. 1a).

By examining outcome in each quartile of median BG over the first 48 h, we observed that the proportion of patients with a poor outcome increased across the four groups (Fig. 2). By comparison with patients in whom a favorable outcome was observed, the median BG level variation during the first 48 h was greater in patients with a poor outcome [9.6 (5.9; 13.6) vs. 7.1 (4.2; 11) mmol/L, $p < 0.01$] (Fig. 1b). When the median BG was below 8.4 mmol/L and BG variations below 8.5 mmol/L, the

Table 1 Baseline characteristics of the 381 out-of-hospital cardiac arrest patients according to the neurologic outcome evaluated with the CPC scale

	All patients ($n = 381$)	CPC 1–2 ($n = 136$)	CPC 3–5 ($n = 245$)	p value
Baseline features				
Median age (Q1; Q3) (years)	60 (51; 73)	57 (48; 71)	63 (52; 74)	**0.03**
Male gender, *n* (%)	271 (71)	92 (68)	179 (73)	0.26
Diabetes, *n* (%)	39 (14)	11 (11)	28 (17)	0.14
Dyslipidemia, *n* (%)	71 (27)	30 (29)	41 (25)	0.52
Hypertension, *n* (%)	109 (40)	38 (36)	71 (43)	0.23
Previous myocardial infarction, *n* (%)	54 (20)	21 (20)	33 (20)	0.93
Current smoking, *n* (%)	46 (13)	18 (14)	28 (13)	0.76
Congestive heart failure, *n* (%)	49 (18)	20 (19)	29 (18)	0.74
Chronic renal failure, *n* (%)	16	3 (3)	13 (8)	0.09
OHCA characteristics				
Location, *n* (%)				**<0.001**
Home	115 (37)	24 (21)	91 (48)	
Public area	102 (33)	46 (39)	56 (29)	
Other	90 (37)	47 (40)	43 (23)	
Initial shockable rhythm, *n* (%)	152 (40)	69 (51)	83 (34)	**<0.01**
No flow >4 min, *n* (%)[a]	155 (46)	39 (33)	116 (53)	**<0.01**
Low flow ≥15 min, *n* (%)[a]	126 (37)	32 (26)	94 (43)	**<0.01**
Epinephrine >2 mg, *n* (%)[a]	108 (42)	27 (30)	81 (49)	**<0.01**
Initial blood lactate >5.7 mmol/L, *n* (%)[a]	174 (50)	32 (26)	142 (63)	**<0.01**
Hypothermia, *n* (%)	308 (82)	105 (78)	205 (84)	**0.12**
Post-CA shock, *n* (%)	244 (66)	84 (63)	160 (67)	**0.40**

Bold values indicate statistical significance ($p < 0.15$)

CPC cerebral performance categories scale, *OHCA* out-of-hospital cardiac arrest, *CPR* cardiopulmonary resuscitation

[a] No flow, low flow, epinephrine dose, and blood lactate level classified according to their medians. Proportions take into account missing data

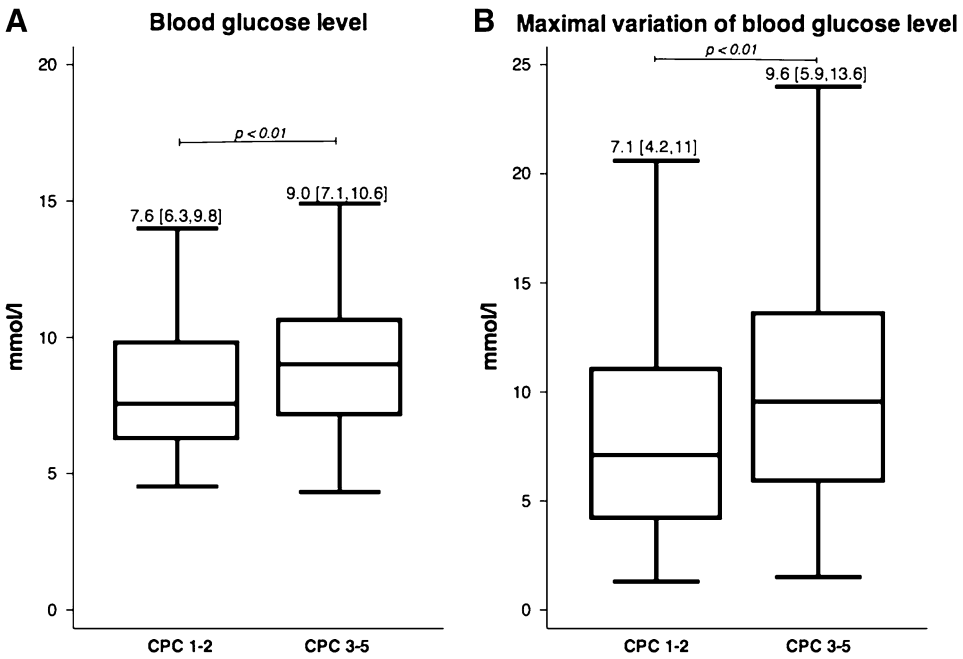

Fig. 1 Blood glucose level and variations of glycemia depending on outcome

proportion of patients with a good outcome was significatively increased (Fig. 3).

Severe hypoglycemia was observed in 22/381 (5.8 %) patients and moderate hypoglycemia in 54/381 (14.2 %) patients. Patients with moderate hypoglycemia had a favorable outcome compared to patients without any hypoglycemia [17/54 (31.5 %) vs. 115/305 (37.7 %), $p = 0.38$]. Patients with severe hypoglycemia had a favorable outcome in similar proportions to those without severe hypoglycemia [4/22 (18.2 %) vs. 132/359 (36.8 %), $p = 0.11$].

Amount of insulin

There was no significant difference in given amount of insulin in patients with favorable and unfavorable outcome (33.5 vs. 34.5 UI, $p = 0.57$).

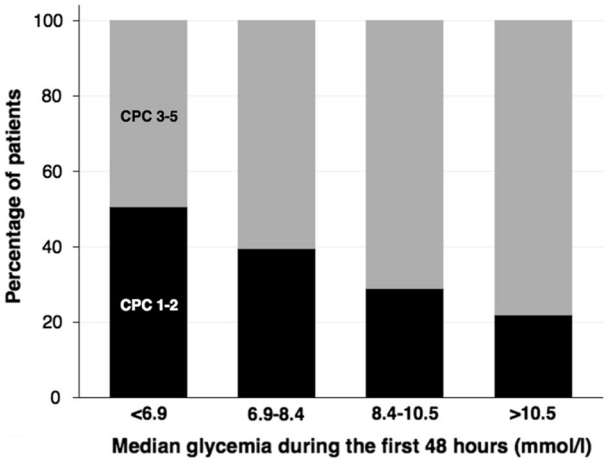

Fig. 2 Outcome according to median blood glucose level during the first 48 h

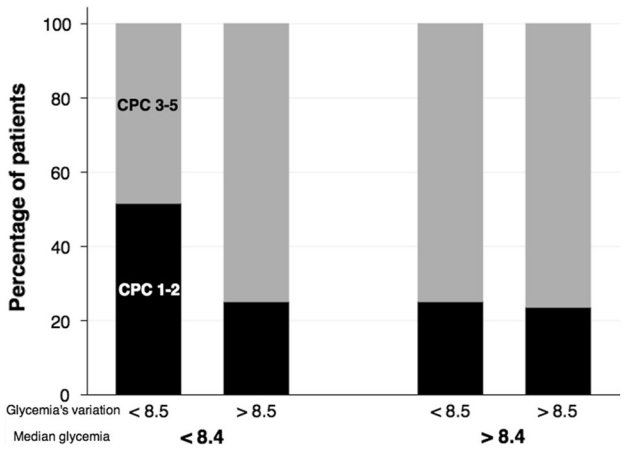

Fig. 3 Blood glucose levels and variations during the first 48 h depending on CPC

Caloric intake

The total caloric intake was not different between the two groups [0 kcal (0–12) range (0–4,716) vs. 0 kcal (0–55) (0–4,217), $p = 0.94$]. During the initial period, there was no relationship between median BG and caloric intake [odds ratio (OR) = 1, 95 % confidence interval (95 % CI) (0.99–1.00), $p = 0.41$]. We did not notice any relationship between the total caloric intake and the final CPC level (OR = 0.99, 95 % CI (0.99–1.00), $p = 0.54$).

Independent predictors of poor neurological outcome

In multivariate analysis, the median BG level over the first 48 h was an independent factor of poor hospital outcome (OR = 0.43; 95 % CI (0.24; 0.78), $p = 0.006$). Other factors associated with a worse outcome were cardiac arrest location and resuscitation intervals (Table 2). In the subset of patients treated by TH, hyperglycemia remained an independent factor of poor outcome (data not shown).

Discussion

The main result of our analysis is that a high glycemia occurring in the post-resuscitation period was associated with a higher risk of unfavorable outcome. We also observed a greater BG variability (as assessed by a higher amplitude of BG variations) in patients with unfavorable outcome, suggesting a possible detrimental influence of these variations on outcome.

Hyperglycemia and neurologic outcome

Our study shows that in patients treated with hypothermia and continuous insulin infusion, a high level of glycemia during the initial phase after cardiac arrest is probably an independent risk factor that could negatively influence outcome at ICU discharge. Beside glycemia disorders, numerous factors can influence the neurological outcome after cardiac arrest. Even if all covariates usually implicated in cardiac arrest prognosis are controlled for, the

Table 2 Multivariate analysis evaluating predictive factors of neurologic outcome after out-of hospital cardiac arrest

	Odds ratio	95 % confidence interval	*p* value
Diabetes mellitus	0.83	0.35; 1.98	0.68
Cardiac arrest location	0.58	0.40; 0.84	0.004
Shockable rhythm	2.40	1.33; 4.33	0.004
No flow <4 min	2.20	1.21; 4.02	0.01
Low flow ≤15 min	2.61	1.40; 4.89	0.003
Median blood glucose during first 48 h >8.4 mmol/L	0.43	0.24; 0.78	0.006

retrospective design of our study cannot firmly establish a direct influence of BG on the outcome. From a physiological point of view, the post-resuscitation period is associated with an intense physiological stress. Action of counter-regulation hormones and inflammatory mediators leads to the production of free oxygenated radicals and stimulation of neuronal apoptosis. Hyperglycemia that results from this stress can also exert systemic harmful effects such as perturbation of the immune system and increased inflammatory response. Experimental studies [18] showed that hyperglycemia decreased phagocytosis and increased blood levels of inflammatory biomarkers. Likewise, in diabetic patients, a chronic hyperglycemic state increases sensitivity to bacterial and fungal infections [5]. Hyperglycemia is already known as an independent risk factor for mortality in patients treated for acute myocardial infarction or stroke [19]. Mechanisms potentially involved in cerebral lesions take place during the ischemic and reperfusion phase [2]. Association between hyperglycemia and neurologic outcome has previously been studied in patients admitted to ICU after cardiac arrest [20, 21]. Even if they show a strong association between worse outcome and hyperglycemia, results from these studies mainly come from patients who were not treated with hypothermia. Finally, the influence of BG level was not controlled for all factors usually involved in the prognosis of the post-cardiac arrest disease. More recently, Cueni-Villoz et al. [11] assessed glucose variability during TH (stable maintenance phase) and normothermia (after rewarming). They showed that mild TH was associated with higher BG levels, increased BG variability, and greater insulin requirements compared to the post-rewarming normothermic phase. These authors found that mean BG level was higher during hypothermia but this was not associated with hospital mortality. These results are important but values of BG that were included in the multivariate analysis were restricted to the effective hypothermia period and were not extended to the whole post-resuscitation period. Finally our analysis was performed in a population who was treated with TH in a large majority of patients. According to current guidelines, the targeted temperature was 33 °C but recent findings suggest that a 36 °C target could also be valuable, leading to similar outcome [22]. It can be hypothesized that such a higher level of temperature targeted can provoke less metabolic disturbances, thus improving the risk–benefit ratio of this treatment. To date, detailed data about hyperglycemia in each group of the TTM Trial are not available, thus it is not possible to assess the role of glycemia in the analysis [22]. Our study highlights that at the 33 °C target that is actually employed in a majority of patients, there is a high incidence of hyperglycemia that is associated with a worse outcome. All together, it suggests that glycemic disorders should be included in the risk–benefit ratio of TH.

Influence of glycemic variations

Our findings concerning glycemic variations suggest that these changes play an important role during the post-resuscitation period even if they do not appear as an independent risk factor of worse outcome when included in multivariate analysis. Our analysis also shows that a low BG level does not protect patients against effects of glycemic changes. We observed that for low level of BG, high variations were more frequently observed in patients with a poor outcome. These results are in accordance with recent findings coming from Cueni-Villoz's study [11] but the mechanisms are not clear. In diabetic patients, dynamic fluctuations between hyperglycemia and normoglycemia are known to induce higher oxidative stress, higher activation of protein kinase C and nuclear factor kappa B, to enhance monocytes adhesion, and to increase apoptosis when compared with sustained hyperglycemia alone [23–26]. Although the exact mechanisms have not been fully elucidated, these findings suggest that increased BG variability may also be potentially deleterious in our critically ill patients. Several metabolic disturbances that occur during inflammatory processes and septic shock may lead to glycemic disorders. Ali et al. [27] retrospectively studied BG variations in patients admitted for septic shock. A strong association between mortality and variations of this parameter was found in multivariate analysis, but regrettably not all the patients were treated with insulin. Different clinical investigations [28, 29] in ICU patients confirmed this relationship, regardless of the reason for admission. In our own study, BG variations were estimated using the difference between maximum and minimum value of BG during the post-resuscitation period. Other methods can be used to assess the behavior of BG changes during the post-resuscitation period that could be more accurate with other statistical tools. We used this method because it is a simple and easy-to-use way to evaluate BG variations at the bedside. Regarding these results, it can be suggested that a BG control based not only on absolute values but also on variation of this parameter could maybe have beneficial effects on the outcome.

Glycemia management

The way BG was controlled during the present study could be challenged, but this management did not change throughout the study period, aiming to maintain BG level between 5.1 and 7.7 mmol/L. Despite this local protocol, reported values of BG were relatively high and this protocol also led to severe hypoglycemia episodes in nearly 20 % of our patients. This could be explained by the lack of enteral or parenteral feeding during the first 48 h following ICU admission in this population. At that time, this was a common practice, driven by the risk of digestive ischemia and feeding intolerance in this population. This

may reflect that control of BG is particularly difficult and that even a trained team could encounter difficulties reaching their goals. Current guidelines from the ILCOR recommend to maintain a BG level around 8 mmol/L in patients admitted after CA, but the level of evidence associated with these guidelines is low. In 2007, Oksanen et al. [30] randomized patients in two groups after resuscitation. One group was submitted to a strict glycemic control (BG between 4 and 6 mmol/L); the other one was treated to achieve a BG level between 6 and 8 mmol/L. Mortality was not different between the two groups and neuron specific enolase (NSE) blood levels were similar in the two groups. These results may be explained by narrow goals that are difficult to obtain in clinical situations. Our results suggest that a BG control aiming to obtain not only a normal BG but also a low variation of this parameter should be tested in this population. Refining algorithms by including dynamic indicators (instead of static measurement) and by increasing the frequency of BG level measurement are two ways that could permit evaluation of decreased BG variability in these patients.

Limitations

Our results come from an observational study, precluding any firm conclusion regarding the best way to manage BG level in post-CA patients. However, patients were treated in the same ward with the same standard of care so our findings could not be reproducible in another ICU. A second limitation is related to the time window used to assess BG influence (during the first 48 h). Influence of subsequent BG level disturbances may also influence the prognostic but this is not firmly confirmed by our results. In patients with a history of diabetes, levels of HbA1C were not assessed in our analysis; therefore we could not determine the possible role of BG disturbances before admission to ICU. Another limitation is that we could not provide data about prehospital BG management. A previous study by Nurmi et al. [10] showed that an increase of BG between CA and ICU admission was associated with a poor prognosis. Finally complications were not extensively assessed in our study. Prevalence of shock, acquired infections, and mode of death were not incorporated in the analysis. It is also known that infections are frequent in this population and probably a consequence of TH [31] that was used for most patients. We did not include patients who died during the first 48 h after cardiac arrest and we did not record the data about their BG level. This could be considered a limitation even if a recent study showed that most of these early deaths were due to a multiorgan failure and post-resuscitation shock, therefore with a probable absence of influence of BG [32]. Finally the way to explore BG control in our study was mainly based on median BG during a selected period. More complex tools could have been used, which were previously described in ICU, but we chose this parameter for its simplicity and because it is a common and easy-to-assess parameter in routine practice [33]. The technique that we used to measure BG has also some limitations because capillary BG measurement in patients with shock could underestimate values of glycemia [34]. A last limitation comes from the main outcome that we employed (CPC level at hospital discharge). Maybe our results would have been more accurate with a neurologic evaluation performed later after the initial event. However, a recent study [15] showed a strong correlation between CPC assessed at hospital discharge and survival at 1 and 5 years. These considerations should be kept in mind when interpreting our findings.

Conclusion

In our population, high BG levels were associated with a poor neurological outcome in post-CA patients treated by therapeutic hypothermia. We also observed higher amplitude of BG variations in patients with poor outcome. As a result of the design of our study, these results do not prove that lowering glycemia will improve outcome, but they strongly suggest the need to test a strategy combining both control of BG and minimization of BG variations for its ability to improve post-resuscitation care.

Conflicts of interest The authors declare no conflict of interest.

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