Increased blood glucose variability during therapeutic hypothermia and outcome after cardiac arrest

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Introduction

- Therapeutic hypothermia (TH) improves the outcome of comatose patients after cardiac arrest (CA)
- Hypothermia alters blood glucose (BG) homeostasis
  - reduced glucose utilization
  - decreased endogenous insulin secretion
  - increased resistance to exogenous insulin

Hypothermia→BG ↑

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Introduction

- Increased BG variability is an independent risk factor of inhospital mortality in various subgroups of critically ill patients
  - exacerbation of oxidative stress
  - enhanced monocyte adhesion
  - increased apoptotic cell death

↑ BG variability → mortality inhospital ↑

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- Analyzed blood glucose variability during therapeutic hypothermia in patients with coma after cardiac arrest and examined its impact on outcome

Hypothermia→BG ↑

↑ BG variability → mortality inhospital ↑

Hypothermia → BG variability ?? →outcome ??

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Methods

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Patients

- Design: Prospective observational databases
- Setting: Two university hospital medical/surgical ICU
  - Lausanne University Hospital, Lausanne, Switzerland
  - Erasme University Hospital, Brussels, Belgium
- Patients: comatose patients successfully resuscitated from CA treated with TH

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TH

- TH was applied following a standardized written algorithm.
- TH to (33 +/- 1)°C for 24hrs
  - irrespective of age
  - initial arrest rhythm
  - postresuscitation hemodynamic status.
- TH was started immediately after admission to the hospital.

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BG Management

- Arterial catheter.
- Taken every 4 hrs,
  - hypoglycemia (BG < 4 mmol/L [72 mg/dL]) was observed earlier
- Target was set to 6–8 mmol/L [110–150 mg/dL]
  - nurse-driven adjustment of insulin infusion rate.
- Glucose-containing solutions were avoided
- Enteral nutrition was generally started only at the end of TH, once core temperature was 35°C (25Kcal/kg/day)

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Data Collection

- Baseline demographics
  - Age
  - Gender
  - initial arrest rhythm
  - etiology of CA
  - time to return of spontaneous circulation (ROSC)
  - presence or absence of diabetes.
- BG variability was defined as the difference between the maximum and the minimum BG during each time period analyzed.

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- Period 1 – induction phase
  - from ICU admission to target core temperature of 33°C
- Period 2 – TH
  - total time ~24 hrs
- Period 3 – rewarming
  - end of TH until core temperature reached 36°C
- Period 4 – postrewarming normothermic (NT) phase
  - total time~24 hrs

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Outcome

- Primary outcome end point
  - survival to hospital discharge
- Secondary outcome end point
  - neurologic recovery
  - assessed using the Glasgow-Pittsburgh Cerebral Performance Categories (CPCs)
- CPC at 3 months

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Results

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Table 1. Patient characteristics (n = 220)

Variable	Value
Median age, yrs (range)	61 (18–88)
Female gender, number (%)	45 (20%)
Initial arrest rhythm, number (%)	
Ventricular fibrillation	127 (57%)
Nonventricular fibrillation	93 (43%)
Asystole	80
Pulseless electrical activity	13
Etiology of cardiac arrest, number (%)	
Cardiac	170 (77%)
Noncardiac	50 (23%)
Median time to return of spontaneous circulation, min (range)	20 (5–75)
Diabetes, number (%)	28 (13%)
Median admission blood glucose, mmol/L (range)	11 (5–40)

- January 2004 – June 2009
- 204 OHCA, 14 IHCA
- 20(early death <48hrs), 44(incomplete BG data or did not receive insulin therapy)

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Median number of BG sample
TH = 9 (range 4-30)
NT = 8 (range 4-22)

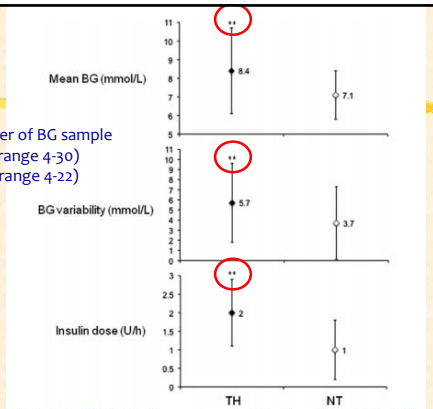

Figure 1. Graphs illustrating the differences of mean (±SD) blood glucose (*BG*) level, BG variability (defined as the difference between the maximum and the minimum BG during each time period), and insulin dose during the maintenance phase of therapeutic hypothermia (*TH*) vs. the postrewarming .4 normothermic phase (*NT*). **$p < .001$ vs. NT.

Table 2. Relationship between blood glucose values during therapeutic hypothermia and survival

Variable	Survival at Hospital Discharge: Survivors (n = 111)	Survival at Hospital Discharge: Nonsurvivors (n = 109)	p
Time to return of spontaneous circulation, min	18 ± 10	25 ± 12	<.001
Etiology of cardiac arrest, cardiac, number (%)	100 (89%)	70 (64%)	<.001
Initial arrest rhythm, ventricular fibrillation, number (%)	85 (76%)	42 (39%)	<.001
Age (yrs)	59 ± 15	60 ± 15	.75
Mean blood glucose (mmol/L)	7.9 ± 1.8	8.7 ± 2.6	.02
Blood glucose variability (mmol/L)	4.9 ± 3.5	6.5 ± 4.1	.003

Data are expressed as mean ± SD.

- No association between survival and increased body temperature variability during TH
- No association between inhospital mortality and dose of norepinephrine received during TH

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Table 3. Relationship between blood glucose values during therapeutic hypothermia and neurologic recovery at hospital discharge and at 3 months

Variable	Neurologic Recovery: At Hospital Discharge: CPC 1–2 (n = 86, 39%)	At Hospital Discharge: CPC 3–5 (n = 134, 61%)	p	At 3 Months[a]: CPC 1–2 (n = 52, 34%)	At 3 Months[a]: CPC 3–5 (n = 103, 66%)	p
Time to return of spontaneous circulation (min)	17 ± 10	24 ± 11	<.001	17 ± 10	23 ± 11	<.001
Etiology of cardiac arrest, cardiac	89%	70%	<.001	85%	66%	.02
Initial rhythm, ventricular fibrillation	79%	45%	<.001	71%	38%	<.001
Age (yrs)	58 ± 16	60 ± 15	.31	56 ± 16	62 ± 14	.07
Mean blood glucose (mmol/L)	7.9 ± 1.8	8.6 ± 2.5	.02	8.3 ± 2.0	8.9 ± 2.6	.13
Blood glucose variability (mmol/L)	4.8 ± 3.6	6.2 ± 4.0	.009	5.4 ± 4.0	6.5 ± 4.2	.03

CPC, Glasgow-Pittsburgh Cerebral Performance Category.
[a]Data were available for 155 patients. Favorable outcome: CPC 1 (good recovery) and 2 (moderate disability). Unfavorable outcome: CPC 3 (severe disability), 4 (vegetative state), and 5 (death). Data are expressed as mean ± SD.

Increased BG variability, but not mean BG levels, was associated with worse long-term neurologic recovery

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Table 4. Blood glucose variability during therapeutic hypothermia, but not mean blood glucose level, is an independent predictor of inhospital mortality

Variable	Odds Ratio for Inhospital Mortality	Confidence Interval	p
Time to return of spontaneous circulation	1.07	1.04–1.10	<.001
Initial rhythm, nonventricular fibrillation	2.52	1.23–5.19	.01
Etiology of cardiac arrest, noncardiac	3.99	1.61–9.89	.003
Blood glucose variability	1.10	1.02–1.19	.016

Nonventricular fibrillation includes asystole and pulseless electrical activity.
All variables with a significance level <0.2 on univariate analysis were included into a logistic regression model, where the dependent variable was mortality at hospital discharge. Backward elimination was used to reach the final model and the joint lack of significance of the removed variables was checked with a likelihood ratio test. Goodness of fit of the final model was evaluated with the Hosmer-Lemeshow test. Mean blood glucose level was not retained as a significant variable by the final multivariable model ($p > .2$).

Increased BG variability during TH was an independent risk factor of inhospital mortality.

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Table 5. The relationship between blood glucose variability and hypoglycemia (defined by arterial blood glucose <4 mmol/L [72 mg/dL])

Variable	Hypoglycemia (% Blood Glucose Samples <4 mmol/L)
Time point	
Stable hypothermic phase	8%
Postrewarming normothermic phase	7.5%
p	.78
Blood glucose variability	
<5 mmol/L (n = 111 patients)	2%
≥5 mmol/L (n = 109 patients)	15%
p	<.001
Neurologic recovery at 3 mos	
Good (Glasgow-Pittsburgh Cerebral Performance Categories 1–2; n = 52 patients)	2%
Poor (Glasgow-Pittsburgh Cerebral Performance Categories 3–5; n = 103 patients)	11%
p	.06

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Discussion

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Main findings

- 1) Mean BG levels, BG variability, and insulin dose are all significantly higher during the maintenance phase of TH;
- 2) higher mean BG levels and increased BG variability are associated with increased mortality and worse neurologic recovery to hospital discharge;

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- 3) only increased BG variability associated with worse 3-month neurologic recovery;
- 4) increased BG variability during TH is an independent risk factor of inhospital mortality,

Increased BG variability is more important than BG levels in predicting prognosis of coma after CA.

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Glucose management during TH

- First time found that:
  - mean BG levels, BG variability, and insulin requirements are significantly increased during TH.
- Reducing core temperature may reduce plasma insulin, induce insulin resistance, and alter BG homeostasis.
  - Difficult to prove

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- Higher BG levels may be due to the use of adrenergic agents
  - norepinephrine and dobutamine
  - no association between BG variability and both adrenergic agents.
- No correlation between increased patient temperature variability and BG variability.

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- Higher BG variability and mean BG may be due to greater injury severity;
  - time to ROSC
- Glucose-containing solutions and nutrition may affect BG variability.
  - caloric intake was less during TH
- Time from initial injury is a confounding factor

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Increased BG variability as an Independent risk factor of worse outcome

- Further studies to confirm and expand our findings in other subgroups of critically ill neurologic patients.
- Increased BG variability was a strong predictor of inhospital mortality
  - use of new systems for continuous closed-loop BG monitorning

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Study Limitations

- Biased by physician's decision of withdrawal of care?
  - Prognostication assessment and decision were based on a standardized algorithm
- Lack of exploration on the exact underlying mechanisms of increased BG variability during TH.

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Conclusions

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Thank you!

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