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Glycemic Management After Resuscitation: Is Glucose The Best Alternative?

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Abstract

Context: Hyperglycemia after resuscitation in both critically-ill adults and preterm newborns is associated with increased mortality and poor brain outcome. Lactose, composed of 50% glucose and 50% galactose is the unique means Nature offers to the newborn, who in absence of modern care suffers from severe bioenergetic impairment, similarly to adults resuscitated after cardiac arrest. Aim of this study is to review these issues, to understand how we may improve outcomes in intensive care units.

Evidence Acquisition: A review study was conducted in 2017 through searching on Science Direct, PubMed, Wiley, and Blackwell databases. The search was performed using bioenergetics, cardiac arrest, critical illness, hyperglycemia, glucose, galactose, newborn and resuscitation, as key words. Finally, 24 articles in English were assessed in this study, thereby comprised 2 guidelines (2015 American heart association and guidelines for both Adult and Neonatal Resuscitation.

Results: Correct glycemic control strategy in extreme ATP deficit conditions, such as after resuscitation from a cardiac arrest or a complicated or preterm birth can improve outcome. 2015 American heart association (AHA) guidelines do not recommend glucose infusion after cardiac arrest. Data on glucose administration following brain insult in newborn are limited. Outcomes of applying the hypothesis allowed to assess that glucose, an excellent substrate, turns to a harmful one, able to worsen brain outcome, likely due to its needing phosphorylation prior to be utilized. Un-phosphorylated galactose can be utilized by Hexose phosphate dehydrogenase.

Conclusions: Awareness that conditions of extreme cellular ATP deficit may lead to a vicious cycle in which glucose would not be freely available as a substrate may rise studies for applying new strategies in clinical practice in the future. The need to balance among the opportunity to avoid both hypo- and hyper-glycaemia tells us that we may have missed the opportunity to learn from Nature how to care for both resuscitated newborns and critically-ill adults. A far-fetched hypothesis arises that to ameliorate long-term brain outcomes, we may imitate Nature which, to start up glucose catabolism, offers a solution composed of 50% glucose and 50% galactose.

Keywords: Resuscitation, Newborn, Cardiac Failure, Glucose, Galactose, Hyperglycaemia

1. Context

Critical illness is common worldwide and is associated with high risk of mortality, and adverse brain outcome. In recent years glycemic management among critically-ill patients, has been a topic of extensive study. Hyperglycaemia after resuscitation in both critically-ill adults and preterm newborns (1) was found to be predictive of poor outcome after brain injury (2) and was identified as a risk predictor for in-hospital mortality (3). What do adults resuscitated after a severe stroke or a cardiac arrest have in common with a newborn requiring resuscitation? Strikingly similar bioenergetic impairment. These conditions are conceivably characterized by a progressively worsening lack of cellular chemical energy (ATP). Lactose, composed of 50% glucose and 50% galactose is the unique means Nature offers to the newborn, who in absence of modern care suffers from severe bioenergetic impairment, similarly to adults resuscitated after cardiac arrest. Aim of this study is to review these issues, to understand how we may improve outcomes in ICU.

2. Evidence Acquisition

A review study was conducted in 2017 through searching on Science Direct, PubMed, Wiley, and Blackwell databases. The search was performed using bioenergetics, cardiac arrest, critical illness, hyperglycemia, glucose, galactose, newborn and resuscitation, as key words. The objective of the review was to evidence a paradox regarding glucose, the best metabolic energy substrate, which apparently becomes harmful in conditions of extreme bioenergetic impairment, such as those regarding adults and newborns after resuscitation. A recent hypothesis on the role of Hexose phosphate dehydrogenase, an enzyme able to utilize also unphosphorylated hexoses, among which especially galactose was also taken into consideration, to

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evaluate whether Nature offers a solution to overcome a bioenergetic impairment such as that consequent to birth.

3. Results

Moderate to severe hyperglycemia is spontaneous in critical ill-patients, due to stress hormone and inflammatory cytokine incretion promoting insulin resistance. Critical illness is also associated with elevated risk of developing type 2 diabetes mellitus (4). In past years, hyperglycemia has been viewed like an epi-phenomenon, until it was found that it associates with increased mortality and worse clinical outcome in both diabetic and non-diabetic patients (5). Concern for the glycemic management in intensive care units (ICU) raised, with a focus on hyperglycemia (6), identified as a risk predictor for in-hospital mortality in nondiabetic patients and poor functional recovery in nondiabetic stroke survivors (3), especially when treated with early reperfusion therapy (7). Hyperglycemia is a primary risk factor of poor outcome after brain injury (2). Results from two single-center studies (8, 9) were in contrast about tight versus moderate glycemic management in critically-ill patients. Intensive insulin treatment seemed to provide no benefit, but there is agreement as to limit the rise in blood glucose after a stroke or cardiac arrest. To date serum glucose tight control is recommended to avoid both hypo- and hyper-glycaemia, according to the NICE-SUGAR trial, the best study on glycemic control strategies among ICU patients (10). There is now general consensus about glycemic management of critically-ill patients; guidelines recommend to maintaining blood glucose lower than 180 mg/dL (11).

Besides adults, also in preterm newborns, hyperglycemia duration and grade is associated with increased mortality and poor outcome (1). Clinical data addressing the optimal glucose concentration following brain insult in newborn are limited. Obviously, hypoglycemia was also associated with adverse neurological outcome (12). Infants at risk for poor glycemic control are preterm, intrauterine growth restriction and small for gestational age ones, as well as term neonates from a diabetic mother. Disturbances of glucose homeostasis, rather than that hypoglycemia per se are more bound to lead to worse outcomes. In neonates requiring resuscitation, Guidelines recommend to treat with 10% glucose solution (D10W) in order to maintain blood glucose in the normal range (13). No specific target glucose concentration can be recommended for newborns (13). In more severely affected infants in ICU, increased mortality was associated to variability of glucose concentration (14). In this regard, hyperglycemia, common among critically ill patients, besides being consequent to therapies, is essentially a salvage means for the body sensing a decline in overall ATP content: an extreme attempt of the body to survive relying on the only carbohydrate it is able to synthesize, Glucose (Glu). However, liver gluconeogenesis has a high metabolic cost (4 moles of ATP each neosynthesized mole of Glu). As is the case for inflammation, beneficial but cause of tissue damage, seemingly Glu can become harmful, paradoxically especially for the brain, the organ that most needs it. Glu is an "expensive" nutrient, in that it requires the use of 2 equivalents of ATP to enter glycolysis, therefore, serious deficit in cellular energy charge renders it difficult to be utilized. This may explain why many clinical studies found that hyperglycemia increases the risk or cerebral injury in adults after stroke (3, 5) and 2015 American Heart Association (AHA) guidelines recommend to avoid glucose infusion in the resuscitation after a cardiac arrest (15, 16), as it causes hyperglycemia due to Glu redistribution, with worse neurological outcomes. Clinical studies ICU patients appeared to support tight Glu concentration control by insulin administration; but subsequent trials showed some potential harm: the goal may not be the mere Glu lowering, as it can cause hypoglycemia. Consistently, the use of the incretin hormone, glucagon-like peptide (GLP) 1 is associated with a lower risk of hypoglycemia (17, 18).

How should we deal with extreme, next-to-death, conditions? Firstly, we should distinguish among normal body conditions and extreme ones like after resuscitation, where the cellular ATP content is severely deficient. In normal conditions, when the cell energy charge is fine, Glu is the body principal carbohydrate, but it can lay beyond reach in conditions of impaired cellular energy charge. Secondly, we may compare, the conditions of resuscitation after a cardiac arrest with those of a birth, which even when uncomplicated encompasses a period of asphyxia. Wat does Nature suggest us? In the scenario of a birth in the absence of care, if the baby survives, he would receive breast milk. In fact, in case of uncomplicated birth, guidelines recommend the baby should be put to the breast within one hour of birth. Mature human milk contains about 5% fat, 0.9% protein, 0.2% minerals and 7.0% lactose. Lactose, the principal macronutrient in human milk, positively correlating with its yield, is composed of 50% Glu and 50% galactose (Gal) (19). There seems to be a bias among those-lucky-babies who did not require resuscitation and those who did, in that the former deserve immediate breast feeding, i.e. administration of a mixture of Glu/Gal, while the latter do not. At best severely ill newborns will receive 10% Glu solution intravenously. While avoidance of hypoglycemia is obviously desirable, how can we be sure that the mere use of glucose instead of a solution of 50% Glu and 50% Gal (like in milk) is better to reduce long-term neurologic morbidity?

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4. Conclusions

A comprehensive glycemic control strategy in extreme ATP deficit conditions, such as after resuscitation from a cardiac arrest or a complicated birth, is lacking, and the range of blood glucose concentration that is associated with the least brain injury following asphyxia cannot be defined based on definite evidence. Current guidelines focus on the need to avoid supplemental glucose during and/or following resuscitation, in both these conditions. In this respect, Gal may be regarded as a rescue substrate the body cannot synthesize on its own, with the exception of the mammary gland, but must assume it from the outside, as in breastfeeding. It is delivered from a mother to the newborn for a limited period: to what end? It is herein proposed that Gal is a rescue nutrient predisposed by Nature after a period of asphyxia, when the cellular ATP content is impaired. Such assumption, needs to consider our previous research that pioneered the hypothesis of myelin aerobically producing ATP, to support axoplasm through the functioning of the ectopic five respiratory complexes, fed by tricarboxylic acid cycle (20). Gal is a better substrate than Glu for aerobic metabolism in myelin *in vitro* (21), consistently with its being a booster of aerobic metabolism. Gal would become the substrate of hexose-6-phosphate dehydrogenase (H6PD, E.C. 1.1.1.47), a membrane-bound enzyme active on many phosphorylated and non-phosphorylated hexoses among whch deoxyglucose catalyzing a pentose phosphate pathway (22). Unphosphorylated Gal is a preferential substrate of H6PD (23). It was shown that Gal can sustain ATP production in myelin where H6PD is expressed and functionally associated to complex I of respiratory chain. Gal was reported to ameliorate glucose oxidative energy metabolism in myotubes (24). This would be especially useful for neurons, that generate ATP by oxidative phosphorylation (OXPHOS), which renders them vulnerable to asphyxia or stroke. A neuroprotective action of Gal on brain oxidative metabolism was postulated. We have hypothesized that the Leloir pathway is essentially devoted to the anabolic D-gal metabolism, considering that in the first days after birth the UDP glucose pathway is quite defective in liver, while H6PD would account for the catabolic one. May it be that we should listen to the cry for help of the body after resuscitating? What if we imitated nature and administer a solution composed of 50% Glu and 50% gal, not only to the infant but even to the adult after cardiac arrest? Wouldn't it be better than administering crystalloids alone? The awareness of the conditions of extreme cellular ATP deficit transforming Glu from an excellent substrate to a dangerous one, too costly to start catabolism with, should let us explore new strategies. In fact, long-term cognitive impairment after critical illness or complicated or preterm birth can become a public health problem, given the growing number of preterm resuscitated newborns and of acutely ill patients treated in ICU, globally.

Footnotes

Authors' Contribution: Isabella Panfoli developed the original idea, provided critical revision, wrote the manuscript, and is guarantor.

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References

1. Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V. Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. *Pediatr Crit Care Med.* 2004;**5**(4):329–36. doi: 10.1097/01.PCC.0000128607.68261.7C. [PubMed: 15215001].
2. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A. The impact of hyperglycemia on patients with severe brain injury. *J Trauma.* 2005;**58**(1):47–50. doi: 10.1097/01.TA.0000135158.42242.B1. [PubMed: 15674149].
3. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke.* 2001;**32**(10):2426–32. doi: 10.1161/hs1001.096194. [PubMed: 11588337].
4. Hsu CW, Lin CS, Chen SJ, Lin SH, Lin CL, Kao CH. Risk of type 2 diabetes mellitus in patients with acute critical illness: a population-based cohort study. *Intensive Care Med.* 2016;**42**(1):38–45. doi: 10.1007/s00134-015-4044-2. [PubMed: 26370689].
5. Baird TA, Parsons MW, Phan T, Butcher KS, Desmond PM, Tress BM, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke.* 2003;**34**(9):2208–14. doi: 10.1161/01.STR.0000085087.41330.FF. [PubMed: 12893952].
6. Nice-Sugar Study Investigators , Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;**360**(13):1283–97. doi: 10.1056/NEJMoa0810625. [PubMed: 19318384].
7. Paolino AS, Garner KM. Effects of hyperglycemia on neurologic outcome in stroke patients. *J Neurosci Nurs.* 2005;**37**(3):130–5. doi: 10.1097/01376517-200506000-00002. [PubMed: 16001816].
8. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;**345**(19):1359–67. doi: 10.1056/NEJMoa011300. [PubMed: 11794168].
9. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006;**354**(5):449–61. doi: 10.1056/NEJMoa052521. [PubMed: 16452557].
10. Nice-Sugar Study Investigators , Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med.* 2012;**367**(12):1108–18. doi: 10.1056/NEJMoa1204942. [PubMed: 22992074].
11. Mitsios JV, Ashby LA, Haverstick DM, Bruns DE, Scott MG. Analytic evaluation of a new glucose meter system in 15 different critical care settings. *J Diabetes Sci Technol.* 2013;**7**(5):1282–7. doi: 10.1177/193229681300700518. [PubMed: 24124955].

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12. Salhab WA, Wyckoff MH, Laptook AR, Perlman JM. Initial hypoglycemia and neonatal brain injury in term infants with severe fetal acidemia. *Pediatrics.* 2004;**114**(2):361–6. doi: 10.1542/peds.114.2.361. [PubMed: 15286217].
13. Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, et al. Part 13: Neonatal Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2015;**132**(18 Suppl 2):S543–60. doi: 10.1161/CIR.0000000000000267. [PubMed: 26473001].
14. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, Wilson DM. Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. *Pediatrics.* 2006;**118**(1):173–9. doi: 10.1542/peds.2005-1819. [PubMed: 16818563].
15. Langhelle A, Tyvold SS, Lexow K, Hapnes SA, Sunde K, Steen PA. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. *Resuscitation.* 2003;**56**(3):247–63. doi: 10.1016/S0300-9572(02)00409-4. [PubMed: 12628556].
16. Peng TJ, Andersen LW, Saindon BZ, Giberson TA, Kim WY, Berg K, et al. The administration of dextrose during in-hospital cardiac arrest is associated with increased mortality and neurologic morbidity. *Crit Care.* 2015;**19**:160. doi: 10.1186/s13054-015-0867-z. [PubMed: 25887120].
17. Nielsen ST, Krogh-Madsen R, Moller K. Glucose metabolism in critically ill patients: are incretins an important player?. *J Intensive Care Med.* 2015;**30**(4):201–8. doi: 10.1177/0885066613503291. [PubMed: 24065782].
18. Clain J, Ramar K, Surani SR. Glucose control in critical care. *World J Diabetes.* 2015;**6**(9):1082–91. doi: 10.4239/wjd.v6.i9.1082. [PubMed: 26265994].
19. Jenness R. The composition of human milk. *Semin Perinatol.* 1979;**3**(3):225–39. [PubMed: 392766].
20. Ravera S, Panfoli I. Role of myelin sheath energy metabolism in neurodegenerative diseases. *Neural Regen Res.* 2015;**10**(10):1570–1. doi: 10.4103/1673-5374.167749. [PubMed: 26692843].
21. Ravera S, Bartolucci M, Calzia D, Morelli A, Panfoli I. Galactose and hexose 6-phosphate dehydrogenase support the myelin metabolic role. *PARIPEX-India J Res.* 2016;**4**(9).
22. Mason PJ, Stevens D, Diez A, Knight SW, Scopes DA, Vulliamy TJ. Human hexose-6-phosphate dehydrogenase (glucose 1-dehydrogenase) encoded at 1p36: coding sequence and expression. *Blood Cells Mol Dis.* 1999;**25**(1):30–7. doi: 10.1006/bcmd.1999.0224. [PubMed: 10349511].
23. Ozols J. Isolation and the complete amino acid sequence of lumenal endoplasmic reticulum glucose-6-phosphate dehydrogenase. *Proc Natl Acad Sci U S A.* 1993;**90**(11):5302–6. doi: 10.1073/pnas.90.11.5302. [PubMed: 8506377].
24. Kase ET, Nikolic N, Bakke SS, Bogen KK, Aas V, Thoresen GH, et al. Remodeling of oxidative energy metabolism by galactose improves glucose handling and metabolic switching in human skeletal muscle cells. *PLoS One.* 2013;**8**(4):e59972. doi: 10.1371/journal.pone.0059972. [PubMed: 23560061].

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