Experience using high-dose Glucose-Insulin-Potassium (GIK) in critically ill patients

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Abstract

Purpose To audit the use of GIK in terms of safety, haemodynamic effects, and impact on catecholamine dosage.

Materials and methods A retrospective, descriptive, evaluative audit of GIK use within the adult ICU of a London teaching hospital was conducted. Rescue therapy of GIK (up to 1.0 Units insulin/kg/hour) was administered to improve cardiac function. Outcomes were ICU survival, change in cardiac index (CI) and blood lactate levels, events of hypoglycaemia, hyperglycaemia, hypokalaemia and hyperkalaemia, and discontinuation time of catecholamine inotropes.

Results Of 85 patients treated with GIK, 13 (15.3%) survived their ICU stay and 9 (10.5%) were discharged home. In patients surviving until 72 hours, a trend of improved CI and lactate levels was seen, often with reductions in catecholamine dosing. Inotropes were discontinued in 35 (54%) patients. Severe hypoglycaemia (<2 mmol/l), hyperglycaemia (>20 mmol/l), hypokalaemia (<2.5 mmol/l) and hyperkalaemia (>7 mmol/l) during GIK affected 1, 6, 8 and 1 patients, respectively. These abnormalities were quickly identified. No measurable harm was noted.

Conclusions High-dose GIK can be safely used in critically ill patients, though blood glucose and potassium levels must be monitored frequently. GIK was associated with improved CI and blood lactate levels. Impact on survival requires prospective evaluation.

Keywords: GIK, critically ill, insulin, glucose, potassium, intensive care

Introduction

Heart failure is a severe disease with a high morbidity and mortality. In 2012/2013, 0.74% of all inpatient episodes in National Health Service hospitals in the United Kingdom were caused by heart failure [1]. In that year, 9.4% of the heart failure patients in England died in-hospital, and 24.6% died within a 1 year follow-up period [2]. Critically ill patients with heart failure and cardiogenic shock are typically treated with catecholamine inotropes as these increase myocardial contractility and myocardial perfusion, and improve cardiac output. If vascular tone is low, drugs with a predominant vasoconstrictor action (norepinephrine, vasopressin, terlipressin) are generally given, whereas inotropes such as epinephrine and dobutamine are commonly used to enhance cardiac output [3].

Use of catecholamines can however be harmful in multiple ways including immunomodulation, increased bacterial growth and virulence, decreased metabolic efficiency, myocardial damage, increased cardiac work, and pro-thrombotic and pro-arrhythmogenic tendencies [4]. Indeed, even adjusting for severity and other factors, these agents are associated with a significantly increased risk of greater morbidity, mortality and rehospitalisation [5-7]. Other options for treating low cardiac output states include phosphodiesterase inhibitors such as enoximone or calcium sensitizers such as levosimendan. Both agents can sometimes cause excessive vasodilation [8], while phosphodiesterase inhibitors have been associated with worse outcomes [9, 10].

Because of the putative beneficial effects of glucose-insulin-potassium (GIK) infusions in patients with low cardiac output states [11], we started to use low dose GIK (with 0.075 Units insulin/kg/hour)

Abbreviations: GIK – glucose-insulin-potassium infusion, ICU – intensive care unit, CI – cardiac index, CO - cardiac output, IV – intravenous, K^+ - potassium, BG – blood glucose, G50% - glucose 50% infusion, ICIP – IntelliVue Clinical Information Portfolio, SOFA – Sequential Organ Failure Assessment, APACHE – Acute Physiology Age Chronic Health Evaluation, FFA – free fatty acids, ATP – adenosine-tri-phosphate, APT-1 – acyl palmitoyltransferase I.

within our intensive care unit 8 years ago [12]. This showed promising results in terms of improving arterial lactate levels and augmenting cardiac output.

The dose response relationship of high dose insulin and hemodynamic effects was shown in pigs after induced poisoning with propranolol, where the cardiac output continued to rise in response to insulin doses exceeding 5 Units/kg/hour [13,14]. The inotropic effect of high-dose insulin after verapamil intoxication in canine models has been shown in several studies, even when standard therapy proved ineffective [15-18]. In short, animal studies showed the ability of high dose insulin to reverse catecholamine and glucagon-refractory overdoses with beta-adrenergic blockers and/or calcium channel blockers, as well as partial reversal of LPS induced shock [13-18].

More recently this lab work has been translated to case series, predominantly in patients being treated for beta-adrenergic and/or calcium channel blocker overdose. High doses of insulin (usually 0.5-1 Units/kg/hour but, sometimes, 3 units/kg/hour or even higher) have been used to augment low output states [19, 20]. The authors reported haemodynamic benefits with an excellent safety profile. Indeed, a recent expert consensus of calcium channel overdose recommends high dose insulin starting at 1 Unit/kg/hour, increasing if necessary to 10 Units/kg/hour [21]. Recent personal correspondence with Dr Lev Krichevskiy (Head, Department of Cardiac Anesthesia and Intensive Care, Yudin's Hospital, Moscow, Russia) reveals impressive hemodynamic rescue therapy in a series of patients with refractory heart failure peri-/post-cardiac surgery using ultra-high doses of insulin (progressive loading boluses of up to 1000 Units and infusion up to 1000 Units/hour titrated to effect).

These positive data encouraged us to move to a high-dose GIK regimen (0.25-1.0 Units insulin/kg/hour) from 2012 onwards as a treatment strategy for patients with low cardiac output who were not responding effectively to high-dose catecholamines. Clearly, the risk of hypo- or hyperglycaemia, as well as hypo- and hyperkalaemia would likely be increased with the use of these high doses. A protocol was thus developed to manage the high-dose GIK regimen safely with a staff

education campaign preceding. As this strategy has become adopted into our routine clinical practice, we decided to audit the use of high-dose GIK, with a focus on safety and haemodynamic effects.

Materials and methods

Setting and study population

This retrospective, descriptive evaluative audit of usual practice was carried out in the mixed adult 35-bed ICU of University College London Hospital, a tertiary care teaching hospital in the United Kingdom. Our protocol aimed to treat patients with myocardial depression who had not responded to conventional catecholamine therapy, with high-dose GIK. All patients treated with GIK with an ICU admission between December 2012 and March 2015 were included, there were no exclusion criteria.

To implement high-dose GIK, staff were asked to follow a protocol aiming to increase cardiac index (CI) (Table 1). This protocol was adapted from Marini *et al* who applied a GIK strategy for treating calcium channel and bèta blocker overdoses (Dr. John Marini, personal communication). The protocol requires patients to be treated with catecholamines and have serum glucose levels >7 mmol/l and potassium levels >4 mmol/l prior to commencing the GIK infusion. After giving glucose and insulin boluses, separate infusions were started at a rate of 0.25 Units insulin/kg/hour, 10 ml/hour 50% glucose solution and 10 mmol/hour potassium. For patients in whom no significant improvement was seen, the insulin dose could be up-titrated after 1 hour to 0.5 Units/kg/hour and, if needed, to 1.0 Units/kg/hour. The 50% glucose infusion rate could be uptitrated to 15 ml/hour and 20 ml/hour, respectively. Glucose and potassium levels were required to be monitored hourly and the infusion rates adjusted to achieve normal blood glucose (4 – 10 mmol/l) and potassium levels (3.8 − 5.0 mmol/l). Once stabilised, the frequency of monitoring could be reduced. When stopping the GIK infusion, insulin should be reduced to half its previous infusion rate at 8-24 hourly intervals. After GIK discontinuation, glucose should be continued for 12-24 hours.

Patient outcomes were manually collected from the Philips IntelliVue Clinical Information Portfolio (ICIP) Electronic Health Record and MUSE Cardiology Information System. Blood gas measurements were carried out with a Roche Cobas B221 blood gas analyser. Cardiac output was monitored using oesophageal Doppler ultrasonography (Deltex Medical, Chichester, Sussex, UK); CI was calculated subsequently by dividing cardiac output by body surface area. We considered 2.6–4.2 l/min/m^2 as a normal range for CI. The underlying reason to start GIK was recorded. Sepsis was defined using standard definitions [22]. A Sequential Organ Failure Assesment (SOFA) score was calculated for each patient [23]. As the central nervous system score could not be defined for sedated patients, they were scored 0 (normal) unless evidence of prior abnormality existed.

Patient consent and Ethical Committee review is not required in the UK for research limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection), provided that the patients or service users are not identifiable to the research team in carrying out the research [24].

Outcomes

The following measures were collected for each individual patient, investigated and analysed interindividually:

1) ICU and in-hospital survival.

2) Daily dose and duration of glucose, insulin and potassium.

3) CI at time points -6, 0, 6, 12, 24, 48 and 72 hours, after starting the GIK infusion where 0 hours represents the start time of GIK.

4) Arterial lactate levels at time points -12, 0, 12, 24 and 48 hours after starting the GIK infusion where 0 hours is the start time of GIK.

5) Incidence, duration and maximum/minimum level of hypoglycaemia (<2.2 mmol/l), hyperglycaemia (>10 mmol/l), hypokalaemia (<3 mmol/l) and hyperkalaemia (>5.4 mmol/l) events before and during GIK. Hyperglycaemic severity was divided in >10, >15 and >20 mmol/l subsets and

hyperkalaemic severity in >5.5, >6 and >7 mmol/l subsets. Asystolic events related to hyperkalaemia were also reported.

6) Time on vasoactive drugs before and during GIK and the total time on vasoactive drugs.

7) Discontinuation and duration of the use of inotropes and norepinephrine.

8) Use of enoximone, levosimendan, terlipressin and vasopressin during GIK.

Statistics

Data analysis was performed using SPSS version 20.0 (IBM). A Shapiro Wilk test with a visual inspection of the histogram, Q-Q plots and boxplots showed that obtained data were not normally distributed, hence nonparametric tests were used. Unless otherwise stated all values are given as median (interquartile range). Diffences between ICU survivors and non-survivors were analysed using Wilcoxon rank sum test (median values) and Fisher's exact test (proportions). Spearman's rho was used to analyse correlations between hyperglycaemic events and mortality, but also between the daily insulin dose and potassium and glucose doses, and between the daily insulin dose and hypoglyceamic and hypokalaemic events. In view of the high early mortality rate in this very sick group of patients, outcome statistics were not performed.

Results

Demographics

During the audit period, 85 patients received GIK commencing a median (IQR) 1 (1–3) days after ICU admission. Patient demographics are presented in Table 2. Seventy (82.4%) patients were primarily admitted to ICU for a medical condition and 15 (17.6%) post-operatively. Overall, baseline cardiac index was low, while SOFA and APACHE II scores were high. Sepsis was present in 83.5%, while 11.8% of the patients had cardiogenic shock.

Thirteen patients (15.3%) survived their ICU stay, and nine were discharged from hospital. ICU survivors stayed for 59 (20–90) days in hospital including 19 (9–39) days in ICU. The ICU non-survivor group had more patients with haematological malignancies than the survivor group, and more patients receiving mechanical ventilation.

Forty-four of the 72 ICU non-survivors (61%) died while the GIK infusion was ongoing, after a median of 23 (10−62) hours. Of the 28 patients who died in ICU after discontinuation of GIK, six died from non-cardiac causes more than seven days later, despite improvement in their myocardial function.

Doses of GIK and use of inotropes and vasopressors

Table 3 shows doses of GIK administered. Forty-nine of the 85 patients remained at the lower dose of 0.25 Units insulin/kg/hour though one patient was commenced at a higher dose. Survivors needed more glucose than non-survivors to maintain normoglycaemia when administered a dose of 0.25 Units insulin/kg/hour, whereas no differences were seen when given higher doses of insulin. Potassium doses were similar at the different doses of insulin. Patients received a daily glucose dose, which comprised GIK, other medications and enteral/parenteral nutrition. Even though potassium and glucose requirements increased in all patients with insulin dosing, only a weak correlation was seen between daily glucose and insulin dose ($\rho=0.47$, $p<0.01$) and no significant correlation was seen between daily potassium supplementation and the insulin dose ($\rho=0.10$, $p=0.36$). The use of inotropes and vasopressors is described in Table 4. Inotropes were discontinued in all survivors and in 26 (46%) of the non-survivors.

Lactate levels and cardiac index

Lactate levels in ICU survivors were 3.3 (1.4-10.9) at the start of treatment and 2.2 (1.4-2.5) mmol/l at 72 hours ($p=0.12$). In decedents who survived more than 72 hours after GIK was started, lactate levels fell from 7.1 (4.3—10.7) to 4.4 (3.4-5.5) mmol/l at 72 hours ($p=0.01$).

Cardiac index rose after 72 hours of GIK therapy, in survivors from 2.6 (1.8-1.8) to 3.6 (2.9-2.9) l/min/m^2 (p=0.18), and in those who ultimately died after 72 hours from 2.3 (2.0−2.9) to 2.7 (3.4−3.5) l/min/m^2 (p=0.06).

Occurrence of hypoglycaemic, hyperglycaemic, hypokalaemic and hyperkalaemic events

Table 5 describes the hypoglycaemic, hyperglycaemic, hypokalaemic and hyperkalaemic events. These events were counted between ICU admission and commencing of GIK and during GIK. No association was found between hypoglycaemic events and the dose of insulin (ρ=0.70, p=1.00).

Before commencing GIK, a total of 101 (80%) hyperglycaemic events exceeded a blood glucose level of 10 mmol/l, 19 (15%) exceeded 15 mmol/l and 6 (5%) exceeded 20 mmol/l. Twenty-one hyperglycaemic events occurred before starting GIK and ended during GIK; correction was achieved within 2 (1–5) hours. No association was found between hyperglycaemic events and mortality (ρ=0.13, p=1.00). Of the hyperglycaemic events during GIK, 89 (78%) exceeded a blood glucose of 10 mmol/l, 17 (15%) exceeded 15 mmol/l and 8 (7%) exceeded 20 mmol/l. Three events occurred while the dose of GIK was decreasing with the intention of stopping GIK, and seven while increasing the dose of glucose.

The patient with the hypokalaemic event during GIK did not have any associated adverse effects. Also, no association was found between insulin dose and the hypokalaemic events (ρ=0.05, p=0.64).

Of the hyperkalaemic events between ICU admission and commencing GIK, 25 (64.1%) patients had a potassium level between 5.5-6.0 mmol/l, 13 (33.3%) between 6.1-7.0 mmol/l and 1 (2.6%) exceeded 7 mmol/l. There were 17 hyperkalaemic events starting before GIK and ending during GIK, needing 2 (2–5) hours to achieve normokalaemia.

Of the hyperkalaemic events during GIK, 47 (72.3%) were between 5.5–6.0 mmol/l, 12 (18.5%) between 6.1–7.0 mmol/l and 6 (9.2%) exceeded 7.0 mmol/l. Levels were corrected by reducing the amount of potassium infused. Ten percent of patients received intravenous calcium. No asystolic events were seen.

Discussion

This evaluation offers insight about the safety and haemodynamic effects of high-dose GIK infusion to augment cardiac performance in patients with severe critical illness requiring high-dose catecholamine infusions. We report overall improvement in blood lactate levels and CI over the first 72 hours. Catecholamine inotropes could be discontinued in more than half of the patients while GIK was being administered. While a minority experienced episodes of severe hypoglycaemia, hyperglycaemia, hypokalaemia and hyperkalaemia, these were quickly identified and corrected, with no obvious harm coming to the patient. Moreover, the dose response curves of insulin to these important variables tend to saturate at relatively low insulin doses, whereas the inotropic and vasodilatation properties continue into a higher range. Clearly, close monitoring of blood glucose and potassium is mandatory during administration of high-dose GIK, particularly around dose transition.

Due to the potential harm induced by exogenous catecholamine therapy [5-7], a less harmful strategy such as GIK may be beneficial. The hyperadrenergic state of heart failure causes plasma free fatty acid (FFA) levels to rise [25-27]. This increases insulin resistance and decreases cellular use of glucose. As a consequence, energy, in the form of adenosine triphosphate (ATP), needs to be liberated from fat instead of glucose and this requires approximately 11-12% more oxygen consumption [28]. As coronary sinus oxygen tensions are normally low, blood flowing through narrowed coronary vessels in ischaemic heart disease must increase further to deliver additional oxygen, and this may not be achievable. A compensatory increase in anaerobic glycolysis occurs, however this is a less efficient producer of ATP compared to aerobic respiration (oxidative phosphorylation). A decrease in oxidative phosphorylation caused by inhibition of the fatty acid transporter, acylpalmitoyltransferase-1 (APT-1), may also result in less oxidation of FFA, thereby

increasing plasma levels still further [29]. High levels of FFA have pro-inflammatory and pro-oxidant actions and reduce mitochondrial efficiency [30, 31].

Such metabolic effects may explain the postulated clinical benefit of GIK in the treatment of heart failure. Firstly, insulin promotes oxidative phosphorylation [32]. Second, insulin inhibits lipolysis, which results in a decrease of circulating FFA and allows the heart to use glucose for ATP production. As glucose is the preferred energy substrate for stressed myocardial cells [26,27], this should be beneficial. Third, insulin induces dose-dependent vasodilation via the L-arginine-NO-pathway; this is hypothesised to improve coronary blood flow and thus contractility of the dysfunctional left ventricle [33,34]. Fourth, insulin starts calcium release in cardiac muscle cells through IP3 production and activation of IP3R. This leads to GLUT4 translocation [35]. In consequence, there is an increase of glucose uptake into cardiac muscle. It remains unclear whether the effect of GIK relies on a decrease of FFA and/or an increase in glucose utilization [36]. As insulin decreases blood glucose and potassium levels, potassium and glucose are integral constituents of the GIK regimen to maintain normoglycaemia and normokalaemia.

GIK has been studied in acute myocardial infarction [11,36,37] and cardiac surgery [38-40], albeit with variable results and thus no overall benefit [41]. Possible reasons include use of different doses of insulin, failure to maintain normoglycaemia, and introduction after thrombolysis where high blood sugar levels may have enhanced the degree of reperfusion injury. A study in 15 septic shock patients showed short-term haemodynamic improvement following a 20-minute GIK infusion [42], while a pilot study in patients with heart failure showed beneficial effects of GIK on systolic function [43].

As high-dose GIK (0.25-1.0 units/kg/hour, but sometimes much higher) now has a recommended role in beta-blocker and/or calcium channel blocker overdose [19,20], we predicted a better response in our patient population with higher doses of insulin than our former practice using 0.075 Units/kg/hour. Our insulin dose regimen was also much higher than in studies using GIK after myocardial infarction and surgery [41].

The inconsistencies of clinical practice were exposed by our audit. The insulin dose remained at 0.25 Units/kg/hour in the majority of patients, rather than being titrated upwards as per our guideline for patients in whom a clinically relevant reduction in catecholamines was not seen within the first few hours. Whether higher doses would have offered better results and/or increased the incidence of adverse events is unknown. Furthermore, little is known about the synergistic effects of high dose insulin and catecholamines and calcium sensitizers, particularly with response to ideal dosing of each and their sequencing.

As we found, higher glucose dosing would be required as insulin causes a net intracellular shift [44]. Whether potassium supplementation would also need to be increased requires further study, as we did not find any correlation between insulin dose and degree of potassium supplementation. A further breach of our ICU protocol was the use of GIK in some patients not receiving inotropes for a low cardiac output state and, in a few instances, not receiving catecholamines. This emphasizes the need for continuing education about its likely biological effects and clinical indications, and closer policing, which have since been instituted.

While mild-to-moderate hyperglycaemic and hyperkalaemic events were common during GIK administration, the incidence was identical to that seen in patients before commencement of the GIK infusion. As described above, severe events were uncommon and promptly corrected.

Regardless of any improvement in haemodynamic and tissue metabolic status, mortality was still very high in this subset of shocked patients. Their baseline APACHE II and SOFA scores and the high incidence of underlying immunosuppression, especially related to haematological malignancy, underlines their poor prognosis.

A limitation of the study is its retrospective nature. Some measurements were missing from our Electronic Health Record at particular timepoints. Furthermore, there is no control group as would be required in a prospective study. However, we do feel there are sufficient grounds in terms of benefits and relatively low risks to proceed to a randomised controlled trial of high-dose GIK in critically ill

septic patients with myocardial depression, in whom the literature is very sparse. It is nonetheless important to carefully characterize the group(s) of patients who would most likely benefit.

Conclusions

High-dose glucose-potassium-insulin infusions can be safely used in critically ill patients, though blood glucose and potassium levels must be monitored frequently. The impact of this therapeutic strategy on survival requires prospective evaluation.

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Conflict of interest

The authors do not have a potential conflict of interest.

References

[1] Townsend N, Williams J, Bhatnagar P, Wickramasinghe K, Rayner M. Cardiovascular disease statistics 2014. British Heart Foundation. 2014. Available at: www.bhf.org.uk/~/media/files/ research/heart- statistics/ bhf_cvd-statistics-2014_web.pdf. Accessed 25 May 2015.

[2] Cleland J, Dargie H, Hardman S, McDonagh T, Mitchell P. National heart failure audit London. NICOR. 2013. [last accessed 25 May 2015]. www.ucl.ac.uk/nicor/audits/heartfailure/ documents/annualreports/hfannual12-3.pdf. Accessed 25 May 2015.

[3] NICE. Acute heart failure: diagnosing and managing acute heart failure in adults. National Institute for Health and Care Excellence. 2014. www.nice.org.uk/guidance/cg187. Accessed 2 June 2015.

[4] Singer M. Catecholamine treatment for shock--equally good or bad? Lancet 2007;370:636-7.

[5] Elkayam U, Tasissa G, Binanay C, Stevenson LW, Gheorghiade M, Warnica JW, *et al*. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. Am Heart J 2007;153:98-104.

[6] Shahin J, DeVarennes B, Tse CW, Amarica DA, Dial S. The relationship between inotrope exposure, six-hour postoperative physiological variables, hospital mortality and renal dysfunction in patients undergoing cardiac surgery. Crit Care 2011;15:162.

[7] Fellahi JL, Parienti JJ, Hanouz JL, Plaud B, Riou B, Ouattara A. Perioperative use of dobutamine in cardiac surgery and adverse cardiac outcome: propensity-adjusted analyses. Anesthesiology 2008;108:979-87.

[8] Bangash MN, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. Br J Pharmacol 2012;165:2015-33.

[9] Abraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, *et al*. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive

medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol 2005;46:57-64.

[10] Cuffe MS, Califf RM, Adams KF, Benza R, Bourge R, Colucci WS, *et al*. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287:1541-7.

[11] Díaz R, Paolasso EA, Piegas LS, Tajer CD, Moreno MG, Corvalán R, *et al*. Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiológicos Latinoamérica) Collaborative Group. Circulation 1998;98:2227-34.

[12] Shulman R, Dhorowa M, Benzaquen D, Davies G, Breen P, Bates I, *et al*. Adjuctive use of glucose-insulin-potassium (GIK) versus control in low cardiac output patients: a case controlled comparison [abstract]. UK Intensive Care Society State of the Art Meeting, London 2011, P146.

[13] Holger JS, Engebretsen KM, Fritzlar SJ, Patten LC, Harris CR, Flottemesch TJ. Insulin versus vasopressin and epinephrine to treat beta-blocker toxicity. Clin Toxicol 2007;45:396-401.

[14] Cole JB, Stellpflug SJ, Ellsworth H, Anderson CP, Adams AB, Engebretsen KM et al. A blinded, randomized, controlled trial of three doses of high-dose insulin in poison-induced cardiogenic shock. Clin Toxicol 2013; 51: 201-7.

[15] Kline JA, Raymond RM, Schroeder JD, Watts JA. The diabetogenic effects of acute verapamil poisoning. Toxicol Appl Pharmacol 1997; 145:357–362.

[16] Kline JA, Tomaszewski CA, Schroeder JD, Raymond RM. Insulin is a superior antidote for cardiovascular toxicity induced by verapamil in the anesthetized canine. J Pharmacol Exp Ther 1993; 267:744–750.

[17] Kline JA, Lenova E, Raymond RM. Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. Crit Care Med 1995; 23:1251–1263.

[18] Kline JA, Lenova E, Williams TC, Schroeder JD, Watts JA. Myocardial metabolism during graded intraportal verapamil infusion in awake dogs. J Cardiovasc Pharmacol 1996; 27:719–726.

[19] Greene SL, Gawarammana I, Wood DM, Jones AL, Dargan PI. Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study. Intensive Care Med 2007;33:2019-24.

[20] Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clin Toxicol 2011;49:277-83.

[21] St-Onge M, Anseeuw K, Cantrell FL, Gilchrist IC, Hantson P, Bailey B et al. Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults. Crit Care Med 2017;45:306-315.

[22] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-74.

[23] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, *et al*. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707-10.

[24] Governance Arrangements for Research Ethics Committees (GAfREC). NHS Health Research Authority. 2014. Available at: http://www.hra.nhs.uk/resources/research-legislation-and-governance/governance-arrangements-for-research-ethics-committees. Accessed 21 December 2015.

[25] Opie LH. The metabolic vicious cycle in heart failure. Lancet 2004;364:1733-4.

[26] Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. Physiol Rev 2005;85:1093–129.

[27] Wang ZV, Li DL, Hill JA. Heart failure and loss of metabolic control. J Cardiovasc Pharmacol 2014;63:302-13.

[28] Opie LH, Knuuti J. The adrenergic-fatty acid load in heart failure. J Am Coll Cardiol 2009;54:1637-46.

[29] Ashrafian H, Frenneaux MP, Opie LH. Metabolic mechanisms in heart failure. Circulation 2007;116:434-48.

[30] Freigang S, Ampenberger F, Weiss A, Kanneganti TD, Iwakura Y, Hersberger M, *et al*. Fatty acid-induced mitochondrial uncoupling elicits inflammasome-independent IL-1α and sterile vascular inflammation in atherosclerosis. Nat Immunol 2013;14:1045-53.

[31] Nogueira AC, Kawabata V, Biselli P, Lins MH, Valeri C, Seckler M, *et al*. Changes in plasma free fatty acid levels in septic patients are associated with cardiac damage and reduction in heart rate variability. Shock 2008;29:342-8.

[32] Stump CS, Short KR, Bigelow ML, Schimke JM, Nair KS. Effect of insulin on human skeletal muscle mitochondrial ATP production, protein synthesis, and mRNA transcripts. Proc Natl Acad Sci U S A 2003;100:7996-8001.

[33] Oliver MF, Opie LH. Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. Lancet 1994;343:155-8.

[34] Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. J Clin Invest 1994;94:1172-9.

[35] Contreras-Ferrat A, Lavandero S, Jaimovich E, Klip A. Calcium signaling in insulin action on striated muscle. Cell Calcium 2014;56(5):390-6.

[36] Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. Circulation 1997;96:1152-6.

[37] Mehta SR, Yusuf S, Díaz R, Zhu J, Pais P, Xavier D, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. JAMA 2005;293:437-46.

[38] Schipke JD, Friebe R, Gams E. Forty years of glucose-insulin-potassium (GIK) in cardiac surgery: a review of randomized, controlled trials. Eur J Cardiothorac Surg 2006;29:479-85.

[39] Shim JK, Yang SY, Yoo YC, Yoo KJ, Kwak YL. Myocardial protection by glucose-insulin-potassium in acute coronary syndrome patients undergoing urgent multivessel off-pump coronary artery bypass surgery. Br J Anaesth 2013;110:47-53.

[40] Duncan AE, Kateby Kashy B, Sarwar S, Singh A, Stenina-Adognravi O, Christoffersen S, *et al*. Hyperinsulinemic normoglycemia does not meaningfully improve myocardial performance during cardiac surgery: a randomized trial. Anesthesiology 2015;123:272-87.

[41] Puskarich MA, Runyon MS, Trzeciak S, Kline JA, Jones AE. Effect of glucose-insulin-potassium infusion on mortality in critical care settings: a systematic review and meta-analysis. J Clin Pharmacol 2009;49:758-67.

[42] Bronsveld W, van den Bos GC, Thijs LG. Use of glucose-insulin-potassium (GIK) in human septic shock. Crit Care Med 1985;13:566-70.

[43] Kalay N, Ozdogru I, Gul A, Yucel Y, Cetinkaya Y, Inanc MT, *et al*. Effects of intermittent and long-term glucose-insulin-potassium infusion in patients with systolic heart failure. Exp Clin Cardiol 2008;13:85-8.

[44] Nguyen TQ, Maalouf NM, Sakhaee K, Moe OW. Comparison of insulin action on glucose versus potassium uptake in humans. Clin J Am Soc Nephrol 2011;6:1533-9.

Table 1. UCLH ICU GIK protocol (adapted from Marini et al)

Monitoring

- **Do NOT change insulin dose in response to blood glucose (BG) or potassium (K^+) levels**
- **Monitor BG every 10 mins and titrate glucose 50% infusion (G50%) to achieve target of 4-10 mmol/l. If BGs are stable, monitor the BG every hour**
- **Monitor blood potassium levels every hour**

Step 1	Step 2	Step 3	Step 4	Step 5	GIK Discontinuation	Hypoglycaemia
Indication for GIK **Low cardiac output (CO), on inotrope**	Bolus:	Stop other crystalloids. Start infusion (first hour):	If no improvement after 1 hour*	If no improvement after 2 hours*	Consider when inotrope weaned and CO restored *	Continue insulin at same dose Glucose BG 2.5 – 3.9 mmol/L: give 10 ml 50% G centrally; recheck BG every 15 min, repeat as needed. BG<2.5mmol/L: give 25 ml 50% glucose centrally; recheck BG every 15 min, repeat as needed. increase G50% rate by 5ml/hr
Stabilise the patient with conventional therapy e.g. mechanical ventilation, inotropes, fluids as needed. Hold feed, inform Dietitian- to review nutrition	Insulin 0.25 U/kg intravenous (IV) 5-10 min	Insulin 0.25 U/kg/h syringe 300u/50ml N/S	Insulin 0.5 U/kg/h	Insulin 1.0 U/kg/h	Halve rates of GIK infusions every 8-24h*. Continue this if CO and perfusion maintained	
Ensure Glucose **> 7 mmol/l (if not: give 15ml 50% bolus centrally)**	Glucose 20ml 50% IV 5-10 min	Glucose 50% 10ml/h centrally	Glucose 50% Increase previous dose by 5 ml/h and adjust to normal target	Glucose 50% Increase previous dose by 5 ml/h and adjust to normal target	Give glucose after insulin discontinuation for 12-24 h . Monitor BG/K^+ every 0.5-2 h (depending on degree of concern about abnormal values – adjust dosing as needed)	
Ensure K^+ **> 4 mmol/l** **(if not: give 20mmol K^+ over 1 hour centrally)**		K^+ 40 mmol / 100ml 10 mmol/h centrally. Adjust to achieve normal levels (3.8-5.0 mmol/l)	K^+ Titrate to achieve normal levels (3.8-5.0 mmol/l)	K^+ Titrate to achieve normal levels (3.8-5.0 mmol/l)		

*** Consultant/Senior doctor decision**

Table 2. Demographic baseline characteristics of included patients[a]

	All patients	ICU survivors	ICU non-survivors
Number of patients	85	13	72
Age	63 (51 – 73)	62 (45 – 73)	63 (51 – 71)
Gender			
Male	62 (72.9%)	10 (76.9%)	52 (72.2%)
Female	23 (27.1%)	3 (23.1%)	20 (27.8%)
Medical or surgical patient			
Medical	70 (82.4%)	11 (84.6%)	59 (81.9%)
Surgical	15 (17.6%)	2 (15.4%)	13 (18.1%)
Underlying immunosuppression			
Haematological malignancy	50 (58.8%)	2 (15.4%)	48 (66.7%)
Oncology	2 (2.4%)	1 (7.7%)	1 (1.4%)
HIV	2 (2.4%)	0 (0%)	2 (2.8%)
Diabetes mellitus	8 (9.4%)	0 (0.0%)	8 (11.1%)
Weight (kg)	75 (67 – 86)	75 (70 – 89)	74 (66 – 87)
Body mass index (BMI)	26 (24 – 29)	27 (24 – 2)	26 (24 – 29)
APACHE II score	25 (19 – 32)	26 (22 – 33)	25 (19 – 31)
SOFA score on GIK day 1	11 (9 – 13)	9 (8 – 11)	11 (9 – 14)
Respiratory score	4 (4 – 4)	4 (2 – 4)	4 (4 – 4)
Cardiovascular score	4 (4 – 4)	4 (4 – 4)	4 (4 – 4)
Liver score	1 (0 – 2)	0 (0 – 0)	1 (0 – 2)
Coagulation score	2 (0 – 3)	0 (0 – 3)	2 (0 – 3)
Renal score	2 (0 – 2)	1 (0 – 2)	2 (1 – 2)
Cognition score	0 (0 – 0)[b]	0 (0 – 0)[b]	0 (0 – 0)[b]
Reason to start GIK:			
- Heart failure/cardiogenic shock	10 (11.8%)	1 (7.6%)	9 (12.5%)
- Sepsis	71 (83.5%)	12 (92.3%)	59 (81.9%)
- Overdose induced heart failure	1 (1.1%)	0 (0%)	1 (1.4%)
- Other	3 (3.5%)	0 (0%)	3 (4.2%)
SvO_2 before GIK (%)	71 (55 – 80)	66 (50 – 79)	71 (57 – 80)
Patients receiving mechanical ventilation during first day of GIK	70 (82%)	8 (62%)	62 (86%)
Patients receiving renal replacement therapy during first day of GIK	49 (58%)	4 (31%)	45 (63%)
Days in ICU before GIK commenced	1 (1 – 3)	1 (0 - 7)	1 (1 – 3)
Cardiac index at start of GIK infusion ($l/min/m^2$)	2.5 (2.0 – 3.2)	2.5 (1.8 – 3.5)	2.6 (2.0 – 3.2)

a Age, APACHE II score, weight and BMI are given as median (interquartile range), all other data are given as n (%)

b Default score as patients were sedated

Abbreviations: HIV=human immunodeficiency virus; BMI=body mass index; SvO_2= mixed venous oxygen saturation.

Table 3. Dose regimen of the GIK infusion[a]

	All patients N=85	ICU Survivors N=13	ICU Non-survivors N=72	p-value
Length of GIK treatment (h)	42 (16 – 88)	77 (52 – 125)	36 (12 – 82)	0.38[b]
Maximum insulin dose 0.25 U/kg/h				
N (%)	49/49(100%)	10/49 (20%)	39/48 (81%)	0.22[c]
Hours	18 (5 – 42)	42 (23 – 72)	22 (6 – 86)	0.09[b]
Maximum insulin dose 0.5 U/kg/h				
N (%)	28/28 (100%)	2/28 (7%)	26/28 (93%)	0.32[c]
Hours	26 (8 – 86)	42[d]	22 (6 – 86)	0.60[b]
Maximum insulin dose 1.0 U/kg/h				
N (%)	8/8 (100%)	1/8 (12.5%)	7/8 (87.5%)	1.00[c]
Hours	30 (10 – 50)	53[d]	21 (8 – 40)	0.18[b]
Dose of insulin (U/24h)	540 (396 – 744)	465 (351 – 691)	540 (401 – 754)	0.75[b]
Glucose dose (g/24h)				
- GIK	407 (262 – 553)	431 (284 – 490)	403 (249 – 575)	0.51[b]
- GIK + other medication	434 (301 – 619)	431 (303 – 535)	436 (299 – 624)	0.53[b]
- GIK, other medication and TPN	439 (313 – 621)	431 (303 – 535)	458 (309 – 624)	0.54[b]
Glucose dose (g/h) (insulin 0.25 U/kg/h)	12 (5 – 19)	16 (10 – 18)	5 (11 – 19)	<0.01[b]
Glucose dose (g/h) (insulin 0.5 U/kg/h)	21 (12 – 31)	31[d]	19 (11 – 30)	0.60[b]
Glucose dose (g/h) (insulin 1.0 U/kg/h)	27 (8 – 47)	6[d]	29 (13 – 48)	0.18[b]
Dose of K^+ (mmol/24h)	111 (56 – 154)	111 (74 – 204)	112 (48 – 152)	0.25[b]
K^+ dose (mmol/h) (insulin 0.25 U/kg/h)	5 (2 – 8)	4 (3 – 9)	5 (1 – 8)	0.35[b]
K^+ dose (mmol/h) (insulin 0.5 U/kg/h)	5 (4 – 9)	6[d]	5 (4 – 8)	0.17[b]
K^+ dose (mmol/h) (insulin 1.0 U/kg/h)	5 (2 – 38)	2[d]	6 (2 – 60)	0.18[b]

a Unless described otherwise, all data are given as median (interquartile range). U=Units, h=hour.
b P-value calculated using Wilcoxon rank sum test
c P-value calculated using Fisher's exact test
d Number of patients too small to give an interquartile range

Table 4. Use of inotropes, norepinephrine (NE) and vasopressors in patients with GIK[a]

	All patients N=85	Survivors N=13	Non-survivors N=72	P-value
Time on vasoactive drugs before GIK infusion (hours)	12 (2 – 30)	3 (0 – 38)	13 (2 – 30)	0.58[c]
Time on vasoactive drugs during GIK (hours)	38 (14 – 121)	42 (0 – 72)	37 (15 – 128)	0.35[c]
Total time on vasoactive drugs (hours)	79 (36 – 159)	50 (0 – 199)	90 (38 – 159)	0.48[c]
Patients on inotropes				
Epinephrine	58/85 (68%)	5/13 (38%)	53/72 (74%)	0.11[b]
Dobutamine	21/85 (25%)	6/13 (46%)	15/72 (21%)	0.73[b]
Levosimendan	7/85 (8%)	3/13 (23%)	4/72 (6%)	1.00[b]
Enoximone	1/85 (1%)	0/13 (0%)	1/72 (1%)	
Patients not on inotropes	20/85 (24%)	6/13 (46%)	14/72 (19%)	0.11[b]
Cessation of inotropes during or after GIK	35/65 (54%)	9/9 (100%)	26/56 (46%)	<0.01[b]
Use of NE before GIK	54/85 (64%)	5/85 (38%)	49/85 (68%)	0.06[b]
Use of NE during GIK				
With inotropes	54/85 (64%)	9/13 (69%)	45/72 (63%)	0.23[b]
Without inotropes	16/85 (19%)	1/13 (8%)	15/72 (21%)	0.29[b]
Use of NE after GIK	12/85 (14%)	3/13 (23%)	9/72 (13%)	0.39[b]
Use of vasopressors during GIK				
Terlipressin	18/85 (21%)	5/13 (38%)	13/13 (18%)	0.06[b]
Vasopressin	2/85 (2%)	0/13 (0%)	2/13 (3%)	1.00[b]

a Data are given as median (interquartile range) or n (%)

b P-value calculated with Fisher's exact test

c P-value calculated with Wilcoxon rank sum test

Table 5. Occurrence of hyperglycaemic, Hypoglycaemic, hyperkalaemic and hypokalaemic events. This table describes the amount events per patient and the median maximum or minimum concentration of glucose or potassium during the event. The length of the event in hours, e.g. between the start of the event to normal glucose or potassium levels is given.

	Amount of patients having an event	Median amount of events per patient	Lowest or highest median level (mmol/l)	Median duration to normalisation (hours)
Events between ICU admission and commencing GIK				
Hypoglycaemic events	0			
Hyperglycaemic events	57	1 (1-2)	13.9 (11.5-15.6)	5 (2-7)
Hypokalaemic events	1	2	1.2	2
Hyperkalaemic events	39	1 (1-2)	6 (5.6-6.4)	4 (2-6)
Events during GIK				
Hypoglycaemic events	3	3	1.9	1
Hyperglycaemic events	55	2 (1-3)	13.3 (11.6-17.7)	3 (2-4)
Hypokalaemic events	1	1	1.2	2
Hyperkalaemic events	41	1(1-2)	6.0 (5.7-6.7)	4 (2-7)