

Perioperative hyperglycemia is associated with postoperative neurocognitive disorders after cardiac surgery

Xiaopeng Zhang¹
 Xiaowei Yan²
 Jennifer Gorman²
 Stuart N Hoffman³
 Li Zhang¹
 Joseph A Boscarino²

¹Department of Anesthesiology, Geisinger Medical Center, ²Center for Health Research, Geisinger Clinic, ³Department of Neurology, Geisinger Medical Center, Danville, PA, USA

Objective: Neurocognitive disorders commonly occur following cardiac surgery. However, the underlying etiology of these disorders is not well understood. The current study examined the association between perioperative glucose levels and other risk factors and the onset of neurocognitive disorders in adult patients following coronary artery bypass and/or valvular surgery.

Methods: Adult patients who underwent their first cardiac surgery at a large tertiary care medical center were identified and those with neurocognitive disorders prior to surgery were excluded. Demographic, perioperative, and postoperative neurocognitive outcome data were extracted from the Society for Thoracic Surgery database, and from electronic medical records, between January 2004 and June 2009. Multiple clinical risk factors and measures associated with insulin resistance, such as hyperglycemia, were assessed. Multivariable Cox competing risk survival models were used to assess hyperglycemia and postoperative neurocognitive disorders at follow up, adjusting for other risk factors and confounding variables.

Results: Of the 855 patients included in the study, 271 (31.7%) had new onset neurocognitive disorders at follow-up. Age, sex, New York Heart Failure (NYHF) Class, length of postoperative intensive care unit stay, perioperative blood product transfusion, and other key factors were identified and assessed as potential risk factors (or confounders) for neurocognitive disorders at follow-up. Bivariate analyses suggested that new onset neurocognitive disorders were associated with NYHF Class, cardiopulmonary bypass, history of diabetes, intraoperative blood product use, and number of diseased coronary vessels, which are commonly-accepted risk factors in cardiac surgery. In addition, higher first glucose level (median =116 mg/dL) and higher peak glucose >169 mg/dL were identified as risk factors. Male sex and nonuse of intra-operative blood products appeared to be protective. Controlling for potential risk factors and confounders, multivariable Cox survival models suggested that increased perioperative first glucose measured in 20 unit increments, was significantly associated with the onset of postoperative neurocognitive disorders at follow-up (hazard ratio [HR] =1.16, $P<0.001$) and that women had an elevated risk for this outcome (HR =4.18, $P=0.01$).

Conclusion: Our study suggests that perioperative hyperglycemia was associated with new onset of postoperative neurocognitive disorders in adult patients after cardiac surgery, and that men tended to be protected from these outcomes. These findings may suggest a need for the revision of clinical protocols for perioperative insulin therapy to prevent long-term neurocognitive complications.

Keywords: insulin resistance, neurocognitive disorders, intensive care, gender

Correspondence: Xiaopeng Zhang
 Department of Anesthesiology, Geisinger Medical Center, 100 North Academy Avenue, Danville, PA, 17822, USA
 Email xzhangl@geisinger.edu

Introduction

Patients undergoing cardiac surgery are at higher risk for developing postoperative neurocognitive disorders,¹ but the etiology of these outcomes remains unclear. Published studies have suggested multifactorial associations in the development of

postoperative neurocognitive disorders, including older age, educational level, preoperative cognitive function, diabetes mellitus,²⁻⁴ cardiac dysrhythmia,⁵ cardiopulmonary bypass surgery,^{1,6,7} post-surgery body temperature and rewarming time,⁸ jugular venous oxygen desaturation,^{9,10} acid-base management strategies,¹¹ microembolic load during surgical bypass,¹² and postoperative intubation time.^{13,14} Clinical trials of perioperative brain-protection protocols have included hypothermia,¹⁵ minimizing aortic manipulation,¹⁶ increasing perfusion pressure,^{17,18} epiaortic ultrasound guided aortic cannulation during cardiopulmonary bypass,¹⁹ intra-aortic filters to prevent gaseous embolism,¹² and use of several pharmacological agents.^{4,20-24} However, none of these preventive measures have proven to be effective.

Stress-induced hyperglycemia is a common perioperative phenomenon that may be caused by temporary insulin resistance from high physiological and psychological stress levels. Perioperative insulin therapy improves overall clinical outcome in patients after cardiac surgery,²⁵ and is frequently given due to the detrimental effects of hyperglycemia. However, the association between perioperative insulin resistance and the onset of postoperative neurocognitive disorders after cardiac surgery, and the role of perioperative insulin therapy in neuroprotection, are not well understood.

In animal studies, diabetic rats have significantly lower scores on cognitive tests.²⁶ Clinical data suggest that patients with type II diabetes mellitus tend to have poorer long-term neurocognitive performance compared to non-diabetic controls,²⁷ and one of the causal mechanisms for this association is thought to be insulin resistance. Data from *in vitro* studies indicate that the insulin signaling pathway is critical for maintaining long-term potentiation in hippocampal neurons, which are likely important in learning and memory.^{28,29} Moreover, activation of the insulin signaling pathway may reduce neuronal programmed cell death under nutritional deprivation, ischemia, and traumatic injury;³⁰⁻³² thus, this pathway may serve a neuroprotective function during physiologic stress. Animal studies have also demonstrated that insulin therapy improved neurological outcome in global and focal brain ischemia.^{33,34} A recent clinical trial showed that intranasal insulin therapy may improve cognitive function in elderly patients with early dementia.³⁵ The potential benefits of perioperative glucose-insulin-potassium therapy have also been under investigation among patients with myocardial infarction and those undergoing cardiac surgery.^{36,37} These data suggest that insulin signaling pathway dysfunction may be an important mechanism in neurocognitive deterioration after neurological injuries. Thus, evidence suggests that

maintaining normal insulin signaling pathway function during perioperative stress may provide important neuroprotective effects.

The focus of the current study is to identify risk factors for new onset neurocognitive disorders after cardiac surgery, with a focus on assessing the association between perioperative insulin resistance, as indexed by perioperative hyperglycemia, and the onset of postoperative neurocognitive disorders. Our hypothesis is that perioperative hyperglycemia is associated with postoperative neurocognitive disorders and that good perioperative glucose control is important for improving neurocognitive outcome. As we note (to follow), the primary risk factor of interest in the current study is glucose level, which we use as a proxy measure for insulin resistance. We hypothesize that glucose level is associated with postoperative neurocognitive outcome, controlling for other risk factors and potential confounders.

Methods

Study population

This is a single medical center, retrospective longitudinal study, with an average patient follow-up time of approximately 4 years. Patients who underwent first-time cardiac surgery from January 2004 to June 2009 at Geisinger Medical Center (Danville, PA, USA) were eligible for the study. Patients who received on or off pump coronary artery bypass graft (CABG) and/or valve repair or replacement under general anesthesia were included in the study. Those who had repeated open sternotomy for CABG and/or valve surgery were excluded from the current study. The study population was restricted to those patients who were 18 years or older at the time of surgery and who had first time open sternotomy for CABG and/or valve surgery only. The study was also restricted to patients who had no prior history of neurocognitive disorders in their medical records, as defined below. The purpose of this neurocognitive disorder restriction was to reduce potential bias at the index date (time of surgery), because patients with prevalent neurocognitive disorders would be more likely to have further recurrences. In addition, this exclusion would potentially reduce confounding related to clinicians' clinical decision-making associated with their patient care approach. For this study, patients' CABG surgery information was retrospectively extracted from the Society for Thoracic Surgery (STS) database maintained at Geisinger Medical Center. This database also includes all cardiac surgery information as well as the presence of key cardiovascular disease measures, such as number of diseased vessels, percent aortic occlusion, and the New York Heart Failure (NYHF) classification. These

were recorded by clinicians in the STS registry as being present at the time of surgery. The STS National Database has more than 250 instructional participants in the US and the Adult Cardiac Surgery Database now contains more than 4.5 million surgical records and represents an estimated 94% of all adult cardiac surgery centers across the US (<http://www.sts.org/national-database>).

Since blood insulin level was not routinely monitored, perioperative (ie, the closest postoperative time point) measurement of glucose was used as a surrogate marker for insulin resistance. In this case, perioperative glucose is defined as the glucose measurement results obtained on the same day of surgery. All non-STS surgery data were extracted from Geisinger's electronic health records (EHR) database. Since information pertaining to the start and end of general anesthesia, aortic cross clamping, and hypothermic cardiopulmonary bypass were not always recorded in the electronic records, the timing of some of these measurement results could not be determined. For our analyses, we assessed each of the following as insulin resistance proxies: first available intra or postoperative glucose, peak glucose, median glucose, and glucose range. Glucose results were all taken within the admission stay for the surgery. In order to control for disease burden, we also assessed key comorbidities for each patient at the time of surgery, which were recorded by clinicians in the STS registry as present at the time of surgery. These comorbidities included infectious endocarditis, immunosuppressive therapy, peripheral vascular disease, cerebrovascular disease, hypertension, and diabetes. The onset of postoperative neurocognitive disorder – the study outcome – was identified from data in the EHR at follow-up. The study outcome was the date of the first *International Classification of Diseases*, Ninth revision, clinical modification (ICD-9 CM) diagnosis code for stroke, cerebrovascular accident, transient ischemic attack, Alzheimer's disease, dementia, memory deficit, coma, encephalopathy, or adult onset neurological conditions after surgery. The first date for any of these disorders was then taken as the date of neurocognitive disorder onset. The study end date was June 30, 2009. This study was approved by the Institutional Review Board of Geisinger Health System (Danville, PA, USA).

Statistical methods

We first present baseline characteristics and comorbidities of the 855 eligible patients. Statistical distributions were assessed for each variable, stratified by postoperative cognitive disorder status. For continuous variables the Student's *t*-test was used, if normally distributed; otherwise,

Mann–Whitney–Wilcoxon or Kruskal–Wallis tests were used. Chi-square test was used for categorical variables. Continuous variables were summarized using means and standard deviation, if normally distributed, otherwise we used the median with interquartile range (IQR; 25th–75th percentiles). Next, we evaluated the association of each variable with postoperative neurocognitive event, using a bivariate Cox proportional hazard model. For patients with multiple glucose measurements, we took the first glucose level as a predictor since it was the one closest to the pre-operation value. We used different strategies to deal with missing data, dependent on measurement level. For variables with more than 30% missing data, the variable was not used in the analysis. Otherwise, we treated missing as a category, if the variable was categorical, and as an indicator measure, if the variable was continuous, with an interaction term for the missing indicator and the variable included in the model for the latter.

For the final model, we included the candidate variables selected from the analyses described above at a significance level of 0.10 or less. An age interaction effect with each of the other variables was tested in the model, followed by sex interaction effect on the variables. Postoperative neurocognitive disorder was the primary outcome of interest, with all-cause mortality included as a competing risk in the model. We utilized this competing-risk proportional hazard model to estimate the cause-specific hazard for onset of postoperative neurocognitive disorders. The advantage of this competing risk method was that the model accounts for the failure time from the competing risk while estimating the hazard ratio, which avoids overestimating the hazard of the disease outcome of interest.³⁸ All statistical tests were two-sided with a *P*-value of less than 0.05 considered as a cut-off for statistical significance. Data analysis was performed using the SAS (version 9.3) statistical package (SAS Institute Inc., Cary, NC, USA).

Results

Among 855 eligible patients, 271 (31.7%) developed postoperative cognitive disorders, and 22 (2.6%) patients died during the follow-up period, which averaged about 4 years in this study (Table 1). Higher percentage of female patients developed postoperative cognitive dysfunction than males ($P=0.005$). The average age at surgery was not significantly different for those who had postoperative cognitive disorders compared to those who did not ($P=0.36$), and while the average age of patients in the mortality group was 3 years older at surgery, this difference was also not significant ($P=0.36$).

Table I Patient characteristics by postoperative neurocognitive outcome results among those with no prior cognitive disorders (N=855)

Study variable	Event (N=271)	No-event (N=562)	Death (N=22)	P-value
Duration of follow-up in years (mean, SD)	4.04 (1.35)	4.08 (1.58)	0.04 (0.03)	<0.001
Age (mean, SD)	66.0 (12.2)	66.5 (11.1)	69.6 (14.1)	0.36
Female sex	88 (32.5)	125 (22.2)	7 (31.8)	0.005
NYHA class of HF (n, %); 85% known*				
Class 1	13 (5.1)	20 (4.4)	0 (0.0)	0.006
Class 2	57 (22.4)	144 (31.9)	1 (5.3)	
Class 3	145 (56.9)	225 (49.9)	11 (57.9)	
Class 4	40 (15.7)	62 (13.7)	7 (36.8)	
Number of diseased coronary vessels (n, %)				
None	52 (19.2)	142 (25.3)	5 (23.7)	0.08
One	22 (8.1)	37 (6.6)	4 (19.1)	
Two	40 (14.8)	100 (17.8)	4 (19.1)	
Three	157 (57.9)	283 (50.4)	8 (38.1)	
Aortic occlusion (n, %)	83 (30.6)	235 (41.8)	17 (77.3)	<0.001
Cardiopulmonary bypass (n, %)	113 (41.7)	271 (48.2)	20 (90.9)	<0.001
Resuscitation after cardiac arrest (n, %)	0 (0.0)	9 (1.6)	1 (5.0)	0.04
ICU length of stay in days (median, IQR)	2 (1.0–3)	2 (1.0–3)	3 (1–13)	0.25
Intra-operative Blood Products applied (n, %) – 83% known*	75 (27.7)	175 (31.1)	13 (59.1)	0.009
Comorbidities				
Diabetes mellitus (n, %)	90 (33.3)	175 (31.1)	9 (45.0)	0.37
Infectious endocarditis (n, %)	5 (1.8)	8 (1.4)	1 (5.0)	0.64
Immunosuppressive therapy (n, %)	0 (0.0)	3 (0.5)	1 (5.0)	0.006
Hypertension (n, %)	196 (72.6)	406 (72.2)	16 (76.2)	0.91
Peripheral vascular disease (n, %)	24 (8.9)	47 (8.4)	1 (5.0)	0.82
Cerebrovascular disease (n, %)	21 (7.8)	23 (4.1)	0 (0.0)	0.04
Cardiac arrhythmia (n, %)	28 (10.3)	84 (15.0)	4 (18.2)	0.15
Among those who had blood transfusion				
# units FFP (median, IQR)	0 (0–4)	0 (0–1)	2 (0–8)	0.002
# units RBC (median, IQR)	2 (2–4)	2 (1–3)	3 (2–8)	0.01
Perioperative glucose				
First glucose (median, IQR)	116 (102–141)	113 (100–133)	128.5 (116–158)	0.02
Median glucose (median, IQR)	135 (121–155)	131 (119–148)	151.5 (134–185)	0.005
Peak glucose (median, IQR)	171 (148–204)	167 (142–199)	203.5 (157–247)	0.01
Glucose range (median, IQR)	59 (37–95)	58 (37–95)	80.5 (61–132)	0.05

Notes: Data are presented as number, mean, median, percentage, or range. *Percentage of patients with information in medical record.

Abbreviations: DM, diabetes mellitus; FFP, fresh frozen plasma; HF, heart failure; ICU, intensive care unit; IQR, interquartile range; NYHA, New York Heart Association; RBC, red blood cell; SD, standard deviation.

However, the mortality group exhibited relatively more severe cardiovascular disease symptoms: 94.7% were in the class 3 or higher heart failure group, compared to 72.6% for the event group, and 63.6% for the no-event group ($P=0.006$). In terms of the number of diseased coronary vessels, the event group appeared to have more coronary-vessel disease than the no-event group (57.9% versus 50.4% had three diseased vessels), while the mortality group appeared to have less coronary vessel disease (38.1% had three diseased vessels; $P=0.08$). In addition, the mortality group had the highest percentage of aortic occlusion (77.3% compared to 30.6% for the event group and 41.8% for the no-event group; $P<0.001$). For surgery-related procedures, the mortality group had the highest percentage of cardiopulmonary bypasses (90.9% compared to 41.7% for the event group and

48.2% for the no-event group; $P<0.001$), and the highest percent of blood product use (59.1% versus 27.7% for the event group and 31.1% for the no-event group; $P=0.009$). However, the three groups had a similar prevalence for most major comorbidities, except immunosuppressive therapy (IMT) and cerebrovascular disease (CEVD): the mortality group had the highest prevalence of IMT (5% compared to 0% in the event group and 0.5% in the no-event group; $P=0.006$), while CEVD was more prevalent in the event-group (7.8% compared to 4.1% for the no-event group and 0% for the mortality group; $P=0.04$). In terms of perioperative glucose measurements, when we compared the first glucose (preoperative measure), median, peak, and range of repeated measurements, it appeared that the mortality group always had the highest glucose level (median of each of the above

measurements was about 20 units higher than the two other groups), followed by the event group, which was typically about 4 units higher than the no-event group ($P<0.05$).

The multivariate hazard ratios (HRs) are presented in Table 2, representing the adjusted hazard of developing postoperative cognitive disorders over time. Patient characteristics and common risk factors were adjusted in the model. As discussed, the hazard for postoperative neurocognitive disorders was significantly greater for women compared to men (HR = 4.18, 95% confidence interval [CI]: 1.33–13.14; $P=0.01$) and older age also presented as an increased hazard for females (HR = 1.04, 95% CI: 1.03–1.05; $P<0.001$). Higher heart failure classification (HFC) was associated with a higher hazard (HFC = 4 versus 1; HR = 4.95, 95% CI: 2.41–10.13; $P<0.001$), as well as utilization of intraoperative blood products (HR = 2.04, 95% CI: 1.77–2.35; $P<0.001$). Several comorbidities, such as diabetes and infectious endocarditis were significantly associated with study outcome (P -values <0.01). Notably, male patients with cardiopulmonary bypass (CPB) were at about a 15 times higher risk for postoperative cognitive disorders than female patients (HR = 15.6, 95% CI: 11.2–21.9, $P<0.001$).

After controlling for other common risk factors, we tested the association of glucose level with postoperative cognitive

disorders. Only the first glucose measurement, which was usually taken before surgery, was significantly associated with the outcome of interest: when measured by 20 unit increases in glucose level, the hazard increased by 16% (HR = 1.16, 95% CI: 1.13–1.20, $P<0.001$). Thus, after adjusting for possible risk factors, survival analysis using Cox-proportional hazard regression with competing risks indicates that patients with first glucose level higher than 170 mg/dL have worse long-term neurocognitive outcomes compared to those who had lower glucose level (Figure 1). Furthermore, we confirmed that the estimated time point where these two glucose levels begin to be statistically significant was at 379 days post-surgery ($P=0.03$).

Discussion

The main research question we sought to answer in this study was whether perioperative hyperglycemia was associated with new onset of postoperative neurocognitive disorders. As was shown, our findings suggest that patients who had perioperative hyperglycemia, as indicated by increased perioperative glucose levels, tended to develop postoperative neurocognitive disorders after cardiac surgery. These findings suggest that de-novo perioperative hyperglycemia may contribute to the mechanism of negative long term neurocognitive outcome.

Hyperglycemia is associated with negative overall outcome in critical care patients, especially neurological outcome after traumatic and ischemic brain injury;^{39,40} however, the mechanism is not well defined. It is unclear if high glucose concentration itself, or the mechanisms involved in glucose dysregulation, promote a negative outcome. Glucose is essential for the survival and growth of brain cells in culture. In fact, the concentration of glucose in optimized neuronal cell cultural media is higher than physiological concentrations,⁴¹ suggesting that neuronal function is better in a high glucose environment. Although an in vitro study did show evidence that high glucose concentrations induced neuronal cell death through oxidative stress and mitochondria dysfunction, it is not clinically relevant since the glucose concentrations in these experiments were much higher than that of clinical hyperglycemia.⁴² Several animal experiments have demonstrated the memory enhancing effects of glucose through facilitating the synthesis and release of acetylcholine in brain.⁴³ In a rat model of traumatic brain injury, intentionally elevated blood glucose prior to injury did not worsen motor or cognitive function post injury, and may have been neuroprotective by reducing edema around injured lesions.⁴⁴ Clamped hyperglycemia increased regional cerebral

Table 2 Multivariate Cox regression results showing risk factors for postoperative neurocognitive disorders

Variable	Level	Hazard ratio (95% CI)	P-value
Age at surgery	In years	1.04 (1.03–1.06)	<0.001
Sex	Female versus male	4.18 (1.33–13.14)	0.01
Age * sex	For female	1.04 (1.03–1.05)	<0.001
Heart failure classification	2 versus 1	0.43 (0.2–0.91)	0.03
	3 versus 1	3.48 (1.72–7.05)	<0.001
	4 versus 1	4.95 (2.41–10.13)	<0.001
Cardiopulmonary bypass (CPB)	Yes versus no	1.17 (0.82–1.68)	0.38
Cardiopulmonary bypass * sex	CPB versus no CPB for males	15.6 (11.2–21.9)	<0.001
Diabetes mellitus	Yes versus no	1.24 (1.08–1.43)	0.002
Infectious endocarditis	Yes versus no	1.44 (1.11–1.87)	0.006
Cardiac arrhythmia	Yes versus no	1.06 (0.91–1.22)	0.46
Intraoperative blood products (BPR)	Yes versus no	2.04 (1.77–2.35)	<0.001
Aortic occlusion	Yes versus no	0.54 (0.43–0.68)	<0.001
ICU stay	In days	1.08 (1.07–1.09)	<0.001
Number of diseased coronary vessels	1 versus 0	0.4 (0.29–0.55)	<0.001
	2 versus 0	1.71 (1.41–2.06)	<0.001
	3 versus 0	0.99 (0.82–1.20)	0.91
First glucose	In 20 units	1.16 (1.13–1.2)	<0.001

Abbreviations: CI, confidence interval; ICU, intensive care unit.

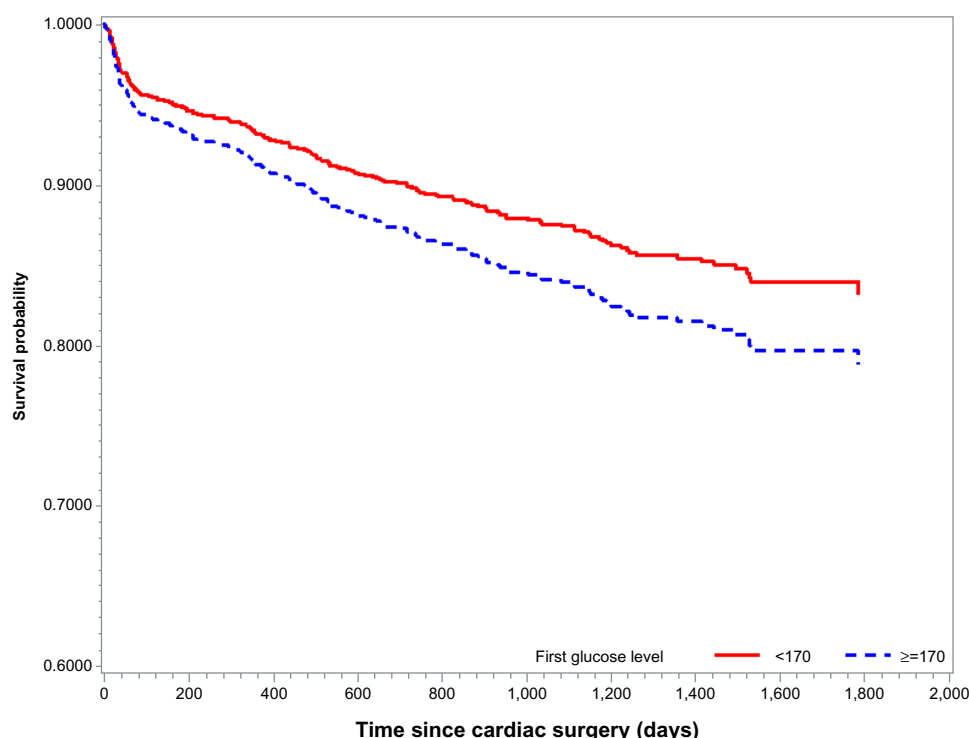


Figure 1 Cox-proportional hazard survival curves with competing risk for study outcome (adjusted for possible risk factors).*

Note: *The estimated time point where these two glucose levels begin to be statistically significant is at 379 days post-surgery ($P=0.03$).

oxygenation in rats subjected to cardiac arrest.⁴⁵ Injection of glucose into the rat hippocampus was found to reverse the memory deficit effect of gamma-Aminobutyric acid (GABA) receptor antagonist.⁴⁶ These research results suggest that glucose, as the obligate energetic fuel for the mammalian brain, is unlikely to be detrimental. Rather, the association between hyperglycemia and negative outcomes may be due to the malfunction of glucose regulation from insulin resistance during specific pathophysiological processes.

Perioperative hyperglycemia is commonly identified in patients with or without diagnosed diabetes mellitus.^{47,48} The mechanism could be stress induced insulin resistance, a neuroendocrine-mediated deterioration in glucose metabolism.⁴⁹ It is well accepted that controlling glucose is important for improving overall outcome in critical care patients, although strict insulin therapy for glucose is not recommended due to the high incidence of severe hypoglycemia.⁵⁰ Clinical studies showed patients with diabetes mellitus type II are subject to long term neurocognitive dysfunction, including Alzheimer's disease later in the life.^{51,52} Clinical studies have indicated that intranasal application of insulin improved cognition in early dementia.³⁵ A study has also shown that insulin resistance generated by knocking out a molecule in the insulin signaling pathway in mice hippocampi disrupts the formation of neuronal long-term potentiation, which

is critical for learning and memory.²⁹ Rats with induced type II diabetes have impaired proliferation of hippocampus neuroprogenitor cells.⁵³ The diabetic animals showed signs of deficits in motor function and spatial learning, had brain neurodegeneration similar to Alzheimer's disease, and had evidence of inhibition of the insulin signaling pathway.^{54,55} Delivery of insulin to the rat hippocampus can enhance spatial memory which is phosphoinositide 3-kinase dependent, and the blockade of endogenous insulin signaling impairs learning and memory.⁵⁶ Insulin resistance is associated with worse long term neurocognitive performance in rats with brain ischemia⁵⁷ and therapeutic intervention of preserving the function of the insulin signaling pathway can reduce hypoxic brain injury and improve behavioral recovery after ischemic insult.⁵⁸ In patients who underwent cardiac surgery, hypothermic cardiopulmonary bypass, which is known to be associated with negative postoperative neurocognitive outcome, exacerbates insulin resistance status.⁵⁹ Although not significant in our study, a history of diabetes was shown to be associated with postoperative cognitive decline in patients who underwent coronary artery bypass, suggesting that preoperative insulin resistance status could contribute to postoperative neurocognitive decline in patients who undergo cardiac surgery.^{4,60} Recent clinical trials found that routine perioperative application of insulin-glucose-potassium in

patients who underwent aortic valve replacement experienced improved outcome; this finding was associated with activation of phosphoinositide 3-kinase/protein kinase B (Akt) and adenosine monophosphate (AMP)-activated protein kinase (AMPK), both of which have an established role in the insulin signaling pathway.³⁷ Although it was not the end point of this study, the activation of insulin signaling suggest that routine, continuous perioperative insulin therapy, in addition to its glycemic effect, may have an advantage in improving neurological outcome.

The relationship between perioperative transfusion of blood products and postoperative neurocognitive outcome is not well studied in cardiac surgery. Studies over the past three decades have demonstrated severe neurological deficits after the transfusion of packed red blood cells.^{61–64} In our study, the negative neurocognitive outcome from fresh frozen plasma and cryoprecipitate transfusions (Table 1) could indicate that coagulopathy has a negative impact on the overall outcome in cardiac surgical patients. At the same time, transfusion of fresh frozen plasma may induce endothelial damage via immune activation in the central nervous system, which contributes to neurocognitive dysfunction. Further studies are warranted in order to confirm this association.

In the current study, NYHF class and longer postoperative intensive care unit (ICU) stay are predictors of postoperative neurocognitive outcome. This suggests that the overall severity of the patient's clinical condition is associated with neurological outcome. This is not surprising given that a patient with severe cardiac dysfunction is subject to hemodynamic instability, which could reduce brain perfusion causing chronic global brain ischemia.¹³ Patients with prolonged ICU stays frequently have a higher incidence of perioperative neurological and psychiatric complications, including ischemic and embolic stroke, and ICU delirium or psychosis.⁶⁵ Lastly, patients with longer postoperative ICU duration may have longer and higher dose exposures to hypnotic and sedative drugs, which may contribute to worse long term neurocognitive outcome.

In addition, our study suggests that female patients may be more vulnerable to postoperative neurocognitive disorders compared to male patients. Sex differences in neurological outcome after brain injury has been under extensive investigation recently. Although animal research suggests that female hormones may be neuroprotective, clinical findings are controversial with regard to sex effects on neurological outcome after brain injury.^{66–68} Recent clinical studies showed that female sex was associated with a reduced likelihood of returning to gainful occupation after stroke.⁶⁹ Hogue et al

found that females had worse performance postoperatively on visuospatial tasks up to 6 weeks after cardiac surgery.⁷⁰ In keeping with clinical studies, our data also suggest that female patients have an increased risk for developing neurocognitive disorders post-cardiac surgery.

The current study is subject to several limitations. First, this is a single center retrospective study and all recruited patients belonged to the cardiac surgery cohort within the study time frame; we were not able to recruit normal and/or non-cardiac surgical patients as control groups due to study limitations. In addition, the types of surgery and anesthesia are two major confounding factors in this study. Second, since the follow up time is equal to or less than approximately 5 years, this may limit the ability to detect the new onset of neurocognitive disorders in some patients. The weaker association after adjusting for other significant covariates in multivariable Cox model could be explained in part by our relatively short follow-up time, leading to an underestimation of the incidence of long-term neurocognitive disorders. Moreover, the eligible cases retrospectively identified in the current study from a single medical center may have biased our study findings. Third, formal neurocognitive tests were not available for analyses in the current study, since these tests are generally neither part of the routine preoperative assessment nor were these tests done during the follow-up period. This limited our ability of identifying short and long term cognitive decline after surgery, especially in a more quantitative way. Fourth, the use of perioperative glucose level as the surrogate marker for insulin resistance status is another limitation; we were not able to directly quantify insulin resistance in the current study due to the fact that blood insulin concentration was unknown in most of the patients undergoing cardiac surgery in our study. Fifth, our perioperative glucose measures did not specifically include only fasting glucose measures; this information was not available for the current study.

In summary, the current study suggests that postoperative neurocognitive disorders may be associated with perioperative insulin resistance in cardiac surgery, with possible contributions of age, sex, transfusion of blood products, significant cardiac dysfunction, and length of postoperative ICU stay. Further clinical and basic research are needed to develop better protocols for improving neurocognitive outcomes by way of improving dysfunctional insulin pathways in the future.

Acknowledgments

This work was funded by the Geisinger Clinic Research Fund. We would like to thank Ms Amanda Bengier and Ms Mary Ann Blosky, RN, for their assistance in data collection

and project management, and Drs Alfred S Casale, Joel J Berberich, Xianren Wu and Thomas M Schieble for making this project possible.

Disclosure

The authors declare no conflicts of interest in this work.

References

- van Dijk D, Spoor M, Hijman R, et al; Octopus Study Group. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA*. 2007;297(7):701–708.
- Kozora E, Kongs S, Collins JF, et al. Cognitive outcomes after on-versus off-pump coronary artery bypass surgery. *Ann Thorac Surg*. 2010;90(4):1134–1141.
- Kadoi Y, Saito S, Fujita N, Goto F. Risk factors for cognitive dysfunction after coronary artery bypass graft surgery in patients with type 2 diabetes. *J Thorac Cardiovasc Surg*. 2005;129(3):576–583.
- Mathew JP, Mackensen GB, Phillips-Bute B, et al; Neurologic Outcome Research Group (NORG) of the Duke Heart Center. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. *Stroke*. 2009;40(3):880–887.
- Stanley TO, Mackensen GB, Grocott HP, et al; Neurological Outcome Research Group; CARE Investigators of the Duke Heart Center. The impact of postoperative atrial fibrillation on neurocognitive outcome after coronary artery bypass graft surgery. *Anesth Analg*. 2002;94(2):290–295.
- Anastasiadis K, Argiriadou H, Kosmidis MH, et al. Neurocognitive outcome after coronary artery bypass surgery using minimal versus conventional extracorporeal circulation: a randomised controlled pilot study. *Heart*. 2011;97(13):1082–1088.
- Porizka M, Sritesky M, Semrad M, Dobias M, Dohnalova A, Korinek J. Standard blood flow rates of cardiopulmonary bypass are adequate in awake on-pump cardiac surgery. *Eur J Cardiothorac Surg*. 2011;39(4):442–450.
- Grigore AM, Grocott HP, Mathew JP, et al; Neurologic Outcome Research Group of the Duke Heart Center. The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. *Anesth Analg*. 2002;94(1):4–10.
- Kawahara F, Kadoi Y, Saito S, Goto F, Fujita N. Slow rewarming improves jugular venous oxygen saturation during rewarming. *Acta Anaesthesiol Scand*. 2003;47(4):419–424.
- Yoshitani K, Kawaguchi M, Sugiyama N, et al. The association of high jugular bulb venous oxygen saturation with cognitive decline after hypothermic cardiopulmonary bypass. *Anesth Analg*. 2001;92(6):1370–1376.
- Venn GE, Patel RL, Chambers DJ. Cardiopulmonary bypass: perioperative cerebral blood flow and postoperative cognitive deficit. *Ann Thorac Surg*. 1995;59(5):1331–1335.
- Gerriets T, Schwarz N, Sammer G, et al. Protecting the brain from gaseous and solid micro-emboli during coronary artery bypass grafting: a randomized controlled trial. *Eur Heart J*. 2010;31(3):360–368.
- Boodhwani M, Rubens FD, Wozny D, et al. Predictors of early neurocognitive deficits in low-risk patients undergoing on-pump coronary artery bypass surgery. *Circulation*. 2006;114(Suppl 1):I461–I466.
- Cheng DC, Karski J, Peniston C, et al. Morbidity outcome in early versus conventional tracheal extubation after coronary artery bypass grafting: a prospective randomized controlled trial. *J Thorac Cardiovasc Surg*. 1996;112(3):755–764.
- Boodhwani M, Rubens F, Wozny D, Rodriguez R, Nathan HJ. Effects of sustained mild hypothermia on neurocognitive function after coronary artery bypass surgery: a randomized, double-blind study. *J Thorac Cardiovasc Surg*. 2007;134(6):1443–1450; discussion 1451–1452.
- Hammon JW, Stump DA, Butterworth JF, et al. Single crossclamp improves 6-month cognitive outcome in high-risk coronary bypass patients: the effect of reduced aortic manipulation. *J Thorac Cardiovasc Surg*. 2006;131(1):114–121.
- Charlson ME, Peterson JC, Krieger KH, et al. Improvement of outcomes after coronary artery bypass II: a randomized trial comparing intraoperative high versus customized mean arterial pressure. *J Card Surg*. 2007;22(6):465–472.
- Siepe M, Pfeiffer T, Gieringer A, et al. Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. *Eur J Cardiothorac Surg*. 2011;40(1):200–207.
- Gold JP, Torres KE, Maldarelli W, Zhuravlev I, Condit D, Wasnick J. Improving outcomes in coronary surgery: the impact of echo-directed aortic cannulation and perioperative hemodynamic management in 500 patients. *Ann Thorac Surg*. 2004;78(5):1579–1585.
- Haljan G, Maitland A, Buchan A, et al. The erythropoietin neuroprotective effect: assessment in CABG surgery (TENPEAKS): a randomized, double-blind, placebo controlled, proof-of-concept clinical trial. *Stroke*. 2009;40(8):2769–2775.
- Holinski S, Claus B, Alaraj N, et al. Cerebroprotective effect of piracetam in patients undergoing open heart surgery. *Ann Thorac Cardiovasc Surg*. 2011;17(2):137–142.
- Hudetz JA, Iqbal Z, Gandhi SD, et al. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. *Acta Anaesthesiol Scand*. 2009;53(7):864–872.
- Silbert BS, Scott DA, Evered LA, et al. A comparison of the effect of high- and low-dose fentanyl on the incidence of postoperative cognitive dysfunction after coronary artery bypass surgery in the elderly. *Anesthesiology*. 2006;104(6):1137–1145.
- Szalma I, Kiss A, Kardos L, et al. Piracetam prevents cognitive decline in coronary artery bypass: a randomized trial versus placebo. *Ann Thorac Surg*. 2006;82(4):1430–1435.
- Ingels C, Debaveye Y, Milants I, et al. Strict blood glucose control with insulin during intensive care after cardiac surgery: impact on 4-years survival, dependency on medical care, and quality-of-life. *Eur Heart J*. 2006;27(22):2716–2724.
- Winocur G, Greenwood CE, Piroli GG, et al. Memory impairment in obese Zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity. *Behav Neurosci*. 2005;119(5):1389–1395.
- Saczynski JS, Jónsdóttir MK, Garcia ME, et al. Cognitive impairment: an increasingly important complication of type 2 diabetes: the age, gene/environment susceptibility – Reykjavik study. *Am J Epidemiol*. 2008;168(10):1132–1139.
- Faivre E, Gault VA, Thorens B, Hölscher C. Glucose-dependent insulinotropic polypeptide receptor knockout mice are impaired in learning, synaptic plasticity, and neurogenesis. *J Neurophysiol*. 2011;105(4):1574–1580.
- Martin ED, Sánchez-Perez A, Trejo JL, et al. IRS-2 Deficiency impairs NMDA receptor-dependent long-term potentiation. *Cereb Cortex*. 2012;22(8):1717–1727.
- Sanderson TH, Kumar R, Murariu-Dobrin AC, Page AB, Krause GS, Sullivan JM. Insulin activates the PI3K-Akt survival pathway in vulnerable neurons following global brain ischemia. *Neurol Res*. 2009;31(9):947–958.
- Suh SW, Gum ET, Hamby AM, Chan PH, Swanson RA. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. *J Clin Invest*. 2007;117(4):910–918.
- Zhang X, Chen Y, Ikonovic MD, et al. Increased phosphorylation of protein kinase B and related substrates after traumatic brain injury in humans and rats. *J Cereb Blood Flow Metab*. 2006;26(7):915–926.
- Hui L, Pei DS, Zhang QG, Guan QH, Zhang GY. The neuroprotection of insulin on ischemic brain injury in rat hippocampus through negative regulation of JNK signaling pathway by PI3K/Akt activation. *Brain Res*. 2005;1052(1):1–9.

34. Voll CL, Auer RN. Insulin attenuates ischemic brain damage independent of its hypoglycemic effect. *J Cereb Blood Flow Metab.* 1991;11(6):1006–1014.
35. Reger MA, Watson GS, Green PS, et al. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. *Neurology.* 2008;70(6):440–448.
36. Bucciarelli-Ducci C, Bianchi M, De Luca L, et al. Effects of glucose-insulin-potassium infusion on myocardial perfusion and left ventricular remodeling in patients treated with primary angioplasty for ST-elevation acute myocardial infarction. *Am J Cardiol.* 2006;98(10):1349–1353.
37. Howell NJ, Ashrafian H, Drury NE, et al. Glucose-insulin-potassium reduces the incidence of low cardiac output episodes after aortic valve replacement for aortic stenosis in patients with left ventricular hypertrophy: results from the Hypertrophy, Insulin, Glucose, and Electrolytes (HINGE) trial. *Circulation.* 2011;123(2):170–177.
38. Fine JP, Gray RJ. A proportional hazards model for the sub-distribution of a competing risk. *J Am Stat Assoc.* 1999;94:496–509.
39. Bruno A, Biller J, Adams HP, et al. Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *Neurology.* 1999;52(2):280–284.
40. Gore DC, Chinkes D, Heggors J, Herndon DN, Wolf SE, Desai M. Association of hyperglycemia with increased mortality after severe burn injury. *J Trauma.* 2001;51(3):540–544.
41. Dennis SH, Jaafari N, Cimarosti H, Hanley JG, Henley JM, Mellor JR. Oxygen/glucose deprivation induces a reduction in synaptic AMPA receptors on hippocampal CA3 neurons mediated by mGluR1 and adenosine A3 receptors. *J Neurosci.* 2011;31(33):11941–11952.
42. Meyer LE, Machado LB, Santiago AP, et al. Mitochondrial creatine kinase activity prevents reactive oxygen species generation: antioxidant role of mitochondrial kinase-dependent ADP re-cycling activity. *J Biol Chem.* 2006;281(49):37361–37371.
43. Degroot A, Kornecook T, Quirion R, DeBow S, Parent MB. Glucose increases hippocampal extracellular acetylcholine levels upon activation of septal GABA receptors. *Brain Res.* 2003;979(1–2):71–77.
44. Hill J, Zhao J, Dash PK. High blood glucose does not adversely affect outcome in moderately brain-injured rodents. *J Neurotrauma.* 2010;27(8):1439–1448.
45. Lennmyr F, Molnar M, Basu S, Wiklund L. Cerebral effects of hyperglycemia in experimental cardiac arrest. *Crit Care Med.* 2010;38(8):1726–1732.
46. Krebs-Kraft DL, Parent MB. Hippocampal infusions of glucose reverse memory deficits produced by co-infusions of a GABA receptor agonist. *Neurobiol Learn Mem.* 2008;89(2):142–152.
47. Dungan K, Hall C, Schuster D, Osei K. Differential response between diabetes and stress-induced hyperglycaemia to algorithmic use of detemir and flexible mealtime aspart among stable postcardiac surgery patients requiring intravenous insulin. *Diabetes Obes Metab.* 2011;13(12):1130–1135.
48. Verhoeven JJ, Hokken-Koelega AC, den Brinker M, et al. Disturbance of glucose homeostasis after pediatric cardiac surgery. *Pediatr Cardiol.* 2011;32(2):131–138.
49. Pei D, Chen TW, Kuo YL, et al. The effect of surgical stress on insulin sensitivity, glucose effectiveness and acute insulin response to glucose load. *J Endocrinol Invest.* 2003;26(5):397–402.
50. Finfer S, Chittock DR, Su SY, et al; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360(13):1283–1297.
51. Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch Neurol.* 2011;68(1):51–57.
52. Williamson JD, Miller ME, Bryan RN, et al; ACCORD Study Group. The Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND): rationale, design, and methods. *Am J Cardiol.* 2007;99(12A):1121–1122.
53. Lang BT, Yan Y, Dempsey RJ, Vemuganti R. Impaired neurogenesis in adult type-2 diabetic rats. *Brain Res.* 2009;1258:25–33.
54. de la Monte SM, Tong M, Nguyen V, Setshedi M, Longato L, Wands JR. Ceramide-mediated insulin resistance and impairment of cognitive-motor functions. *J Alzheimers Dis.* 2010;21(3):967–984.
55. Tong M, Neusner A, Longato L, Lawton M, Wands JR, de la Monte SM. Nitrosamine exposure causes insulin resistance diseases: relevance to type 2 diabetes mellitus, non-alcoholic steatohepatitis, and Alzheimer's disease. *J Alzheimers Dis.* 2009;17(4):827–844.
56. McNay EC, Ong CT, McCrimmon RJ, Cresswell J, Bogan JS, Sherwin RS. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. *Neurobiol Learn Mem.* 2010;93(4):546–553.
57. Moreira T, Cebers G, Pickering C, Ostenson CG, Efendic S, Liljequist S. Diabetic Goto-Kakizaki rats display pronounced hyperglycemia and longer-lasting cognitive impairments following ischemia induced by cortical compression. *Neuroscience.* 2007;144(4):1169–1185.
58. Zhong J, Zhao L, Du Y, Wei G, Yao WG, Lee WH. Delayed IGF-1 treatment reduced long-term hypoxia-ischemia-induced brain damage and improved behavior recovery of immature rats. *Neurol Res.* 2009;31(5):483–489.
59. Anderson RE, Brismar K, Barr G, Ivert T. Effects of cardiopulmonary bypass on glucose homeostasis after coronary artery bypass surgery. *Eur J Cardiothorac Surg.* 2005;28(3):425–430.
60. Nötzold A, Michel K, Khattab AA, Sievers HH, Hüppe M. Diabetes mellitus increases adverse neurocognitive outcome after coronary artery bypass grafting surgery. *Thorac Cardiovasc Surg.* 2006;54(5):307–312.
61. Heo K, Park S, Lee JY, Lee BI, Lee SK. Post-transfusion posterior leukoencephalopathy with cytotoxic and vasogenic edema precipitated by vasospasm. *Cerebrovasc Dis.* 2003;15(3):230–233.
62. Nagasawa H, Kurita K, Wada M, Kawanami T, Kato T. Blood transfusion-induced irreversible brain damage. *J Neurol.* 2005;252(12):1541–1542.
63. Smith MJ, Le Roux PD, Elliott JP, Winn HR. Blood transfusion and increased risk for vasospasm and poor outcome after subarachnoid hemorrhage. *J Neurosurg.* 2004;101(1):1–7.
64. Yamada S, Koizumi A, Iso H, et al; JACC Study Group. History of blood transfusion before 1990 is a risk factor for stroke and cardiovascular diseases: the Japan collaborative cohort study (JACC study). *Cerebrovasc Dis.* 2005;20(3):164–171.
65. Nuttall GA, Kumar M, Murray MJ. No difference exists in the alteration of circadian rhythm between patients with and without intensive care unit psychosis. *Crit Care Med.* 1998;26(8):1351–1355.
66. Brazinova A, Mauritz W, Leitgeb J, et al. Outcomes of patients with severe traumatic brain injury who have Glasgow Coma Scale scores of 3 or 4 and are over 65 years old. *J Neurotrauma.* 2010;27(9):1549–1555.
67. Iverson KM, Hendricks AM, Kimerling R, et al. Psychiatric diagnoses and neurobehavioral symptom severity among OEF/OIF VA patients with deployment-related traumatic brain injury: a gender comparison. *Womens Health Issues.* 2011;21(Suppl 4):S210–S217.
68. Leitgeb J, Mauritz W, Brazinova A, et al. Effects of gender on outcomes after traumatic brain injury. *J Trauma.* 2011;71(6):1620–1626.
69. Hannerz H, Holbæk Pedersen B, Poulsen OM, Humle F, Andersen LL. A nationwide prospective cohort study on return to gainful occupation after stroke in Denmark 1996–2006. *BMJ Open.* 2011;1(2):e000180.
70. Hogue CW, Lillie R, Hershey T, et al. Gender influence on cognitive function after cardiac operation. *Ann Thorac Surg.* 2003;76(4):1119–1125.

Neuropsychiatric Disease and Treatment**Dovepress****Publish your work in this journal**

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the 'PsycINFO' database and CAS.

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>