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SCIENTIFIC ARTICLE

The effect of two different glycemic management protocols on postoperative cognitive dysfunction in coronary artery bypass surgery

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Abstract
Introduction: Postoperative cognitive dysfunction (POCD) is an adverse outcome of surgery that is more common after open heart procedures. The aim of this study is to investigate the role of tightly controlled blood glucose levels during coronary artery surgery on early and late cognitive decline.
Methods: 40 patients older than 50 years undergoing elective coronary surgery were randomized into two groups. In the ''Tight Control'' group (GI), the glycemia was maintained between 80 and 120 mg dL^{-1} while in the ''Liberal'' group (GII), it ranged between 80–180 mg dL^{-1}. A neuropsychological test battery was performed three times: baseline before surgery and follow-up first and 12th weeks, postoperatively. POCD was defined as a drop of one standard deviation from baseline on two or more tests.
Results: At the postoperative first week, neurocognitive tests showed that 10 patients in the GI and 11 patients in GII had POCD. The incidence of early POCD was similar between groups. However the late assessment revealed that cognitive dysfunction persisted in five patients in the GII whereas none was rated as cognitively impaired in GI ($p = 0.047$).
Conclusion: We suggest that tight perioperative glycemic control in coronary surgery may play a role in preventing persistent cognitive impairment.
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PALAVRAS-CHAVE
Controle glicêmico;
Disfunção cognitiva;
Cirurgia de revascularização do miocárdio

Efeito de dois protocolos de controle glicêmico diferentes sobre a disfunção cognitiva após cirurgia de revascularização do miocárdio

Resumo

Introdução: A disfunção cognitiva pós-operatória (DCPO) é um resultado adverso cirúrgico que é mais comum após cirurgias cardíacas abertas. O objetivo deste estudo foi investigar o papel dos níveis de glicose no sangue rigorosamente controlados durante a cirurgia coronariana no declínio cognitivo precoce e tardio.

Métodos: Quarenta pacientes com idades acima de 50 anos e submetidos à cirurgia coronariana eletiva foram randomizados em dois grupos. No grupo ''controle rigoroso'' (GI), a glicemia foi mantida entre 80-120 $mg.dL^{-1}$; enquanto no grupo ''liberal'' (GII), variou entre 80-180 $mg.dL^{-1}$. A bateria de testes neuropsicológicos foi realizada três vezes: fase basal, antes da cirurgia e na primeira e décima segunda semana de acompanhamento no pós-operatório. DCPO foi definida como uma queda de um desvio padrão da fase basal em dois ou mais testes.

Resultados: Na primeira semana de pós-operatório, os testes neurocognitivos mostraram que 10 pacientes no GI e 11 pacientes no GII apresentaram DCPO. A incidência de DCPO precoce foi semelhante entre os grupos. No entanto, a avaliação tardia revelou que a disfunção cognitiva persistiu em cinco pacientes no GII, enquanto nenhum paciente foi classificado como cognitivamente prejudicado no GI ($p = 0,047$).

Conclusão: Sugerimos que o controle glicêmico rigoroso no perioperatório de cirurgia coronariana pode desempenhar um papel na prevenção da deterioração cognitiva persistente.
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Introduction

Postoperative cognitive dysfunction (POCD) is an intellectual decline related to surgery. Older patients undergoing major surgery are at increased risk of POCD that covers a broad clinical spectrum ranging from mild concentration difficulties to serious behavioral problems that can be easily confounded with delirium.[1,2] The problem can be transient but also persist for a longer period. In the early phase, POCD causes prolonged hospitalization and can disrupt quality of life by complicating the rehabilitation period. POCD also affects the mortality rate in the long term.[3,4] Finally, although the mechanisms are not clear, POCD is a debatable risk factor for delayed and chronic changes associated to dementia and Alzheimer's disease.[5]

Cognitive decline after cardiac surgery is more frequent compared to non-cardiac major surgery. The incidence rate varies between 25% and 80% according to various studies.[6,7] Recent advances in the perioperative management including surgical techniques, anesthetic choice, and perfusion strategies have decreased the incidence rate of major complications. However, the frequency of cognitive decline after open heart surgery has not improved. The etiology of POCD related to cardiac surgery is multifactorial, and various preoperative and intraoperative factors are associated with the disorder. Cerebral hypoperfusion due to microembolization or systemic hypotension, serious inflammatory response to extracorporeal circulation and to surgical stimuli, temperature perturbations, and metabolic instability are the most common etiologic factors.[8,9]

Hyperglycemia induced by open heart procedures causes a series of adverse events, including serious arrhythmias, low output state, and infections, and results in a prolonged stay in the intensive care unit with delay in hospital discharge.[10,11] The hyperglycemic state triggered by cardiac surgery may also be harmful to the hypoperfused brain and worsen the neurologic status analogous to that stroke patients.[12] Cognitive deterioration in cardiac surgery can be associated and/or aggravated by this ''diabetic state'' of those patients and be restrained to some extent by controlling glucose levels during the operative period.

The aim of the present study is to investigate the role of tightly controlled blood glucose levels during coronary artery surgery in order to prevent early and late postoperative cognitive dysfunction.

Methods

The study was designed and conducted as a prospective, double-blind, randomized clinical trial. The physician performing the neuropsychological tests and the patients were blinded to the perioperative glycemic management.

Patients older than 50 years with preserved left ventricular systolic function undergoing coronary artery bypass (CABG) surgery who had at least primary school education, were included in the study after institutional ethical committee approval (1571/1405-09) and written informed consent from each patient were obtained. The exclusion criteria was determined as; drug and alcohol addiction, major psychiatric and central nervous system diseases, major antidepressive treatment, American Society of Anesthesiologists (ASA) status higher than III, preoperative infection, serious organ failure, and combined or urgent operations.

In addition to these medical conditions, patients with communication problems due to serious sight and hearing defects, inadequate use of native language, and lack of reading and writing skills were excluded. Finally, patients who scored less than 23 on the Mini-Mental State Examination (MMSE) at the initial evaluation were excluded in order to eliminate the population who already had cognitive impairment.

Anesthesia induction was achieved with 10–15 $\mu g\,kg^{-1}$ fentanyl, 0.1–0.2 $mg\,kg^{-1}$ midazolam, and 0.1 $mg\,kg^{-1}$ vecuronium bromide. Sevoflurane based inhalational anesthesia and fentanyl infusion with supplemental vecuronium bromide doses were used for maintenance including the cardiopulmonary bypass period. Pressure-controlled mechanical ventilation with FiO_2: 0.5, inspiratory pressure level to obtain a tidal volume of 8 $mL\,kg^{-1}$, respiratory frequency to obtain an $ETCO_2$ of 40–45 mmHg, and 5 cm H_2O PEEP were adjusted. During the cardiopulmonary bypass, the lungs were passively deflated.

All patients were operated on by the same surgical team at 32 °C and a mild level of hemodilution (Hct: 26–28%). Pump flow rates were adjusted to 2.5 $L\,min^{-1}$ per m^2 for the normothermic phase and 2.25–2.5 $L\,min^{-1}$ per m^2 for the hypothermic phase during which the target systemic arterial pressure was 70 mmHg. Intermittent antegrade blood cardioplegia was applied in a 20 $mL\,kg^{-1}$ induction dose and 10 $mL\,kg^{-1}$ in every 30 min as maintenance. At the end of the intervention, patients were transferred to the intensive care unit under propofol and midazolam sedation and controlled ventilation. The weaning process from sedation, mechanical ventilation, and inotropic support was managed by the intensive care team according to their routine clinical procedure. Regarding to study protocol all abnormal (lower or higher than the limits) laboratory results of any parameter during routine measurements of any parameter which can possibly affect the glucose level, such as blood Na level has been observed. Finally the need for postoperative inotropic support and mechanical ventilation time were recorded for every patient.

Glucose control

After anesthesia induction, patients were randomized into two groups according to the sealed envelope system. Diabetic patients were included to the same randomization process regardless of the type of the disease. The GIK solution, which is our routine application for intraoperative management of diabetic patients during cardiac and noncardiac surgery, is used for all diabetic patients in both groups before the initiation of additive insulin infusion to achieve targeted glucose levels.

In the tight glucose control group (GI), the blood glucose level was maintained between 80 and 120 $mg\,dL^{-1}$ while in the second group, named the liberal glucose control (GII), the blood glucose level ranged between 80 and 180 $mg\,dL^{-1}$. This is a similar way of grouping to previous study to examining ''tight glucose control'' strategy.[13]

In order to achieve this target, Group I patients received an insulin infusion when their blood glucose level exceeded 120 $mg\,dL^{-1}$. The rate was adjusted in response to their actual blood glucose level (Table 1). A glucose–insulin–potassium (GIK) solution (10 U insulin and 10 mEq KCl added to 500 mL; 5% dextrose in water) was applied to the GI patients with diabetes mellitus. The infusion rate was set to 40 $mL\,h^{-1}$ when the blood glucose level was between 80 and 100 $mg\,dL^{-1}$. The rate was increased to 60 $mL\,h^{-1}$ when the blood glucose level was between 100 and 120 $mg\,dL^{-1}$. When the blood glucose level was higher than 120 $mg\,dL^{-1}$, additional insulin infusion was started as shown in Table 1.

Table 1 Insulin infusion rates for the tight glucose control group (GI).

Blood glucose level ($mg\,dL^{-1}$)	Insulin rate ($U\,h^{-1}$)
120–149	1.5
150–179	2
180–209	3
210–239	4
240–269	5
270–299	6
300–329	7
330–359	8
>360	12

Table 2 Insulin infusion rates for the liberal glucose control group (GII).

Blood glucose level ($mg\,dL^{-1}$)	Insulin rate ($U\,h^{-1}$)
180–239	2
240–299	3
300–359	5
>360	6

Liberal glucose regimen was maintained in the GII by starting the insulin infusion when blood glucose level was greater than 180 $mg\,dL^{-1}$. Insulin infusion was applied according to the rates shown in Table 2. Diabetic patients in the liberal group were managed with an infusion of the GIK solution at a rate adjusted to their glucose level. The infusion rate was 40 $mL\,h^{-1}$ when the blood glucose level was between 80 and 100 $mg\,dL^{-1}$, 60 $mL\,h^{-1}$ when the blood glucose level was between 100 and 120 $mg\,dL^{-1}$, 80 $mL\,h^{-1}$ when the blood glucose level was between 120 and 150 $mg\,dL^{-1}$, and 100 $mL\,h^{-1}$ when the blood glucose level was between 150 and 180 $mg\,dL^{-1}$. Additional insulin infusion was started when the blood glucose level was higher than 180 $mg\,dL^{-1}$ as shown in Table 2.

Following surgery, patients received an insulin regimen applied as shown in Table 3. Blood glucose levels were measured in every 30 min during the study period from an arterial blood sample which was obtained from the patient's arterial line. The sample was analyzed in a standard blood gas analyzer (ABL 707, Radiometer, Copenhagen, Denmark). Intraoperatively, whenever the blood glucose level was below 60 $mg\,dL^{-1}$, 50 mL bolus of 50% dextrose in water was used. Postoperatively, when the blood glucose level was <80 $mg\,dL^{-1}$, 50 mL bolus of 30% dextrose in water was used for the patients. The insulin protocol was continued during first 24 h postoperatively.

Table 3 Postoperative glucose control infusion for all patients.

Blood glucose level (mg dL^{-1})	Insulin rate (U h^{-1})	Insulin bolus (U)
80–99	0.5	–
100–124	1	–
125–159	2	–
160–199	4	–
200–234	6	–
235–274	8	3
> 274	8	5

Neuropsychological assessment

Cognitive function was assessed by an investigator blinded to the perioperative glycemic approach. An initial MMSE was performed, and patient eligibility was determined according to the score obtained on this first assessment. The MMSE is a quantitative and practical testing used to detect a patient's cognitive status such as orientation, memory, attention, language, and visuo-spatial functioning. If patients scored more than 23 on the MMSE, they were considered eligible for the study and were assessed with a comprehensive neuropsychological test battery that included the Weschler Memory Scale (WMS) – Logical Memory subtest (detects short-term and long-term memory, with two different stories pre-and postoperatively), the Clock Drawing Test (detects planning ability), the Word List Generation Test (detects sustained attention also called perseverance), the Digit Span subtest (detects global attention, concentration) and the Visuo-Spatial Skills Test (detects perceptual functions).

Except for the MMSE, all patients were examined the day before surgery (baseline), postoperatively at the first week (early), and at 12th week (late). All evaluation was conducted by the same anesthesiologist who was blinded to perioperative glycemic management and who was trained and supervised by the faculty's Neurology Clinic's consultants during the entire study period. The neuropsychological test battery lasted approximately 45 min. All tests were administered in same time of day and same location, a private room at surgical service.

Postoperative cognitive dysfunction (early or late) was defined as a drop of 1 standard deviation from baseline on two or more neuropsychological tests as described by Höcker et al. in their recent study.[14] Because of the lack of a non-surgical control group, the cognitive function evaluation was performed only as a between-group comparison. The standard deviation (SD) of each preoperative test was calculated, and the number of patients who deteriorated or improved postoperatively was determined.[14]

The primary outcome was determined as the incidence of early and late POCD and secondary was the frequency of hypoglycemic episodes seen during study period. Data were analyzed with the Prisma 5.0 statistic package (Graphpad Software Incorp, Layola, CA, USA). All values are presented as the mean ± standard deviation. Categorical data were analyzed with Fisher's exact test and the Mann–Whitney *U* test and repeated measures of ANOVA test was used for comparing continuous data. A *p*-value less than 0.05 was accepted as significant.

Table 4 Demographic and preoperative data.

	Tight control ($n = 20$)	Liberal control ($n = 20$)
Age (year)	58.5 ± 8.5	60 ± 8
Sex (M/F)	19/1	19/1
Body mass index	26.9 ± 3.14	28.2 ± 3.64
Diabetes mellitus (P/NP)	10/10	10/10
Duration of DM (years) Min-max (median)	4–22 (9)	2–16 (8.5)
Diabetes type (I/II)	7/3	4/6
Creatinine (mg dL^{-1})	1.05 ± 1.01	1.02 ± 0.63
Documented carotid stenosis (P/NP)	1/19	1/19
Euroscore	3.3 ± 1.68	3.8 ± 2.14
Average education level (year)	8.2 ± 2.7	8.8 ± 3.2

P, present; NP, not present.

Table 5 Operative data.

	Tight control ($n = 20$)	Liberal control ($n = 20$)
Operation time (min)	304.7 ± 53.4	280 ± 51
CPB time (min)	119 ± 17.6	110 ± 9.7
Cross clamp time (min)	59.75 ± 10.6	56.8 ± 7.9
Minimum temperature during CPB (°C)	29.05 ± 0.97	28.95 ± 1.2
Minimum hematocrit during CPB (%)	29.29 ± 1.72	29.46 ± 1.65
Proximal anastomosis number	2.7 ± 0.73	3.0 5 ± 0.75
Need for defibrillation at the end of CPB (P/NP)	5/15	4/16
Inotrope use (patients)	17	18
Fluid balance at the end of surgery (mL)	1758 ± 580	1424 ± 414
Mechanical ventilation time in ICU (h)	6.85 ± 1.42	6.95 ± 1.6

P, present; NP, not present; CPB, cardiopulmonary bypass.

Results

Forty patients for elective coronary surgery were included in this study. The demographic and operative data of 40 participants are shown in Tables 4 and 5. The patients in the two groups were comparable according to the demographic characteristic and educational level. The preoperative medical status of patients, including the incidence and insulin dependency of diabetes mellitus and carotid stenosis diagnosed by Doppler ultrasonography were comparable. Similarly, the statistical analysis of operative data that could influence the

Table 6 Blood glucose levels ($mg\,dL^{-1}$) during study period.

	Tight control: GI ($n=20$)	Liberal control: GII ($n=20$)
T0 – baseline	124.65 ± 26.09[a]	125.08 ± 24.50
T1 – 30 min	110.95 ± 19.69[a,c]	156.75 ± 22.08[b]
T2 – 60 min	108.15 ± 22.86[a,c]	167.25 ± 25.63[b]
T3 – 120 min	108.20 ± 29.21[a,c]	153 ± 25.29[b]
T4 – 180 min	118.6 ± 27.17[a,c]	169.83 ± 28.93[b]
T5 – 240 min	117.2 ± 22.87[a,c]	164.33 ± 29.50[b]
T6 – End of surgery	115.45 ± 12.74[a,c]	163.08 ± 25.63[b]
T7 – ICU 1st hour	108.75 ± 12.36[a,c]	169.5 ± 28.55[b]
T8 – ICU 12th hour	121.20 ± 15.81[a,c]	164.16 ± 25.49[b]
T9 – ICU 24th hour	142.90 ± 17.90[d]	160.41 ± 26.83[b]

[a] $p<0.001$ compared to T9.
[b] $p<0.01$ compared to T0.
[c] $p<0.0001$ compared to GII.
[d] $p=0.03$ compared to GII.

neuropsychological prognosis during coronary artery surgery did not show any significant difference between the tight (GI) and liberal glucose control (GII) groups. There was no major cardiac (new myocardial ischemia, serious arrhythmias, refractory low output state) or neurologic (stroke) complications observed during perioperative period in any patients.

Blood glucose values obtained during study period is shown in Table 6. Hypoglycemic episodes (<60 $mg\,dL^{-1}$ intraoperatively, <80 $mg\,dL^{-1}$ in the postoperative period) were recorded in 4 patients in the tight control group during the study period and appropriately treated according to the protocol. None of the liberal group experienced hypoglycemic attack. All 4 hypoglycemia cases were observed during surgery, and no hypoglycemia occurred in the postoperative period. The statistical comparison of the incidence of perioperative hypoglycemic attacks between groups showed no difference ($p=0.104$). Although statistically without significance, the difference in hypoglycemia frequency between the groups seems notable.

At the postoperative first week, neuropsychological testing revealed that 10 patients (50%) in GI and 11 patients (55%) in GII had a cognitive decline according to pre-defined criteria described.[12] The incidence of early POCD at the first postoperative week was similar and independent of glycemic management.

Late neuropsychological evaluation 3 months after surgery revealed that the cognitive dysfunction persisted in 5 patients (25%) in GII while all patients in GI had returned to normal cognition ($p=0.047$). Two of these stable POCD patients had a history of diabetes type II. Scrutiny of the neuropsychological tests for this stable POCD of GII showed that one patient was impaired in all of 5 tests, followed by one in 3 of 5, and the remaining three in 2 of 5 (Table 7).

Discussion

In this pilot study examining the effect of perioperative glycemic management on postoperative cognitive dysfunction (POCD) in patients undergoing coronary artery surgery, no difference in the incidence of early POCD was found between the tight and liberal control groups. However, assessments at 3 months after surgery showed a return to preoperative levels in all patients in the tight control group. Conversely 5 of the liberal group had persistent POCD at late assessment. As expected, hypoglycemic episodes were more frequent in the tight glucose control group during the study period, although the difference did not reach statistical significance.

Cognitive impairment occurring after cardiac surgery is thought to result from a combination of factors such as global hypoperfusion, cerebral microembolism, imbalance between cerebral oxygen demand and consumption during rewarming, and possible blood-brain barrier dysfunction.[8,15] It is estimated that POCD occurs in 7–28% of patients 7–10 days after general surgery.[16] In patients undergoing cardiac surgery, much higher incidence rates such as 20–70% have been observed.[17] Concordant with these reports, 52.5% of our patients (21/40) in the overall study population had POCD during the early postoperative period without any difference between groups. This finding appears to suggest at first glance the absence of an association between early postoperative cognitive decline and perioperative glycemic control; this is probably due to the major role of hypoperfusion and microembolism in the development of early POCD.

This study was based on the hypothesis that glycemic control could influence the subsequent course of early POCD, which occurs in nearly half of the cases, either assuming a course toward recovery or persistence at 3 months after the surgical procedure. Intermediate and long-term assessments of cognitive functions generally span a period of 3–12 months, and the reported long-term incidence rates for POCD are as low as 24% at 6 months

Table 7 Test results for patients with late POCD in the liberal control group.

Patient	Weschler Memory Scale	Clock Drawing Test	Word List Generation Test	Digit Span Test	Visuo-Spatial Skills Test
No. 4	**	**	**	**	**
No. 6	++	—	**	—	**
No. 7	—	**	**	++	—
No. 10	++	—	**	—	**
No. 16	**	**	—	++	**

**, deteriorated; —, not affected; ++, ameliorated.

compared to early postoperative results.[18] In our study, cognitive dysfunction was present in 25% of the patients (5/20) in the liberal control group, while no patients in the tight glucose control group had identifiable cognitive dysfunction at 3 months after surgery. We believe that this, i.e., significantly better cognitive status in the tight glucose control group, is the most important finding of our study.

Lactate accumulation and intracellular acidosis due to hyperglycemia have been shown to exert direct toxic effects on the ischemic brain in stroke cases which is further complicated by the neurotoxic effects of increased circulatory free fatty acid concentration due to inadequate insulin secretion.[19] Although the mechanisms responsible for cerebral ischemia during cardiac surgery are different, avoidance of hyperglycemia in a hypoperfused brain during cardiopulmonary bypass may be expected to attenuate some of the undesired effects of hyperglycemia. Clinical or experimental studies examining the adverse effects of hyperglycemia on ischemic and/or inflammatory cerebral injury have suggested that the principal mechanisms of hyperglycemia-induced neurotoxicity include the disruption of the blood-brain barrier[20] and increased concentration of excitatory amino acids.[21] Although debatable, cognitive decline persisting at third months postoperatively could easily accepted as permanent, and due to aforementioned mechanisms tight glucose control looks like improve neurocognitive recovery.

In a retrospective study by Puskas et al. that examined the association between intraoperative hyperglycemia and cognitive dysfunction, intraoperative hyperglycemia was shown to correlate with late (6 weeks) cognitive dysfunction in patients without diabetes.[22] The untoward effects of hyperglycemia on focal and global cerebral injury, which occurs commonly during cardiac surgery, have been proposed as a possible explanatory mechanism for their results. Interestingly, non-diabetic patients experienced more severe cognitive dysfunction compared to diabetics in that study. The latter finding was attributed to the low threshold value (200 $mg\,dL^{-1}$) of hyperglycemia for diabetic patients for whom the central nervous system may be rather accustomed to glycemia of this level.[22] In our study, there was homogeneous distribution of diabetic and non-diabetic patients across the groups, and early POCD occurred at a similar frequency in both subjects. However, of the 5 patients with late POCD in the liberal group 3 were diabetic, and 2 were non-diabetic.

In another study by Butterworth et al.[23] involving non-diabetic patients undergoing cardiac surgery, insulin infusion or placebo was given for blood glucose levels exceeding 100 $mg\,dL^{-1}$ during the cardiopulmonary bypass (CPB), and new occurrence of neurological, neuro-ophtalmological, and neurobehavioral disorders were assessed at weeks 1 and 6 and at month 6 post-surgically. The authors concluded that the glucose control strategy used for preventing hyperglycemia during CPB had no effect on the neurologic prognosis. The disagreement between these results with ours and Puskas et al.'s may arise from differences in defining POCD and methodological differences such as the restriction of the blood sugar control strategy to the duration of CPB.

Neuropsychological tests are an essential part of the assessment of cognitive functions. However, learnability of cognitive tests, particularly of those assessing the memory, is a well-known phenomenon. Not surprisingly, in our study, participants scored higher when they were exposed to memory and digit tests again later in the study. Research has suggested that preoperative anxiety or depression may also explain lower initial scores.[24] Despite the divergence of the conclusions in studies examining whether the diagnosis of POCD represents a real ''disorder'' or it is a diagnostic category derived from the invalidity of the tests, no other methods producing more objective and/or valid data than those currently available have been developed despite their limitations. In our study tests are predisposed to evaluate all intellectual domains such as memory, vigilance, mathematical thinking, and psychomotor abilities. Although the improvement in subsequent test results compared to the baseline can be explained based on a ''learning effect'',[25] this improvement was limited to patients in the tight glucose group in our study, suggesting that the perioperative glycemic control strategy might have contributed to the improvement.

Educational level is an important preoperative factor for POCD but conflicting data exists in this area. Newman et al. indicated that higher level of education can play a protective role against late POCD as seen in Alzheimer's disease[18] although higher level of education was found an independent risk factor for POCD in low risk CABG patients in Boodhwani et al.'s study.[26] Our study population, with an average of educational period consisting 8 years in both groups represents well the typical profile of the country which is stated as 7.6 years in a recent report.[27]

Other considerations in studies examining the glycemic management are target glucose levels, the treatment approach to reach or maintain these targets, and monitoring methods. Previously, target blood glucose levels between 80 and 110 $mg\,dL^{-1}$ were used, and a significant reduction in mortality was observed in intensive care unit patients when these targets are adopted.[28] However, since more recent studies suggested that such tight control not only fails to provide a prognostic advantage but also is associated with an increased risk of hypoglycemia, new target values, i.e., between 140 and 180 $mg\,dL^{-1}$, have been defined.[13] Generally, the current definition of ''tight glucose control'' involves blood glucose values between 110 and 200 $mg\,dL^{-1}$ in cardiac surgery and in intensive care unit patients.[29] In our study, blood glucose targets similar to those proposed by Ouattara et al. were used.[30] The Portland insulin infusion protocol[31] was adopted for blood glucose regulation in which monitoring was performed every 30 min. More patients in the tight glucose control group experienced episodes of hypoglycemia with this protocol, although the difference was not significant.

Our study has some limitations. First, the sample size is relatively small and further investigation with larger population is certainly required. The absence of a non-surgical control group that would allow us to rule out a learning effect must be addressed as another concern. We excluded urgent operations and patients with impaired left ventricular function so our results cannot be extrapolated to these situations and/or patients. Finally the late assessment for

POCD made at third postoperative month due to organizational difficulties can be considered relatively short. On the other hand, a recent systematic review revealed that the range for late POCD assessment after cardiac surgery vary between 6 weeks to 1 year.[32]

In conclusion, regardless of the method used for perioperative blood glucose control, almost half of patients undergoing coronary artery surgery, showed a significant decline in cognitive performance one week after surgery, meeting the diagnostic criteria for POCD. However, 3 months after the procedure, patients in the tight glucose control group were more likely to return to their baseline cognitive function compared to those in the liberal control group. These results suggest that intraoperative blood glucose control with established positive effects on neurological functions and wound healing in patients undergoing coronary artery surgery may also play a similar role in the preservation and quick recovery of cognitive functions.

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Conflicts of interest

The authors declare no conflicts of interest.

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