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Does uncontrolled diabetes mellitus affect cerebral hemodynamics in heart surgery?

Kalp cerrahisinde kontrolsüz diabetes mellitus serebral hemodinamikleri etkiler mi?

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ABSTRACT

Background: In this study, we aimed to investigate the effects of poor blood glucose control on the intraoperative cerebral system in patients undergoing coronary artery bypass grafting using various neuromonitors.

Methods: Between January 2011 and December 2011, a total of 40 adult patients (31 males, 9 females; mean age 58.8±9.2 years; range, 38 to 78 years) who were scheduled for elective coronary artery bypass grafting were included in the study. The patients were divided into four groups according to hemoglobin A1c levels as follows: Group 1 including non-diabetic controls (n=11); Group 2 including those with a hemoglobin A1c value of <7% (n=10); Group 3 including those with a hemoglobin A1c value of 7 to 10% (n=11); and Group 4 including those with a hemoglobin A1c value of ≥10% (n=8). Cerebral monitoring was performed with near-infrared spectroscopy and transcranial Doppler. Measurement periods were defined as follows: Before anesthesia induction (period 1), 10 min after anesthesia induction (period 2), during cannulation (period 3), 10 min after cardiopulmonary bypass (period 4), at 32°C temperature during cardiopulmonary bypass (period 5), at 36°C temperature during cardiopulmonary bypass (period 6), and at the end of the operation (period 7).

Results: There was a significant difference in the near-infrared spectroscopy values in the cannulation period for both right (p<0.001) and left (p=0.002) sides and the mean transcranial Doppler flow velocity (p=0.002) in Group 4, compared to Group 1. The heart rate was found to be significantly lower in Group 4 in the cannulation period. The near-infrared spectroscopy values and transcranial Doppler blood flow velocity decreased in Group 4 in all measurement periods.

Conclusion: The results of our study show that, in patients with severe diabetes undergoing open heart surgery, heart rate decreases in the cannulation period due to possible autonomic neuropathy, and cerebral blood flow and oxygenation decrease. For these patients, particularly in the cannulation period, perfusion of both cerebral and other organs should be closely monitored and necessary interventions should be performed.

Keywords: Cardiac anesthesia, cardiac surgery, diabetes mellitus, near-infrared spectroscopy, transcranial Doppler.

ÖZ

Amaç: Bu çalışmada, koroner arter baypas greftleme yapılan hastalarda çeşitli nöromonitörler ile kötü kan glukoz kontrolünün ameliyat sırası serebral sistem üzerine etkisi araştırıldı.

Çalışma planı: Ocak 2011 - Aralık 2011 tarihleri arasında elektif koroner arter baypas greftleme planlanan toplam 40 erişkin hasta (31 erkek, 9 kadın; ort. yaş 58.8±9.2 yıl; dağılım, 38-78 yıl) çalışmaya alındı. Hastalar hemoglobin A1c düzeylerine göre şu şekilde dört gruba ayrıldı: Grup 1, diyabetik olmayan kontroller (n=11); Grup 2, hemoglobin A1c düzeyi <%7 olanlar (n=10); Grup 3, hemoglobin A1c düzeyi %7 ila %10 olanlar (n=11) ve Grup 4, hemoglobin A1c düzeyi ≥%10 olanlar (n=8). Yakın kızılötesi spektroskopi ve transkraniyal Doppler ile serebral monitörizasyon yapıldı. Ölçüm dönemleri şu şekilde belirlendi: Anestezi indüksiyonundan önce (periyod 1), indüksiyondan 10 dk. sonra (periyod 2), kanülasyon sırasında (periyod 3), kardiyopulmoner baypastan 10 dk. sonra (periyod 4), kardiyopulmoner baypas sırasında 32°C'de (periyod 5), kardiyopulmoner bypass sırasında 36°C'de (periyod 6) ve operasyon sonunda (periyod 7).

Bulgular: Grup 1'e kıyasla Grup 4'te kanülasyon periyodunda yakın kızılötesi spektroskopi değerlerinde hem sağ (p<0.001) hem de sol (p=0.002) taraflarda ve ortalama transkraniyal Doppler kan akış hızında (p=0.002) anlamlı fark bulundu. Kanülasyon periyodunda Grup 4'te kalp hızı anlamlı düzeyde düşüktü. Tüm ölçüm periyotlarında yakın kızılötesi spektroskopi değerleri ve transkraniyal Doppler kan akış hızı Grup 4'te azalmıştı.

Sonuç: Çalışma sonuçlarımız, açık kalp ameliyatı geçiren ciddi diyabetli hastalarda kanülasyon periyodunda muhtemel otonom nöropati nedeniyle kalp hızının düştüğünü ve serebral kan akımı ve oksijenasyonun azaldığını göstermektedir. Bu hastalarda, özellikle kanülasyon periyodunda, hem serebral hem de diğer organların perfüzyonları yakından izlenmeli ve gerekli girişimler yapılmalıdır.

Anahtar sözcükler: Kardiyak anestezi, kalp cerrahisi, diyabetes mellitus, yakın kızılötesi spektroskopi, transkraniyal Doppler.

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Despite recent improvements in surgical and anesthesia methods, a high number of patients still experience neurological problems after cardiac surgery. Neurological sequelae in the postoperative period result in delayed discharge, impaired quality of life, and increased morbidity and mortality.[1] In the perioperative period, stroke affects about 1.5 to 5.2% of patients, encephalopathy about 8.4 to 32% of patients, and neurocognitive impairment about 20 to 30% of patients.[2-6] The main risk factor is diabetes mellitus (DM) in this patient population, which not only increases the tendency for cardiac diseases, but also disturbs cerebral perfusion and autoregulation during cardiopulmonary bypass (CPB), thereby, increasing the incidence of neurological problems.[7]

Near-infrared spectroscopy (NIRS) is a non-invasive, continuous trend-monitoring device in brain oxygenation monitoring. Compared to baseline values, more than 20% change in the regional oxygen saturation (rSO_2), more than 20% difference between two hemispheres, or a rSO_2 value of <45% indicate an impaired brain perfusion.[8] The main advantages of NIRS include its feasibility during hyperthermia, low flow perfusion, and cardiopulmonary arrest, as it is not dependent on pulse, pressure, or temperature.[8]

Transcranial Doppler (TCD) is a non-invasive ultrasound which provides neuromonitoring and measures from the thinnest temporal bone window of the scull with Doppler principles. In cardiac surgery, evaluation of the middle cerebral artery flow velocity, which carries 75 to 80% of the carotid artery blood flow, provides direct data on the cerebral blood flow. A reduction in the flow velocity by 70%, compared to baseline, indicates malperfusion.[9]

In the present study, we aimed to investigate the effects of poor blood glucose control on intraoperative cerebral hemodynamics in patients undergoing coronary artery bypass grafting (CABG).

PATIENTS AND METHODS

Between January 2011 and December 2011, a total of 40 adult patients (31 males, 9 females; mean age 58.8±9.2 years; range, 38 to 78 years) who were scheduled for elective CABG were included in this prospective, observational study. Exclusion criteria were as follows: emergency surgeries, previous cerebrovascular accident or neurological disorders, coronary surgeries in conjunction with other procedures. All patients were divided into four groups according to the hemoglobin A1c (HbA1c) levels. Group 1 consisted of non-diabetic control subjects (n=11); Group 2 consisted of patients with a HbA1c of <7% (n=10); Group 3 consisted of patients with a HbA1c of 7 to 10% (n=11); and Group 4 consisted of patients with a HbA1c of ≥10% (n=8). Demographic and clinical data, intraoperative data, postoperative complications, mortality, duration of intubation, intensive care unit (ICU) stay, and time to discharge were recorded. A written informed consent was obtained from each patient. The study protocol was approved by the institutional Ethics Committee of Ankara Yüksek İhtisas Training and Research Hospital (No: 20-412, Date: 13-12-2010). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Anesthetic management

All patients were administered 0.15 mg/kg^{-1} oral diazepam the night before surgery and 0.1 mg/kg^{-1} morphine 30 min before surgery. The patients were, then, taken to the operating room, and two peripheral veins and the left radial artery were cannulated. Pulse oximetry and electrocardiography were performed, and invasive artery pressure was monitored. Before anesthesia induction, the forehead skin was cleaned and the NIRS (INVOS Somanetics, 5100, Troy MI, USA) optods were placed into the bilateral frontal area, 1 cm above the eyebrow line. The velocity from the middle cerebral artery was examined with TCD. After preoxygenation anesthesia induction with 10 $\mu g/kg^{-1}$ fentanyl, 0.1 mg/kg^{-1} midazolam, 0.6 mg/kg^{-1} rocuronium bromide, and 1 mg/kg^{-1} lidocaine were administered. During the anesthesia maintenance, fentanyl, midazolam, and rocuronium bromide were applied through total intravenous anesthesia. After intubation, the respiration rate was set with 50% fraction of inspired oxygen, 6 mL/kg^{-1} tidal volume, and 35 to 45 mmHg partial pressure of carbon dioxide. Arterial oxygen pressure was optimized at 100 to 150 mmHg. Nasopharyngeal temperature was monitored. For the blood gas management during CPB, alpha-stat strategy was used. During surgery, no fresh frozen plasma was used, and no erythrocyte transfusion was applied, if hemoglobin value was not below 8 mg/dL^{-1}. Blood glucose regulation at a value of 120 to 180 mg/dL^{-1} was maintained using insulin infusion.

Surgical technique

After the left internal mammary artery was harvested with heparinization, venous and aortic cannulation were conducted. Cardiopulmonary bypass was initiated using a roller-pump, open reservoir, and Nipro® oxygenator with a target flow of 2.4 $L/min^{-1}/m^2$ at 36°C. Prime volume composition was composed of ringer lactate and other additives. The patient was

Table 1. Demographic and clinical characteristics of patients

	Group 1					Group 2					Group 3					Group 4					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			54.9±10.2					58.8±9.3					60.6±8.7					61.8±8.0			0.367
Body mass index (kg/m²)			28.8±5.0					29.2±4.4					30.7±6.3					28.7±3.2			0.388
Gender																					0.163
Male	8	25.8				6	19.8				11	35.5				6	19.4				
Female	3	33.3				4	44.4				0	0				2	22.2				
Hypertension	8	72.7				7	70				7	63.6				6	75				1.000
Duration of diabetes (year)			0					8.9±3.4					8±8.1					15±6.1			0.162
Oral anti-diabetic use	0	0				8	80				8	72				3	37				<0.001*
Insulin use	0	0				0	0				1	9.1				6	75				<0.001*
Hyperlipidemia	5	45				4	40				4	36				5	62				0.777
Ejection fraction				60	50-60				60	38-65				60	45-65				55	40-65	0.582

SD: Standard deviation; Min: Minimum; Max: Maximum; Kruskal-Wallis test was conducted for continuous variables and chi-square test for the categorical variables to assess the differences among four groups * p<0.05.

Table 2. Intra- and postoperative data

	Group 1			Group 2			Group 3			Group 4			
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*
Duration of surgery (min)		240	150-275		240	210-390		270	180-360		255	210-480	0.36
CPB time (min)	86±22.2			93±34			104±21.5			113.8±25.3			0.12
Cross-clamp time (min)	52.7±12.5			60.7±24.6			63.3±11.7			68.2±21.4			0.28
Extubation time (hour)		10	6-24		7.75	5-11		10	4-17		10.5	8-20	0.35
Length of ICU stay (day)		1	1-1		1	1-1		1	1-2		1	1-3	0.30
Time to discharge (day)		6	4-8		5.5	4-20		7	4-28		6.5	5-15	0.46
Mortality		0	0		0	0		0	0		0	0	

SD: Standard deviation; Min: Minimum; Max: Maximum; CPB: Cardiopulmonary bypass; ICU: Intensive care unit; Kruskal-Wallis test was conducted for continuous variables to assess the differences among four groups.

Table 3. Postoperative complications

	Group 1		Group 2		Group 3		Group 4		
	n	%	n	%	n	%	n	%	*p*
Inotropic support	1	9.1	2	20	1	9.1	4	50	0.139
IABP use	-	-	-	-	-	-	-	-	-
Pacemaker use	-	-	-	-	1	9.1	2	25	0.142
Myocardial infarction	-	-	-	-	-	-	-	-	-
Atrial fibrillation	-	-	-	-	-	-	1	12.5	0.20
Stroke	-	-	-	-	-	-	-	-	-
Hemodialysis	1	9.1	-	-	-	-	-	-	1.000
Delirium	-	-	-	-	-	-	-	-	-
Gastrointestinal bleeding	-	-	-	-	1	9.1	-	-	1.000

IABP: Intra-aortic balloon pump; Chi-square test was conducted for the categorical variables to assess the differences among four groups.

cooled at 32°C. After cardiac arrest was performed with anterograde crystalloid cardioplegia (Plegisol®), surgery was continued with 1:4 ratio mixed blood by retrograde cardioplegia with a-20-min interval. After distal anastomosis, cross-clamp was removed using hot blood cardioplegia, and proximal anastomosis was performed by side clamping. After decannulation, heparin effect was reversed by protamine, and CPB was terminated.

Neuromonitoring

The right and left rSO_2 values obtained with NIRS and hemodynamic data, blood gas analysis, temperature and blood glucose values were followed on a regular basis. The middle cerebral artery flow velocity obtained with TCD was recorded in prespecified time points. Measurement periods were set as follows: Before anesthesia induction (period 1), 10 min after anesthesia induction (period 2), during cannulation (period 3), 10 min after CPB (period 4), at 32°C temperature during cardiopulmonary bypass (period 5), at 36°C temperature during CPB (period 6), and at the end of the operation (period 7). For tracking cerebral oxygenation with NIRS, the flow chart described by Denault et al.[10] was used. When the rSO_2 value decreased more than 20%, compared to baseline, or the rSO_2 value was below 40%, the pallet locations, head position, and cannula positions were initially controlled and hemodynamic parameters and blood gas values were, then, analyzed. Accordingly, an intervention was made, if indicated.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 15.0 software (SPSS Inc., Chicago, IL, USA). Distribution of the variables were assessed using the Kolmogorov-Smirnov test and visual assessment were conducted via histograms. Descriptive data were expressed in mean ± standard deviation (SD) for normally distributed variables, median (min-max) for abnormally distributed variables, and in number and frequency for categorical variables. As the demographical variables were not distributed normally, the Kruskal-Wallis test was used to analyze median values among the groups. Categorical variables were evaluated using the Pearson chi-square or Fisher's exact test, and Bonferroni correction was conducted, if there was a significant difference among the groups. The Spearman's correlation test was used to analyze the correlation between the abnormally distributed continuous variables, while the Pearson's correlation test was used to analyze the correlation between the normally distributed variables. Repetitive measurements of continuous variables were done to analyze intra- and inter-group significant differences at prespecified time points using the general linear model repeated measures (for the differences between the groups), and Friedman test (for the differences within the group). In case of significant differences, post-hoc analyses were done for multiple comparisons at prespecified time points. P values of <0.05 and <0.008 for the Bonferroni correction were considered statistically significant.

RESULTS

Demographic data including age, gender, body mass index (BMI), and clinical characteristics including the presence of preoperative hypertension and hyperlipidemia and the mean preoperative ejection fraction were similar among four groups (Table 1). All groups, except Group 1, received oral antidiabetics and insulin. The highest rate of insulin use was in Group 4 (Table 1). Duration of cross-clamp, CPB, and operation were also found to be similar among the groups in the intraoperative period. In addition, extubation time, duration of ICU stay, and time to discharge were similar among the groups in the postoperative period (Table 2). Also, there was no significant differences in postoperative complications among the groups (Table 3). At all prespecified time points, the mean artery pressure was similar among the groups (Figure 1). However, the heart rate values were found to be significantly lower in Group 4 compared to the control group, in the cannulation period (period 3) ($p=0.045$) (Figure 2). On the other hand, hematocrit values did not significantly differ among the groups (Figure 3).

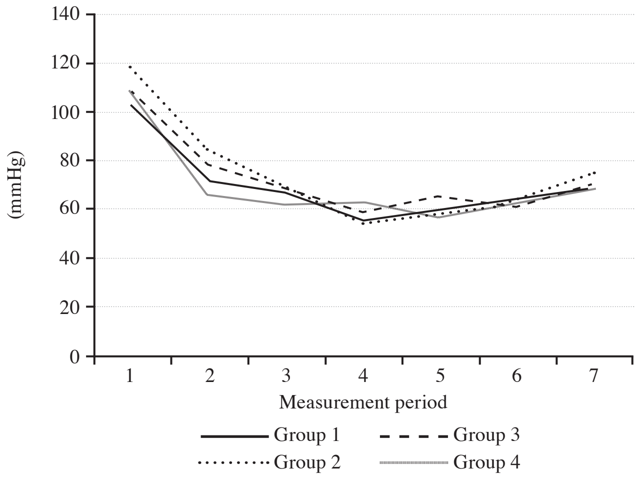

Figure 1. Mean arterial pressure (mmHg) for all measurement periods in four groups. There was no significant difference among the groups.

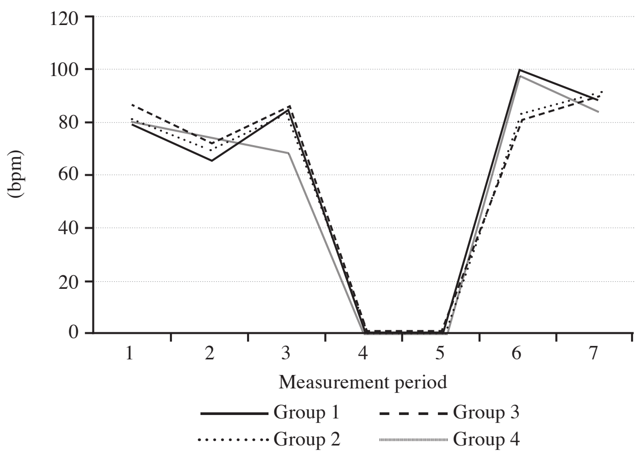

Figure 2. Heart rate (bpm) for all measurement periods in four groups. There was a difference between non-diabetic group 1 and uncontrolled diabetic Group 4 ($p=0.045$) in the measurement period 3. There were no data during the fourth and fifth measurment periods due to cardiopulmonary bypass.

The right and left rSO_2 values obtained by NIRS did not indicate bihemispheric lateralization among the groups. In general, rSO_2 values reduced in Group 4, compared to the other groups. However, this reduction was found to be significant only at the third measurement time point, which was the cannulation (the right rSO_2 $p<0.001$) and the left rSO_2 $p=0.002$, (Figure 4). In the cannulation period, the mean TCD flow velocity was found to be significantly lower in Group 4, compared to Group 1 ($p=0.002$) (Figure 5). However, there was no critical reduction in the NIRS values in any groups in any time points. Also, no reduction in the TCD measurements by 70% was seen, compared to the baseline values.

DISCUSSION

In the present study, we examined the effects of poor blood glucose control on intraoperative cerebral hemodynamics in patients undergoing CABG. Our study results showed that the heart rate, cerebral oxygenation values, and middle cerebral artery flow velocities significantly reduced in uncontrolled diabetic patients, compared to the non-diabetic patients, particularly in the cannulation period of open heart surgery.

It is well-established that cell functions of diabetic patients which are impaired due to hyperglycemia adversely affect the cerebrovascular circulation and vasodilatation reserves.[11,12] Cerebral vascular endothelial function, which is interrupted on nitric oxide pathway, results in impaired flow-perfusion system during CPB.[7] In addition to the expected cerebral changes in diabetic patients during CPB, several studies examined the periods in which cerebral desaturation occurred in patients who underwent heart surgery, irrespective of comorbidities. In these

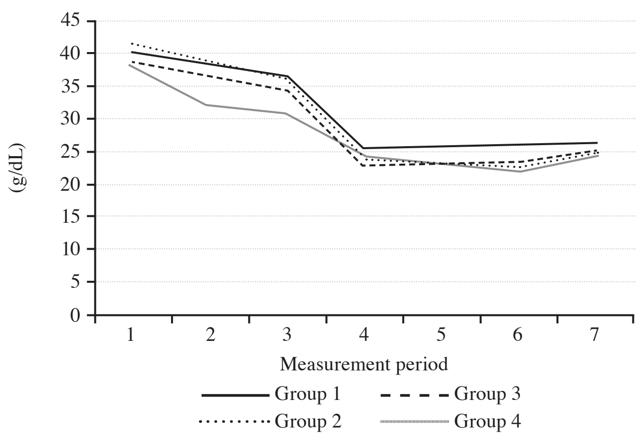

Figure 3. Hemotocrit levels (g/dL) for all measurement periods in four groups. There was no significant difference among the groups.

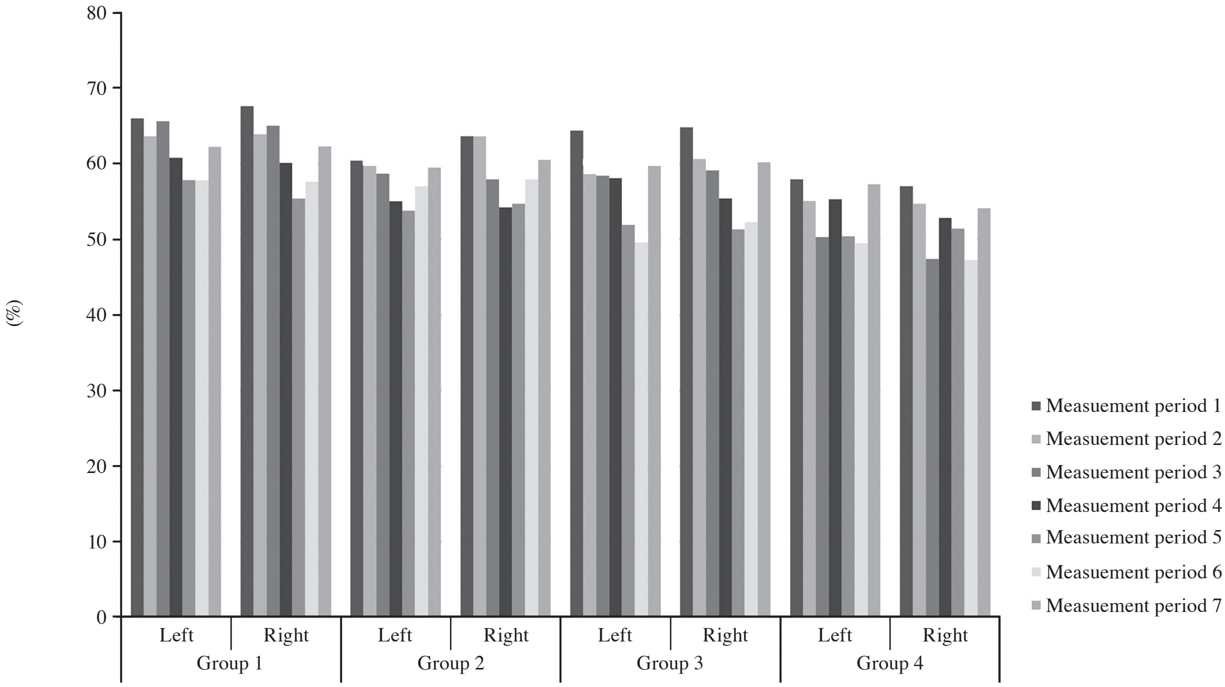

Figure 4. Bilateral near-infrared spectroscopy values (%) for all measurement periods in four groups. There was a difference between non-diabetic Group 1 and uncontrolled (advances) diabetic Group 4 in the measurement period 3 (left rSO2 p=0.00, right rSO2 p=0.003).

studies, cerebral oxygen saturation was found to be altered in periods such as anesthesia induction, acute normovolemic hemodilution, sternal retractor localization, initiation of CPB, and aortic cross-clamping and all these periods were considered critical periods.[13] Induction of general anesthesia resulted in a steep increase in cerebral rSO_2, which may be

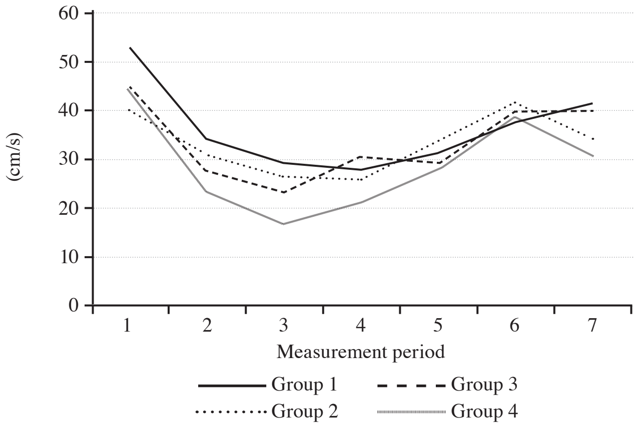

Figure 5. Transcranial Doppler middle cerebral artery flow velocity values (cm/s) for all measurement periods in four groups. There was a difference between non-diabetic Group 1 and uncontrolled (advances) diabetic Group 4 in the measurement period 3 (p=0.01).

explained by pre-oxygenation with a high-inspired fraction of oxygen, decreased consumption and unchanged cardiac output. Conversely, a significant decrease in the mean rSO_2 occurred with the onset of CPB, which can be explained by acute hemodilution, as the hematocrit values dropped. Accordingly, it can be speculated that sternal retractor is a factor influencing the cerebral saturation as measured by NIRS. One of the hypotheses is that the change in cerebral saturation is caused by strong pain signals transported via the spinal cord during the event and this results in an immediate elevation in blood pressure. However, this effect is not observed in the cases due to adequate anesthesia and analgesia. Another theory is that opening the thoracic cavity affects intrathoracic pressures and venous return, resulting in an increased cerebral saturation. On the other hand, removal of the sternal retractor did not show a significant difference in rSO_2. A plausible explanation for this observation is that the hypothesized pain signals were not activated or not in an extent large enough to cause a significant difference. In our study, during aforementioned critical periods, no desaturation was observed; however, we found reduced cerebral blood flow and oxygenation in the cannulation period in patients with uncontrolled diabetes. To the best of our knowledge, there is no study reporting changes in the cerebral blood flow in the cannulation period of heart surgery in the literature. In our study, signs of brain blood flow reduction in severely diabetic patients, which were not seen in non-diabetic patients, indicated a diabetes-related hemodynamic impairment. Meanwhile, we observed a significant reduction in the heart rate in these patients. It is not surprising that autonomic neuropathy, which is frequently seen in diabetic patients, may cause heart rate variability and fluctuations in the vasomotor tone. In particular, it was more apparent in the uncontrolled diabetic patients with reduced heart rate.[14] On the other hand, decrease in the cerebral saturation and heart rate in our study has not been previously reported in other cardiac surgery studies, which is an interesting aspect of the current study. Manipulation of nodal areas, which controls the heart rate in the right atrium during cannulation, may cause arrhythmia and heart rate alterations.[15] In diabetic patients, the possibility of manipulation and heart rate changes during cannulation due to autonomic neuropathy is higher. Furthermore, several studies examined the effects of heart rate on cerebral oxygenation in laparoscopic cases and investigated the detectability of the heart rate with NIRS devices. These studies demonstrated that increased heart rate increased the rSO_2 values.[16] In a similar but opposite way, in the present study, we observed that reduced heart rate decreased the rSO_2 values. Accordingly, the middle cerebral artery flow velocity, which was measured in the same period with reduced rSO_2, decreased. Recent data have shown that NIRS for monitoring of cerebral blood flow changes is strongly correlated with the TCD, and these two methods yield favorable results, when used in combination.[17,18] In our study, cerebral hemodynamics, which were evaluated with both NIRS and TCD methods, decreased in the cannulation period in patients with severe DM. Although not significant, blood pressure was lower in the cannulation period than the other groups such as heart rate in severe diabetic patients. Static cerebral autoregulation shows steady state changes in blood pressure and cerebral blood flow, while dynamic cerebral autoregulation is a cerebral blood flow response to a sudden change in pressure and flow. The main responsible mechanism in diabetic patients is dynamic cerebral autoregulation, which demonstrates the ability to rapidly adapt to sudden hemodynamic changes in CPB.[19,20] Arrhythmias that occur as a result of direct contact with the pacemaker cells in the right atrium of the heart during cannulation are quickly tolerated in non-diabetic individuals and no hemodynamic deterioration is observed. In our opinion, the decrease in the heart rate caused measurable cerebral changes due to the deterioration of rapid adaptation ability in severe diabetics.

In a study that intraoperative cerebral oximetry monitoring was performed in cardiac surgical patients who were randomly assigned to an intervention group in which episodes of cerebral oxygen desaturation, the mean memory change scores were significantly better in the intervention group at six months. However, the presence, duration, and severity of cerebral desaturation were not found to be associated with cognitive change scores. Perioperative outcomes did not significantly differ between the intervention and control groups.[21] These findings suggest that targeted therapy has a protective effect on the likelihood of neurological reasons. This is an important aspect of the neuroprotection strategy, but further research is needed to identify specific aspects of the treatment algorithm, such as optimizing perfusion pressure, hemoglobin concentration, and carbon dioxide.

Although NIRS provides a very rapid representation of cerebral oxygen saturation and can identify unpredictable changes from standard hemodynamic monitoring during cardiovascular procedures, evidence for improved patient outcomes is currently limited which precludes to offer a general recommendation for the use of NIRS for all cardiologic procedures.[22] In the light of these data regarding the limited nature of NIRS, no monitor is perfect, and data must be interpreted in the context of the global clinical picture.[23] On the other hand, it was previously claimed that impaired cerebrovascular autoregulation was an independent risk factor for postoperative delirium.[24] Unfortunately, we were unable to evaluate cognitive functions in this study. Another limitation in this study is its relatively small sample size that may have adversely affected the study power. Therefore, further large-scale, prospective studies are required to establish a conclusion.

In conclusion, our study results suggest that heart rate may be reduced due to autonomic neuropathy in severely diabetic patients undergoing open heart surgery, thereby, reducing the brain blood flow and cerebral oxygenation in the cannulation period, eventually. For these patients, particularly in the cannulation period, perfusion of both cerebral and other organs should be closely monitored and necessary interventions should be performed. As a result, blood glucose management, and intraoperative hemodynamic and cerebral parameters should be closely followed in uncontrolled diabetes patients undergoing cardiac surgery.

Declaration of conflicting interests

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