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Original Article

Dynamics of heart rate variability in patients with type 2 diabetes mellitus during spinal anesthesia using dexmedetomidine

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Abstract: Objective The aim of this study was to investigate the heart rate variability (HRV) in patients with Type 2 diabetes mellitus (T2DM) who underwent spinal anesthesia using dexmedetomidine for lower limb surgery. Methods: T2DM patients were divided into two groups, namely the controlled group (HbA1c < 7%) and the uncontrolled group (HbA1c > 7%) according to the glycosylated hemoglobin (HbA1c) level, and patients with non-T2DM as the normal group, 30 cases in each group. The HRV, including low-frequency (LF) power, high-frequency (HF) power, total power (TP) and LF/HF ratio, was measured 10 min before spinal anesthesia (T0) and 10 min (T1), 20 min (T2) and 30 min (T3) after spinal anesthesia with dexmedetomidine. Results: We observed that TP, LF, and HF power in the uncontrolled group were remarkably lower than that in the other two groups at T0 ($P < 0.05$). In the controlled group, the LF power dropped markedly at T1-2 than the normal group. The LF power in the uncontrolled group did not show significant change at all time points, but was significantly lower than the level in the controlled group at T1-3. The HF power in the three groups did not alter markedly at different time points, but the HF power in the uncontrolled group was markedly lower than that in the normal group and the controlled group. In all three groups, the LF/HF ratio dropped markedly at T1-3 with no markedly difference between the groups. The heart rhythms in the three groups showed a decrease trend after spinal anesthesia with no markedly difference between the groups. The SBP and DBP at T1-3 in the three groups were markedly lower than that at T0, and the systolic blood pressure (SBP) and diastolic blood pressure (DBP) at T1-3 in the uncontrolled group were markedly higher than those in the normal group and the controlled group. Conclusion: Spinal anesthesia with dexmedetomidine affects autonomic nerve function in patients whose glycemic control is better during the lower limb surgery in T2DM patients, but has no significant effect on patients who fail to do so. For such patients, spinal anesthesia can result in a markedly increase in SBP and DBP.

Keywords: Type 2 diabetes mellitus (T2DM), spinal anesthesia, heart rate variability (HRV), glycemic control, glycosylated hemoglobin

Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disease in the middle-aged and elderly population, and could lead to a higher risk of cardiovascular disease, perioperative hypotension, intraoperative complications, and autonomic dysfunction. Neuropathy is a common complication of T2DM, and serious autonomic failure induced by parasympathetic dysfunction is usually reported in the patients with poorly controlled chronic T2DM [1]. Previous studies have reported cases of autonomic dysfunction in T2DM patients during general anesthesia with dexmedetomidine [2, 3]. Studies have also shown that strict glycemic control has the potential to reduce the incidence for diversified complications of T2DM. Hence, glycosylated hemoglobin (HbA1c) level is suggested below 7 % in T2DM patients during clinical treatment [4].

Heart rate variability (HRV) serves as a typical screening parameter for the determination of autonomic dysfunction [5], which reflects the balance of vagus nerve in patients. The total power is an objective reflection of overall autonomic modulation [6] and is also thought to be a key indicator for the evaluation of how the sympathetic and parasympathetic nerve activi-

ties are balanced. There are numerous studies that indicated a significant correlation between HRV and chronic hyperglycemia [7]. The preganglionic sympathetic fibers and cardiac sympathetic innervation during spinal anesthesia are blocked, which will trigger central sympathetic. Therefore, it is speculated that the effects of sympathetic block on cardiac autonomic function in T2DM may be different from that in normal subjects. Additionally, the changes of low-frequency (LF) power/high-frequency (HF) ratio have been previously reported to predict hypotension when spinal anesthesia is conducted [8].

At present, it is known that sympathetic blockade induced by spinal anesthesia in patients with T2DM has a great influence on the cardiac autonomic nervous system; however, there is little knowledge about the pattern of changes in cardiac autonomic function in T2DM patients during spinal anesthesia. Besides, it is still unclear whether the difference exists in bradycardia and hypotension and patients with uncontrolled diabetes and other patients during spinal anesthesia. Therefore, how to effectively inhibit the stress response during the induction of anesthesia has become a key point to ensure the safety of vital signs during the perioperative period of diabetic patients. At present, there is a paucity of trial on this. In our study, we used dexmedetomidine, a highly selective α2 adrenergic receptor agonist, and demonstrated that it plays a pivotal role in analgesic, sedative, anti-sympathetic activity and stable perioperative blood. As a consequence, the aim of this article was to assess the changes of HRV and cardiac autonomic system in T2DM patients at the time of spinal anesthesia, with a view to guide the clinical management of T2DM.

Methods and materials

Participants

A total of 60 T2DM patients scheduled for lower limb surgery admitted to our hospital from March 2017 to December 2018 were selected as the objects of study. The type of lower limb surgeries for patients in this study included open reduction of fracture, amputation (toe or knee), debridement, arthroscopic surgery, removal of fixation device, and bipolar hemiarthroplasty. Since HbA1c level was recommended below 7% in T2DM patients during clinical treatment, HbA1c 7% was used as the criteria for grouping T2DM patients in this study, and patients with HbA1c < 7% were classified into the controlled group and the patients with HbA1c > 7% were classified into the uncontrolled group, with 30 cases in each group. Another 30 non-T2DM patients who underwent surgery during the same period were randomly selected as the normal group, with normal blood glucose levels.

Inclusion criteria (1) diagnosed with T2DM [9] and underwent unilateral lower limb surgery as required; (2) absence of malignant tumors, coagulation dysfunction, arrhythmia, severe systemic diseases or organ lesions; (3) absence of contraindications to spinal anesthesia; (4) haven't taken drugs affecting the autonomic nervous system recently; (5) classified as American Society of Anesthesiologists (ASA) grade I-III; (6) complete case data and provided informed consent form. The ethics committee of our hospital approved this study.

Exclusion criteria: (1) complicated with arrhythmia, coagulation dysfunction, severe lesion of other organs and systems; (2) presence of contraindications to spinal anesthesia; (3) recent use of drugs affecting the autonomic nervous system like antidepressants, β-adrenergic receptor blockers and hypnotics. (4) pregnant women; (5) incomplete medical records; (6) failed to provide informed consent form.

Anaesthetic management

All patients were not pre-medicated and monitored by non-invasive BP measurements, electrocardiography and pulse oximetry before the arrival to the operating room. For the purpose of HRV analysis, PowerLab data acquisition and analysis system (AD Instruments) was used for electrophysiology measurements. On the day before the treatment, patients were maintained under fasted conditions at night and hydrated with 5 mL/kg of sodium chloride solution prior to spinal anesthesia. All patients were under a stabilized state about 20 min before they had spinal anesthesia with dexmedetomidine, and were then positioned laterally. A 22 g spinal needle was used to target the lumber L3-4 or L4-5 of the inter-vertebral space. Afterwards, 10-12 mg of 0.5% bupivacaine (Shanghai Harvest Pharmaceutical Co., Ltd, GYZZ H310-

22840) was injected into the subarachnoid space. An acupuncture test was conducted to confirm the level of spinal block through the severity of pain, with T6-8 as the target level. The pulse rate and baseline BP in the supine position were documented at T0 before and at T1, T2 and T3 after spinal anesthesia. Hypotension was defined as a SBP < 90 mmHg, and managed by the gradual injection of 4 mg of ephedrine. Bradycardia was that an HR < 50 beats/min and the continuous recording was ≥ 15 s, and it was also managed by the administration of 0.25-0.5 mg of atropine via injection.

HRV analysis

LabChart v7 software (AD Instruments) was used for the HRV analysis according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [4]. The LF power (0.04-0.15 Hz) in HRV is induced by the two, the first was the sympathetic and the second is the parasympathetic nerve activities, whereas the HF power (0.15-0.4 Hz) was primarily dominated by the vagus nerve activity alone. TP (0-0.4 Hz) showed how the overall autonomic activity was and LF/HF ratio indicated the balance of the sympathetic and the parasympathetic nerve activities. Time points for HRV detection were set at T0 before and at T1, T2, and T3 after spinal anesthesia.

Statistical processing

SPSS 20.0 was employed to conduct the statistical processing. Enumeration data were expressed as frequency or percentage, inter-groups comparisons were carried out by the chi-square test. The measurement data were presented by mean ± standard deviation, and t-test and the one-way ANOVA were conducted for inter-groups comparisons. A repeated measure ANOVA was performed for intra-group comparisons of the HRV and the hemodynamic parameters. $P < 0.05$ was taken as statistically significant difference.

Results

Baseline data of subjects

T2DM patients were divided into two groups, one is the controlled group (HbA1c < 7%) and the other group is the uncontrolled group (HbA1c > 7%) according to the glycosylated hemoglobin (HbA1c) level, and patients with non-T2DM as normal group. Baseline data of subjects in the three groups was shown in **Table 1**. There were no markedly differences in terms of age, gender, height, weight, BMI, ASA classification and type of surgery (P > 0.05). However, the T2DM duration was remarkably poorer in the controlled group (7.55 ± 4.43 years) than in the uncontrolled group (12.53 ± 5.42 years) (P < 0.05). In addition, the HbA1c level (5.05 ± 0.62%) of the normal group was markedly poorer than the level in the case group, and the HbA1c level (6.38 ± 0.38%) in the controlled group was notably poorer than the uncontrolled group (8.76 ± 1.22%), which suggested that there were notably significant differences all among these three groups (P < 0.05).

Changes in HRV

Studies have shown that TP, LF power, and HF power in the uncontrolled group were notably lower than the rest two groups at T0 (P < 0.05), and the TP in the controlled group was markedly lower than the level of the normal group. The TP in the normal group decreased significantly at T3. The TP in the controlled group and uncontrolled group did not decrease significantly at T1-3. But the TP in the controlled group was remarkably lower than the research level of the normal group at T1, and the TP at all time points in the uncontrolled group was remarkably lower than in the level of the normal group. The LF power in the controlled group dropped remarkably at T1-2 and was lower than the normal group at T1-2. The LF power in the uncontrolled group did not change remarkably at all time points, but was remarkably lower than that in the normal group at T1-3. The HF power in the three groups did not alter markedly at different time points, but the HF power in the uncontrolled group was remarkably lower than the level of the normal group and the controlled group. The LF/HF ratio in the three groups was reduced markedly at T1-3, whereas the difference between the groups was not remarkable (**Table 2**; **Figure 1**).

Changes in hemodynamics

The HR, SBP and DBP didn't show any differences in all the three research groups at T0. In uncontrolled group, the HR reduced at T3 from T0 and decreased at T2 and T3 from T0 in

Table 1. Baseline data of subjects

Data	Normal group (n = 30)	Controlled group (n = 30)	Uncontrolled group (n = 30)	$F/t/X^2$	P
Age (years)	56.34 ± 9.32	58.32 ± 8.54	57.43 ± 10.29	12.547	0.365
Gender (n)				1.634	0.578
Male	14	13	13		
Female	16	17	17		
Height (cm)	162.35 ± 8.32	163.53 ± 8.66	162.19 ± 8.76	11.745	0.785
Weight (kg)	64.64 ± 8.46	63.34 ± 10.95	63.75 ± 11.17	10.254	0.635
BMI (kg/m^2)	24.60 ± 4.58	25.03 ± 6.32	24.83 ± 6.35	17.631	0.712
T2DM duration (years)	NA	7.55 ± 4.43	12.53 ± 5.42	2.365	0.001
HbA1c (%)	5.05 ± 0.62	6.38 ± 0.38*	8.76 ± 1.22*,#	10.487	0.002
ASA classification				1.697	0.523
I	13	14	8		
II	11	12	13		
III	6	4	9		
Type of surgery				2.458	0.536
Amputation (toe or knee)	2	3	8		
Open reduction of fracture	11	9	4		
Arthroscopic surgery	4	6	3		
Debridement	3	4	6		
Removal of fixation device	5	2	2		
Bipolar hemiarthroplasty	5	6	7		

Notes: *$P < 0.05$ compared to normal group; #$P < 0.05$ compared to controlled group.

another two groups. However, the differences between the groups were not notable. The SBP and DBP at T1-3 in the three groups were remarkably poorer than the level at T0, and the SBP and DBP at T1-3 in the uncontrolled group were remarkably better than the same level of the normal group and the controlled group (**Table 3**).

Discussion

As a normal complication of T2DM, neuropathy can lead to myocardial infarction, sudden death, and hypotension. Several studies have reported cases of autonomic dysfunction in T2DM patients during general anesthesia with dexmedetomidine [3]. Studies have shown that strict glycemic control has the potential to reduce the incidence for various complications such as microangiopathy in T2DM patients. Thus, HbA1c level of below 7% is regarded clinically as a cut-off point for glycemic control in T2DM patients [4]. HRV is the change in HR rhythm over time, and decreased HRV is a sensitive indicator for the diagnosis of early autonomic dysfunction in patients [1-4]. The LD power of HRV is predominantly innervated by the parasympathetic and sympathetic nerves, whereas the HF power is primarily innervated by the vagus nerve. TP (0-0.4 Hz) can really present all the autonomic activity, and the LF/HF ratio can also indicate the equilibrium in both sympathetic and vagal activities. Other studies stated that more severe hyperglycemia represents more decreased TP, and the correlations between blood glucose level and TP, LF and HF power are observed [9-12]. Chronic hyperglycemia affects hemodynamics as well as oxidative stress, and it exerts a crucial effect in the pathogenesis of atherosclerosis and autonomic neuropathy [13-16].

This study investigated changes in rhythm variability in T2DM patients during spinal anesthesia. T2DM patients were divided into two groups, the one is the controlled group (HbA1c < 7%) and the other one is the uncontrolled group (HbA1c > 7%) according to the glycosylated hemoglobin (HbA1c) level, and patients with non-T2DM as the normal group. Studies have shown that TP, LF power and HF power in the uncontrolled group were notably poorer than

Table 2. Changes of heart rate variability

Parameters	Group	T0	T1	T2	T3	F_{Time}	P_{Time}	F_{Group}	P_{Group}	$F_{Time×Group}$	$P_{Time×Group}$
Total power (ms^2)	Normal group (n = 30)	728.32 ± 212.75	576.43 ± 146.53*	478.1 ± 146.36*	503.23 ± 157.42*	356.7	< 0.001	301.5	< 0.001	297.3	< 0.001
	Controlled group (n = 30)	479.5 ± 164.85$^{\#}$	463.48 ± 176.25$^{\#}$	404.96 ± 175.85	399.55 ± 147.64						
	Uncontrolled group (n = 30)	331.46 ± 143.75$^{\#,\&}$	342.64 ± 120.35$^{\#,\&}$	337.05 ± 82.56$^{\#}$	344.64 ± 76.36$^{\#}$						
LF power (ms^2)	Normal group (n = 30)	335.64 ± 146.07	253.67 ± 146.57	278.66 ± 167.24	299.62 ± 133.68	333.458	< 0.001	334.5	< 0.001	309.4	< 0.001
	Controlled group (n = 30)	298.24 ± 154.46	147.85 ± 112.45$^{*,\#}$	159.68 ± 83.60$^{*,\#}$	245.62 ± 144.25						
	Uncontrolled group (n = 30)	171.85 ± 82.32$^{\#,\&}$	125.34 ± 81.85$^{\#}$	136.48 ± 73.35$^{\#}$	129.56 ± 46.06$^{\#}$						
HF power (ms^2)	Normal group (n = 30)	117.25 ± 57.58	174.52 ± 53.17	203.04 ± 87.54	196.94 ± 70.25	298.5	< 0.001	287.6	< 0.001	297.4	< 0.001
	Controlled group (n = 30)	128.56 ± 44.36	144.92 ± 48.47	166.67 ± 74.35	162.54 ± 77.65						
	Uncontrolled group (n = 30)	61.83 ± 19.85$^{\#,\&}$	63.55 ± 24.05$^{\#,\&}$	64.63 ± 32.33$^{\#,\&}$	55.32 ± 28.13$^{\#,\&}$						
LF/HF ratio	Normal group (n = 30)	3.23 ± 1.01	1.78 ± 0.82*	1.68 ± 0.89*	2.31 ± 1.22*	304.6	< 0.001	354.7	< 0.001	307.6	< 0.001
	Controlled group (n = 30)	3.12 ± 1.20	1.66 ± 0.55*	1.62 ± 0.72*	2.27 ± 1.07*						
	Uncontrolled group (n = 30)	3.27 ± 1.13	1.83 ± 0.79*	1.75 ± 0.68*	2.35 ± 1.03*						

Notes: T0-T3 represents 10 min before spinal anesthesia (T0), 10 min (T1), 20 min (T2) and 30 min (T3) after spinal anesthesia; $^{*}P < 0.05$ compared with T0; $^{\#}P < 0.05$ compared with normal group; $^{\&}P < 0.05$ compared with the controlled group.

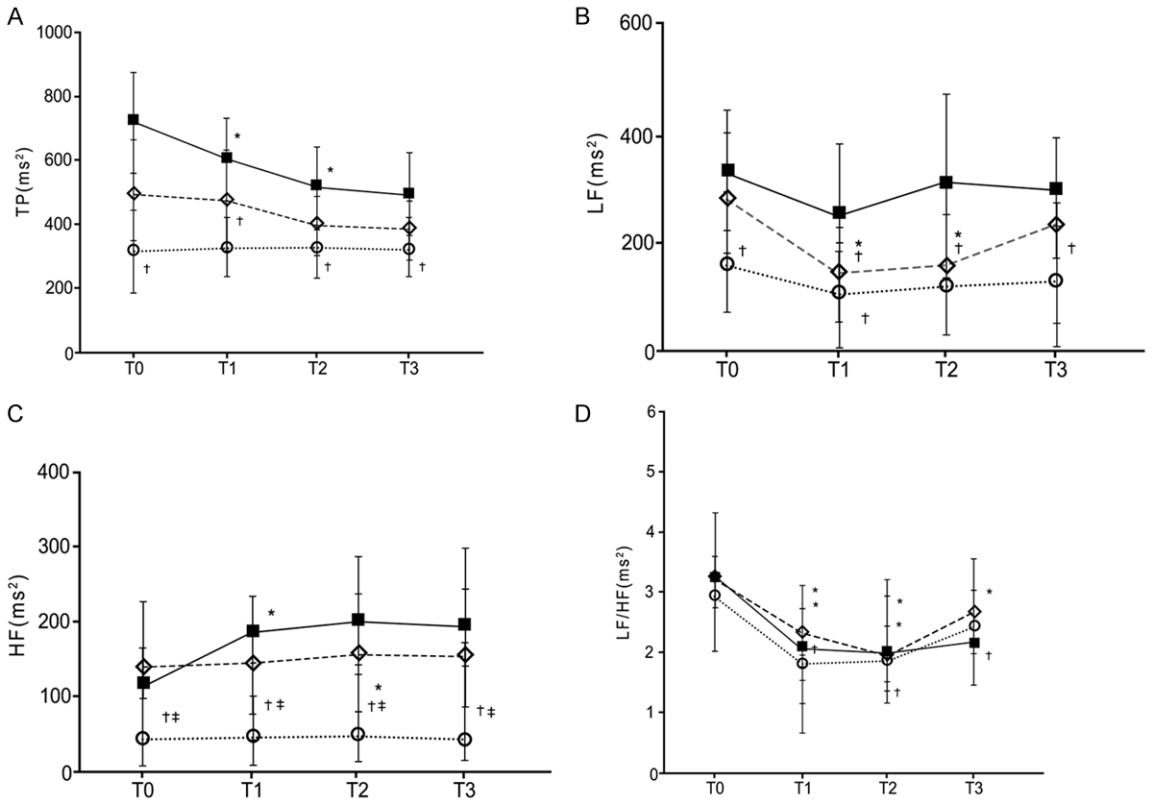

Figure 1. Heart rate variability measurement (A) total power (B) low-frequency (LF) power (C) high-frequency (HF) power (D) LF/HF ratio. Data are mean with error bars showing SD. T0, 10 min before spinal anaesthesia; T1, 10 min; T2, 20 min; T3, 30 min after spinal anaeshthesia; normal group N (●),controlled DM group (□), uncontrolled DM group (○). *P < 0.05 compared to T0; †P < 0.05 compared to normal group; ‡P < 0.05 compared to controlled DM group.

the study result in the controlled group and the normal group at T0, and the TP in the controlled group was remarkably poorer than that of the conventional-treatment group. Furthermore, the TP was markedly reduced in the uncontrolled group compared with the normal group at all time points. It suggests that autonomic activity is diminished and both sympathetic and vagal activities are inhibited in T2DM patients with poor glycemic control. However, the LF power in the controlled group dropped notably at T1-2 and was substantially different from level of the normal group at T1-2. At all time points, the LF power in the uncontrolled group did not change remarkably, but was notably poorer than the level of the normal group at T1-3. The HF power in the three groups did not alter markedly at different time points, whereas no significant difference was found in the LF/HF ratio for all the three groups. It was shown that spinal anesthesia affects sympathetic nerve function in patients with good glycemic control, but not in patients with poor glycemic control. Patients with poor glycemic control during spinal anesthesia had reduced cardiac autonomic activity, but no significant changes in sympathetic-vagal balance appeared.

To best of knowledge, changes in blood pressure are closely related to neuroendocrine function, and activation of the sympathetic nervous system acts as an essential regulator for blood pressure, thus there is an intrinsic link between HRV and blood pressure levels [17-21]. Our study showed that the HR at T3 was remarkably poorer than T0 in the normal group, while it was decreased at T2-3 from T0 in the other two groups. However, the differences between the groups were not significant. This indicated that spinal anesthesia both affects the HR of the subject, but there is no distinct correlation of HR changes with glycemic control for diabetic sufferers. The SBP and DBP at T1-3 were remarkably poorer than the data at T0 in

Table 3. Changes in hemodynamics

Parameters	Group	T0	T1	T2	T3	F_{Time}	P_{Time}	F_{Group}	P_{Group}	$F_{Time×Group}$	$P_{Time×Group}$
Heart rate	Normal group (n = 30)	71.32 ± 12.21	71.32 ± 11.74	67.55 ± 13.32	61.35 ± 11.66*	378.7	< 0.001	363.5	< 0.001	300.3	< 0.001
	Controlled group (n = 30)	72.75 ± 11.84	72.54 ± 14.02	64.43 ± 13.15*	65.32 ± 13.45*						
	Uncontrolled group (n = 30)	76.54 ± 13.33	75.11 ± 14.23	72.35 ± 11.32*	71.76 ± 12.05*						
Systolic blood pressure (mmHg)	Normal group (n = 30)	143.14 ± 12.34	124.32 ± 11.05*	120.14 ± 13.16*	122.04 ± 13.42*	323.458	< 0.001	304.5	< 0.001	307.4	< 0.001
	Controlled group (n = 30)	145.25 ± 17.24	118.53 ± 16.35*	117.64 ± 19.66*	117.53 ± 14.95*						
	Uncontrolled group (n = 30)	155.03 ± 14.46	133.46 ± 21.17*,#,&	135.23 ± 21.05*,#,&	136.27 ± 22.12*,#,&						
Diastolic blood pressure (mmHg)	Normal group (n = 30)	83.78 ± 8.06	73.43 ± 7.35*	71.64 ± 8.44*	71.67 ± 9.10*	308.5	< 0.001	317.6	< 0.001	304.4	< 0.001
	Controlled group (n = 30)	83.40 ± 9.46	72.04 ± 7.95*	72.53 ± 11.14*	71.17 ± 9.73*						
	Uncontrolled group (n = 30)	84.18 ± 11.05	78.32 ± 13.45*,#,&	78.42 ± 11.23*,#,&	78.88 ± 11.23*,#,&						

Notes: T0-T3 represents 10 min before spinal anesthesia (T0), 10 min (T1), 20 min (T2) and 30 min (T3) after spinal anesthesia; *P < 0.05 compared with T0; #P < 0.05 compared with normal group; &P < 0.05 compared with the controlled group

both all the three groups, whereas they are increased at T1-3 in the uncontrolled group compared to that of the conventional-treatment group and the controlled group. It suggested that hyperglycemia regulated endothelial and peripheral nerve function through interactions with vascular and metabolic factors, leading to decreased sympatho-vagal activity and increased blood pressure in patients with poor glycemic control. However, there may have potential selection bias due to it's a retrospective study. The absence of the consideration of multiple confounding factors, the results may need to be yielded accurately by performing prospective study.

In conclusion, our study indicates that spinal anesthesia affects autonomic nerve function in patients with satisfactory glycemic control during the lower extremity surgery in T2DM patients, but has no significant effect on patients with poor glycemic control. For the latter, spinal anesthesia can result in a remarkable augment in SBP and DBP.

Disclosure of conflict of interest

None.

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