



Original Article

Different Effects of Volatile Anesthetics on Cardiovascular Neural Regulation of the Autonomic Nervous System in the Streptozotocin-induced Diabetic Rat

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Abstract

Objective: Inhalation anesthetics increase heart rate (HR) *in vivo* in both animals and humans but decrease heart rate in isolated hearts. Clinical studies indicate that insulin-dependent diabetes mellitus is associated with alterations in autonomic nervous system control of cardiovascular function. The specific aim of this study was to elucidate the effects of different inhalation anesthetics on cardiovascular autonomic function in diabetic rats.

Materials and Methods: We measured blood pressure variability (BPV) in streptozotocin (STZ, 60 mg/kg, i.p.)-induced diabetic Sprague-Dawley rats and vehicle control groups exposed to different inhalation anesthetics (halothane, desflurane and sevoflurane) and BPV was recorded until the recovery stage. Frequency-domain analysis of telemetric systemic arterial pressure and pulse-pulse interval were applied to quantify the parameters of BPV. High frequency power (HF) was regarded as cardiac vagal modulation. Low frequency power of BPV (BLF) was referred to as vascular sympathetic modulation. Normalized low-frequency power (LF%) of the spectrogram of the RR interval was regarded as cardiac sympathetic modulation.

Results: STZ-induced diabetes was associated with a significant reduction of HR but not consistently with a higher HF among these volatile anesthetics. BLF was significantly decreased at one minimum alveolar concentration (MAC) of desflurane when compared with halothane and sevoflurane in the STZ-induced diabetic group. We found an early recovery of the BLF to awake stage baseline values 30 minutes post-anesthesia for sevoflurane, although it was not significant when compared with the other two anesthetics. However, the LF% significantly recovered to 80% of awake baseline values with desflurane and sevoflurane when compared with halothane 30 minutes post-anesthesia.

Conclusion: The components of sympathetic regulation (BLF and LF%) may be an early sign of hemodynamic recovery to the awake stage during anesthesia in STZ-induced diabetic rats. Our results provide an indication for clinical anesthetic choice in diabetes patients receiving anesthesia. (*Tzu Chi Med J* 2009;21(4):302–309)

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1. Introduction

Insulin-dependent diabetes mellitus (IDDM) alters systemic autonomic function and autonomic nervous system (ANS) control of cardiovascular function. Clinical studies suggest that parasympathetic nervous control of the heart is diminished in diabetics and sympathetic neuropathy often occurs in these individuals (1–4). Evidence shows that both branches of the ANS are impaired (4). In addition, IDDM is associated with neuronal alternations that develop progressively with the duration of disease (1). Subclinical changes have been observed early after diagnosis in young individuals with overt neuropathy (5,6). In animal studies, streptozotocin (STZ)-induced diabetes has been shown to result in resting bradycardia, a diminished circadian variation in heart rate (HR) and decreased cardiac sympathetic and parasympathetic control under resting conditions (7,8).

Several studies have reported hemodynamic instability in patients with autonomic dysfunction during anesthetic induction and maintenance (9–14). Impaired regulation of blood pressure and HR may cause imbalances in myocardial oxygen demand and supply, and these may increase surgical risks in diabetic patients. Brian et al have shown that the minimal alveolar concentration (MAC) values of halothane, isoflurane, and enflurane are diminished in diabetic rats compared with control rats (9). However, Hattori et al suggested that the myocardium of diabetic rats could be less sensitive to halogenated agents than the myocardium of healthy rats (15). Recently, it was reported that halothane and sevoflurane have greater negative inotropic effects in diabetic rats, mainly because of a significant decrease in myocardium Ca^{2+} sensitivity (16). All of these results may explain some of the reasons for hemodynamic instability in diabetes mellitus (DM) patients during anesthesia.

Power spectral analysis of HR variability (HRV) has proven useful in evaluating cardiovascular autonomic activity in diabetic patients (17–19). The main advantage of spectral analysis is the possibility of assessing not only the amount of overall variability, but also frequency-specific oscillations and the relative impact on variability of sympathetic and vagal modulation in

the heart (19). The purpose of this study was to investigate the effects of different volatile anesthetics on the neural cardiovascular autonomic regulation in STZ-induced diabetic rats.

2. Materials and methods

2.1. Animal preparation

The subcommittee on Research Animal Care of Buddhist Tzu Chi University and Tzu Chi General Hospital approved the experimental protocol. Experiments were carried out on adult male Sprague-Dawley (200–250g) rats. The rats were obtained from the Animal Center of Tzu Chi University with guidelines established by the Position of the American Heart Association on Research Animal Use. Diabetes was induced in the rats by administration of 60 mg/kg STZ i.p. (Sigma, St. Louis, MO, USA) with pH 4.5, and 0.1 M citrate buffer. Diabetic mellitus was then confirmed by Diastix semiquantitative urine sugar test strips = 10g/L (20). The control group was given an intraperitoneal injection of 1 mL/kg citrate buffer solution.

In the telemetry system (model TA11PA-C40; Data Sciences, St. Paul, MN, USA), a pressure transmitter was implanted to record arterial pressure signals according to the methods of Kuo et al (21). One week after diabetes was induced, the rats were anesthetized with pentobarbital sodium (50 mg/kg i.p.) and a flexible transmitter catheter was secured surgically in the abdominal aorta below the renal arteries pointing against the flow. The tip of the probe catheter was inserted rostrally by a small hole in the abdominal wall and fixed in position with a drop of tissue glue. The transmitter body was positioned in the abdominal cavity and sutured to the inside of the muscle. After surgery, the rats were given antibiotics (chlortetracycline) and housed individually in cages for 1 week of recovery. On the day of the recording, a 30-minute period was allowed for the rat to become familiar with the chamber and the experimental apparatus. At the time of the arterial pressure measurements, each cage was placed over the receiver panel and connected to a computer for collection of data.

The biological signals were then synchronously recorded in every rat during the experiment.

STZ-induced diabetes and control rats were divided into groups for exposure to halothane, desflurane, or sevoflurane. We continuously recorded awake, control biological signals (AW) for 30 minutes, and then administered 1.0 MAC of the inhalation anesthetics (0.8% halothane, 6.0% desflurane and 2.0% sevoflurane) for 30 minutes while still recording. We then increased the anesthetic concentration to 1.3 MAC (1.2% halothane, 7.8% desflurane and 2.6% sevoflurane) for 30 minutes and recorded data. After recording the data, the anesthetics were stopped and recording was carried out at 30, 60 and 90 minutes post-anesthesia (PA30, PA60 and PA90, respectively) until the animals were fully awake.

2.2. Cardiovascular variability analysis

Biotelemetry techniques were utilized to monitor cardiovascular parameters and changes in STZ-induced diabetes and control rats during anesthetic exposure. Spectral analysis of the mean arterial pressure (MAP) and interpulse interval (PPI) signals were monitored as an index of autonomic nervous function as previously reported by Kuo et al [21,22]. The stationary MAP and PPI signals were resampled and interpolated at a rate of 64 Hz to provide continuity in the time domain and were then truncated into successive 16-second (1024 points) time segments (windows or epochs) with 50% overlap. These sequences were analyzed with fast Fourier transform after application of the Hamming window. We analyzed the MAP and PPI signal spectral data according to the following frequency bands. Low-frequency power (BLF; 0.06–0.6 Hz) of the MAP spectrogram, high-frequency power (HF; 0.6–2.4 Hz), and normalized low-frequency power (ν) (representing the relative value of the LF power component in proportion to the total power minus the very low frequency component) of the PPI spectrogram were quantified. BLF, LF%, and HF provide markers of sympathetic vasomotor activity, cardiac sympathetic modulation, and cardiac vagal activity, respectively [22–24]. The data length for the sequence analysis is 56 seconds, which is synchronous with the spectral analysis.

2.3. Statistical analysis

Different effects of the same inhalation anesthetic between the control and STZ-induced group were assessed by unpaired Student *t* test. The neural regulation effects of the different inhalation anesthetics on STZ-induced diabetic rats were analyzed by one-way ANOVA, with *post hoc* comparisons using the

Student-Newman-Keuls method. Data are presented as mean \pm standard error of the mean and $p < 0.05$ indicates statistical significance.

3. Results

The use of telemetric arterial pressure recordings allowed complete and simultaneous measurement of arterial pressure signals from which the awake, anesthesia and recovery stages of arterial pressure variability could be analyzed. There were no significant differences in mean blood pressure (MBP; except with 1.3 MAC sevoflurane, STZ: 96 ± 3 mmHg vs. control: 86 ± 3 mmHg) or LF% between the control and STZ-induced diabetic groups (Figs. 1A, 2A, 3A and 1E, 2E, 3E). HR was significantly decreased in the diabetic rats compared with the control group with all three anesthetics. This phenomenon occurred not just at the awake stage but also during all anesthetic periods and recovery stages until PA90 (Figs. 1C, 2C, 3C). The HF component in the STZ-induced group was significantly higher than that in the control group with halothane exposure in the awake, 1.0 MAC, 1.3 MAC and PA30 stages (Fig. 1D), but in the desflurane and sevoflurane groups this was not significant, although there was a trend towards it being higher (Figs. 2D, 3D). The effects of the three volatile anesthetics on BLF were different between the groups, especially at the recovery stage. BLF in the diabetic rats was significantly lower than in the control rats at the awake and PA90 stages with exposure to halothane (Fig. 1B). Nevertheless, BLF was persistently significantly lower in the diabetic group than in the control group at PA30 and PA60 with desflurane exposure (Figs. 2B, 3B) and at PA30, PA60 and PA90 with sevoflurane (Fig. 3B).

When we compared the effects of these anesthetics in the STZ-induced diabetic rats, we used the awake stage (AW) baseline value as the standard and compared each stage as a percentage of the AW value. We found that the MBP change was not significant (except at the 1 MAC stage where MBP of the desflurane group was significantly lower than that in the halothane group) among the three anesthetics during all stages in diabetic rats (Table 1). BLF decreased most at 1 MAC in the desflurane group and was significantly lower than that in the halothane group. BLF had an early recovery to the AW stage value in the sevoflurane group compared to the halothane and desflurane groups (but this was just a trend and was not statistically significant). The halothane and desflurane groups did not recover to the same percentage of AW baseline values until the PA90 stage. There were no significant changes in HF and HR among the anesthetics in the STZ-induced diabetic rats. LF% was significantly higher at PA30 in the desflurane and

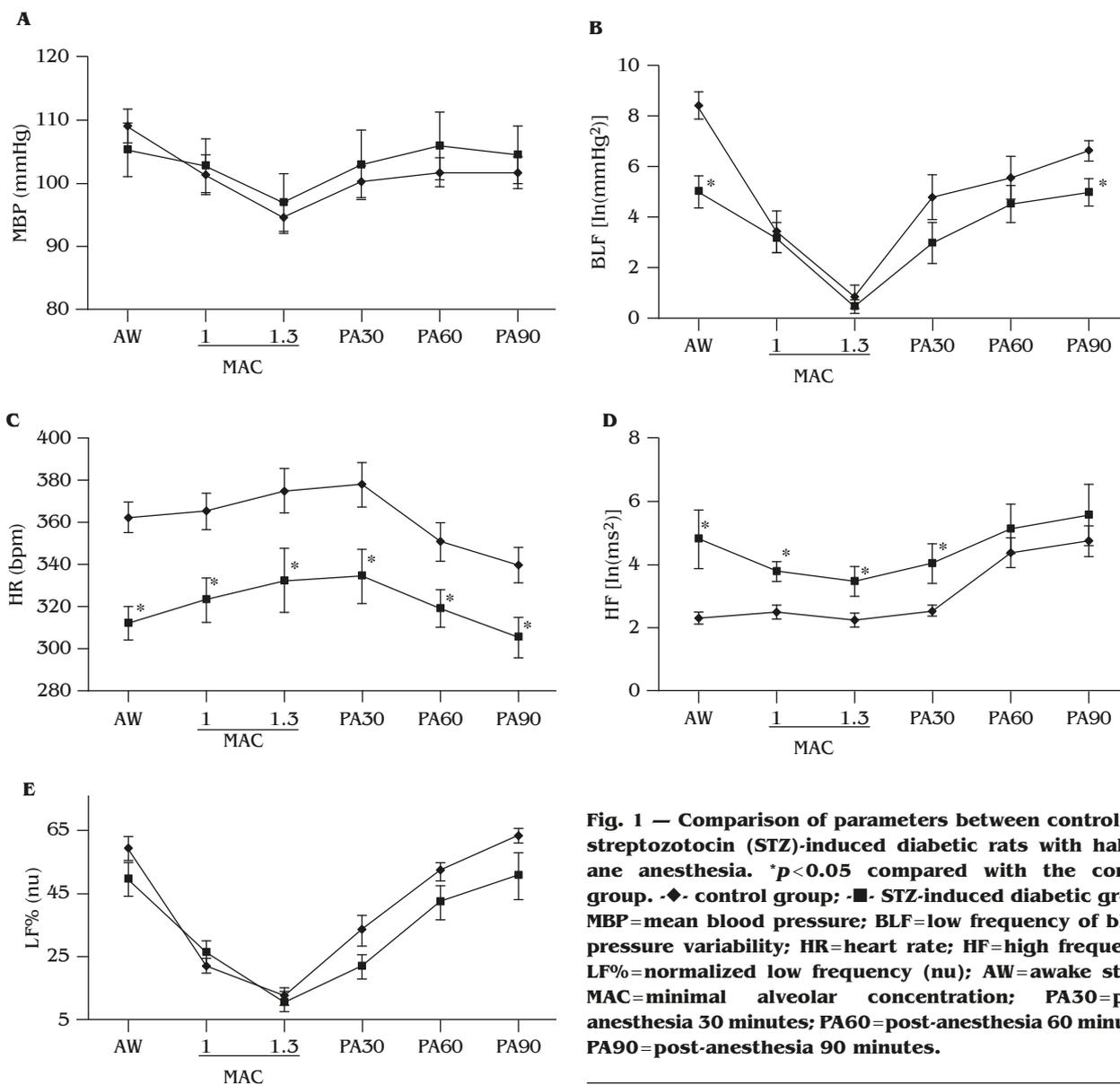


Fig. 1 — Comparison of parameters between control and streptozotocin (STZ)-induced diabetic rats with halothane anesthesia. * $p < 0.05$ compared with the control group. \blacklozenge — control group; \blacksquare — STZ-induced diabetic group. MBP=mean blood pressure; BLF=low frequency of blood pressure variability; HR=heart rate; HF=high frequency; LF%=normalized low frequency (nu); AW=awake stage; MAC=minimal alveolar concentration; PA30=post-anesthesia 30 minutes; PA60=post-anesthesia 60 minutes; PA90=post-anesthesia 90 minutes.

sevoflurane groups compared with that in the halothane group (Table 1).

4. Discussion

Data from our study successfully demonstrated the dose- and time-dependent effects of inhalation anesthetics on sympathetic vasomotor activity and cardiac sympathetic modulation in control and STZ-induced diabetic rats. However, the effects of different anesthetics on cardiac vagal activity were not the same in the two groups.

Autonomic neuropathy and cardiovascular dysregulation are common complications of DM (1). Diabetic patients with autonomic neuropathy have a higher mortality than those without autonomic neuropathy (25,26). ANS dysregulation can be detected

by modern sensitive methods, even in the early stages of DM (1,26). Javorka et al used spectral analysis of BPV in young patients with IDDM and found impaired parasympathetic control of the HR but no difference in blood vessel sympathetic control (1). Previous studies have shown that STZ-induced diabetic rats demonstrate lower basal systolic arterial pressure and HR and reduced mid-frequency band variability of BPV (7,8). These findings suggested that sympathetic modulation of the cardiovascular system was impaired. In our study, the diabetic rats also showed ANS dysregulation, including lower sympathetic (BLF) vasomotor activity, a lower HR and higher parasympathetic (HF) modulation of the cardiovascular system when compared with the controls in the awake state. This is consistent with previous studies of STZ-induced diabetic rats with ANS dysregulation, although there was no significant difference in MBP

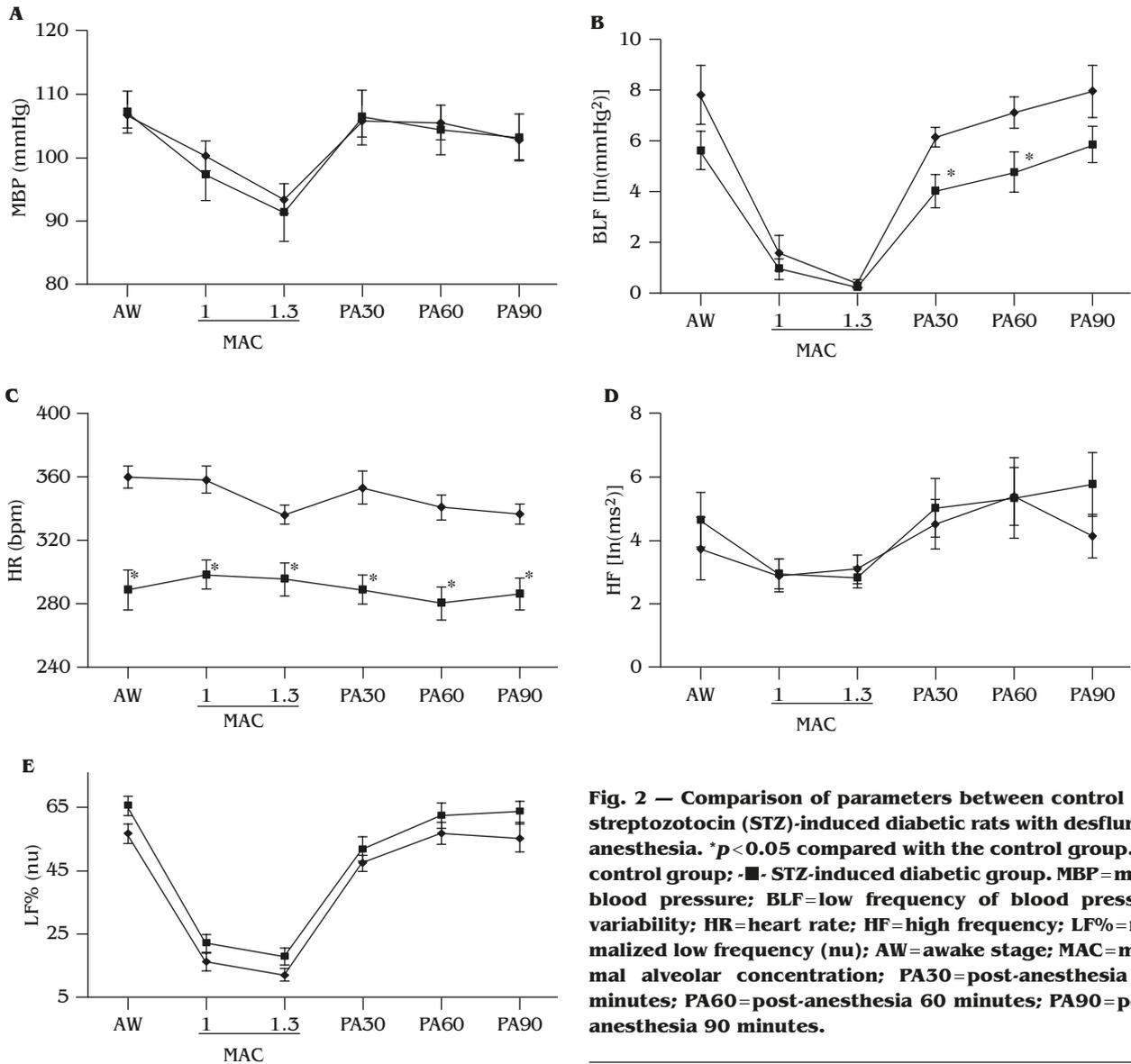


Fig. 2 — Comparison of parameters between control and streptozotocin (STZ)-induced diabetic rats with desflurane anesthesia. * $p < 0.05$ compared with the control group. ◆—control group; ■—STZ-induced diabetic group. MBP=mean blood pressure; BLF=low frequency of blood pressure variability; HR=heart rate; HF=high frequency; LF%=normalized low frequency (nu); AW=awake stage; MAC=minimal alveolar concentration; PA30=post-anesthesia 30 minutes; PA60=post-anesthesia 60 minutes; PA90=post-anesthesia 90 minutes.

between our groups. However, when we compared the effects of the three volatile anesthetics in the diabetic rats, the results showed a different regulation of vascular (BLF) and cardiac (LF%) sympathetic effects during the anesthetic and recovery stages. Sympathetic vasomotor activity regulation seemed deepest at 1 MAC with desflurane but not with halothane and sevoflurane. With desflurane and sevoflurane, cardiac sympathetic modulation recovered early to almost 80% of the awake state just 30 minutes post-anesthesia. This finding suggested there is decreased vasomotor sympathetic activity soon at 1 MAC with desflurane in STZ-induced diabetic rats. When these rats were given sevoflurane, vasomotor sympathetic activity did not decrease as quickly and cardiac sympathetic activity recovered early at 30 minutes post-anesthesia. These results may help clinicians determine which anesthetics to use when IDDM patients have surgery.

Volatile anesthetics increase HR *in vivo* both in animals and humans (27–31). Activation of the sympathetic nervous system may explain the increase in HR during volatile anesthesia, which may be caused by an increase in traffic of the sympathetic nerves innervating skeletal muscle in humans (32–34). However, activation of the sympathetic nervous system is more pronounced during transient than steady state conditions (32). In our steady state experiments, we saw no signs of tachycardia in either group (except in the halothane group). Fazan et al showed that basal systolic arterial pressure and HR were reduced in STZ-induced diabetic animals in a power spectral analysis of BPV and HRV (7). They suggested that reduction of mid-frequency band variability of arterial pressure might indicate that sympathetic modulation of the cardiovascular system is impaired. In our study, STZ-induced diabetic rats also had a reduced HR from the awake state to 90 minutes post-anesthesia. In STZ-induced

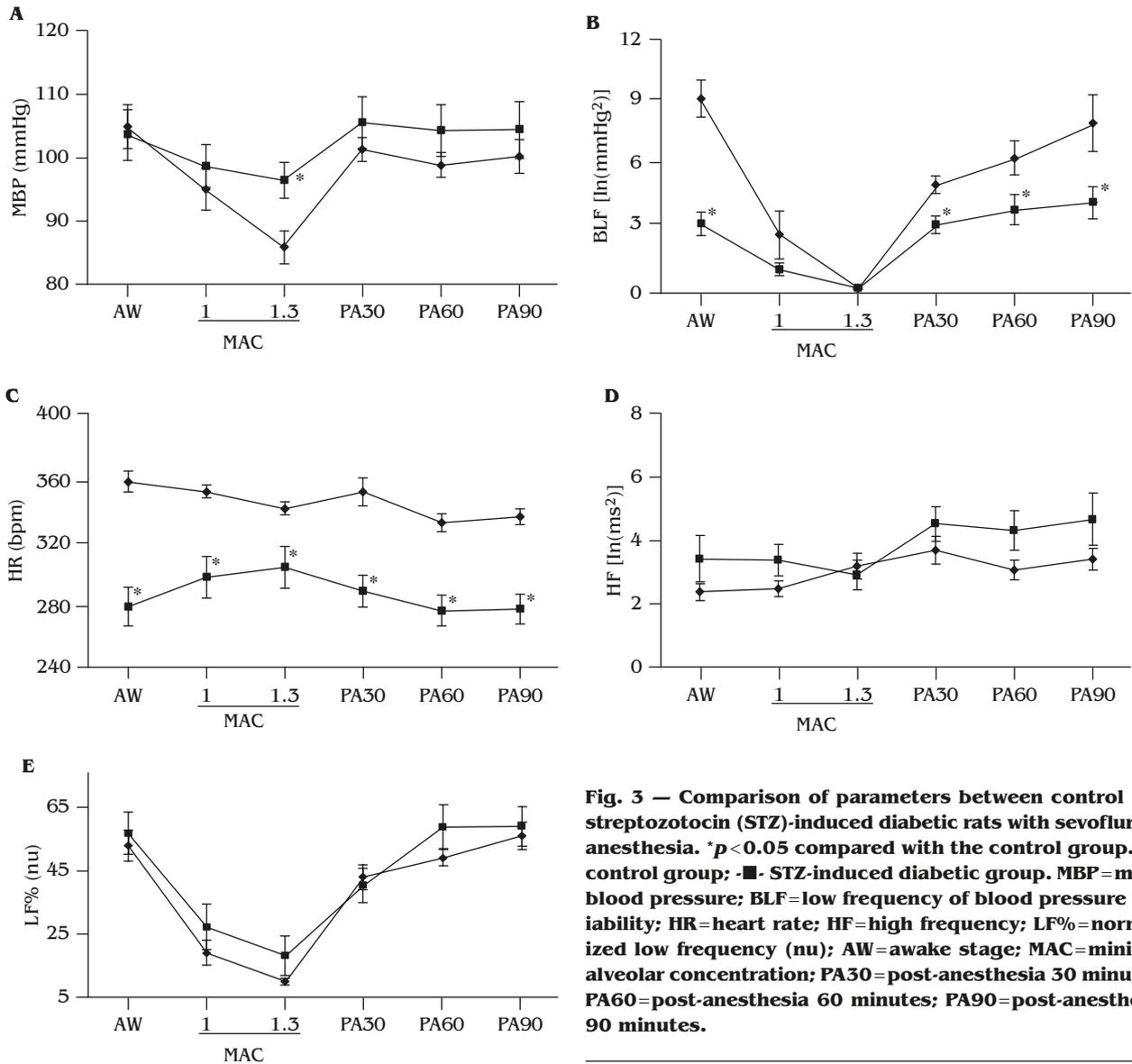


Fig. 3 — Comparison of parameters between control and streptozotocin (STZ)-induced diabetic rats with sevoflurane anesthesia. **p* < 0.05 compared with the control group. ◆- control group; ■- STZ-induced diabetic group. MBP=mean blood pressure; BLF=low frequency of blood pressure variability; HR=heart rate; HF=high frequency; LF%=normalized low frequency (nu); AW=awake stage; MAC=minimal alveolar concentration; PA30=post-anesthesia 30 minutes; PA60=post-anesthesia 60 minutes; PA90=post-anesthesia 90 minutes.

diabetic rats, MAP was significantly decreased with desflurane at 1.0 MAC, which is compatible with significantly early depressed vasomotor sympathetic activity (BLF) with the lowest trend of cardiac sympathetic activity (LF%). BLF recovered quickly to the awake state just 30 minutes after stopping sevoflurane. Cardiac sympathetic activity also returned to almost 80% of the awake state 30 minutes post-anesthesia in both the sevoflurane and desflurane groups. These results suggest that the effects of different volatile anesthetics on autonomic neuromodulation in STZ-induced diabetic rats are different, even though the clinical hemodynamic signs may not be different.

Picker et al found an increase in HR and a significant correlation between decreased HRV and a decrease in HF power, and concluded that the primary effect of sevoflurane anesthesia was decreased parasympathetic activity (35). It has also been reported

that there is an increase in HR with sevoflurane and a correlation between the decrease in HF power and HRV (36). Feld et al reported the effect of desflurane on vagal tone, and HRV was attenuated in a manner similar to sevoflurane (37). All of these studies suggest that volatile anesthetics decrease vagal tone and HRV in a similar way, although there may be subtle differences between the drugs. Our results are different from previous studies in that the three volatile anesthetics did not show dose-dependent decreased vagal tone and HRV in either group. However, the volatile anesthetic effects on sympathetic vasomotor activity and cardiac sympathetic modulation were more consistent in both groups. These volatile anesthetics dose-dependently inhibit sympathetic nervous activity but have mild effects on parasympathetic modulation during inhalation anesthesia. The variability between our study and previous studies may have

Table 1 — Comparison of parameters among the different inhalation anesthetics in streptozotocin-induced diabetic rats*

STZ		AW	1 MAC	1.3 MAC	PA30	PA60	PA90
MBP (% of AW)	Halothane	100	98±2	92±3	98±3	100±2	99±1
	Desflurane	100	91±2 [†]	85±3	99±3	97±2	96±1
	Sevoflurane	100	96±1	94±2	102±2	101±2	101±1
BLF (% of AW)	Halothane	100	78±20	9±4	72±28	95±14	110±16
	Desflurane	100	14±4 [†]	5±1	77±13	92±13	118±15
	Sevoflurane	100	51±19	9±2	114±19	132±25	136±15
HR (% of AW)	Halothane	100	98±2	95±4	95±4	98±2	103±3
	Desflurane	100	97±2	98±3	100±3	103±2	101±2
	Sevoflurane	100	94±2	92±2	97±2	101±2	100±2
HF (% of AW)	Halothane	100	94±11	87±16	123±34	123±16	128±14
	Desflurane	100	77±15	86±19	118±17	126±27	131±12
	Sevoflurane	100	113±19	104±21	147±16	147±25	158±31
LF% (% of AW)	Halothane	100	54±8	23±6	45±7	85±9	99±11
	Desflurane	100	33±4	27±4	79±5 [†]	96±6	98±5
	Sevoflurane	100	45±8	28±6	76±10 [†]	108±9	109±8

*Data presented as mean±standard error of the mean of the percentage of the AW baseline value; [†] $p < 0.05$ compared with the halothane group. AW=awake stage; MAC=minimal alveolar concentration; PA30=post-anesthesia 30 minutes; PA60=post-anesthesia 60 minutes; PA90=post-anesthesia 90 minutes; MBP=mean blood pressure; BLF=low frequency of blood pressure variability; HR=heart rate; HF=high frequency; LF%=normalized low frequency (nu).

been caused by a difference in experimental species and methods of collection and analyzing data. Future studies need to extend our methods to clinical patients.

In conclusion, we demonstrated the effects of three different volatile anesthetics on autonomic regulation in STZ-induced diabetic animals. Sympathetic vasomotor activity (BLF) and cardiac sympathetic activity (LF%) may be early signs of hemodynamic change in IDDM patients during anesthesia and emergence. These results may provide some suggestions on the clinical choice of anesthetic in IDDM patients receiving anesthesia.

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