Anesthesiology 2007; 107:45–52

Effects of Isoflurane and Sevoflurane Anesthesia on Arteriovenous Shunt Flow in the Lower Limb of Diabetic Patients without Autonomic Neuropathy

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Background: **Failure of sympathetic nerve control caused by diabetic neuropathy results in vasodilation of arteriovenous shunts. The aim of this study was to test the hypothesis that the function of arteriovenous anastomoses was disordered in mild diabetic patients without apparent neuropathy, and that volatile anesthetics opened arteriovenous shunts more greatly in nondiabetic patients than diabetic patients.**

Methods: **Autonomic system function was assessed by cardiovascular reflex tests. Arterial–venous oxygen content difference ($A\text{-}V\Delta O_2$) and partial oxygen pressure index (Pvo_2/Pao_2, the ratio of oxygen tension in femoral vein blood to that in femoral artery blood) were measured before and during isoflurane or sevoflurane anesthesia in 16 diabetic and 22 nondiabetic patients. Skin temperatures of the foot and leg were measured in 14 diabetic and 15 nondiabetic patients using thermography before and during anesthesia.**

Results: **Pvo_2/Pao_2 before anesthesia was significantly higher in diabetic patients. In nondiabetics, venous oxygen content significantly increased and $A\text{-}V\Delta O_2$ markedly decreased during anesthesia, but these parameters were unchanged in diabetics. Foot temperatures were higher in diabetics before anesthesia, and increased gradually and significantly in both groups during anesthesia, but with a greater increase in nondiabetic patients. Induction of anesthesia caused a larger decrease in leg temperature in diabetics than in nondiabetics.**

Conclusions: **Diabetic patients have a higher Pvo_2/Pao_2 and a small core-to-peripheral temperature gradient before anesthesia, suggesting latent dysfunction of the autonomic nerve system, even in the absence of autonomic neuropathy. Volatile anesthesia opens the arteriovenous shunt in nondiabetics to a greater extent than in diabetic patients.**

DIABETES mellitus (DM) is one of the commonest endocrine disorders encountered in anesthesia, and complications of DM are major perioperative causes of mortality and morbidity.[1] Macroangiopathies and microangiopathies derived from DM are the major causative factors of complications in important organs, including the heart, brain, kidney, and peripheral and autonomic nervous system. Peripheral and autonomic neuropathy is one of the important complications of DM, and diabetic patients with neuropathy have arteriovenous shunts; such shunts originate from arteriovenous anastomoses that regulate body temperature and are tonically closed by sympathetic nerve activity under normal conditions.[2] Failure of sympathetic control caused by diabetic neuropathy results in vasodilation and increased blood flow through arteriovenous shunts, thereby increasing venous oxygen saturation and oxygen contents.[3–5] In such patients, although total peripheral blood flow increases, flow in nutritional capillaries is reduced (capillary steal). This is considered to be one of the etiologies in that some patients with neuropathy have warm feet and that cutaneous ulceration coexists with increased peripheral skin blood flow, resulting in cutaneous ulceration despite the increased peripheral blood flow.

Volatile anesthetics have been shown to dilate vessels directly or indirectly, and isoflurane and sevoflurane both reduce peripheral vascular resistance.[6,7] Such vascular effects of anesthetics affect normally closed arteriovenous anastomoses.[8] It is thought that volatile anesthetics may not show strong vasodilative action for the arteriovenous anastomoses that have already opened with autonomic neuropathy.

However, most diabetic patients who undergo surgery have mild conditions without neuropathy, and diabetic patients may still have vascular abnormalities such as endothelial dysfunction or atherosclerotic changes, even in the absence of neuropathy.[9,10] Vascular function of the arteriovenous anastomoses has not been known, and the effect of volatile anesthetics on arteriovenous shunts in the foot has not been examined in such patients. Therefore, the aim of the current study was to prove the hypothesis that the function of arteriovenous anastomoses was disordered in mild diabetic patients without apparent symptoms of neuropathy, and that volatile anesthetics opened arteriovenous shunts more greatly in nondiabetic patients than in diabetic patients.

The arteriovenous shunt flow was estimated based on measurements of arterial–venous oxygen content difference ($A\text{-}V\Delta O_2$), partial oxygen pressure index (Pvo_2/Pao_2),[2] and regional leg skin temperature. The opening of arteriovenous anastomoses was estimated by change of skin temperature using thermography.

Materials and Methods

Patients and Preoperative Assessment

The study was approved by the ethical committee of Wakayama Medical University, Wakayama, Japan, and written informed consent was obtained from 45 patients

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Received from the Department of Anesthesiology, Wakayama Medical University, Wakayama, Japan. Submitted for publication July 3, 2006. Accepted for publication March 13, 2007. Support was provided solely from institutional and/or departmental sources.

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with type 2 diabetes mellitus (the DM group) and 41 age-matched nondiabetic patients (the non-DM group) who were scheduled to undergo elective surgery during general anesthesia. Four diabetic patients with apparent symptoms of neuropathy (*e.g.*, toe ulcer, reports of a cold sensation of the foot and abnormal sweating of the lower extremities) subsequently received surgery during local or regional anesthesia and were excluded from the study. Therefore, 41 diabetic patients without apparent symptoms of diabetic neuropathy were selected as subjects for the study. The criteria for diabetes mellitus were an elevated fasting plasma glucose level of 140 mg/dl or higher or a glycosylated hemoglobin (HbA_{1c}) level of 5.8% or higher. HbA_{1c} was measured in patients who had already diagnosed DM or who had abnormal values in fasting blood sugar. Exclusion criteria were dysautonomia, Raynaud syndrome, other endocrine disorders, significant dysrhythmia, congestive heart failure, ischemic heart disease or peripheral vascular disease, pregnancy, a history of alcoholism or drug abuse, and taking β-adrenergic antagonists or central sympatholytic agents. The patients had apparent neurologic symptoms such as abnormal sensations, burning pain, loss of vibration sensation, and reduced tendon reflex of the lower extremities were excluded. The 41 DM patients and 41 non-DM patients were randomly assigned to two experimental protocols: measurement of arteriovenous oxygen content ($n = 25$ in each group) and thermographic measurement of leg skin temperature ($n = 16$ in each group). We performed the study of arterial and venous blood gas analyses when the operation day was even numbered, and the study of leg skin temperature when the operation day was odd numbered. In each protocol, DM and non-DM patients were randomly allocated to an isoflurane or a sevoflurane group. Examiners were not informed about the groups of the patients.

Autonomic Function Test

Autonomic system function was assessed by means of standardized cardiovascular reflex tests[11] before the scheduled anesthesia and surgery. All tests were performed by a physician who was blinded to the experimental protocol. Patients with hypertension were asked to refrain from taking antihypertensive agents in the morning of the test day.

Variation in R-R Interval with Deep Breathing

The patient sat quietly and then breathed deeply and evenly at a rate of 6 breaths/min. The maximum and minimum R-R intervals during each breathing cycle were measured with a ruler and converted to beats/min. The result was then expressed as the mean value of the difference (beats/min) between maximum and minimum heart rates for the six measured cycles. Differences of less than 10 beats/min were considered abnormal.

Arterial Blood Pressure in Response to Standing

Blood pressure was measured while the subject was lying down in a supine position. The patient was then asked to stand up quickly, and blood pressure was measured again. The change in systolic blood pressure in moving from a supine position to a standing position was calculated and used as an indicator of sympathetic nervous system function. A decrease in systolic blood pressure of more than 30 mmHg after reaching a standing position was considered abnormal.

Anesthetic Technique

Antihypertensive agents were not administered from the night before surgery, and diabetic patients who had been treated with insulin did not receive insulin on the morning of surgery because of preoperative fasting. Premedication consisted of oral diazepam (5–10 mg), intramuscular meperidine (25–50 mg), and atropine (0.5 mg) 1 h before induction of anesthesia. Electrocardiography, noninvasive oscillometric blood pressure, and percutaneous oxygen saturation were monitored. End-tidal carbon dioxide and anesthetic concentration were measured with an anesthetic gas monitor (Ultima; Datex Engstrom, Helsinki, Finland). Preoxygenation was not performed. Anesthesia was induced with intravenous thiopental sodium (4 mg/kg), and nitrous oxide (50%) and isoflurane (1.8%) or sevoflurane (2.5%) were added to a fresh gas flow (at a total of 6 l/min) immediately by facemask ventilation after induction. The trachea was intubated approximately 3 min after induction with previous administration of vecuronium bromide (0.1 mg/kg). Anesthesia was then maintained with isoflurane (1.8%) or sevoflurane (2.5%), and nitrous oxide (50%) in oxygen. Ventilation was controlled to maintain an end-tidal carbon dioxide of approximately 35 mmHg.

Study 1: Arterial and Venous Blood Gas Analyses. Arterial and venous gas analyses were scheduled in 25 non-DM and 25 DM patients. Each group was divided into an isoflurane group and a sevoflurane group. Blood samples for analysis were obtained from the femoral artery and vein with local infiltration of 1% lidocaine before induction of anesthesia. After the anesthetic induction and tracheal intubation, the second blood samplings were performed at the point when the end-tidal anesthetic concentration reached 1 minimal alveolar concentration (MAC) for isoflurane (1.2%) and sevoflurane (1.7%). Rectal temperature was measured immediately after tracheal intubation and at the point of blood sampling. Automated noninvasive oscillometric blood pressure and heart rate were recorded simultaneously with blood sampling. After all blood samplings, the surgical procedure was started. Arterial and venous blood gas analyses were performed using a blood gas analyzer (Chiba Corning 286; Medfield, MA). Pvo_2/Pao_2 was defined as the ratio of the oxygen tension of the blood from the femoral vein to that of the blood from the femoral

artery. Hemoglobin (g/dl) and blood gas were determined, and the blood oxygen content (Cao_2 or Cvo_2) was calculated as follows: O_2 content (Cao_2 or Cvo_2: vol%) = 1.34 × hemoglobin × O_2 saturation + 0.0031 × Po_2. A-VΔO_2 was calculated as $Cao_2 - Cvo_2$.

Study 2: Measurement of Leg Skin Temperature. Measurement of leg skin temperature was designed in 16 DM patients and 16 non-DM patients using infrared thermography (TH3108ME; NEC San-ei, Tokyo, Japan). Each group was divided into an isoflurane group and a sevoflurane group. The temperature of the operating room was controlled from 25° to 26°C, and humidity was maintained at 60%. The air conditioner and operating lights were switched off before the arrival of patients in the operating room because a cold or warm current of air and incandescent lamps were likely to prevent accurate thermography measurements. Only fluorescent lamps were used throughout the experiment, and the door of the operating room was closed during the experimental procedure to keep the room temperature constant. Patients wore an operating gown and were covered with a cotton cloth from shoulder to foot. Upon arrival in the operating room, the leg skin temperature was continuously measured by thermography, and the body core temperature was recorded at the tympanic membrane using a Mon-a-Therm thermocouple probe (Mallinckrodt, St. Louis, MO).

Upon entering the operating room, patients were asked to expose their leg, and then the leg skin temperature was continuously measured for 10 min using thermography. After the leg skin temperature of each patient had stabilized, anesthesia was induced. Induction and maintenance of anesthesia was performed in an identical fashion to study 1.

Thermal images were recorded digitally just before induction of anesthesia and at intervals of 3 min thereafter until 15 min after induction. Therefore, six images were obtained for each patient. All measurements were performed before surgery. Each image was divided into two segments: the "foot" and "leg" segments. The foot segment was defined as the region below the ankle, and consisted of the toe and heel, and the leg segment was the defined as the region above the ankle and below the knee, and consisted of the shin and calf. The average temperature of each segment was calculated using software that computes an average temperature from data obtained from the thermal image (NEC San-ei).

Statistical Analysis

A power analysis based on data of Pvo_2/Pao_2 and foot skin temperature before anesthesia in preliminary study indicated that sample sizes of 10 and 7 subjects in each group, respectively, were needed to detect differences of 0.09 in Pvo_2/Pao_2 and 1.3°C in foot skin temperature with a power of 0.80 and α of 0.05. Therefore, at least 68 subjects were needed based on this analysis. We prepared 86 subjects, taking into consideration that some subjects might drop out. Four DM patients were excluded form these studies because of their apparent symptom of neuropathy. Eleven DM patients and 4 non-DM patients were excluded from the statistical analysis because of an abnormal R-R interval during deep breathing on the autonomic function test. The changes in arterial pressure in moving from a supine to a standing position were −3.5 ± 5.9 mmHg (range, −19 to 7 mmHg; n = 37) and −3.0 ± 5.4 mmHg (range, −15 to 10 mmHg; n = 30) in non-DM and DM patients, respectively. The final group sizes used in the analysis for study 1 were n = 16 for the DM group (isoflurane group, n = 9; sevoflurane group, n = 7) and n = 22 for the non-DM group (isoflurane group, n = 11; sevoflurane group, n = 11); the final group sizes used in the analysis for study 2 were n = 13 for the DM group (isoflurane group, n = 7; sevoflurane group, n = 7) and n = 14 for the non-DM group (isoflurane group, n = 8; sevoflurane group, n = 7).

Data are expressed as mean ± SD. Comparison of data between the DM and non-DM groups were performed using an unpaired *t* test or Mann–Whitney U test. For A-VΔO_2, changes in values within each group and differences between groups were analyzed by paired and unpaired *t* tests, respectively.

For leg skin temperature, comparison of baseline temperatures before anesthesia was performed using an unpaired *t* test, and changes in temperature were compared with baseline values using analysis of variance for repeated measurements. $P < 0.05$ was considered to be statistically significant. Data were analyzed using StatView 5 software (SAS Institute Inc., Cary, NC) and StatMate III software (ATMS Co. Ltd., Tokyo, Japan) on an Apple Macintosh computer (Apple Computer, Inc., Cupertino, CA).

Results

The demographic characteristics of the patients finally participated in the studies are shown in table 1. Age, body weight, sex distribution, and hemoglobin of the DM and non-DM patients did not have a significant difference in the isoflurane and sevoflurane anesthesia groups. Fasting blood sugar levels of DM patients were significantly higher than those of non-DM patients ($P < 0.01$), but those of DM patients in the isoflurane and sevoflurane groups did not differ significantly. In DM patients, there were no significant differences in the values of HbA_{1c} and mean duration of diabetes in the isoflurane and sevoflurane groups, and diabetes treatments were similar in the isoflurane and sevoflurane groups. Diabetes treatment included diet alone, oral hypoglycemic agents, and insulin. Four DM patients had not received any treatment.

Table 1. Profiles of Patients

	Study 1		Study 2	
	Non-DM (n = 22)	DM (n = 16)	Non-DM (n = 15)	DM (n = 14)
Age, yr	58.1 ± 11.4	60.8 ± 9.1	62.1 ± 10.1	63.3 ± 11.1
Sex, male/female	12/10	9/7	7/8	6/8
Body weight, kg	59.8 ± 11.9	61.3 ± 8.4	57.5 ± 10.5	60.1 ± 13.4
Height, cm	160.0 ± 8.5	158.9 ± 9.6	159.1 ± 12.1	163.1 ± 10.0
Volatile anesthetics, Iso/Sev	11/11	9/7	8/7	7/7
Fasting blood sugar, mg/dl	96.5 ± 8.3	141.2 ± 41.4*	94.2 ± 9.1	135.2 ± 31.1*
Hb, g/dl	13.5 ± 2.1	12.9 ± 2.6	13.5 ± 2.4	13.2 ± 1.8
HbA_{1C}, %	—	7.5 ± 1.9	—	8.0 ± 1.4
Insulin	—	10	—	7
Oral hypoglycemics	—	4	—	4
Diet therapy	—	3	—	3
No therapy	—	2	—	2

Data are mean ± SD.

* $P < 0.05$ *vs.* non-DM group. There was no significant difference between the isoflurane group and the sevoflurane group.

DM = diabetes mellitus group; Hb = hemoglobin; HbA_{1c} = glycosylated hemoglobin; Iso = isoflurane; non-DM = control group; no therapy = number of diabetic patients who did not receive any therapy (some of them did not know they had diabetes mellitus); Sev = sevoflurane; study 1 = arterial and venous blood gas analyses; study 2 = measurement of leg skin temperature.

Arterial–Venous Oxygen Content Difference

There were no differences in age, sex, weight, or height between the non-DM and DM groups. Rectal temperatures measured immediately after tracheal intubation and at the point of blood sampling during anesthesia were 36.6° ± 0.7° and 36.5° ± 0.6°C, respectively. Table 2 shows changes in mean arterial pressure and heart rate before induction of anesthesia and at the point when the end-tidal anesthetic concentration reached the 1 MAC level. There were no significant differences in mean arterial pressure and heart rate between non-DM and DM patients in the isoflurane and sevoflurane groups before anesthesia. Although mean arterial pressure significantly decreased in each group during anesthesia with isoflurane or sevoflurane at 1 MAC, the extent of change in mean arterial pressure was comparable among the four groups. In contrast, heart rate significantly decreased in DM patients during anesthesia with isoflurane but not with sevoflurane ($P < 0.05$).

Data for the Pvo_2/Pao_2 ratio before anesthesia, venous oxygen content (Cvo_2) of the femoral vein before and during anesthesia, and $A\text{-}V\Delta O_2$ are summarized in table 3. The Pvo_2/Pao_2 ratio before anesthesia was significantly greater in DM patients ($P < 0.05$), whereas Cvo_2 values before anesthesia were similar in non-DM and DM patients. Cvo_2 significantly increased during anesthesia in non-DM patients, but not in DM patients. Although $A\text{-}V\Delta O_2$ values before anesthesia were slightly higher in non-DM patients than in DM patients, this tendency did not reach statistical significance. During anesthesia, $A\text{-}V\Delta O_2$ markedly decreased in non-DM patients but not in DM patients. There were no significant differences in changes in Cvo_2 and $A\text{-}V\Delta O_2$ between the isoflurane and sevoflurane groups for DM and non-DM patients.

Leg Skin Temperature

There were no differences in age, sex, weight, or height between the non-DM and DM groups. Hemodynamic parameters measured during anesthesia, including heart rate, and systolic and diastolic blood pressure, did not differ between the non-DM and DM groups or between the isoflurane and sevoflurane groups.

Representative thermal images after induction of anesthesia are shown in figure 1; similar thermal images to

Table 2. Mean Arterial Pressure and Heart Rate before and during Anesthesia

	Mean Arterial Pressure, mmHg		Heart Rate, beats/min	
Group	Before Anesthesia	During Anesthesia	Before Anesthesia	During Anesthesia
Iso				
Non-DM (n = 12)	102.0 ± 5.0	72.8 ± 11.6*	84.1 ± 18.2	82.1 ± 12.9
DM (n = 10)	105.3 ± 6.1	70.8 ± 9.2*	83.2 ± 17.6	76.4 ± 14.3*
Sev				
Non-DM (n = 9)	102.2 ± 11.5	73.9 ± 14.2*	76.5 ± 16.0	72.9 ± 11.5
DM (n = 7)	101.4 ± 9.8	74.4 ± 16.1*	83.1 ± 20.1	78.1 ± 12.1

Data are mean ± SD.

* $P < 0.05$ *vs.* before anesthesia.

DM = diabetes mellitus group; Iso = isoflurane; non-DM = control group; Sev = sevoflurane.

Table 3. Blood Oxygen Data in Non-DM and DM Patients before and during Anesthesia

	Before Anesthesia			During Anesthesia	
Group	Pvo_2/Pao_2	Cvo_2, ml/dl	A-VΔO_2, ml/dl	Cvo_2, ml/dl	A-VΔO_2, ml/dl
Non-DM (n = 22)	0.47 ± 0.08	12.5 ± 2.7	4.8 ± 2.1	14.6 ± 2.7†	3.0 ± 1.5†
DM (n = 16)	0.54 ± 0.08*	13.7 ± 2.0	4.1 ± 1.5	14.3 ± 2.8	3.9 ± 2.0

Data are mean ± SD.

* $P < 0.05$ *vs.* non-DM. † $P < 0.05$ *vs.* before anesthesia.

A-VΔO_2 = difference in arteriovenous oxygen content; Cvo_2 = venous oxygen content; DM = diabetes mellitus group; non-DM = control group; Pvo_2/Pao_2 = partial pressure index.

those shown in figure 1 were obtained for all patients. Just before induction, the average skin temperature in the foot segment was below 32°C, which was lower than that in the leg segment, which was above 34°C (0 min in fig. 1). Three minutes after induction, a hot area (above 34°C, yellow and red in the image) emerged in the toe and heel, showing that the skin temperature in the foot segment was increasing gradually. The change in temperature was greater in the first 6 min after induction of anesthesia than in the following period. In thermal images of the leg segment, we found a "trail" line that was obviously at a different temperature to that of the adjacent skin (shown with an arrow in fig. 1); this trail was identified as the great saphenous vein. Three minutes after induction, the temperature of the trail was approximately 34°C, which was lower than that of the adjacent area, which was approximately 35°C (3 min in fig. 1). The temperature of the trail then increased and exceeded the adjacent skin temperature 6 min after induction of anesthesia. The blood temperature in the great saphenous vein may reflect the skin temperature of the trail.

Although the core temperature measured from the tympanic membrane after induction of anesthesia decreased gradually from induction until 15 min later, there were no significant differences between non-DM and DM patients in the isoflurane and sevoflurane groups. End-tidal concentrations of isoflurane and sevoflurane reached the 1 MAC level at 8.6 ± 1.8 and 5.9 ± 1.1 min after induction of anesthesia, respectively.

The average temperatures in the foot and leg segments in DM and non-DM patients before and during anesthesia are compared in figure 2. Before induction of anesthesia, the foot temperature in non-DM patients was 31.0° ± 1.3°C, which was significantly lower than that in DM patients (32.8° ± 0.9°C; $P < 0.05$). In contrast, the leg temperature was similar in both groups. There was no significant difference in the temperatures before anesthesia between isoflurane and sevoflurane group.

During anesthesia, the average foot temperature in both non-DM and DM patients gradually increased, with the increase in temperature in non-DM patients being greater than that in DM patients (fig. 2; $P < 0.05$). On the other hand, the average leg temperature in both groups gradually decreased, with the decrease in temperature being greater in DM patients than in non-DM patients ($P < 0.05$). Skin temperature changed significantly in comparison with baseline before anesthesia in all groups

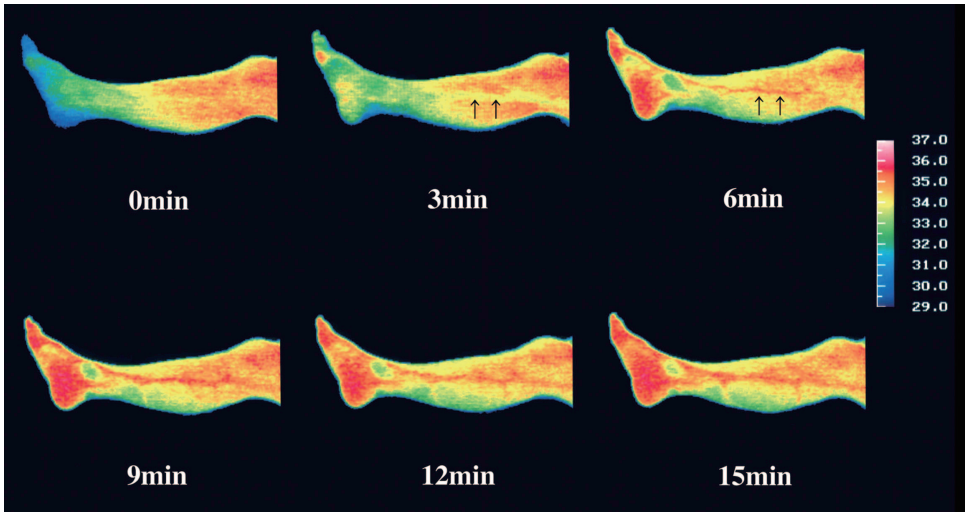

Fig. 1. Representative example of a thermal image showing the change in lower limb temperature after induction of anesthesia. These images were obtained for a 54-yr-old non–diabetes mellitus patient during isoflurane anesthesia. The *right color bar* indicates the temperature. Images were taken just before induction of anesthesia and every 3 min thereafter for 15 min, to give a total of six images. *Arrows* show the line of the great saphenous vein.

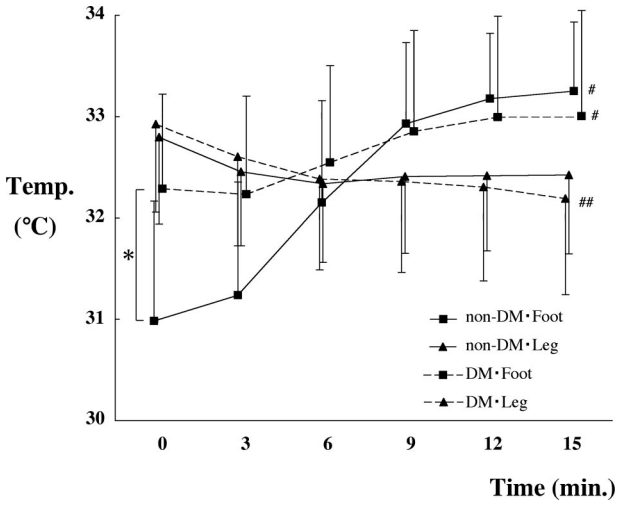

Fig. 2. The change in the foot and leg temperature in each group during general anesthesia. The *horizontal axis* shows elapsed time from induction of anesthesia. 0 min = just before anesthesia. Foot temperature in the non–diabetes mellitus (DM) group was significantly lower than in the DM group (* $P < 0.05$) before anesthesia. Foot temperature in the non-DM and DM groups increased gradually and significantly (# $P < 0.05$); the increase was significantly greater in the non-DM group than in the DM group ($P < 0.05$). Leg temperature in the DM groups decreased gradually and significantly (## $P < 0.05$).

except the non-DM leg group ($P < 0.05$). No significant differences in changes in foot and leg temperature occurred between the isoflurane and sevoflurane groups for non-DM and DM patients.

Discussion

The key findings of the current study are as follows. Before anesthesia, DM patients had a higher Pvo_2 of femoral venous blood and a higher Pvo_2/Pao_2 ratio, compared with non-DM patients, and infrared thermography showed a higher foot skin temperature in DM patients. During anesthesia with isoflurane or sevoflurane, the Cvo_2 increased and the A-VΔO_2 of the leg decreased in non-DM patients, but not in DM patients. Although isoflurane or sevoflurane induced an elevation of foot skin temperature and a decrease in leg skin temperature in both groups, these changes were greater in non-DM patients.

Core body temperature is strictly regulated by positive and negative feedback systems, as with many other control systems, and its afferent responses include sweating, shivering, vasodilation, and vasoconstriction. Thermoregulatory arteriovenous shunts that control peripheral blood flow are found in the foot[8] and are regulated by α-adrenergic sympathetic nerves. At normal body temperature, sympathetic vasoconstrictive nerves maintain these anastomoses in an almost totally closed state. In diabetic patients, the higher oxygen tension in femoral venous blood and the higher foot skin temperature suggest malfunction of local sympathetic control, resulting in vasodilation and a subsequent increase in blood flow through the arteriovenous anastomoses. High venous oxygen saturation and a subsequent decrease in A-VΔO_2 have been reported in diabetic patients with symptomatic neuropathy and foot ulceration,[12] and Boulton *et al.*[5] also showed that the mean venous blood Po_2 in the foot of diabetic subjects with neuropathy and foot ulceration was higher than that in nondiabetics or in diabetic subjects without neuropathy. These findings are consistent with our finding that the Pvo_2/Pao_2 ratio was higher in DM patients than in non-DM patients.

None of the diabetic patients showed neurologic symptoms such as abnormal sensations, burning pain, loss of vibration sensation, and reduced tendon reflex of the lower extremities, all of which are often seen in diabetic peripheral neuropathy. The patients also showed normal changes in arterial blood pressure in moving from a supine to a standing position and a normal tendon reflex, although 11 of the 41 diabetic patients showed abnormal R-R variation during deep breathing. The change in blood pressure in moving from a supine to a standing position is a specific test for assessing sympathetic function, whereas evaluation of R-R variation during deep breathing is commonly used for assessment of parasympathetic function. R-R variation is, however, influenced by many physiologic factors, including age, body weight, respiratory rate, and arterial blood pressure[13]; in fact, it has been demonstrated that 15% of healthy volunteers show at least one abnormal result in repeated autonomic function tests.[14] Therefore, taken together, these results suggest that the diabetic patients in the current study can be classified as having no neuropathy or asymptomatic neuropathy, according to Dyck's diabetic neuropathy staging.[15] However, the higher Pvo_2/Pao_2 ratio and higher foot skin temperature in the diabetic patients suggest that possible dysfunction of the local sympathetic nerve system may cause an increase in blood flow through arteriovenous shunts, even in diabetic patients without clinical autonomic neuropathy.

Skin temperature in conscious patients before anesthesia can be variable depending on their surroundings and emotional state. We observed skin temperature with thermography continuously at least 10 min before anesthesia. Consequently, we confirmed that the range of skin temperature variability was smaller than the difference of foot temperature of the DM and non-DM patients and that the speed of thermal change before anesthesia was slower than after induction of anesthesia. We considered an influence of temperature variability before anesthesia to be small.

The volatile anesthetics isoflurane and sevoflurane induced a rapid elevation of foot skin temperature in both DM and non-DM patients. It is possible that this thermal change is due to an increase in peripheral blood flow *via* arteriovenous anastomoses induced by the anesthetics.

The vasodilation effect of volatile anesthetics leads to redistribution of body heat, and infrared thermographic imaging showed the emergence of hot areas (yellow and red in the images) in the toe and heel after induction of anesthesia; this hot area corresponds to the anatomical location of the thermoregulatory arteriovenous anastomosis.[8,16] Interestingly, a lower skin temperature over the great saphenous vein was observed 3 min after induction of anesthesia, relative to the adjacent area, but the temperature corresponding to the vein then became higher than the adjacent area 6 min after induction. This may reflect changes in blood temperature in the toe and heel regions: Just after induction of anesthesia, increased blood flow through arteriovenous shunts caused by the anesthetics may have pushed cold blood from the foot to the saphenous vein, and therefore, the blood temperature of the saphenous vein rose after the foot temperature increased. It was unexpected to us that leg temperature decreased after induction of anesthesia. According to the theory of redistribution of body heat, core temperature decreases, and leg temperature should increase. However, leg temperature decreases, too. It suggested that redistribution of body heat was not as simple as we had expected. It was thought that a decrease of leg temperature might be due to a blood steal phenomenon that occurred for increased blood flow of arteriovenous anastomoses. Elevation of foot skin temperature after induction of anesthesia in the DM group was apparently smaller than that in non-DM group, and Cvo_2 significantly increased and A-VΔO_2 significantly decreased only in non-DM patients during anesthesia with isoflurane or sevoflurane; these variables were almost unchanged in DM patients. These findings suggest that the increase in local blood flow through arteriovenous anastomoses induced by anesthetics may be greater in non-DM than in DM patients, perhaps because in diabetic patients the arteriovenous shunts are already opened before anesthesia, and therefore, there is less potential for further anesthetic-induced vasodilation. Also, it was suggested that the effect of vasodilation by volatile anesthetics might make arteriovenous anastomoses open like autonomic neuropathy, and that blood flow in nutritional capillaries might be reduced.

Intraoperative hypothermia primarily results from core to peripheral redistribution of body heat.[17] Opening of arteriovenous shunts can lead to redistribution of body heat and to an increase in peripheral temperature and a decrease in core temperature. In the current study, core temperature measured at the tympanic membrane gradually decreased during anesthesia, but no difference between DM and non-DM patients was found over an experimental period of at least 15 min after induction of anesthesia. Kitamura *et al.*[18] demonstrated that diabetic autonomic neuropathy is associated with intraoperative hypothermia because of impaired thermoregulatory vasoconstriction, and showed that diabetic patients become more hypothermic 120 min after induction of anesthesia. This suggests that impaired peripheral blood flow regulation in diabetic patients may contribute to delayed hypothermia during anesthesia.

The use of thiopental as an induction agent is a limitation of the current study, because thiopental is an ultrashort-acting barbiturate that is known to have a vasodilatory effect on arteries and veins[19]; therefore, thiopental may influence changes in skin temperature and venous blood oxygen content after induction of anesthesia. We used thiopental as an induction drug to keep the patients immobilized during induction, because anesthetic induction with an inhaled agent alone often causes involuntary movement, making it difficult to make precise measurements of skin temperature by infrared thermography. However, we have confirmed that thiopental alone does not induce an increase in skin temperature in the toe and heel regions, as seen during isoflurane or sevoflurane anesthesia ($n = 3$; data not shown). Thus, we conclude that our findings are mainly due to the inhaled anesthetic agents, although effects induced by thiopental cannot be formally excluded. Furthermore, anesthetic induction with thiopental is commonly used clinically, and therefore, the findings in the current study are relevant to common clinical anesthetic practice.

In summary, diabetic patients without apparent neuropathy had a higher oxygen content in femoral venous blood and a higher foot skin temperature compared with nondiabetic patients. Induction of anesthesia with isoflurane or sevoflurane increased Cvo_2 and foot skin temperature in nondiabetic patients to a greater extent than in diabetic patients, suggesting that thermoregulatory shunt flow controlled by the sympathetic nervous system is impaired in diabetic patients, even in the absence of symptomatic neuropathy, and that peripheral vasodilation in response to inhaled anesthetics may be altered in these patients.

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