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# Preliminary Measurement of Intraoperative Sympathetic Nerve Activity Using Microneurography and Laser Doppler Flowmetry During Surgical Resection of Suprasellar Tumors

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## Abstract

**Intraoperative microneurography (enabling direct measurement of sympathetic outflow) and laser Doppler flowmetry were used to measure skin sympathetic nerve activity (SSNA) and skin blood flow (SBF) as indicators of hypothalamic damage during resection of 12 suprasellar tumors, 6 craniopharyngiomas, 4 meningiomas, 1 pituitary adenoma, and 1 germ cell tumor. SSNA was measured from a tungsten microelectrode inserted into the peroneal nerve, and SBF was measured from the foot innervated by the peroneal nerve. SBF reduction was induced by nociceptive procedures and non-nociceptive procedures before tumor exposure, on exposed tumors, and directly on the hypothalamus. SSNA could be reliably recorded in only 4 patients because of technical difficulties. In these patients, SSNA bursts appeared, followed by SBF reduction. The number of SSNA bursts was 37% to 100% of the number of SBF reduction events. Various surgical procedures involving painful stimuli or mechanical stress on the hypothalamus induced SSNA bursts and SBF reduction. The present findings suggest that SSNA and SBF can be used to detect sympathetic nerve activity, as an indicator of hypothalamic function, during neurosurgical procedures.**

Key words: intraoperative monitoring, laser Doppler flowmetry, microneurography, suprasellar tumor, sympathetic nerve activity

## Introduction

Resection of suprasellar tumors, such as craniopharyngiomas, optic or hypothalamic gliomas, germ cell tumors, or pituitary adenomas with suprasellar extension, frequently results in anhidrosis, intolerance of cold or heat exposure, and uncontrollable weight gain.[1,6,18,19] Hypothalamic damage due to tumor extension or intraoperative procedures is probably the cause of these manifestations of autonomic dysfunction.[1,18] However, prevention of iatrogenic hypothalamic damage is difficult because no effective methods for intraoperative monitoring of hypothalamic function are available.

Microneurography can be used to measure skin sympathetic nerve activity (SSNA) under many extreme conditions.[3,5,7] Microneurography now allows direct measurement of sympathetic outflow, and can separately assess SSNA and muscle sympathetic nerve activity.[11,17] SSNA regulates the sweat glands and precapillary sphincters of the arterioles. These sudomotor and vasoconstrictor/vasodilator functions are important in human thermoregulatory control. The vasomotor component can be monitored as the effector response of SSNA on skin blood flow (SBF) which is easily measured using laser Doppler flowmetry. Our previous study used microneurography for quantitative evaluation of the sympathetic component of hypothalam-

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ic function in patients with hypothalamic dysfunction following surgical resection of large suprasellar tumors.[18] We directly demonstrated abnormal sympathetic outflow in these patients.

In this study, microneurography and laser Doppler flowmetry were performed during resection of suprasellar tumors to measure sympathetic nerve function as an indicator of surgical stress on the hypothalamus.

## Materials and Methods

### I. Patients

Twelve patients, 7 women and 5 men aged from 4 to 80 years, underwent resection of suprasellar tumors in our institution over a period of 18 months (Table 1). The tumors were 6 craniopharyngiomas, 4 meningiomas, 1 pituitary adenoma, and 1 germ cell tumor. Five tumors, 4 craniopharyngiomas and 1 germ cell tumor, were removed using an interhemispheric trans-lamina terminalis approach, which may elicit direct mechanical stress on the hypothalamus. Seven tumors, 4 tuberculum sellae meningiomas, 2 craniopharyngiomas, and 1 pituitary adenoma, were removed using pterional, orbitozygomatic, or interhemispheric approaches without opening the lamina terminalis, which elicit only indirect mechanical stress on the hypothalamus.

SBF was measured by laser Doppler flowmetry and SSNA by microneurography during surgery. The study was approved by the Ethics Committees on Human Research of Nagoya University Hospital. Patients were informed of the purpose, procedure, and the risks of the protocol, and gave consent in written form.

### II. Microneurography and laser Doppler flowmetry

Patients were positioned supine on the operating table. A tungsten microelectrode with a shaft diameter of 120 $\mu$m, a tip diameter of approximately 1 $\mu$m, and an impedance of 3–5 M$\Omega$ was inserted percutaneously into the peroneal nerve prior to induction of general anesthesia. Nerve discharges were conducted from the microelectrode into an amplifier (Kohno IV; Kohno Instruments, Nagoya, Aichi) with high-impedance input and band-pass filtering from 500 to 5000 Hz, and were observed on a cathode-ray oscilloscope (Hitachi Electronics, Tokyo) with audio monitoring. The nerve discharges were then full-wave rectified, integrated with a time constant of 0.1 seconds, and recorded by a digital audio tape recorder (PC-216AX; Sony Precision Technology, Tokyo), with simultaneous visualization using a thermal pen recorder (Recti-Horiz; NEC-Sanei, Tokyo).[11,17,18] Identification of SSNA was based on the criteria described previously.[11]

**Table 1 Clinical characteristics of 12 patients**

| Case No. | Age (yrs)/ Sex | Micro-neurography | Diagnosis | Tumor size (mm) | | Approach | Removal | Hypothalamo-pituitary symptoms | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Width | Height | | | Preoperative | Postoperative |
| 1 | 4/F | | craniopharyngioma | 25 | 40 | BFBIH, TLT | total | none | DI, hypopit |
| 2 | 52/M | performed (poor record) | recurrent craniopharyngioma | 20 | 20 | BFBIH, TLT | total | hypopit | hypopit |
| 3 | 5/F | | craniopharyngioma | 40 | 40 | BFBIH, TLT | total | none | DI, hypopit |
| 4 | 23/F | | craniopharyngioma | 30 | 25 | pterional, TLT | total | none | none |
| 5 | 7/F | | immature teratoma | 20 | 35 | BFBIH, TLT | total | DI, hypopit | DI, hypopit |
| 6 | 67/M | performed | craniopharyngioma | 40 | 30 | BFBIH | total | none | none |
| 7 | 47/M | | prolactinoma | 40 | 25 | orbito-zygomatic | partial | none | none |
| 8 | 14/F | performed | recurrent craniopharyngioma | 15 | 15 | BFBIH | total | hypopit | hypopit |
| 9 | 58/M | performed | clinoidal meningioma | 40 | 25 | pterional | total | none | none |
| 10 | 37/F | performed (poor record) | TS meningioma | 25 | 25 | pterional | total | none | none |
| 11 | 69/F | performed | TS meningioma | 25 | 25 | pterional | total | none | none |
| 12 | 80/M | | TS meningioma | 30 | 30 | pterional | subtotal | none | none |

BFBIH: bifrontal basal interhemispheric, DI: diabetes insipidus, hypopit: hypopituitarism, TLT: trans-lamina terminalis, TS: tuberculum sellae.

Briefly, SSNA was recognized as irregular efferent nerve activity asynchronous with the heartbeat, followed by reduction of SBF with a consistent latency, elicited by mental or physical stimuli or a sudden deep breath. The probe of the laser Doppler flowmeter was affixed with paste on the area of the skin innervated by the peroneal nerve (on the foot of the same side) to monitor SBF. Unfortunately we experienced technical difficulties with electrode insertion and electrical noise in our operating theater, so microneurography was performed in only 6 patients and SSNA was reliably recorded in only 4 patients.

After confirming the recording of SSNA and SBF, anesthesia was induced with propofol, fentanyl, and vecuronium, and maintained with oxygen, isoflurane, propofol, fentanyl, and vecuronium.[4,14] Core body temperature and electrocardiography were monitored. Room temperature was maintained stable. The legs of the patient were kept warm. SSNA and SBF were continuously recorded together with heart rate and arterial blood pressure by a pen recorder throughout the operation. The streaming data on the pen recorder were captured with an 8 mm video camera, and simultaneously recorded with the surgical video in picture-in-picture style. During surgery, performance of special procedures such as tumor dissection or retraction was noted by the surgeon and marked on the record. All other surgical procedures which elicited SSNA bursts and SBF reduction were identified by observation of the TV monitor in the operating room or from the surgical video.

## III. Data analysis

SSNA bursts are followed by episodic reduction of SBF with a latency of about 4 seconds.[8,9] In this study, SBF reduction following SSNA burst was confirmed several seconds after each operative procedure. The duration of SBF reduction was usually less than 10 seconds. SSNA was measured as the height (mm) of the integrated wave pattern.[8,11] Reduction of SBF was expressed as a percentage of the SBF value immediately before the reduction.

Surgical procedures eliciting reduction of SBF were classified into two groups: Procedure 1 included nociceptive procedures such as incision of skin, muscle, or dura, and Procedure 2 included non-nociceptive intradural procedures. Non-nociceptive procedures were subdivided into three groups: procedures before tumor exposure such as dissection of the interhemispheric fissure (Procedure 2A), procedures on exposed tumors such as retraction or compression of the tumor (Procedure 2B), and procedures directly involving the hypothalamus such as dissection of tumor from the hypothalamus after opening the lamina terminalis (Procedure 2C).

Data were expressed as mean ± standard error, and were compared between procedures using repeated measures analysis of variance and Student-Newman-Keuls test. The Spearman rank correlation was calculated to compare SBF reduction and SSNA burst height. P values less than 0.05 were considered significant.

**Table 2 Numbers of skin blood flow (SBF) reduction events and skin sympathetic nerve activity (SSNA) bursts**

| Case No. | Procedure 1 | | Procedure 2A | | Procedure 2B | | Procedure 2C | No procedure |
|---|---|---|---|---|---|---|---|---|
| | SBF reduction [a] | SSNA burst (% of [a]) | SBF reduction [a] | SSNA burst (% of [a]) | SBF reduction [a] | SSNA burst (% of [a]) | SBF reduction | SBF reduction |
| 1 | 291 | | 132 | | 100 | | 29 | 8 |
| 2 | 122 | | 25 | | 83 | | 105 | 9 |
| 3 | 83 | | 76 | | 48 | | 88 | 3 |
| 4 | 243 | | 73 | | 86 | | 60 | 16 |
| 5 | 248 | | 313 | | 62 | | 58 | 20 |
| 6 | 87 | not recorded | 44 | 40 (91%) | 64 | 24 (38%) | | 0 |
| 7 | 902 | | 72 | | 385 | | | 18 |
| 8 | 32 | 19 (59%) | 23 | 23 (100%) | 73 | 46 (63%) | | 0 |
| 9 | 122 | 45 (37%) | 100 | 66 (66%) | 330 | 232 (70%) | | 31 |
| 10 | 101 | | 34 | | 66 | | | 23 |
| 11 | 39 | 38 (97%) | 3 | 3 (100%) | 76 | 39 (51%) | | 0 |
| 12 | 153 | | 30 | | 161 | | | 0 |

Procedure 1: nociceptive procedures, Procedure 2: non-nociceptive procedures before tumor exposure (2A), on exposed tumors (2B), and directly involving the hypothalamus (2C).

## Results

Table 1 shows the clinical and radiological findings, surgical approach, and surgical outcome for the 12 patients. Table 2 and Fig. 1A show the numbers of SBF reduction events and SSNA bursts during nociceptive (Procedure 1) and non-nociceptive (Procedures 2A, 2B, and 2C) surgical procedures. SBF reduction was also detected without specific surgical procedures in 8 patients (Table 2). The number of SBF reduction events varied among patients and was significantly higher during Procedure 1 compared to Procedure 2A ($p < 0.05$). The number of SSNA bursts was 37% to 100% of the number of SBF reduction events, and did not differ significantly between procedures. Figure 1B shows the mean SBF reduction and mean SSNA burst heights. SBF reduction ranged between 12.0% and 61.4%. The mean SBF reduction in Procedure 1 was significantly higher than in Procedure 2A ($p < 0.05$). The SSNA burst height ranged between 19.4 and 58.6 mm, and did not differ significantly between procedures.

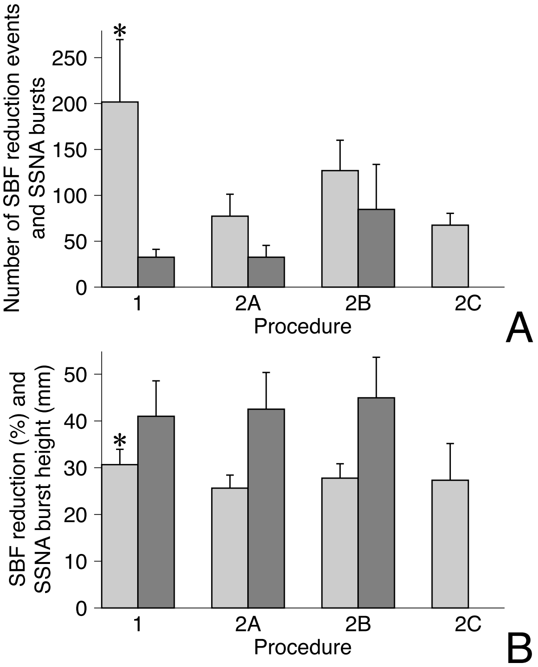

**Fig. 1** **Numbers of skin blood flow (SBF) reduction events (*gray bars*) and skin sympathetic nerve activity (SSNA) bursts (*black bars*) (A) and mean SBF reduction (*gray bars*) and mean SSNA burst heights (*black bars*) (B) during nociceptive (Procedure 1) and non-nociceptive (Procedures 2A, 2B, and 2C) surgical procedures. The number of SBF reduction events (A) and mean SBF reduction (B) were significantly higher in Procedure 1 than in Procedure 2A by repeated measures analysis of variance and Student-Newman-Keuls test (*$p < 0.05$).**

## Illustrative Cases

**Case 1 with SBF measurement**: A 4-year-old girl presented with complaints of headache and vomiting. Magnetic resonance (MR) imaging revealed a partly cystic mass extending into the third ventricle (Fig. 2A, B). Baseline SBF was 29.7 ± 5.8 ml/min/100 g tissue, the mean duration of SBF reduction episodes was 3.9 ± 1.9 sec, and SBF reduction was 22.7 ± 13.5%. Large changes in SBF were noted during nociceptive procedures such as skin incision and craniotomy and dissection of tumor from the hypothalamus. Figure 3 shows video records during tumor resection. The tumor was exposed using an interhemispheric trans-lamina terminalis approach. SBF decreased with short latency after the tumor was compressed, and recovered gradually following release of compression. The tumor adhered more to the left side of the hypothalamus than to the right side. Dissection from the right hypothalamus induced 6 events of SBF reduction whereas dissection

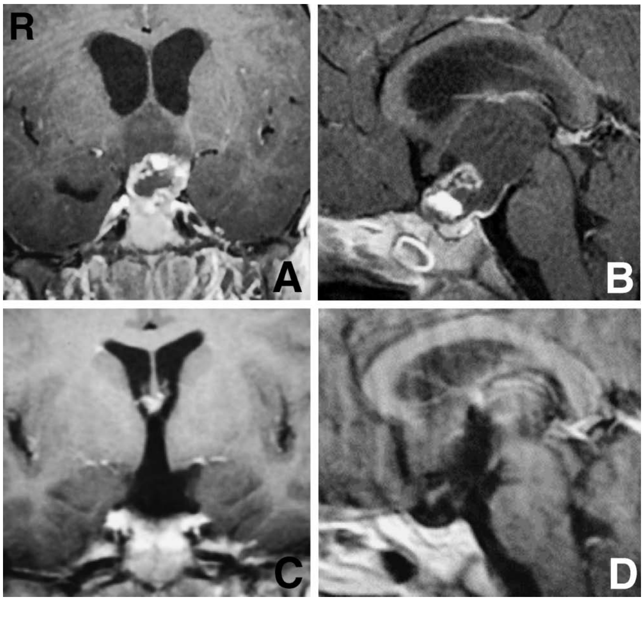

**Fig. 2** **Case 1. Preoperative $T_1$-weighted magnetic resonance (MR) images with contrast medium (A, B) showing a retrochiasmatic, partly cystic craniopharyngioma extending into the third ventricle, and postoperative $T_1$-weighted MR images with contrast medium (C, D) showing removal of the tumor and slight damage to the left hypothalamus.**

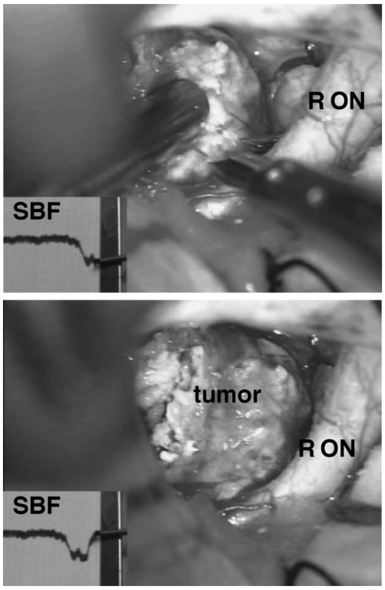

**Fig. 3** **Case 1. Video records during tumor resection through a basal interhemispheric approach showing skin blood flow (SBF) reduction shortly after compression of the tumor (*upper*) and gradual recovery following release of compression (*lower*). R ON: right optic nerve.**

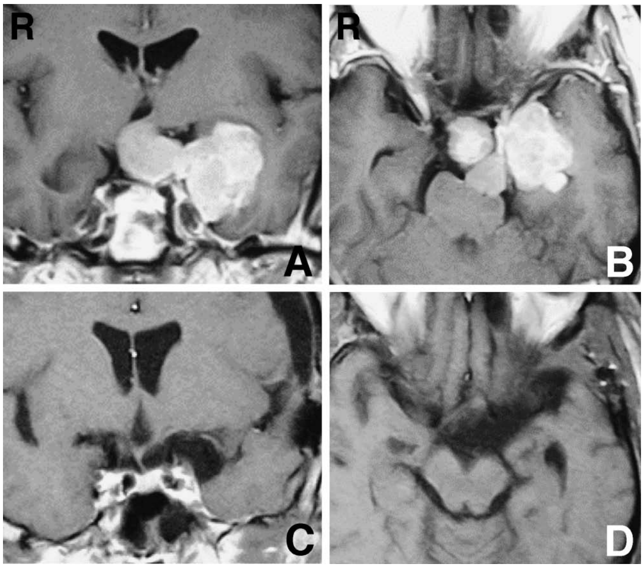

**Fig. 4** **Case 9. Preoperative $T_1$-weighted magnetic resonance (MR) images with contrast medium (A, B) showing a suprasellar meningioma extending to the left, and postoperative $T_1$-weighted MR images with contrast medium (C, D) showing removal of the tumor.**

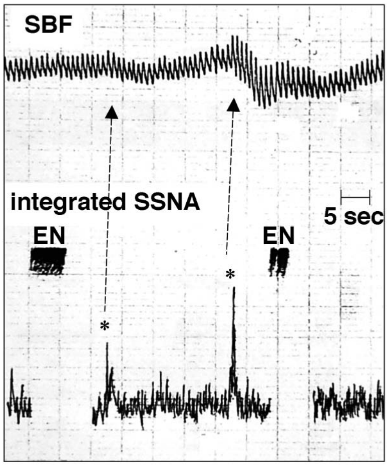

**Fig. 5** **Case 9. Records during tumor resection through a left pterional approach showing skin sympathetic nerve activity (SSNA) bursts (*asterisks*), followed by reduction of skin blood flow (SBF). EN: electrical noise.**

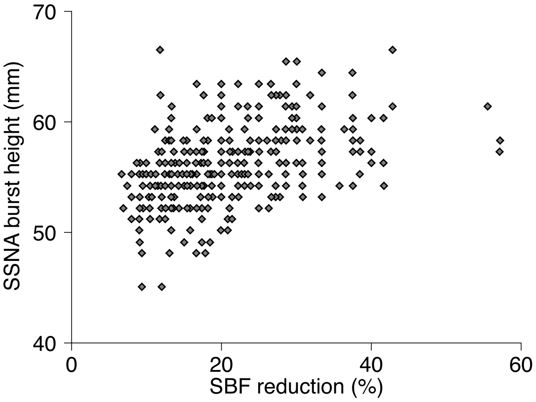

**Fig. 6** **Case 9. Spearman rank correlation of SBF reduction and corresponding SSNA burst height revealed a significant correlation (rs $= 0.465$, $p < 0.0001$).**

on the left side induced 23 events. Postoperatively the patient showed hypopituitarism and diabetes insipidus. The postoperative course was otherwise uneventful. MR imaging revealed slight damage to the left hypothalamus (Fig. 2C, D).

**Case 9 with SBF and SSNA measurements**: A 58-year-old man was admitted with gradual decrease in left visual acuity. MR imaging revealed a suprasellar meningioma extending to the left (Fig. 4A, B). SSNA bursts were consistently recorded throughout surgery. Figure 5 shows records during tumor resection through a left pterional approach. Pressure on the tumor beneath the hypothalamus caused an SSNA burst, followed by SBF reduction. Figure 6 shows the relationship between SBF reduction and corresponding SSNA burst height. These parameters showed a significant correlation in this patient ($rs = 0.465$, $p < 0.0001$). The postoperative course was uneventful. MR imaging revealed complete removal of the tumor (Fig. 4C, D).

## Discussion

The present study used SBF measurement as a substitute for SSNA measurement. Episodes of SBF reduction were found throughout the surgical procedures. SSNA bursts were recognized ahead of 37% to 100% of SBF reduction events. These SSNA bursts were probably indicative of specific changes in sympathetic nerve activity. Episodes of SBF reduction were induced by both nociceptive procedures and non-nociceptive procedures around the hypothalamus. Non-specific episodes of SBF reduction were also detected without surgical procedures. Episodes of SSNA bursts and SBF reductions were immediately and consistently induced by surgical procedures during dissection of suprasellar tumors, such as traction or compression of tumor and dissection of the tumor from the hypothalamus regardless of the tumor pathology. Comparison of procedures on the right and left sides of the hypothalamus in the same patients found that dissection of tumor adhering to the hypothalamus induced increased numbers of episodes. Therefore, SSNA and SBF are sensitive methods for monitoring changes in sympathetic nerve activity induced by both nociceptive and non-nociceptive procedures around the hypothalamus during surgery.

### I. Pathophysiology of procedures on the hypothalamus

Our previous study using microneurography found that after resection of suprasellar tumors, patients exhibited hypothalamic dysfunction.[18] Sudomotor and vasodilatative nerve activities during heating were markedly impaired in such patients. Animal studies have shown that the preoptic area of the hypothalamus occupies a crucial position in the neuronal circuit for thermoregulation, detecting local brain temperature as well as receiving thermal information from the body core and the skin.[20] Approximately 30% of neurons in the preoptic area were heat-sensitive and less than 5% were cold-sensitive. Somatosensory information from skin and spinal thermoreceptors is sent to the preoptic heat-sensitive neurons and allows these neurons to integrate central and peripheral thermal information. Heat-sensitive neurons produce the predominant effector output, regulating heat loss and heat production.[2] The descending pathway from the heat-sensitive neurons passes through the median forebrain bundle.[10] The periaqueductal gray matter is important for the transmission of efferent signals to thermoregulatory effectors in the rat.[20] The rostral periaqueductal gray matter receives input from the median preoptic nucleus activated by heat exposure. The medullary raphe area receives inhibitory signals from the preoptic area and may serve as a vasoconstriction center for thermoregulation.[16] Prostaglandin $E_2$ suppresses the tonic firing of preoptic area neurons (which may be GABAergic), disinhibits the medullary raphe neurons, stimulates the sympathetic nervous system, and induces fever via stimulation of thermogenesis in the brown adipose tissue.[12] Electrical or chemical stimulation of the preoptic area suppresses shivering and facilitates vasodilation in anesthetized rats.

In this study, direct or indirect mechanical stress on the hypothalamus probably suppressed the activity of neurons in the preoptic area and induced vasoconstriction through activation of the medullary raphe. SBF reductions were brief and reversible, probably because the effects on the hypothalamus were transient. Since our patients suffered no sequelae suggestive of significant hypothalamic damage, we could not confirm the presence of intraoperative SSNA responses and SBF changes induced by irreversible hypothalamic damage. However, our previous study did find that permanent damage of the hypothalamus resulted in impaired response of SSNA to systemic heat exposure.[18]

### II. Pathophysiology of nociceptive stimuli

The medullary raphe neurons also control the cutaneous vasoconstriction induced by noxious stimuli.[13] Changes in cutaneous blood flow are largely sympathetically mediated and occur without increases in arterial pressure. Electrical stimulation of the amygdala or hypothalamus causes vasoconstriction of the skin via the medullary raphe area in the rabbit.[13] Similar selective decreases in cutaneous blood flow occur when conscious rabbits detect salient environmental events eliciting an alert response, and these decreases are entirely abolished by bilateral pharmacological inactivation of the amygdala region.[21] Selective cutaneous vasoconstriction is also observed in response to painful stimuli in anesthetized humans.[15] A significant correlation was found between the intensity of noxious stimuli and the magnitude of vasomotor responses. In the present study, noxious stimuli such as incision or coagulation of the skin, muscle, or meninges probably activated the vasoconstriction center in the medullary raphe through the limbic system.

### III. Limitations of the present study

Microneurography is the only method enabling direct measurement of sympathetic nerve activity, but is technically difficult. Insertion of a tungsten microelectrode into a peripheral nerve is an extremely demanding procedure and must be performed prior to induction of general anesthesia with the cooperation of the patient. Therefore, this procedure cannot be performed in children. We sometimes failed to obtain SSNA records due to strong electrical noise from surgical and anesthetic equipment. We obtained a statistically significant correlation between the SSNA burst heights and SBF reduction in only one patient (Case 9). Monitoring of SSNA bursts using microneurography is very specific, but difficult to perform consistently in the operating theater. On the other hand, SBF measurement is simple and does not add stress to the patient. SBF is mainly controlled by SSNA but is also affected by various conditions such as room temperature, agents and depth of anesthesia, and blood pressure. The finding of a positive correlation between the SSNA burst heights and SBF reduction suggests that more invasive stress induces higher SSNA bursts and greater reduction of SBF.[9] Therefore, monitoring of SBF reduction may provide an alternative to microneurography.

Another drawback of this study was our inability to distinguish responses induced by hypothalamic stress from those induced by nociceptive stimuli. SBF reduction by nociceptive procedures was rather higher than SBF reduction by non-nociceptive intradural procedures. Further study is needed to identify the specific pattern of SSNA bursts and SBF changes suggestive of hypothalamic origin of modification of sympathetic nerve activity, and those suggestive of irreversible hypothalamic damage.

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## *Commentary*

*The authors measured skin sympathetic nerve activity (SSNA) and skin blood flow (SBF) as indicators of hypothalamic damage during resection of 12 suprasellar tumors, 6 craniopharyngiomas, 4 meningiomas, 1 pituitary adenoma, and 1 germ cell tumor by using intraoperative microneurography (enabling direct measurement of sympathetic outflow) and laser Doppler flow meter. They found that SBF reduction was induced by nociceptive procedures and non-nociceptive procedures before tumor exposure, on exposed tumors, and directly on the hypothalamus. They found that SBF reduction was observed following the SSNA bursts and the number of SSNA bursts was 37% to 100% of the number of SBF reduction events in four patients whose SSNAs were reliably recorded. Based on their observations, the authors suggested that less invasive SBF can be used to detect sympathetic nerve activity instead of more invasive SSNA, as an indicator of hypothalamic function, during neurosurgical procedures.*

*To avoid hypothalamic damage is one of the most important things in the surgical resection of the tumors located in the suprasellar area, 3rd ventricle adjacent the hypothalamus. Since the impact of hypothalamic damage during the operation is too detrimental to the patient, preservation of the hypothalamus should be put first on the list to be avoided during the surgery. Unfortunately, however, there was no feasible and reliable monitoring method for the hypothalamus during the surgery. In that sense, this paper reported a good preliminary data of the clinical application of SSNA and SBF as a could-be-useful indicator to monitor hypothalamic function during the surgical resection of the tumors surrounding hypothalamus. However, the results in this study should be cautiously interpreted to validate the applicability of measurement of SSNA and SBF as an indicator of hypothalamus injury.*

*Traditionally, vital signs such as arterial blood pressure or heart rate have been frequently used to detect the sympathetic response to surgical stress during general anesthesia. Although the cardiovascular response to surgical stress is directly influenced by inhaled anesthetics, vasodilators, beta-adrenergic blockers or sympathomimetics infused during the anesthesia, the change of the vital signs should have been analyzed with the monitoring of SSNA and SBF in this study.*[1,2,4)]

*Secondly, the sudden reduction of SBF might be a nonspecific phenomenon unrelated with the hypothalamic injury. Since the sudden reduction in skin tissue blood flow measured by using laser Doppler may have some relationship to the sympathetic nervous responses (i.e. increase in plasma norepinephrine levels and cardiovascular response) even to surgical incision under halothane or isoflurane anesthesia.*[3)]

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*The authors present a novel method of intraoperative monitoring for potential hypothalamic damage as a result of operations for suprasellar lesions. The basis for the monitoring is the measurement of sympathetic changes potentially derived from hypothalamic manipulation, and measured by intraneural electrodes in the peroneal nerve and skin surface electrodes on the food in the peroneal distribution. Sympathetic nerve activity and changes in cutaneous blood flow are the end points, with bursts of sympathetic response as the indicator of hypothalamic distortion.*

*The small number of patients in whom these difficult measurements were successfully obtained is a limitation of the study. The findings would be reinforced by a larger series, particularly in craniopharyngiomas where the most promising results were obtained. The influence of pre-existing hormonal deficits from the tumors involved also merits additional study. This is a provocative paper in an area which has received little previous attention.*

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