Am J Physiol Heart Circ Physiol 291: H1761–H1767, 2006.
First published May 26, 2006; doi:10.1152/ajpheart.00280.2006.

Effects of sympathetically induced vasomotion on tissue-capillary fluid exchange

Terumi Sakurai and Naohito Terui

Department of Physiology, Institute of Basic Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

Submitted 17 March 2006; accepted in final form 7 May 2006

Sakurai, Terumi, and Naohito Terui. Effects of sympathetically induced vasomotion on tissue-capillary fluid exchange. *Am J Physiol Heart Circ Physiol* 291: H1761–H1767, 2006. First published May 26, 2006; doi:10.1152/ajpheart.00280.2006.—The spontaneous and rhythmic constriction of peripheral arterioles, which is not associated with the cardiac or respiratory cycles, is called vasomotion. Vasomotion is observed in various tissues of various species, but the physiological role of vasomotion has not been clarified because of the difficulty in controlling the appearance of vasomotion in in vivo preparations. We developed a method of controlling vasomotion in in vivo experiments. The electrical stimulation of the cervical sympathetic nerve could reproducibly evoke vasomotion in rabbit ear skin. The frequencies of the evoked vasomotion were 0.04–0.07 Hz, which corresponded to spontaneously occurring vasomotion that has been reported before. Vasomotion was always evoked between 25 and 35°C. At lower than 17°C or higher than 37°C, vasomotion was not evoked. With the use of this method of evoking vasomotion in vivo, the role of vasomotion in tissue perfusion was examined. A tracer (Cr-EDTA) was injected into the ear tissue, and tracer fading was then measured by using a camera. The rates of fading (clearance) of the tracer with vasomotion were significantly greater (1.7 to 8.1 times) than those without vasomotion. These results provided evidence that vasomotion enhanced tissue perfusion.

flow motion; microcirculation

A SPONTANEOUS RHYTHMIC CHANGE in vascular diameter, termed vasomotion, is a typical feature of arteriolar networks. Vasomotion has been observed in various tissues of mammals, including humans (1, 5, 8, 18, 21, 33). It is not correlated with other physiological rhythms, such as breathing movements or heartbeat (13). Vasomotion causes a rhythmic variation in blood flow (flow motion) (2, 7), which can be detected by laser-Doppler flowmetry (3, 14, 19, 25, 29).

The main function of the microvasculature is the transport of materials. Water and solutes in blood are carried through microvessels and exchanged, through vessel walls, with those in surrounding tissues. It has been suggested in theoretical models that oscillatory perfusion may confer specific advantages over steady-state flow (12, 16, 24, 28), but the physiological significance of vasomotion in microcirculatory flow remains the subject of investigations and considerable debate (3, 26, 27). Because vasomotion disappears readily upon anesthesia (6) and the appearance of vasomotion cannot be controlled, the examination of vasomotion in in vivo preparations has been difficult.

The temperature of a preparation was reported to affect the frequency of vasomotion. As temperature increases, the frequency of vasomotion increases (4, 5), until disappearing at a certain temperature (17, 25, 29). Vasomotion is also abolished by decreasing temperature to a certain level (5). Vasomotion occurs in response to the application of α-receptor agonists in vitro (22). It seems that vasomotion is evoked by sympathetic nerve stimulation and controlled by temperature in in vivo preparations. To our knowledge, however, no experimental trials have been carried out.

The effects of muscle capillary blood flow in the steady state on the permeability of water-soluble substances are examined by the microscopic tissue clearance method (30). In this method, a muscle tissue is stained with a test tracer by suffusing the tracer solution around the tissue, and then subsequent changes in tissue concentration attributable to tracer washout by capillary flow are recorded. With the use of this clearance method, the effects of vasomotion on tissue-fluid material exchanges can be evaluated.

To clarify the physiological significance of vasomotion, we *1*) developed a method for the reproducible induction of vasomotion in anesthetized rabbits in vivo and *2*) examined the effects of vasomotion on material exchanges between tissue and blood.

METHODS

Preparation

Experiments were performed on Japanese White rabbits (3.35 ± 0.11 kg) of both sexes. All experiments were approved by the Animal Experiment Committee of the University of Tsukuba. Animals were initially anesthetized with 3% halothane (Takeda), administered through a face mask. After the administration of halothane, hair was shaved from the ear, and the right femoral vein and artery were then exposed for the insertion of polyethylene catheters with local anesthesia using xylocaine (80 mg/1 ml lidocaine hydrochloride, Astra). Urethane (1 g/kg body wt, Tokyo Kasei) was administered intravenously through the catheter of the femoral vein. By monitoring the fluctuation of arterial pressure and heart rate, the level of anesthesia was checked at all stages, and an additional dose of the anesthetic was given when necessary. After the injection of urethane, the right femoral artery was cannulated for the measurement of systemic arterial pressure (AP). The arterial line was filled with heparin (heparin sodium salt, 200 units/ml in 0.9% saline, Wako). After the trachea was cannulated, the animal was immobilized with gallamine triethiodide (Sigma), initially at 30 mg and thereafter at 20 mg/h iv with an infusion pump (STC-521, Terumo). Animals were ventilated artificially with a gas mixture of 20% O_2-80% room air using a

Address for reprint requests and other correspondence: N. Terui, Dept. of Physiology, Institute of Basic Medical Sciences, Graduate School of Comprehensive Human Sciences, Univ. of Tsukuba,. 1–1-1 Tennodai, Tsukuba-shi, Ibaraki-ken 305–8575, Japan (e-mail: terui@md.tsukuba.ac.jp).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

respiratory pump (model 661E, Harvard Apparatus). End-expiratory CO_2 concentration was monitored continuously (RespinaIH26, Sanei-NEC) and maintained at between 3.8 and 4.2% by adjusting ventilation volume. Rectal temperature was maintained at 39–40°C with a thermostatically regulated heating pad and an infrared lamp connected to a thermocouple inserted into the rectum. Room temperature was maintained at 26 ± 3°C. To change the temperature solely of an ear, the ear was covered with a thermally insulated box in which temperature-controlled air was circulated. Temperature in the box was measured with a thermocouple thermometer. At the end of the experiment, the animal was euthanized by the administration of an overdose of the anesthetic.

Stimulation of Cervical Sympathetic Nerve

The cervical sympathetic nerve was exposed unilaterally by a flank incision of the neck and isolated from the surrounding tissue. The distal cut end of the nerve was placed across a pair of silver-wire electrodes spaced 2–3 mm apart. Electrical stimuli were square-wave pulses of 0.5-ms duration. For monitoring ear blood flow (EBF) decrease using a laser-Doppler flowmeter, stimulus intensity (4.5–16.5 V) was adjusted to be 1.5 times the maximal strength as determined by continuous electrical stimulation at 20 Hz for 10 s. Response thresholds ranged between 0.38 and 2.00 V. All these stimulus pulses were delivered from a pulse generator (SEN-7103, Nihon Kohden) through an isolation unit (SS-201J, Nihon Kohden). The exposed cervical sympathetic nerve was covered with mineral oil to prevent drying.

Data Recordings

AP, end-expiratory CO_2 concentration, EBF, ambient temperature of the ear, and rectal temperature were recorded online (the sampling rate of AP was at 140 Hz, whereas other parameters were at 12 Hz) using the CED 1401 plus interface and Spike2 software (Cambridge Electronic Design, Cambridge, UK).

Recordings of Vasomotion and Flow Motion

Changes in the diameter of an arteriole (vasomotion) were observed through the dorsal skin of the ear under a video microscope (TW-CM10, Sony). Hair was removed from the ear with a hair remover (thioglycolic acid, Kanebo), and the observed area of the ear was transilluminated with a halogen lamp. To determine the association of diameter changes of a vessel with blood flow changes, time marks at 1-s intervals were generated as sounds (for videotape recordings) and as pulses (for flowmeter recordings). The videos were converted to audio video interleaving (AVI) files using a digital video (DV) converter (ADVC100, Canopus). The diameter changes of an arteriole were measured every 1 s from frame pictures of the AVI files.

To measure changes in blood flow (flow motion), a probe of a laser-Doppler flowmeter (1-s time constant, ALF21D, Advance) was placed on the skin over an arteriole. We selected arteries from first-, second-, or third-order branches, so that the diameter of arterioles was in the range of 30 to 100 μm.

Recordings of Tissue Perfusion

Tissue perfusion was measured by the clearance method (30). As the indicator for clearance, we employed Cr-EDTA, which is often used to examine capillary permeability (23, 32). Cr-EDTA is an inert blue dye with a molecular weight of 341, approximately equal to sucrose (342 mol wt), and does not bind to albumin. Cr-EDTA (0.1 M, 20 μl) was injected into the skin of the rabbit ear. As previously noted (30), the tracer was washed out by capillary flow, and then the blue color of the tissue faded gradually. The fading of the blue color of the tissue indicates a concentration change of Cr-EDTA in the tissue. Therefore, we recorded color fading with a color CCD digital camera (DXC-S500, Sony), which took an image (640 × 480 pixels) of the injected part of the ear every 30 s. The exposure and white balance of the digital camera were set manually and remained fixed throughout the experiment. The injected part of the ear was transilluminated with a halogen lamp. The color images were converted to an eight-bit gray scale (0–255) using Photoshop (Adobe systems), and the gray-scale images were then analyzed using Scion Image (Scion). Tracer concentration was estimated as the mean value of the gray scale within the region of interest.

Experimental Procedure

Vasomotion and flow motion. To establish the relationship between vasomotion and flow motion, a simultaneous recording was performed. A probe of the laser-Doppler flowmeter was placed on the skin of the ear on the ventral side, and changes in the diameter of the arteriole onto which the probe was attached were observed from the dorsal side under the video microscope. Because of the low resolution, no movements of arterioles with a diameter of <30 μm could be observed by this video microscopy method.

Experiment 1: frequency of stimulation and flow motion. To establish the relationship between the frequency of electrical stimulation and induced flow motion, stimuli of various frequencies (a burst of 5 pulses at 20 Hz every 0.5–20 s or a continuous stimulation with pulses of 2–25 Hz) were applied to the cervical sympathetic nerve.

Experiment 2: temperature and flow motion. To establish the relationship between temperature and the frequency of induced flow motion, the ambient temperature of the ear was decreased in a stepwise manner from room temperature to ~10°C, then increased to 42°C, and decreased again to room temperature. The temperature inside the box was kept constant (±0.5°C) during the electrical stimulation of the cervical sympathetic nerve.

Experiment 3: effects of flow motion on tissue perfusion. Before the electrical stimulation, Cr-EDTA (0.1 M, 20 μl) was injected into the skin of the rabbit ear. The ear was placed in the box for the control of ambient temperature. Measurements were carried out at low or high ambient temperatures at which flow motion could be induced and at lower or higher temperatures at which flow motion could not be induced.

Statistical Analysis

The results of *experiment 2* were statistically analyzed using Pearson's correlation coefficient. The Wilcoxon signed-ranks test was used to determine the significance of differences in *experiment 3*. The level of significance was $P < 0.05$. Results were expressed as means ± SE.

RESULTS

Vasomotion and Flow Motion

The electrical stimulation of the cervical sympathetic nerve induced vasomotion in most arterioles at the center, medial edge, lateral edge, and tip of the ear. Vasomotion was observed from the first to fourth branched arterioles (~30 μm in diameter) (Fig. 1 and *supplemental video 1*, *A* and *B*; note: all supplemental videos cited in this article are available online at the *American Journal of Physiology-Heart and Circulatory Physiology* web site). The contraction of the vessel seemed to start and spread (1–4 mm/s) from one branching point to the next. The direction of propagation was not necessarily toward the periphery.

As shown in Fig. 2, the electrical stimulation of the cervical sympathetic nerve immediately decreased the diameter of the arteriole and EBF. The decrease in EBF was maintained throughout the stimulation. Rhythmical changes in the diame-

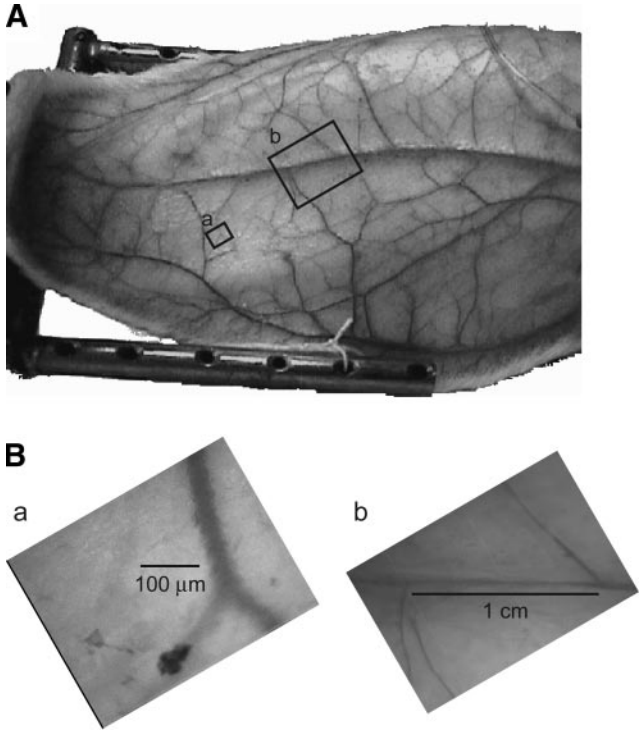

Fig. 1. Stimulation-induced vasomotion. Electrical stimulation of cervical sympathetic nerve elicited vasomotion of arterioles. *A*: dorsal surface of rabbit ear. Squares [third bifurcated arterioles (*a*) and first bifurcated arterioles (*b*)] indicate regions shown in *B*.

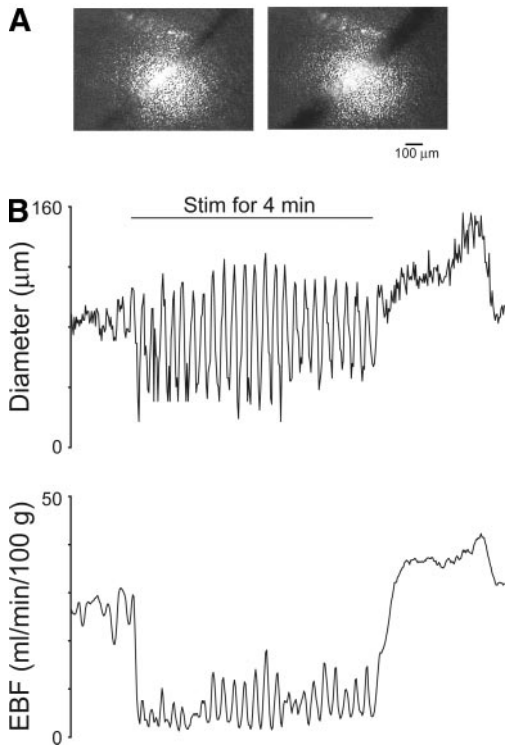

Fig. 2. Simultaneous recording of vasomotion and flow motion. Simultaneous recording with a video microscope and using laser-Doppler flowmeter. *A*: samples of pictures from video microscope: constricted state (*left*) and dilated state (*right*). To measure changes in ear blood flow (EBF), a flowmeter probe (bright areas in video pictures) was placed on the skin of the ear on ventral side. *B*: electrical stimulation (9 V, 10 Hz continuous) of cervical sympathetic nerve induced vasomotion (*top*) and flow motion (*bottom*).

ter of the arteriole and EBF started after the onset of the stimulation. After the cessation of stimulation, these rhythmical changes disappeared, and the diameter of the arteriole and EBF returned to the prestimulus level (*supplemental video 2*). Simultaneous recordings showed that a decrease in diameter always corresponded to a decrease in EBF; that is, the frequency of diameter changes was always consistent with that of EBF changes. However, there was a poor correlation between the amplitude of diameter changes and that of EBF changes (one out of three showed a correlation; data not shown).

Experiment 1

To examine the effects of stimulus frequency, a burst of 5 pulses at 20 Hz every 0.5–20 s (burst stimulation) or a continuous stimulation with pulses of 2–25 Hz for 500 s was applied to the cervical sympathetic nerve at room temperature in three rabbits. Two-hundred seconds before the end of stimulation was taken as the period of analysis, because sometimes flow

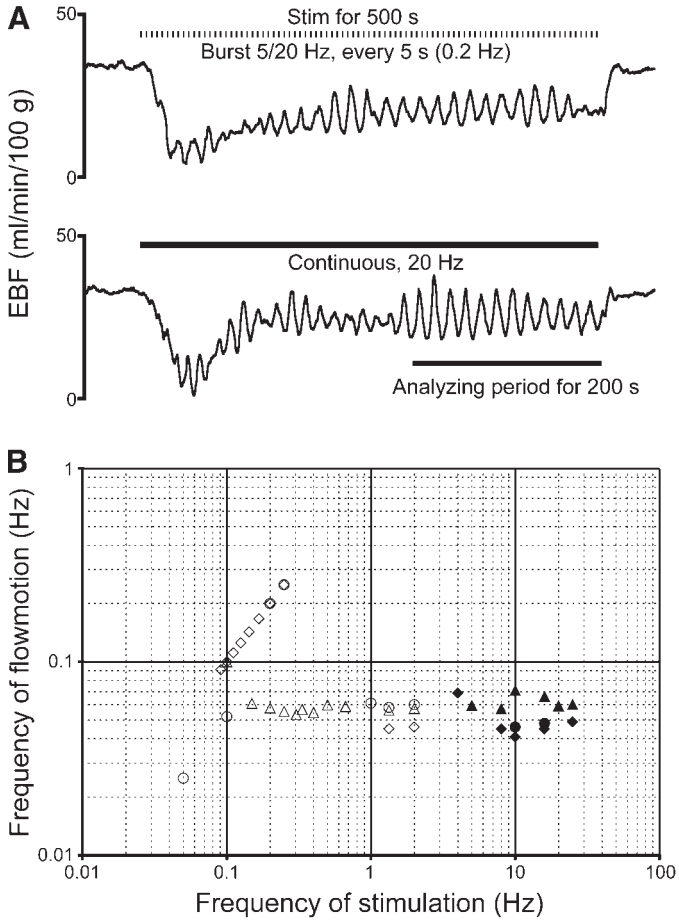

Fig. 3. Relationship between frequency of stimulation and that of flow motion. *A*: EBF responses to electrical stimulation (9 V) of cervical sympathetic nerve. Five pulses at 20 Hz every 0.5 s (*top*) and continuous 20 Hz (*bottom*) were applied, respectively. *B*: various frequencies of stimuli (abscissa) were applied to cervical sympathetic nerve: a burst of 5 pulses at 20 Hz every 0.5–20 s (the reciprocal of the burst interval was taken as the frequency, open symbols) or a continuous stimulation of 2–25 Hz (solid symbols). Because continuous stimulation with pulses of 2 Hz did not evoke flow motion, those data were eliminated. Different symbols represent different rabbits ($n = 3$).

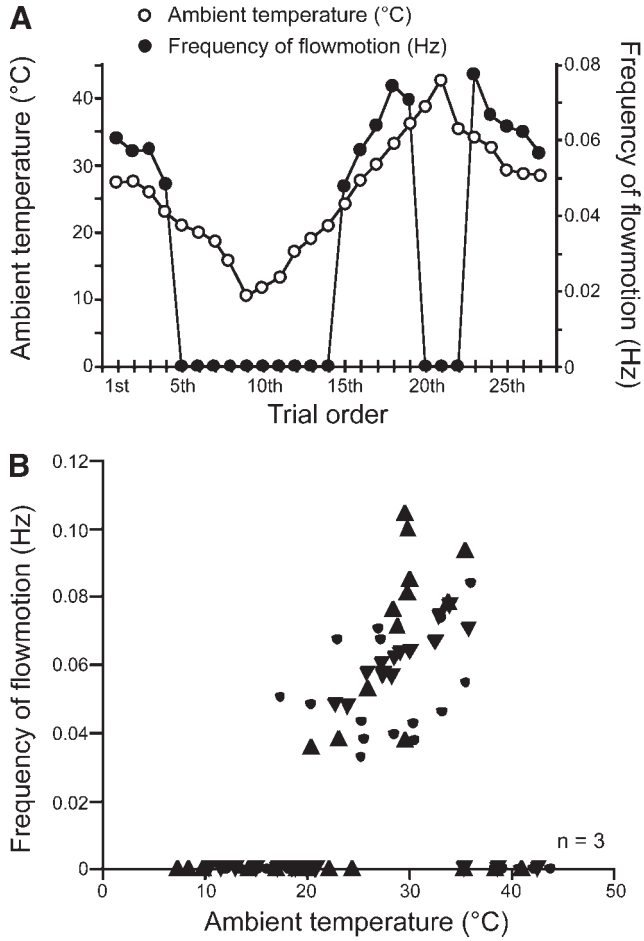

Fig. 4. Relationship between ambient temperature and frequency of flow motion. *A*: left ordinate (ambient temperature; ○) and right ordinate (frequency of flow motion; ●). If flow motion was not induced, the result was plotted at 0 Hz. Abscissa represents trial order. Each trial (measurement) was separated by ~20 min. *B*: different symbols represent different rabbits ($n = 3$).

motion was not stable at the initial period of stimulation. Typical results are shown in Fig. 3*A*.

At frequencies <0.25 Hz (reciprocal of burst interval) of burst stimulation, EBF fluctuated at the same frequency of stimulation in two rabbits, whereas EBF fluctuation, which was independent of stimulus frequency, was observed in one rabbit. Burst stimulation at >0.30 Hz always induced flow motion with a frequency that was independent of stimulus frequency. Continuous stimulation at frequencies >4 Hz induced flow motion with a frequency that did not correlate with electrical stimulus frequency (Fig. 3*B*). Because the frequencies of evoked flow motion did not differ between stimulation methods (burst or continuous stimulation), we pooled them. The frequencies of flow motion ranged between 0.04 and 0.07 Hz [mean, 0.055 ± 0.001 Hz, number of experiments (n) = 29].

Experiment 2

The effects of temperature on flow motion were examined in three rabbits. The stimuli (continuous stimulation with pulses of 2–16 Hz) were applied for 500 s. The ear was covered with a box to keep ambient temperature constant. The frequency of flow motion induced by electrical stimulation was measured. Typical results are shown in Fig. 4*A*.

Flow motion was always induced at ambient temperatures between 25° and 35°C after electrical stimulation. Between 17° and 25°C or between 35° and 37°C, the induction of flow motion after electrical stimulation depended on the rabbit. At <17°C or >37°C, electrical stimulation decreased EBF, but flow motion was not evoked (Fig. 4*B*). The frequency of evoked flow motion significantly correlated with ambient temperature in two out of the three [Pearson's correlation coefficients: 0.705 ($P < 0.05$), 0.288 ($P = 0.30$), and 0.934 ($P < 0.05$), respectively].

Experiment 3

To examine the effects of vasomotion on tissue perfusion, Cr-EDTA was injected into the ear skin of eight rabbits, and tracer fading was measured. One of the examples is shown in Fig. 5. In this experiment, ambient temperatures were maintained at 37°C (with flow motion) and at 47°C (without flow

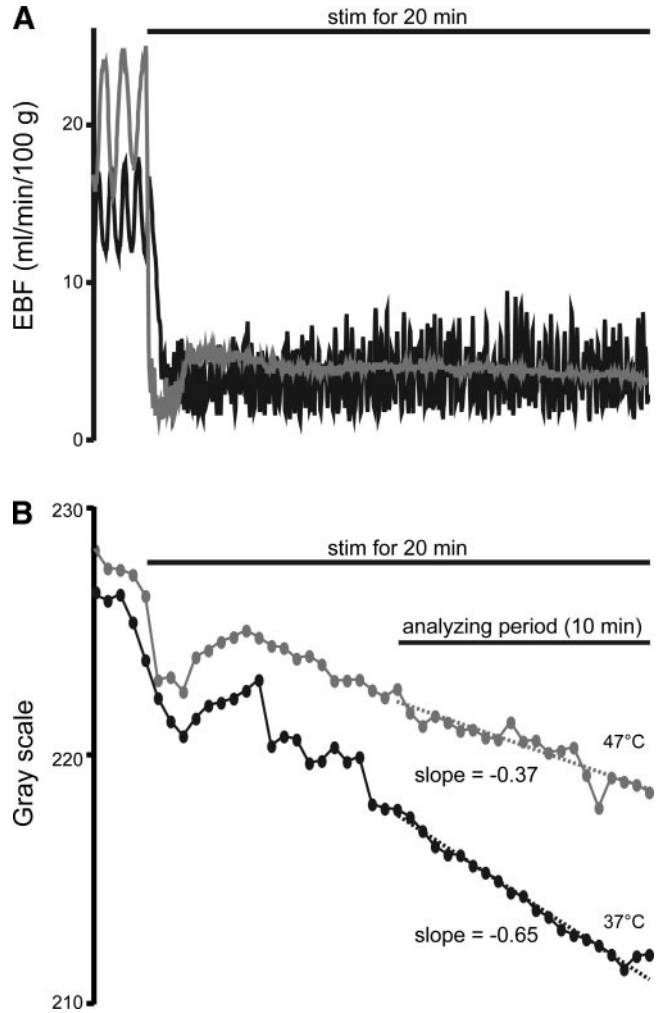

Fig. 5. Tracer fading and EBF with or without flow motion. Time courses of EBF (*A*) and tracer fading (*B*) from same animal are shown. Stimulation (9 V, 10 Hz continuous) was applied for 20 min. Black curves represent EBF or tracer fading with flow motion at an ambient temperature of 37°C. Gray curves represent EBF or tracer fading without flow motion at ambient temperature of 47°C. Dotted lines in *B* represent the linear regression lines during analysis period. Rates of tracer fading were calculated at 0.65 (37°C) and at 0.37 (47°C), respectively. In this experiment, very slow fluctuation of EBF was observed before stimulation.

motion). Four rabbits were subjected to this warm protocol (41–47°C), and the other four rabbits were subjected to a cold protocol (20–12°C) to prevent the generation of flow motion. The stimuli were applied for 20 min. The rate of tracer fading was estimated as the slope of the linear regression line (per min), applied to the time course of the tracer fading. Ten minutes before the end of the stimulation was taken as the period of analysis, because the mean EBF was sometimes not stable at the initial period of stimulation. During the analysis period, the mean EBF with flow motion was not different from that without flow motion (Fig. 5*A*). However, tracer fading with flow motion decreased faster than that without flow motion (decrease slope, −0.65 vs. −0.37 in Fig. 5*B*).

Although ambient temperature was decreased or increased to prevent the generation of flow motion, the fading rates with flow motion were higher (1.7 to 8.1 times) than those without flow motion ($P < 0.05$, one-tailed test, Fig. 6*B*). There were no significant differences between mean EBFs with flow motion and those without flow motion ($P = 0.78$, two-tailed test, Fig. 6*A*).

DISCUSSION

The most significant contribution made by this study is to prove that vasomotion promoted material exchange between tissue and blood in in vivo preparations.

We could reproducibly evoke vasomotion in arterioles of an anesthetized rabbit ear by electrical stimulation of the cervical sympathetic nerve. The cervical sympathetic nerve contains preganglionic fibers projecting to the superior cervical ganglion and postganglionic fibers from the stellate ganglion (10, 11). Because of the mixture of myelinated preganglionic and unmyelinated postganglionic fibers, stimulus intensities (3.0 to 11.0 V) of more than five times higher the threshold intensities (0.38 to 2.00 V) were required to elicit maximal responses. Although there are selective projections from the superior cervical and stellate ganglia to different regions of the ear (20), in our experiments postganglionic fibers in both ganglia were activated after the stimulation of the cervical sympathetic nerve, with the result that the evoked vasomotion was observed in a wide area of the ear.

Bertgulia et al. (2) attempted simultaneous recordings of spontaneous vasomotion and flow motion, but a probe of the laser-Doppler flowmeter was not positioned at the microscope objective to avoid the interference of fluorescence microscopy. Ours is the first study to carry out the simultaneous recordings of vasomotion and flow motion from the same point of an arteriole. The frequency of flow motion coincided with that of vasomotion. From this result, we also concluded that the rhythmical fluctuation of blood flow (flow motion), measured by using a laser-Doppler flowmeter, was the result of the rhythmical contraction of the arteriole (vasomotion) (2, 7). Consequently, we hereinafter refer to flow motion that was measured with a laser-Doppler flowmeter as vasomotion.

In general, the continuous electrical stimulation of sympathetic nerves generates a tonic vasoconstriction (31). However, it has been reported that a prolonged in vivo electrical stimulation of the lumbar sympathetic chain often produces a rhythmic (0.03 Hz) constriction in the cat tenuissimus muscle (9). In the present study, we also observed that electrical stimulation induced vasomotion at a frequency of ~0.06 Hz despite the wide range of frequencies of stimulation. This observed frequency agreed with the frequency of spontaneous vasomotion of the rabbit ear (13). The frequency of vasomotion is inversely related to the diameter of the vessel (8, 12). Because the diameter was not exactly measured in each experiment, we could not confirm the relationship between arteriole diameter and flow-motion frequency. However, the diameters of the arterioles used in our experiments ranged from 30 to 100 μm, and the observed frequencies of flow motion ranged between 0.04 and 0.07 Hz. These values corresponded to the relationship between arteriole diameter and vasomotion frequency in hamster skin preparation (8). Although the continuous stimulation at low frequencies (<2 Hz) did not induce vasomotion, the continuous stimulation at higher frequencies (≥2 Hz) and burst stimulation did. The α_1-receptor agonist induces rhythmical vasomotion, such as the constriction of arterioles in in

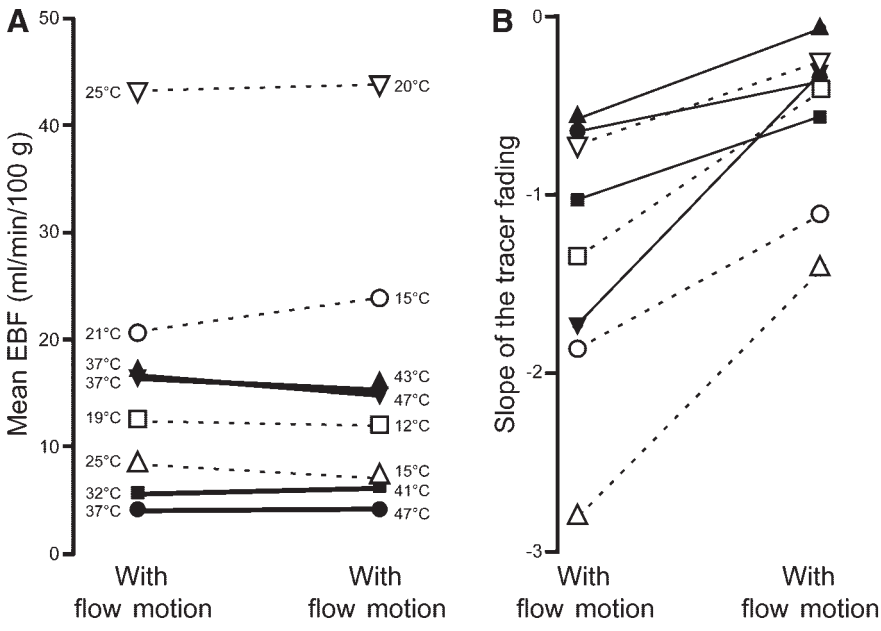

Fig. 6. Comparison of mean EBF and rate of tracer fading. Each plot represents different animals ($n = 8$). Solid line and solid symbols show experiments in which temperature was raised to stop flow motion. Broken line and open symbols show experiments in which temperature was reduced to stop flow motion. *A*: mean EBF with and without flow motion. *B*: slope of tracer fading with and without flow motion.

vitro preparations (22). In in vivo preparations, vasomotion was sometimes observed during hemorrhagic shock (3); in this case, the sympathetic nerve was activated greatly by the baroreceptor reflex. Therefore, it is not surprising that the activation of the sympathetic nerve, as observed in this experiment, evokes vasomotion.

The induction of vasomotion was affected by ambient temperature. Electrical stimulation always induced vasomotion at ambient temperatures between 25° and 35°C. To avoid interference in the observation and to prevent tissue damage, we did not directly measure the temperature of the skin in the area of interest using a plate-type or a needle-type thermosensor. Instead of direct measurements, we measured ambient temperature. The observed area was always the edge or tip of the ear, which is thin, and the stimulation reduced blood flow continuously. Therefore, the temperature of the observed area of the skin must be very close to ambient temperature. At ambient temperatures <17°C or >37°C, electrical stimulation decreased EBF but did not evoke vasomotion. It has been reported that the frequency of spontaneous vasomotion in the human skin (25) or bat wing (4) depends on temperature. Spontaneous vasomotion in the hamster cheek pouch was abolished when the superfusing solution temperature was decreased from 36.5° to 15°C (5). Vasomotion induced by electrical stimulation had the same features as those of responses to temperature.

As described above, vasomotion evoked by electrical stimulation was almost the same as spontaneously occurring vasomotion with respect to frequency and temperature dependencies. Therefore, we concluded that the vasomotion induced in this study by electrical stimulation was the same as the spontaneous vasomotion observed in nature. The method of vasomotion induction used in this study is concluded to be valuable for in vivo experiments because of its reproducibility, a low physical burden to animals, and easier control with temperature.

Some theoretical models have been constructed regarding the role of vasomotion in capillary function, particularly in tissue-fluid exchange. Tissue-fluid motion attributable to vasomotion is the motion propelling tissue fluid into terminal lymphatics (16). Vasomotion results in less tissue dehydration when flow rate is decreased by steady-state contraction (24). Iida (15) found that the net capillary-tissue fluid fluxes under vasomotion flow are higher than those under a steady flow and that the capillary fluid exchange is almost constant regardless of vasomotion frequency. Although the physiological roles of vasomotion have been speculated in theoretical models as mentioned above, there have been very few experimental approaches. We showed that the fading rate (clearance) with vasomotion was significantly larger than that without vasomotion. We measured EBF on a single arteriole that did not always perfuse the tissue where Cr-EDTA was injected. However, the electrical stimulation of the cervical sympathetic nerve induced vasomotion in almost all of the ear arterioles. Therefore, it was reasonable to postulate that the electrical stimulation also reduced blood flow and evoked vasomotion in the area of interest to us. Clearance of Cr-EDTA is affected not only by blood flow but also by the microvascular permeability and area of the effective microvascular wall. At present, there is no information about the sympathetic effects on the latter two factors. Because vasomotion at arterioles must periodically move blood at the peripheral capillaries, this movement must enhance the material exchange. Small solutes, such as Cr-EDTA, can cross the microvascular wall mainly by diffusion. Therefore the clearance is dependent on temperature: the higher the temperature, the larger the clearance. As shown in our experiments on temperature effects, the clearance was larger at lower temperatures (with vasomotion) than at higher temperatures (without vasomotion). This result indicates vasomotion must exert a greater effect on clearance than temperature does.

In summary, we developed a method of controlling vasomotion in in vivo preparations. With the use of this method, it is possible to clarify further the physiological significance of vasomotion. We have shown here that vasomotion enhanced the tissue-capillary exchange of small water-soluble solutes.

ACKNOWLEDGMENTS

We thank Kazumi Bunzui for technical help, F. Miyamasu for professional comments in proofreading the manuscript, and Sony Manufacturing Systems for providing a video microscope (TW-CM10).

REFERENCES

1. **Asano M and Branemark PI.** Microphotoelectric plethysmography using a titanium chamber in man. *Adv Microcirc* 4: 131–160, 1972.
2. **Bertuglia S, Colantuoni A, Arnold M, and Witte H.** Dynamic coherence analysis of vasomotion and flowmotion in skeletal muscle microcirculation. *Microvasc Res* 52: 235–244, 1996.
3. **Borgstrom P, Schmidt JA, Bruttig SP, Intaglietta M, and Arfors KE.** Slow-wave flowmotion in rabbit skeletal muscle after acute fixed-volume hemorrhage. *Circ Shock* 36: 57–61, 1992.
4. **Bouskela E.** Vasomotion frequency and amplitude related to intraluminal pressure and temperature in the wing of the intact, unanesthetized bat. *Microvasc Res* 37: 339–351, 1989.
5. **Bouskela E and Grampp W.** Spontaneous vasomotion in hamster cheek pouch arterioles in varying experimental conditions. *Am J Physiol Heart Circ Physiol* 262: H478–H485, 1992.
6. **Colantuoni A, Bertuglia S, and Intaglietta M.** Effects of anesthesia on the spontaneous activity of the microvasculature. *Int J Microcirc Clin Exp* 3: 13–28, 1984.
7. **Colantuoni A, Bertuglia S, and Intaglietta M.** Microvascular vasomotion: origin of laser Doppler flux motion. *Int J Microcirc Clin Exp* 14: 151–158, 1994.
8. **Colantuoni A, Bertuglia S, and Intaglietta M.** Quantitation of rhythmic diameter changes in arterial microcirculation. *Am J Physiol Heart Circ Physiol* 246: H508–H517, 1984.
9. **Eriksson E and Lisander B.** Changes in precapillary resistance in skeletal muscle vessels studied by intravital microscopy. *Acta Physiol Scand* 84: 295–305, 1972.
10. **Feldberg W.** The peripheral innervation of the vessels of the external ear of the rabbit. *J Physiol* 61: 518–529, 1926.
11. **Fletcher WM.** The vaso-constrictor fibres of the great auricular nerve in the rabbit. *J Physiol* 22: 259–263, 1898.
12. **Funk W, Endrich B, Messmer K, and Intaglietta M.** Spontaneous arteriolar vasomotion as a determinant of peripheral vascular resistance. *Int J Microcirc Clin Exp* 2: 11–25, 1983.
13. **Funk W and Intaglietta M.** Spontaneous Arteriolar Vasomotion. *Prog Appl Microcirc* 3: 66–82, 1983.
14. **Gustafsson U, Wardell K, Nilsson GE, and Lewis DH.** Vasomotion in rat skeletal muscle induced by hemorrhage as recorded by laser-Doppler flowmetry. *Microvasc Res* 42: 224–228, 1991.
15. **Iida N.** Effects of vasomotion and venous pressure elevation on capillary-tissue fluid exchange across hetero-porous membrane. *Biorheology* 27: 205–224, 1990.
16. **Intaglietta M and Gross JF.** Vasomotion, tissue fluid flow and the formation of lymph. *Int J Microcirc Clin Exp* 1: 55–65, 1982.
17. **Kastrup J, Bulow J, and Lassen NA.** Vasomotion in human skin before and after local heating recorded with laser Doppler flowmetry. A method for induction of vasomotion. *Int J Microcirc Clin Exp* 8: 205–215, 1989.

18. **Minamiyama M and Hanai S.** Propagation properties of vasomotion at terminal arterioles and precapillaries in the rabbit mesentery. *Biorheology* 28: 275–286, 1991.
19. **Morita Y, Hardebo JE, and Bouskela E.** Influence of cerebrovascular sympathetic, parasympathetic, and sensory nerves on autoregulation and spontaneous vasomotion. *Acta Physiol Scand* 154: 121–130, 1995.
20. **Morris JL, Zhu BS, Gibbins IL, and Blessing WW.** Subpopulations of sympathetic neurons project to specific vascular targets in the pinna of the rabbit ear. *J Comp Neurol* 412: 147–160, 1999.
21. **Nicoll PA and Webb RL.** Blood circulation in the subcutaneous tissue of the living bat's wing. *Ann NY Acad Sci* 46: 697–711, 1946.
22. **Peng H, Matchkov V, Ivarsen A, Aalkjaer C, and Nilsson H.** Hypothesis for the initiation of vasomotion. *Circ Res* 88: 810–815, 2001.
23. **Rippe B, Kamiya A, and Folkow B.** Simultaneous measurements of capillary diffusion and filtration exchange during shifts in filtration-absorption and at graded alterations in the capillary permeability surface area products (PS). *Acta Physiol Scand* 104: 318–336, 1978.
24. **Salathe EP and Salathe EP Jr.** Transcapillary fluid exchange during arteriolar vasomotion. *Microvasc Res* 31: 115–118, 1986.
25. **Salerud EG, Tenland T, Nilsson GE, and Oberg PA.** Rhythmical variations in human skin blood flow. *Int J Microcirc Clin Exp* 2: 91–102, 1983.
26. **Schmidt JA, Intaglietta M, and Borgstrom P.** Periodic hemodynamics in skeletal muscle during local arterial pressure reduction. *J Appl Physiol* 73: 1077–1083, 1992.
27. **Schmidt-Lucke C, Borgstrom P, and Schmidt-Lucke J.** Low frequency flowmotion/(vasomotion) during patho-physiological conditions. *Life Sci* 71: 2713–2728, 2002.
28. **Secomb TW, Intaglietta M, and Gross JF.** Effects of vasomotion on microcirculatory mass transport. *Prog Appl Microcirc* 15: 49–61, 1989.
29. **Setchell BP, Bergh A, Widmark A, and Damber JE.** Effect of testicular temperature on vasomotion and blood flow. *Int J Androl* 18: 120–126, 1995.
30. **Shibata M, Yoshida M, and Kamiya A.** Measurement of local capillary permeability in skeletal muscle by microscopic clearance method. *Jpn J Physiol* 41: 725–734, 1991.
31. **Stauss HM, Stegmann JU, Persson PB, and Habler HJ.** Frequency response characteristics of sympathetic transmission to skin vascular smooth muscles in rats. *Am J Physiol Regul Integr Comp Physiol* 277: R591–R600, 1999.
32. **Wahlander H, Friberg P, and Haraldsson B.** Capillary diffusion capacity for Cr-EDTA and cyanocobalamine in spontaneously beating rat hearts. *Acta Physiol Scand* 147: 37–47, 1993.
33. **Wiedeman MP.** Contractile activity of arterioles in the bat wing during intraluminal pressure changes. *Circ Res* 19: 559–563, 1966.