

# Vestibular stimulation leads to distinct hemodynamic patterning

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**Kerman, I. A., B. A. Emanuel, and B. J. Yates.** Vestibular stimulation leads to distinct hemodynamic patterning. *Am J Physiol Regulatory Integrative Comp Physiol* 279: R118–R125, 2000.— Previous studies demonstrated that responses of a particular sympathetic nerve to vestibular stimulation depend on the type of tissue the nerve innervates as well as its anatomic location. In the present study, we sought to determine whether such precise patterning of vestibulo-sympathetic reflexes could lead to specific hemodynamic alterations in response to vestibular afferent activation. We simultaneously measured changes in systemic blood pressure and blood flow (with the use of Doppler flowmetry) to the hindlimb (femoral artery), forelimb (brachial artery), and kidney (renal artery) in chloralose-urethane-anesthetized, baroreceptor-denervated cats. Electrical vestibular stimulation led to depressor responses,  $8 \pm 2$  mmHg (mean  $\pm$  SE) in magnitude, that were accompanied by decreases in femoral vasoconstriction ( $23 \pm 4\%$  decrease in vascular resistance or  $36 \pm 7\%$  increase in vascular conductance) and increases in brachial vascular tone (resistance increase of  $10 \pm 6\%$  and conductance decrease of  $11 \pm 4\%$ ). Relatively small changes ( $<5\%$ ) in renal vascular tone were observed. In contrast, electrical stimulation of muscle and cutaneous afferents produced pressor responses ( $20 \pm 6$  mmHg) that were accompanied by vasoconstriction in all three beds. These data suggest that vestibular inputs lead to a complex pattern of cardiovascular changes that is distinct from that which occurs in response to activation of other types of somatic afferents.

blood flow; vascular resistance; vascular conductance; sympathetic nervous system

RECENT WORK DEMONSTRATED that activation of vestibular afferents leads to specific patterning of vestibulosympathetic reflexes (VSR) (10–12, 20). It has been suggested that activity of vasoconstrictor sympathetic efferents is preferentially influenced by electrical activation of vestibular afferents (11). As discussed in the previous paper (12), the responses of vasoconstrictor efferents to electrical vestibular stimulation are not homogeneous but depend on their innervation targets as well as their anatomic location. These findings suggest that the vestibular system has the potential to alter the tone of vascular beds located throughout the body. However, it is likely that these changes are not uniform but instead are patterned and lead to specific

hemodynamic alterations. The goal of the present study was to determine whether electrical vestibular stimulation leads to patterned changes of regional vascular tone. In particular, this investigation had three specific objectives. The first aim was to determine whether changes in vascular resistance and conductance elicited by vestibular stimulation are greater in the limbs or in the kidney. The second aim was to establish whether there is a difference between forelimb and hindlimb vascular resistance changes to vestibular stimulation, as would be predicted by a previous observation that VSR recorded from forelimb and hindlimb vasoconstrictor fibers are qualitatively different (12). The third aim was to determine whether regional vascular resistances are affected in a similar manner by vestibular signals as by inputs from muscle and skin. To address these aims, systemic blood pressure and blood flow to the hindlimb, forelimb, and kidney were simultaneously measured during stimulation of either the vestibular nerve or limb nerves containing skin and muscle afferents.

## METHODS

All the procedures used in this study conformed to the American Physiological Society's *Guiding Principles for the Care and Use of Animals* and were approved by the University of Pittsburgh's Animal Care and Use Committee.

**Surgical procedures.** Experiments were performed on nine adult cats weighing between 3.3 and 5.1 kg (supplied by Liberty Laboratories, Waverley, NY). Animals were premedicated with a mixture of ketamine (15–20 mg/kg im) and xylazine (0.1–0.2 mg/kg im) and were then anesthetized with a mixture of  $\alpha$ -chloralose (40 mg/kg iv) and urethane (200 mg/kg iv). The depth of anesthesia was determined as adequate if withdrawal reflexes to noxious stimuli were absent and the pupils remained constricted. Chloralose-urethane supplements ( $\sim 10\%$  of the initial dose) were administered as necessary to maintain this level of anesthesia.

A tracheostomy was performed, and a blood pressure transducer (Millar Instruments, Houston, TX) was inserted into the right femoral artery. The right femoral vein was cannulated for drug delivery. Rectal temperature was monitored and maintained near  $38^\circ\text{C}$  with the use of a heating pad and heat lamp. The bladder was catheterized and emptied.

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In five cats, the carotid sinus and aortic depressor nerves were transected bilaterally to produce baroreceptor denervation. In the other animals, bilateral carotid sinus nerve transection was combined with bilateral vagotomy (2 cats) or unilateral vagotomy and contralateral aortic depressor nerve transection (2 cats) to eliminate baroreceptor inputs. To ensure completeness of the carotid sinus denervation, the common carotid artery and the carotid sinus were painted with 10% phenol. Effectiveness of this procedure was confirmed in six animals by observing elimination of bradycardic responses to pressor challenges induced by metaraminol bitartrate (Aramine, Merck; 10–20  $\mu\text{g}/\text{kg}$  iv, 5 animals) or L-phenylephrine hydrochloride (Janssen Chimica; 20  $\mu\text{g}/\text{kg}$  iv, 1 animal) after the denervation procedure.

The left femoral and brachial arteries were dissected from a ventral approach, and Doppler flow cuffs (20-MHz signal frequency, 0.8- to 1.3-mm lumen diameter; Iowa Doppler Products, Iowa City, IA), which allow continuous blood flow measurements, were placed on both vessels. The left kidney (right kidney in one case) was dissected retroperitoneally via a flank incision, and a Doppler flow cuff was placed around the renal artery. Care was taken to preserve the nerves running alongside each artery, and all of the flow cuffs were positioned as close to the abdominal aorta as possible. Measurements from all three vessels were performed simultaneously, except in one animal in which reliable recordings could only be made from the renal and femoral arteries.

Vestibular afferents on one or both sides were prepared for bipolar electrical stimulation with the use of a previously described method (11, 21, 28). The tympanic bulla was dissected with the use of a ventral approach and was opened to expose the promontory. The anterior wall of the promontory was opened to gain access to the scala vestibuli. One silver-silver chloride ball electrode, insulated except at the tip, was inserted through the round window into the scala vestibuli in the direction of the vestibule. The second electrode was placed 1–2 mm away, in the vicinity of the oval window. In all but two animals, the effectiveness of vestibular nerve stimulation was assessed by monitoring eye movements and neck contractions, which occur as part of vestibular-ocular and vestibular-colic reflexes. These reflexes were elicited with the use of a train of 50 shocks with a pulse width of 0.2 ms and a 3-ms separation repeated every 0.5–2 s. The position of the electrodes was adjusted to produce a large differential between the stimulus intensity required to produce eye movements and that which resulted in facial twitching. The facial nerve runs just outside the labyrinth and is the first target to be affected by stimulus spread (26). Previous studies have shown that stimulation of the vestibular nerve with the use of intensities that are subthreshold for activating facial efferents selectively activates vestibular afferents (11, 21). Tips of the electrodes were insulated with wax, and the wires were fixed to the adjacent bone with dental acrylic.

To stimulate muscle and cutaneous afferents, either the right ulnar (8 cats) or the right median (1 cat) nerve was dissected in the forelimb. The isolated nerve was crushed peripherally, placed on a bipolar silver hook electrode, and covered with a mixture of Vaseline and mineral oil.

Before the start of recording sessions (but after all surgical procedures were complete), animals were paralyzed with gallamine triethiodide (Sigma, St. Louis, MO) administered intravenously (10-mg/kg initial dose, supplemented hourly or as needed with 5–10-mg/kg iv injections) and artificially ventilated. End-tidal  $\text{CO}_2$  was monitored and maintained between 3.5 and 4.0%. Paralysis was allowed to wear off every 2–4 h at which time the depth of anesthesia was

evaluated and, if necessary, additional anesthetic was administered.

At the end of recording sessions, animals were euthanized with an overdose of pentobarbital sodium (120 mg/kg iv).

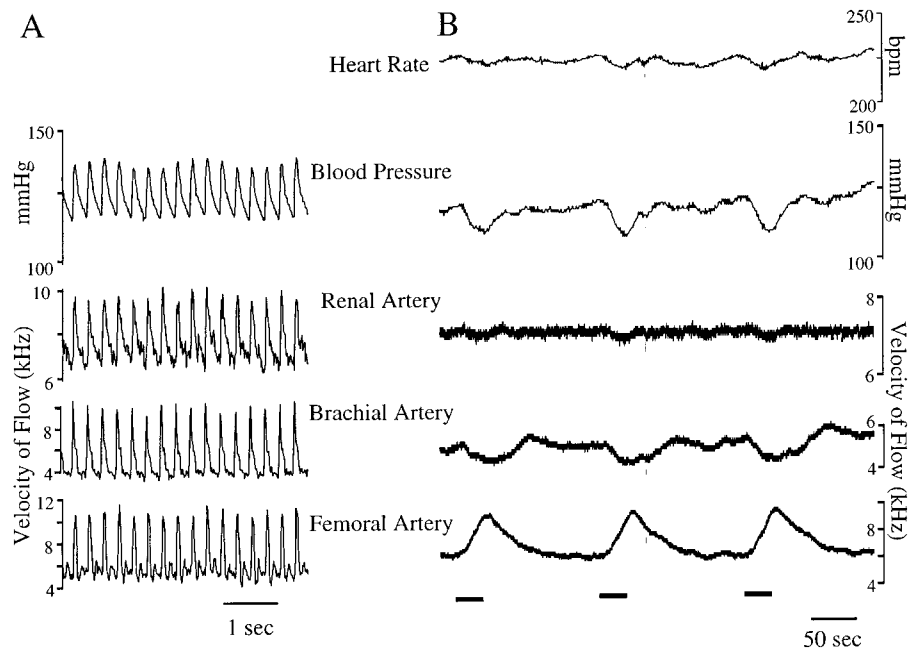
*Data recording procedures.* Blood flow cuffs were connected to a directional pulsed Doppler flowmeter (model 545C, University of Iowa Bioengineering, Iowa City, IA). Doppler frequency shift (in kHz) in blood flow velocity as measured by the flowmeter correlates well with regional blood flow changes (5). The range of the blood flow transducer was adjusted so that the strongest phasic signal from each flow cuff was recorded (see Fig. 1A for examples). Afterward, the mean flow signal was sampled from the mean output port of the flowmeter. Mean blood flow and pulsatile blood pressure signals were digitized at 100 Hz (with the use of a model 1401-plus analog-to-digital converter, Cambridge Electronic Design, Cambridge, UK) and fed into a computer (Macintosh Quadra 800) to allow continuous online measurement. Data sampling and subsequent analyses were performed with the use of Spike2 software (Cambridge Electronic Design). Mean arterial pressure was determined over 1-s bins; heart rate was also calculated over 1-s intervals on the basis of the average interval between systolic blood pressure peaks. To determine whether changes in blood flow were due to active constriction or relaxation of local vasculature (as opposed to passive changes in flow resulting from systemic blood pressure alterations), resistance was calculated off-line by dividing blood pressure (in mmHg) by the Doppler shift (kHz) of the blood flow velocity signal for each vascular bed. To ensure that possible changes in baseline flow rates did not bias our conclusions regarding changes in local vascular tone (18), conductance was also calculated by dividing the blood flow velocity signal by blood pressure. Resistance and conductance measurements were expressed as percent change from mean control values (taken during the 10- or 20-s period immediately preceding stimulation onset).

*Stimulation procedures.* To elicit cardiovascular responses, vestibular afferents on one side were activated with stimulus trains of square-wave shocks (0.2-ms pulse duration, 333-Hz stimulus frequency, 30- to 40-s train duration) repeated every 2–5 min. Responses of up to 15 stimulus repetitions were recorded and averaged. In seven cats, stimulation intensity was set just below the facial movement threshold at  $470 \pm 92 \mu\text{A}$  (mean  $\pm$  SE), which was  $3.3 \pm 0.4$  times the threshold for eliciting eye movements. In three animals, lower intensity stimuli were also shown to elicit cardiovascular responses that were qualitatively similar, although smaller in magnitude than those elicited by stimuli that were just below facial nerve threshold. In one animal, eye and facial movements were not measured, and in another cat eye movements could not be elicited, presumably due to the depth of anesthesia. In the latter animal, activation of vestibular afferents was confirmed by recording field potentials from the ipsilateral vestibular nuclei. In both of these animals, the intensity of vestibular stimulation was set to 500  $\mu\text{A}$ , a value that was close to mean intensity of vestibular stimulation used in the other animals.

Skin and muscle afferents in the ulnar or median nerve were activated with the use of similar stimulus parameters as those employed to elicit vestibulocardiovascular responses. Stimulus intensity ranged from 3 to 10 mA but was set at a constant level within each experiment. We previously determined that stimulation intensities in this range lead to maximal sympathetic nerve responses (10) and therefore would likely produce maximal cardiovascular changes.

*Statistical methods.* Differences in response sizes and response latencies were evaluated with the use of a one-way

Fig. 1. Regional blood flow alterations in response to electrical vestibular stimulation. After verifying stability of phasic blood flow signals (A), continuous mean blood flow recordings were made from the renal, brachial, and femoral arteries (B). Phasic blood pressure was also recorded (A, top) and used to determine heart rate and mean arterial pressure (B, top and middle). In this example, ipsilateral vestibular stimulation (30-s continuous train, 0.2-ms pulse width, 333 Hz, 1.7 times vestibuloocular reflex threshold) was delivered during times indicated by thick bars at bottom of B. This stimulus produced depressor responses that were accompanied by small heart rate changes, increases in blood flow to the hindlimb, decreases in flow to the forelimb, but no change in renal blood flow. bpm, Beats/min.



ANOVA (InStat 1.12 for Macintosh). Post hoc statistical testing was performed with the use of the Bonferroni multiple comparisons test. Significance was set at  $P < 0.05$ . Pooled data are presented as means  $\pm$  SE.

## RESULTS

Electrical stimulation of vestibular afferents led to depressor responses in all nine animals (see Fig. 1B for an example), whose baseline blood pressure was  $116 \pm 5$  mmHg and baseline heart rate was  $253 \pm 11$  beats/min. The magnitude of the depressor response elicited by the maximal stimulus intensity employed in each experiment ranged from 2 to 16 mmHg (Table 1); the mean decrease in blood pressure was  $8 \pm 2$  mmHg. Lower stimulus intensities elicited qualitatively similar, although smaller, decreases in blood pressure. The latency of peak depressor responses was  $13.7 \pm 9.0$  s. In five of the animals, these peak depressor effects were accompanied by decreases in heart rate of 2–9 beats/min (latency of  $12.0 \pm 7.5$  s; Fig. 1B), whereas no heart rate changes were observed in the other animals.

The mean decrease in heart rate elicited by vestibular stimulation in all animals was  $3 \pm 1$  beats/min.

Changes in blood pressure elicited by vestibular stimulation were typically accompanied by increases in blood flow to femoral vasculature, decreases in blood flow to brachial vasculature, and relatively small changes in renal arterial blood flow (Fig. 1B). Examples of vascular resistance changes elicited by vestibular stimulation are illustrated in Fig. 2. Resistance changes occurred within a few seconds and reached their maximum 10–25 s after the onset of vestibular stimulation. The mean latencies of peak responses were  $14.6 \pm 2.5$ ,  $18.3 \pm 4.2$ , and  $16.0 \pm 3.3$  s for femoral vascular resistance (FVR), brachial vascular resistance (BVR), and renal vascular resistance (RVR), respectively. The differences in response latencies were not statistically significant ( $P > 0.05$ , ANOVA). The response patterns were similar across the range of stimulus intensities used in this study (which were subthreshold for producing current spread to nonves-

Table 1. Cardiovascular changes elicited by electrical vestibular stimulation in each experiment

Animal	BP, mmHg	HR, beats/min	FVR, %	BVR, %	RVR, %	FVC, %	BVC, %	RVC, %
1	-6	0	-22	44	-3	47	-32	3
2	-5	0	-22	10	2	28	-10	-3
3	-14	-5	-15	13	-10	35	-12	10
4	-3	-2	-22	7	3	29	-6	-4
5	-9	-4	-37	15	-6	45	-12	6
6	-2	0	2	17	-5	-2	-15	7
7	-11	-4	-44	-9	1	81	10	-2
8	-16	-9	-25	-17	-15	35	-10	7
9	-3	0	-20		-2	27		-2

Changes in blood pressure (BP) and heart rate (HR) as well as those in regional vascular resistances and conductances (expressed as percent change from control values) are presented. BVR, brachial vascular resistance; FVR, femoral vascular resistance; RVR, renal vascular resistance; BVC, brachial vascular conductance; FVC, femoral vascular conductance; RVC, renal vascular conductance.

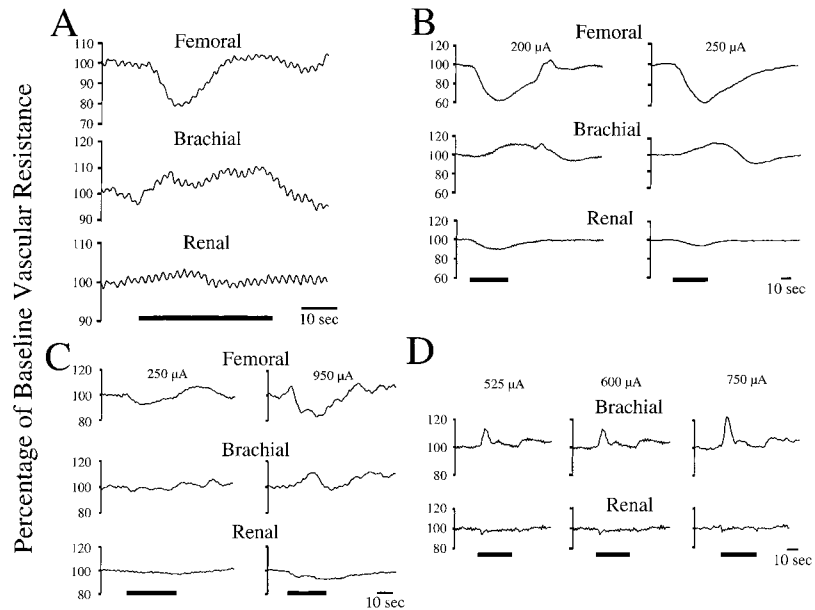


Fig. 2. Changes in vascular resistance elicited by vestibular stimulation. Resistance was calculated as blood pressure divided by blood flow velocity signal, which was simultaneously measured from left femoral, left brachial, and left renal arteries. Values are expressed as a percentage of baseline vascular resistance, which was calculated over the 20-s period preceding each stimulus train. Vestibular stimuli were comprised of trains of pulses of 0.2-ms duration that were delivered at 333 Hz and are demarked by dark bars at *bottom*. Data from different animals are illustrated. *A*: changes in vascular resistance elicited by stimulation of the contralateral labyrinth at 500  $\mu\text{A}$ ; each trace is the average of 5 responses. Note that vestibular stimulation produced a decrease in femoral vascular resistance (FVR), an increase in brachial vascular resistance (BVR), but only a relatively small change in renal vascular resistance (RVR). *B*: in another animal, stimulation of ipsilateral vestibular afferents at 200 (*left*) and 250  $\mu\text{A}$  (*right*) produced a similar response pattern; traces represent the average of 9 responses. *C*: in this animal, contralateral vestibular stimulation at 250  $\mu\text{A}$  (*left*) produced a selective decrease in femoral resistance (average of 6 responses). Reversing stimulus polarity and increasing current intensity to 950  $\mu\text{A}$  (*right*) produced a larger decrease in femoral resistance and also elicited an increase in brachial resistance; traces are the average of 3 responses. *D*: in this case, contralateral vestibular stimulation at intensities of 525 (*left*; average of 10 responses), 600 (*middle*; average of 8 responses), and 750  $\mu\text{A}$  (*right*; average of 4 responses) produced brachial vasoconstriction. Note that the shape of the response elicited by each stimulus intensity was similar. FVR was unaffected by current intensities that were subthreshold for producing stimulus spread to nonvestibular afferents and is not shown.

tibular afferents), although in some cases the threshold for producing a detectable change in resistance in a particular vascular bed was slightly lower than for others (e.g., see Fig. 2C).

Maximal changes in vascular resistance and conductance were calculated in each animal and are presented in Table 1. In five cats (*animals 1-5* in Table 1), vestibular stimulation elicited decreases in FVR of 15–37% in magnitude, whereas BVR increased by 7–44%. Changes in flow in one of these cats (*animal 5*) are illustrated in Fig. 1B. In three of these animals, relatively small decreases (3–10%) in RVR were observed, whereas in two other animals, increases of ~3% in RVR were measured. However, in two animals (*animals 6 and 7* in Table 1), vestibular stimulation produced either a selective increase in BVR or a selective decrease in FVR, whereas little change in resistance occurred in the other vascular beds. In one of these animals, BVR increased by 17%, whereas only a 2% change in FVR was observed. In the other animal, FVR decreased by 44%, whereas BVR showed a relatively small decrease of 9%. In both of these animals, relatively small changes in RVR were observed. Only in one cat (*animal 8* in Table 1) were qualitatively and

quantitatively similar changes in FVR, BVR, and RVR observed. In the remaining cat (*animal 9* in Table 1), vestibular stimulation led to a selective decrease in FVR of 20%, whereas no change in RVR was observed. Brachial artery flow was not measured in this cat. Changes in conductance during vestibular stimulation typically paralleled the changes in vascular resistance, reflecting decreased vascular tone in the femoral vasculature, increased vascular tone in the brachial vascular bed, and little alteration in the tone of the renal vasculature.

Overall, FVR decreased and femoral vascular conductance (FVC) increased in eight of nine animals. The average maximal decrease in resistance in response to vestibular stimulation was  $23 \pm 4\%$  in all animals, whereas conductance increased by  $36 \pm 7\%$  (Fig. 3). BVR increased in six and decreased in two of eight animals, whereas brachial vascular conductance (BVC) decreased in seven of eight animals. The mean maximal BVR increase for all animals was  $10 \pm 6\%$ , and the mean decrease in maximal BVC was  $11 \pm 4\%$  (Fig. 3). RVR decreased in five of nine animals, whereas only small (<3%) changes were observed in the other animals, and similar but reciprocal alterations in renal

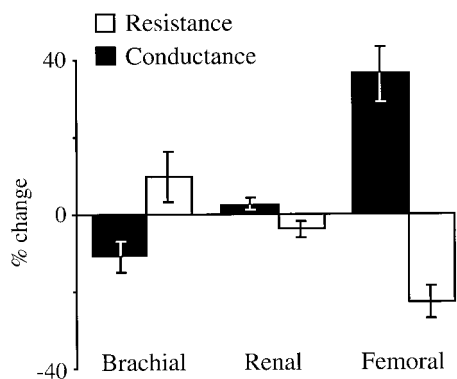


Fig. 3. Average change in vascular resistance and conductance elicited by vestibular stimulation in 9 cats. This stimulus led to qualitatively different changes in femoral and brachial vascular resistance and conductance but little alteration in renal vascular resistance or conductance. Error bars indicate SE.

vascular conductance (RVC) were also noted. RVR decreased by  $4 \pm 2\%$  across all of the animals, whereas RVC increased by only  $2 \pm 2\%$  (Fig. 3). Both resistance and conductance changes elicited by vestibular stimulation in the renal, brachial, and femoral vascular beds were significantly different ( $P < 0.001$ , ANOVA). Post hoc statistical testing confirmed that differences between FVR and RVR as well as between FVC and RVC were statistically significant ( $P < 0.05$ , Bonferroni test). Likewise, differences between FVR and BVR and between FVC and BVC were also significant ( $P < 0.05$ ). Differences in changes of RVR and BVR exhibited a trend toward significance (uncorrected  $P = 0.05$ ) as did the difference between RVC and BVC (uncorrected  $P = 0.08$ ).

To determine whether observed changes in regional hemodynamics were specific to vestibular stimuli, we also examined resistance and conductance changes produced by activation of skin and muscle afferents. These responses were studied in the same animals that were used for determination of hemodynamic alterations elicited by vestibular stimulation. Muscle and cutaneous afferents were activated by delivering a high-intensity electrical stimulus to the right ulnar (8 cats) or the right median (1 cat) nerve. In response to these stimuli, blood pressure increased by  $20 \pm 6$  mmHg ( $11.4 \pm 1.8$ -s latency), whereas heart rate increased by  $7 \pm 2$  beats/min ( $14.5 \pm 1.8$ -s latency; see Fig. 4 for examples of responses). These changes were accompanied by alterations in vascular resistance and conductance in all of the animals that peaked within 5–15 s of stimulus onset (Fig. 4). Overall, the latencies of peak increases in vascular resistance elicited by limb nerve stimulation were  $11.0 \pm 1.8$ ,  $9.1 \pm 1.4$ , and  $14.6 \pm 2.4$  s for FVR, BVR, and RVR, respectively; these differences did not reach statistical significance ( $P > 0.05$ , ANOVA).

Limb nerve stimulation elicited a marked increase in FVR and a large decrease in FVC in all of the animals. However, in two cases, the flow signal decreased to zero during stimulus periods, likely due to strong vasoconstriction, and recovered after each stimulus. This de-

crease in flow saturated resistance measurements and prevented us from accurate quantification of this parameter. In the other animals, the magnitude of changes in FVR ranged from 28 to 1,120%, whereas FVC decreased by 24–90%. Changes in BVR and BVC during limb nerve stimulation were qualitatively similar to those in FVR and FVC, respectively. These parameters were measured in every animal; the increase in BVR ranged from 18 to 200%, whereas the decrease in BVC ranged from 15 to 59%. RVR increased by 8–78% in six of the animals and decreased by 10% in another. In two of the animals, no appreciable changes in renal artery resistance were observed (change  $\leq 4\%$ ) in three animals.

Overall, simultaneous activation of skin and muscle afferents led to increases of  $406 \pm 155$  and  $62 \pm 23\%$  for FVR and BVR, respectively (Fig. 5). The mean change in RVR was  $17 \pm 9\%$  (Fig. 5). The differences in the magnitude of these peak resistance changes were statistically significant ( $P < 0.001$ , ANOVA). Post hoc statistical analysis confirmed that differences between changes in FVR and BVR as well as those between

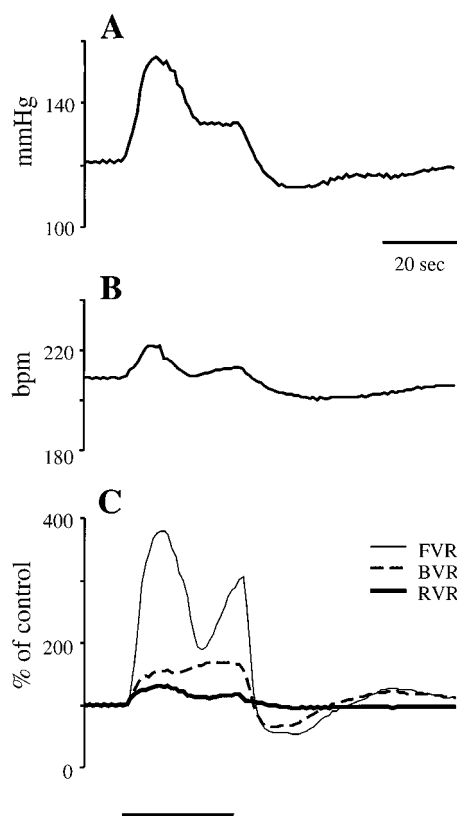


Fig. 4. Changes in vascular resistance (C) elicited by ulnar nerve stimulation (30-s continuous train, 0.2-ms pulse width, 333 Hz, 5 mA); values are expressed as percent of control (taken as 10-s period preceding stimulus onset). Plots represent averages of 5 stimulus trials. In contrast to vestibular stimulation, activation of skin and muscle afferents produced increases in blood pressure (A) and heart rate (B). These effects were accompanied by simultaneous increases of FVR, BVR, and RVR.

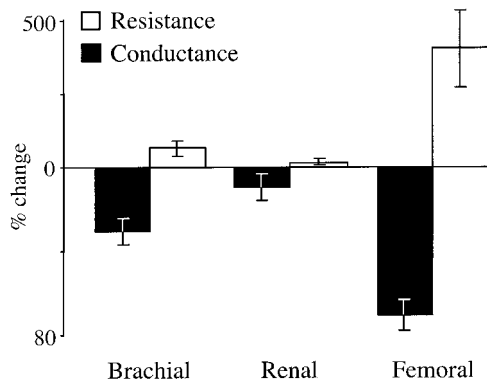


Fig. 5. Average vascular resistance and conductance changes elicited by stimulation of skin and muscle afferents in the ulnar ( $n = 8$ ) and median nerve ( $n = 1$ ). Data were collected in the same animals that were used for determination of changes in vascular resistance elicited by vestibular stimulation (see Fig. 3). Parallel increases in FVR, BVR, and RVR and decreases in conductance in these vascular beds were observed in response to limb nerve stimulation. Error bars indicate SE.

FVR and RVR were significant ( $P < 0.05$ , Bonferroni test). The differences in magnitude of changes between RVR and BVR did not reach statistical significance ( $P > 0.05$ ). Similarly, limb nerve stimulation elicited decreases in FVC, BVC, and RVC of  $70 \pm 7$ ,  $31 \pm 6$ , and  $10 \pm 6\%$ , respectively (Fig. 5). These differences in mean peak conductances were statistically significant ( $P < 0.05$ , ANOVA), and post hoc statistical analysis confirmed that differences between changes in FVC and BVC as well as those between FVC and RVC were significant ( $P < 0.05$ , Bonferroni test), whereas those between RVC and BVC were not ( $P > 0.05$ ).

## DISCUSSION

The major new finding of the present study is that vestibular stimulation has the potential to produce patterned hemodynamic alterations that preferentially affect the limb vasculature as opposed to that of the kidney. Additionally, in many animals, changes in hindlimb and forelimb vascular resistance and conductance elicited by electrical vestibular stimulation are qualitatively different such that the hindlimb resistance decreases (and conductance increases), whereas the forelimb resistance increases (and conductance decreases). In contrast, activation of skin and muscle afferents produces a different pattern of hemodynamic responses that includes a parallel increase in forelimb and hindlimb vascular resistance (or a decrease in conductance) in the three vascular beds. Although a previous study showed that stimulation of the A5 area of the brain stem can produce changes in blood flow to muscles in some parts of the body but not others (23), the present data indicate that inputs from a particular sensory system (the vestibular system) can also elicit patterned hemodynamic responses.

One caveat in our data analysis is that we calculated vascular resistance and conductance from measurements of blood pressure and Doppler frequency shift in blood flow velocity. These calculations rely on the as-

sumption that venous pressure does not change independent of arterial blood flow. Because we did not measure venous pressure in this study, we are uncertain that this assumption is completely valid. Nonetheless, it seems highly unlikely that in the paralyzed animals used in this study changes in venous pressure could account for the patterning of blood flow that was observed during vestibular stimulation. Another limitation in these experiments is that blood flow to the muscle and skin could not be distinguished, so that reciprocal changes in blood flow to the muscle and skin of a limb would appear as the absence of a local hemodynamic alteration. Follow-up studies will be required to determine whether electrical vestibular stimulation alters blood flow to the muscle, skin, or to both tissues.

Other investigators have reported that unilateral electrical vestibular stimulation produces blood pressure decreases of  $>20$  mmHg in baroreceptor-intact cats (7, 16, 25), whereas bilateral vestibular stimuli produce even larger decreases in blood pressure (6). In the present study, vestibular-elicited depressor responses were considerably smaller in magnitude ( $\sim 8$  mmHg), although qualitatively similar to those reported earlier (6). Several factors may have accounted for smaller response sizes in this study. First, we limited the current intensities applied to the vestibular nerve to assure that nonlabyrinthine afferents were not activated; it is likely that larger stimuli would have produced greater changes in blood pressure. The anesthetic regimen employed in these experiments as well as the frequency of vestibular stimulation delivered could also have diminished response sizes. Presumably, different parameters of vestibular stimulation delivered in unanesthetized animals would produce larger changes in vascular resistance than were observed in this investigation. Additionally, it is feasible that vestibular inputs act on the baroreceptor reflex circuitry to produce cardiovascular responses. Such is the case with inputs that are activated as part of the autonomic response of the defense reaction (22). It is therefore possible that larger cardiovascular changes would be observed in baroreceptor-intact cats than were elicited in the present experiments.

In the companion manuscript, we reported anatomic differences in responses of muscle vasoconstrictor sympathetic efferents to electrical vestibular stimulation (12). Specifically, activity of single muscle vasoconstrictor efferents located in the hindlimb was typically initially inhibited by vestibular stimulation; these inhibitory responses were typically followed by "rebound" excitation. In contrast, responses of muscle vasoconstrictor units located more rostrally (in the head and forelimb) often included a short duration excitatory phase that preceded the inhibition. In the present study, we found that vascular resistance changes elicited by vestibular stimulation parallel the shortest latency responses of muscle vasoconstrictor fibers. It is thus tempting to speculate that the observed hemodynamic effects reflected sympathetically mediated changes in blood flow to muscle but not to skin. However, it cannot be ruled out that activation of sympa-

thetic vasodilator fibers in the hindlimb as well as liberation of adrenal catecholamines contributed to the responses observed in the present study.

The small magnitude of changes in RVR and RVC elicited by vestibular stimulation suggests that this vascular bed is relatively unresponsive (as compared with the hindlimb) to labyrinthine inputs. This finding is somewhat surprising given the fact that renal nerve activity is much more powerfully affected by vestibular stimulation than that of other visceral sympathetic nerves that have been examined (11). One reason for this discrepancy may be differences between the characteristics of vestibular stimulation used in the present study and in the previous experiment in which sympathetic nerve activity was recorded. In the nerve recording study, responses to 200–400 brief (15 ms) stimulus trains repeated every 1–2 s were averaged (11). In the present study, stimulus trains were much longer, were repeated fewer times, and were separated by longer periods. It is feasible that the former parameters of vestibular stimulation would elicit more pronounced changes in vasoconstrictor activity than would the latter. An alternative possibility is that sympathetic nerve responses and those of vascular smooth muscle are dissociated in the kidney during vestibular stimulation. Several lines of evidence suggest that renal blood flow can remain constant during increases or decreases in renal sympathetic nerve activity. For example, occlusion of the common carotid arteries leads to a large increase in renal sympathetic nerve activity (19), but it fails to appreciably change renal blood flow (4, 13). Likewise, other baroreceptor stimuli (such as loading or unloading of the atrial stretch receptors) produce little or no change in blood flow to the kidney (4), although renal sympathetic nerve activity is altered markedly (11, 19). In contrast, stimuli such as hypoxia and those that lead to alerting and defensive behaviors produce considerable sympathetically mediated renal blood flow alterations (3, 9, 14). Further experiments will be required to determine the functional significance of vestibular effects on sympathetic outflow to the kidney.

Electrical stimulation was used to activate vestibular afferents in this study, as this method powerfully and selectively elicits vestibular inputs to the central nervous system. Many previous studies (e.g., 7, 16, 24, 25) have examined the effects of electrical vestibular stimulation on blood pressure and have shown that this method elicits depressor responses. In contrast, stimulation of a subset of vestibular afferents (in decerebrate, unanesthetized cats) signaling a head-up movement produces pressor responses (27). Thus the results of this study cannot be used to conclusively predict the pattern of hemodynamic changes that would be elicited by a particular direction of movement. Nonetheless, because stimulation of the whole vestibular nerve produces patterned hemodynamic responses, it seems likely that selective activation of subsets of vestibular afferents (either through body movements in space or electrical stimulation of individual branches of the vestibular nerve) would also

generate patterned changes in blood flow to different tissues and body regions. Because vestibular afferents are activated during the act of falling in the cat (26), it is possible that electrical stimulation of the whole vestibular nerve elicits a hemodynamic response that would typically be associated with vestibulospinal reflexes during such body translations in space. These responses could require an increase in blood flow to the large hindlimb muscles that the animal predominantly uses to “catch” itself after a fall. However, stimulation of the subset of vestibular afferents that would be activated during nose-up body rotations may produce a different pattern of blood flow in the body that is appropriate to offset an orthostatic challenge.

In contrast to vestibular afferents, stimulation of limb nerves elicited an increase in resistance and a decrease in conductance in all three vascular beds that were studied, accompanied by tachycardia and blood pressure increases. These observations are consistent with findings from other studies (2, 8, 17), indicating that pressor responses accompanied by widespread sympathetically mediated vasoconstriction occur in response to electrical stimulation of somatic nerves in anesthetized cats and dogs. In an earlier study, we reported that the pattern of responses of visceral sympathetic nerves to vestibular stimulation is different from that elicited by activation of limb afferents (10). The current study extends those findings by demonstrating that differences in sympathetic nerve responses to stimulation of vestibular and other somatic afferents are also reflected in distinct cardiovascular responses, which may involve complicated redistributions of blood flow to different body regions.

### *Perspectives*

The present study has demonstrated that electrical vestibular stimulation produces patterned alterations in the hemodynamics of limb vasculature, which include hindlimb vasodilation and forelimb vasoconstriction with relatively small changes in renal circulation. Taken together with the findings of the preceding paper, it is most likely that this reciprocal patterning is produced by withdrawal of sympathetic vasoconstrictor drive to the hindlimb muscle vasculature together with increased activity of forelimb muscle vasoconstrictor efferents. Because the vestibular system plays an important role in controlling motoneuron activity during unexpected postural changes (26), it is possible that the sympathetic patterning described in the present studies represents a complementary and preparatory autonomic response to motor activation that occurs during postural adjustments (e.g., righting). Accordingly, previous studies have suggested a role of the vasomotor sympathetic outflows for blood flow redistribution to muscle immediately before the onset of muscle contraction during willful dynamic exercise (1) or in response to emotional stimuli that produce fighting behavior (15). In addition, vestibular inputs may participate in eliciting regional changes in vas-

cular tone to offset venous pooling during movements that challenge orthostatic stability (27). These possibilities will require further investigation with the use of more natural stimuli than were employed in the present experiments. Likewise, the integration of vestibular inputs with feedforward (i.e., central command) and feedback (i.e., afferent input from contracting muscles) mechanisms that regulate sympathetic activity during movement and exercise needs to be further explored.

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