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Neurovascular responses to sequential deep inspirations assessed via laser-Doppler perfusion changes in dorsal finger skin

Harvey N. Mayrovitz and Edye E. Groseclose

Departments of Physiology and Biochemistry, College of Medical Sciences, Nova Southeastern University, FL, USA

Correspondence

Harvey N. Mayrovitz, Department of Physiology, College of Medical Sciences, Nova Southeastern University, 3200 S University Drive, Fort Lauderdale, FL 33328, USA
Fax: +1 954 262 1802

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Summary

A vasomotor reflex triggered by a rapid and deep inspiration causes arteriolar vasoconstriction and a transient decrease in skin blood flow in most people. This is the inspiratory gasp vascular response (IGVR). The most common site of its measurement has been on the palmar or plantar aspect of the digits and little is known about its features in skin with few or any arterial venous anastomoses (AVAs). A basic aspect of this response that has not been systematically studied is its temporal pattern associated with multiple sequential inspiratory gasps (IG) in the same person. Such information would provide insight as to whether there is any form of adaptation or temporal dependence and may serve as a basis for judging response variability. Thus, the present study was undertaken to characterize the normal pattern of responses in finger dorsum skin in a group of 28 normal persons who performed 21 sequential, uniformly spaced IG, over an interval of 42 min. The results show that IGVR measured on the finger dorsum have a magnitude comparable with that obtained on finger pulp, in spite of the relative dearth of sympathetically controlled AVAs on the dorsum. It was also found that the magnitude of the IGVR displays little if any tendency for sequential adaptation or temporal trending. Finally, the results indicate that the largest component of response variability is associated with subject-to-subject differences as compared with sequential variability within subjects.

Introduction

A vasomotor reflex triggered by a rapid and deep inspiration causes arteriolar vasoconstriction and a transient decrease in skin blood flow in most people. This phenomenon was first reported in detail by Bolton and coworkers (Bolton *et al.*, 1936), who also showed that it depends on an intact peripheral sympathetic system, because the vasoconstrictor response was absent in the digits of limbs that were either denervated or sympathectomized. As the inspiratory gasp vascular response (IGVR) depends on sympathetic activity, it has been used to study aspects of neurovascular function in various conditions including diabetes (Wilson *et al.*, 1992; Abbot *et al.*, 1993), Raynaud's phenomenon (Wollersheim *et al.*, 1991), erythromelalgia (Littleford *et al.*, 1999) and leprosy (Abbot *et al.*, 1993). The vasoconstrictor response was present with a complete occlusion of the arm circulation, indicating no major role of local circulation in the reflex. These early workers concluded that the afferent stimulus was caused by chest wall expansion during deep inspiration. However others, who were able to induce the reflex with either deep inspiration or with negative pressure breathing without chest wall expansion, argued for an increase in stretch of intrathoracic veins as the principal initiating factor (De Lalla, 1948). Gilliatt *et al.* (1948) concluded that the IGVR represents a purely spinal reflex mediated by afferent fibres that enter the spinal cord mainly in the upper thoracic region, because they observed a vasoconstrictor reflex in paraplegic patients who had a full break in functional continuity of the spinal cord above the level of sympathetic outflow to the hands. This group also demonstrated that the reflex vasoconstriction was not because of inspiration-induced hypotension, with its associated carotid sinus reflex (Gilliatt, 1946).

Many details of the afferent and efferent pathways remain to be clarified. That the reflex causes a significant reduction in blood flow has been clearly demonstrated by plethysmography, which showed hand blood flow to be reduced by 83% during deep inspiration, and by nailfold capillaroscopy, which showed a rapid and complete cessation of capillary flow during a deep inspiration in most subjects (Mulinos & Shulman, 1939). Interestingly, when capillary flow was stopped by a suprasystolic

arm occlusion, a subsequent deep inspiration caused a transient forward capillary flow, presumably because of the expelled contents of the vasoconstricted proximal arterioles. In more recent times this inspiratory gasp vascular response (IGVR) has most often been measured on the plantar aspect of the toes and fingers, using either laser-Doppler perfusion monitoring (Khan *et al.*, 1991; Netten *et al.*, 1996) or photoplethysmography (Barron *et al.*, 1993). Although the reflex causes vasoconstriction, there may be an initial small flow increase that precedes the flow decrease, and often a flow increase follows (see Fig. 3 later). Factors that may affect the magnitude of the vasoconstrictive component include skin temperature, age, gender and vital capacity (Lau *et al.*, 1995; du Buf-Vereijken *et al.*, 1997).

An important basic issue that has not been systematically studied is the temporal pattern of evoked response magnitudes associated with multiple sequential inspiratory gasps in the same person. Such information would provide insight as to whether there is any form of adaptation or temporal dependence of the response. It would also serve to provide a basis for judging response variability based on data from more than two or three sequential measures, which is common practice. Thus, the present study was undertaken to characterize the normal pattern of responses in a group of 28 normal persons who performed 21 sequential, uniformly spaced inspiratory gasps over an interval of 42 min.

Methods

Experimental

Subjects: Twenty-eight volunteers participated in this study after signing an institutional review board approved informed consent. Subjects were equally divided by gender and were drawn from the university medical student population and sta. No subject had a history of any form of cardiovascular or respiratory abnormality, hypertension or diabetes. However in five male subjects, the measured diastolic blood pressure following the testing interval was greater than 90 mmHg (102–110 mmHg). Although it was not a requirement for entry into this study, the right hand turned out to be the dominant hand of all subjects. Pertinent summary data is shown in Table 1.

Table 1 Summary of subject data.

	Male (n = 14)	Female (n = 14)	Total group (n = 28)
Age (years)	32·9 ± 7·9	33·3 ± 13·2	33·1 ± 10·7
Height (cm)*	177 ± 6·3	167 ± 5·8	172 ± 8·0
Weight (kg)*	82·4 ± 11·0	62·2 ± 9·0	72·3 ± 14·3
Pressures (mmHg)			
Systolic	128 ± 20	117 ± 13	123 ± 17
Diastolic*	89 ± 13	79 ± 8	85 ± 12

Values are mean ± sd.
* Parameter values significantly greater for males ($P<0.01$).

Initial preparations: Subjects were seated in a comfortable, height adjustable arm-chair with their hands placed palm down on a soft support surface placed across the front of the chair. A laser-Doppler probe (Vasamedics, Softflo no. 4409, St Paul, MN, USA) was placed on the dorsum of the index finger of the right hand, with its sensing area approximately 4 mm proximal to the nailfold (Fig. 1a). The probe was connected to a laser-Doppler monitor (Vasamedic Model 403a) and its output perfusion data recorded by a laptop computer. A small thermocouple was placed under the probe near the site of measurement and the combination of probe and thermocouple wire were secured by gentle wrapping with an elastic cohesive bandaging material (Coban$^{R.}$ 3M company, MN, USA) as shown in Fig. 1b. In addition to providing support, the wrapping served to provide thermal insulation and render the finger relatively insensitive to potential drafts or direct effects of ambient temperature changes. The hand was then covered with a towel to further insulate the test area and to provide for a more stable local skin temperature. Skin temperature was continuously monitored and testing did not begin until it had reached a steady state level; typically this took 15–20 min

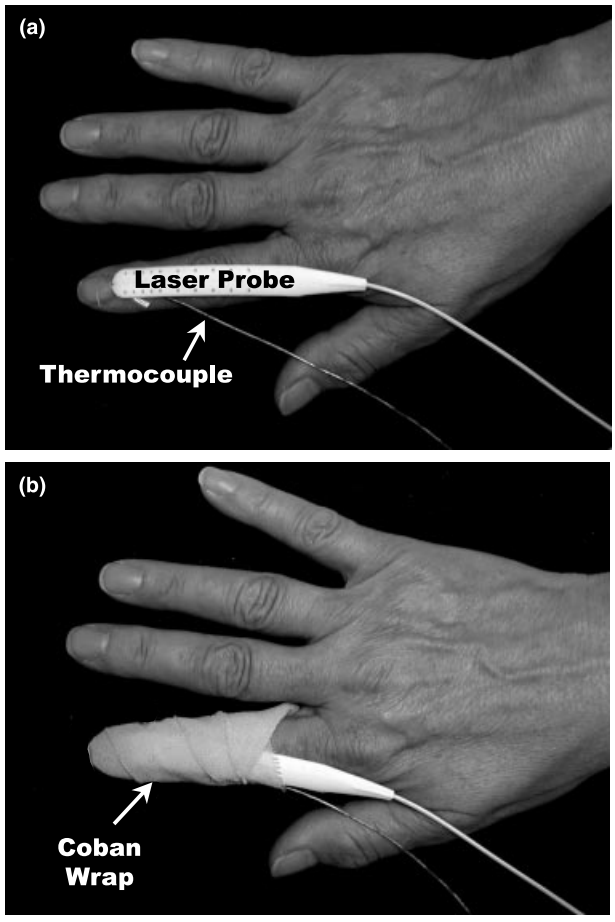

Figure 1 Laser-Doppler probe on finger.

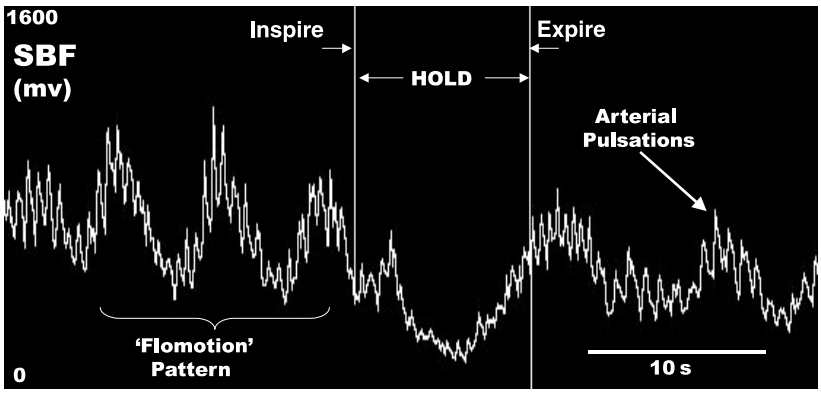

Figure 2 Skin blood perfusion (SBF) before, during and after a single inspiration. Subjects were instructed to take a deep and rapid inspiration starting at the end of a normal quiet expiration and hold it for 10 s. In some subjects a rhythmical flow motion pattern was present. Time constant for laser-Doppler recording was 0·1 s which allowed detection of arterial pulsations.

During this interval the subject was instructed about the breathing manoeuvre that was required and was given multiple chances to practice these. The instruction was to take a deep and rapid inspiration starting at the end of a normal quiet expiration and hold it for 10 s (Fig. 2). Subjects were instructed to first sense their breathing pattern so that they could feel comfortable in identifying the end-expiratory point and then to take the gasp when comfortable. During testing, the experimenter quietly informed the subject that their next gasp was in 20 s and, when the time arrived, they were instructed to 'gasp when ready'. Following this last instruction, subjects usually initiated the gasp within 10 s.

Test procedures and perfusion parameters

The test protocol consisted of a series of 21 sequential inspiratory gasps taken at uniform intervals of 2 min between adjacent gasps. The average finger skin blood perfusion (SBF) during the 2-min interval immediately preceding each successive gasp was used as the reference perfusion for its following inspiratory gasp vascular response (IGVR). The IGVR was determined from the minimum perfusion during the gasp (SBF_{min}) and its reference perfusion (SBF_0) according to the relationship: $IGVR = 100 \times (SBF_0 - SBF_{min})/SBF_0$ (Fig. 3). Accordingly the maximum range of IGVR was 0–100%. Skin and room temperatures were continuously monitored and recorded every 2 min corresponding to each of the inspiratory gasps. At the end of the procedure, blood pressure was measured in the right arm and a suprasystolic occlusion (200 mmHg) of the brachial artery for 3-min was used to determine the laser-Doppler biological zero at the finger site. This value was routinely subtracted from all raw SBF data prior to analyses.

Analytical

All data reduction was done from the computer-acquired and -stored perfusion signals. The total data set consisted of 21 IGVR for each of the 28 subjects representing a total of 588 data points. All data points were included in the subsequent analyses. The complete data set was analysed using a full factorial repeated measures model (SPSS version 6·1) to determine within-subject and between-subject response properties. Correlational properties of sequential IGVR were tested by determining the Pearson correlation coefficient for all pairs of IGVR and testing these for overall within- and between-subject differences using the full factorial repeated measures model. The possibility of a sequential trend in responses was further tested by regression analysis of IGVR against inspiratory gasps (IG) number. Additional

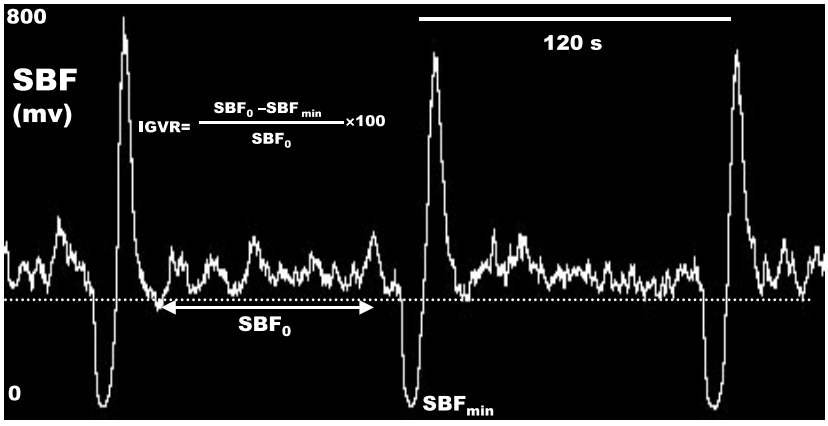

Figure 3 Determination of inspiratory gasp vascular response (IGVR). In this subject the gasp induced vasoconstriction was followed by a large transient hyperaemic peak in SBF.

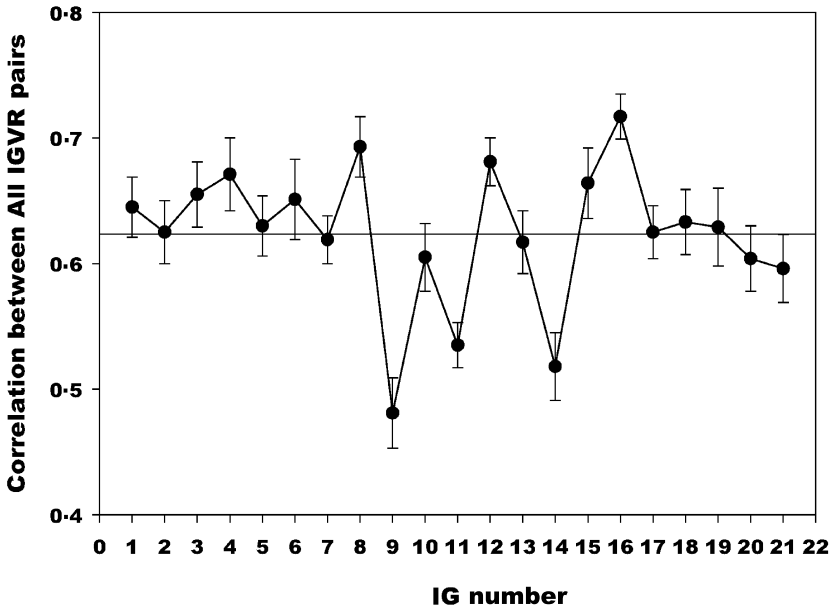

Figure 4 Correlations between sequential IG. Circles are mean Pearson correlation coecients between each IG and all other IG; Bars are SEM.

analyses were done to test for possible differences in the responses of subjects of different genders and ages.

Results

Overall sequential response features

The correlation among sequential IG, as expected, was significant among all pairs of IG (0·63 ± 0·05 SD, $P < 0·01$) and ranged from 0·48 to 0·72 (Fig. 4). There was an overall difference ($P < 0·01$) among the full set of paired correlations both within and between subjects, but there was no significant sequential trend or time related difference in the correlation between paired IG. Response magnitudes between subjects had a large scatter but there was no sequential trend during the 42 min experimental interval (Fig. 5); regression analysis indicated an r^2 value of 0·004 with upper and lower 95% confidence intervals of 66·4–73·5, respectively.

The overall grand mean IGVR (28 subjects with 21 responses each) was 72·2% (Fig. 6) with no detectable within-subjects significant difference ($MS = 251$, $F = 1·45$, $P = 0·095$). However, a highly significant overall difference between subjects was present ($MS = 5995$, $F = 511$, $P < 0·001$).

During the 42-min experimental interval, the average of the 21 reference SBF values (SBF0) across IG samples was 54·8 ± 3·0 a.u and skin temperature (34·3 ± 0·18 °C) and room temperature (24·6 ± 0·15 °C) varied only slightly.

Gender and age as factors

There was no significant difference in IGVR between gender ($n = 14$ each group, $F = 0·80$, $P = 0·72$) but a small significant inverse dependence of IGVR on age was detected in the present group ($r = -0·382$, $P = 0·045$, age range 19–57 years).

Discussion

The present findings show that IGVR induced by an inspiratory gasp and measured on the finger dorsum is large in magnitude and displays little if any tendency for sequential adaptation or temporal trending. The results further indicate that the largest component of response variability is associated with subject-to-subject differences as compared with sequential variability within subjects.

The overall IGVR determined in the present study (72%) is in close agreement with a value of 77% obtained in a group of 20 young healthy people (Khan *et al.*, 1991). The fact that these workers used the finger tip pulp whereas the finger dorsum was used in our study, suggests that in spite of a much lower density of arterial venous anastomoses (AVAs) in finger dorsum, the net vasoconstrictor activity induced by the IG sympathetic reflex is similar. We believe that the present report is the first to describe the IGVR using finger dorsum skin, a site which was specifically chosen for two reasons. First, because of the extensive sympathetic control of the AVAs, it is reasonable to assume that IGVR magnitude depends on reflex activation of these vessels. Thus by choosing to study the dorsum skin we are now able to suggest that, although AVA activation is probably predominant on the digit plantar surfaces, the IGVR is not generally dependent on this process. The second reason was a practical one. Certain experimental treatments of the hand vasculature that are being developed require placement of the palmar surface directly on the treatment device's surface. This hampers, and may preclude, proper placement of laser Doppler probes on the palmar surface. The present findings

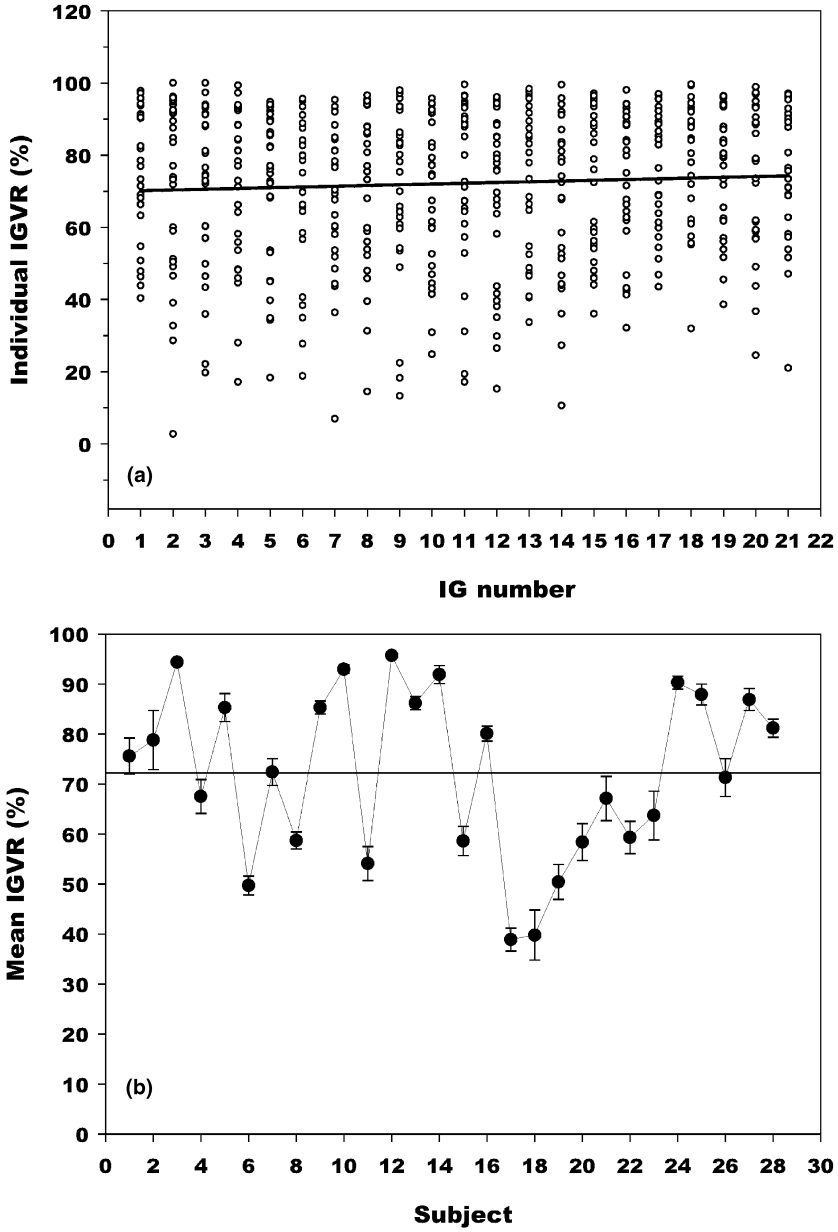

Figure 5 Individual IGVR. (a) Circles are all individual IGVR with line showing the near zero regression of seqential IG. Significant scatter of IGVR between subjects is evident. (b) Mean and SEM for IGVR by subject. Horizontal line shows grand mean across all subjects and IG.

show that such placement is not necessary to obtain suitable IGVR for testing purposes.

It is also noteworthy that the present findings and those of Khan *et al.* (1991) were obtained at skin temperatures very close to 34 °C. Skin temperature is a consideration because of its reported effect on the magnitude of the IVGR when measured on palmar or plantar digits (Oberle *et al.*, 1988). These workers initially found no significant age difference in IGVR between a young group (mean age = 26 years) and a group of 10 normal subjects (mean age = 51 years) in whom a mean IGVR of 71% was reported. However by expanding the group size in later work (Khan *et al.*, 1992), an age-related, 32% reduction in IGVR was detected when triplicate IGVR were used to compare 28 elderly persons (mean age of 68 years) with the responses of the 20 young subjects. The present finding of a small age related decrease in IGVR would be consistent with their results.

Using finger pulp IGVR, comparisons have also been made between normal subjects and patients with advanced diabetes who also had copresent retinal complications (Wilson *et al.*, 1992). Reported results indicated that although the mean IGVR was less in the diabetics (48 vs. 68%), there was no significant difference between these groups of 15 subjects each. Although the present work has focused on finger responses, it is relevant to note that related work has been done using the great toe pulp for assessments of IGVR. This site has been used to compare normal subjects with patients with diabetes (Wilson *et al.*, 1992) and considerable work has been done regarding the reproducibility of this response (Netten *et al.*, 1996; du Buf-Vereijken *et al.*, 1997). To date

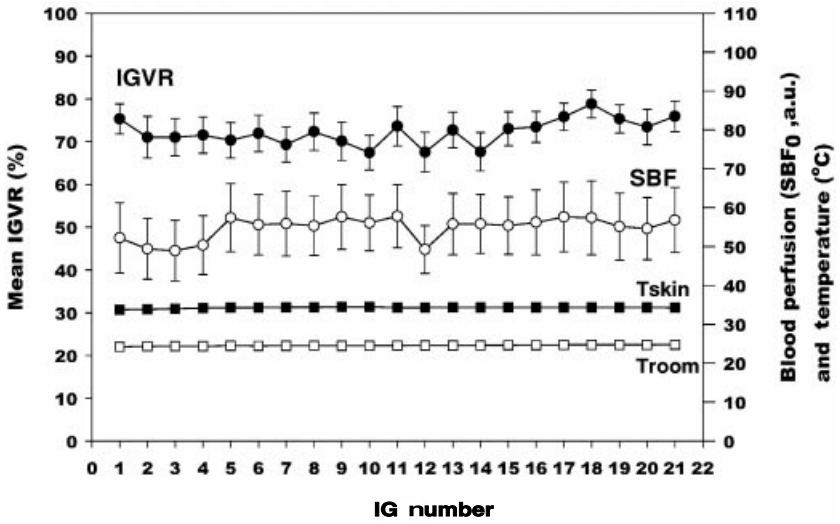

Figure 6 Sequential parameter values. Points are the mean of all 28 subjects for IGVR, skin blood perfusion (SBF), skin temperature (T_{skin}) and room temperature (T_{room}) and bars are SEM. There were no significant trends in any parameter over the experimental interval.

however, studies of the responses of the foot dorsum have not been reported.

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