Sympathoexcitation causes differing responses in supraorbital vs. peripheral skin nerves: implications for rosacea

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Abstract

Previous studies indicate that common fibular, tibial, and radial skin sympathetic nerve activity (SSNA) increases with physical stress in an exercise intensity-dependent manner but abates during ischemia when class III & IV muscle afferents are stimulated without the engagement of the motor cortex. It is currently unknown if these peripheral nerve responses are similar to nerves of the face. Rosacea, a fascial flushing disorder, results in substantially higher physical and mental stress-induced increases in SSNA, but it is unknown if this is modifiable. We hypothesize that physical stress increases supraorbital SSNA in an intensity-dependent manner. Furthermore, we hypothesize that post-exercise muscle ischemia (PEMI) will not modulate supraorbital SSNA. Nine healthy subjects (5M/ 4F) participated in a series of physical stressors known to be symptom-triggering in individuals with rosacea. Forehead SSNA (supraorbital microneurography) was measured during handgrip exercise for 1 minute at 15%, 30%, and 45% of their maximum hand grip strength. Additionally, 2 minutes of hand grip at 30% of maximum, followed by 2 minutes of PEMI (upper-arm arterial occlusion) were completed to assess the role of muscle afferents in the SSNA response. Skin blood flow (laser-Doppler flowmetry) and transepithelial water loss/sweat rate (TEWL/SR; capacitance hygrometry) were measured on both the forehead and the ventral forearm during procedures. Heart rate (HR; ECG) and mean arterial pressure (MAP; finger photoplethysmography) were also recorded. All intensities of handgrip increased HR and MAP, and these responses were positivity correlated with intensity. Handgrip also increased SSNA, but there was no association with intensity. No changes in skin blood flow or TEWL/SR were observed across trials. PEMI maintained handgrip-induced elevations of MAP and SSNA, albeit at a reduced magnitude compared to baseline. Contrary to our hypothesis, physical stress did not increase supraorbital SSNA in an intensity-dependent manner (15%, 30%, and 45% of maximum handgrip strength). Furthermore, unlike peripheral SSNA which increases during physical stress but abates during PEMI, these data indicate that ischemia or ischemic pain increases supraorbital SSNA. These data imply that supraorbital SSNA differs in control and regulation from peripheral nerves, and these differences could potentially account for altered supraorbital SSNA results observed in individuals with rosacea.

Introduction

- It is estimated that rosacea affects 16 million Americans[1]. This disease can be very costly and drastically reduce quality of life[2,3]. The etiology of rosacea is currently unknown, though physical stress can trigger symptoms which include facial flushing[4,5].
- Physical stress increases skin sympathetic outflow[6], which can be quantified directly via postganglionic SSNA in several superficial nerves.
- Previous studies indicate that common fibular, tibial, and radial SSNA increases with physical stress in an exercise intensity-dependent manner but abates during ischemia when class III & IV muscle afferents are stimulated without the engagement of the motor cortex[7,8].
- It is currently unknown if these peripheral nerve responses are similar to nerves of the face. Rosacea results in substantially higher physical and mental stress-induced increases in SSNA[9], but it is unknown if this is modifiable.

Figure 1: Skin sympathetic neurogram obtained via microneurography

- **Hypothesis: We hypothesize that physical stress increases supraorbital SSNA in an intensity-dependent manner. Furthermore, we hypothesize that post-exercise muscle ischemia (PEMI) will not modulate supraorbital SSNA.**

Methods

Human subjects: 9 healthy subjects (4 females, 5 males) completed the study. A medical history and vital signs were used to screen all participants for health.

Instrumentation/Measurements: Supraorbital SSNA was measured by inserting a custom sterile tungsten microneurography electrode (impedance 2 MΩ, shaft diameter 0.2 mm; FHC, Bowdoin, ME) through the skin without local anesthesia (Figure 2 & 3). Capacitance hygrometry capsules (with custom ventilated chambers perfused with N_2) measured sweat rate and TEWL while laser-Doppler flowmetry (Moor Instruments, Wilmington, DE) assessed skin blood flow. Heart rate was calculated via 2-lead ECG (CWE) and beat-by-beat arterial blood pressure (Finapres Medical Systems, Amsterdam, The Netherlands) was measured by finger photoplethysmography. A skin thermistor (YSI, Yellow Springs, OH) measured skin temperature.

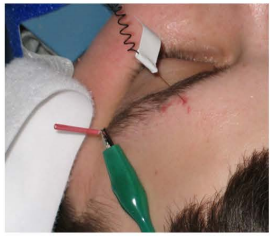

Figure 2: Supraorbital microneurography

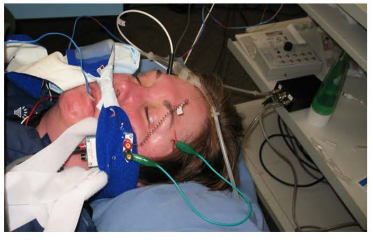

Figure 3: Supraorbital microneurography

Protocol 1: SSNA was measured in the supraorbital nerve throughout the experiment. Laser-Doppler flow probes for skin blood flow, ventilated capsules for TEWL/sweat rate, and a thermistor for skin temperature were placed within the typical area of supraorbital innervation on the contralateral forehead because ipsilateral sensory-related mechanoreceptive afferents could not be avoided. Laser-Doppler flow probes and hygrometry capsules were also placed on the ventral forearm contralateral to the handgrip. The placement of the recording electrode within the nerve fascicle was verified until SSNA bursts were identified using previously established criteria[10,11], which included 3:1 signal-to-noise ratio; skin afferent recordings; non-pulse-synchronous SSNA induction by startle, inspiratory gasp, and handgrip; and no relation to chemoreflex or baroreflex perturbations. Baseline measurements were obtained, followed by the handgrip protocol. To induce physical stress, participants performed a series of isometric handgrip exercises. Participants performed maximal voluntary contractions while force was measured via compression dynamometry (Biopac Systems) to determine target submaximal forces of 15%, 30%, and 45%. Handgrip force feedback was provided via verbal cues. These tasks increase fibular SSNA in an effort-dependent manner that is not related to the amount of muscle mass involved[12,13,14,15]. Forehead SSNA was then measured during the handgrip exercises for 1 minute at 15%, 30%, and 45%.

Protocol 2: Following a similar set up to Protocol 1, subjects underwent training to determine target submaximal forces. Upper-arm arterial occlusion with a manually inflated blood pressure cuff created post-exercise muscle ischemia (PEMI). 2 minutes of hand grip at 30% maximum followed by 2 minutes of PEMI were completed.

Data Analysis: Data were acquired at 1,000 Hz with the use of a data acquisition system and analyzed with commercially available software (Biopac Systems). Data are means ± SE unless otherwise noted. Supraorbital SSNA was calculated as the integral of the integrated SSNA neurogram[16], averaged in 30-s bins, normalized to baseline, and expressed as percent change from baseline. Normalization accounts for individual SSNA variation and electrode locations within the nerve. Cutaneous vascular conductance (CVC) as calculated as red blood cell flux divided by mean arterial pressure (MAP). HR, cardiac output, MAP, CVC, and sweat rate were also averaged in 30-s bins. Group differences analyzed via RM ANOVA utilizing SNK post hoc analysis when significant main effects were observed.

Results

Table 1: Heart rate and arterial blood pressure changes during handgrip protocol. Values are reported in the table as an absolute change from each protocol's baseline, where a (+) indicates an increase and (–) a decrease.

	Protocol #1				Protocol #2		
	Base/IHG	15%	30%	45%	Base	2 min HG	PEMI
HR (bpm)	53±1	+1±1	+6±2	+7±1	55±2	+3±2	-2±1
MAP (mmHg)	87±2	+8±1	+12±2	+11±2	90±2	+22±2	+12±1
SV (ml/beat)	92±2	-6±1	-9±2	-6±1	92±2	-16±2	-2±1

Skin blood flow as indexed by CVC was greater in the forehead compared to the arm (60±8 vs. 40±6 flux/mmHg, respectively). These site differences persisted but there were no significant differences were noted between protocol, treatment.

No differences between site, protocol, or treatment were noted for TEWL/Sweat rate.

SSNA in Protocol #1 increased during IHG but this increase was not significantly different between 15, 30, and 45% of MVC (maximal responses range from 117-134%) change from baseline across the different grip efforts.

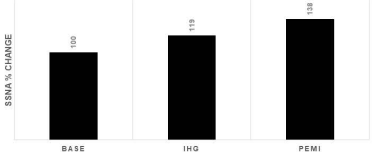

Figure 4: SSNA responses during Protocol #2.

Discussion

- There was a positive correlation with HR and MAP compared to handgrip intensity. Physical stress did not increase supraorbital SSNA in an intensity dependent manner (15%, 30%, and 45% of maximum handgrip strength).
- PEMI maintained handgrip-induced elevations of MAP, though at a reduced magnitude compared to baseline. Similarly, PEMI maintained elevations of SSNA.
- **These data indicate that supraorbital SSNA differs in control and regulation from peripheral nerves. Unlike peripheral SSNA which increases during physical stress but abates during PEMI, these data indicate that ischemia or ischemic pain increases supraorbital SSNA.**
- These differences could potentially account for altered supraorbital SSNA results observed in individuals with rosacea.

Acknowledgements & References

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