

Syncopal attack alters the burst properties of muscle sympathetic nerve activity in humans

Satoshi Iwase*, Tadaaki Mano, Atsunori Kamiya, Yuki Niimi, Qi Fu, Akio Suzumura

Department of Autonomic Neuroscience, Research Institute of Environmental Medicine, Nagoya University, Nagoya 464-8601, Japan

Received 13 August 2001; received in revised form 5 October 2001; accepted 9 October 2001

Abstract

This study aimed at examining whether the properties of microneurographically recorded muscle sympathetic nerve activity (MSNA) were altered during hypotensive attacks. A retrospective study was performed on 74 subjects who participated in tilt studies when vasodepressive syncope was induced incidentally in six subjects. The specific features of MSNA that distinguish this activity from skin sympathetic nerve activity are (1) rhythmic pulse synchronous burst discharge, (2) a duration of approximately 150–300 ms, and (3) no response to arousal stimuli were abolished during the syncopal attack. The altered features observed during the syncopal attack in these six subjects were (1) scattered reflex latencies of MSNA peak from the ECG R-wave, (2) elongated burst duration twice to five times as long as that in conscious state, and (3) response to arousal stimuli. The reduced input from the baroreceptors due to suppression on the central sympathetic volley proximal to the nucleus tractus solitarius might be attributed to the lost features characteristic of MSNA. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Muscle sympathetic nerve activity; Microneurography; Vasovagal syncope; Baroreflex

1. Introduction

The present study was conducted to test the hypothesis that vasoconstrictive sympathetic outflow to muscles (muscle sympathetic nerve activity, MSNA) is losing its characteristic features in the course of ongoing fainting.

MSNA plays an important role in regulating systemic blood pressure in humans, especially in a positional change from lying to standing (Burke et al., 1977; Iwase et al., 1991). MSNA possesses specific features, usually being utilized to distinguish this sympathetic outflow to muscle from that of the skin (skin sympathetic nerve activity, SSNA). They are (1) a rhythmic, pulse synchronous discharge pattern, (2) a duration of 150–300 ms, and (3) a failure to respond to arousal stimuli (Mano, 1998; Wallin, 1999). It is reported that arterial and cardiopulmonary baroreceptor inputs generate these characteristic properties of MSNA presumably by an inhibitory processing in the caudal and rostral ventrolateral medulla (CVLM and RVLM) (Benarroch, 1999).

In our past tilt studies, we have sometimes experienced the subjects suffering from fainting or hypotensive attacks during which the specific properties of MSNA were altered. In this survey, we examined the quantitative changes in MSNA bursts retrospectively when the subject is fainting or suffering from hypotensive attack in order to predict the ongoing fainting even before the fall by observing the MSNA bursts.

2. Subjects and methods

Out of 74 subjects who participated in the tilt studies, six of them suffered from vasovagal syncopal attack. They were all men aged 19 to 28 years old (mean \pm SD, 22 ± 3), height: 171.3 ± 4.7 cm, weight: 64.2 ± 4.2 kg, body fat percentage: $16.2 \pm 4.0\%$. They were all normotensive in the supine position ($116 \pm 7.2/77 \pm 7.6$ mm Hg) and their heart rate was normal (60 ± 2.6 min⁻¹). All subjects were instructed to refrain from drinking alcohol or caffeinated beverages from 21:00 the previous night, and to come to the laboratory at 10:00. The protocol of the study was approved by the Human Research Committee, Research Institute of Environmental Medicine, Nagoya University.

* Corresponding author. Tel.: +81-52-789-3883; fax: +81-52-789-5047.
E-mail address: iwase@riem.nagoya-u.ac.jp (S. Iwase).

The subjects reclined on a tilt bed for > 1 h. A tungsten microelectrode with a tip diameter of 1 μm, shaft diameter of 100 μm and an impedance of 3–5 MΩ was inserted into the muscle fascicle of the tibial nerve at the popliteal fossa. The MSNA, which satisfies the above-mentioned criteria, was identified and recorded. The sympathetic nerve signals were fed into a high impedance input preamplifier (World Precision Instruments, DAM-6A, New Haven, CT) and band-pass filters (NF Circuit Design E-3201A, Yokohama) with a band width of 500–5000 Hz and an attenuation rate of 24 dB/octave. They were monitored on a cathode ray oscilloscope (Tektronix 5113, Beaverton, OR) with a loud speaker for sound monitoring.

ECG and respiration were monitored and pulsatile finger blood pressure was continuously measured with Finapres (Ohmeda Finapres 2300, Madison, WI). All data were stored in a 14-channel FM data recorder (Sony-Magnescape, KS-616U, Tokyo).

Subjects were requested to lie down on a tilt bed. After recording MSNA, they were rested in a supine position for a control reading >30 min. The bed was passively and gradually tilted from 0° to 90° (upright standing). The subjects who suffered from a fainting attack or a hypotensive attack by vasovagal syncope were retrospectively extracted from the whole tilt studies, and changes in their MSNA burst

properties were analyzed during the time course of the attack from the data recorder. These attacks happened incidentally while the maneuvering was being conducted, and were wholly unintentional. The consciousness states were classified into four stages: conscious, presyncopal, fainting and recovery. The *conscious* state was defined as conscious with no blood pressure drop, *presyncopal* as drowsy with a blood pressure drop >15 mm Hg, *fainting* as drowsy with fainting symptoms (nausea, grayout, bradycardia >20 bpm, etc.), and *recovery* as the conscious state after the fainting episode. In each state, MSNA bursts were measured and analyzed.

The reflex latency from the R-wave of ECG to the corresponding MSNA burst peak in the integrated MSNA with a time constant of 1 s was determined for the quantification of MSNA linkage to the heartbeat. The latency is defined as the delay from the ECG R-wave to the peak of the corresponding MSNA burst in the mean voltage neurogram, the peak being interpreted as the beginning of the inhibition to the sympathetic discharge (Fagius and Wallin, 1980). The burst duration from the initial impulse to the termination of MSNA multifiber bursts was measured in the four consciousness states. The data were estimated as mean ± SD and *p* values less than 0.05 were considered significant. Burst duration and reflex latency were examined in the above four states (conscious, prefainting, fainting and

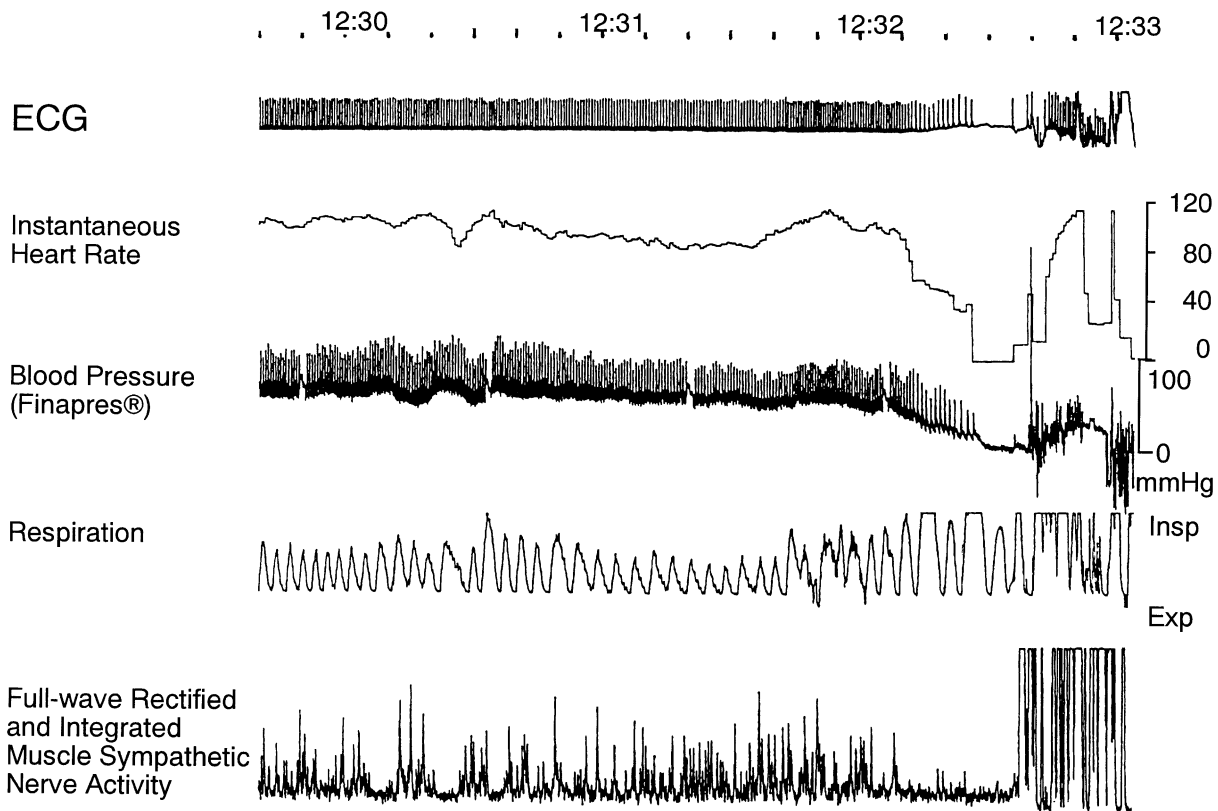


Fig. 1. Polygraphic recordings of ECG, heart rate, blood pressure waves, respiration curve, and full-wave rectified and integrated muscle sympathetic nerve activity. For details, see text. The alphabets A to D correspond to the consciousness states in Fig. 2.

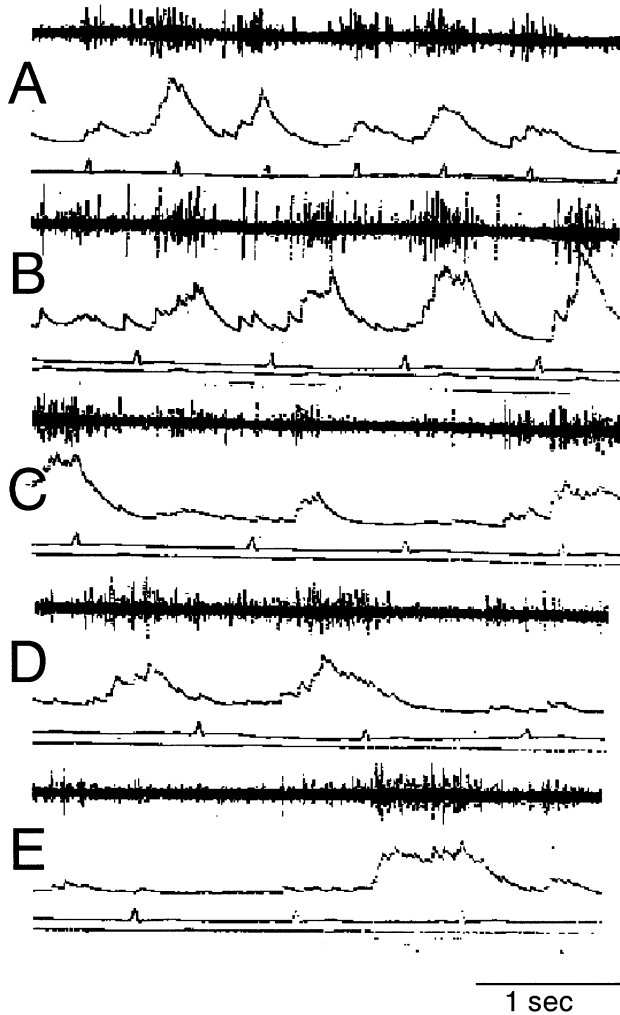


Fig. 2. Changes in muscle sympathetic nerve activity in fainting: (A) when the subject is conscious; (B) when the subject complains of a fainting sensation; (C) when the subject complains of nausea and becomes pale with sweating; (D) when the subject loses consciousness; and (E) when the subject is laid down after the reinsertion. From A to E, upper trace is original MSNA, middle trace is full-wave rectified and integrated MSNA, and lower trace is electrocardiogram. B and C are prefaint states, and D and E are fainting states. In B, burst duration became elongated, although pulse synchronicity is still maintained. In C, D and E, pulse synchronicity disappears and burst duration becomes elongated more and more as the fainting proceeds.

recovery) and the effects of consciousness were analyzed by repeated measures ANOVA.

3. Results

Fig. 1 shows the polygraphic recording of the syncopal attack of a typical subject. All variables were normal until 12:31:00, when a gradual decrease in blood pressure was observed. Enhanced MSNA was observed, then an increase in heart rate, coarse respiration, and MSNA reached its maximum. Then sudden bradycardia, muscle sympathetic

silence, and hypotension occurred. Cardiac standstill was observed, and the subject fainted. By taking a recumbent position, the subject recovered consciousness.

At the same time, as the hypotensive attack began, the subject complained of nausea and exhibited pallor with sweating, and there was a disappearance of pulse synchronicity of MSNA and an elongated burst duration (Fig. 2). After complete recovery, the electrode was reinserted to obtain an MSNA burst at the satisfactory level.

The burst duration of a typical subject in a conscious state was 246 ± 32 ms, whereas it was elongated to 556 ± 157 ms in prefainting, and was further elongated in the fainting state to 771 ± 123 ms (Fig. 3). After a complete recovery of consciousness, it recovered to a fairly constant value of 303 ± 51 ms. The averaged burst duration in the six subjects was significantly reduced by the fainting event from 279 ± 52 ms in a conscious state to 619 ± 92 ms in prefainting, 834 ± 78 ms in fainting, and recovered to 349 ± 59 ms (Fig. 4, $F=75.793$, $p<0.0001$). The reflex latency in a conscious state in a typical subject was 1062 ± 41 ms. When the subject complained of a fainting sensation and nausea (presyncopal state), it became short-

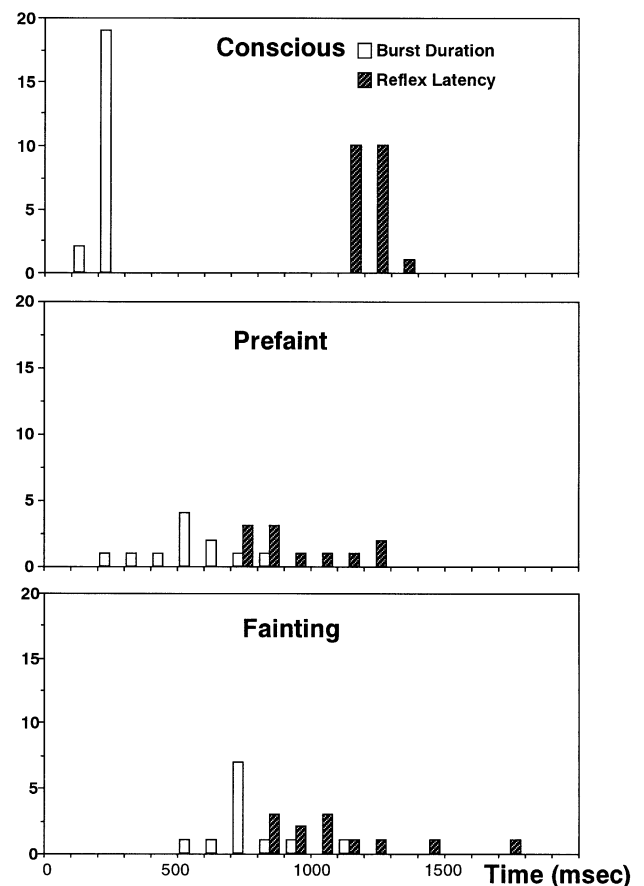


Fig. 3. Histogram of burst duration and reflex latency in fainting. Conscious, prefaint and fainting correspond to A, B–C, and D–E, respectively. The reflex latency becomes more scattered, and burst duration becomes elongated as the fainting proceeds. For the detailed values, see text.

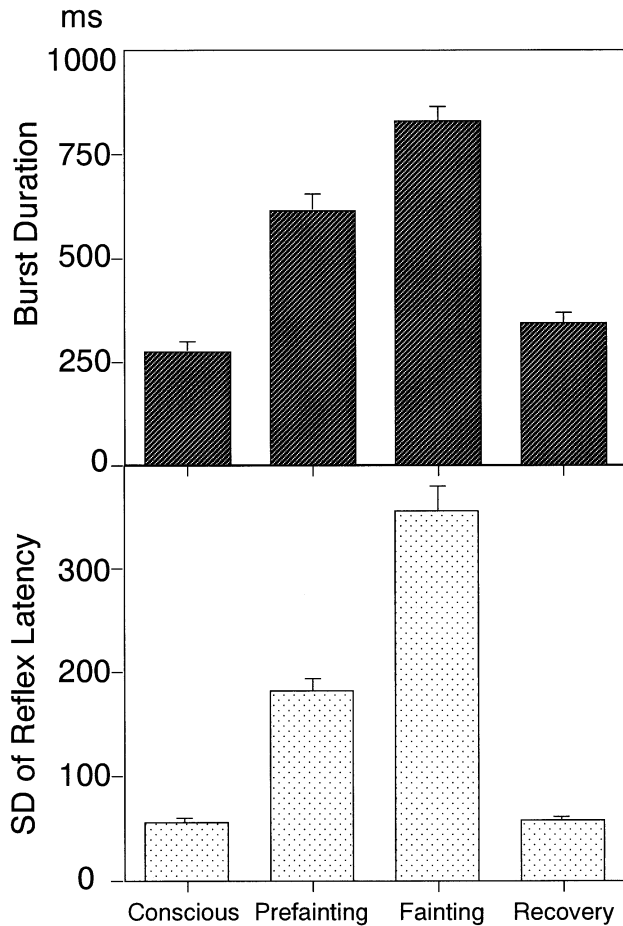


Fig. 4. Changes in burst duration (upper plate) and standard deviations of reflex latency (lower plate). As the fainting attack develops progressively, burst duration is more elongated and reflex latency is more scattered.

ened but scattered to 740 ± 139 ms, becoming further shortened and scattered to 723 ± 289 ms in the fainting state (Fig. 3). The SD of reflex latencies in the six subjects were significantly increased by the fainting event from 57 ± 12 to 182 ± 33 ms in prefainting, 357 ± 58 ms in fainting, and recovered to 59 ± 8 ms (Fig. 4, $F=102.329$, $p<0.0001$).

During the syncopal attack, we called the subjects' name. By this arousal stimuli, the subject discharged an MSNA burst during prefainting and fainting states with elongated burst duration ~ 1 s after name calling. This phenomenon disappeared during name calling in the recovered state.

4. Discussion

This study demonstrated that the MSNA-specific burst properties were altered into those of SSNA during the syncopal attack. They are: (1) a rhythmic pulse synchronous pattern was disorganized to scattered reflex latency during the attack; (2) burst duration of 150–300 ms was elongated to 400–700 ms; and (3) no response to arousal stimuli in

conscious state became responsive with a latency of ~ 1 s during the attack.

The reflex latencies were scattered during the presyncopal period and the latencies in the fainting state were more scattered in the course of the attack. Since the reflex latency from the R-wave of ECG to the peak in the correspondent MSNA burst is fairly constant (Fagius and Wallin, 1980), these scattered reflex latencies indicate that pulse synchronicity was lost during the attack. This MSNA-specific burst property of R-wave locked discharge was considered to be configured by inhibitory input from the baroreceptors (Kumada et al., 1990). The impulses from the baroreceptors enter the brainstem at the nucleus tractus solitarius and are transmitted to the caudal ventrolateral medulla, where the inhibitory impulses are input to the RVLM, thus forming the pulse synchronicity of MSNA bursts. The collapse of this pulse synchronicity suggests the diminished input of the inhibitory rhythmic and pulse synchronous to the RVLM.

Prolongation of MSNA burst duration was also observed in the course of fainting, and the MSNA responses elicited by arousal stimuli might be attributed to deafferentation from the baroreceptors (Fagius et al., 1985). The above-mentioned properties of the burst are the specific features of MSNA, by which we routinely distinguish MSNA from the sympathetic outflow to skin. These alterations in MSNA burst properties indicate that inhibitory input from the baroreceptors is diminished in the course of fainting. In spite of this diminished inhibitory input to the caudal ventrolateral medulla, the central sympathetic outflow was incapable of enhancing MSNA that was inadequate to compensate for the blood pressure fall. This was then followed by progressive MSNA inhibition until its complete disappearance and syncope (Wallin and Sundlöf, 1982).

Similar phenomena were observed in MSNA during glossopharyngeal and vagal anesthesia by lidocaine (Fagius et al., 1985) and during non-REM sleep (Takeuchi et al., 1994), in which the burst duration of MSNA became elongated, some bursts were outside the constant reflex latency, and MSNA bursts were elicited by arousal stimuli. The time lapse from the arousal stimuli to the MSNA burst was considered to be the conduction time in the spinal cord and the postganglionic efferent C-fibers, which was calculated to be ~ 1 s during stage I of non-REM sleep (Okada et al., 1991).

The deafferentation from the baroreceptors during the fainting might be attributed to the suppression of the central sympathetic outflow proximal to the RVLM (Ziegler et al., 1986). The abrupt sympathetic silence is proposed to be due to initial exaggerated sympathetic activation, in combination with relative ventricular hypovolemia and stimulated myocardial ventricular afferents (Öberg and Thorén, 1972; Walker et al., 1978). In the case of tilt-induced fainting, MSNA bursts were gradually but not immediately diminished during fainting. It is probable that the inhibitory vagal suppression on the sympathetic volley was not sufficiently strong to completely suppress the MSNA bursts but was

rather mild and altered only the specific features of MSNA, which are the elongation of burst duration, disappearance of pulse synchronicity and burst elicitation by arousal stimuli. Greater suppression on the central sympathetic outflow suppressed the burst discharge (Kumada et al., 1990; Mosqueda-Garcia et al., 1997), then it progressed to the hypotensive with a cardiac standstill (Wallin and Sundlöf, 1982).

We suggest that the reduced inputs from baroreceptors due to suppression occurring in a site proximal to the nucleus tractus solitarius during the syncopal attack alter the burst properties specific to MSNA, and the observation of changes in MSNA burst properties can provide a predictive sign of fainting before serious falls occur.

References

- Benarroch, E.E., 1999. Central neurotransmitters and neuromodulators in cardiovascular regulation. In: Mathias, C.J., Bannister, R. (Eds.), *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System*, 4th edn. Oxford Univ. Press, Oxford, pp. 37–44.
- Burke, D., Sundlöf, G., Wallin, B.G., 1977. Postural effects on muscle nerve sympathetic activities in man. *J. Physiol.* 272, 399–414.
- Fagius, J., Wallin, B.G., 1980. Sympathetic reflex latencies and conduction velocities in normal man. *J. Neurol. Sci.* 47, 433–448.
- Fagius, J., Wallin, B.G., Sundlöf, G., Nerhed, C., Englesson, S., 1985. Sympathetic outflow in man after anaesthesia of the glossopharyngeal and vagus nerves. *Brain* 108, 423–438.
- Iwase, S., Mano, T., Watanabe, T., Saito, M., Kobayashi, F., 1991. Age-related changes of sympathetic outflow to muscles in humans. *J. Gerontol.* 46, M1–M5.
- Kumada, M., Terui, N., Kuwaki, T., 1990. Arterial baroreceptor reflex: its central and peripheral neural mechanisms. *Prog. Neurobiol.* 35, 331–361.
- Mano, T., 1998. Microneurographic research on sympathetic nerve responses to environmental stimuli in humans. *Jpn. J. Physiol.* 48, 99–114.
- Mosqueda-Garcia, R., Furlan, R., Fernandez-Violante, R., Desai, T., Snell, M., Jarai, Z., Ananthram, V., Robertson, R.M., Robertson, D., 1997. Sympathetic and baroreceptor reflex function in neurally mediated syncope evoked by tilt. *J. Clin. Invest.* 99, 2736–2744.
- Öberg, B., Thorén, P., 1972. Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat—a possible cause of the vasovagal reaction. *Acta Physiol. Scand.* 85, 164–173.
- Okada, H., Iwase, S., Mano, T., Sugiyama, Y., Watanabe, T., 1991. Changes in muscle sympathetic nerve activity during sleep in humans. *Neurology* 46, 1961–1966.
- Takeuchi, S., Iwase, S., Mano, T., Okada, H., Sugiyama, Y., Watanabe, T., 1994. Sleep-related changes in human muscle and skin sympathetic nerve activities. *J. Auton. Nerv. Syst.* 47, 121–129.
- Walker, J.L., Thames, M.D., Abboud, F.M., Mark, A.L., Kopfenstein, H.S., 1978. Preferential distribution of inhibitory cardiac receptors in left ventricle of the dog. *Am. J. Physiol.* 235, 287–291.
- Wallin, B.G., 1999. Intraneural recordings of normal and abnormal sympathetic activity in man. In: Mathias, C.J., Bannister, R. (Eds.), *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System*, 4th edn. Oxford Univ. Press, Oxford, pp. 224–231.
- Wallin, B.G., Sundlöf, G., 1982. Sympathetic outflow to muscles during vasovagal syncope. *J. Auton. Nerv. Syst.* 6, 287–291.
- Ziegler, M.G., Echon, C., Wilner, K.D., Specho, P., Lake, C.R., McCutchen, J.A., 1986. Sympathetic nervous withdrawal in the vasodepressor (vasovagal) reaction. *J. Auton. Nerv. Syst.* 17, 273–278.