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SHORT COMMUNICATION

Cardiovagal and somatic sensory nerve functions in healthy subjects

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Abstract
Purpose Heart rate response to deep breathing (HR_{DB}), which depends on the integrity of cardiac vagal preganglionic neurons and efferent fibers, and the function of sural nerve fibers are both associated with an age-related decline process. The aim of this study was to determine whether the effects attributed to aging on cardiovagal and sural nerve function decline are associated.
Methods HR_{DB} and sural sensory nerve action potential (SNAP) amplitude, latency, and conduction velocity (SCV) were measured in one hundred healthy asymptomatic subjects (aged 14–92 years, 41 women). Multiple and simple linear regressions were used to analyze the relationships between the variables.
Results There were significant linear relationships between sural SNAP amplitude and HR_{DB} with age. There was also a significant linear relationship between sural SNAP amplitude and HR_{DB} (correlation coefficient 0.46, $p<0.0001$), but the model explained only 21.5 % of the variability in HR_{DB}.
Conclusion Cardiovagal function assessed by HR_{DB} is associated with sural SNAP amplitude in healthy subjects. Age-related decline only partially explained the variability seen in the association. Other genetic and environmental factors may also play a role.

Keywords Cardiovagal · Sural · Nerve · Healthy · Subjects

Introduction

Heart rate (HR) increase during inspiration and decrease during expiration occurs during normal breathing and is called respiratory sinus arrhythmia. It is related to direct modulation of the cardiac vagal preganglionic neurons by central respiratory drive and inhibition of cardiac vagal efferent activity by lung inflation [1, 4]. Deep breathing (DB) is used to magnify the HR variability with respiration to measure sinus arrhythmia in the HR_{DB} test, which is considered a clinical index of cardiovagal function [2–4]. Other research methods use statistical analysis in the time frequency domain to study sympathovagal cardiac modulation [4]. Respiratory sinus arrhythmia shows an age-related decline, with progressive loss of cardiac parasympathetic control in the absence of disease [1–4]. A low respiratory sinus arrhythmia may also be associated with cardiac heart failure, hypertension, diabetes mellitus, and psychosocial factors [1], and also with a number of autonomic disorders [4].

Somatic sensory nerve function, as indexed by the sural sensory nerve action potential (SNAP) amplitude, also shows an age-related decline [5–7]. Reduced sural SNAP amplitude may be related to a primary loss of dorsal root ganglia cells and axons, or it may be related to a slowing of sensory conduction velocity of somatic myelinated sensory fibers.

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Table 1 Sural nerve and cardiovagal parameters in different age groups of 100 healthy subjects

Age groups (years) (*n*, M/F)	Sural nerve SNAP				Cardiovagal (HR_{DB})			
	Amplitude (μV) mean (±SD)	Range	Latency (m/s)[a] mean (±SD)	Range	SCV (ms) mean (±SD)	Range	Beats/min mean (±SD)	Range
10–19 (6/5)	14.6 ± 7.8	7–29	2.8 ± 0.3	2.7–3.6	42.4 ± 4.9	39–52	27.2 ± 6.7	19–40
20–29 (10/9)	15.7 ± 6.1	6–29	2.8 ± 0.4	2.2–3.8	46.6 ± 6.7	37–63	25 ± 10.7	11–49
30–39 (8/7)	14.7 ± 5.9	7–25	3.0 ± 0.4	2.1–3.7	43.3 ± 7.5	38–67	19.2 ± 6.1	12–32
40–49 (9/11)	15.1 ± 5.2	8–28	3.0 ± 0.3	2.5–3.6	46.4 ± 5.1	39–56	19.5 ± 7.2	10–35
50–59 (4/6)	15.6 ± 7.9	4.7–33	2.5 ± 0.6	2.7–3.9	43.5 ± 5.8	36–56	12.7 ± 4.0	8–19
60–69 (5/6)	9.4 ± 4.7	3.5–20	3.2 ± 0.4	2.6–3.9	44.5 ± 6.4	36–54	13.1 ± 7.9	2–32
≥70 (6/8)	7.7 ± 4.3	0–12	2.6 ± 1.3	2.8–3.8	39 ± 17	37–50	9.3 ± 6.5	1–24

SNAP sensory nerve action potential, *n M/F* number of male/female, *SD* standard deviation, *SCV* sensory conduction velocity, HR_{DB} heart rate response to deep breathing (beats/min)

[a] Latency from onset

Cardiovagal and peripheral nerve functions' age-related decline could be a consequence of the aging process alone or it could be related to other factors, or both. If similar factors are involved in both age-related declines, a strong association between both functions would be expected.

We tested whether age-related diminished respiratory sinus arrhythmia indexed by HR_{DB} and reduced somatic sensory nerve function indexed by sural SNAP amplitude in healthy subjects were associated.

Participants and methods

We studied 100 healthy voluntary subjects aged 14–92 years; Table 1 shows the genders and age groups of all participants. The mean body mass index (BMI) was 23.55 SD 0.56 (range 17–26.1).

Inclusion criteria: (1) subjects without symptoms of peripheral neuropathy such as weakness, sensory, or autonomic complaints; (2) normal neurological examination. Exclusion criteria: (1) insulin resistance; (2) diabetes mellitus; (3) subjects with a BMI of 30 or greater; (4) systemic diseases including cardiovascular diseases; (5) hypertension; (6) history of alcoholism; (7) history of exposure to environmental toxins; (8) neuromuscular disorder or family history of peripheral neuropathy; (9) history of treatment for vitamin B12 deficiency; (10) diseases affecting autonomic nervous system function; (11) drugs that produce peripheral neuropathy; (12) drugs that interfere with autonomic function (e.g., anticholinergics, antidepressants, antihistamines, β-blockers, and other antihypertensives). All subjects gave informed consent. The informed consent was obtained from parents or legal tutors for subjects under 18 years old. The study was approved by the local ethics committee.

Study protocol

The autonomic testing was completed first. After 20 min of rest the nerve conduction test was done. Both studies were performed in the morning of the same day (start time: 9:00 AM).

Autonomic studies

The test was performed with the subject supine and rested. No food, coffee, or nicotine was permitted for 3 h before the procedure. The room temperature was 22–24 °C. The patient was connected to an electrocardiograph monitor. The HR_{DB} was performed with the patient lying quietly and breathing deeply at six breaths per minute (inspiratory and expiratory cycles of 5 s each) during six successive breathing cycles. The procedure was repeated after 5 min of rest. The maximum–minimum HR during each 10 s breathing cycle was measured and the mean of the five largest differences was calculated [2].

Sural nerve studies

Sural nerve studies were performed on a Nihon Kohden, Neuropack S1 electromyograph. The skin temperature was recorded on the dorsum of the foot; it was maintained at or above 32 °C. The subjects remained lying on their side while sensory conduction velocity, latency, and SNAP amplitude were measured. Antidromic supramaximal stimuli were delivered 14 cm proximal to the recording electrode. The SNAP amplitude was recorded using disc electrodes on the outer side of the foot below the lateral malleolus and was measured as peak to peak and latency to the onset of the first peak.

Statistics

A multiple linear regression model was used first to describe the relationship between the variability of heart frequency during deep breathing and four independent variables (age, sural SNAP amplitude and latency to onset, and sex). BMI was excluded because subjects were selected to have BMIs <30. Variables that showed significant associations were subsequently studied with simple regressions.

Results

Table 1 summarizes the sural SNAP amplitude and latency to onset and HR_{DB} organized by age group and gender.

The sural SNAP amplitude and HR_{DB} were not correlated with BMI (correlation coefficients of 0.132, $p = 0.665$ and 0.306, $p = 0.231$, respectively).

A multiple regression (with HR_{DB} as dependent variable; and age, sural SNAP amplitude and latency, sensory conduction velocity, and gender as independent variables) showed a significant association between the variables at the 95 % confidence level with a p value of 0.0076. However, only age and sural SNAP amplitude had significant p values at <0.0001 and 0.0045, respectively. The p values for latency, SCV, and gender were 0.36, 0.92 and 0.44, respectively.

A simple regression of HR_{DB} as a dependent variable with age (Fig. 1a) gave a correlation coefficient of -0.63, $p < 0.0001$, and an R^2 of 40.2 %, indicating that the model explained 40.2 % of the variability in HR_{DB}. A regression of sural SNAP amplitude as a dependent variable with age (Fig. 1b) gave a correlation coefficient of -0.39, $p = 0.0001$, and an R^2 of 15.2 %, indicating that the model explained 15.23 % of the variability in amplitude.

A regression of HR_{DB} as a dependent variable with sural SNAP amplitude (Fig. 1c) gave a correlation coefficient of 0.46, $p < 0.0001$, and an R^2 of 21.6 %, indicating that only 21.6 % of the variability in HR_{DB} was explained by sural SNAP amplitude.

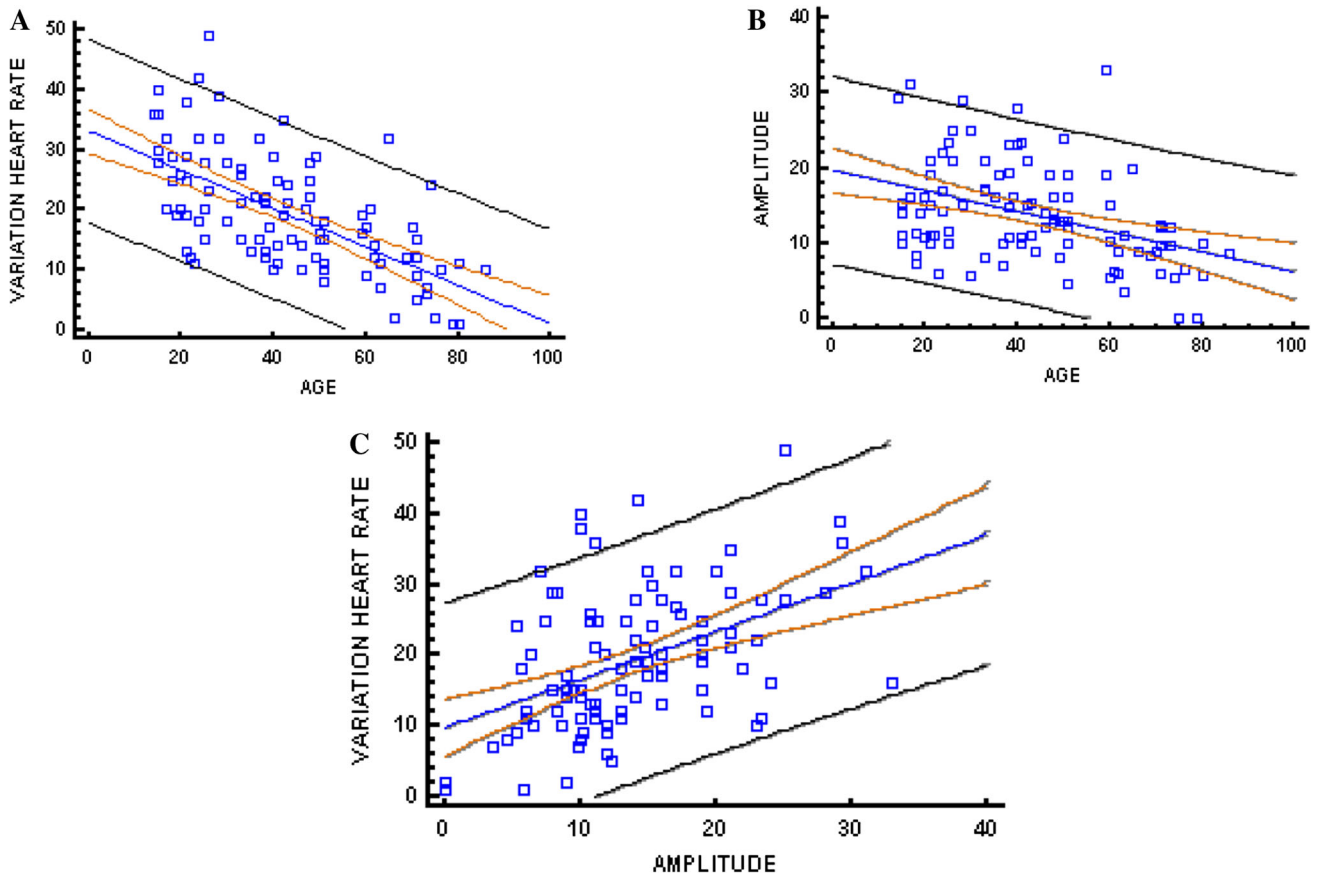

Fig. 1 Linear regressions with 95 % confidence limits in healthy subjects (see text). **a** Age-related decline in variation in heart rate response to deep breathing (HR_{DB}). **b** Age-related decline in sural sensory nerve action potential (SNAP) amplitude. **c** Linear regression of variation in heart rate response to deep breathing (HR_{DB}) and sural SNAP amplitude

Discussion

We have not found a direct comparison between cardiovagal autonomic and sensory nerve function in healthy adult subjects in the literature [PUBMED, 1980–2013]. The main findings of this study were that: (1) there is an association between cardiovagal function, as measured by HR_{DB}, and somatic sensory nerve function, as measured by sural SNAP amplitude and (2) the model can only explain 21.6 % of the HR_{DB} variability, although sural SNAP amplitude and HR_{DB} are both significantly associated with age. Therefore, there must be other unknown factors that contribute to such variability.

The negative linear or log-linear association between cardiovagal function (measured by HR_{DB}) and age has also been found by others [2, 3]. Cardiovagal function measured by HR variability (frequency domain) showed a decline with age, which was thought to be related to the aging process per se, and less so to aged-related conditions such as obesity, blood pressure, fitness, and metabolic factors [1].

The precise causes of the age-related decline of cardiovagal function are uncertain. Although human functional studies showed blunted cardiovagal responses with age, it is not known in which proportion a diminished vagus nerve efferent function, a sinus node compromise, or a decreased acetylcholine release in M2 cardiac receptors contributed to the cardiovagal age-related decline. Structural changes in cardiac vagal efferent axons have been shown in aged rats, though cardiac vagal function studies in aged rats have reported controversial results [8].

Nonneural factors acting on the target organ response, such as cardiac arrhythmias and heart failure, could influence respiratory sinus arrhythmia; we excluded subjects with such conditions.

The sural SNAP amplitude linear regression with age has been extensively described. Guiloff et al. [5–7] reported a significant negative linear correlation of both sural and medial plantar SNAP amplitudes with age with a wide range of amplitude values in each decade. Factors that might influence sural SNAP amplitude such as height, gender, and BMI are controversial [6, 7]. Technical factors that may contribute to sural nerve SNAP amplitude variability such as conduction distance, skin temperature, and distance between recording electrodes were carefully monitored in our study. Loss of sural nerve myelinated and unmyelinated fibers with age has been reported in humans [9]. The influence of height, gender, and BMI on HR_{DB} in healthy subjects has not been documented [2–4].

Associations between somatic and autonomic nerve functions have also been reported in pathological conditions. Patients with diabetic polyneuropathy showed a correlation between sural SNAP amplitude and cardiovagal function decline [10]. None of our subjects had neuropathic symptoms and nerve conduction studies did not fulfill minimal criteria for the electrodiagnostic confirmation of polyneuropathy.

The gene expression pattern of neurotrophic factors' (NTF) complex interactions influences the development and maintenance of parasympathetic and sensory neurons [11]. Reactive oxygen species generated by intracellular or exogenous stimulus may decrease NTF activity [12], so that both sensory and autonomic neurons could be affected by NTF balance. A model of increased oxidative stress shows functional and morphological changes similar to normal aging in peripheral nerves [13]. An accelerated aging process may affect sensory and autonomic parasympathetic neurons in healthy subjects and result in increased vulnerability to those peripheral neuropathies affecting both autonomic and sensory functions.

In conclusion, our findings suggest that in healthy subjects, both sensory and cardiovagal nerve function declines are associated. However, environmental and genetic factors other than age may contribute to the variability in the association between HR_{DB} and sural SNAP amplitude declines.

Conflict of interest On behalf of all authors, the corresponding authors state that there is no conflict of interest.

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