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Quantification of autonomic regulation in patients with sudden sensorineural hearing loss

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ABSTRACT

Previous studies have proposed varying causes for idiopathic sudden sensorineural hearing loss (SSNHL), including vascular occlusion, ruptured inner ear membrane, acoustic tumours and circulatory disturbances in the inner ear.

The objective of this study was to characterise the autonomic regulation in 19 SSNHL patients in comparison to 19 healthy age-gender matched normal-hearing control subjects (CON) in order to improve the diagnostics of vascular caused hearing loss in SSNHL patients. A high-resolution short-term electrocardiogram (ECG) and the continuous noninvasive blood pressure signal were simultaneously recorded under resting conditions (30 min). Linear and nonlinear indices of heart rate- and blood pressure variability (HRV, BPV) were calculated to characterise autonomic regulation. The results showed that HRV analysis did not produce significantly different results between SSNHL and CON, whereas linear and nonlinear BPV indices showed significant differences between both groups ($p<0.01$).

This study was the first to show an altered cardiovascular regulation in SSNHL patients when compared to CON subjects, based on continuous blood pressure analysis. This was characterised by reduced variability, complexity and dynamics of blood pressure time series in SSNHL. These findings may contribute to an improved classification of the controversially discussed causes of SSNHL and, in addition, may lead to improved diagnostic strategies for a subgroup of SSNHL patients whose hearing loss is caused by cardiovascular factors.

1. Introduction

The causes of idiopathic sudden sensorineural hearing (SSNHL), i.e. the unexplained unilateral sensorineural hearing loss with an onset lasting over a period of less than 72 h, still remain uncertain, as does the specific site of inner ear disease (Rauch, 2008). The global incidence of sudden hearing loss is quoted to be 5–20 new cases/100,000 inhabitants per year (Germany ~200,000) (Olzowy et al., 2005). There is a high variability of severity of hearing loss as well as its spontaneous improvement and response to medical treatment. This high variability can presumably mean that SSNHL is a collective term for a multicausal disease. Previous studies have proposed differing causes for SSNHL which include vascular occlusion, viral- or bacterial infection, ruptured inner ear membrane, autoimmune diseases and acoustic tumours. There is currently a revived discussion that, at least within a subgroup, SSNHL might be associated with cardiovascular risk factors. ,A large cohort-control study recently estimated the risk of stroke development among SSNHL patients and revealed that the risk of getting a stroke during a five-year follow-up period was 1.64-times higher for SSNHL patients than for control subjects (Lin et al., 2008). Hence, SSNHL in general seems to be a modest predictor for stroke risk. It appears that a subgroup of SSNHL patients exist for which hearing loss is caused by cardiovascular factors, confirming the theory of vascular involvement in the aetiology (Marcucci et al., 2005; Ballesteros et al., 2009; Mosnier et al., 2011). The association of SSNHL with hypertension, however, is a point of controversial discussion (Pirodda et al., 1997; Chau et al., 2010). A growing number of studies describe an association between autonomic nervous system (sympathetic and parasympathetic) dysfunction and the risk of cardiovascular diseases as myocardial infarction, sudden death or stroke (Cook et al., 2006; Thayer et al., 2010; Hilz et al., 2011). The objective of this study is to characterise the autonomic regulation in SSNHL patients in comparison to healthy age-gender matched normal hearing control subjects (CON). Our main goal is to assess a basic characteristic of autonomic regulation in SSNHL patients. These findings may lead to improved diagnostic strategies especially for SSNHL patients with vascular impairments. We assume that a subgroup of SSNHL patients exist in

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which hearing loss is caused by cardiovascular factors, confirming the theory of vascular involvement in the aetiology. The questions that arise are:

do patients with SSNHL have an autonomic dysfunction accompanied by an impaired blood pressure variability that might lead to disturbances of blood flow to the inner ear, and could an autonomic dysfunction also act as an indicator/link for stroke risk in SSNHL patients.

2. Materials and methods

2.1. Patients

In this study, 19 patients suffering from idiopathic sudden sensorineural hearing loss (SSNHL, 59.6 ± 15.3 years, 13 male) and 19 healthy age-gender matched normal-hearing control subjects (CON, 58.5 ± 9.5 years, 13 male) were enrolled. The investigation fulfilled the recommendations of the Declaration of Helsinki. All participants gave a written informed consent to a protocol approved by the Ethics Committee of the University Hospital Jena. Selection criteria included: being 18–80 years of age, being at the onset of hearing loss ≤14 days and having sudden unilateral hearing loss with a hearing threshold of ≥15 dB HL in three or more frequencies in a standard pure tone, air-conducted audiogram with a range of 0.125 to 8 kHz. Patients were excluded if they had a middle- or external ear disease, bilateral hearing loss or an acute hearing loss other than SSNHL. Patients with either a history of autoimmune disease, a severe psychiatric illness or a neurological disease were also excluded from the study. Nineteen patients fulfilled the inclusion criteria and agreed to participate. All patients were treated according to the guidelines of the German Society of Otorhinolaryngology — Head and Neck Surgery with descending doses of prednisolone. The starting dosage was 250 mg/d prednisolone for 3 days, followed by a dose reduction of 50% every 2 days for a period of 7 days.

2.2. Data acquisition and data preprocessing

All participants were given a high-resolution short-term ECG (1000 Hz sampling frequency) during which their blood pressure (BP) was simultaneously and continuously recorded in a non-invasive way using the third and fourth fingers and recorded over a 30-minute period with the Task Force monitor® (CNSystems, Graz, Austria). All recordings (ECG, BP) were obtained prior to the administration of medication (prednisolone) to exclude any possible confounding effects before the final results were interpreted. All measurements were performed under resting conditions (supine position, a quiet environment and the same time of day and location).

From the 30-minute data records, heart rate time series consisting of the following three items were extracted: 1) successive beat-to-beat intervals (tachograms, BBI), 2) systograms as the maximum end-systolic blood pressure (SBP) amplitude values over time in relation to the previous R-peak and 3) diastograms as the minimum end-diastolic blood pressure (DBP) amplitude values over time in relation to the previous R-peak. All times series were subsequently filtered by an adaptive filter algorithm to remove and interpolate ventricular premature beats and artefacts to obtain normal-to-normal beat time series (NN) (Wessel et al., 2000).

2.3. Methods of heart rate- and blood pressure variability

We applied some of the most commonly used indices in cardiovascular variability analysis in the time-, frequency- and nonlinear dynamics domains. These indices have shown relevance to clinical research and have proven their suitability to explore dynamic and structural features of cardiovascular regulation. They are based on various concepts, thereby revealing multiple aspects of cardiovascular variability (Voss et al., 2009).

2.3.1. Time- and frequency domain

Heart rate variability (HRV) and blood pressure variability (BPV) were quantified by calculating indices from each tachogram, systogram (sys_) and diastogram (dia_) of the time- and frequency domains (TD, FD) according to the recommendations of the Task Force of the European Society of Cardiology (Task Force, 1996). The following standard HRV indices from the TD were calculated:

- *meanNN* — the mean value of the BBI-intervals [ms], systolic (sys_) and diastolic (dia_) blood pressure [mm Hg] values;
- *sdNN* — standard deviation of the BBI-intervals [ms], systolic (sys_) and diastolic (dia_) blood pressure [mm Hg] values;
- *rmssd* — square root of the mean squared differences of successive BBI intervals [ms], systolic (sys_) and diastolic (dia_) blood pressure values [mm Hg].

The power spectra of equidistant linear interpolated (10 Hz) NN interval time series (resampled to 2 Hz) were obtained by applying the fast Fourier transformation using the Blackman Harris window function to reduce leakage effects. The following frequency domain indices were calculated:

- o *LF*, *sys_LF*, *dia_LF* — low-frequency power (0.04–0.15 Hz) [arbitrary units, a.u.];
- o *HF*, *sys_HF*, *dia_HF* — high-frequency power (0.15–0.4 Hz) [arbitrary units, a.u.];

2.3.2. Symbolic dynamics

The concept of symbolic dynamics (SD) is based upon a coarse-graining of the dynamics within time series. Thus, the study of the dynamics is simplified to point of becoming a description of symbol sequences. In this way, some detailed information is lost, however the more general dynamic behaviour of the time series can be analysed (Kurths et al., 1995). SD has been proven to be sufficient for the investigation of complex systems and describes nonlinear aspects within time series (BBI, SBP, DBP) (Voss et al., 1996). To this end and as a first step, all NN interval time series (BBI, SBP, and DBP) were transformed into a symbol sequence of four symbols with the given alphabet $A = \{0,1,2,3\}$ to classify dynamic changes (changes of the i-th NN interval in relation to the mean value of all NN intervals) according to the rules of transformation:

$$0 : \mu < NN_i \le (1+\alpha) * \mu$$

$$1 : (1+\alpha) * \mu < NN_i < \infty$$

$$2 : (1-\alpha) * \mu < NN_i \le \mu$$

$$3 : 0 < NN_i \le (1-\alpha) * \mu$$

Here μ is the mean NN interval, n is the time series length, α is a special scaling parameter equal to 0.1 and NN_i is the NN interval at the time point i, where $i = 1,2,3\ldots n$.

From this new alphabet (symbol string), words were created consisting of three successive symbols which allow for 64 different word type combinations (bins) (000, 001,…, 333). The following SD indices from the probability distribution of each word type within the symbol sequence were estimated:

- *wpsum02*, *sys_wpsum02*, *dia_wpsum02* — relative portion (sum/total) of words consisting only of the symbols '0' and '2', a measure for reduced HRV/ BPV [a.u.];
- *wpsum13*, *sys_wpsum13*, *dia_wpsum13* — relative portion (sum/total) of words consisting only of the symbols '1' and '3', a measure for increased HRV/ BPV [a.u.];
- *SD_Shannon*, *sys_SD_Shannon*, *dia_SD_Shannon* — Shannon entropy of word type distribution [bit] as $^{SD_{Shannon}} = -\sum_{i=1}^{k} p_i \ln p_i$, where p is the probability distribution of every word type and k (=64) is the total number of word types (Voss et al., 1996).