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Altered cardiovascular coupling in patients with sudden sensorineural hearing loss in comparison to healthy subjects*

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Abstract— **The causes of idiopathic sudden sensorineural hearing loss (SSNHL) are still unclear while SSNHL seems to be a multicausal disease. To date limited information about autonomic regulation and, especially, cardiovascular coupling (CVC) are available for those patients. The objective of this study was to characterize short-term (30min) CVC in 23 SSNHL patients in comparison to 23 healthy age and gender matched normal hearing control subjects (CON). Further on, the results from CVC should be compared with those from standard heart rate variability (HRV) and blood pressure variability (BPV) analyses. The results showed that HRV is not affected by the disease whereas BPV analysis revealed significant differences between both groups ($p<0.01$) whereby SSNHL exhibit a decreased short-term BPV. Results from CVC analysis demonstrated that especially the applied nonlinear methods exhibit an increased short-term CVC in SSNHL patients ($p<0.01$) indicating more complex interactions of short-term HR and BP regulatory processes. In conclusion, this study was the first to show a changed and decreased short-term BPV and increased nonlinear CVC in SSNHL patients. Our findings might help to improve diagnostic strategies for hearing loss caused by vascular factors.**

I. Introduction

The global incidence of sudden hearing loss is quoted to be 5-20 new cases/100,000 inhabitants per year [5]. Idiopathic sudden sensorineural hearing (SSNHL) is defined as the unexplained unilateral sensorineural hearing loss (a specific inner ear site disease) with an onset lasting over a period of less than 72 hours [8]. However, it is assumed that SSNHL can be understood as multicausal disease due to the high variability of severity of hearing loss, its spontaneous improvement and response to medical treatment. To date, the causes of SSNHL are unclear. However, previous studies have proposed different causes for SSNHL as vascular occlusion, viral- or bacterial infection, ruptured inner ear membrane, autoimmune diseases and acoustic neuromas.

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In general, there is less information available about a possible impairment of the autonomic nervous system (ANS) in SSNHL patients. Especially, to our knowledge, there exists no study about short-term cardiovascular coupling (CVC) in those patients. The bivariate coupling analysis of heart rate (HR) and systolic blood pressure (BP) as well as of heart rate and diastolic BP time series, respectively, might therefore provide additional diagnostic and prognostic information about a possible autonomic dysregulation in SSNHL patients. For the characterization of CVCs (linear, nonlinear) several concepts are available based on Granger causality; nonlinear prediction; entropies; symbolization and phase synchronization to detect direct and indirect couplings between time series. While nonlinear coupling approaches analyze complex signal interactions the linear methods favor the frequency domain representation of biological signals (characterization of connectivity between specific oscillatory components) [3].

The objective of this study was to characterize the CVC in SSNHL patients in comparison to healthy age and gender matched normal hearing control subjects. We assume that SSNHL patients in comparison to normal hearing healthy subjects exhibit alterations in their CVCs and thus, supporting the theory of vascular involvement in the etiology [1].

II. Materials And Methods

A. Patients

23 patients suffering from idiopathic sudden sensorineural hearing loss (SSNHL, 59.2±15.6 years, 15 male) and 23 healthy age-gender matched normal-hearing control subjects (CON, 57.3±9.2 years, 16 male) were investigated in this study. 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≥ 15dB HL in three or more frequencies in a standard pure tone, air-conducted audiogram with a range of 0.125 to 8kHz. Exclusion criteria for patients were the existence of a middle- or external ear disease, bilateral hearing loss or an acute hearing loss other than SSNHL and if they had an autoimmune, a psychiatric or a neurological disease. 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.

B. Data Recording and Data Preprocessing

From all participants a high-resolution short-term ECG (1000 Hz sampling frequency) and simultaneously the non-

invasive BP from the third and fourth fingers were continuously recorded over a period of 30 minutes using the Task Force monitor® (CNSystems, Graz, Austria). All recordings were performed under resting measurement conditions (supine position, quiet environment, same time of day and location). From the raw data records automatically (i) time series of heart rate consisting of successive beat-to-beat intervals (BBI) and (ii) time series of systolic and diastolic blood pressure (SBP, DBP) values were extracted using in-house software (programming environment Delphi 3). Thereafter, all time series were visually inspected and if necessary edited. Finally, before biosignal analyses were performed all time series were filtered by applying an adaptive variance estimation algorithm to remove and interpolate ventricular premature beats and artifacts to get normal-to-normal beat time series (NN) [12].

C. Standard indices from heart rate- and blood pressure variability in the time- and frequency domains

For the quantification of heart rate variability (HRV) and blood pressure variability (BPV) we calculated some of the most commonly used indices in clinical settings to quantify cardiovascular variability and autonomic modulation (sympathetic, vagal) [9].

In the time domain (TD), the following standard indices were calculated:

- *meanNN* - the mean value of the NN-intervals of BBI [ms] and SYS [mmHg];
- *sdNN* - standard deviation of the NN-intervals of BBI [ms] and SYS and DIA [mmHg].

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

- *LFn* - normalized low-frequency power (0.04–0.15Hz) of BBI and SYS and DIA [arbitrary units, a.u.];
- *HFn* - normalized high-frequency power (0.15–0.4Hz) of BBI and SYS and DIA [a.u.];

D. Baroreflex sensitivity

Analysis of baroreflex sensitivity (BRS) can be used as an indicator of autonomic short term blood pressure control. We applied the Dual Sequence Method [4] for estimating the spontaneous short-term baroreflex sensitivity. Thereby, a minimum change of 1mmHg in SYS and 5ms in BBI was defined for including the representative fluctuations into the calculations. Two BRS responses related to the BBI regulation were quantified: the bradycardic (an increase in SYS causes an increase in BBI - *bslope,* [ms/mmHg]) and tachycardic (a decrease in SYS causes a decrease in BBI - *tslope* [ms/mmHg]) fluctuations.

E. Joint Symbolic Dynamics

The method of Joint Symbolic Dynamics (JSD) [11] was applied to quantify the short-term bivariate nonlinear behavior of CVC. JSD transforms BBI and SYS time series into symbol sequences of different words *w* according to the transformation rules using an alphabet $A=\{0,1\}$. Thereby, symbol '1' represents increasing values and symbol '0' decreasing and unchanged values applying a threshold level equal to zero. Afterwards, short patterns (words of length 3) were formed (k=64). Following indices were estimated:

- normalized probability occurrences of bivariate word type combinations (*JSD1-JSD64*) '*xxx'* of BBI and simultaneous '*yyy'* of SYS (e.g. *BBI001/SYS101*) within an 8x8 word distribution density matrix *W*,
- sum of each row (combinations with equal BBI word: *BBIxxx*) and the sum of each column (combinations with equal SYS word: *SYSyyy*) and
- sums of diagonals within *W*: *SumSym* - symmetric word types (including baroreflex pattern) and *SumDiam* - diametric word types.

F. Segmented Poincaré Plot Analysis

The Segmented Poincaré Plot Analysis (SPPA) is an enhancement of the standard Poincaré Plot Analysis (PPA) [2]. The advantage of SPPA in comparison to PPA is that it avoids linear correlation and analyzes nonlinear features of dynamic systems [10]. The bivariate SPPA plots BBI time series over SYS or DIA time series. For the graphical representation the cloud of points is segmented into 12x12 equal rectangles whose size (height and width) depends on the standard deviations of BBI and SYS or DIA time series. From each rectangle the number of points related to the total number of points was counted to get the single point probabilities. Based on these single point probabilities two segmentation algorithms are used: summarizing all single probabilities of rows (*row*) and columns (*col*). As an example, we calculated the following index:

- *BBI_SYS_col5* - percentage of points in the fifth column of the Poincaré plot of BBI_n vs. synchronous systolic BP values (SYS_n).

G. Cross Conditional Entropy

Cross Conditional Entropy (CCE) quantifies the degree of CVC [7]. Thereby, the two time series are embedded into multiple dimensions and for each dimension the conditional entropy (CE) is calculated. CE is a process of sorting and counting mixed patterns and describes the amount of information included in the sample *y* when the pattern *u* is given. Applying CE, a synchronization index (*SI*) can be calculated which quantifies the amount of information exchanged between two signals (e.g. *SI_BBI-SYS* quantifies the coupling between HR and the systolic BP) [7]. The larger *SI* the more coupled are the two signals.

H. Statistics

For the statistical evaluation of significant differences between SSNHL and CON the nonparametric Mann-

Whitney U-test was applied. Significances were considered for values of $p<0.01$ (Bonferroni-Holm correction; $p<0.00016$). Descriptive statistics was used to describe the basic features of the data.

III. Results

A. HRV in TD/ FD

None of the HRV indices revealed any significant difference between SSNHL and CON neither in the TD and nor FD (not shown).

TABLE I. INDICES FROM SYSTOLIC AND DIASTOLIC BLOOD PRESSURE VARIABILITY (SYS BPV, DIA BPV) FOR THE DISCRIMINATION BETWEEN PATIENTS SUFFERING FROM SUDDEN IDIOPATHIC SENSORINEURAL HEARING LOSS (SSNHL) AND NORMAL HEARING HEALTHY CONTROL SUBJECTS (CON). DESCRIPTIVE STATISTICS WERE USED AS THE MEAN VALUE ± STANDARD DEVIATION. (* P<0.01; ** P<0.00016, BONFERRONI-HOLM CORRECTION,)

	index	p	SSNHL mean ± std	CON mean ± std
SYS BPV	*meanNN*	n.s.	128.0 ± 16.4	126.9 ± 18.0
	sdNN	**	5.4 ± 2.0	8.3 ± 2.3
	LFn	*	0.69 ± 0.17	0.82 ± 0.13
	HFn	*	0.31 ± 0.17	0.18 ± 0.13
DIA BPV	*meanNN*	**	82.0 ± 13.4	67.1 ± 9.5
	sdNN	n.s.	3.6 ± 1.4	3.9 ± 1.5
	LFn	*	0.76 ± 0.12	0.85 ± 0.10
	HFn	*	0.24 ± 0.12	0.15 ± 0.10

B. BPV in TD/ FD

BPV analysis of SYS in TD showed a significant decreased *sdNN* ($p<0.01$) for SSNHL compared to CON. BPV analysis of DIA revealed a significant increased *meanNN* ($p<0.00016$) for SSNHL in comparison to CON (Table 1). Analysis of BPV (SYS and DIA) in the FD both indices *LFn* and *LFn* revealed significant differences between SSNHL and CON ($p<0.01$). Thereby, the indices from the low frequency band were significant reduced and for the high frequency band significant increased in SSNHL.

C. BRS

Both BRS indices for all bradycardic (*bslope*) and tachycardic (*tslope*) baroreflex fluctuations did not reveal significant differences between both groups.

D. JSD

Eleven bivariate word types (normalized probability occurrences of each single bivariate word type) revealed significant differences between SSNHL and CON ($p<0.01$, $n=10$; $p<0.00016$, $n=1$) (Table 2, JSD1…JSD64). Nine of these 11 bivariate word types were significantly reduced in SSNHL (e.g. JSD43: 101/010; JSD55: 110/110). The sum of 3 from 8 columns (*SYS000*, *SYS011*, *SYS110*) revealed significant differences between SSNHL and CON ($p<0.01$) whereas sum of each row (*BBIxxx*) did not reveal significant differences between both groups. The symmetric (*SumSym*) and diametric word types (*SumDiam*) did not significantly differentiate between both groups.

E. SPPA

Analyzes of coupling of BBI with SYS two bivariate SPPA indices (*BBI_SYS_row5*, *BBI_SYS_row8*) revealed significant differences ($p<0.01$) between both groups. The coupling between both BP time series revealed significant differences in the indices *SYS_DIA_col5* and *SYS_DIA_col8* comparing SSNHL with CON (Table 2). Further on, all indices were significant reduced in the SSNHL group.

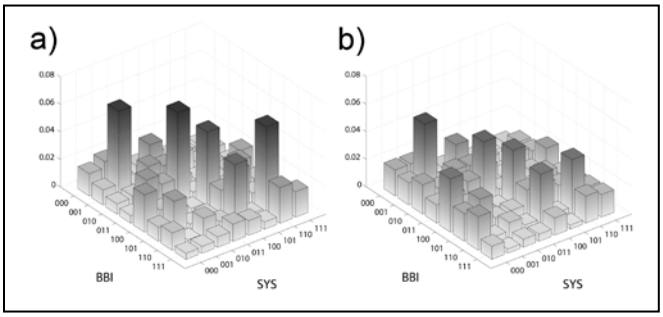

Figure 1. Probability distributions of word types within the 8x8 word distribution density matrix for cardiovascular coupling for idiopathic sudden sensorineural hearing patients (a) and ormal-hearing control subjects (b); BBI: beat-to-beat intervals, SYS: systolic blood pressure.

F. CCE

All synchronization indices from CCE (*SI_BBI-SYS*, *SI_BBI-DIA*, *SI_SYS-DIA*) quantifying the coupling (synchronization) between BBI and SYS (and DIA) as well as between SYS and DIA did not present significant values between SSNHL and CON.

TABLE II. INDICES FROM JOINT SYMBOLIC DYNAMICS (JSD) AND SEGMENTED POINCARÉ PLOT ANALYSIS (SPPA) FOR THE DISCRIMINATION BETWEEN PATIENTS SUFFERING FROM SUDDEN IDIOPATHIC SENSORINEURAL HEARING LOSS (SSNHL) AND NORMAL HEARING HEALTHY CONTROL SUBJECTS (CON). DESCRIPTIVE STATISTICS WERE USED AS THE MEAN VALUE ± STANDARD DEVIATION. (* P<0.01; ** P<0.00016, BONFERRONI-HOLM CORRECTION)

	index	p	SSNHL mean ± std	CON mean ± std
JSD	*JSD1-JSD64*	*…**	-	-
	SYS000	*	9.4 ± 5.5	16.1 ± 8.0
	SYS011	*	15.8 ± 2.7	13.0 ± 2.8
	SYS110	*	15.8 ± 2.7	13.0 ± 2.8
	JSD43	*	0.4 ± 0.6	0.8 ± 0.8
	JSC55	*	6.3 ± 3.3	3.9 ± 2.4
SPPA	*BBI_SYS_row5*	*	12.0 ± 2.6	14.3 ± 2.4
	BBI_SYS_row8	*	12.5 ± 2.9	15.3 ± 2.0
	SYS_DIA_col5	*	12.5 ± 2.9	15.3 ± 2.0
	SYS_DIA_col8	*	12.0 ± 2.6	14.3 ± 2.4

IV. Discussion And Conclusion

In this study we demonstrated the presence of an altered

CVC in SSNHL patients, differing from healthy age-gender matched, normal-hearing control subjects.

None of the HRV indices differed when comparing SSNHL patients and CON that means that HR regulation is not affected by SSNHL. BPV analysis in the TD revealed reduced variability of systolic BP regulation (*sdNN*) whereas the mean systolic BP seems to be not affected in SSNHL. The decrease of the *LFn* (SYS and DIA) components of BP oscillations in SSNHL may partly reflect an inhibition of sympathetic modulation [6]. The increase of the *HFn* (SYS and DIA) components suggests an intensified short-term variability of BP regulation (increased vagal modulation).

The results from coupling analyses showed that BRS (*bslope*, *tslope*) is not significant different in SSNHL patients compared to CON and suggests that linear cardiovascular regulatory processes are not altered in those patients. However, *bslope* was increased in SSNHL patients and exhibited a trend (12.5±6.3 vs. 8.2±3.2, $p<0.016$).

For the assessment of nonlinear couplings we applied different methods based on different mathematical concepts (JSD, SPPA and CCE) because it has been proven in several studies that the success of a specific method depends on different circumstances as e.g. patients, preprocessing and data. In these specific patients the CCE did not show any significant difference between both groups. The significant reduction of bivariate word type combinations from JSD analysis indicated to a more concentrated (e.g. JSD 43, JSD 55) short-term coupling between HR and systolic BP regulation in SSNHL than in CON. JSD results revealed a few dominating but rather an increased and not equally distributed number of bivariate word types (*JSD1-JSD64*) in the patients. This result might be a sign for an increased short-term nonlinear CVC in SSNHL patients. The significant reduced index *SYS000* (a monotonous word type with unchanging or decreasing values "000" of systolic BP) indicated a higher amount of uncoupling in the CON. In contrast to *SYS000* all other SYS word types in SSNHL are characterized by more fluctuation patterns (higher values). Especially the SYS patterns "*011*, *110*" occurred more frequently and were much more pronounced in combination with all other BBI word types (HR regulation) in SSNHL than in CON. The decrease in *SYS000* and the increase in *SYS011* and *SYS110* represent a reduced systolic BPV in SSHNL. This is accompanied with a increased CVC (specific systolic BP pattern over BBI) in SSNHL patients. In addition, *SumSym* (representing baroreflex-like response patterns) was in trend significant different (0.34±0.14 vs.0.26±0.11, $p<0.04$) and increased in SSNHL patients in comparison to CON. JSD43 and JSD55 are significant bivariate word types that are parts of the traditional bradycardic (JSD43) and the tachycardic (JSD55) baroreflex (SumSym resp. SumDia). That could be interpreted as a much stronger effort of the ANS to increase perfusion due to an increased blood pressure. This finding further suggests an increase in short-term CVC (baroreflex mediated regulation pattern). The reduced bivariate SPPA indices *BBI_SYS_row5* and *BBI_SYS_row8* also reveal an increased CVC in SSNHL. The stronger baroreflex like coupling patterns in JSD might be partly caused by antihypertensive drugs [3], however, this is not clear confirmed by the traditional baroreflex sensitivity indices. The vascular coupling between SYS and DIA (*SYS_DIA_col5*, *SYS_DIA_col8*) showed comparable results as between BBI and SYS and supports the finding of increased CVC in SSNHL.

Limitations of this study are that the influence of administered antihypertensive drugs on CVC indices was not (yet) investigated and that we have to examine if some of the revealed significant changes might be induced by drugs. Additionally, we did not apply methods for analyzing local flow in the inner ear.

In conclusion, we could demonstrate that SSNHL patients show an altered and increased short-term nonlinear CVC and a decreased short-term BPV. These findings may lead to improved diagnostic strategies for "vascular-caused" hearing loss at least within a subgroup of SSNHL patients.

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