Effects of awareness and nociception on heart rate variability during general anaesthesia*

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Abstract

During anaesthesia awareness and nociception are serious complications that may further lead to haemodynamic instability. Specific monitoring of depth of hypnosis and depth of analgesia based on heart rate variability (HRV) analysis is eligible to improve patient safety and reduce efforts in post-operative care. Consequently, in this analysis we assess the applicability of HRV parameters during surgical interventions with standardized intravenous propofol-remifentanil-anaesthesia. Peri-operative electrocardiograms were recorded from cardiovascular stable patients (ASA Score I/II, $N = 32$, age: 36.4 ± 11.23 a, BMI: 25.2 ± 3.16) scheduled for trauma and dentofacial surgery. HRV time- and frequency-domain parameters, measures of complexity and nonlinear dynamics were compared by analysing longitudinally distributed 300 s intervals preceding/following induction of anaesthesia (BL–I1), intubation (I1–I2) and extubation (E1–E2). Mean value (meanNN) and standard deviation (sdNN) of the heart rate are influenced in BL–I1 ($p < 0.001$), I1–I2 ($p < 0.05$) and E1–E2 ($p < 0.001$). The number of forbidden words of symbolic dynamics changes significantly for BL–I1 ($p < 0.001$) and not for I1–I2 and E1–E2 ($p > 0.05$). Probability of low-variability POLVAR10 is significantly altered in all comparisons (BL–I1: $\Delta = 0.032, p < 0.01$, I1–I2: $\Delta = 0.12, p < 0.05$, E1–E2: $\Delta = 0.169, p < 0.01$) but especially during nociception. While standard time-domain parameters lacked selectivity, parameters of symbolic dynamics appear to be specifically influenced by changes in depth of hypnosis and nociception, respectively. However, the lack of steady-state ventilation/breathing in this study needs to be considered in

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future research. To be used for clinical anaesthesia monitoring our results have to be prospectively validated in clinical studies.

Keywords: heart rate variability (HRV), analgesia, anaesthesia, entropy, nonlinear dynamics, symbolic dynamics

(Some figures may appear in colour only in the online journal)

1. Introduction

During surgical interventions, administration of anti-nociceptive and hypnotic drugs is necessary. Side effects such as reduction of blood pressure or long post-operative recovery periods force a tentatively minimal dosage of both drugs. Demanding the minimal dosage, in turn, can lead to peri-operative awareness as well as extensive cardiovascular instability during noxious stimuli. To assure an optimal dosage, specific measures to monitor depth of analgesia as well as depth of hypnosis are of particular research interest (Heller and Burghardt 2006).

Depth of hypnosis monitoring is commercially available through a number of devices that extract spectral parameters from processed electroencephalographic ([p]EEG) signals. However, the usability is under debate as they show a sigmoidal relation towards drug dosage and depth of hypnosis (Palanca *et al* 2009) and do not necessarily decrease the incidence of anaesthesia awareness in high-risk patients (Avidan *et al* 2008). Furthermore, it has to be noted that EEG-based signal parameters increase the complexity of the device set-up in the operating room. From both, the persisting functional limitations and an increased complexity in devic set-ups, the motivation originates to extract parameters from routinely measured cardiovascular signals to assess the depth of analgesia and hypnosis.

One frequently recorded standard-of-care biosignal is the electrocardiogram (ECG) which is primarily used to assess the heart rate and detect arrhythmias. Consequently, ECG-based parameters which allow an effective monitoring of depth of hypnosis are of high interest but may suffer from minor influences of the brain on cardiovascular dynamics. Additionally, the nociceptive input into the central nervous system, which integrates the effects of noxious stimuli on one hand and effects analgesic drugs on the other hand cannot be measured directly. However, the effects of nociception on cardiovascular dynamics, as the activation of the sympathetic branch of the central nervous system, could potentially be used as specific parameters for the degree of nociception (Kenwright *et al* 2011).

Previous publications address the ECG-based monitoring during anaesthesia. Early research on the usage of heart rate variability (HRV) parameters, particularly the statistical time-domain as well as frequency-domain parameters, to indirectly assess the depth of hypnosis is summarized by Fleisher (1996). In particular, low-frequency (LF) and high-frequency (HF) parameters show significant alterations during induction of anaesthesia; the LF to HF ratio in turn might be a better parameter to assess a sympatho-vagal balance. In conclusion, Fleisher (1996) states that there are significant limitations to the depth of anaesthesia monitoring because of several confounding effects through drugs, secondary diagnosis (as diabetes mellitus) and painful stimuli throughout the process of surgery. From the aspect of signal processing, these parameters are confounded by non-stationarity as well as short-term artefacts.

Recently, the qualification of HRV frequency-domain parameters has been studied to assess the effects of nociception and depth of anaesthesia. Jeanne *et al* (2009) and Tarvainen

et al (2010) confirmed similar effects of inducing anaesthesia and nociception through a decrease of total power, LF and HF bands. Furthermore, the normalized HF power, HFn, did increase during induction, probably caused by the transition from spontaneous to controlled mechanical ventilation, while normalized LF power, LFn, did decrease. During painful stimuli the opposite was observed.

Alternatively, the analysis of measures of nonlinear dynamics, complexity, or chaos may contribute to a more profound assessment of the patient state. The effects of vagal blockade and different breathing patterns on complexity and fractal measures (approximate entropy and detrended fluctuation analysis, respectively) of HRV were investigated by Penttilä *et al* (2003). Thereby, neither the influences of nociception nor the effects of analgetic drugs were considered. Mäenpää *et al* (2011) developed δ-entropy to reduce confounding effects due to LF oscillations but neither tested for effects of nociception nor breathing patterns. Balocchi *et al* (2005) reported the superiority of Poincaré plot measures over standard time-domain HRV parameters to investigate the effect of painful stimulation.

Even though today's research is aware of different confounding factors, HRV parameters to specifically monitor nociception and depth of anaesthesia are still lacking. Finding such specific parameters constitutes one precondition for a successful ECG-based anaesthesia monitoring. Owing to the differences in study populations and settings, a comprehensive comparative assessment of the proposed parameters is difficult based on the literature. Thus, in order to assess the suitability and specificity of linear and nonlinear HRV parameters regarding the assessment of nociception and deepening of anaesthesia, we compare those parameters in a peri-operative study in cardiovascular healthy subjects during general propofol/remifentanil anaesthesia.

2. Methods

2.1. Study recordings

This work attends to the longitudinal analysis of HRV parameters during general peri-operative intravenous anaesthesia using propofol and remifentanil as hypnotic and analgetic, respectively. Thereto, we analysed study data recorded during the DFG funded project 'Measurement of heart rate variability using continuous wavelet transformation' conducted in 2008. After approval by the Institutional Review Board (Ethikkommission der Medizinischen Fakultät Carl Gustav Carus, Dresden [reference no 194082007]) and written informed consent, cardiovascular stable (ASA[4] Score I or II) patients of age 18–60 years scheduled for trauma or dentofacial surgery were included. Exclusion criteria were specified as follows: present or past diabetes mellitus, drug therapy with beta-blocker or clonidine/moxonidine, chronic analgesic therapy, BMI < 18 or BMI > 32, alcoholic or drug abuse. We acquired records of 72 patients. After the exclusion of protocol violations and artefact, flawed dataset records were selected for further analysis to assure a minimal mean BMI and age. This resulted in the following study on population characteristics: $N = 32$ patients with the following general properties: age: 36.4 ± 11.23, gender: 25 male and BMI: 25.2 ± 3.16. The average time of intervention measured between induction of anaesthesia and extubation was 02:23:08 (hours:minutes:seconds), ranging from 00:55:32 to 05:15:48.

Continuous six channel ECG recording with a sampling rate of 4.8 kHz and a resolution of 16 Bit (gUSBamp, gTec, Graz, Austria) was initiated before induction of anaesthesia and was continued until after extubation. Anaesthesia was performed by target-controlled infusion of propofol and remifentanil. Target effect site concentrations during induction were 4.5 μg ml^{-1}

[4] American Society of Anaesthesiology.

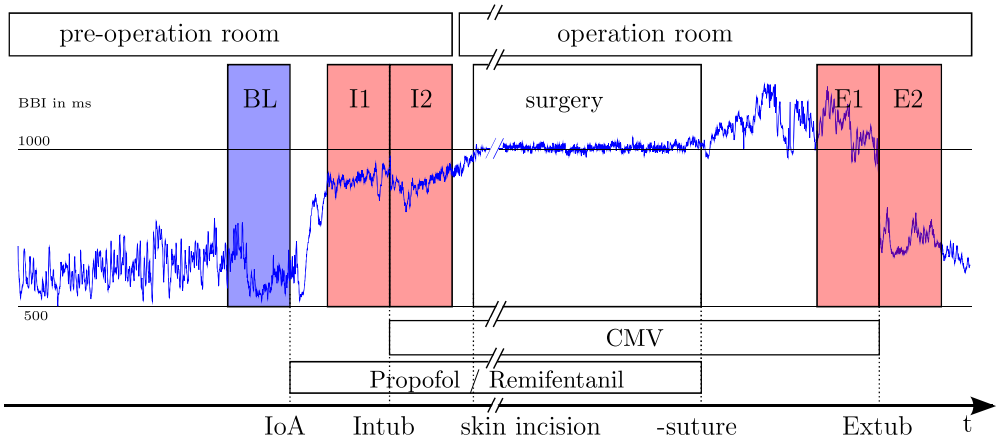

Figure 1. Overview of beat-to-beat intervals and location of 300 s intervals relative towards different periods of surgical intervention. CMV—controlled mechanical ventilation; IoA—induction of anaesthesia; In/extub—intubation/extubation; BL—baseline before induction of anaesthesia; I1/I2—intervals before/after intubation; E1/E2—intervals before/after extubation.

(model by Schnider *et al* (1998)) and 5 ng ml^{-1} for remifentanil (model by Minto *et al* (1997)). After intubation and before skin incision, propofol target concentration was lowered to 3.5 μg ml^{-1}. The protocol allowed for modification in target concentrations of both drugs at the discretion of the attending anaesthesiologist. Furthermore, different intervals of anaesthesia were logged through specific markers during the recording using the software accompanying the ECG recorder.

To assess the depth of hypnosis and nociception, we extracted windows of length 300 s each before/after the following markers: before induction of anaesthesia (BL), before start (I1) and after end (I2) of intubation, before start (E1) and after end (E2) of extubation (figure 1). We hypothesize that any specific parameter dependence on the depth of hypnosis manifests between the induction of anaesthesia BL and intubation I1, whereas specific influences of nociception on HRV parameters become visible in the comparisons I1–I2 and E1–E2, respectively. Skin incision was not considered as an appropriate event because of differences with regard to the accomplished surgeries on nociception. Intubation and extubation, on the other hand, cause comparable noxious stimuli in all patients.

2.2. Parameter extraction

For each of the extracted intervals heart beat, detection by signal adaptive threshold (Suhrbier *et al* 2006) was done based on the Einthoven II signal. After filtering the tachogram with an adaptive filter to detect and replace non-sinusoidal heart beats (Wessel *et al* 2000), linear and nonlinear time- and frequency-domain (Malik *et al* 1996) as well as a number of parameters derived by symbolic dynamics were calculated as described in Wessel *et al* (2007)(table 1).

While time and frequency space parameters of HRV were selected for their widespread usage and to ensure comparability to other publications, special linear and nonlinear complexity measures were chosen as they showed dedicated differences in other applications in biosignal processing (Wessel *et al* 2007).

Within the 300 s intervals each parameter was calculated once. The respective values of all records are summarized by median, first and third quartiles. The non-parametric Wilcoxon

Table 1. Analysed HRV time and frequency parameters and parameters derived by symbolic dynamics (Wessel *et al* 2007) and by Malik *et al* (1996)

Parameter	Description	Unit
meanNN	Mean value of beat to beat intervals NN[a]	ms
sdNN	Standard deviation of beat to beat intervals	ms
RMSSD	Root mean square of NN intervals	ms
Shannon	Shannon entropy of NN intervals	None
VLF	Power in very low-frequency band $0.0033 - 0.04$ Hz	ms^2
LF	Power of low-frequency band $0.04 - 0.15$ Hz	ms^2
HF	Power of high-frequency band $0.15 - 0.4$ Hz	ms^2
LF/HF	Quotient of LF power to HF power	None
FORBWORD	Number of forbidden words	None
FWShannon	Shannon entropy of word distribution	None
POLVAR10	Probability of low variability $<$ 10 ms	None

[a] NN—normal to normal beat interval.

rank-sum test was used for significance analysis between pairs of groups BI–I1, I1–I2 and E1–E2 ($p < 0.05$ is regarded as significant [$*$], $p < 0.01$ is regarded as highly significant [$**$] and $p < 0.001$ is regarded as very highly significant [$***$]).

3. Results

3.1. HRV parameter during induction of anaesthesia

The parameters meanNN, sdNN and RMSSD are influenced, not necessarily significantly, by the induction of anaesthesia as suggested by p-values in BL–I1 (table 2, figures 2(a)–(c)). Furthermore, the results suggest that tachogram-based measures of time-series complexity (Shannon entropy) are not or at least to a low degree affected by the induction of anaesthesia (BL–I1, figure 2(d)). All frequency parameters except VLF were significantly altered by the induction of anaesthesia (table 2). However, relative frequency band power measures of LF and HF like LF/HF did not change significantly, although a reduced sympathetic activity is expected through the action of propofol (Kochs *et al* 2008). FORBWORD shows a significant increase during the induction of anaesthesia and seems to be largely independent of noxious stimuli. This suggests a potential influence of the depth of anaesthesia (figure 2(f)). POLVAR10 does highly significantly increase after the induction of anaesthesia (figure 2(g)). In particular, not only frequency-domain parameters but also parameters of symbolic dynamics show significant alteration from pre-induction (BL) to post-induction (I1) intervals, while tachogram complexity appears to be independent. For all parameters, a high scatter of analysed parameters can be seen potentially due to inter-subject variability.

3.2. HRV parameter during noxious stimulation

The results when comparing HRV parameters before and after noxious stimulation through intubation and extubation are summarized in table 2. The majority of statistical linear HRV parameters is influenced during periods of nociception as suggested by p-values in I1–I2 and E1–E2 (table 2, figures 2(a)–(c)). The reason for all p-values being lower in E1–E2 compared to I1–I2 can be explained by a reduced anti-noxious effect after the end of medication before extubation (cf figures 2(a)–(g), table 2). Further on, the results suggest that tachogram-based measures of time-series complexity (Shannon entropy) are significantly lowered by the standardized painful stimuli through intubation and extubation (see p-values of I1–I2

Table 2. Influences of the induction of anaesthesia on HRV parameters analysed in time interval windows. BL—baseline preceding induction of anaesthesia, I1—before intubation and influences of nociception on HRV parameters analysed by I1—before intubation, I2—after intubation, E1—before extubation and E2—after extubation. Values are Median $^{1^{st}Q}_{3^{rd}Q}$ and interval comparison is characterized by the difference in median and significance levels of the non-parametric Wilcoxon rank sum test with ∗—$p < 0.05$, ∗∗—$p < 0.01$ and ∗∗∗—$p < 0.001$.

	BL			I1			I2		E1			E2	
meanNN	793.45	713.8	***	923.34	872.8	NS	882.10	791.2	1002.78	944.3	***	757.76	678.0
		883.2			1046.3			1000.2		1070.1			822.3
sdNN	56.38	41.7	NS	65.07	45.4	*	48.71	38.4	78.76	55.5	***	48.19	34.0
		74.9			84.9			62.2		119.3			60.8
RMSSD	26.75	18.8	*	17.83	13.6	NS	14.39	9.7	24.59	16.9	**	12.49	7.5
		40.1			27.2			20.2		36.2			30.7
Shannon	2.40	2.1	NS	2.33	2.0	**	1.94	1.8	2.44	2.1	*	2.09	1.8
		2.7			2.6			2.3		2.7			2.4
VLF	173.87	104.2	NS	161.82	82.5	NS	107.62	79.4	132.27	36.2	NS	82.40	37.9
		356.1			307.6			191.9		394.3			197.5
LF	51.29	27.7	***	17.15	8.3	NS	10.58	5.5	39.39	17.6	NS	22.75	9.6
		134.5			33.6			18.4		60.2			97.8
HF	19.61	10.4	***	4.11	2.3	NS	2.24	1.3	6.16	2.1	NS	4.15	0.8
		45.7			7.4			4.9		19.4			10.1
LF/HF	2.84	1.9	NS	3.45	2.4	NS	4.27	2.6	4.71	3.1	*	8.81	4.7
		4.7			5.0			6.7		9.2			12.4
FORBWORD	28.50	21.5	***	41.00	38.0	NS	41.00	36.0	41.00	31.3	NS	40.00	33.3
		35.0			44.0			44.0		44.0			43.0
FWSHANNON	2.87	2.7	***	2.21	2.0	NS	2.08	1.8	2.32	2.0	NS	2.31	2.1
		3.2			2.4			2.4		2.7			2.7
POLVAR10	0.003	0.000	**	0.035	0.002	*	0.155	0.03	0.032	0.000	**	0.211	0.017
		0.012			0.175			0.53		0.078			0.520

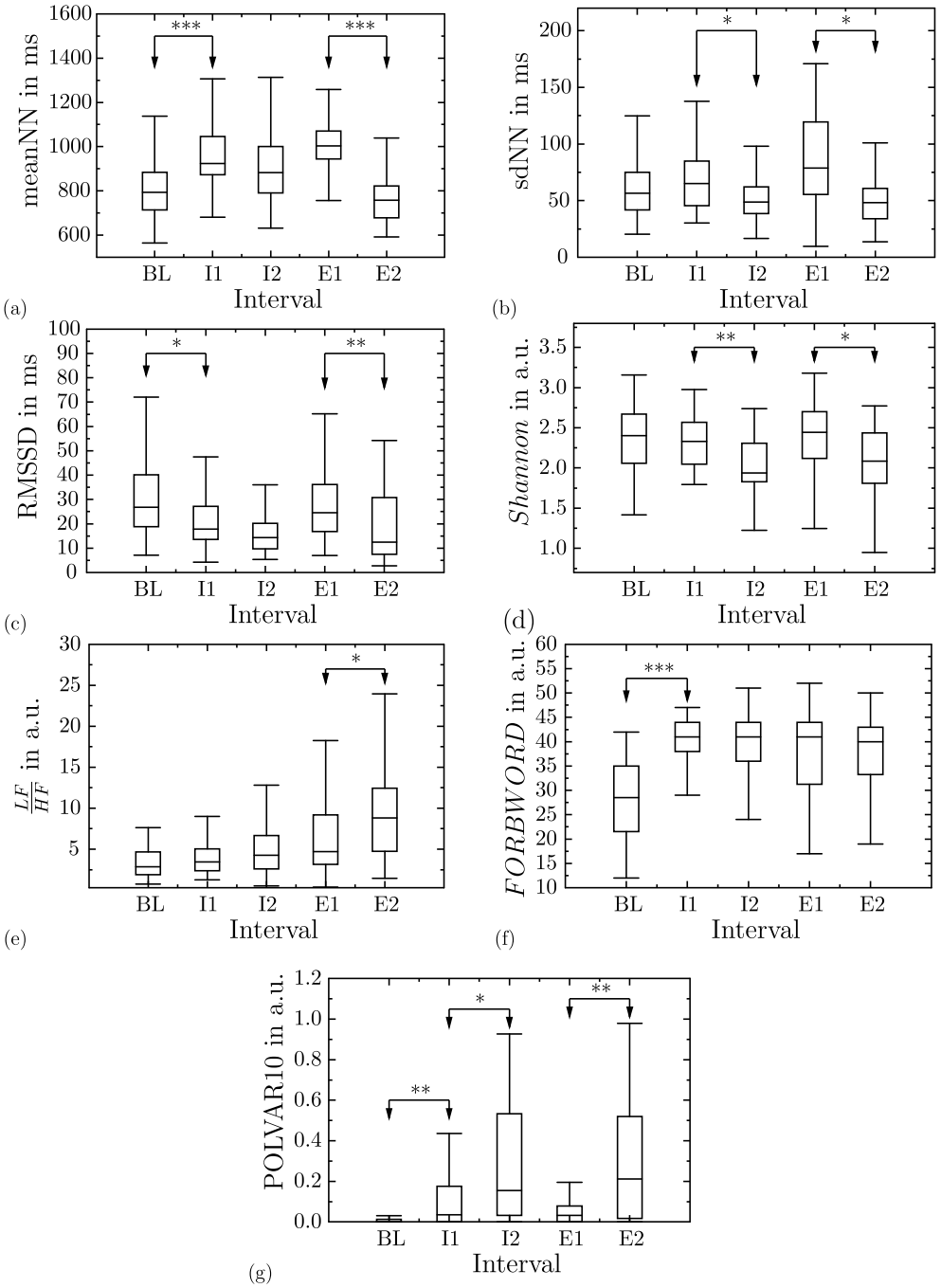

Figure 2. Longitudinal comparison of parameter values between intervals BL—baseline preceding induction of anaesthesia, I1/I2—before/after intubation, E1/E2 extubation. (a) meanNN, (b) sdNN, (c) RMSSD, (d) Shannon, (e) LF/HF, (f) FORBWORD, (g) POLVAR10. Box plot displays median, first and third quartile with significance levels $*$—$p < 0.05$, $**$—$p < 0.01$ and $***$—$p < 0.001$.

and E1–E2). Frequency-domain HRV parameters show no significant alteration between the states pre- and post-nociception (I1 and I2). HF and LF power content is reduced (but not significantly) due to intubation and extubation. The VLF power showed no significant alterations. POLVAR10 does increase after the induction of anaesthesia and furthermore shows a significant elevation after intubation and extubation. This is presumably caused by sympathetic activation in consequence of the painful stimuli and is consistent with the reduced tachogram variability (sdNN, RMSSD) and reduced complexity (Shannon entropy). However, parameter differences accumulate and POLVAR10 reaches a distinct co-domain which is not the case in sdNN and RMSSD. The increase of POLVAR10 during intubation is nearly one order of magnitude higher than that during the induction of anaesthesia (figure 2(g)).

4. Discussion

The specificity of single parameters regarding both influence factors, nociception and depth of anaesthesia, is of major interest. Concerning specificity for monitoring nociception the entropy parameter *Shannon* shows promising results (figure 2(d)) as *Shannon* is not affected by induction but significantly alters through intubation/extubation. Thus it can be assumed that the Shannon entropy of HRV did significantly reduce in consequence of painful stimuli. This can be explained by increased sympathetic activity after the noxious stimulation resulting in a less complex time series as also documented by Stubsjøen *et al* (2010). In the context of analgesic monitoring tachogram, complexity measures documented in the literature are approximate entropy (Penttilä *et al* 2003) and δ-entropy (Mäenpää *et al* 2011). Both are sensitive towards different depths of hypnosis (Mäenpää *et al* 2011). The results of the presented analysis, however, suggest that there is no or at least a considerably low influence of depth of hypnosis on tachogram complexity. However, Shannon entropy appears more suitable for monitoring nociception. It must be noted that the complexity measures used in this study differ from the ones reported in the literature.

The symbolic dynamics parameter POLVAR10 (figure 2(g)) alters significantly during the induction of anaesthesia and intubation/extubation, but the change of median is one magnitude higher during intubation and extubation. Hence, this analysis suggests that influences of nociception and depth of awareness are discriminable by POLVAR10. POLVAR10 assesses the influences of sympathetic activity caused by nociception and sympathetic blockage due to the effects of propofol (Kochs *et al* 2008) on HRV complexity and amplitude, respectively. In contrast to simple time-domain measures (sdNN, RMSSD), POLVAR10 is arguably more robust against episodic high variability.

LF and HF parameters do change during the induction of anaesthesia but not during intubation/extubation. Particularly, HF undergoes highly significant alterations due to the induction of anaesthesia which might be caused by the transition from spontaneous to mechanically controlled ventilation. This can indirectly be confirmed by the smaller inter-individual scatter as represented by $\frac{1^{st}}{3^{rd}}$-quartiles of I1 (table 2). All HF-band-related parameters and all fraction of these have to be considered to be heavily influenced by the transition from autonomous to artificial ventilation. Nonetheless, LF power shows significant alteration due to the induction of anaesthesia. Additionally, LF is not influenced directly by ventilation assuming respiration frequency being above 0.14 Hz. Also, frequency-based parameters are corrupted by in-stationarity within the signal interval.

To circumvent confounding effects of breathing on the HRV parameters analysed here, special ventilation-related parameters assessing the sympathetic effect on the respiratory sinus arrhythmia (RSA) represent a good approach. Simple time-domain parameters as the area under the curve of RSA oscillations in the tachogram can be used as the latest results show

promising specific alterations during sympathetic activation forced through noxious stimuli (Logier *et al* 2006, ,2010). However, assessing this effect by more sophisticated signal-processing techniques like the concept of coupled oscillators (Musizza *et al* 2007, Stefanovska 2007) or wavelet correlation analysis (Brouse *et al* 2010) might allow for a deeper insight and deliver more robust indices. For profound research on this aspect, further clinical studies with specific set-ups to assess ventilation rhythm even before the induction of anaesthesia are necessary.

Specificity can also be observed in the parameter of symbolic dynamics FORBWORD (figure 2(f)) that alters significantly between intervals BL and I1 but not during intubation and extubation.

This study used intubation as nociceptive stimulus, which represents a reliable pain stimulus. It was assumed that intubation/extubation result in inter-individually comparable nociceptive stimuli; however, the level of nociception cannot be measured directly. Thus, additional studies are required to investigate on further defined stimuli. Furthermore, it has to be noted that different levels of effect site concentration could not be considered in this analysis which could yield further insight.

The results of this study do not consider different confounding effects in respect of the depth of hypnosis influences on HRV. Essentially, the two intervals BL and I1 do differ not only at the level of hypnosis but also at the level of analgesia and in the present ventilation regime. Regardless of significant differences, a high overlapping of parameter values between intervals can be observed. This overlapping was meant to be reduced by preselecting a uniform, cardiovascular healthy study population. However, this overlapping is still present and might be originated in different underlying confounding effects on HRV and are thus subject to further investigations on the path towards usable parameters for monitoring depth of anaesthesia.

5. Conclusion

The results of this analysis evidence the feasibility of monitoring nociception based on heart rate variability (HRV) parameters. While a simple time-based HRV parameter shows significant alteration through nociception and anaesthesia, specific parameters for monitoring nociception were found. The data suggest the specific influence of nociception on the HRV amplitude which results in alterations of sdNN. However, this parameter is not appropriate since induction and intubation have inverse effects on sdNN. The HRV measure of the probability of reduced variability POLVAR10 is more adapted for monitoring the effects of nociception and changes in the depth of anaesthesia. Further research has to be launched to compare different entropy measures and their suitability for monitoring depth of anaesthesia and nociception.

The induction of anaesthesia does specifically manifest in a number of frequency parameters and in parameters of symbolic dynamics, especially FORBWORD and FwShannon. Our results on frequency parameters are in-line with the results reported by Jeanne *et al* (2009). The consideration of specific effects of breathing and of induction of anaesthesia is not possible within the presented pilot approach. Thus, for an ultimate conclusion on the usage of HRV parameters to monitor the depth of hypnosis, additional data on the change of respiration patterns during induction of anaesthesia are compulsory.

Due to the lack of specificity, simple statistical time-domain measures of HRV are not sufficient to monitor the effects of anaesthesia separately. However, complex nonlinear symbolic dynamics derived parameters such as POLVAR10 show significant alterations for both the induction of anaesthesia and nociception. One challenge of the probability of limited variability POLVAR10 that has to be encountered in further research is the relatively large scatter as observed by comparing respective first/third quartiles and median values. High

variability, overlapping of parameters and especially the effects of different breathing patterns could potentially limit the reliability of these results. This has to be investigated in further research to adapt these nonlinear symbolic parameters for these confounding effects.

However, the results obtained here suggest that the usage of the nonlinear symbolic dynamics parameter provide additional specific information of cardiovascular variability during anaesthesia.

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