Technische Universität München

Klinik für Anästhesiologie und Intensivmedizin

Klinikum rechts der Isar

Technische Universität München

(Prof. Dr. Gerhard Schneider)

Heart rate variability as a correlate of anaesthetists' workload

Frederick Schneider

Vollständiger Abdruck der von der *Fakultät für Medizin* der Technischen Universität München zur Erlangung des akademischen Grades eines *Doktors der Medizin* genehmigten Dissertation.

Vorsitzender: Prof. Dr. Jürgen Schlegel

Prüfer der Dissertation:

1. apl. Prof. Dr. Klaus J. Wagner
2. Prof. Dr. Adnan Kastrati

Die Dissertation wurde am 04.04.2019 bei der Technischen Universität München eingereicht und durch die Fakultät für Medizin am 05.11.2019 angenommen.

ABSTRACT

Background: Heart rate variability (HRV) defines the beat to beat variation of heart rate and has been linked to alterations in health and performance. In research on human factors and ergonomics, HRV was studied during shift-work, surgery and medical skills training. However, the role of HRV under high workload circumstances (e.g. emergency medicine or anaesthesia) and its abilities as a correlate of workload remain unknown.

Methods: Electrocardiograms of physicians were obtained during their work as anaesthetists during real cases in the operation theatre, during a simulated critical incident or when providing primary healthcare as emergency physicians. The software tools ARTiiFACT, Kubios HRV and LabView were used to extract heart rate variability metrics from the electrocardiograms.

Results: Non-linear HRV metrics, especially Permutation entropy, are the most valuable parameters for the separation of various workload levels during pre-hospital emergency care. HRV was not linked to performance, sex, and work experience in neither simulated critical incidents nor during the induction of general anaesthesia.

Conclusion: The evaluation of anaesthesiologists' HRV metrics is a promising tool to assess workload in medical environments such as simulated critical incidents and emergency care. Especially non-linear HRV metrics and Permutation Entropy might have a high potential to classify workload levels. In order to avoid patient harm and adverse events, future research needs to focus on the real-time analysis of health care providers' heart rate variability and the identification of individual thresholds of excessive workload.

„Es gibt tausend Krankheiten, aber nur eine Gesundheit.“

Carl-Ludwig Börne, deutscher Journalist (1786-1837)

Meinen Eltern gewidmet.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

All images and figures are reproduced and printed with the kind permission of the respective copyright owners.

LIST OF ABBREVIATIONS

Abbreviation	Description
α_1, α_2	Short-term (α_1) and long-term (α_2) fluctuations of detrended fluctuation analysis
ApEn	Approximate entropy
AR	Autoregressive
ASD	Acute stress disorder
AUC	Area under the receiver operating characteristics curve
CIS	Critical incident stress syndrome
D_2	Correlation dimension
DET	Determinism (percentage of recurrence points which form diagonal lines in the recurrence plot)
DFA	Detrended fluctuation analysis
ECG	Electrocardiogram
HF	High frequency (0.15-0.4 Hz)
HRV	Heart rate variability
HRV triangular index	The integral of the RR interval histogram divided by the height of the histogram
Hz	Hertz
IBI	Interbeat interval
LF	Low frequency (0.04-0.15 Hz)
LF and HF powers [n.u.]	Powers of LF and HF bands in normalized units
LF/HF	Ratio between LF and HF band powers
Lmax	Maximum line length of the diagonal lines in the recurrence plot
Lmean	Mean line length of the diagonal lines in the recurrence plot
Mean HR	The mean heart rate
Mean RR	The mean of all RR intervals
Ms	Milliseconds

Abbreviation	Description
NASA	National Aeronautics and Space Administration
NASA-tlx	National Aeronautics and Space Administration task load index
NN50	Number of successive RR interval pairs that differ more than 50 Ms
PeEn	Permutation entropy
pNN50	NN50 divided by the total number of RR intervals
REC	Recurrence rate (percentage of recurrence points in the recurrence plot)
RMSSD	Square root of the mean squared differences between RR intervals
RR-interval	Time span ranging from an R peak to the subsequent R peak in an electrocardiographic signal
SampEn	Sample entropy
SD1, SD2	Standard deviations of the Poincaré plot
SDNN	Standard deviation of normal-to-normal RR intervals
ShanEn	Shannon entropy of diagonal line lengths' probability distributions
STDHR	Standard deviation of instantaneous heart rate values
TINN	Baseline width of the RR interval histogram, evaluated by triangular interpolation
Tlx	Task load index
VLF	Very low frequency (0-0.04 Hz)
VLF, LF and HF peaks	Peak frequencies for VLF, LF and HF bands
VLF, LF and HF powers	Absolute powers of VLF, LF and HF bands
VLF, LF and HF powers [%]	Relative powers of VLF, LF and HF bands

Descriptions for heart rate variability metrics adapted from Tarvainen, Niskanen et al., 2014.

INTRODUCTION

“Exercise to begin with – and as long as it is practiced in moderation – renders the pulse vigorous large, quick, and frequent”, states *Galen of Pergamon* in his work “The pulse for beginners” (Galen, around 129-205 AD) [1] . With this characterization, the ancient physician was among the first who linked alterations of the pulse to the prognosis and diagnosis of maladies (Billman 2011). Two millennia later, with the invention of the electrocardiogram (ECG), the systematic evaluation of beat-to-beat changes in the cardiac rhythm became a viable scientific technique (Billman 2011).

These beat-to-beat changes and their statistical assessment are commonly referred to as heart rate variability (HRV). Along with improved processing capacities and statistical computing, the number of publications regarding HRV has been steadily increasing over the last years. Today, HRV is known to be a result of complex interactions between parasympathetic and sympathetic nerve fibres, respiration, and other influences on the pacemaker in the sinoatrial node (Billman 2011, Shahrestani, Stewart et al. 2015). HRV has been linked to workload in various psychophysiological concepts (Porges 2007, Thayer, Hansen et al. 2009). One of them, the polyvagal theory, proposes that in situations experienced as safe and without threat, the parasympathetic influence on the cardiac pacemaker increases. This results in slower mean heart rate (*mean HR*) and increased HRV (Porges 2007). During stressful events and in challenging situations the parasympathetic influence on the sinoatrial node diminishes while an increased sympathetic activation prepares the organism for a ‘fight-or-flight’ reaction (Porges 2007, Shahrestani, Stewart et al. 2015).

[1] Cited according to the transcript of his *‘Selected Works’,* Oxford University Press, 1997; see Galen (1997). The pulse for beginners. Galen: Selected Works. New York, Oxford University Press**:** 332..

WORKLOAD IN THE ENVIRONMENT OF ANAESTHESIOLOGY AND EMERGENCY MEDICINE

The health care professionals' stress reaction that accompanies a critical incident is known to impair an individual's capacity to adequately react to the challenges of the critical situation as well as to negatively affect problem-solving (Flannery and Everly 2000). Maximum levels of stress can overpower the individual's coping mechanisms, and hence lead to inappropriate and adverse reactions like the critical incident stress syndrome (CIS) or acute stress disorder (ASD) (Caine and Ter-Bagdasarian 2003). As a negative result, lowered productivity, disability and inability to work ultimately increase costs (Kalia 2002, Caine and Ter-Bagdasarian 2003).

A methodological approach to describe an individual's reaction to stress and challenging circumstances is the concept of workload which has been reviewed for anaesthesia by Leedal and Smith (Leedal and Smith 2005). The authors defined workload as a construct that includes the challenges of a situation and an individual's response to them (Leedal and Smith 2005).

Conclusions drawn from several studies suggest a correlation among high workload and an increased rate of adverse events (Cohen, O'Brien-Pallas et al. 1999, Weinger and Slagle 2002). High mental workload, for instance, has been associated with poor performance that can result in cognitive overload and human errors (Gaba and Lee 1990, Byrne, Oliver et al. 2010). In an interview-study by Gaba and Howard, more than 60 percent of the anaesthetists reported personal mistakes due to high workload before; nearly 50 percent observed unsafe actions undertaken by anaesthetists due to demanding pressure for effective and efficient performance (Gaba, Howard et al. 1994).

After all, it seems necessary and crucial to identify critical levels of individual workload *before* cognitive overload may impair patient safety (Gaba and Lee 1990). This can only be achieved with non-intrusive methods for the assessment of workload which neither disturb the individual nor interfere with the individual's activity. Finally, the applied method should not require interruptions of the individual's current actions that are needed to handle any critical situation.

TECHNIQUES OF WORKLOAD EVALUATION

The assessment of workload can be divided into subjective and objective methods. *Subjective* methods typically include retrospective, recall-related questionnaires that are administered post-hoc, whereas *objective* methods aim to evaluate workload from an external point of view primarily using physiological parameters or additional secondary tasks, such as response times to optical stimuli (Weinger, Herndon et al. 1994) or arithmetic questions (Gaba and Lee 1990).

A method to assess subjective workload is the National Aeronautics and Space Administration task load index (NASA-tlx) that has been developed for aeronautics by Hart and Staveland. The NASA-tlx is a six-dimensional questionnaire that consists of ratings for mental, physical, and temporal demands as well as performance, effort, and frustration perceived during a stressful task (Hart and Staveland 1988). Besides aeronautics, the NASA-tlx has been evaluated to be useful and appropriate under high workload circumstances, in the field of anaesthesia (Leedal and Smith 2005, Levin, France et al. 2006, Byrne, Oliver et al. 2010), and in trauma patient care (Parsons, Carter et al. 2012) Additionally, the questionnaire is regularly used to quantify subjective workload in the standardized environment of anaesthesia in the operation theatre (Leedal and Smith 2005, Martin, Schneider et al. 2016).

Objective methods typically evaluate workload via secondary tasks the anaesthetists has to complete on top of his routine work (Leedal and Smith 2005). These secondary tasks may vary from *keeping an accurate anaesthetic record* (Byrne, Sellen et al. 1998) to response-time to optical stimuli (Weinger, Herndon et al. 1994) or problems in mathematical addition (Gaba and Lee 1990). Usually performance on the secondary task was impaired when workload in the primary task increased (Gaba and Lee 1990, Weinger, Herndon et al. 1994, Byrne, Sellen et al. 1998, Leedal and Smith 2005). Since many objective methods report performance on a secondary task, objective methods may also be a surrogate for spare mental capacity (Leedal and Smith 2005). However, their benefit is impaired and less sensitive if the individual compensates changes in workload by increased effort (Leedal and Smith 2005).

Besides objective workload assessment, physiological parameters like the *mean HR* have been used to objectify workload. It has first been linked to workload in the context of aeronautics, where *mean HR* could index dynamic responses to variations in workload (Jorna 1993). In the environment of anaesthesiology, *mean HR* was used to quantify workload under various circumstances: Weinger and colleagues as well as Martin and co-workers found *mean HR* a good correlate for the workload of anaesthetists providing general anaesthesia in the operation theatre (Weinger, Reddy et al. 2004, Martin, Schneider et al. 2016). Schulz and colleagues were able to demonstrate differences in heart rate between uneventful anaesthesia and critical incidents in a human patient simulation (Schulz, Schneider et al. 2011).

Beyond *mean HR*, the beat-to-beat variations in either heart rate or the duration of the peak-to-peak interval (also entitled N-N- or RR-interval) have been investigated beginning in the 1960s (Billman 2011). Alterations in N-N- or RR-intervals are commonly referred to as HRV (Billman 2011).

HRV can be used for cardiovascular risk stratification after myocardial infarction, and a reduced HRV is recognized as a major risk factor for cardiovascular disorders (Kamath, Ghista et al. 1987, Löllgen 1999). It has also been used in psychophysiological research, where Kimhy and colleagues could demonstrate an association between measures of HRV and superior performance on executive function tasks (Kimhy, Crowley et al. 2013). Furthermore, shift work and job strain in physicians have been related to reduced HRV during shift-work (Wong, Ostry et al. 2012, Hernandez-Gaytan, Rothenberg et al. 2013).

In the framework of workload, likewise mean HR, HRV has been investigated in combat flying and aeronautics (Lindqvist, Keskinen et al. 1983, Jorna 1993, Lahtinen, Koskelo et al. 2007). Mansikka, Simola and co-workers' research investigated the HRV of fighter pilots during an instrument approach. They revealed that mean HR and HRV were able to identify the level of pilots' mental workload at which the subjects were no longer able to cope with task demands (Mansikka, Simola et al. 2016). Field research in the environment of anaesthesia done by Martin and colleagues revealed HR and measures of HRV to be promising tools for workload differentiation (Martin, Schneider et al. 2016). More precisely, they found anaesthetists' HRV parameters significantly correlated to different workload stages during general anaesthesia (Martin, Schneider et al. 2016). Beyond, job strain and the perception of work stressors – both not directly related to workload, however – have been documented to reduce HRV (Lee, Yoon et al. 2010, Clays, De Bacquer et al. 2011). According to Thayer and Hansens' neurovisceral integration model, HRV mediated by vagal tone is a major influence on cognitive and executive performance under stressful conditions (Thayer, Hansen et al. 2009). However, in the neurovisceral integration model, these conclusions are limited to mathematical parameters assumed to be correlates of cardiac vagal tone (Thayer, Hansen et al. 2009, Laborde, Mosley et al. 2017). Little is known about new methods of HRV computation and their capability to monitor sympathetic and vagal influences on the heart (Porta, Gnecchi-Ruscone et al. 2007, Sassi, Cerutti et al. 2015). Among these new methods, entropy-based computations have been considered an alternative measurement of vagal influences on the heart (Porta, Gnecchi-Ruscone et al. 2007, Sassi, Cerutti et al. 2015).

HYPOTHESIS AND AIMS OF THE RESEARCH PROJECT

As mentioned earlier, high levels of workload might lead to stress reactions and cognitive overload and may hence impair patient safety. Thus, measuring workload and avoiding work-overload is of specific interest. So far, HRV was only used to assess workload in standardized settings. However, it is unclear whether the parameters of HRV are valid outside protected environments like the operation theatre. This is of particular interest as the hazard for high workload and critical incidents is even higher in settings such as emergency medicine, where a standardised environment is absent.

Except for the NASA-tlx (Parsons, Carter et al. 2012), little is known about the construct validity of workload correlates in much less standardized settings like emergency medicine. Veltman and Gaillard as well as others suggest that HRV, for example, was less valid in field than in laboratory studies (Jorna 1992, Wilson 1992, Veltman and Gaillard 1996). Furthermore, a review by Laborde and co-workers proposed that environmental influences like movement, activity and respiration can affect the HRV under real-life circumstances (Laborde, Mosley et al. 2017).

Martin and colleagues identified *mean HR* and certain parameters of HRV as valuable correlates of workload during general anaesthesia in the operation theatre (Martin, Schneider et al. 2016). However, their study focussed on uneventful general anaesthesia in ASA I[2] patients. This can be considered as a low level of workload for anaesthesiologists in the standardised setting of the operation theatre. Hence, little is known about the validity of these parameters under the circumstances of emergency medicine and during high workload situations such as critical incidents.

Thus, the aim of our research was to identify linear and non-linear HRV metrics that highly correlate with workload in field settings like emergency medicine as well as during simulated critical incidents. Accordingly, we hypothesized that workload during pre-hospital emergency care is associated with HRV and measures of HRV can discriminate between various workload levels. To date, the neurovisceral integration model limits correlations between HRV, performance and executive function to these measures of HRV that are correlates of vagal modulation (Thayer, Hansen et al. 2009). Thus, we aimed to extend this model towards non-linear HRV metrics that might – according to a review – also reflect vagally mediated influences on the cardiac pacemaker (Sassi, Cerutti et al. 2015).

[2] Referring to the ASA-Classification of the American Society of Anaesthesiologists, ASA I represents a healthy patient.

MATERIAL AND METHODS

HEART RATE VARIABILITY

The HRV parameters (hereafter referred to as HRV metrics) can be divided into three main sections: time domain, frequency domain (both also known as linear methods), and non-linear methods. The time domain HRV metrics include simple statistical variabilities of the intervals between two adjacent QRS complexes. Frequency domain methods analyse the power spectral density in order to describe how variance distributes as a function of frequency (1996). In 1981, Akselrod, Gordon and colleagues showed that especially parasympathetic and sympathetic modulation of the cardiac rhythm can be evaluated by their frequency-specific contribution to the frequency domain measures of HRV (Akselrod, Gordon et al. 1981). Finally, non-linear methods have been used to capture the structure and complexity of heart rate time series. (Stein, Domitrovich et al. 2005)

ELECTROCARDIOGRAM GATHERING AND PROCESSING

ECGs have been used as a basis for HRV computations; those ECGs were recorded using the corresponding function of the Zephyr Bio Harness 3™ chest belt (Zephyr Technology Corp., Annapolis, MD, USA; hereafter referred to as chest belt). The reliability and validity of the generated ECG under laboratory and field conditions has been demonstrated by Johnstone, Ford and co-workers (Johnstone, Ford et al. 2012). The ECG data was extracted from the chest belt using the Zephyr Log Downloader Software that is part of the enclosed software package.

The raw ECGs were processed and corrected for artefacts using the software tool ARTiiFACT 2.2 (Biosignal Analysis and Medical Imaging Group, Department of Applied Physics, University of Eastern Finland, Kuopio, Finland; Kaufmann, Sutterlin et al. 2011). First, a high pass filter of 10 Hz was applied on ECG data sets and a global threshold of approximately 50 μV (selected depending on optimized R-peak detection) was used to enhance the automated detection of R peaks in the ECG data. Following the guidelines of the *Task Force*[3], the ECG raw data were checked for inaccurately detected R-peaks, afterwards. R-peaks were controlled visually, using the integrated peak detection function of the ARTiiFACT software (Kaufmann, Sutterlin et al. 2011). In a final step, ARTiiFACT extracted the interbeat intervals (IBIs) from the visually checked ECG data. To identify invalid IBIs within the diversity of correct IBIs, ARTiiFACT used the artifact identification algorithm for heart period data that has been established by Berntson, Quigley and colleagues (Berntson, Quigley et al. 1990). This algorithm deduced an artifact criterium (individual threshold) from the normal distribution of successive heart period differences within the data. Since they are less sensitive for corrumption than least square estimates, percentile based distributions were used for the computations of the algorithm (Berntson, Quigley et al. 1990). IBIs that conformed to the artifact criterion were marked as incorrect and the cubic spline interpolation was applied on the IBIs to correct them (Figure 1). The algorithm of the cubic spline interpolation used piecewise polynomials (“splines“) to interpolate the link of predefined points (McKinley and Levine 1998). The IBI data prepared in such a manner were imported into the software ‘Kubios HRV’ for further procession (Tarvainen, Niskanen et al. 2014).

[3] Guidelines proposed by the *Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology* (1996). "Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology." European Heart Journal **17**(3): 354-381.

FIGURE 1 – INCORRECT INTERBEAT INTERVALS AND THEIR CORRECTION IN ARTiiFACT

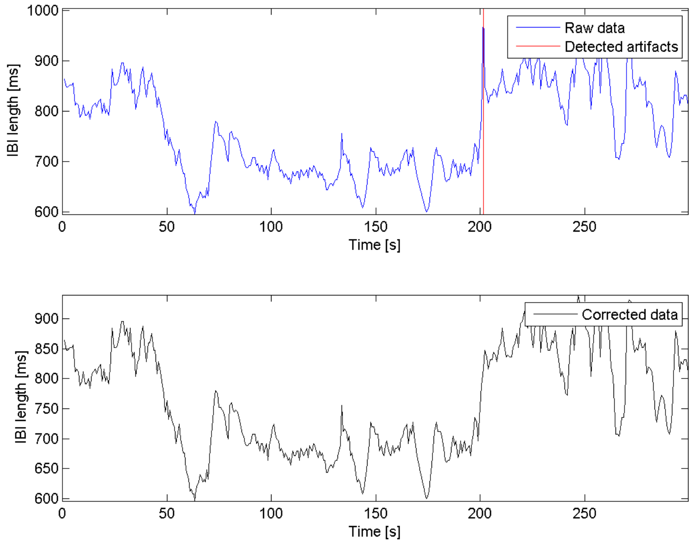

Figure 1 – The top graph shows the interbeat interval (IBI) lengths over time; the red line marks an IBI that is detected as incorrect. The bottom graph represents the data corrected by ARTiiFACT using a cubic spline interpolation. The graphs are generated during the IBI correction step of ARTiiFACT (Kaufmann, Sutterlin et al. 2011).

HRV METRICS AND HRV COMPUTING

All HRV computations were done using the software "Kubios HRV" (Tarvainen, Niskanen et al. 2014). The software performs computations for time domain, frequency domain and non-linear HRV metrics. To compute Permutation Entropy (*PeEn*) the software tool LabView 8.5 (National Instruments LabVIEW, National Instruments, Austin, TX, USA) was used.

Time domain methods were applied to the successive RR intervals directly; they include the mean heart rate (*mean HR*) and the mean value of RR intervals (*mean RR*). Furthermore, a variety of time domain HRV metrics describes the variability within the RR series (Tarvainen, Niskanen et al. 2014). These include the standard deviation of normal-to-normal RR intervals (*SDNN*), the root mean square of successive differences (*RMSSD*), the number of successive intervals differing more than 50 ms (*NN50*), and the corresponding relative amount (*pNN50*) (Tarvainen, Niskanen et al. 2014). Furthermore, based on the RR interval histogram the HRV triangular index as the integral of the histogram divided by its height (dependent on the bin width, in this case 1/128s) as well as the *TINN* – the baseline width of the histogram evaluated by triangular interpolation – are computed (Tarvainen, Niskanen et al. 2014).[4] For further details and the respective units of the frequency based HRV metrics, see the table.

For the computation of frequency domain HRV metrics, the time-based RR interval series were converted into equidistantly sampled series using polynomial functions (cubic spline interpolation) (Litvack, Oberlander et al. 1995, Tarvainen, Niskanen et al. 2014). To obtain frequency spectra from the continuous ECG signals, the software 'Kubios HRV' takes advantage of two different methods: 1) Welch's periodogram that divides RR series into overlapping segments, and 2) autoregressive (AR) modelling of RR series with an AR model of specific order (Tarvainen, Niskanen et al. 2014). Frequencies were divided in the three frequency bands 1) very low frequencies (VLF) ranging from 0 to 0.04 Hz, 2) low frequencies (LF) from 0.04 to 0.15 Hz, and 3) high frequencies from 0.15 to 0.4 Hz.[4]

Since two distinct computations were used, all HRV metrics of the frequency spectrum are delivered based on Welch's periodogram as well as the AR model. From the frequency domain HRV metrics, the *peak frequencies* (frequency values related to maximum power; for VLF, LF, and HF), *absolute* and *relative powers* (of VLF, LF, and HF), *normalized powers* of LF and HF, *LF/HF* power ratio, and the *total spectral power* were included. The software calculates the corresponding powers as the integral of the spectrum estimates over the frequency bands, or the integral of the whole spectrum for total power, respectively (Tarvainen, Niskanen et al. 2014).[4] See the table for more detailed information about computation, units and calculations of frequency based HRV metrics.

Since the cardiac autonomous regulation is complex and variously influenced, non-linear methods are an attempt to measure the structure and complexity of

[4] According to the guidelines proposed by the *Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology* (1996).

heart rate time series. 'Kubios HRV' uses different non-linear methods. First, a Poincaré plot is deployed as a graphic presentation of correlations among consecutive RR intervals. Within the Poincaré plot, *SD1* results from the width and, respectively, *SD2* from the length of the plot's shape (Tarvainen, Niskanen et al. 2014).

FIGURE 2 – EXAMPLE OF A POINCARÉ PLOT COMPUTED BY KUBIOS HRV

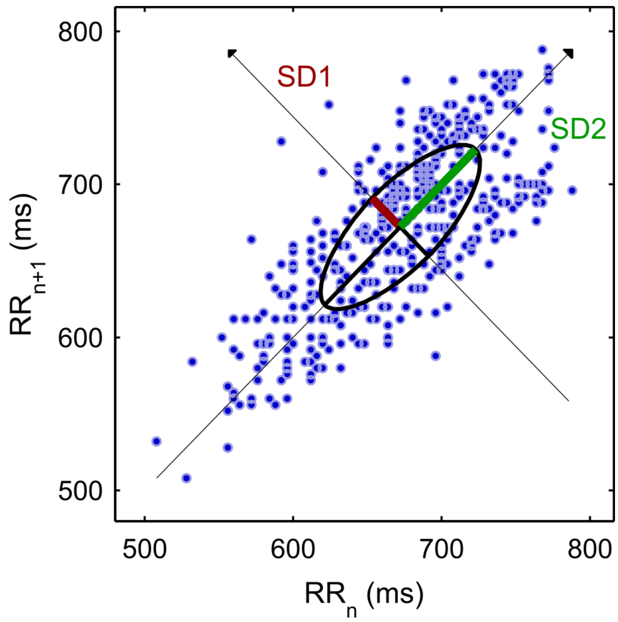

Figure 2 – Example of a Poincaré plot as computed using the software tool Kubios HRV (Tarvainen, Niskanen et al. 2014). SD1 (red) results from the width, and SD2 (green) from the length of the plot's shape, respectively.

Second, approximate entropy (*ApEn*) and sample entropy (*SampEn*) are calculated based on an embedding dimension *m* and the tolerance *r* (Richman and Moorman 2000). To ensure inter-individual comparability, the software determines the tolerance *r* to be 0,2 SDNN (Tarvainen, Niskanen et al. 2014). Another method, the *detrended fluctuation analysis* (DFA), measures correlations within the data for different time scales; in HRV analysis, these are divided into short-term and long-term fluctuations (displayed by the variables α_1 and α_2, respectively) (Tarvainen, Niskanen et al. 2014). To characterize the complexity and strangeness of the data, the correlation dimension (D_2) provides the minimum number of dynamic variables that are needed to model the underlying system (Tarvainen, Niskanen et al. 2014). The correlation dimension model uses the embedding dimension *m* (default value *m*=10) and the threshold *r* (default value r=$\sqrt{m}\mathrm{SDNN}$) (Tarvainen, Niskanen et al. 2014).

FIGURE 3 - EXAMPLE OF THE DETRENDED FLUCTUATION ANALYSIS DONE BY KUBIOS HRV

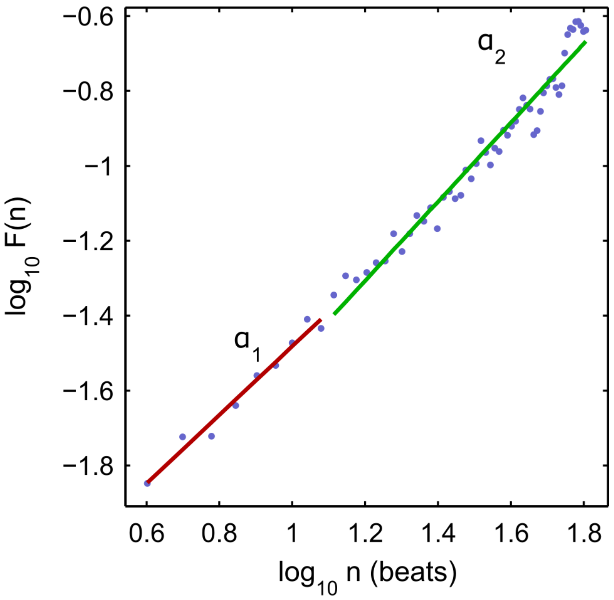

Figure 3– Example of a detrended fluctuation analysis as computed by Kubios HRV (Tarvainen, Niskanen et al. 2014). α_1 correlates with the short-term and α_2 with the long-term changes in HRV, respectively.

Last, the recurrence plot analysis – using the same embedding dimension *m* and threshold *r*, as the correlation dimension – is a binary square matrix resulting in a graphic of short lines parallel to a main diagonal (Tarvainen, Niskanen et al. 2014). From this, the software obtains the variables mean line length (*Lmean*), maximum line length (*Lmax*), recurrence rate (*REC*), determinism (*DET*), and Shannon entropy of line length distribution (*ShanEn*) (Tarvainen, Niskanen et al. 2014).

Finally, the non-linear HRV metric Permutation Entropy is computed using the software tool “LabView 8.5” (National Instruments LabVIEW, National Instruments, Austin, TX, USA). Permutation entropy is a mathematical construct that can be used as a non-linear HRV metric; it is believed to be unimpaired by high signal dimensions and seems to be robust for the detection of unusual patterns in complex time lines (Bandt and Pompe 2002, Cao, Tung et al. 2004, Jordan, Stockmanns et al. 2008).

Supplementary details for all computed HRV metrics, their verbal description, and their units are provided in the table.

***TABLE** – DETAILED DESCRIPTION OF ALL HEART RATE VARIABILITY METRICS COMPUTED BY KUBIOS HRV SOFTWARE.*

Parameter	Units	Description
Time Domain		
Mean RR	[ms]	The mean of all RR-intervals
SDNN	[ms]	Standard deviation of normal-to-normal RR-intervals
Mean HR	[1/min]	The mean heart rate
STDHR	[1/min]	Standard deviation of instantaneous heart rate values
RMSSD	[ms]	Square root of the mean squared differences between successive RR-intervals
NN50	[count]	Number of successive RR-interval pairs that differ more than 50 ms
pNN50	[%]	NN50 divided by the total number of RR-intervals
HRV triangular index	-	The integral of the RR-interval histogram divided by the height of the histogram
TINN	[ms]	Baseline width of the RR-interval histogram, evaluated by triangular interpolation
Frequency Domain	*All frequency domain heart rate variability metrics are delivered based on two distinct spectrum estimates (Welch's periodogram and autoregressive modelling, respectively – for details see full text).*	
VLF, LF, and HF peaks	[Hz]	Peak frequencies for VLF, LF, and HF bands
VLF, LF, and HF powers	[ms^2]	Absolute powers of VLF, LF, and HF bands
VLF, LF, and HF powers	[%]	Relative powers of VLF, LF, and HF bands VLF [%] = VLF [ms^2]/total power [ms^2] x 100 % LF [%] = LF [ms^2]/total power [ms^2] x 100 % HF [%] = HF [ms^2]/total power [ms^2] x 100 %

Parameter	Units	Description
LF and HF powers	[n.u.]	Powers of LF and HF bands in normalized units LF [n.u.] = LF [ms^2]/(total power [ms^2] - VLF [ms^2]) HF [n.u.] = HF [ms^2]/(total power [ms^2] - VLF [ms^2])
LF/HF	-	Ratio between LF and HF band powers
Total Power	[ms^2]	Total spectral power
Non-linear		
SD1, SD2	[ms]	Standard deviations of the Poincaré plot
ApEn	-	Approximate entropy
SampEn	-	Sample entropy
D_2	-	Correlation dimension
α_1, α_2	-	Short-term and long-term fluctuations of detrended fluctuation analysis
Lmean	[beats]	Mean line length of the diagonal lines in recurrence plot (RP)
Lmax	[beats]	Maximum line length of diagonal lines in RP
REC	[%]	Recurrence rate (percentage of recurrence points in RP)
DET	[%]	Determinism (percentage of recurrence points which form diagonal lines in RP)
ShanEn	-	Shannon entropy of diagonal line lengths' probability distribution
PeEn	-	Permutation Entropy

Overview on the heart rate variability metrics computed by the software used for analysis. Abbreviations: ms, miliseconds; min, minutes; VLF, very low frequencies; LF, low frequencies; HF, high frequencies. Modified version of the table delivered in Tarvainen, Niskanen et al. 2014.

STUDY DESIGN AND DATA ACQUISITION

SETTING 1: THE VALIDITY OF LINEAR AND NON-LINEAR HEART RATE METRICS AS WORKLOAD INDICATORS OF EMERGENCY PHYSICIANS, PLOS ONE (2017)

During a period of five months in 2015, emergency physicians were asked to wear the chest belt during their 24-hour shifts as emergency physician on the emergency physician response vehicle operated by the Department of Anaesthesiology and Intensive Care at the Klinikum rechts der Isar, Technical University of Munich. The local Ethics Committee approved the study (N° 5771/13; May 11th, 2015). Based on the timestamps from the physicians' protocols, four different time segments during the emergency sorties were distinguished: The first segment included the five minutes before the alarm, the second segment was the drive to the emergency site. The third segment was the time between the arrival on the scene and the handover of the patient to an emergency physician at the admitting emergency ward and the fourth segment were the five minutes just after the sortie was finished. These four time segments were defined as different levels of workload. The time before the alarm represented a baseline level, the drive to the emergency site was the mental preparation of the physician, the primary patient care was the time of highest workload, and the time after the alarm was defined as the physicians' recovery. See figure 4 for details about the time segments and their median durations. ECG raw data were extracted from the chest belt's 24-hour recordings and based thereupon, HRV metrics were calculated for each of those segments (Schneider, Martin et al. 2017).

To adjust for repeated measurements within subjects on a single shift as well as for subjects working on different days, linear mixed-effects models were fitted to explore differences of the HRV metrics between the time segments (Schneider, Martin et al. 2017). To explore the HRV metrics' ability to discriminate between the various workload stages, receiver operating characteristics (ROC) analysis for clustered data were used (Schneider, Martin et al. 2017).

FIGURE 4 – ANALYSED TIMESPANS DURING AN EMERGENCY SORTIE

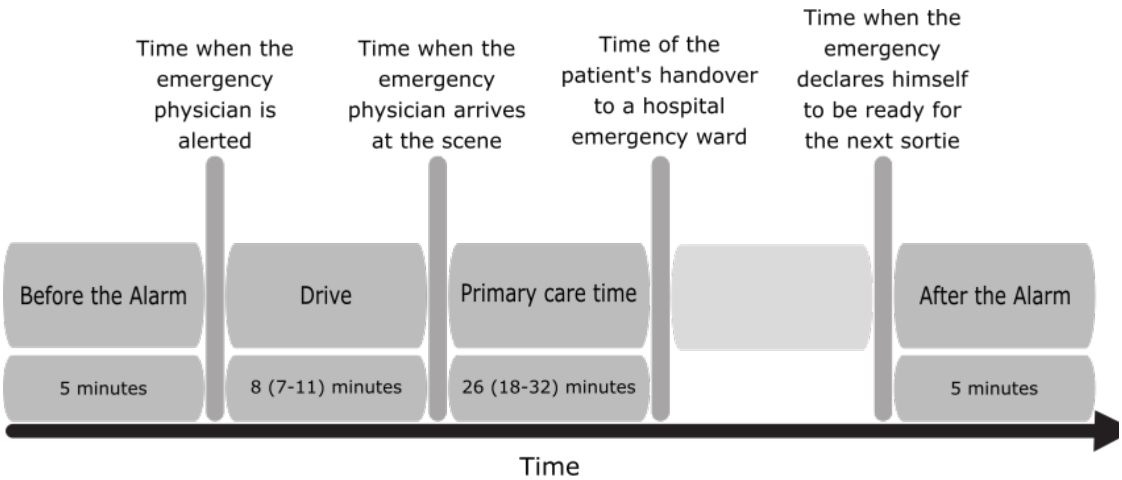

Figure 4 – Schematic presentation of the work sequence during a primary care emergency physician's sortie and description of the timespans exported for HRV metric computation. The times are presented as median times (interquartile-range). In the absence of definitive time markers, a time interval of 5 minutes was chosen for the segments before and after the alarm. Modified figure originally published in Schneider, Martin et al., 2017.

SETTING 2: ANAESTHETISTS' HEART RATE VARIABILITY AS AN INDICATOR OF PERFORMANCE DURING INDUCTION OF GENERAL ANAESTHESIA AND SIMULATED CRITICAL INCIDENTS, JOURNAL OF PSYCHOPHYSIOLOGY (2018)

Anaesthetists working at the Department of Anaesthesiology at the Klinikum rechts der Isar, Technical University of Munich were exposed to a simulated hypotension scenario. The study was approved by the local Ethics Committee (N° 5761/13; April 22nd, 2013). During this scenario anaesthetists' ECGs were recorded using the chest belt. To generate a realistic simulation environment, a high-fidelity human patient simulator (HPS® Human Patient Simulator, CAE Healthcare Corp., Montreal, Quebec, Canada) presented a severe intra-operative hypotension during general anaesthesia. The HRV metrics were computed from the five-minute segment after the onset of hypotension. The overall duration and depth of hypotension was used as a correlate of the anaesthetist's performance (mmHg*s).

These data were compared to the HRV metrics of anaesthetists during the induction of general anaesthesia in ASA I patients gathered for a prior study (Martin, Schneider et al. 2016). The Ethics Committee at Klinikum rechts der Isar, Technical University of Munich approved the study (N° 5771/13; April 29th, 2013).

Here, the time needed for induction of general anaesthesia was used as a marker of the anaesthetist's performance.

Based on the medians of the time needed for anaesthesia induction and the length and depth of hypotension, participants with high and low performance were identified and grouped to a low- and high-performance group. The Mann-Whitney-U test was applied to assess differences of the HRV metrics' medians between groups.

RESULTS AND DISCUSSION

The research project aimed to investigate linear and non-linear HRV metrics and their potential to discriminate different levels of workload. First, based on Martin and colleagues' findings from the operation theatre (Martin, Schneider et al. 2016), the suitability of HRV metrics in a pre-hospital emergency care setting was investigated (Schneider, Martin et al. 2017). Second, the analysis of HRV during the induction of general anaesthesia and simulated critical incidents (Schneider, Martin et al. 2018) intended to explore the connection of non-linear HRV metrics and performance based on the neurovisceral integration model (Thayer, Hansen et al. 2009).

LINEAR AND NON-LINEAR HRV METRICS AND THEIR VALIDITY IN PRE-HOSPITAL EMERGENCY MEDICINE

In pre-hospital emergency care, non-linear HRV metrics (AUC for grouped analysis = 0.998) and among the analysis of single HRV metrics especially PeEn separated workload best (Schneider, Martin et al. 2017). In contrast to the findings by Martin and co-workers (Martin, Schneider et al. 2016), mean HR was not a valuable parameter for the separation of different workload levels (AUC = 0.558). The high-performing non-linear HRV metric PeEn has first been introduced as a measurand for a signal's complexity by Bandt and Pompe in 2002 (Bandt and Pompe 2002). Ever since, it has been used in different settings, including the separation of consciousness from unconsciousness through the analysis of electroencephalographic data (Jordan, Stockmanns et al. 2008). Due to its computation, PeEn is unimpaired by high signal dimensions and limitations in signal length as well as enabled to detect patterns in complex time lines (Bandt and Pompe 2002, Cao, Tung et al. 2004, Jordan, Stockmanns et al. 2008).
Though they performed good in the highly standardized environment of general anaesthesia (Martin, Schneider et al. 2016), time domain HRV metrics did not perform satisfactorily in pre-hospital care (Schneider, Martin et al. 2017). In a comparable setting, Rieger, Stoll and co-workers divided surgeons in a stressed and non-stressed group (based on the short form of the State Trait Anxiety

Inventory[5]) before assessing their HRV during surgeries. The heart rate (*mean HR*, referred to as a part of the time domain HRV metrics) of surgeons from the stressed group was higher during surgeries, their HRV was decreased during sleep (Rieger, Stoll et al. 2014). This was the first approach to HR and HRV metrics as a possible categorisation tool for perceived stress during work (i.e. in the operation theatre).

In contrast to the time domain HRV metrics, more of the frequency domain HRV metrics correlated with changes of workload in pre-hospital emergency care (Schneider, Martin et al. 2017). This was in line with findings by Crewther, Shetty and colleagues: They demonstrated that decreasing HRV (indicated by reduced LF and HF components) might predict improved performance and reduced stress during laparoscopic surgery simulations (Crewther, Shetty et al. 2015). However, their findings were not significant ($p<0.10$) (Crewther, Shetty et al. 2015). Pagani and colleagues as well as Hjortskov and co-workers proposed that mental stress induces changes in parasympathetic regulation of the cardiac pacemaker; they found these changes to be represented by frequency domain HRV metrics (Pagani, Mazzuero et al. 1991, Hjortskov, Rissén et al. 2004). However, compared to the performance of non-linear HRV metrics, the performance of frequency domain HRV metrics remained low (Schneider, Martin et al. 2017).

INTER-INDIVIDUAL DIFFERENCES IN HRV AND THEIR RELATION TO PERFORMANCE DURING INDUCTION OF ANAESTHESIA AND SIMULATED CRITICAL INCIDENTS

The comparison of HRV metrics between a group of low and high performing individuals during the induction of general anaesthesia in the operation theatre as well as during a simulated critical incident did not show significant differences between the two groups (Schneider, Martin et al. 2018). However, HRV was not recorded under resting conditions which limits the comparability with other

[5] The short State Trait Anxiety Inventory (STAI) is a psychological inventory that measures anxiety; It is well validated and consists of 6 instead of 40 questions compared to the State Trait Anxiety Index (Marteau, T. M. and H. Bekker (1992). "The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI)." Br J Clin Psychol **31 (Pt 3)**: 301-306.).

studies. Hansen and co-workers, for example, separated individuals based on their resting HRV and found a higher HRV under resting conditions related to improved performance (Hansen, Johnsen et al. 2003, Hansen, Johnsen et al. 2009). Most of these studies refer to time domain HRV metrics like SDNN and RMSSD (Thayer, Hansen et al. 2009, Beaumont, Burton et al. 2012, Luque-Casado, Zabala et al. 2013); others, however, found a correlation of the frequency domain's high frequency (HF) component and performance (Elliot, Payen et al. 2011). Yet, these results are not necessarily objecting the lack of significant findings, as Schneider et al. compared inter-individual differences, while the aforementioned studies focussed on intra-individual changes of HRV in comparison to resting HRV (Schneider, Martin et al. 2018).

Besides HRV metrics, work-experience was not related to performance markers (Schneider, Martin et al. 2018). Alike, DeAnda and Gaba, as well as Schulz and co-workers found great variance in the performance of unexperienced anaesthesia providers but not in group-wise comparison with more experienced anaesthetists (DeAnda and Gaba 1991, Schulz, Schneider et al. 2014). The majority of studies, however, found work-experience positively correlated with performance (Quińones, Ford et al. 1995).

HEART RATE VARIABILITY ANALYSIS IN OTHER ENVIRONMENTS

Apart from our own research in settings related to anaesthesiology, various researchers studied heart rate variability (HRV) in a hospital-like environment using staff-physicians as their object of investigation (Karhula, Henelius et al. 2014, Crewther, Shetty et al. 2015). Most of these studies focussed on a human factors approach and investigated the human body's response to shift-work, job strain, and increasing complexity of the work environment. This is important to identify factors that contribute to physicians' low job satisfaction and increased burnout rates, and hence, improve their overall wellbeing (Tyssen 2007, Markwell and Wainer 2009, Feeney, O'Brien et al. 2016). Accordingly, for example, reduced HRV in young residents related to high job strain and work stressors (Hernandez-Gaytan, Rothenberg et al. 2013). Furthermore, Tobaldini, Cogliati and co-workers observed a sympathetic modulation and a parasympathetic withdrawal in their analysis of residents' HRV metrics after one night of duty. Beyond, they also observed increased levels of plasmatic inflammatory cytokines related to sympathetic activation (Tobaldini, Cogliati et al. 2013). Further research pointed out similar results regarding sympathetic modulation following night shifts and duty days (Amirian, Toftegard Andersen et al. 2014); Lee, Lo and colleagues found decreasing HRV correlated with increasing duty loads (Lee, Lo et al. 2016). These results reinforce the adverse effects of shift-work and sleep deprivation observed earlier: Irwin and colleagues found evidence for elevated catecholamine levels during acute sleep deprivation (Irwin, Thompson et al. 1999), The authors considered these effects of sympathetic modulation to contribute to the onset of cardiovascular diseases (Irwin, Thompson et al. 1999). Besides cardiovascular diseases, working night shifts has been linked to an increased risk for diabetes mellitus (Strohmaier, Devore et al. 2018). Under these circumstances, mostly HRV metrics of the frequency domain are used for the interpretation of parasympathetic and sympathetic activity (Hernandez-Gaytan, Rothenberg et al. 2013, Amirian, Toftegard Andersen et al. 2014, Lee, Lo et al. 2016). Our own research suggests that these changes in cardiac autonomous regulation may not only be observed as an adverse effect of shift-work in general, but also among rest and activity within a single duty (Schneider, Martin et al. 2017), as well as within different workload levels of a single activity (Martin, Schneider et al. 2016, Schneider, Martin et al. 2017). Thus, besides shift-work permanent occupation with high workload tasks could also contribute to a sympathetic modulation and the subsequent predisposition for cardiovascular disease and diabetes.

Besides ergonomics and human factors, HRV has been studied in the context of workload generated by differing task demands under experimental and simulator conditions (Henelius, Hirvonen et al. 2009, Luque-Casado, Perales et al. 2016) In simulator environments HRV analysis has a long tradition; particularly, in the field of aviation and flight simulation (Lindqvist, Keskinen et al. 1983, Jorna 1993). A study on simulated flight maintenance unveiled that HRV metrics were sensitive to different workload phases (Tattersall and Hockey 1995). Also, in experimental settings, researchers already classified workload using HRV parameters

(Henelius, Hirvonen et al. 2009). Based on their research with various tasks in the laboratory, Luque-Casado, Perales and co-workers suggested that HRV was sensitive to sustained attention demands and varies as a function of task demands (Luque-Casado, Perales et al. 2016).

Mean heart rate and heart rate variability have rarely been investigated in anaesthetists in the operation theatre (Weinger, Reddy et al. 2004, Martin, Schneider et al. 2016) and during simulated critical incidents before (Schulz, Schneider et al. 2011). Apart from our research, heart rate variability in pre-hospital emergency care has not been investigated, so far. Likewise, research on objective workload in anaesthesia as a *per se* highly challenging domain, was limited to workload evaluation using additional tasks (i.e. mathematical addition) or response time to vibrotactile stimuli to create high workload situations, so far (Gaba and Lee 1990, Byrne, Oliver et al. 2010, Byrne, Murphy et al. 2013). Notwithstanding, the benefit of additional tasks for workload assessment was impaired since they were rather considered a surrogate of mental spare capacity and performance might be influenced by an individual's effort to compensate changes in workload (Leedal and Smith 2005).

After all, HRV analysis is a valuable non-intrusive method for workload assessment in challenging environments like anaesthesia. Particularly, modern entropy-based HRV metrics could improve the value of HRV for workload analysis, since they are considered to be unimpaired by high signal dimensions and limitations in signal length (Bandt and Pompe 2002, Cao, Tung et al. 2004, Jordan, Stockmanns et al. 2008). Additionally, their ability to detect dynamical changes in complex time lines makes a real-time analysis of workload and thus prevention of work-overload possible (Bandt and Pompe 2002, Cao, Tung et al. 2004). Nevertheless, these methods have not yet been validated in terms of predictive value, reproducibility and robustness (Sassi, Cerutti et al. 2015). To date, this compromises their widespread use in HRV analysis.

SUMMARY AND CONCLUSIONS

High levels of workload and stress can impair patient safety. Hence, it is of particular interest to measure workload and prevent work overload. Physiological workload correlates such as HRV have so far only been validated in standardized settings like the operation theatre (Martin, Schneider et al. 2016). Hence, the aim of this research project was to apply their analyses to high workload environments like emergency medicine. Moreover, we intended to find non-linear HRV metrics that correlate with performance during simulated critical incidents.

It has been shown that in the operation theatre anaesthetists' mean HR and several linear and non-linear HRV metrics significantly differ between various anaesthesia stages. Accordingly, non-linear HRV metrics discriminated workload levels during different time segments of a sortie in the more liberal environment of pre-hospital emergency medicine best. Among them, especially PeEn performed extraordinarily. Furthermore, the combination of the AUCs from the logistic regression models showed that the non-linear HRV metrics perform better than time- or frequency-domain HRV metrics. Not surprisingly, PeEn as a correlate of workload was highest during primary patient care (time between the physician's arrival at the emergency site and the handover of a patient to the hospital's emergency ward).

During simulated critical incidents and the induction of general anaesthesia in the operation theatre, inter-individual differences in HRV metrics were not related to the anaesthetists' performance.

Hence, HRV metrics are a promising tool for the assessment of workload in a medical environment, particularly, in challenging fields like anaesthesiology and emergency medicine, where high workload is predominant. Future research should concentrate on the real-time analysis of heart rate variability and the definition of individual thresholds; so that adverse events caused by work-overload may be prevented.

APPENDIX

SUMMARY OF EACH PUBLICATION AND INDIVIDUAL CONTRIBUTION OF THE CANDIDATE

THE VALIDITY OF LINEAR AND NON-LINEAR HEART RATE METRICS AS WORKLOAD INDICATORS OF EMERGENCY PHYSICIANS (PLOS ONE)

Based on our work that examined heart rate variability (HRV) of different levels of workload in the operation theatre (Martin, Schneider et al. 2016), this study was the first approach to transfer these publications' findings to a more liberal work environment where high workload is predominant without simulation. We hypothesised that non-linear HRV metrics are more capable to differentiate workload levels than linear HRV metrics of the time- and frequency-domain.

Hence, we gathered electrocardiograms (ECG) from 13 physicians during a 24h duty as primary out-of-hospital emergency care providers. Furthermore, we obtained their subjective workload from NASA task load index queries and obtained additional information on times and patient characteristics from the physicians' protocols.

We found Permutation entropy to discriminate best between the time before the alarm and primary patient care. In the multivariable approach, the non-linear HRV metrics provided a higher area under the receiver operating curve compared to the frequency domain and to the time domain HRV metrics.

Non-linear heart rate metrics and, specifically, PeEn provided good validity for the assessment of different levels of a physician's workload in the inherently low structured setting of pre-hospital emergency care.

Under my responsibility essential parts of this study (e.g. study design, statistical analysis) were planned and discussed. In cooperation with the co-workers of my research group I have been responsible for the conception and realisation of the study, the data acquisition and data presentation, as well as for the design of tables and figures. Furthermore, the first draft of the manuscript was written by me. In cooperation with my colleagues from the research group I constantly worked on the elaboration of the final manuscript.

ANESTHETISTS' HEART RATE VARIABILITY AS AN INDICATOR OF PERFORMANCE DURING INDUCTION OF GENERAL ANESTHESIA AND SIMULATED CRITICAL INCIDENTS: AN OBSERVATIONAL STUDY (JOURNAL OF PSYCHOPHYSIOLOGY)

To extend the conclusions drawn from earlier work on HRV metrics published by our research group, we tried to meter the inter-individual relation among heart rate variability and performance. Furthermore, we tried to assess the impact of sex and work experience on performance in anaesthesia. Hence, we investigated anaesthetist heart rate variability in an environment simulating high workload as well as during the induction of general anaesthesia in the operation theatre. For the statistical analysis we focussed on the *inter*-individual changes in heart rate variability rather than *intra*-individual differences compared to baseline HRV. We investigated, whether anaesthetists' vagally-mediated HRV is correlated with performance during the induction of general anaesthesia and the management of simulated critical incidents.

We found performance to be independent from anaesthetists' heart rate variability, sex and work experience.

Because we solely compared the HRV metrics of different activity levels, the comparability of our results to others is impaired. Our results regarding sex and work experience were consistent to most studies under various circumstances.

During data analysis, it was my responsibility to process the data gathered in the simulator environment. This included sequencing of ECG raw data, computation of heart rate variability analysis and data preparation for the statistical breakdown. Likewise, I composed and wrote the first draft of the manuscript. In collaboration with the colleagues from my research group, I revised the manuscript and prepared it for submission. Furthermore, I adapted the manuscript according to the reviewers' comments and created the graphic that is part of the publication.

ADDITIONAL CO-AUTHORSHIP: LINEAR AND NON-LINEAR HEART RATE METRICS FOR THE ASSESSMENT OF ANAESTHETISTS' WORKLOAD DURING GENERAL ANAESTHESIA (BRITISH JOURNAL OF ANAESTHESIA)

In order to research new abilities for workload assessment, this exploratory study analysed the anaesthesiologists' heart rate variability during the induction, maintenance and emergence of general anaesthesia in healthy patients. We found mean HR as well as several linear and non-linear HRV parameters to significantly discriminate between various anaesthesia stages. In a multiparametric approach non-linear HRV metrics unveiled a better AUC than the linear HRV metrics.

This exploratory approach was the basis for later studies that are part of this dissertation. I analysed the raw data gathered from the ECGs recorded in the operation theatre and prepared them for statistical analysis; this included the computation of HRV metrics. Beyond, the first draft of the manuscript and the revision of the same were written with my support.

BIBLIOGRAPHIC DETAILS OF THE PUBLICATIONS THAT ARE PART OF THIS CUMULATIVE DISSERTATION

SCHNEIDER, F., MARTIN, J., HAPFELMEIER, A., JORDAN, D., SCHNEIDER, G. & SCHULZ, C. M. (2017). The validity of linear and non-linear heart rate metrics as workload indicators of emergency physicians. *PLOS ONE,* 12**,** e0188635.

DOI: doi.org/10.1371/journal.pone.0188635
Pubmed ID: 29190808

SCHNEIDER, F., MARTIN, J., SKRZYPCZAK, M., HINZMANN, D., JORDAN, D., WAGNER, K. J., & SCHULZ, C. M. (2018). Anesthetists' Heart Rate Variability as an Indicator of Performance During Induction of General Anesthesia and Simulated Critical Incidents. *Journal of Psychophysiology*.

DOI: doi.org/10.1027/0269-8803/a000225

MARTIN, J., **SCHNEIDER, F.,** KOWALEWSKIJ, A., JORDAN, D., HAPFELMEIER, A., KOCHS, E. F., ... SCHULZ, C. M. (2016). Linear and non-linear heart rate metrics for the assessment of anaesthetists' workload during general anaesthesia. *British Journal of Anaesthesia, 117*(6), 767-774.

DOI: doi.org/10.1093/bja/aew342
Pubmed ID: 27956675

BIBLIOGRAPHY

(1996). "Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology." European Heart Journal **17**(3): 354-381.

Akselrod, S., D. Gordon, F. A. Ubel, D. C. Shannon, A. C. Berger and R. J. Cohen (1981). "Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control." Science **213**(4504): 220-222.

Amirian, I., L. Toftegard Andersen, J. Rosenberg and I. Gogenur (2014). "Decreased heart rate variability in surgeons during night shifts." Can J Surg **57**(5): 300-304.

Bandt, C. and B. Pompe (2002). "Permutation entropy: a natural complexity measure for time series." Phys Rev Lett **88**(17): 174102.

Beaumont, A., A. R. Burton, J. Lemon, B. K. Bennett, A. Lloyd and U. Vollmer-Conna (2012). "Reduced cardiac vagal modulation impacts on cognitive performance in chronic fatigue syndrome." PLoS One **7**(11): e49518.

Berntson, G. G., K. S. Quigley, J. F. Jang and S. T. Boysen (1990). "An approach to artifact identification: application to heart period data." Psychophysiology **27**(5): 586-598.

Billman, G. E. (2011). "Heart rate variability - a historical perspective." Frontiers in Physiology **2**: 86.

Byrne, A. J., A. Murphy, O. McIntyre and N. Tweed (2013). "The relationship between experience and mental workload in anaesthetic practice: an observational study." Anaesthesia **68**(12): 1266-1272.

Byrne, A. J., M. Oliver, O. Bodger, W. A. Barnett, D. Williams, H. Jones and A. Murphy (2010). "Novel method of measuring the mental workload of anaesthetists during clinical practice." Br J Anaesth **105**(6): 767–771.

Byrne, A. J., A. J. Sellen and J. G. Jones (1998). "Errors on anaesthetic record charts as a measure of anaesthetic performance during simulated critical incidents." Br J Anaesth **80**(1): 58-62.

Caine, R. M. and L. Ter-Bagdasarian (2003). "Early identification and management of critical incident stress." Crit Care Nurse **23**(1): 59-65.

Cao, Y., W. W. Tung, J. B. Gao, V. A. Protopopescu and L. M. Hively (2004). "Detecting dynamical changes in time series using the permutation entropy." Phys Rev E Stat Nonlin Soft Matter Phys **70**(4 Pt 2): 046217.

Clays, E., D. De Bacquer, V. Crasset, F. Kittel, P. de Smet, M. Kornitzer, R. Karasek and G. De Backer (2011). "The perception of work stressors is related to reduced parasympathetic activity." Int Arch Occup Environ Health **84**(2): 185-191.

Cohen, M. M., L. L. O'Brien-Pallas, C. Copplestone, R. Wall, J. Porter and D. K. Rose (1999). "Nursing workload associated with adverse events in the postanesthesia care unit." Anesthesiology **91**(6): 1882-1890.

Crewther, B. T., K. Shetty, D. Jarchi, S. Selvadurai, C. J. Cook, D. R. Leff, A. Darzi and G. Z. Yang (2015). "Skill acquisition and stress adaptations following laparoscopic surgery training and detraining in novice surgeons." Surg Endosc.

DeAnda, A. and D. M. Gaba (1991). "Role of experience in the response to simulated critical incidents." Anesthesia and Analgesia **72**(3): 308-315.

Elliot, A. J., V. Payen, J. Brisswalter, F. Cury and J. F. Thayer (2011). "A subtle threat cue, heart rate variability, and cognitive performance." Psychophysiology **48**(10): 1340-1345.

Feeney, S., K. O'Brien, N. O'Keeffe, A. N. Iomaire, M. E. Kelly, J. McCormack, G. McGuire and D. S. Evans (2016). "Practise what you preach: health behaviours and stress among non-consultant hospital doctors." Clin Med (Lond) **16**(1): 12-18.

Flannery, R. B., Jr. and G. S. Everly, Jr. (2000). "Crisis intervention: a review." Int J Emerg Ment Health **2**(2): 119-125.

Gaba, D. M., S. K. Howard and B. Jump (1994). "Production pressure in the work environment. California anesthesiologists' attitudes and experiences." Anesthesiology **81**(2): 488-500.

Gaba, D. M. and T. Lee (1990). "Measuring the workload of the anesthesiologist." Anesth Analg **71**(4): 354-361.

Galen (1997). The pulse for beginners. Galen: Selected Works. New York, Oxford University Press: 332.

Hansen, A. L., B. H. Johnsen and J. F. Thayer (2003). "Vagal influence on working memory and attention." International Journal of Psychophysiology **48**(3): 263-274.

Hansen, A. L., B. H. Johnsen and J. F. Thayer (2009). "Relationship between heart rate variability and cognitive function during threat of shock." Anxiety Stress & Coping **22**(1): 77-89.

Hart, S. G. and L. E. Staveland (1988). Development of NASA-TLX (Task Load Index): Results of Empirical and Theoretical Research. Advances in Psychology. A. H. Peter and M. Najmedin, North-Holland. **Volume 52:** 139-183.

Henelius, A., K. Hirvonen, A. Holm, J. Korpela and K. Muller (2009). "Mental workload classification using heart rate metrics." Conf Proc IEEE Eng Med Biol Soc **2009**: 1836-1839.

Hernandez-Gaytan, S. I., S. J. Rothenberg, P. Landsbergis, L. C. Becerril, G. De Leon-Leon, S. M. Collins and F. J. Diaz-Vasquez (2013). "Job strain and heart rate variability in resident physicians within a general hospital." Am J Ind Med **56**(1): 38-48.

Hjortskov, N., D. Rissén, A. Blangsted, N. Fallentin, U. Lundberg and K. Søgaard (2004). "The effect of mental stress on heart rate variability and blood pressure during computer work." European Journal of Applied Physiology **92**(1-2): 84-89.

Irwin, M., J. Thompson, C. Miller, J. C. Gillin and M. Ziegler (1999). "Effects of sleep and sleep deprivation on catecholamine and interleukin-2 levels in humans: clinical implications." J Clin Endocrinol Metab **84**(6): 1979-1985.

Johnstone, J. A., P. A. Ford, G. Hughes, T. Watson and A. T. Garrett (2012). "Bioharness(™) Multivariable Monitoring Device: Part. II: Reliability." Journal of Sports Science & Medicine **11**(3): 409-417.

Jordan, D., G. Stockmanns, E. F. Kochs, S. Pilge and G. Schneider (2008). "Electroencephalographic order pattern analysis for the separation of consciousness and unconsciousness: an analysis of approximate entropy, permutation entropy, recurrence rate, and phase coupling of order recurrence plots." Anesthesiology **109**(6): 1014-1022.

Jorna, P. G. (1992). "Spectral analysis of heart rate and psychological state: a review of its validity as a workload index." Biological Psychology **34**(2-3): 237-257.

Jorna, P. G. (1993). "Heart rate and workload variations in actual and simulated flight." Ergonomics **36**(9): 1043-1054.

Kalia, M. (2002). "Assessing the economic impact of stress--the modern day hidden epidemic." Metabolism **51**(6 Suppl 1): 49-53.

Kamath, M. V., D. N. Ghista, E. L. Fallen, D. Fitchett, D. Miller and R. McKelvie (1987). "Heart rate variability power spectrogram as a potential noninvasive signature of cardiac regulatory system response, mechanisms, and disorders." Heart Vessels **3**(1): 33-41.

Karhula, K., A. Henelius, M. Harma, M. Sallinen, H. Lindholm, M. Kivimaki, J. Vahtera and S. Puttonen (2014). "Job strain and vagal recovery during sleep in shift working health care professionals." Chronobiology International **31**(10): 1179-1189.

Kaufmann, T., S. Sutterlin, S. M. Schulz and C. Vogele (2011). "ARTiiFACT: a tool for heart rate artifact processing and heart rate variability analysis." Behavior Research Methods **43**(4): 1161-1170.

Kimhy, D., O. V. Crowley, P. S. McKinley, M. M. Burg, M. E. Lachman, P. A. Tun, C. D. Ryff, T. E. Seeman and R. P. Sloan (2013). "The association of cardiac vagal control and executive functioning--findings from the MIDUS study." Journal of Psychiatric Research **47**(5): 628-635.

Laborde, S., E. Mosley and J. F. Thayer (2017). "Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for

Experiment Planning, Data Analysis, and Data Reporting." Frontiers in Psychology **8**: 213.

Lahtinen, T. M., J. P. Koskelo, T. Laitinen and T. K. Leino (2007). "Heart rate and performance during combat missions in a flight simulator." Aviation, Space, and Environmental Medicine **78**(4): 387-391.

Lee, H. H., S. H. Lo, B. Y. Chen, Y. H. Lin, D. Chu, T. J. Cheng, P. C. Chen and Y. L. Guo (2016). "Increased night duty loading of physicians caused elevated blood pressure and sympathetic tones in a dose-dependent manner." Int Arch Occup Environ Health **89**(3): 413-423.

Lee, K. H., K. Yoon, M. Ha, J. Park, S. H. Cho and D. Kang (2010). "Heart rate variability and urinary catecholamines from job stress in korean male manufacturing workers according to work seniority." Ind Health **48**(3): 331-338.

Leedal, J. M. and A. F. Smith (2005). "Methodological approaches to anaesthetists' workload in the operating theatre." Br J Anaesth **94**(6): 702-709.

Levin, S., D. J. France, R. Hemphill, I. Jones, K. Y. Chen, D. Rickard, R. Makowski and D. Aronsky (2006). "Tracking workload in the emergency department." Hum Factors **48**(3): 526-539.

Lindqvist, A., E. Keskinen, K. Antila, L. Halkola, T. Peltonen and I. Valimaki (1983). "Heart rate variability, cardiac mechanics, and subjectively evaluated stress during simulator flight." Aviation, Space, and Environmental Medicine **54**(8): 685-690.

Litvack, D. A., T. F. Oberlander, L. H. Carney and J. P. Saul (1995). "Time and frequency domain methods for heart rate variability analysis: A methodological comparison." Psychophysiology **32**(5): 492-504.

Löllgen, H. (1999). "Herzfrequenzvariabilität." Deutsches Ärzteblatt **96**(31-32): A-2029-2032.

Luque-Casado, A., J. C. Perales, D. Cardenas and D. Sanabria (2016). "Heart rate variability and cognitive processing: The autonomic response to task demands." Biol Psychol **113**: 83-90.

Luque-Casado, A., M. Zabala, E. Morales, M. Mateo-March and D. Sanabria (2013). "Cognitive performance and heart rate variability: the influence of fitness level." PLoS One **8**(2): e56935.

Mansikka, H., P. Simola, K. Virtanen, D. Harris and L. Oksama (2016). "Fighter pilots' heart rate, heart rate variation and performance during instrument approaches." Ergonomics: 1-9.

Markwell, A. L. and Z. Wainer (2009). "The health and wellbeing of junior doctors: insights from a national survey." Med J Aust **191**(8): 441-444.

Marteau, T. M. and H. Bekker (1992). "The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI)." Br J Clin Psychol **31 (Pt 3)**: 301-306.

Martin, J., F. Schneider, A. Kowalewskij, D. Jordan, A. Hapfelmeier, E. F. Kochs, K. J. Wagner and C. M. Schulz (2016). "Linear and non-linear heart rate metrics for the assessment of anaesthetists' workload during general anaesthesia." British Journal of Anaesthesia **117**(6): 767-774.

McKinley, S. and M. Levine (1998). "Cubic spline interpolation." College of the Redwoods **45**(1): 1049-1060.

Pagani, M., G. Mazzuero, A. Ferrari, D. Liberati, S. Cerutti, D. Vaitl, L. Tavazzi and A. Malliani (1991). "Sympathovagal interaction during mental stress. A study using spectral analysis of heart rate variability in healthy control subjects and patients with a prior myocardial infarction." Circulation **83**(4 Suppl): Ii43-51.

Parsons, S. E., E. A. Carter, L. J. Waterhouse, A. Sarcevic, K. J. O'Connell and R. S. Burd (2012). "Assessment of workload during pediatric trauma resuscitation." J Trauma Acute Care Surg **73**(5): 1267-1272.

Porges, S. W. (2007). "The polyvagal perspective." Biological Psychology **74**(2): 116-143.

Porta, A., T. Gnecchi-Ruscone, E. Tobaldini, S. Guzzetti, R. Furlan and N. Montano (2007). "Progressive decrease of heart period variability entropy-based complexity during graded head-up tilt." Journal of Applied Physiology **103**(4): 1143-1149.

Quińones, M. A., J. K. Ford and M. S. Teachout (1995). "The relationship between work experience and job performance: a conceptual and meta-analytic review." Personnel Psychology **48**(4): 887-910.

Richman, J. S. and J. R. Moorman (2000). "Physiological time-series analysis using approximate entropy and sample entropy." Am J Physiol Heart Circ Physiol **278**(6): H2039-2049.

Rieger, A., R. Stoll, S. Kreuzfeld, K. Behrens and M. Weippert (2014). "Heart rate and heart rate variability as indirect markers of surgeons' intraoperative stress." Int Arch Occup Environ Health **87**(2): 165-174.

Sassi, R., S. Cerutti, F. Lombardi, M. Malik, H. V. Huikuri, C. K. Peng, G. Schmidt and Y. Yamamoto (2015). "Advances in heart rate variability signal analysis: joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society." Europace **17**(9): 1341-1353.

Schneider, F., J. Martin, A. Hapfelmeier, D. Jordan, G. Schneider and C. M. Schulz (2017). "The validity of linear and non-linear heart rate metrics as workload indicators of emergency physicians." PLOS ONE **12**(11): e0188635.

Schneider, F., J. Martin, M. Skrzypczak, D. Hinzmann, D. Jordan, K. J. Wagner and C. M. Schulz (2018). "Anesthetists' heart rate variability as an indicator of performance during induction of general anesthesia and simulated critical incidents: an observational study." Journal of Psychophysiology.

Schulz, C. M., E. Schneider, L. Fritz, J. Vockeroth, A. Hapfelmeier, M. Wasmaier, E. F. Kochs and G. Schneider (2011). "Eye tracking for assessment of workload: a pilot study in an anaesthesia simulator environment." Br J Anaesth **106**(1): 44-50.

Schulz, C. M., E. Schneider, S. Kohlbecher, A. Hapfelmeier, F. Heuser, K. J. Wagner, E. F. Kochs and G. Schneider (2014). "The influence of anaesthetists' experience on workload, performance and visual attention during simulated critical incidents." Journal of Clinical Monitoring and Computing **28**(5): 475-480.

Shahrestani, S., E. M. Stewart, D. S. Quintana, I. B. Hickie and A. J. Guastella (2015). "Heart rate variability during adolescent and adult social interactions: A meta-analysis." Biological Psychology **105**(0): 43-50.

Stein, P. K., P. P. Domitrovich, H. V. Huikuri and R. E. Kleiger (2005). "Traditional and nonlinear heart rate variability are each independently associated with mortality after myocardial infarction." Journal of Cardiovascular Electrophysiology **16**(1): 13-20.

Strohmaier, S., E. E. Devore, Y. Zhang and E. S. Schernhammer (2018). "A Review of Data of Findings on Night Shift Work and the Development of DM and CVD Events: a Synthesis of the Proposed Molecular Mechanisms." Curr Diab Rep **18**(12): 132.

Tarvainen, M. P., J. P. Niskanen, J. A. Lipponen, P. O. Ranta-Aho and P. A. Karjalainen (2014). "Kubios HRV--heart rate variability analysis software." Computer Methods and Programs in Biomedicine **113**(1): 210-220.

Tattersall, A. J. and G. R. Hockey (1995). "Level of operator control and changes in heart rate variability during simulated flight maintenance." Human Factors **37**(4): 682-698.

Thayer, J. F., A. L. Hansen, E. Saus-Rose and B. H. Johnsen (2009). "Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health." Annals of Behavioral Medicine **37**(2): 141-153.

Tobaldini, E., C. Cogliati, E. M. Fiorelli, V. Nunziata, M. A. Wu, M. Prado, M. Bevilacqua, D. Trabattoni, A. Porta and N. Montano (2013). "One night on-call: sleep deprivation affects cardiac autonomic control and inflammation in physicians." Eur J Intern Med **24**(7): 664-670.

Tyssen, R. (2007). "Health problems and the use of health services among physicians: a review article with particular emphasis on Norwegian studies." Ind Health **45**(5): 599-610.

Veltman, J. A. and A. W. K. Gaillard (1996). "Physiological indices of workload in a simulated flight task." Biological Psychology **42**(3): 323-342.

Weinger, M. B., O. W. Herndon, M. H. Zornow, M. P. Paulus, D. M. Gaba and L. T. Dallen (1994). "An objective methodology for task analysis and workload assessment in anesthesia providers." Anesthesiology **80**(1): 77-92.

Weinger, M. B., S. B. Reddy and J. M. Slagle (2004). "Multiple measures of anesthesia workload during teaching and nonteaching cases." Anesth Analg **98**(5): 1419-1425, table of contents.

Weinger, M. B. and J. Slagle (2002). "Human Factors Research in Anesthesia Patient Safety." Techniques to Elucidate Factors Affecting Clinical Task Performance and Decision Making **9**(Supplement 6): S58-S63.

Wilson, G. F. (1992). "Applied use of cardiac and respiration measures: practical considerations and precautions." Biological Psychology **34**(2-3): 163-178.

Wong, I. S., A. S. Ostry, P. A. Demers and H. W. Davies (2012). "Job strain and shift work influences on biomarkers and subclinical heart disease indicators: a pilot study." J Occup Environ Hyg **9**(8): 467-477.

CURRICULUM VITAE

Frederick Schneider, geboren am 11.08.1992 in München.

Bildung

10/1999 - 07/2011	Grundschule Egmating-Oberpframmern und Gymnasium Ottobrunn
01.07.2011	Allgemeine Hochschulreife
10/2011 - 07/2013	Ludwig-Maximilians-Universität München, Humanmedizin
23.09.2013	Erster Abschnitt der ärztlichen Prüfung
10/2013 - 11/2017	Technische Universität München - Klinikum rechts der Isar, Humanmedizin
13.10.2016	Zweiter Abschnitt der ärztlichen Prüfung)
11/2016 - 10/2017	Student im Praktischen Jahr:
	Klinikum rechts der Isar (Kinderchirurgie), München
	The Royal London Hospital (Trauma Surgery), London
	Schulthess Klinik (Orthopädie), Zürich
	Rotkreuzklinikum (Innere Medizin), München
13.11.2017	Dritter Abschnitt der ärztlichen Prüfung
22.11.2017	Approbation als Arzt

Berufserfahrung

10/2014 - 11/2015	Studentische Hilfskraft beim Giftnotruf München (Abteilung für Klinische Toxikologie und Giftnotruf München, 2. Medizinischen Klinik, Universitätsklinikum rechts der Isar, München)
seit 01/2018	Assistenzarzt, Klinik für Anästhesiologie und Intensivmedizin (Univ. Prof. Dr. Gerhard Schneider), Klinikum rechts der Isar der Technischen Universität München, München

Mitgliedschaften

Deutsche Gesellschaft für Berg- und Expeditionsmedizin (BExMed)

Berufsverband Deutscher Anästhesisten (BDA)

Deutsche Gesellschaft für Anästhesie und Intensivemdizin (DGAI)