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I. Medizinische Klinik und Poliklinik

Klinikum rechts der Isar

Risk prediction after myocardial infarction by cyclic variation of heart rate, a surrogate of sleep-disordered breathing assessed from Holter ECGs.

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Abstract

Aims

Ischemic cardiovascular diseases are becoming the leading cause of death and disability all over the word. Sleep-disordered breathing (SDB) is documentarily common among cardiac patients. However, its role as an independent risk predictor after myocardial infarction (MI) is unclear. SDB was proved to be associated with cyclic variation of heart rate (CVHR), and can be detected from Holter recordings with a positive and negative predictive accuracy of 86% and 100%, respectively. The aim of this study was to apply this detection algorithm to Holter recordings from a large cohort of survivors of acute MI to assess the value of SDB and CVHR for mortality prediction after acute MI.

Method

1590 survivors of acute MI in sinus rhythm were prospectively enrolled and followed for 5-year all-cause mortality. Standard Holter ECGs were recorded at a median of 5 days after MI. Heart rate (HR) tachograms were generated from nocturnal (00:00-06.00 am) segments and analyzed using a previously-described and validated algorithm. Briefly, CVHR was defined as ≥3 successive HR increases (arousals) of at least 6 bpm and at least 10 seconds duration, with ≤2 min between two successive arousals. According to a pre-specified cutpoint, SDB was assumed if CVHR was

present >20% of the recording.

Results

77 patients (4.8%) had flat HR tachograms which prohibited analysis for SDB. Of the remaining 1513 patients, 584 (38.6%) were classified as having SDB. Mortality rates in groups stratified according to ECG-derived SDB did not differ significantly. Taken as a continuous variable, low CVHR duration was associated with increased mortality.

The mortality of patients with flat HR tachograms was significantly increased, even after adjustment for age, sex, LVEF, GRACE score and diabetes mellitus. Mortality prediction by a flat HR tachogram was also independent of heart rate variability, heart rate turbulence, and deceleration capacity.

Conclusion

In Holter ECG recordings of survivors of acute MI, signs suggestive of SDB were frequently present, however, this specific pattern is not associated with altered mortality rate. A flat nocturnal HR tachogram was a strong, independent predictor of 5-year all-cause mortality. Low CVHR duration-as a continuous variable-was also associated with increased mortality.

Zusammenfassung

Ziele

Ischämische Herz-Kreislauf-Erkrankungen werden weltweit zur Hauptursache für Tod und Behinderung. Schlafbezogene Atemstörungen (*sleep-disordered breathing,* SDB) treten bei Herzpatienten bekanntermaßen auf. Ihre Rolle als unabhängiger Risikoprädiktor nach Myokardinfarkt (MI) ist jedoch unklar. Es wurde nachgewiesen, dass SDB mit der zyklischen Variation der Herzfrequenz (*cyclic variation of heart rate,* CVHR) in Zusammenhang steht und mit Holter-Aufzeichnungen mit einer positiven und negativen Vorhersagegenauigkeit von 86% bzw. 100% detektiert werden kann. Das Ziel dieser Studie war es, diesen Detektionsalgorithmus auf Holter-Aufzeichnungen einer großen Gruppe von Überlebenden akuter MI anzuwenden, um den Wert von SDB und CVHR für die Mortalitätsvorhersage nach akutem MI zu bestimmen.

Methode

1590 Überlebende eines a kuten MI im Sinusrhythmus wurden prospektiv eingeschlossen und in Bezug auf die 5-jährige Gesamtmortalität verfolgt. Standard-Holter-EKGs wurden im Mittel 5 Tage nach MI aufgezeichnet. Herzfrequenz- (*heart rate,* HR) -Tachogramme wurden aus nächtlichen Segmenten (00: 00-06.00 Uhr) erstellt und unter Verwendung eines zuvor beschriebenen und

validierten Algorithmus analysiert. CVHR wurde definiert als ≥3 aufeinanderfolgende HR-Erhöhungen (Arousals) von mindestens 6 Schlägen pro Minute und einer Dauer von mindestens 10 Sekunden, wobei zwischen zwei aufeinanderfolgenden Arousals ≤2 min liegen mussten. Gemäß einer zuvor festgelegten Dichotomie wurde SDB angenommen, wenn CVHR in > 20% der Aufzeichnung vorhanden war.

Ergebnisse

77 Patienten (4,8%) hatten flache HR-Tachogramme, die eine Analyse in Hinblick auf auf SDB unmöglich machten. Von den verbleibenden 1513 Patienten wurden 584 (38,6%) als SDB klassifiziert. Die Mortalitätsraten in nach EKG-detektierter SDB stratifizierten Gruppen unterschieden sich nicht signifikant. Als kontinuierliche Variable ausgedrückt war eine niedrige CVHR-Dauer mit einer erhöhten Mortalität assoziiert.

Die Mortalität von Patienten mit flachen HR-Tachogrammen war signifikant erhöht, auch nach Adjustierung für Alter, Geschlecht, LVEF, GRACE-Score und Diabetes mellitus. Die Mortalitätsvorhersage durch ein flaches HR-Tachogramm war auch unabhängig von Herzfrequenzvariabilität, *Heart rate turbulence* und *Deceleration capacity*.

Fazit

In den Holter-EKG-Aufzeichnungen von Überlebenden eines akuten MI

traten häufig Anzeichen für SDB auf. Dieses spezifische Muster stand jedoch nicht im Zusammenhang mit einer veränderten Mortalitätsrate. Ein flaches nächtliches HR-Tachogramm war ein starker, unabhängiger Prädiktor der 5-Jahres-Gesamtmortalität. Eine niedrige CVHR-Dauer - als kontinuierliche Variable - war ebenfalls mit einer erhöhten Mortalität verbunden.

Table of contents

Abbreviations

MI	Myocardial infarction
CAD	Coronary artery disease
EMS	Emergency medical service
SDB	Sleep-disordered breathing
CVHR	Cyclic variation of heart rate
ECGs	Eletrocardiograms
ICD	Implantable cardioverter-defibrillator
HR	Heart rate
HRV	Heart rate variability
SDNN	Standard deviation of normal-to-normal intervals
SDANN	Standard deviation of the 5 minute average NN intervals
RMSSD	root mean square of successive differences
pNN50	Percentage of successive RR intervals that differ by more than 50 ms
SAF	Severe autonomic failure
HRT	Heart rate turbulence
DC	Cardiac deceleration capacity

LVEF	Left ventricular ejection fraction
NRR	Mean nocturnal respiratory rate
GRACE Score	Global Registry of Acute Coronary Events score
OSA	Obstructive sleep apnea
CSA	Central sleep apnea
PLM	Periodic limb movements
Acv	Amplitude of CVHR
BPM	Beats per minute
IQR	Interquartile range
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass grafting
CKmax	Maximal creatine kinase plasma concentration
TAVI	Transcatheter aortic valve implantation
TMVI	Transcatheter mitral valve implantation
AHI	Apnea – hypopnea Index

Part 1 Introduction

1.1 Post-MI and risk stratification

Ischemic vascular diseases are becoming the leading cause of death and disability all over the world (Thom T et al. 2006). Myocardial infarction (MI), characterized by the presence of myocardial ischemia, death of cardiomyocytes and problems of vascular structures due to the occlusion of a coronary artery, may mostly occur due to coronary artery disease (Stanley D et al. 2010). As the comprehensive management of patients with MI is continually improved, if the symptoms of MI of patients can be recognized early, with the activation of the emergency medical service (EMS) system for the life-saving intervention, the morbidity and mortality from MI can be largely decreased. However, after the strike of MI, re-infraction, arrhythmias, or progressive heart failure (Stanley D et al. 2010, Reed GW et al. 2017) still can menace the recovery of survivors from MI. Therefore, cardiac rehabilitation and subsequent therapy are still of great significance to suppress the death rate after MI. And before that, identification and selection of high-risk survivors of MI is a prerequisite for subsequent prophylactic therapy. Whereas the present prognostic evaluation is far from perfect, more research is thus still needed for novel risk markers complementary to currently applied risk scores, for saving more medical resources and avoiding unnecessary therapies (Malik

M et al. 2011). Current approaches to assess the mortality risk of these patients include clinical scores (e.g. GRACE risk score) (Eagle KA et al. 2004), screening for co-morbidities (e.g. diabetes mellitus (Akirov A et al. 2016), renal impairment (Smith GL et al. 2008)), measurement of the left-ventricular ejection fraction (LVEF) (Dagres N et al. 2013), or evaluation for parameters of cardiac electric instability or cardiac autonomic dysfunction (e.g. heart rate variability (HRV) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996), heart rate turbulence (HRT) (Schmidt G et al. 1999), deceleration capacity of heart rate (DC) (Bauer A et al. 2006), or severe autonomic failure (SAF, a combination of abnormal HRT and abnormal DC) (Bauer A et al. 2009). Cardiac autonomic descriptors, due to their simplicity, practicality and non-invasiveness, have a great potential scientific value in mortality risk prediction. Such parameters may be helpful for risk stratification in different types of heart disease, e.g,. MI, heart failure and cardiac channelopathies such as catecholaminergic polymorphic ventricular tachycardia, congenital long QT syndrome, Brugada syndrome, etc. (Schmidt G et al. 2017, Malik M et al. 2017, Lopshire JC et al. 2012, Singh JP et al.2014)

1.2 Respiration-related autonomic function

Recently, several parameters related to respiration such as the respiratory rate (Barthel P et al. 2013) (which can be also measured from Holter ECG recordings as the nocturnal respiratory rate) (Dommasch M et al. 2014, Sinnecker D et al. 2014) or respiratory sinus arrhythmia (Sinnecker D et al. 2016) have been demonstrated to be strong predictors of the mortality risk of MI survivors.

Beside the respiration rate, sleep-disordered breathing (SDB), characterized by pauses in breathing or periods of shallow breathing during sleep, often disrupting the normal sleep and making the patients experience sleepiness and tiredness in the day-time, has been reported to be an important risk factor for cardiovascular events such as MI (Marin JM et al. 2005), and is frequently found in MI survivors (Porto F et al. 2017). The question whether the presence of sleep-disordered breathing in survivors of acute MI bears implications for the patients' prognosis has been so far investigated in some small clinical studies, with conflicting results (Shah N et al. 2013, Ludka O et al. 2017). It has been recognized that SDB is accompanied by a typical pattern of heart rate decelerations (during apnea episodes) followed by accelerations (during arousals) which has been termed cyclic variation of heart rate (CVHR) (Guilleminault C et al. 1984), and proprietary algorithms to assess the likelihood of SDB from standard Holter ECG recordings have been implemented into Holter

analysis equipment from various companies. Interestingly, a simple method to manually score RR interval tachograms generated from ECG recordings obtained during polysomnography for the presence of CVHR (Stein PK et al. 2003) was able to predict the presence or absence of SDB (as assessed by standard polysomnography) with a positive and negative predictive accuracy of 86% and 100%, respectively.

Hence, the aim of this work was to assess whether CVHR, assessed with the mentioned method (Stein PK et al. 2003) from nocturnal Holter ECG recordings in a large cohort of post-infarction patients, bears prognostic information, and, if so, whether the previously-described association of an increased nocturnal respiratory rate with an increased risk of non-sudden cardiac death (Dommasch M et al. 2014) is related to sleep-disordered breathing.

Part 2 Materials and Methods

2.1 Study cohort

The study is a retrospective analysis of a previously-described prospective cohort study (Bauer A et al. 2009, Dommasch M et al. 2014, Sinnecker D et al. 2014) aimed at assessing risk predictors of subsequent mortality in survivors of the acute phase of myocardial infarction. Patients admitted with acute MI at one of two centers (German Heart Centre and Klinikum rechts der Isar, both in Munich, Germany) were enrolled between May 2000 and March 2005. Inclusion criteria were (i) age ≤80 years, (ii) sinus rhythm at admission, (iii) MI within 4 weeks before enrollment, (iv) survival until hospital discharge, (v) no indication for ICD implantation for secondary prophylaxis at the time of enrolment. Diagnosis of acute MI required two or more findings of: (i) chest pain for ≥20 min, (ii) creatine kinase more than twice the upper limit of normal, (iii) and ST-segment elevation ≥0.1 mV in two or more limb leads or ≥ 0.2 mV in two or more contiguous precordial leads on admission. All study subjects underwent Holter ECG recordings during the first days after MI. Patients were followed-up for all-cause mortality for five years. The study was approved by the local ethics committee, and informed consent was obtained from all participants.

2.2 ECG analysis

24h Holter ECG recordings (Oxford Excel Holter system, Oxford instruments; Pathfinder 700, Reynolds Medical; and Mortara Holter system, Mortara Instrument) were performed on the survivors of of acute MI. In order to study the risk-predicting potential of SDB, and meanwhile, to minimize the influences of physical activity and external interference on respiratory movement, only the hours between midnight and 6 am were used for the measurement. The Holter ECGs were recorded at a median of 5 days (IQR: 4-7 days) when the patients were stabilized after the acute MI phase, with a median recording period of 21h (IQR 19-23h) (Bauer A et al. 2009, Barthel P et al. 2013, Dommasch M et al. 2014, Sinnecker D et al. 2014).

2.3 Assessment of Cyclic Variation of Heart Rate (CVHR) indicating SDB

SDB was assessed from the Holter ECGs using a previously-published and validated algorithm (Stein PK et al. 2003). Analysis was restricted to the above-described nocturnal six-hour segments of the recordings. A custom-written analysis software plotted the instantaneous heart rate (i.e. the inverse of normal-to-normal R-R intervals) to a computer screen, on which CVHR episodes were manually marked and stored in a database.

As previously described (Stein PK et al. 2003), some patients had a flat HR tachogram, defined as no visible respiratory sinus arrhythmia and no instantaneous heart rate changes of ≥5 beats/min (Figure 1). In those patients, it is not possible to obtain information on the presence of SDB from ECG recordings (Stein PK et al. 2003). Consequently, we assessed for every study subject whether a flat tachogram according to the above definition was present (see Figure 1).

Recordings with a non-flat tachogram were evaluated for episodes of CVHR, which were defined as previously described (Stein PK et al. 2003) as ECG segments containing ≥3 successive HR increases (arousals) of at least 6 bpm and at least 10 seconds duration, with ≤2 min between two successive arousals. According to the pre-specified cutpoint, SDB was assumed if CVHR episodes were present in ≥20% of the recording, i.e. ≥ 72 minutes of the nocturnal 6-hour segment.

2.4 Mean nocturnal respiratory rate (NRR)

NRR was automatically derived from Holter recordings by a previously-described algorithm (Dommasch M et al. 2014, Sinnecker D et al. 2014) analyzing beat-to-beat changes in QRS amplitudes, QRS vectors, and RR intervals.

2.5 Severe autonomic failure (SAF)

According to a previous report (Bauer A et al. 2009), SAF was defined as the combination of both abnormal Heart Rate Turbulence (HRT) (slope <2.5 ms/RR and onset >0%) and abnormal cardiac Deceleration Capacity (DC) (<4.5 ms).

2.6 Left-ventricular ejection fraction

Left-ventricular ejection fraction (LVEF) was measured within 2 weeks after MI by angiography or biplane echocardiography (Sono 5500, Hewlett Packard) based on Simpson's method.

2.7 GRACE score

The clinical GRACE score to predict the long-term mortality risk was calculated based on age, history of past heart failure and MI, serum creatinine and the cardiac biomarker status at admission, pulse and systolic blood pressure at admission, ST segment deviation and in-hospital percutaneous coronary intervention as described previously (Eagle KA et al. 2004).

2.8 Endpoint of the study

The primary endpoint was all-cause mortality within five years after index MI. Follow-up was conducted with clinical appointments every 6 months. Participants who missed these appointments were contacted by

letter, telephone, or through their General Practitioner. If necessary, the local population registry was contacted to obtain the new address in case participants changed residence, or to confirm death in case participants deceased.

2.9 Statistical analysis

Continuous variables are presented as median and inter-quartile range (IQR), and categorical data are presented as frequency and percentage.

The linear correlation of two sets of data points was assessed by Pearson correlation coefficient. Survival curves were generated using the Kaplan-Meier method and compared with the log-rank test. Univariable or multivariable Cox analysis was performed to calculate hazard ratios (with 95% confidence intervals) for 5-year all-cause mortality.

R 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical calculations. Differences were considered statistically significant if $P<0.05$.

Part 3 Results

3.1 Selection and Clinical characteristics of patients

1590 patients hospitalized for acute MI met the inclusion criteria and were included in the analysis. Out of these, 1513 patients had a "non-flat tachogram", i.e. it was possible to score the heart rate tachogram for SDB-related CVHR (**Figure 1**). Of these patients, 584 had CVHR episodes in ≥ 72 minutes of the analyzed 6-hour segment, indicating presence of SDB, while 929 were classified as not having SDB. The remaining 77 patients showed a "flat tachogram" (see **Figure 1**).

The clinical and demographic characteristics of patients with "flat" and "non-flat" HR tachograms are shown in **Table 1**. Patients with a "flat tachogram" were older, more often female, had a higher GRACE score, a lower LVEF, and a higher prevalence of diabetes mellitus. The first part of the Results section will focus on the patients with a "non-flat tachogram" to assess the prognostic implications of Holter-derived screening for SDB. The second part will investigate the prognostic implications of a "flat tachogram".

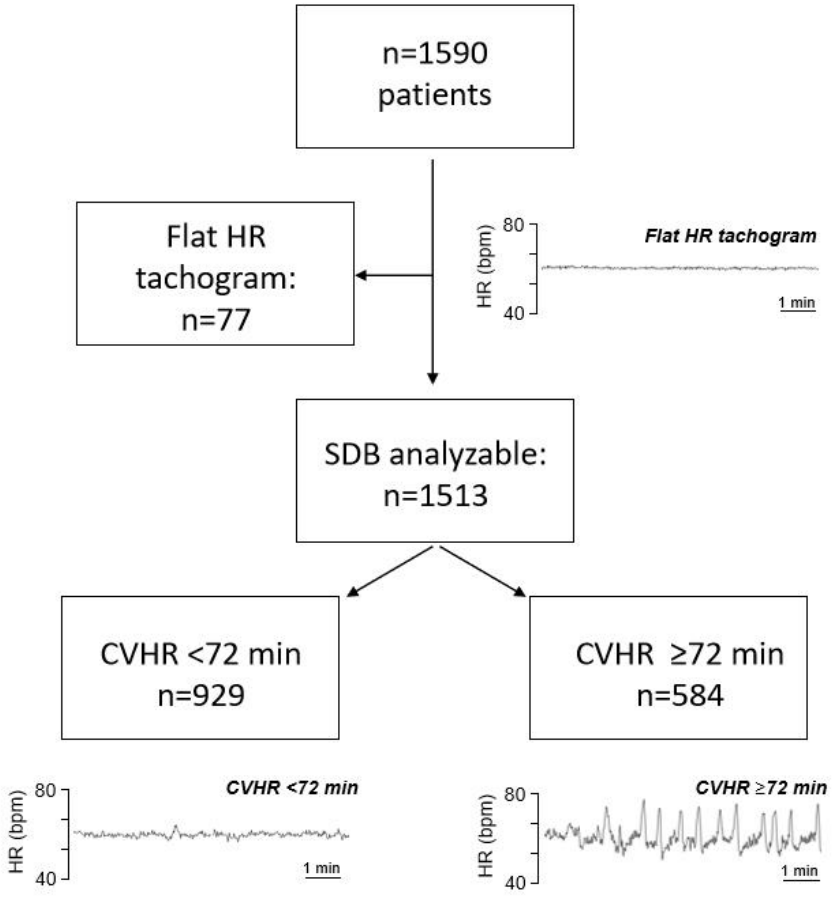


Figure 1: Patient flow chart. Typical Examples of nocturnal HR tachogram segments from patients with a flat tachogram, with CVHR<72 min, and with CVHR ≥72 min are shown as indicated. HR, heart rate; bpm, beats per minute; SDB, sleep-disordered breathing; CVHR, cyclic variation of heart rate.

Table 1: Baseline Characteristics

Variable	All patients (n=1590)	"non-flat tachogram" (n=1513)	"flat tachogram"(n=77)	P value ("flat" vs."non-flat" tachogram)	"non-flat tachogram"		P value (CVHR <72min vs. CVHR ≥72 min)
					CVHR<72 min (n=929)	CVHR≥72 min (n=584)	
Age (median [IQR])	59.2 [51.6–66.8]	58.6 [51.2–66.3]	67.2 [59.7–73.3]	<0.001	60.3 (54.0–67.7)	55.9 (48.5–64.1)	<0.001
Females, n (%)	327 (20.6)	302 (20.0)	25 (32.5)	0.012	216 (23.3)	86 (14.7)	<0.001
Acute Intervention,n (%)				0.051			0.47
PCI	1451	1384	67		840	544	
	(91.3)	(91.5)	(78.0)		(90.4)	(93.2)	
CABG	33 (2.1)	30 (2.0)	3 (3.9)		22 (2.4)	8 (1.4)	
Thrombolysis	54 (3.4)	53 (3.5)	1 (1.3)		37 (4.0)	16 (2.7)	
None	52 (3.3)	46 (3.0)	6 (7.8)		30 (3.2)	16 (2.7)	
Diabetes mellitus, n (%)	270 (17)	249 (16.2)	32 (41.6)	<0.001	158 (17.0)	80 (13.7)	0.099
LVEF (median [IQR])	55 [45–63]	55 [45–63]	48 [39–57]	<0.001	55 [45–63]	56 [46–63]	0.836
GRACE Score (mean (sd))	96 (80–113)	96 (79–112)	114 (103–125)	<0.001	99 (82–113)	90 (75–108)	<0.001
CK_{max}, U/l (median [IQR])	1140 [569–2478]	1140 [569–2478]	1082 [566–2420]	0.856	1110 [560–2429]	1200 [586–2518]	0.33
Creatinine, mg/dl (median [IQR])	1.1 [0.9–1.3]	1.1 [0.9–1.3]	1.2 [1.0–1.5]	0.002	1.1 [1.0–1.3]	1.1 [0.9–1.2]	0.019

IQR, inter-quartile range; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left-ventricular ejection fraction; GRACE, Global Registry of Acute Coronary Events; CKmax, maximal creatine kinase plasma concentration

3.2 Patients with a "non-flat tachogram"

CVHR ≥72 minutes, indicating presence of SDB, was found in 584/1513 patients (38.6%). Compared to the group with <72 minutes of CVHR, indicating absence of SDB, these patients were younger, more often male, and had a significantly lower GRACE score, whereas no significant differences were present regarding other risk factors (**Table 1**). Five-year all-cause mortality did not differ significantly between these two groups (**Figure 2**).

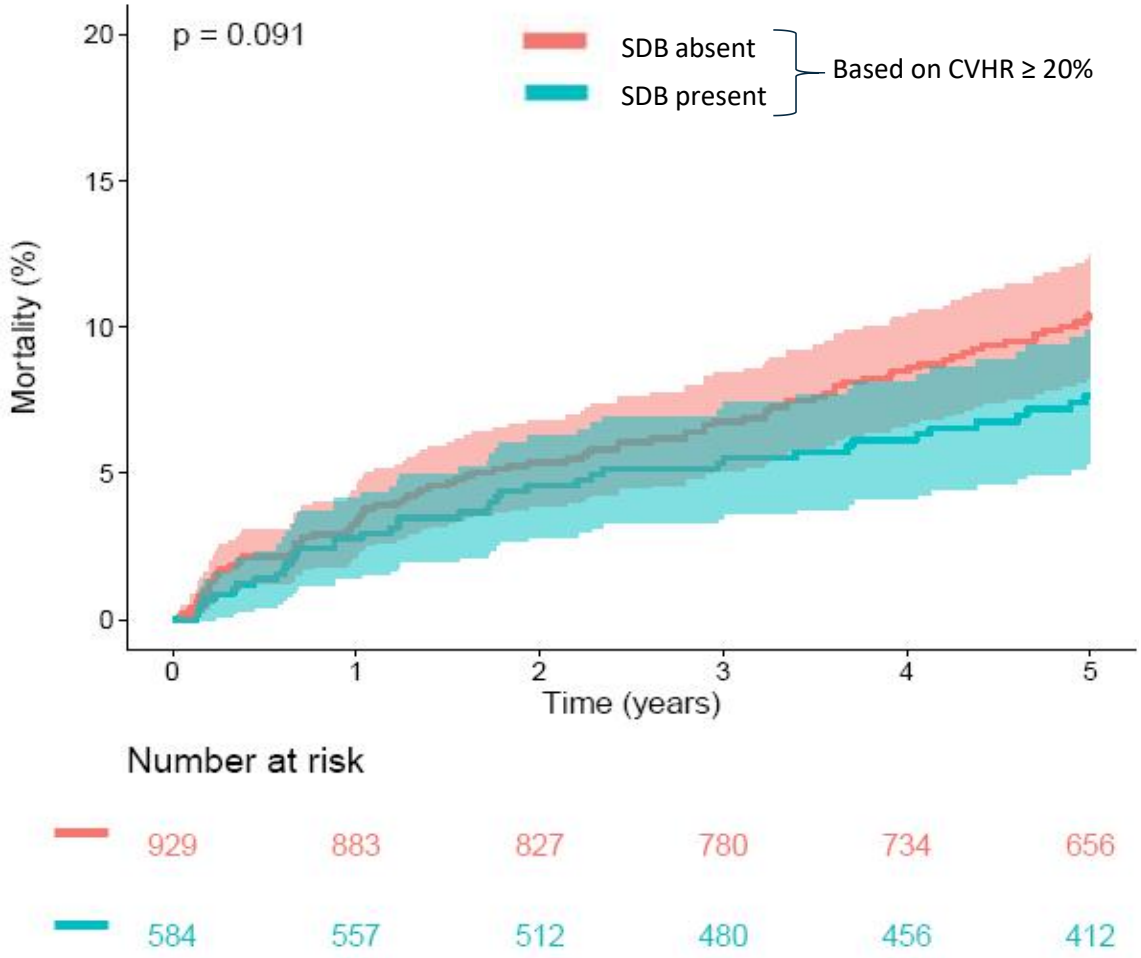
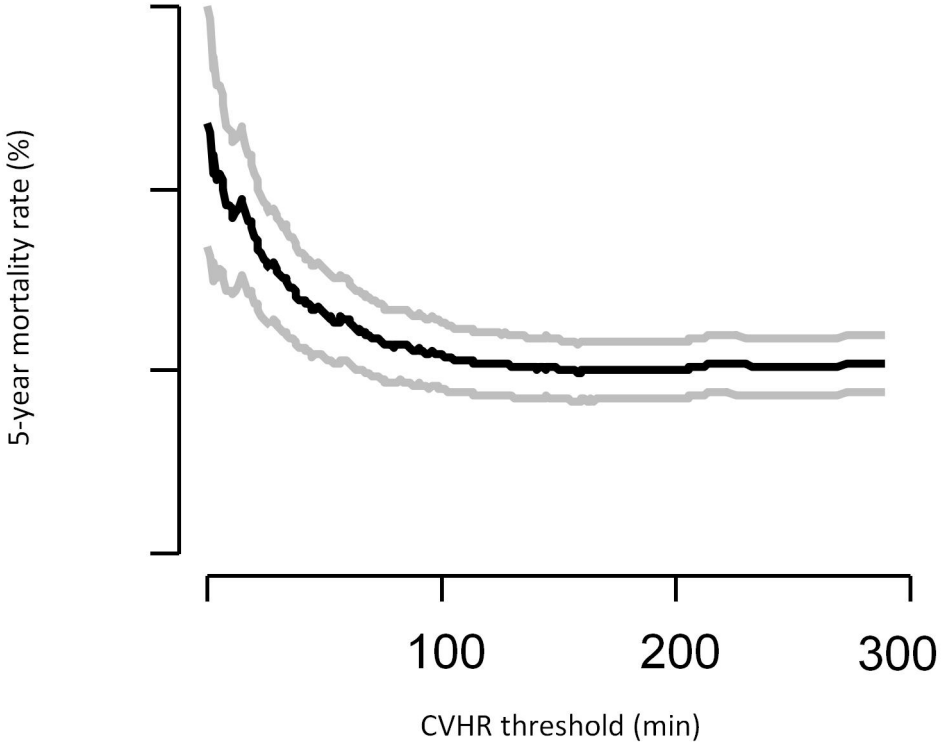
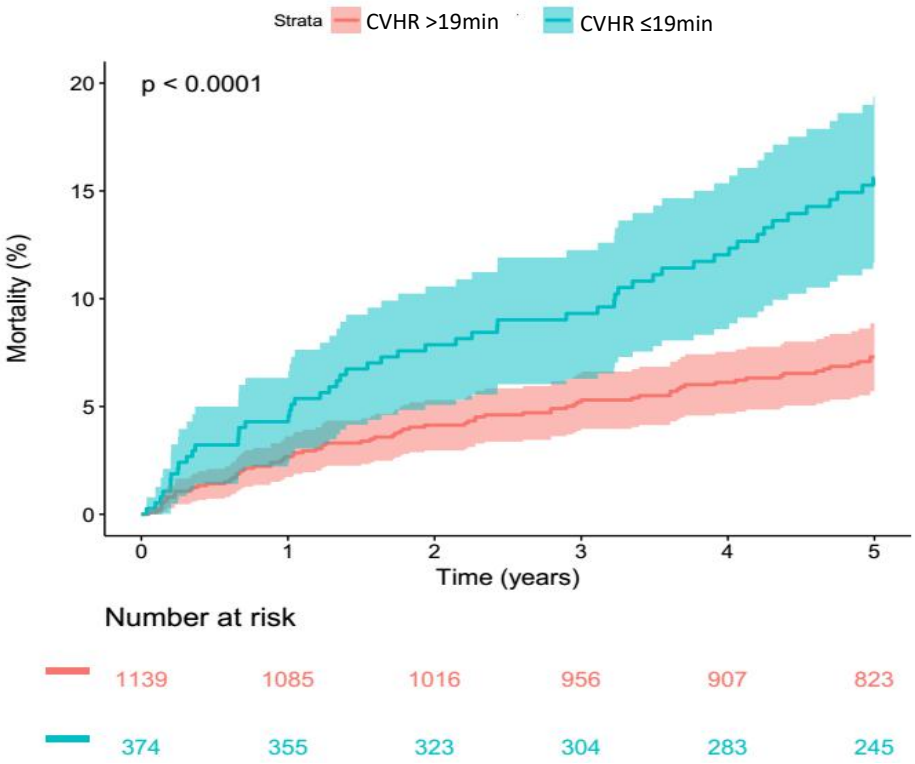


Figure 2: Survival in patients stratified according to CVHR. Kaplan-Meier curves along with 95% confidence intervals are shown for patients with CVHR <72 min ("SDB absent") and ≥72 min ("SDB present"). The numbers of patients at risk in the respective groups are shown below the graph. CVHR, cyclic variation of heart rate; SDB, sleep-disordered breathing.

As an exploratory analysis, we investigated the effect of the overall duration of CVHR episodes, treated as a continuous variable, on 5-year mortality **(Figure 3a)**. Interestingly, very short CVHR durations, markedly below the threshold of 72 minutes that indicates absence of sleep apnea, were associated with substantially increased mortality rates (see **Figure 3b**). In our patients, the optimum threshold for mortality prediction was CVHR ≤19 minutes within the 6-hour segment.


5-year mortality rate (%)
100
200
300
CVHR threshold (min)

(a)


Strata
CVHR >19min
CVHR ≤19min
p < 0.0001
Mortality (%)
20
15
10
5
0
0
1
2
3
4
5
Time (years)
Number at risk
1139
1085
1016
956
907
823
374
355
323
304
283
245

(b)

Figure 3: (a) Continuous association of CVHR with mortality. The 5-year mortality rate (black curve) estimated by the Kaplan-Meier method in patients with a non-flat tachogram with a CVHR duration less than or equal to a certain threshold are plotted as a function of this threshold. Grey curves show 95% confidence limits of the mortality estimate.

(b) Significant association between optimal cutpoint CVHR ≤19 minutes within the 6-hour segment and 5-year mortality. The optimal cutpoint with regard to risk stratification would be rather ≤19 minutes within the 6-hour segment. Using the optimal cutpoint, cumulative Kaplan-Meier curves for the patients with “non-flat tachograms” was present. The number of survival patients of individual groups analyzed at the year of 0,1,2,3,4 and 5 year are respectively shown below the graph.

There was no substantial correlation between continuous CVHR duration and the nocturnal respiratory rate (NRR) determined from the identical segment of the ECG recording (**Figure 4**; correlation coefficient -0.068). In multivariable Cox regression, NRR (hazard ratio 3.1; p=<0.0001), but not CVHR (hazard ratio 0.99; p=0.31) was a significant mortality predictor in our cohort.

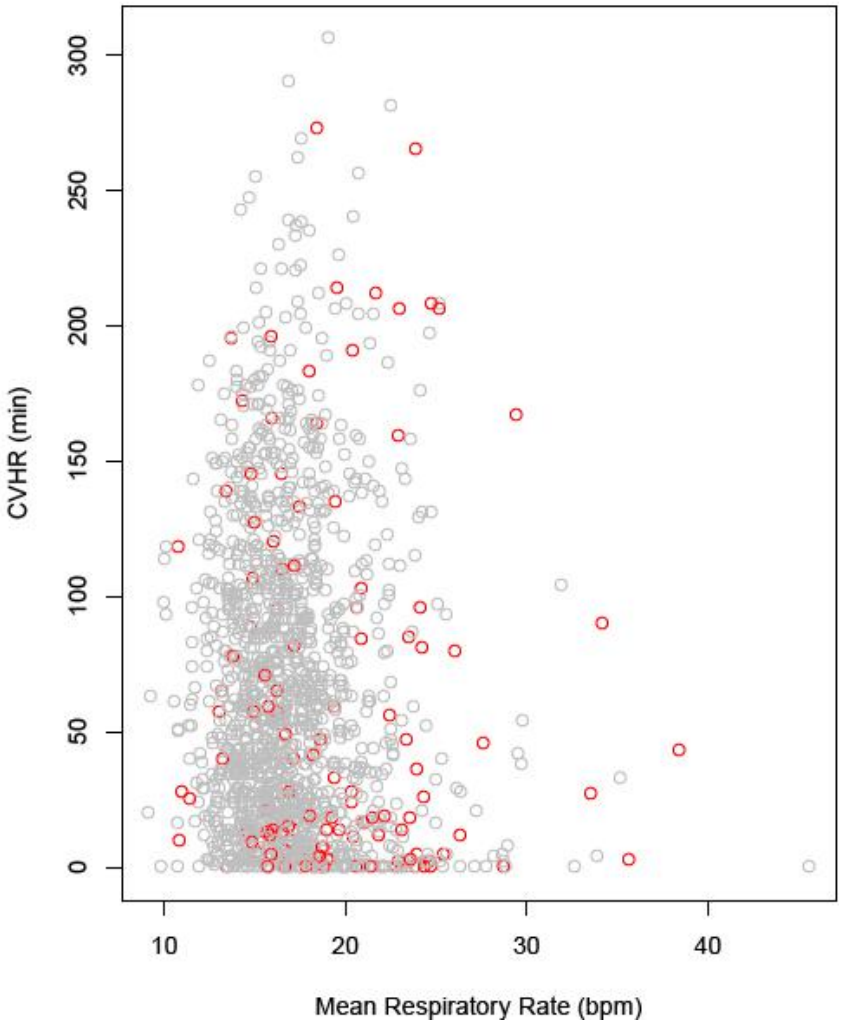


Figure 4: Correlation between nocturnal CVHR and respiratory rate. CVHR is expressed as the number of minutes with CVHR within the nocturnal 6-hour segment, respiratory rate as the mean value over the same segment. Data points from patients who were alive at 5 years are printed in grey, data points from deceased patients in red. CVHR, cyclic variation of heart rate; bpm, breaths per minute.

3.3 Patients with a “flat tachogram”

A comparison of the mortality rates in patients with a “flat tachogram” and in the remaining patients revealed that a “flat tachogram” identifies a high-risk population with a substantially increased 5-year mortality rate (29.1% (95% CI 17.7–38.9) vs. 9.4% (95% CI 7.8–10.9); p<0.0001; **Figure 5**). This may be partly explained by the above-mentioned differences in baseline risk factors. However, in multivariable Cox analysis considering also age, sex, LVEF, GRACE score and diabetes mellitus, a “flat tachogram” was independently associated with mortality with a hazard ratio of 1.7 (p=0.023) (**Table 2**).

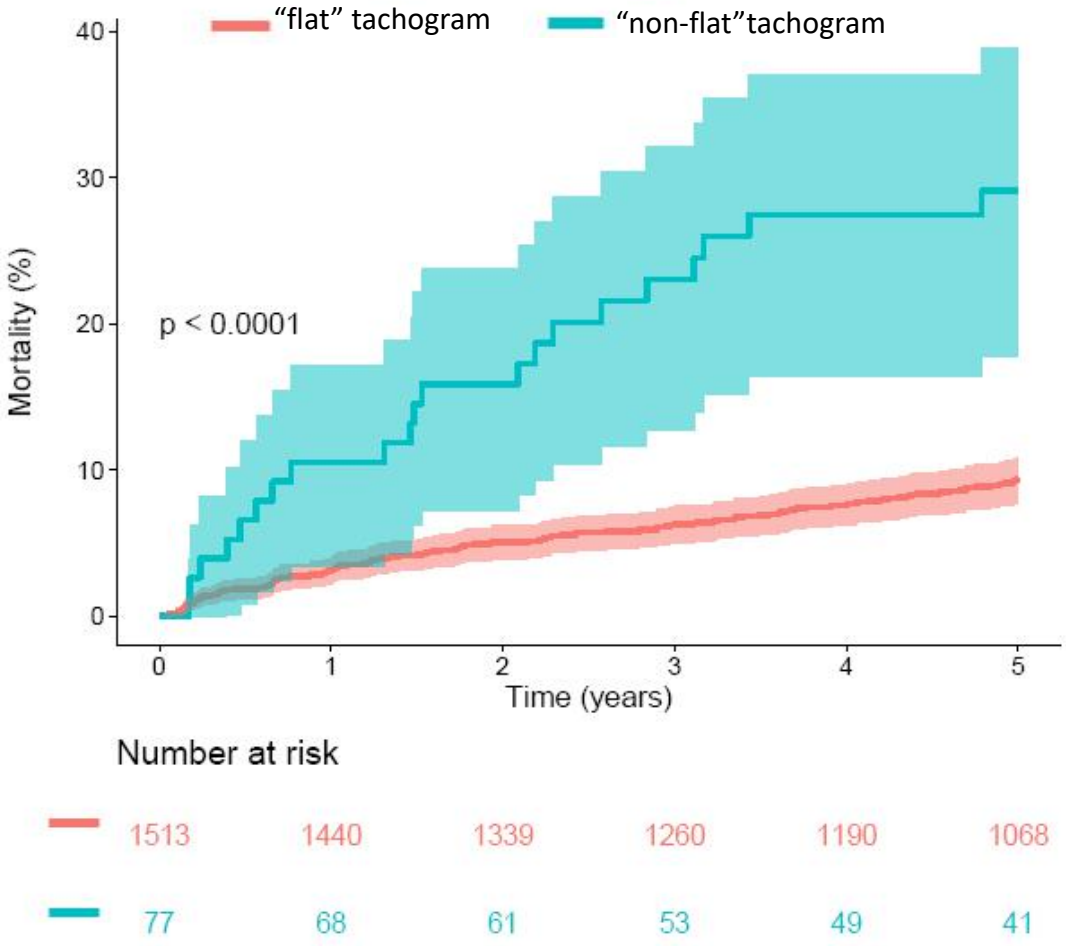


Figure 5: Survival in patients stratified according to presence or absence of a flat heart rate tachogram. Kaplan-Meier curves along with 95% confidence intervals are shown. The numbers of patients at risk in the respective groups are shown below the graph. CVHR, cyclic variation of heart rate; SDB, sleep-disordered breathing.

Table 2: multivariable Cox analysis

Variable	Hazard ratio (95% CI)	P value
Flat HR tachogram	1.73 (1.08-2.78)	0.022
Age (per year)	1.06 (1.03-1.08)	<0.0001
Female sex	0.98 (0.67-1.44)	0.92
LVEF (per %)	0.95 (0.93-0.96)	<0.0001
GRACE score (per point)	1.004 (0.99-1.01)	0.47
Diabetes mellitus	1.66 (1.17-2.35)	0.005

HR, heart rate; LVEF, left-ventricular ejection fraction; GRACE, Global Registry of Coronary Events.

A “flat tachogram” can be considered indicative of a markedly-reduced heart rate variability (HRV). Since it is well-known that reduced HRV signifies an increased risk in cardiac patients, we tested whether the prognostic information provided by the presence of a “flat tachogram” is independent of classical HRV parameters (SDNN, SDANN, rmssd, pNN50) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996). Indeed, in a multivariable Cox model incorporating all these parameters, presence of a “flat tachogram” remained a significant mortality predictor with a hazard ratio of 2.6 (p=0.00011). More recently introduced parameters based on the variation of RR intervals such as heart rate turbulence (Schmidt G et al. 1999) or deceleration capacity (Bauer A et al. 2006) provide much stronger risk stratification information than classical heart rate variability

parameters. However, in our cohort, presence of a “flat tachogram” even provided additional prognostic value when added to “severe autonomic failure” (SAF), a parameter combining heart rate turbulence and deceleration capacity (Bauer A et al. 2009): of the 1590 patients in our cohort, 111 had SAF, and 77 had a “flat tachogram”. The overlap between these two groups was small; only 18 patients had both, a “flat tachogram” and SAF. Presence of SAF identified a high-risk group of 111 patients who had a 5-year mortality risk of 40% (**Figure 6**). However, the presence of a “flat tachogram” in patients without SAF identified another high-risk group of 59 patients with an almost similarly-high mortality rate (see **Figure 6**). In a multivariable Cox model considering also LVEF and GRACE score, SAF and a “flat tachogram” were independent risk predictors with hazard ratios of 2.9 ($p<0.001$) and 1.9 ($p=0.013$), respectively, indicating that the presence of a “flat tachogram” provides additional prognostic information in survivors of acute myocardial infarction.

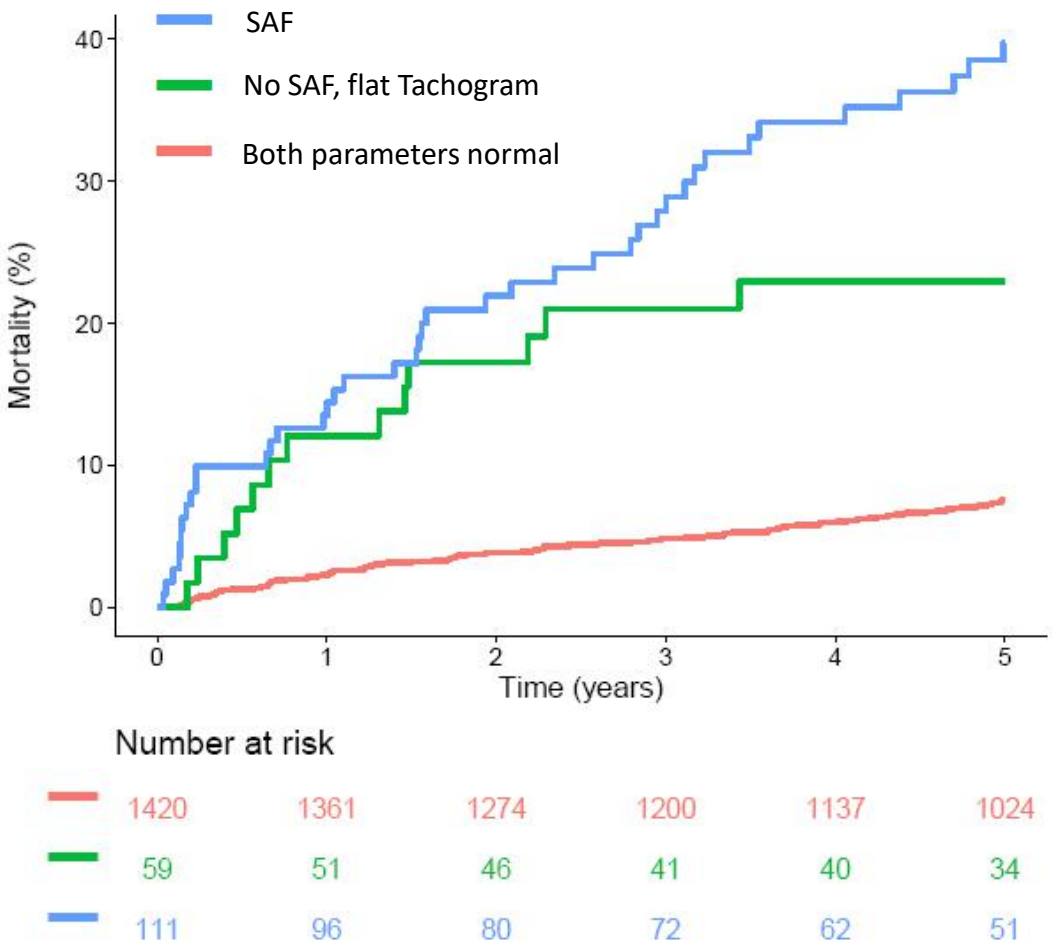


Figure 6: Survival in patients stratified according to presence of a flat heart rate tachogram and severe autonomic failure (SAF). Kaplan-Meier curves are shown for patients without a flat tachogram and SAF ("Both parameters normal"), for patients with SAF regardless of flat tachogram status ("SAF") and for the subgroup of patients without SAF, but with a flat nocturnal HR tachogram ("No SAF, flat tachogram"). The numbers of patients at risk in the respective groups are shown below the graph.

Part 4 Discussion

In this study, we applied a previously-described and validated algorithm to screen nocturnal segments from Holter recordings of a large cohort of survivors of acute myocardial infarction for SDB based on CVHR. The primary result of our study was that a nocturnal ECG pattern indicative of SDB did not have prognostic implications regarding 5-year mortality rate in this patient cohort (see **Figure 2**).

Of those patients in whom the algorithm to detect SDB from the ECG could be applied, 38.6% had a nocturnal ECG pattern indicative of SDB in this cohort of post-infarction patients. This fits well with numerous evidence referring to a high prevalence of SDB among cardiac patients (e.g., 30–50% of patients with coronary heart disease (Hayano J et al. 2017)) and underscores the importance of this disease entity in post-infarction patients.

In some patients (4.8% in our cohort), a "flat" heart rate tachogram does not allow an evaluation for signs of SDB. Considering that reduced heart rate variability, as a sign of cardiac autonomic dysfunction, is a known predictor of adverse outcome (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996), it might be speculated that the "flat tachogram" is also indicative of cardiac autonomic dysfunction and poor prognosis. Indeed, patients with

a "flat tachogram" were characterized by a higher burden of cardiovascular risk factors at baseline (see **Table 1**). Interestingly, however, this "flat tachogram" was a strong risk predictor even after adjustment for baseline risk factors (see **Figure 5, Table 2**), providing prognostic information independent from both, "classical" HRV parameters and more recently introduced parameters such as heart rate turbulence and deceleration capacity. This unexpected result warrants further investigation. We hypothesize that SDB is a strong stimulus for the sympatho-vagal regulatory circuits influencing the heart rate, and that some patients with SDB cannot react to this stimulus (i.e. do not develop CVHR) because of severe impairment of the cardiac autonomic system. This hypothesis is in line with a recent report in which the amplitude of the HR fluctuations related to CVHR was investigated by phase-rectified signal averaging (Hayano J et al. 2017). This amplitude, rather than the frequency of CVHR episodes, was associated with mortality in different patient cohorts with MI, chronic heart failure, and end-stage renal disease, with a lower amplitude of CVHR indicating an increased mortality risk (Hayano J et al. 2017). Interestingly, also in this study, 3.6% of the patients did not have enough CVHR episodes to calculate CVHR amplitude (similar to our 4.8% "flat tachogram" patients, even though the definition of this patient group was slightly different). The mortality risk of this subgroup, however, was not reported.

An exploratory analysis of our data was also consistent with the hypothesis that, at least in a substantial fraction of patients, reduced CVHR might signify cardiac autonomic impairment rather than absence of SDB: For the above-reported results, we used the pre-defined cutoff of CVHR in ≥ 72 minutes of the analyzed time segment to assume presence of SDB (Stein PK et al. 2003). However, in our data, there was a continuous association of between CVHR duration and increased mortality risk (see **Figure 3a**), and the optimal cutpoint with regard to risk stratification would be rather ≤ 19 minutes within the 6-hour segment. Using this cutpoint, a significant association between CVHR and 5-year mortality was present **(Figure 3b**). Notably, a lower CVHR duration was associated with increased risk, i.e. the high-risk group consisted of those patients with CVHR in 19 minutes or less of the analyzed time segment. We hypothesize that cardiac autonomic impairment, by blunting the heart rate response to CVHR, reduces the number of apnea episodes detectable by CVHR.

Presence of a "flat nocturnal heart rate tachogram" can be easily assessed from standard Holter ECG recordings. It would be interesting to investigate whether its presence provides similar independent prognostic information in other cohorts, or whether the prognostic implications of other ECG-derived parameters profit from only investigating them during a nocturnal time segment.

However, since no polysomnograms were performed in our patients, we do not know how many of the patients actually had SDB. Thus, the study does not allow to make any statement on whether the presence of SDB (as opposed to "a nocturnal ECG pattern suggestive of SDB") is an independent risk factor in survivors of acute MI. It would be very informative to obtain polysomnogram data from a similar cohort and subsequently follow the patients for endpoints such as mortality, which could answer this question.

Nonetheless, our results suggest that screening for SDB by means of ECG analysis does not provide any meaningful prognostic information in addition to the "classical" risk factors. The fact that the patients with a "flat tachogram" – in whom ECG-based screening for SDB is not possible – are a patient population with an extraordinarily-high 5-year mortality risk should raise caution regarding the use of ECG-based SDB detection tools in post-MI patients. If they are used, one should consider performing additional tests, e.g. portable cardiorespiratory polygraphy or polysomnography, in patients with a "flat tachogram" in the Holter ECG to avoid missing possibly important information in a particularly vulnerable patient group. However, even in patients who have a "non-flat" tachogram, one cannot decide, based on the ECG recordings alone, whether a very infrequent occurrence of CVHR solely signifies absence of SDB, or rather severe cardiac autonomic dysfunction.

In our previous study, which revealed that post-MI patients with an increased nocturnal respiratory rate are at increased risk of non-sudden cardiac death (Dommasch M et al. 2014, Sinnecker D et al. 2014), we could not exclude the possibility that this association is (at least partly) mediated by SDB. But our present study indicates that there is no correlation between SDB and the nocturnal respiratory rate.

4.1 Merits and demerits of the study

Our study showed that a “flat tachogram” and low values of CVHR can predict the post-MI mortality risk, but we cannot exclude other factors interfering with this association.

It was documented that (Hayano J et al. 2017) there is a positive correlation of amplitude of CVHR (Acv) with sleep-time mean normal R-R interval, even if it was stated that the mortality risk prediction of Acv was only partially affected by mean normal R-R interval. Based on this, further studies may be needed to investigate the relationship between our novel parameters and mean normal R-R intervals in sleep-time.

All the patients enrolled in our study were in sinus rhythm. Thus, we cannot make any statement on the utility of the algorithm in patients with atrial fibrillation. Similarly, we only investigated patients with a recent MI, and it may not be valid to extrapolate our findings to patients with other cardiac conditions.

Since we did not directly measure respiration in our patients, we cannot exclude that sleep-disordered breathing that escaped detection by the screening algorithm (possibly in the patients with a "flat tachogram") bears prognostic information after myocardial infarction. Similarly, since our algorithm does not allow to discriminate between patients with obstructive (OSA) and central (CSA) sleep apnea, we cannot make any statement on differential prognostic implications of these two forms of SDB.

Manual evaluation of RR interval tachograms is operator-dependent, not entirely objective, and somewhat time-consuming. However, given that the manual detection algorithm was previously validated, we deliberately decided against developing a new, fully-automated algorithm.

Additionally we have not included the subjects exceeding 80 years, therefore, we cannot give a risk assessment to the elders (>80 years), even if the SDB may be more prevalent in them.

However, there are still several advantages in our study design and implementation. Firstly, our cohort was also previously used to asssess the risk predictive power of NRR and SAF, therefore, due to the common background of same cohort, the interference of confounding factors derived from clinical, demographic characteristics and enrollment

criteria can be considered minimal. The fact that the assessment for CVHR can be carried out simply and directly from ECG recordings is a laudable merit, comparing with many known predictors, e.g. post exercise heart rate recovery (Lacasse M et al. 2004) which need to be assessed through exercise. Moreover, the 6h duration in night-time measurement was also of importance, since during this period, most of the subjects were very likely asleep, eliminating many possible disturbations of the HR pattern. Meanwhile, comparing with the 3h nocturnal measurement by Stein et al. (Stein PK et al. 2003), the 6h segment used in our study may result in a higher information content in the recordings, and a reduction of noise influences.

4.2 Clinical application and scenario

In spite of these limitations, the results of our cohort study are robust and might benefit future risk stratification in the clinical practice. Research for novel risk predictors, serving as a starting point for subsequent studies, may at least partially contribute to improving clinical practice by optimizing treatment strategies and guidelines, including selection of high-risk patients, individualized medicine application, etc. A better risk stratification, aided by parameters like those developed in this study, might result in higher clinical attention, more strict diagnostic procedures, more frequent follow-up visity, or more intensive treatment

management in patient groups predicted to have a high mortality risk, which might ultimately result in better outcomes.

Conclusion

In survivors of acute MI, Holter recordings suggesting SDB are frequently seen. In our cohort, this specific pattern was not associated with an altered mortality rate. A nocturnal "flat tachogram" — indicating impaired autonomic control of heart rate, and making Holter-based screening for SDB impossible — was a strong and independent mortality predictor after myocardial infarction. In the remaining patients with non-flat tachograms, a trend to higher mortality rates in patients with very few CVHR episodes (CVHR≤19min within the 6-hour segment) may be also related to impaired autonomic function. Thus, Holter-based detection methods for sleep apnea should be used with caution in cardiac patients.

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Hiermit erkläre ich, Xu Cao, dass die vorliegende Dissertation zum Thema: ‘Risk prediction after myocardial infarction by cyclic variation of heart rate, a surrogate of sleep-diaordered breathing assessed from Holter ECGs. ’ selbstständig verfasst wurde und keine anderen als die angegebenen Quellen und Hilfsmittel verwendet wurden.

München, 14. 05. 2019

XU CAO