Low heart rate variability predicts stroke and other complications in the first six postoperative months after a hip fracture operation.

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Abstract

Background 1-year mortality after hip fractures is underestimated and is reported as 25%. An improved risk stratifying could contribute to a better follow up of these patients. Heart Rate Variability (HRV) is an easy point-of-care investigation and is used in cardiology, endocrinology and perioperative care. This observational study intended to explore relevant associations between HRV parameters and 6-months mortality and morbidity after a hip fracture. Methods 165 patients admitted to two hospitals were included and short-time HRV measurements were obtained. Mortality data were gathered from the Norwegian central address register. Patients, close relatives of patients and in some cases their general physicians or nursery home physicians were interviewed six months postoperatively regarding the incidence of pneumonia, cardiac events or stroke. Results 157 (95.2%) patients were followed up after six months. 21 (13%) died during this period. Twenty patients (13%) developed pneumonia, eight (5%) stroke and four (2%) myocardial infarction. No HRV parameter was associated with six-month general mortality. However, patients who developed stroke, had significantly lower High Frequency Power (HF, $p< 0.001$) and lower Very Low Frequency Power (VLF, $p=0.003$) at inclusion compared to patients without complications. Patients who developed pneumonia had at inclusion lower root mean square of successive differences (RMSSD, $p = 0.044$). Patients with a history of coronary heart disease ($n = 41$) showed a mortality of 7%. Mortality in this group was associated with the standard deviation of the NN intervals (SDNN, $p = 0.006$), Total Power (TP, $p = 0.009$), HF ($p = 0.026$), and Low Frequency Power (LF, $p = 0.012$). Beta-blocker intake was not associated with differences in HRV parameters. Conclusions We present for the first time significant associations between different preoperative HRV parameters and stroke, myocardial infarction and pneumonia during a 6-month period after hip fracture. HRV might be a simple and effective tool to identify patients at risk that would warrant better follow-up.

Background

Hip fractures occur frequently in older people and the incidence is increasing [1]. The normal therapeutic approach is surgery. This is associated with a significant proportion of complications both perioperatively and during the hospital stay until discharge [2]. Moreover, a hip fracture may also have effects on many aspects of the patient's well-being after they are discharged from the hospital [3, 4]. Long-term mortality after hip fractures has to a large extent been neglected for many years. Some studies report a 5-year mortality of 55–68%% (compared to 12% in population based controls adjusted for age and previous hospitalization for serious disease). The highest mortality is reported during the first six months [5–7]. 1-year mortality rates of hip fractures in Norway are 25 % according to the Norwegian Hip Fracture Register [8]. The fact that one third of all postoperative complications and 50% of postoperative mortality are due to cardiac events, underlines the importance of risk estimation [9]. Currently, no ideal risk estimation tool to predict long term mortality exists [9, 10]. Thus, simple risk estimation tools to identify low-risk and high-risk groups are needed.

Short-term heart rate variability (HRV) is a simple point-of-care investigation. Patient's heart rhythm is evaluated by an ECG measurement over five to ten minutes. The beat-to-beat variance measured by QRS distances shows variability in different frequency areas. This time series can be analysed with several mostly simple algorithms which can be differentiated between time domain, frequency domain, fractal analysis or measures of entropy[11]. Since 1996, a general accepted standard procedure has been used which makes studies comparable[12]. In *time domain* the standard recommends standard deviation of beat-to-beat intervals (SDNN), and root mean square of successive differences (rMSSD). In *frequency domain,* one determines the frequency bands Total Power (TP), Very Low Frequency (VLF), Low Frequency (LF), High Frequency (HF), and the ratio of LF/HF. After this standard was established, HRV has been investigated as risk estimator in cardiology, perioperative care, and diabetes, among others [13]. Short-term heart rate variability has been tested perioperatively in unselected patients[14, 15] and patients at risk of coronary artery disease[16], but not in patients undergoing surgery after hip fractures during a long-time follow up.

This prospective observational study intended to explore relevant associations between HRV parameters and mortality and morbidity six months after hip fracture surgery. We hypothesized that decreased heart rate variability parameters might be associated with 6-months mortality, and 6-months incidence of pneumonia, stroke and myocardial infarction. We anticipated that myocardial infarction would be especially prominent in patients with known coronary heart disease. Since Beta-blockers might influence HRV results[17, 18], we also planned to look specifically into possible effects of these drugs.

Methods

Patients with hip fractures admitted to Oslo University Hospital (OUS) and Kongsberg Hospital between 2008 and 2013 and with sinus rhythm in ECG were eligible for inclusion in the study. The patients at OUS were at the same time participating in another randomized study investigating the effect of geriatric care on cognitive function [19]. Exclusion criteria were technical problems to take a short-time ECG (e.g. due to delirium), patients with unstable circulation, patients with operations the last month before admission, neoplasms, high energy trauma, and patients with short life expectancy. Patients signed written informed consent. In Oslo, substitute decision-makers were allowed to consent if the patients were not capable. An ECG signal was obtained within the first day after admission before operation and digitalized. We used Biocom ECG recorders (Biocom 3000 in Kongsberg, Biocom 4000 in Oslo), equipped with dry silver/ silver chloride ECG electrodes being mounted on the index fingers of the right and the left hand, respectively. After a relaxing period of five minutes an ECG signal was recorded over 5 minutes (Oslo) or 10 minutes (Kongsberg). All ECGs were manually edited. Ectopic beats and noisy events were interpolated on preceding and successive beats. Patients with more than 10% of ectopic beats or noise events were also excluded at this stage. Linear parameters (time domain: SDNN, rMSSD; frequency domain: HF, LF, VLF, LF/HF) were calculated by a Heart Rhythm Scanner - Version 2.0—(Biocom Technologies—U.S.A). Both signal measurement and processing was done according to recommendations the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology [12]. HRV was analyzed both in time domain and frequency domain. Methods are described in detail in recent publications [20, 21].

The sample size was estimated according to reference values reported earlier [22]. The calculation was based on mortality. Assuming a 6-months mortality between 3 and 8% according to Dahl [23], 150 patients were expected to be sufficient to test the hypothesis of a significant association between mortality and HRV.

To test univariate associations, the independent samples T test was applied, and ANOVA for multivariate analysis. The Chi-Square test or Fisher's exact test were used in case of nominal data, as appropriate. The nonparametric Mann-Whitney-U-test was used when very different group sizes (in the case of postoperative pneumonia) were analyzed. Statistical analyses were conducted by the Statistical Package for Social Sciences (SPSS), release 18.0.3 (September 2010). Values are given in mean +/- SEM.

Every person in Norway is identified by a unique number in the Central Personal Register. Deceased patients were identified by the Norwegian central address register which provides exact data for the time of death. In addition, patients, close relatives of patients and in some cases their general physicians or nursing home physicians were interviewed six months postoperatively in the Kongsberg group regarding pneumonia, cardiac events and stroke. In the Oslo group patients, close relatives of patients and in some cases their general physicians or nursing home physicians were interviewed regarding pneumonia, cardiac events and stroke within the first six months postoperatively. In both groups the results of the interviews were cross-validated by the hospital journals and—if relevant—nursery home journals regarding new hospital admissions within six months after the operation date.

The study protocol was reviewed and approved of the Regional Committee for Medical and Health Research Ethics of Southern Norway (11.1.2008, S–07307b) and the Data Protection Officer of Oslo University Hospital.

Results

165 patients (123 females and 42 males, mean age 80.9 ± 9.9 Std. dev.) were included (Figure 1). At admission, one in four patients had an established diagnosis of coronary heart disease, one in three had hypertension and nearly one fifth COPD. Patient details are reported in tables 1–2.

Illness	Number	%
Coronary heart disease	41	25
Hypertension	62	38
Diabetes (insulin)	7	4
Diabetes (tablets)	15	9
Arrhytmias	34	21
COPD	31	19

Table 1: Preoperatively identified illnesses according to the case notes (n= 165)

Drug treatment	Number	%
Beta blocking agents	47	29
AT2 antagonists	23	14
ACE inhibitors	27	16
Calcium channel blockers	22	13
Diuretics	37	22
Glucocorticoids	13	8
Lipid lowering drugs	37	22
Sedatives	25	15
Antidepressive drugs	35	21
Antiepileptic drugs	7	4

Table 2: Preoperative drug treatment (n=165)

157 (95%) patients were followed up at six months (with a similar proportion of illnesses, medication, ECG abnormalities and blood sample results compared to the original group). Death dates for all patients were obtained by the central address register.

There were no significant associations between intake of beta-blockers and HRV parameters. Thus, we did not include beta blockers as a variable in the statistical models.

Twenty one patients (13 %) died during the study period of six months after operation. Twenty patients (13 %) developed pneumonia, eight (5 %) stroke and four (3 %) myocardial infarction.

No HRV parameter was associated with six-month mortality.

Patients who developed stroke had at inclusion substantial lower HF (p< 0.001), and lower VLF (p = 0.003, figure 2), compared to patients without complications. Patients who developed pneumonia had at inclusion lower RMSSD (p = 0.044, figure 3) compared to patients without complications. Patients with coronary heart disease (n = 41) had a mortality of 7 %. Mortality within this patient group was associated with SDNN (p = 0.006), TP (p = 0.009), HF (p = 0.026), and LF (p = 0.012, figure 4). All HRV results are presented in table 3.

Mean (S.E.M.)	No complications (n= 131)	Stroke (n = 8)	Pneumonia (n = 21)	Myocardial Infarction (n = 4)
SDNN	35.9 (± 2.67)	54.8 (± 20.3)	49.1 (± 10.4)	28.8(± 11.8)
rMSSD	17.5 (± 0.86)	14.7 (± 1.5)	**13.7 (± 1.7)***	19.6 (± 6.4)
TP	1515.6 (± 331.4)	2436.9 (± 1718.8)	2486.1 (± 1260.8)	263.7 (± 195.1)
LF	164.1 (± 27.7)	101.3 (± 63.9)	131.6 (± 41.3)	56.3 (± 38.5)
HF	54.4 (± 7.8)	**14.6 (± 3.0)****	59.6 (± 21.8)	24.2 (± 15.7)
VLF	101.9 (± 11.6)	**31.9 (± 11.5)*****	105.9 (± 36.4)	56.3 (± 38.5)
LF/HF	1.88 (± 0.18)	2.61 (± 1.06)	1.82 (± 0.30)	1.50 (± 1.00)

Table 3: HRV results in hip fracture patients without and with complications during the first six months postoperatively (* = p < 0.05, ** p< 0.005, *** = p < 0.001, SDNN = standard deviation of all normal QRS-distances, rMSSD = square root of the mean squared differences of successive NN intervals, TP = Total Power, LF = Low Frequency Power, HF = High Frequency Power, VLF: Very Low Frequency Power. Higher numbers indicate higher variability

Discussion

This prospective study showed strong associations between the incident of stroke and lower HF and VLF at time of admission. Pneumonia was associated with lower RMSSD. Mortality in patients with coronary heart disease was associated with lower SDNN, TP, LF, and HF. We found no association between HRV parameters and six months overall mortality.

Our study has some limitations. Due to practical circumstances, we recorded ECG for ten minutes in Kongsberg, and five minutes in Oslo. Previous studies reported no relevant differences in HRV assessments of five or ten minutes[24]. Mortality was analyzed by retrieving data from the central address register and can be considered as very reliable. Our follow up percent was high (95 %). Since the diagnosis of stroke, myocardial infarction and pneumonia was made at different places, different criteria might have been used. On the other hand, especially diagnosis of stroke and myocardial infarction are highly standardized and most patients were treated for these illnesses in the same two hospitals. The diagnosis of pneumonia, however, was established in hospitals, nursing homes or by general physicians. It is possible that we were not able to identify all patients with milder forms of pneumonia, either because they were not recognized as pneumonia or because some patients did not contact a physician. The HRV measurements were carried out according to international standards [12] which secures a sufficient quality. This is an exploratory study where we tried to identify relevant HRV parameters as predictors of mortality and morbidity. Many associations were tested. Thus, we should consider some associations with caution. However, the p-values of the associations between stroke and HF and VLF are very low, indicating a high probability. The association between pneumonia and rMSSD was in accordance with previous findings seen during the hospital stay of the patients [21].

This is the first study showing an association between HRV parameters and stroke incidence during a six-month postoperative period. Only two studies have reported HRV as a predictor of stroke previously. The Copenhagen Holter study followed 678 healthy persons between age 65 and 75 and calculated night-time SDNN between 2.00 and 2.15 a.m. based on 15 minutes measurement. In contrast to 24 hours SDNN and Mean NN, night-time SDNN was significantly associated with stroke in the follow up period [25]. In the Atherosclerosis Risk in Communities (ARIC) study, lower HRV was associated with higher risk of stroke, but only in participants with prevalent diabetes mellitus [26]. HRV has else only been used to characterize patients after stroke [27].

Reduced HF is associated with reduced parasympathetic tone. Reduced parasympathetic tone has been associated with hypercoagulation and increased blood viscosity, and is possibly associated with arrhythmias [28]. The VLF-component is a major determinant of physical activity and reflects possibly sympathetic activity, though its origin is controversial [29]. Decreased VLF is often associated with increased inflammatory parameters like CRP, Il–6 and WBC [30]. Increased inflammation and coagulation have often been associated with development of stroke[31]. Since both lower HF and VLF are also associated with these factors, they might reflect an increased tendency to inflammation and coagulation in patients predisposed to develop stroke.

Increased incidence of pneumonia during the first 6 months of operation was associated with decreased rMSSD. A decreased rMSSD may indicate a lower parasympathetic activity and has been associated with immunologic changes in patients with hypertension [32], and in an experimental model where healthy human participants were treated with low dose endotoxin infusions [33]. Decreased rMSSD has been suggested as an early marker of multiple organ dysfunction [34]. The observed lower rMSSD in our patients with pneumonia might indicate an increased vulnerability to develop infections.

In patients with known coronary disease there was an association between mortality and lower SDNN, TP LF, and HF. This is not surprising. SDNN, LF and HF are all associated with increased risk for sudden cardiac death [35]. In risk populations with coronary heart disease these HRV parameters are correlated with long term mortality [36]. Filipovic et al. followed patients scheduled for major elective non-cardiac surgery (e.g. vascular procedures of the abdominal aorta or lower limb, open intraperitoneal or intrathoracic procedures, major orthopaedic procedures of the hip or spinal column or major procedures on the neck). They observed an association between LF/HF < 2 and mortality, but did not measure SDNN or TP [16]. In our study, we did not find a significant lower LF/HF ratio, probably because LF and HF were reduced similarly. Our results confirm these earlier results.

We did not find associations between HRV parameters and overall mortality. This is in contrast with other earlier studies. A recent metanalysis including at all 21 988 participants without cardiac disease at baseline and followed up in cohort studies, demonstrated a robust association between decreased HRV and later cardiovascular events. Individuals with low HRV have about 40% increased risk of fatal or non-fatal CVD compared to individuals with high HRV. Recent studies had a follow-up of 9 and 15 years [30, 37, 38], as opposed to our study of only six months follow-up. However, we did find associations between HRV parameters, stroke and pneumonia. Presence of stroke and recurrent pneumonia are associated with increased mortality [39, 40]. Thus, we could expect a further increase in mortality in our study group after six months, secondary to events like stroke and pneumonia.

Conclusions

We present for the first time a significant association between preoperative low HF, VLF, and stroke during a 6-month period after hip fracture. Pneumonia in this period was associated with low preoperative rMSSD. Mortality in cardiac patients was associated with low SDNN, TP, HF and LF preoperatively. If these results can be confirmed, HRV might be a simple and effective tool to identify patients at risk. A better and more targeted follow-up of these patients might decrease morbidity and mortality.

List Of Abbreviations

COPD - Chronic Obstructive Pulmonary Disease

HRV - Heart Rate Variability

HF - High Frequency Power

LF - Low Frequency Power

RMSSD - Lower Root Mean Square of Successive Differences

SDNN - Standard Deviation of the NN intervals

TP - Total Power

VLF - Very Low Frequency Power

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved of the Regional Committee for Medical and Health Research Ethics of Southern Norway (11.1.2008, S–07307b) and the Data Protection Officer of Oslo University Hospital. Written consent was obtained from all participants in the Kongsberg subgroup. In the Oslo subgroup, written informed consent was obtained from the patients or substitute decision-makers if patients did not have the capacity to consent, according to the study protocol of the orthogeriatric study (Watne et al 2014)

Consent to publish

Not applicable

Availability of data and materials

The clinical data from the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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The study was funded with internal funds. The funding body was not involved in the design of the study, neither in the collection, analysis, and interpretation of data and in writing the manuscript.

Authors contributions

GE has designed the study, collected data in the Kongsberg group, analysed the data, drafted the manuscript, revised it and wrote the final version

LOW collected data in the Oslo group and revised the manuscript.

FF revised the manuscript.

TBW revised the manuscript.

AD analysed the data and revised the manuscript.

MR has designed the study, analysed the data, drafted the manuscript, revised it and wrote the final version together with Gernot Ernst

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Figures

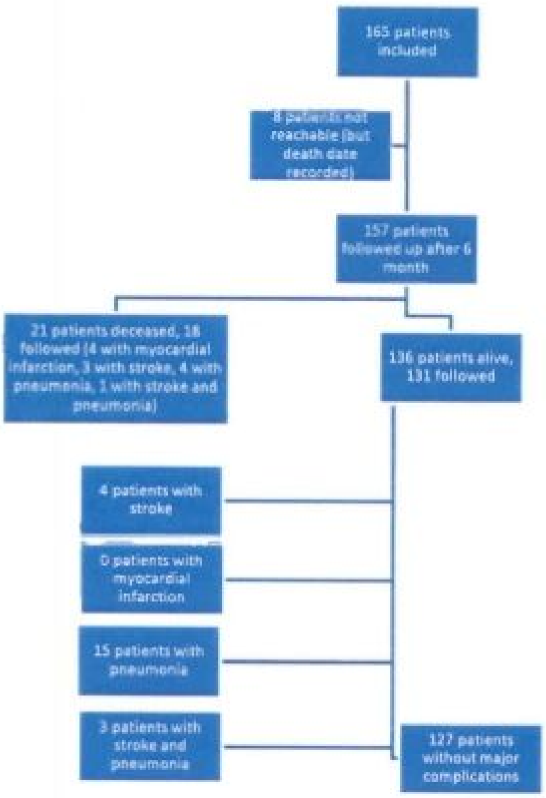

Figure 1

Flow chart of the follow-up after six months of all 165 included patients

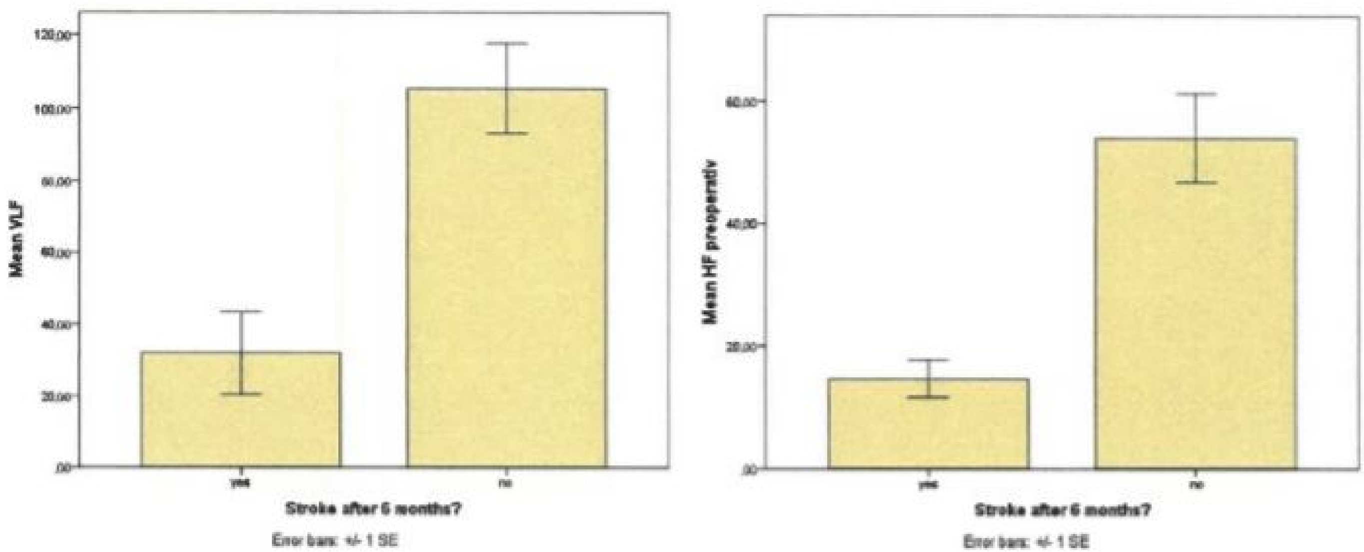

Figure 2

Very Low Frequency (VLF) (left panel) and High Frequency (HF) (right panel) power assessed in the acute phase in patients who did versus did not develop a cerebral stroke during the six months follow up period.

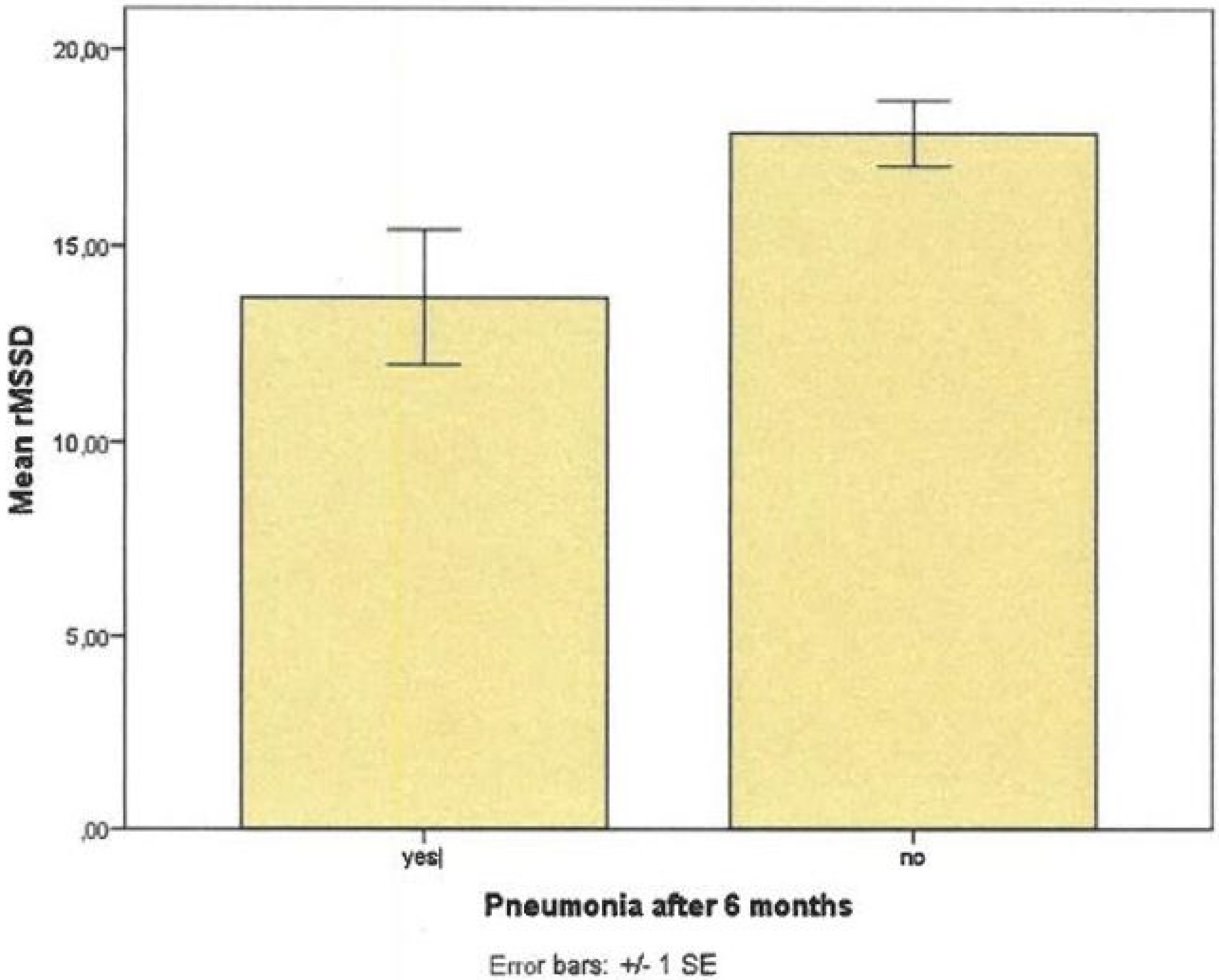

Figure 3

Square root of the mean squared differences of successive NN intervals (RMSSD) assessed in the acute phase in patients who did versus did not develop pneumonia during the six months follow up period.

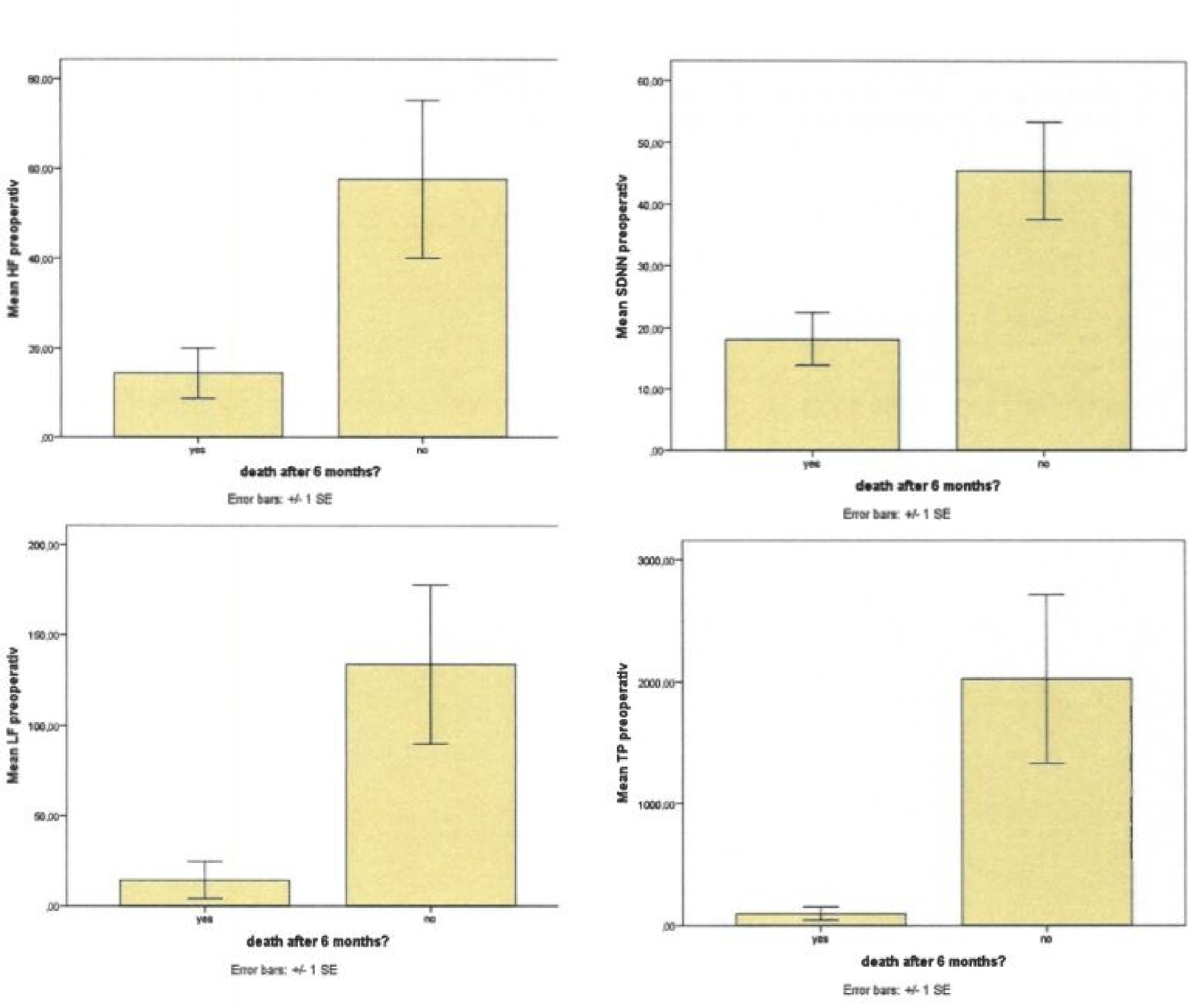

Figure 4

High Frequency (HF) (right panel), standard deviation of all normal QRS-distance (SDNN), low frequency power (LF) and total power (TP), assessed in the acute phase in the subgroup of patients with coronary heart disease who deceased during the six months follow up period compared to the survivors.