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# Low heart rate variability in patients with clinical burnout

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ABSTRACT

Several studies have shown that acute psychosocial stress and chronic psychosocial stress reduce heart rate variability (HRV). It is likely that individuals suffering from burnout have reduced HRV, as a consequence of the long-term stress exposure. This study investigated HRV in 54 patients with clinical burnout (40 women and 14 men) and in 55 individuals reporting low burnout scores (healthy; 24 women and 31 men) and 52 individuals reporting high burnout scores (non-clinical burnout; 33 women and 19 men). The participants underwent a 300 s ECG recording in the supine position. Standard deviation of normal R-R intervals (SDNN) and the root mean square of successive normal interval differences (RMSSD) were derived from time domain HRV analysis. Frequency domain HRV measures; total power (TP), low frequency power (LF), high frequency power (HF), and LF/HF ratio were calculated. All HRV measures, except LF/HF ratio, were lower in the clinical burnout patients compared to both the non-clinical burnout group and the healthy group. The difference was larger between the patients and the healthy group than between the patients and the non-clinical burnout group. HRV did not differ significantly between the non-clinical burnout group and the healthy group. Low HRV in burnout patients may constitute one of the links to associated adverse health, since low HRV reflects low parasympathetic activity – and accordingly low anabolic/regenerative activity.

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## 1. Introduction

Burnout has been defined as a negative affective state consisting of emotional exhaustion, cognitive weariness and physical fatigue which is caused by chronic psychosocial stress (Melamed et al., 1992). Besides the mental health burden and consequences for quality of life, burnout is associated with adverse physical health (Honkonen et al., 2006; Lerman et al., 1999; Melamed et al., 1992; Melamed et al., 2006b; Sheiner et al., 2002; Toker et al., 2005). Melamed and co-workers concluded that the evidence from prospective cohort studies suggests a link between burnout/vital exhaustion and cardiovascular related events (Melamed et al., 2006a). Several studies have been performed to explore plausible biological mechanisms mediating the risk of cardiovascular disease (CVD) in people reporting burnout and work-related stress (Chandola et al., 2008; Steptoe and Kivimäki, 2013). One of the most commonly suggested mechanisms is a dysregulation of the autonomic nervous system, with sustained enhanced sympathetic activity and reduced parasympathetic activity (Schwartz et al., 2003). The present study investigates cardiac parasympathetic activity through the measurements of heart rate variability (HRV) in burnout.

HRV is, as the name indicates, a measure of variations in the heart rate. A significant part of the beat-to-beat fluctuations in the heart rate are caused by fluctuations in cardiac sympathetic and parasympathetic activity. Therefore, examination of variations in the heart rate can provide information about the state of the autonomic nervous system. HRV is based on measuring the intervals between instantaneous heart beats, the RR intervals in the QRS complex in the ECG. There are several measures of HRV, and these can be divided into time domain measures (based on arithmetic calculations of RR intervals) and frequency domain measures (based on spectral analysis). In the present study, in which short-term measurements (5 min) has been performed, we use the time domain HRV measures SDNN (standard deviation of all normal RR intervals) and RMSSD (root mean square of successive differences in RR intervals) and the frequency domain HRV measures HF (high frequency component:0.18–0.4 Hz) and LF (low frequency component: 0.04–0.15 Hz). All HRV measures mentioned above, except LF, reflect parasympathetic activity. There is disagreement about the interpretation of the LF component of HRV. Some researchers consider LF as a marker of sympathetic activity, while most investigators believe that

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**Table 1**
Descriptives.

| | | Clinical burnout | Non-clinical burnout | Healthy controls | p-Value[b] |
|---|---|---|---|---|---|
| | | N = 54 | N = 52 | N = 55 | |
| Sex, n (%) | Women | 40 (74) | 33 (62) | 24 (44) | 0.005 |
| | Men | 14 (26) | 20 (38) | 31 (56) | |
| Age, mean (SD) | | 41 (9) | 40 (7) | 40 (9) | 0.730 |
| BMI, mean (SD) | | 23.6 (4.6) | 23.4 (2.8) | 23.9 (2.4) | 0.808 |
| Nicotine use, n (%) | Yes | 13 (28) | 12 (25) | 8 (15) | 0.257 |
| | No | 33 (72) | 36 (75) | 45 (85) | |
| Antidepressant use n (%) | | 25 (46) | 0 | 0 | na |
| Physical activity, n (%) | Sedentary | 13 (25) | 17 (35) | 3 (6) | <0.001 |
| | Light physical activity | 27 (52) | 19 (40) | 18 (34) | |
| | Regular moderate or intense physical activity | 12 (23) | 12 (25) | 32 (60) | |
| Burnout score, mean (SD)[a] | | 5.5 (0.9) | 4.6 (0.7) | 1.6 (0.3) | <0.001 |
| RR interval (ms), mean (SD) | | 930 (121) | 1041 (154) | 1050 (173) | <0.001 |

[a] N = 44 in the clinical burnout group.
[b] Sex, nicotine use, and physical activity tested by chi-square test and age, BMI, burnout score and RR interval tested by one-way ANOVA.

the LF component of HRV is a reflection of fluctuations in both sympathetic and vagal activity (Berntson et al., 1997). From here on, when referring to low HRV, we mean low values of the HRV measures that reflect parasympathetic activity.

Low HRV has been associated with a wide range of somatic (Koenig et al., 2016; Thayer and Lane, 2007; Thayer et al., 2010) and mental diseases (Chalmers et al., 2014; Kawachi et al., 1995; Kemp and Quintana, 2013; Sgoifo et al., 2015; Thayer and Sternberg, 2006). The parasympathetic nervous system is responsible for governing anabolic/regenerative and recovery activities, thus activities that build and repair cells and tissues. Several studies have shown that acute (Delaney and Brodie, 2000; Hamer and Steptoe, 2007; Lin et al., 2001; Sgoifo et al., 2003) and chronic psychosocial stress (Chandola et al., 2010; Lucini et al., 2005; Vrijkotte et al., 2000; Zanstra et al., 2006) reduce HRV. It is likely that individuals suffering from burnout have reduced HRV, as a consequence of the long-term stress exposure. Low HRV, and accordingly high sympathetic activity, in individuals who report chronic burnout might constitute one link to associated adverse health. However, publications of HRV measurements in burnout subjects are very limited. One publication reported a relationship between burnout symptoms and HRV in (healthy) males (Teisala et al., 2014). We found two publications in which HRV was compared between burnout subjects and controls, one reported no differences in HRV (Zanstra et al., 2006) and the other reported reduced HRV in the patients (de Vente et al., 2015). Thus, more studied are needed within this field. The aim of the present study was to investigate HRV in patients with clinical burnout. The reference groups constituted of individuals who reported low (<2) and high (≥3.75) scores on the Shirom-Melamed Burnout Questionnaire (SMBQ). In this way, we were able to compare the burnout patients with both individuals without burnout symptoms and with individuals who reported non-clinical burnout. We predicted lower HRV in burnout subjects compared with healthy individuals and a negative relationship between burnout severity and HRV.

## 2. Material and methods

### 2.1. Participants

We included 54 consecutive patients (40 women and 14 men) who were referred from occupational healthcare and primary care physicians in Region Västra Götaland in Sweden, to a specialized outpatient clinic at the Institute of Stress Medicine in Gothenburg, Sweden due to symptoms of severe clinical burnout. Inclusion criteria were; age 20–65 years and BMI 18.5–30 kg/m$^2$. All patients were diagnosed with Exhaustion Disorder (ED) with the ICD-10 code F43.8 (n = 49) as previously described by Jonsdottir et al. (2009) or "Reaction to severe stress, unspecified" with the ICD-10 code F43.9 (n = 5). Since burnout is not an established diagnosis, these are the diagnoses used for clinical burnout in Sweden (Grossi et al., 2015). ED is defined as physical and mental exhaustion experienced for at least two weeks, caused by exposure to one or more stressors for a minimum of six months. Cardinal features are markedly reduced energy, impaired cognitive functioning and reduced capacity to meet demands. Over 90% of the patients scored above 4.4 on the Shirom-Melamed Burnout Questionnaire (SMBQ), indicating severe burnout (Lundgren-Nilsson et al., 2012). Patients with severe psychiatric disease or a somatic disease that could explain the clinical burnout symptoms were not admitted to the clinic. Full-time sick-leave was reported by 57% of the patients, 26% reported part-time sick-leave and 17% reported no sick-leave. Cognitive impairments in terms of memory loss were reported by 83% of the patients. Furthermore, 86% had sleeping problems and 98% reported fatigue. The self-reported duration of symptoms before seeking medical help was >5 years

**Table 2**
Two-way analyses of variance of HRV in the three groups (clinical burnout, non-clinical burnout, and healthy) and Tukey's post-hoc tests of variables with significant group differences.

| | Uncorrected | | | | | | | | | | | | Corrected[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Group | | | Sex | | | Group * sex | | | Clinical vs. non-clinical burnout | Clinical burnout vs. healthy | Non-clinical burnout vs. healthy | Group | | | Sex | | | Group * sex | | |
| | F | p | $\eta^2$ | F | p | $\eta^2$ | F | p | $\eta^2$ | p[b] | p[b] | p[b] | F | p | $\eta^2$ | F | p | $\eta^2$ | F | p | $\eta^2$ |
| lnSDNN (ms) | 10.1 | <0.001 | 0.115 | 4.7 | 0.032 | 0.029 | 3.0 | 0.054 | | 0.002 | <0.001 | 0.551 | 7.7 | 0.001 | 0.102 | 3.1 | 0.079 | | 2.7 | 0.072 | |
| lnRMSSD (ms) | 8.3 | <0.001 | 0.097 | 0.3 | 0.596 | | 2.9 | 0.058 | | 0.009 | 0.002 | 0.903 | 7.1 | 0.001 | 0.095 | 0.0 | 0.990 | | 2.8 | 0.062 | |
| lnTP (ms$^2$) | 9.0 | <0.001 | 0.104 | 3.1 | 0.081 | | 2.4 | 0.094 | | 0.004 | <0.001 | 0.525 | 6.6 | 0.002 | 0.090 | 1.7 | 0.200 | | 2.3 | 0.105 | |
| lnLF (ms$^2$) | 4.8 | 0.010 | 0.058 | 9.7 | 0.002 | 0.059 | 2.5 | 0.085 | | 0.058 | 0.001 | 0.442 | 4.5 | 0.013 | 0.063 | 4.7 | 0.031 | 0.034 | 3.4 | 0.035 | 0.048 |
| lnHF (ms$^2$) | 7.0 | 0.001 | 0.083 | 0.1 | 0.893 | | 1.7 | 0.187 | | 0.017 | 0.005 | 0.923 | 6.2 | 0.003 | 0.084 | 0.4 | 0.524 | | 1.7 | 0.192 | |
| lnLF/HF | 1.1 | 0.333 | | 13.3 | <0.001 | 0.079 | 0.3 | 0.731 | | | | | 1.4 | 0.239 | | 9.2 | 0.003 | 0.064 | 0.4 | 0.666 | |

[a] Corrected for age, BMI, nicotine use, and physical activity.
[b] Adjusted for multiple comparisons.

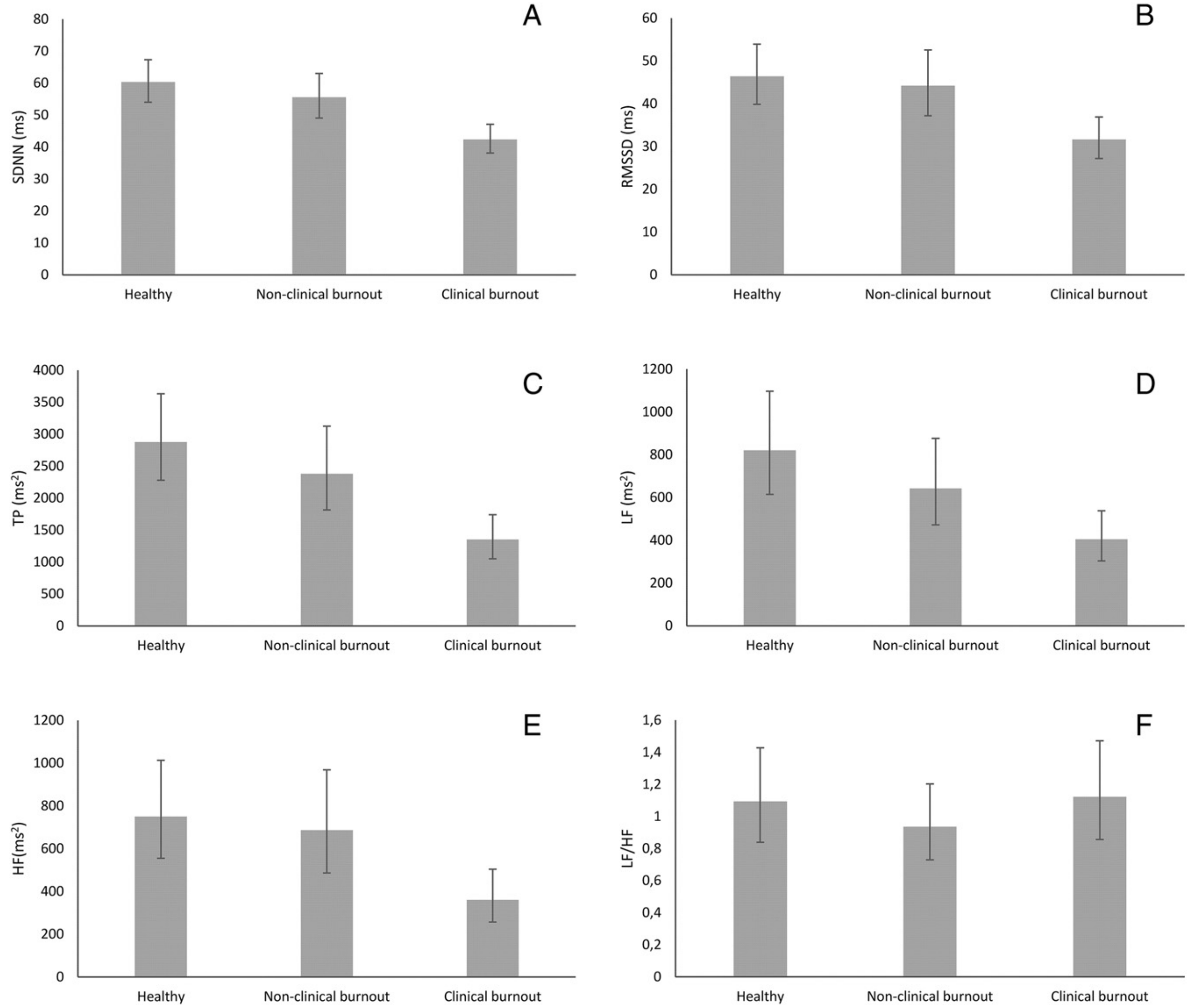


**Fig. 1.** Geometric mean (95% CI) heart rate variability in healthy referents (n = 55), non-clinical burnout referents (n = 52), and clinical burnout patients (n = 54).

for 11% of the patients, 3–5 years for 20%, 1–2 years for 28% and <1 year for 41%. The ECG recording used for HRV calculations was part of the regular examination for the patient group.

The reference groups were recruited from a study with the overall aim of exploring the relationship between different aspects of self-rated stress and mental health outcome measures and plausible biological measures of stress in healthy individuals. Inclusion criteria were; self-reported good health (i.e., no known somatic or psychiatric disease), age 25–50 years and BMI 18.5–30 kg/m$^2$. Initially, 200 participants (100 women and 100 men) with varying levels of self-reported

**Table 3**
Sex-specific one-way analyses of variance of HRV in the three groups (clinical burnout, non-clinical burnout, and healthy) and Tukey's post-hoc tests of variables with significant group differences.

| | Women | | | | | | Men | | | | | | Men | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Uncorrected | | | Corrected[a] | | | Uncorrected | | | | | | Corrected[b] | | |
| | Group | | | Group | | | Group | | | Clinical vs. non-clinical burnout | Clinical burnout vs. healthy | Non-clinical burnout vs. healthy | Group | | |
| | F | p | $\eta^2$ | F | p | $\eta^2$ | F | p | $\eta^2$ | p[b] | p[b] | p[b] | F | p | $\eta^2$ |
| lnSDNN (ms) | 2.1 | 0.127 | | 1.0 | 0.388 | | 8.7 | <0.001 | 0.219 | 0.009 | <0.001 | 0.626 | 6.9 | 0.002 | 0.213 |
| lnRMSSD (ms) | 1.2 | 0.302 | | 0.7 | 0.505 | | 7.3 | 0.001 | 0.192 | 0.006 | 0.001 | 0.965 | 6.2 | 0.004 | 0.196 |
| lnTP (ms$^2$) | 2.1 | 0.123 | | 1.0 | 0.375 | | 7.9 | 0.001 | 0.202 | 0.023 | 0.001 | 0.489 | 5.9 | 0.005 | 0.188 |
| lnLF (ms$^2$) | 0.5 | 0.582 | | 0.4 | 0.674 | | 6.1 | 0.004 | 0.165 | 0.070 | 0.002 | 0.460 | 7.1 | 0.002 | 0.218 |
| lnHF (ms$^2$) | 1.5 | 0.223 | | 1.1 | 0.340 | | 5.8 | 0.005 | 0.157 | 0.021 | 0.005 | 0.926 | 5.2 | 0.009 | 0.170 |
| lnLF/HF | 0.7 | 0.519 | | 1.9 | 0.163 | | 0.7 | 0.487 | | | | | 0.2 | 0.798 | |

[a] Corrected for age, BMI, nicotine use, and physical activity.
[b] Adjusted for multiple comparisons.

**Table 4**
Model 1 is a simple linear regression between HRV measures and burnout score. Model 2 and 3 are generalized linear regressions with HRV measures as the dependent variable and burnout score and group belonging (clinical burnout (n = 44), non-clinical burnout (n = 52)) as the independent variables. Model 1 and 2 are uncorrected and model 3 is corrected for confounding variables (sex, age, BMI, antidepressants, nicotine, and physical activity) according to the purposeful variable selection method.

| | lnSDNN (ms) | | | | lnRMSSD (ms) | | | | lnTP (ms$^2$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ | p | B | 95% CI | $R^2$ | p | B | 95% CI | $R^2$ | p | B | 95% CI |
| ***Model 1*** | .136 | <.001 | | | .089 | .003 | | | .098 | .002 | | |
| **Intercept** | | | 4.82 | 4.33 – 5.30 | | | 4.68 | 4.00 – 5.36 | | | 9.29 | 8.18 – 10.34 |
| **Burnout score** | | | -0.18 | -0.28 - -0.09 | | | -0.21 | -0.34 - -0.07 | | | -0.35 | -0.57 - -0.13 |
| | **$X^2$** | **p** | **B** | **95% CI** | **$X^2$** | **p** | **B** | **95% CI** | **$X^2$** | **p** | **B** | **95% CI** |
| ***Model 2*** | 16.1 | .001 | | | 10.2 | .017 | | | 11.7 | .008 | | |
| **Intercept** | 278.1 | <.001 | 4.52 | 3.73 – 5.32 | 128.3 | <.001 | 4.32 | 3.19 – 5.45 | 192.6 | <.001 | 8.70 | 6.87 – 10.53 |
| **Burnout score** | 7.1 | .008 | -0.14 | -0.29-0.00 | 4.5 | .035 | -0.15 | -0.36 – 0.05 | 4.5 | .034 | -0.27 | -0.60 – 0.06 |
| **Group** | 0.12 | .734 | | | 0.1 | .722 | | | 0.1 | .818 | | |
| Non-clinical burnout | | | 0.19 | -0.90 – 1.27 | | | 0.28 | -1.26 – 1.82 | | | 0.29 | -2.21 – 2.79 |
| Clinical burnout | | | 0[a] | | | | 0[a] | | | | 0[a] | |
| **Burnout score*group** | 0.01 | .925 | | | 0.0 | 0.867 | | | 0.0 | .997 | | |
| Non-clinical burnout*burnout score | | | -0.01 | -0.22 – 0.20 | | | -0.03 | -0.33 – 0.28 | | | 0.0 | -0.49 – 0-49 |
| Clinical burnout*burnout score | | | 0[a] | | | | 0[a] | | | | 0[a] | |
| ***Model 3*** | 28.9 | <.001 | | | 23.8 | <.001 | | | 22.2 | .001 | | |
| **Intercept** | 183.0 | <.001 | 5.58 | 4.62 – 6.54 | 109.5 | <.001 | 5.94 | 4.58 – 7.30 | 143.2 | <.001 | 10.23 | 8.19 – 12.27 |
| **Burnout score** | 3.9 | .047 | -0.08 | -0.22 – 0.06 | 2.4 | .125 | -0.09 | -0.28 – 0.11 | 3.0 | .083 | -0.17 | -0.49 – 0.15 |
| **Group** | 0.7 | .419 | | | 0.5 | .478 | | | 0.4 | .515 | | |
| Non-clinical burnout | | | 0.43 | -0.62 – 1.49 | | | 0.53 | -0.93 – 1.98 | | | 0.80 | -1.62 – 3.22 |
| Clinical burnout | | | 0[a] | | | | 0[a] | | | | 0[a] | |
| **Burnout score*group** | 0.2 | .663 | | | 0.1 | .700 | | | 0.1 | .746 | | |
| Non-clinical burnout*burnout score | | | -0.05 | -0.25 – 0.16 | | | -0.06 | -0.34 – 0.23 | | | -0.08 | -0.55 – 0.39 |
| Clinical burnout*burnout score | | | 0[a] | | | | 0[a] | | | | 0[a] | |
| **Sex** | | | | | | | | | | | | |
| Women | | | | | | | | | | | | |
| Men | | | | | | | | | | | | |
| **Age** | 5.8 | .016 | -0.01 | -0.02 - -0.00 | 6.3 | .012 | -0.02 | -0.03 - -0.00 | | | | |
| **BMI** | 6.6 | .010 | -0.04 | -0.06 - -0.01 | 9.1 | .003 | -0.06 | -0.09 - -0.02 | 6.2 | .013 | -0.08 | -0.14 - -0.02 |
| **Nicotine use** | | | | | | | | | | | | |
| Yes | | | | | | | | | | | | |
| No | | | | | | | | | | | | |
| **Physical activity** | 5.3 | .071 | | | | | | | 5.6 | .060 | | |
| Sedentary | | | -0.25 | -0.47 - -0.03 | | | | | | | -0.59 | -1.08 - -0.10 |
| Light physical activity | | | -0.10 | -0.29 – 0.10 | | | | | | | -0.25 | -0.70 – 0.20 |
| Regular moderate or intense physical activity | | | 0[a] | | | | | | | | 0[a] | |

[a] Set to zero because this parameter is redundant.

stress symptoms were recruited, as described in detail by Lindwall et al. (2012). In this HRV study, we included two sub-samples to serve as reference groups to the patients; one sub-sample reporting high burnout scores and one sub-sample reporting very low or no burnout. The cut-off for high burnout was ≥3.75 on the SMBQ, i.e., the limit for non-clinical burnout that has been used in other studies (Grossi et al., 2003), and the cut-off for being considered as healthy was ≤2.0 on the SMBQ. The non-clinical burnout group comprised 52 participants (33 women and 19 men) and the healthy reference group comprised 55 participants (24 women and 31 men).

Both patients and referents underwent a screening examination, including anthropometric measurements and blood samples to assess the following exclusion criteria; current infection, pregnancy, breastfeeding, medication with substances having systemic effects (except for antidepressants for the patients), vitamin B12 deficiency, and excessive consumption of alcohol. Physical activity level was assessed with a question developed by Saltin and Grimby (Grimby et al., 2015). The participants reported the level that best corresponded to their physical activity during the last three months: 1) mostly sedentary; 2) light physical activity at least 2 h a week; 3) moderate physical activity at least 2 h a week; 4) intense physical activity at least 5 h a week. In this study, levels 3 and 4 were merged.

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden, and was conducted in accordance with the Declaration of Helsinki. All participants included in the study gave written informed consent.

### 2.2. Procedure

The participants underwent a 300 s ECG recording in the supine position. All recordings were performed in the morning after fasting since 10 pm the night before. They were instructed to abstain from tobacco use on the test day and to avoid heavy physical exertion and alcohol consumption the day before the HRV assessment. Upon arrival, the participants were prepared for recordings and surface electrodes were placed in the standard configuration for a 12-lead ECG. They lay on a bed for a minimum of 5 min before the recording started, while the signal quality was checked and heart rate was allowed to stabilize. Effort was made to ensure all procedures were carried out in a quiet laboratory. Data were collected with a sampling rate of 600 Hz using a CardioPerfect Pro Recorder and software version 1.6.4 (Welch Allyn AB, Danderyd, Sweden).

### 2.3. HRV analysis

R-peak detection, editing of RR interval data and analyses of variability were performed using the automated editing and HRV features of the CardioPerfect software. In accordance with Task Force recommendations (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996), the standard deviation of normal intervals (SDNN) and the root mean square of successive normal interval differences (RMSSD) were derived from time domain analysis.

| lnLF (ms$^2$) | | | | lnHF (ms$^2$) | | | | lnLF/HF | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $R^2$ | p | B | 95% CI | $R^2$ | p | B | 95% CI | $R^2$ | p | B | 95% CI |
| .064 | .013 | | | .092 | .003 | | | .014 | .254 | | |
| | | 7.85 | 6.59 – 9.10 | | | 8.44 | 7.01 – 9.86 | | | -0.59 | -1.65 – 0.47 |
| | | -0.32 | -0.56 - -0.07 | | | -0.44 | -0.72 - -0.16 | | | 0.12 | -0.09 – 0.33 |
| **$X^2$** | **p** | **B** | **95% CI** | **$X^2$** | **p** | **B** | **95% CI** | **$X^2$** | **p** | **B** | **95% CI** |
| 7.1 | .068 | | | 10.3 | .016 | | | 2.0 | .564 | | |
| 108.3 | <.001 | 7.67 | 5.59 – 9.75 | 95.2 | <.001 | 7.66 | 5.29 – 10.02 | 0.6 | .432 | 0.01 | -1.75 – 1.77 |
| 3.1 | .076 | -0.30 | -0.67 – 0.08 | 4.9 | .026 | -0.32 | -0.74 – 0.11 | 0.8 | .374 | 0.02 | -0.30 – 0.33 |
| 0.0 | .863 | | | 0.2 | .653 | | | 0.7 | .419 | | |
| | | -0.25 | -3.09 – 2.59 | | | 0.74 | -2.49 – 3.97 | | | -0.99 | -3.39 – 1.41 |
| | | 0[a] | | | | 0[a] | | | | 0[a] | |
| 0.1 | .751 | | | 0.1 | .777 | | | 0.6 | .450 | | |
| | | 0.09 | -0.47 – 0.65 | | | -0.1 | -0.73 – 0.55 | | | 0.18 | -0.29 – 0.66 |
| | | 0[a] | | | | 0[a] | | | | 0[a] | |
| 33.2 | <.001 | | | 22.3 | <.001 | | | 28.0 | <.001 | | |
| 113.3 | <.001 | 11.03 | 8.70 – 13.36 | 86.3 | <.001 | 11.00 | 8.15 – 13.86 | 4.4 | .037 | -0.38 | -1.96 – 1.20 |
| 0.9 | .345 | -0.08 | -0.42 – 0.27 | 2.9 | .089 | -0.19 | -0.60 – 0.22 | 5.2 | .022 | 0.17 | -0.12 – 0.46 |
| 0.4 | .513 | | | 0.6 | .454 | | | 0.6 | .430 | | |
| | | 0.86 | -1.71 – 3.42 | | | 1.17 | -1.89 – 4.22 | | | -0.86 | -2.99 – 1.27 |
| | | 0[a] | | | | 0[a] | | | | 0[a] | |
| 0.1 | .715 | | | 0.2 | .634 | | | 0.6 | .450 | | |
| | | -0.09 | -0.59 – 0.41 | | | -0.15 | -0.75 – 0.46 | | | 0.16 | -0.26 – 0.58 |
| | | 0[a] | | | | 0[a] | | | | 0[a] | |
| | | | | | | | | 5.4 | .021 | | |
| | | | | | | | | | | -0.43 | -0.80 - -0.07 |
| | | | | | | | | | | 0[a] | |
| 10.4 | .001 | -0.04 | -0.06 - -0.02 | 4.9 | .027 | -0.03 | -0.06 - -0.00 | | | | |
| 10.2 | .001 | -0.11 | -0.17 - -0.04 | 9.1 | .003 | -0.12 | -0.20 - -0.04 | | | | |
| | | | | | | | | 7.0 | .008 | | |
| | | | | | | | | | | 0.50 | 0.13 – 0.86 |
| | | | | | | | | | | 0[a] | |
| 15.2 | .001 | | | | | | | 12.6 | .002 | | |
| | | -1.00 | -1.52 - -0.47 | | | | | | | -0.41 | -0.86 – 0.04 |
| | | -0.78 | -1.26 - -0.30 | | | | | | | -0.73 | -1.14 - -0.32 |
| | | 0[a] | | | | | | | | 0[a] | |

A discrete Fourier transformation was employed to calculate frequency domain HRV measures. The RR interval time series was resampled at a sampling frequency of 4 Hz using cubic spline interpolation. Smoothing of the spectrum was performed with a Hann window. Total power (TP) and absolute power in the low frequency (LF) range (0.04–0.15 Hz) and high frequency (HF) range (0.15–0.40 Hz) were calculated. LF/HF ratio was also computed.

### 2.4. Assessment of burnout symptoms

Burnout symptoms were measured using the Shirom-Melamed Burnout Questionnaire (SMBQ). The original questionnaire includes 22 items measuring five different aspects of burnout, including physical fatigue, emotional exhaustion, tension, listlessness and cognitive weariness (Melamed et al., 1992). We used the shortened 18-item SMBQ, excluding the tension subscale, as suggested by Lundgren-Nilsson et al. (2012). A mean burnout index is calculated for each participant. The index can range from 1 to 7. Commonly used cut-off value for burnout is 3.75 (Grossi et al., 2003).

### 2.5. Statistical analyses

Statistical analyses were conducted in IBM SPSS statistics version 22. A p-value of $<0.05$ was considered statistically significant. Variables that showed a non-normal distribution according to the Kolmogorov–Smirnov test were converted by logarithmic transformation. Background variables were compared between groups using one-way ANOVA and Chi-square tests. Since antidepressant use has been linked to reduced HRV (Kemp and Quintana, 2013), we performed a Student's *t*-test to check if HRV was different in patients using and not using antidepressants. Two-way ANOVA was used to compare HRV measures between groups (clinical burnout, non-clinical burnout, and healthy), also taking sex and sex*group interaction into consideration, since men generally have higher HRV than women (Koenig and Thayer, 2016). Significant group differences were further scrutinized by pairwise comparisons of the three groups using Tukey's honestly significant difference test. Age, body mass index (BMI), nicotine use (yes or no), and physical activity level were identified as potential confounders. They were included in the two-way ANCOVA analyses, separately and together, to control for confounding. The sex ratios varied between groups, resulting in an unbalanced design. Hence, as a second step, men and women were analysed separately in the same manner as described above. The relationship between burnout symptoms and HRV was analysed using simple linear regression and generalized linear regression, with burnout score and group (clinical or non-clinical burnout) as the independent variables. The final regression models were fitted according to the purposeful variable selection method (Bursac et al., 2008). In the first step, each variable was evaluated separately. In the next step, variables that had p-values $< 0.25$ in the first step were included in the model. In the third step, using Wald statistics, variables with p-values $> 0.1$ were removed from the model. In the fourth step, the likelihood ratio test of reduced and full model was performed to assess the significance of the removed variables. If parameter estimates changed >15%, removed variables were added back. In the fifth step, any variable not originally selected from the first step was added to the model, one at a time, and kept if the p-value was <0.05. The healthy reference group was not included in the regression analyses since they were recruited based on low burnout scores.

## 3. Results

HRV was not significantly different between patients using antidepressant medication ($n = 26$) and patients not using antidepressants ($n = 29$) (all *t*-test p-values $> 0.4$). Furthermore, excluding antidepressant users from the main analysis of differences between groups did not change the results (data not shown). Both users and non-users were thus included in the analyses of group differences in HRV. Age, BMI and nicotine use did not differ between groups (Table 1). Age and BMI were negatively correlated to HRV, i.e. the higher the age or BMI, the lower the HRV (data not shown). *t*-Test revealed that lnLF ($p = 0.041$) and lnLF/HF ($p = 0.032$) were significantly lower in nicotine users compared to non-users. No other significant results were found regarding nicotine use. Physical activity differed significantly between groups (Table 1) and lnSDNN ($p < 0.001$), lnRMSSD ($p = 0.010$), lnTP ($p < 0.001$), lnLF ($p < 0.001$), lnHF ($p = 0.025$) and lnLF/HF ($p = 0.001$) were all significantly related to physical activity level (results from one-way ANOVA). Thus, participants reporting higher levels of physical activity generally had higher HRV. Results from both uncorrected and corrected tests are presented below.

### *3.1. Comparison of HRV between groups*

SDNN, RMSSD, TP, LF, and HF were significantly different between groups according to two-way ANOVA (Table 2). LF/HF was not significantly different between groups. Pairwise comparisons revealed that SDNN, RMSSD, TP, and HF were lower in the clinical burnout patients compared to non-clinical burnout and SDNN, RMSSD, TP, LF, and HF were lower in the clinical burnout patients than in the healthy group (Table 2). The difference was larger between the patients and healthy group than between the patients and the non-clinical burnout group (Fig. 1). HRV did not differ significantly between non-clinical burnout subjects and healthy subjects.

SDNN, LF, and LF/HF were significantly higher in males than in females. The group*sex interaction was significant for LF in the corrected tests, indicating larger group differences in LF among the males than among the females.

Statistical analyses of men separately revealed that male patients with clinical burnout had significantly lower SDNN, RMSSD, LF and HF compared to both non-clinical burnout and healthy referents (Table 3). LF/HF was similar in patients and reference groups. In the statistical analyses of women separately, the differences between groups did not reach statistical significance, although the pattern was the same as for males (Table 3).

### *3.2. Relationship between burnout symptoms and HRV*

Burnout scores were negatively related to SDNN, RMSSD, TP, LF, and HF in clinical burnout patients and non-clinical burnout, irrespective of group belonging, i.e., higher burnout scores were associated with lower HRV (Table 4). Introducing group belonging to the model resulted in significant relationships between burnout scores and SDNN, RMSSD, TP, and LF. No significant group differences emerged, indicating that the relationship between level of burnout symptoms and HRV was similar in clinical and non-clinical burnout. After controlling for confounders, SDNN was negatively related to burnout scores and LF/HF was positively related to burnout scores.

## 4. Discussion

Heart rate variability (HRV) was investigated in patients with clinical burnout, and in reference groups scoring low or high burnout symptoms according to the Shirom-Melamed Burnout Questionnaire (SMBQ). We found that HRV was significantly lower in the clinical burnout patients compared to the other two groups. The largest difference in HRV was between the patients and the healthy participants with low burnout symptoms. However, HRV in the patients was also significantly lower than in the reference group that reported high burnout scores. Reduced HRV has been observed during acute (Delaney and Brodie, 2000; Hamer and Steptoe, 2007; Lin et al., 2001; Sgoifo et al., 2003) and chronic psychosocial stress (Chandola et al., 2010; Jarczok et al., 2013; Lucini et al., 2005; Vrijkotte et al., 2000; Zanstra et al., 2006). The observed lower HRV in the burnout patients is plausibly a consequence of the psychosocial stress that those individuals have experienced. Low HRV in burnout patients may constitute one of the links to associated adverse health, since low HRV reflects low parasympathetic activity – and accordingly low anabolic/regenerative activity.

There are two previous studies comparing HRV between burnout patients and healthy individuals (de Vente et al., 2015; Zanstra et al., 2006). Zanstra et al. (2006), did not show any differences between burnout patients and the reference group in HRV (HF-HRV was studied). It can be noted that their reference group consisted of a larger proportion of women than the patient group (67.5% vs. 53.8%). Since HRV is shown to be lower in women (Koenig and Thayer, 2016), the reference group may have exhibited lower HRV than would be expected with comparable numbers of men and women. Zanstra et al. did not include sex specific statistical analyses. In the present study, we performed additional analyses on men and women separately. The results remained the same for the male sample as for the whole sample, but in women the differences between the burnout patients and the reference groups did not reach statistical significance. We found indications of larger stress-related decreases of HRV in males, although the group*sex interaction effect was only significant for LF in the corrected model. Further studies will be needed to elucidate possible sex differences in the effects of chronic stress on HRV. Such sex differences could be part of the explanation to the more pronounced associations found in the literature between stress and CVD in males compared to females (Belkic et al., 2004). In the other previous study comparing HRV between burnout patients and healthy individuals, de Vente et al. (2015) found that basal HRV (RMSSD) was reduced in the patients compared to the reference group, in both males and females. They used a photoplethysmographic signal for HRV analyses, and therefore only estimations of HRV could be calculated. Our use of a standard 12 lead ECG with a sampling frequency of 600 Hz provides a more reliable signal for HRV analyses.

In addition to the previous studies comparing HRV between patients and reference groups, we found one publication reporting data on HRV in relation to burnout symptoms in healthy individuals. Teisala et al. (2014) investigated the correlation between physical activity, fitness and body composition with heart rate variability in 81 healthy males in the age 26–40 years. In an additional analysis, it was found that higher burnout scores (Occupational burnout measured by Bergen Burnout Inventory (BBI)) were associated with lower HRV. The regression analysis between burnout scores and HRV in the present study showed a significant negative association between HRV and burnout scores. However, the relationships were rather weak and most of them did not remain after controlling for confounders.

There are several points to be considered when discussing the clinical relevance of our results. Present results suggest that changes in vagal tone may occur after long-term stress exposure, but only in those who have developed clinical symptoms of burnout. The severity of symptoms studied could perhaps to some extent explain why some studies, relating stress exposure to autonomic dysfunction show significant relationship and other studies do not (Jarczok et al., 2013). Autonomic imbalance has been shown to be a strong predictor of future cardiovascular and metabolic disturbances (Wulsin et al., 2015). There is a large body of data to suggest that low vagal function is an independent risk factor for all-cause mortality and a common factor in all of the major risk factors for CVD (Thayer et al., 2010). Previously, burnout has been shown to be associated with several mental and physical health problems including cardiovascular disease (Honkonen et al., 2006; Melamed et al., 2006a), which could to some extent be mediated by diminished adaptation of the autonomic nervous system to environmental stress.

Thayer et al. (2012) have proposed that HRV may provide a proxy measure of the brain-peripheral integration involved in the adaptation to changing environments. They argue that HRV may be more than just a marker of heart function, as HRV may serve as an index of how appraisals of threat, mediated by cortical-subcortical pathways, influence brainstem activity and subsequently autonomic responses in the body. The medial prefrontal cortex (mPFC) regulates emotional responses to environmental challenges by inhibition of the amygdala, and hence of the fight-or-flight response. Under conditions of threat, the mPFC becomes hypoactive and allows sympathetic dominance and parasympathetic withdrawal. Thayer et al. (2012) suggest that there is a large negativity bias in stressed patients, i.e., they show exaggerated threat responses to neutral or harmless stimuli. Such threat responses are not inhibited by the mPFC, causing a dysregulated brain-peripheral integration which is manifested as reduced vagal influence of the heart rhythm and thus lower HRV. Accordingly, individuals with lower resting HRV have been shown to react with less appropriate physiological responses to stressors, and they show a delayed recovery afterwards (Weber et al., 2010).

Clinical burnout/exhaustion is a condition that should be treated seriously within the health care system. Patients with clinical burnout risk future health problems and measures to promote health and prevent stress-related exhaustion should be focused on. Several activities/lifestyle changes, such as physical exercise, meditation, dietary changes, and smoking cessation, are known to increase HRV (Kemp and Quintana, 2013; Olex et al., 2013; Thayer et al., 2010). For instance, weight loss in obese individuals is accompanied by increased HRV and increased physical activity decreases resting heart rate and increases vagal tone (Thayer et al., 2010). Indeed, in this study we found that physical activity was significantly related to HRV. Including lifestyle changes in the treatment of stress-related diseases would likely have beneficial effects on the autonomic nervous system and accordingly heart rate variability. In addition, some of the activities that increase HRV are also effective in the treatment of burnout symptoms. Engaging in physical activity has proven to be beneficial for the recovery from burnout and to lower burnout symptoms (Gerber et al., 2013; Lindegård et al., 2015).

Treatment with antidepressants is common in clinical burnout populations. In patients with major depressive disorder, the use of antidepressants (all types) is known to cause a decrease in HRV (measured as RSA) (Licht et al., 2010). Thus, although there were no significant differences in HRV between antidepressant users and non-users in our sample, there is a plausible risk of additional negative consequences in antidepressant users. The patients in this study had recently been diagnosed with clinical burnout and were tested at their very first visit to the clinic. Therefore, the long-term effects of antidepressant use in this patient population are unknown. Taken together, this implicates that HRV-increasing treatment regimens should be considered, especially in antidepressant users.

There are some limitations of the study that should be noted. This study was cross-sectional and future studies on this topic should ideally assume a prospective design to further elucidate the relationship between chronic stress and adverse health. In the subgroup analyses, the sample sizes were quite small. A larger sample size could better reveal any group differences within women. Additionally, we did not measure breathing patterns, and respiratory rate and depth are known to influence HRV (Berntson et al., 1997).

## 5. Conclusions

Low HRV in burnout patients may constitute one of the links to associated adverse health, since low HRV reflects low parasympathetic activity – and accordingly low anabolic/regenerative activity. Promoting lifestyle changes that have the potential to increase HRV as part of the treatment for patients with stress-related diseases may have beneficial effects on future CVD risk.

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