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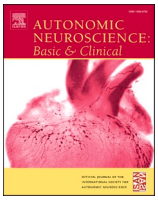

Heart rate variability and cardiovascular risk factors in patients with rheumatoid arthritis: A longitudinal study

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ABSTRACT

Background: It is established that the risk of cardiovascular disease (CVD) is increased in patients with Rheumatoid Arthritis (RA). Heart rate variability (HRV) is a method for evaluating the activity in the cardiac autonomic nervous system. Our aim was to assess the longitudinal development of HRV in patients with RA and compare with healthy controls. Furthermore, we wanted to investigate associations between HRV, inflammatory disease activity and cardiovascular complications in patients with RA over time.

Method: HRV was assessed with frequency-domain analysis at baseline and after five years in 50 patients with early RA, all being younger than 60 years. HRV indices were age-adjusted based on the estimated age-dependency in 100 age and sex matched healthy controls. Additionally, clinical data including serological markers, disease activity, and blood pressure were collected from the patients. Eleven years after inclusion CVD was assessed.

Results: At baseline, patients with RA presented with lower HRV compared to controls during deep breathing (6 breaths/min), paced normal breathing (12 breaths/min) and after passive tilt to the upright position. No significant change in HRV was observed at the five-year follow-up. A significant negative correlation was found between HRV parameters and systolic blood pressure (SBP) at baseline. A significant positive correlation was found between heart rate and inflammatory markers at baseline but not after five years. Nine patients had developed CVD after 11 years, but no significant association was found with baseline HRV data.

Conclusion: This study showed that patients with RA have autonomic imbalance both at an early stage of the disease and after five years, despite anti-rheumatic medication, but no correlation between HRV and inflammation markers were observed. Reduced HRV was also significantly negatively correlated with increased SBP. Hypertension is a common finding in patients with RA. Thus, significant decline of HRV could be a useful early marker for development of hypertension in patients with RA.

1. Introduction

Rheumatoid arthritis (RA) is a common chronic inflammatory disease. Approximately 1 % of the adult population worldwide is affected. Inflammation leads to the gradual destruction of bones and cartilage, in the body's synovial joints (Gravallese and Firestein, 2023). The disease progression does not only engage the joints but can also affect different parts of the body such as lungs, skin, eyes, nerve tissue, kidneys, and the cardiovascular (CV) system. Symptoms and clinical signs can start at any time of life, but most often appear between the age of 45 and 55 years (Gravallese and Firestein, 2023), with the most common symptoms being swollen joints, pain, and fatigue. If not treated, or if the treatment is insufficient, the disease leads to pain, joint deformity, and disabilities.

Patients with RA have an increased risk of cardiovascular disease (CVD) including myocardial infarction (Avina-Zubieta et al., 2008; Avina-Zubieta et al., 2012), as well as a high rate of CV mortality. An autonomic nervous system (ANS) imbalance has been suggested as a risk factor influencing the development of CVD in patients with RA (Thayer

Abbreviations: ANS, Autonomic Nervous System; BMI, Body Mass Index; CRP, C-Reactive Protein; CVD, Cardiovascular Disease; DAS28, Disease Activity Score based on 28-joint count; DBP, Diastolic Blood Pressure; ESR, Erythrocyte Sedimentation Rate; HF, High Frequency; HR, Heart Rate; HRV, Heart Rate Variability; IL-6, Interleukin 6; LF, Low Frequency; RA, Rheumatoid Arthritis; SBP, Systolic Blood Pressure.

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et al., 2010). Impaired autonomic function has been found in patients with RA based on analysis of heart rate variability (HRV) in many observational studies, both cross-sectional and case-control type, still several studies have reported normal HRV findings as well (Adlan et al., 2014; Vlcek et al., 2012; Dekkers et al., 2004). The predictive value of impaired autonomic function for the long-term development of CVD has been scarcely studied in this patient group (Schwemmer et al., 2006).

It has become evident that the nervous system has several anatomical and physiological associations with the immune system (Koopman et al., 2011). The central nervous system and the immune system communicate with each other, and their main function is to preserve the homeostasis. There are two pathways between the immune system and the brain: the neuroendocrine system and the ANS. The ANS may impact expressions of inflammatory diseases, such as RA, by an assortment of mechanisms, for example through mediating the release of the neurotransmitter norepinephrine which activates the immune system (Elenkov et al., 2000). A considerable number of previous studies have shown that a modification of ANS function contributes to development of CVD, and it is also an important predictor of CV death (Adlan et al., 2014; Fisher et al., 2009; Abboud et al., 2012).

HRV is a method used to indirectly assess autonomic dysregulation since ANS activity directly regulates the initiation of heart beats. The analysis is based on the successive changes in the time interval between two heart beats, which is often measured using the RR interval. HRV reflects how the ANS changes the heart rate (HR) in response to different physiological processes, such as respiration and regulation of blood pressure, as well as other conditions including mental stress and physical activity. Decreased HRV is a risk factor for cardiac arrhythmias and death (Malik et al., 1996).

The mechanisms explaining why patients with RA have reduced HRV compared to healthy controls are still not fully understood (Adlan et al., 2014). The pathogenesis of RA is undetermined, but it is well-known that disease progress is due to inflammation (Gravallese and Firestein, 2023). An inverse association has been found between HRV and inflammation parameters interleukin 6 (IL-6) and highly sensitive C-reactive protein (hs-CRP) in patients with RA (Adlan et al., 2017), but the longitudinal association of these parameters has not been established. Increased sympathetic control of HR in patients with RA has also been reported, with the authors suggesting that it may lead to ventricular tachyarrhythmia's and sudden cardiac death (Evrengül et al., 2004).

The aim of this study was to investigate the longitudinal development of cardiac autonomic function in a cohort of patients with RA, where HRV was recorded at baseline and at a 5-year follow-up. Further aims were to investigate possible associations between HRV and RA disease activity, and between HRV and the long-term development of CVD as well as hypertension.

2. Material and methods

2.1. Participants

The material in this study consists of 50 patients with RA (38 women and 12 men) from northern Sweden, region Västerbotten. The patients were included in a prospective study and were newly diagnosed with RA at the time of inclusion (2000–2004). The main focus of that study was on atherosclerosis as identified by intima media thickening in the common carotid artery by ultrasound and this data has since then been published (Södergren et al., 2015a; Södergren et al., 2015b; Södergren et al., 2019; Björsenius et al., 2020; Södergren et al., 2010a). HRV was also recorded at the baseline examination and five years after inclusion in accordance with the design of this longitudinal study, however, this data has not been previously presented or investigated. All patients fulfilled the classification criteria for RA used at the time of inclusion (Arnett et al., 1988), where the criteria were based on patients with established disease. One hundred age and sex matched controls (76 women and 24 men) were included from the HRV reference material used at the department of Clinical Physiology, Umeå University Hospital. The controls were randomly selected from the population register, medical students and hospital staff. The controls did not have any neurological disorders, diabetes mellitus, cardiac disease or arrhythmias. They were normotensive and not treated with medications affecting heart function or blood pressure. This study was approved by the regional ethics review board in Umeå, Dnr 05-068 M. All subjects were coded. All participants gave their written informed consent to participate, in accordance with the Declaration of Helsinki.

2.2. Clinical data

Blood samples were collected from all patients in order to identify biomarkers of endothelial activation. All blood samples were separated into plasma, serum, and buffy coat cells by centrifugation at 4400 $\times g$ for 15 min and stored at −80 °C. After thawing the levels of IL-6 (ng/L) were measured in serum using ELISA (R&D Systems, Abingdon UK). Soluble CRP levels (mg/L) were measured according to routine methods at Umeå University Hospital, erythrocyte sedimentation rate (ESR) (mm/h) was measured according to the Westergren method. Calculation of the Disease Activity Score based on 28-joint count (DAS28) was carried out according to Prevoo et al. (Prevoo et al., 1995). Pain was assessed using the visual analogue pain scale score (0−100). Body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP, respectively), and use of medications that could affect the cardiovascular system were collected in both patients and controls in conjunction with each HRV recording. The definition for hypertension was blood pressure $\geq$ 140/90 mmHg, previous diagnose with hypertension and/or using antihypertensive medication at the time of measurement.

2.3. HRV

HRV was recorded with the subject in supine position on a tilt table. Beat-to-beat changes in HR was continuously recorded based on a single-channel electrocardiogram (ECG) measurement. The patients and the controls were informed not to smoke, drink tea or coffee, or eat a larger meal 2 h prior to the HRV recording. The test started with 6 min of quiet rest in the supine position with spontaneous normal breathing. This was followed by two maneuvers with paced breathing for 1 min, where the operator used a clock to instruct the subjects when to inhale and exhale: a) a deep breathing test at a rate of six breaths/min, corresponding to the breathing frequency 0.1 Hz, and b) with paced normal breathing at a rate of 12 breaths/min. Subsequently a passive tilt to an upright position of 70° was maintained for 4 min during spontaneous breathing. HRV was assessed by power spectrum analysis based on autoregressive modelling of arrhythmia free RR interval data from 2-min sequences in the supine and upright position and 1-min sequences from the procedures with paced breathing, as described before (Wiklund et al., 2010). The unevenly sampled RR intervals were converted to equidistant samples by cubic spline interpolation and resampling at 2 Hz.

In this study we analyzed HRV in the frequency domain with spectral analysis (Malik et al., 1996). The power in the spectrum between 0.005 and 0.50 Hz was defined as total power (PTOT) and the power spectrum was divided into two components: the low frequency component (LF) in the region 0.05–0.15 Hz. The low frequency (LF) component is considered to reflect parasympathetic modulation of HR as a response to blood pressure regulation *via* the baroreflex, for example blood pressure fluctuations due to sympathetic regulation of peripheral resistance vessels. The high frequency component (HF) in the region 0.15–0.50 Hz normally reflects the fluctuations in HRV due to spontaneous breathing and represents parasympathetic modulation of the HR *via* the vagus nerve (Malik et al., 1996). Also, the ratio of low-to-high frequency power (LF/HF) was calculated. The LF/HF ratio is a commonly used marker of sympathetic-vagal balance, and although this interpretation has been questioned, a high LF/HF value is suggestive of dominant sympathetic activity. We also calculated two commonly used time domain indices in

studies of HRV in patients with RA: SDNN (standard deviation of normal RR intervals) and RMSSD (root mean square of successive differences in RR intervals). SDNN is correlated with PTOT, and RMSSD is strongly correlated with HF. Before HRV analysis, errors in the series of detected heart beats were manually corrected, and spurious ectopic heartbeats were replaced by linear interpolation. HRV was not analyzed in recordings with frequent arrhythmias.

All recordings and analyses were performed by biomedical scientists and engineers with long experience (>20 years) of the respective modality.

2.4. Cardiovascular events

Eleven years after inclusion, a review of the patient's medical records from the hospital and primary care was carried out to assess for the following cardiovascular events: transient ischemic attack, stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism and if the patient had undergone a coronary artery bypass graft or a heart valve surgery classified according to International Classification of Diseases, 10th ed. as I21–23, I61–64, I74, I80–82. All events were verified by experienced clinicians (co-author AS and two other) by review of the patient's medical records. The review was performed as described by earlier publications (Södergren et al., 2015a; Björsenius et al., 2020; Södergren et al., 2010b).

2.5. Statistical analysis

All HRV indices were log transformed. HRV data were age-adjusted based on the age-dependency in controls, where the slope of the estimated linear regression line was used to adjust all indices to age 50 years. Additional information concerning the determination of the age-dependency is presented in the Supplementary materials.

Continuous data are presented as mean and standard deviation. Independent and paired *t*-tests were used for comparisons between controls and study patients at baseline and follow-up. HRV parameters were also compared with clinical variables (CRP, ESR, DAS28 and IL-6) using the nonparametric Spearman correlation analysis at baseline and follow up. $P \leq 0.05$ was considered statistically significant. Data processing and statistical analyses were performed in Matlab R2021b (Mathworks Inc., Natick, Ma, USA) and SPSS version 28 (IBM, Armonk NY, USA).

3. Results

3.1. HRV at baseline

The patient clinical data of the 50 included patients with RA is summarized in Table 1. Table 2 shows the results of the HRV analysis where 45 patients were included in the statistical analysis of data from the baseline recording; one patient was excluded from HRV analysis because of arrhythmia and four patients due to use of betablockers. Before age-adjustment, HRV decreased with increasing age, examples are shown in Supplementary Materials. In the supine position during spontaneous breathing patients with RA had a higher HR than controls, but no significant differences in HRV were noted. During deep breathing, patients with RA had lower total HRV as well as LF compared to the controls. Note that since HRV is known to be concentrated in the LF range during deep breathing, HF, LF/HF and RMSSD were not analyzed for this sequence. Patients with RA displayed lower total HRV and HF during paced normal breathing, as well as lower total HRV and LF) in the upright position (Table 2, Fig. 1). Note that reductions of HRV with 0.10 and 0.30 in logarithmic units correspond to reductions of 20 % and 50 % respectively.

3.2. HRV at 5 years follow-up

HRV at the five-year follow-up was analyzed in 42 patients with RA: four RA patients did not participate in the follow-up (one had moved from the region, one declined, one did not come to the follow-up and one patient had died), in addition four patients were excluded from the HRV analysis due to use of betablockers at the follow-up recording. No statistically significant differences in HRV were seen between baseline and follow-up in the patients with RA (Table 2). In the supine position during normal breathing there were still no significant differences in HRV between patients with RA and controls. During both deep and paced normal breathing total HRV, LF and HF were significantly lower in patients than controls, however no significant differences were found in HR between patients and controls during these two procedures. HR had significantly decreased in patients with RA between baseline and follow-up during paced normal breathing. In the supine position patients with RA continued to present with significantly higher HR compared to controls.

Table 1
Clinical characteristics of patients with RA and controls at baseline.

Variable	*Patients with RA at baseline (n = 50)*	*Patients with RA at 5 y-follow-up (n = 46)*	*Controls (n = 100)*
Age (years)	46.6 (11.2)	51.7 (10.7)	46.9 (12.2)
Females/Males	38/12	37/9	76/24
BMI (kg/m^2)	25.8 (4.2)	25.8 (4.6)	24.9 (6.3)
SBP supine (mm Hg)	124.5 (16.7)	120.2 (13.9)	125.1 (17.3)
DBP supine (mm Hg)	73.5 (9.2)	86.7 (9.3)	75.8 (9.9)
SBP upright (mm Hg)	118.6 (14.1)	115.8 (16.1)	119.8 (18.9)
DBP upright (mm Hg)	77.4 (14.3)	77.4 (10.8)	81.4 (10.3)
Mean disease duration (months)	16 (6.7)		
CRP (mg/L)	16.4 (15.8)	8.8 (8.2)	
ESR (mm/h)	17.6 (18.0)	13.8 (10.9)	
DAS28	3.6 (1.5)	2.9 (1.5)	
IL-6 (ng/L)	15.6 (26.7)	17.3 (33.8)	
VAS pain (mm)	28.9 (24.0)	26.5 (20.8)	

Data is given as mean (standard deviation). Body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), Disease Activity Score based in 28-joint count (DAS28), Interleukin 6 (IL-6).

3.3. Correlation between HRV and clinical data

There were no significant correlations between HRV parameters (in all four procedures) and disease activity at baseline nor at follow-up (Table 3). There were, however, a significant positive correlation between HR and the inflammation markers IL-6 (in all four procedures) and CRP (in the supine position) during baseline examinations (Table 3) and between DAS28 and HR (in the supine position and during deep breathing) at follow-up. No correlation was seen between HRV scores and the pain score during deep breathing at baseline nor at follow-up (data not shown).

Significant negative correlations between HRV parameters, (PTOT, LF and HF) during both normal and deep breathing in the supine position, and SBP were seen in patients with RA (Table 4). Also, there was a significant positive correlation between HR and SBP during deep breathing in the patient group and during normal breathing in the control group (Table 4).

3.4. Baseline HRV and cardiovascular findings at the 11-year follow-up

In total, nine patients presented with hypertension at baseline. However, two of those were not followed-up and were excluded from this analysis. Eleven other patients had developed hypertension between the baseline examination and the 11-year follow-up. These patients

Table 2
Comparison of spectral components based on power spectrum analysis of HRV between patients with RA at baseline and follow-up and controls.

	RA patientsbaseline (n = 45)	*RA patients 5y follow-up (n = 42)*	*Controls (n = 98)*	*RA patients baseline vs Controls (p-value)*	*RA patients 5y follow-up vs Controls (p-value)*	*RA patients baseline vs 5y follow-up (p-value)*
Spontaneous normal breathing, supine						
PTOT (ms^2, log)	2.91 (0.47)	2.83 (0.53)	2.97 (0.42)	0.42	0.08	0.57
LF (ms^2, log)	2.36 (0.50)	2.24 (0.55)	2.45 (0.50)	0.30	**0.03**	0.51
HF (ms^2, log)	2.27 (0.59)	2.30 (0.62)	2.40 (0.50)	0.17	0.28	0.62
LF/HF	0.08 (0.47)	−0.05 (0.45)	0.04 (0.38)	0.60	0.20	0.15
Heart rate (beats/min)	71.0 (9.3)	70.3 (10.0)	66.0 (10.2)	**0.005**	**0.02**	0.39
SDNN (ms, log)	1.49 (0.24)	1.45 (0.25)	1.51 (0.21)	0.53	0.13	0.61
RMSSD (ms, log)	1.32 (0.29)	1.32 (0.33)	1.40 (0.26)	0.12	0.16	0.93
Deep breathing (6 breaths/min), supine						
PTOT (ms^2, log)	3.44 (0.38)	3.34 (0.51)	3.67 (0.43)	**0.003**	**<0.001**	0.38
LF (ms^2, log)	3.32 (0.38)	3.20 (0.51)	3.55 (0.43)	**0.002**	**<0.001**	0.25
Heart rate (beats/min)	69.1 (9.5)	67.9 (10.9)	66.3 (10.2)	0.13	0.42	0.12
SDNN (ms, log)	1.75 (0.18)	1.70 (0.25)	1.86 (0.21)	**0.003**	**<0.001**	0.39
Paced normal breathing (12 breaths/min), supine						
PTOT (ms^2, log)	2.78 (0.47)	2.80 (0.54)	3.03 (0.49)	**0.005**	**0.02**	0.64
LF (ms^2, log)	2.17 (0.49)	2.14 (0.49)	2.33 (0.46)	0.06	**0.03**	0.95
HF (ms^2, log)	2.45 (0.57)	2.52 (0.59)	2.77 (0.56)	**0.002**	**0.02**	0.48
LF/HF	−0.28 (0.49)	−0.38 (0.39)	−0.43 (0.41)	0.054	0.47	0.46
Heart rate (beats/min)	70.8 (9.9)	68.3 (11.1)	68.2 (10.3)	0.17	0.97	**0.02**
SDNN (ms, log)	1.46 (0.23)	1.46 (0.25)	1.57 (0.22)	**0.01**	**0.01**	0.98
RMSSD (ms, log)	1.36 (0.28)	1.39 (0.32)	1.49 (0.29)	**0.02**	0.08	0.92
Spontaneous normal breathing, upright						
PTOT (ms^2, log)	2.77 (0.46)	2.76 (0.57)	2.94 (0.38)	**0.02**	0.08	0.06
LF (ms^2, log)	2.33 (0.47)	2.24 (0.64)	2.54 (0.45)	**0.01**	**0.003**	0.60
HF (ms^2, log)	1.87 (0.63)	1.77 (0.71)	1.99 (0.46)	0.19	**0.03**	0.26
LF/HF	0.47 (0.49)	0.47 (0.47)	0.55 (0.43)	0.30	0.32	0.56
Heart rate (beats/min)	80.0 (11.1)	80.1 (13.4)	76.1 (10.6)	0.07	0.07	0.71
SDNN (ms, log)	1.43 (0.22)	1.44 (0.27)	1.51 (0.19)	**0.03**	0.11	0.47
RMSSD (ms, log)	1.13 (0.29)	1.10 (0.34)	1.21 (0.22)	0.09	0.06	0.33

Data is given as mean (standard deviations). HRV are log-transformed and age-corrected (to age = 50 years). *P*-values are derived from groupwise and paired *t*-tests. HRV = heart rate variability; PTOT = total power; LF = power of low frequency component; HF = power of high frequency component.
Bold values indicate significance at $p < 0.05$.

presented with significantly lower HF in the supine position and also a tendency to lower baseline HRV (PTOT, and LF) during deep breathing than the group that did not develop hypertension (Table 5).

At the 11-year follow-up, one patient had died due to myocardial infarction and nine presented with cardiovascular events: four stroke or transient ischemic attack, three myocardial infarction and one deep vein thrombosis or pulmonary embolism. Out of these nine, HRV data could not be analyzed in one patient due to arrhythmias. HRV components reflecting parasympathetic modulation (LF during deep breathing and HF in the upright position) was lower at baseline in RA patients with CVD at 11-year follow-up than in those without CVD, but the difference was not significant (Table 6).

4. Discussion

This study evaluated the longitudinal development in cardiac autonomic function in a group of patients with RA by analysis of HRV, where a comparison was made with the expected age-dependency in healthy controls of the same sex. Patients with RA had significantly reduced HRV during breathing provocations at the baseline examination, but the most noteworthy finding was that a further reduction was noted, and it was detected during deep breathing in the supine position at the five-year follow-up. To the best of our knowledge, longitudinal changes in HRV have not been previously reported in this patient group. A significant negative correlation between HRV and SBP was also found. Patients with RA presented a positive correlation between HR, but not HRV, and inflammatory biomarker levels but only at baseline.

4.1. HRV at baseline and 5-year follow-up

We detected a lower HRV in patients with RA during both procedures with paced breathing, a finding which persisted, and was even more pronounced, after five years. These results indicate reduced parasympathetic modulation of the HR and are in line with many, but not all, earlier studies (Adlan et al., 2014; Adlan et al., 2017; Evrengül et al., 2004). The mechanism for reduced HRV in patients with RA is unclear, and we only found a significant correlation between HRV and one clinical variable-systolic blood pressure. Hypertension is knowingly associated with abnormal HRV (Adlan et al., 2017; Khan et al., 2021; Singh et al., 1998). In our study 11 patients with RA (24 %) had developed hypertension at the 11-year follow-up. These patients presented with lower HRV at baseline compared to patients that did not develop hypertension during the same time interval. Thus, the reduced HRV seen both at baseline and after five years could be an early sign of longitudinal development of hypertension.

Inflammation could also be one influencing factor of reduced HRV. In this study, we did not find any significant correlation between HRV parameters and inflammation markers, however it has been observed in some previous studies but the results are conflicting (Adlan et al., 2014). Adlan et al. described that inflammatory cytokines seem to reduce HRV

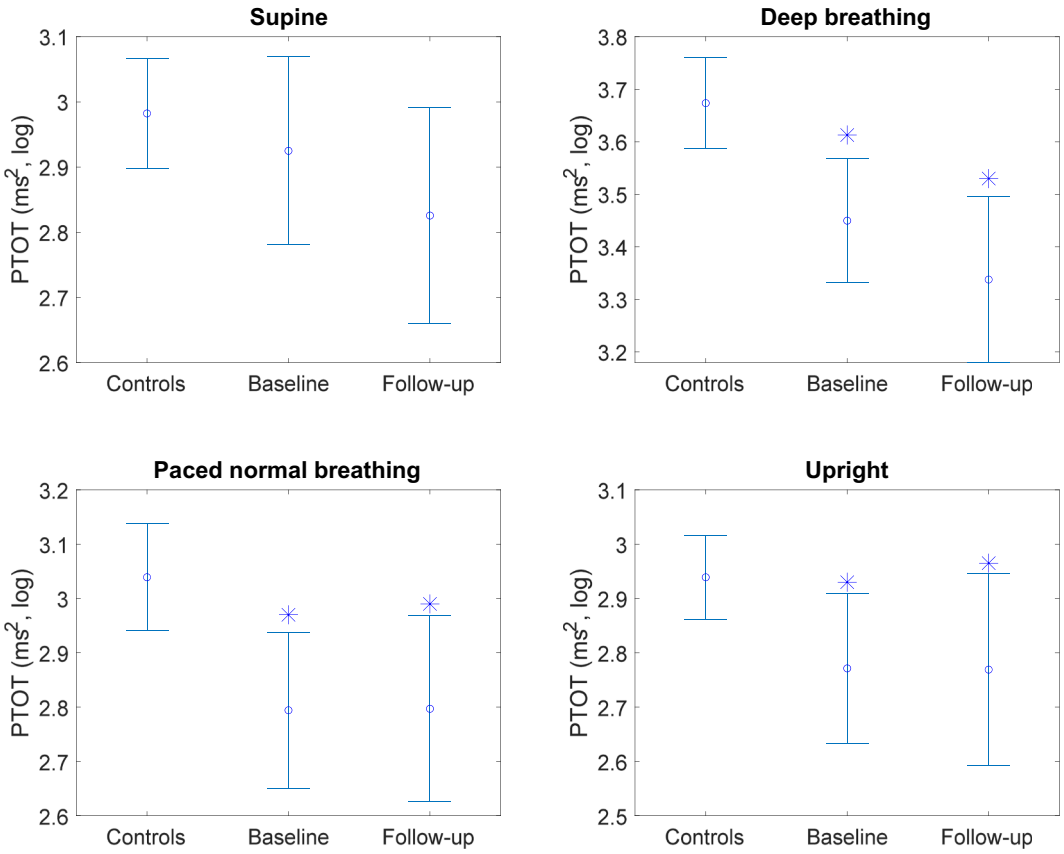

Fig. 1. HRV in patients with RA at baseline and follow-up and controls. Error bars show mean and 95 % confidence intervals, * indicates significant differences compared to controls.

Table 3
Correlation between heart rate and inflammation in patients with RA.

	Heart rate supine		*Heart rate deep breathing test (6/min)*		*Heart rate paced normal breathing (12/min)*		*Heart rate upright*	
	Rho	*P value*	*Rho*	*P-value*	*Rho*	*P-value*	*Rho*	*P-value*
Baseline examination N = 45								
CRP	0.32	**0.04**	0.22	0.16	0.24	0.12	0.26	0.10
ESR	0.04	0.80	0.03	0.85	−0.04	0.78	0.02	0.91
DAS28	0.01	0.93	−0.001	0.99	−0.02	0.90	0.07	0.66
IL-6	0.47	**0.002**	0.38	**0.01**	0.43	**0.004**	0.55	**<0.001**
VAS pain	−0.04	0.80	−0.04	0.82	−0.03	0.85	0.05	0.76
Follow-up examination N = 42								
CRP	−0.27	0.17	−0.11	0.61	−0.17	0.42	−0.32	0.11
ESR	−0.28	0.15	−0.21	0.30	−0.19	0.34	−0.24	0.23
DAS28	−0.41	**0.04**	−0.47	**0.01**	−0.36	0.07	−0.21	0.29
IL-6	−0.02	0.90	0.02	0.89	0.04	0.80	0.04	0.82
VAS pain	−0.05	0.80	−0.10	0.59	−0.002	0.99	0.08	0.68

P-values are derived from nonparametric correlation test. C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), Disease Activity Score based in 28-joint count (DAS28), Interleukin 6 (IL-6).
Bold values indicate significance at $p < 0.05$.

via efferent and afferent pathways (Adlan et al., 2017) and Jae et al. reported in their study that an acute inflammation is correlated with a transient decline in the parasympathetic nervous system (Jae et al., 2010). While these two studies found correlations between decreased HRV and inflammatory response, a specific association between the immune and autonomic systems has yet to be solidified. It has been suggested that autonomic dysfunction precede inflammation but also that the reduced HRV is a consequence of inflammation (Bellocchi et al., 2022; Ingegnoli et al., 2020).

Another explanation for reduced HRV in patients with RA may be pain. In this study no relationship between pain (measured by VAS) and HRV was observed. However, a correlation between self-reported pain and a reduction in HRV has been reported by others (Adlan et al., 2017). As mentioned earlier, both the parasympathetic and sympathetic nervous system are involved in several regulation states in the body, including pain. Tracy et al. found that chronic pain was concomitant

Table 4
Correlation between baseline HRV and systolic blood pressure in RA patients and controls.

	Patients with RA (n = 45)		*Controls (n = 95)*	
	Rho	*p-Value*	*Rho*	*p-Value*
Spontaneous normal breathing, supine				
PTOT	−0.39	**0.01**	−0.18	0.08
LF	−0.39	**0.01**	−0.16	0.13
HF	−0.40	**0.01**	−0.22	**0.04**
Heart rate	0.21	0.18	0.24	**0.02**
SDNN	−0.38	**0.01**	−0.18	**0.08**
RMSSD	−0.38	**0.01**	−0.22	**0.04**
Deep breathing (6 breaths/min), supine)				
PTOT	−0.53	**<0.001**	−0.23	**0.04**
LF	−0.51	**<0.001**	−0.21	**0.04**
Heart rate (beats/min)	0.36	**0.02**	0.24	**0.02**
SDNN	−0.54	**<0.001**	−0.24	**0.02**

p-Values are derived from nonparametric correlation test.
HRV = heart rate variability; PTOT = total power; LF = power of low frequency component.
Bold values indicate significance at $p < 0.05$.

Table 5
Comparison of baseline HRV and the development of hypertension at the 11-year follow-up. RA patients with hypertension at baseline were excluded from this analysis.

	Patients without HT at 11-y follow-up (n = 29)	*Patients with HT at 11-y follow-up (n = 11)*	*p-Value*
Spontaneous normal breathing, supine			
PTOT (ms^2, log)	2.98 (0.51)	3.07 (0.31)	0.10
LF (ms^2, log)	2.43 (0.51)	2.25 (0.48)	0.16
HF (ms^2, log)	2.35 (0.63)	2.01 (0.42)	0.06
Heart rate (beats/min)	70.5 (9.1)	71.8 (8.5)	0.35
Deep breathing (6 breaths/min), supine			
PTOT (ms^2, log)	3.75 (0.28)	3.53 (0.58)	0.07
LF (ms^2, log)	3.63 (0.28)	3.43 (0.59)	0.08
Heart rate (beats/min)	68.3 (9.7)	69.4 (7.9)	0.37

Data is given as mean (standard deviation). HRV scores are log-transformed and age-corrected. *P*-values are derived from groupwise one-sided *t*-tests.
HRV = heart rate variability; PTOT = total power; HF = power of high frequency component LF = power of low frequency component.

Table 6
Comparison of baseline HRV during deep breathing between RA patients with and without CVD at the 11-year follow-up.

	Patients without CVD (n = 40)	*Patients with CVD (n = 9)*	*p-Value*
Deep breathing (6 breaths/min), supine			
PTOT (ms^2, log)	3.42 (0.41)	3.25 (0.61)	0.16
LF (ms^2, log)	3.29 (0.42)	3.10 (0.69)	0.15
Heart rate (beats/min)	69.7 (10.3)	67.7 (9.5)	0.30
Spontaneous normal breathing, upright			
PTOT (ms^2, log)	2.76 (0.51)	2.70 (0.32)	0.38
LF (ms^2, log)	2.31 (0.52)	2.21 (0.37)	0.30
HF (ms^2, log)	1.90 (0.70)	1.54 (0.41)	0.07
LF/HF	0.41 (0.50)	0.67 (0.39)	0.08
Heart rate (beats/min)	78.5 (11.6)	81.8 (12.7)	0.23

Data is given as mean (standard deviation). HRV scores are log-transformed and age-corrected. *P*-values are derived from groupwise one-sided *t*-tests.
HRV = heart rate variability; PTOT = total power; LF = power of low frequency component.

with autonomic dysregulation as shown by reduced HRV and increased HR (Tracy et al., 2016). Measuring pain can be difficult since it depends on the patient's approximation of their pain as well as the nonlinear design of the VAS scale, adding considerable uncertainty to the assessment. Pain may nevertheless be an explanation for findings of low HRV and increased HR in the patients with RA.

In our study patients with RA had lower HRV than controls during paced normal breathing but not during spontaneous 'free' breathing. Both reduced and normal HRV has been observed in patients with RA during spontaneous breathing at rest (Adlan et al., 2014). One possible confounder may be a weaker parasympathetic stimulation during spontaneous breathing than during paced deep breathing. Another potential confounder is differences in HF due to varying respiratory frequency. Parasympathetic activity is normally associated with the HF component during spontaneous breathing, but there are subjects where the respiratory related fluctuations in HRV occur in the LF region due to slow breathing. Therefore, to mitigate this we added the sequence with paced normal breathing with 12 breaths/min, which corresponds to HF component at the same frequency in all subjects (at 0.2 Hz).

4.2. Heart rate in patients with RA

During spontaneous breathing in the supine position at baseline and in the upright position at follow-up, we found that patients with RA had higher HR than controls, which also has been seen in previous studies (Aydemir et al., 2010; Johannes et al., 2003; Piha and Voipio-Pulkki, 1993). However, no difference in HR was found between RA patients and controls in the tests with paced breathing where HRV differences were observed. The increased HR in patients may reflect autonomic dysfunction, but it could also be a consequence of a higher disease activity due to inflammation (Adlan et al., 2014). We found a positive correlation between the inflammation marker IL-6 and HR at baseline, but not at the follow-up examination. This is what could be expected since the patients were treated according to guidelines with the aim to reach remission and hereby loosing power to see any correlations due to lower levels of disease activity at follow-up.

4.3. HRV and cardiovascular events

In general, an abnormal HRV is associated with predisposition of arrhythmias. A reduced HRV has also been shown to be a strong independent risk factor for cardiovascular events in a variety of medical conditions, including RA (Evrengül et al., 2004; Lazzerini et al., 2013; Malliani et al., 1994; Ewing et al., 1980). Patients with RA that developed CVD during the study time presented with lower HRV at baseline, the differences were however not significant. Hypertension is also a contributing factor for the development of CVD (Fuchs and Whelton, 2020). In this study, four of the nine patients that developed CVD also presented with hypertension at the 11-year follow-up.

4.4. Methodology and protocol

HRV decreases with age in adult subjects, with a linear relationship between log transformed HRV indices and age. Therefore all HRV indices were age-adjusted based on the age-dependency in controls. Without this adjustment, the changes in all HRV indices would have become statistically significant when comparing the two recordings in patients. Reduced HRV is normally associated with increased HR, and different methods have been suggested to adjust HRV for basal HR (de Geus et al., 2019; Monfredi et al., 2014). However, to the best of our knowledge, no study has suggested any dual correction of HRV indices for both basal heart rate and age, which could be difficult since they are strongly correlated as heart rate increases with increasing age. There were no differences in HR between patients with RA and controls during the two provocations with deep and paced breathing. Thus, it is unlikely that the reduced HRV in patients with RA is explained by heart rate. A

smaller breathing volume could also be one reason for a reduced HRV in patients during deep breathing, but all our recordings were performed by very experienced research nurses that encouraged all subjects to perform forceful and complete deep breathing.

The choice of protocol and provocations could have affected the results regarding assessment of the cardiac ANS. Measurement of ANS function in patients with RA have been analyzed in multiple earlier studies. A systematic review including 40 studies presented different methods including clinical cardiovascular reflex tests, biomarkers of sympathetic activity, cardiac baroreflex sensitivity and HRV (Adlan et al., 2014). Many HRV studies in patients with RA have been based on measures of the HR changes during deep breathing (Adlan et al., 2014), a test that is also included in the Ewing test battery (Ewing et al., 1985). In most of these studies patients with RA presented findings consistent with parasympathetic dysfunction. A weakness is that the scoring of autonomic function during deep breathing traditionally is based on the difference between the highest and lowest HR during each breathing cycle. The advantage of our approach, based on power spectrum analysis, is that HR changes of non-autonomic origin, such as subtle arrhythmias, can be detected as spectral components at frequencies other than the breathing frequency (Wiklund et al., 2018). No subject presented with arrhythmias during deep breathing in our study. Instead, our results clearly show that the patients with RA presented with less variability during deep breathing.

4.5. Strengths and limitations

The longitudinal outlining of this study enables the investigation of autonomic dysfunction over time in a patient group known to have a higher rate of myocardial infarctions and cardiovascular mortality. In addition to the longitudinal HRV analysis, another strength of this study is that we could explore if the HRV findings at baseline were associated with the long-term development of hypertension and cardiovascular events. Although the sample size was relatively small, the number of included subjects is typical for studies of HRV in patients with RA. The long-term substudies are probably underpowered, therefore larger studies are needed to investigate if HRV is predictive of future cardiovascular complications in this patient group. Unfortunately HRV was not recorded at the 11-year follow-up, thus changes in HRV could not be assessed. Another strength is that we performed HRV in controls and patients with RA under the same controlled conditions with several types of provocations, including paced breathing and posture changes. Limitations to this study include that controls were only investigated once, thus the estimated age-dependency in HRV controls might be somewhat biased since the corresponding within subject changes due to age could not be evaluated. The included patients were treated according to clinical routine at all timepoints, still since the patients were included during the years 2000–2004 nearly none of the patients were treated with biologics.

Different provocations have been applied during the HRV recordings in this study, to assess the activity in both parts of the ANS. This has proven to be beneficial since HRV analysis during spontaneous breathing might miss to detect autoregulatory problems that arise with any form of strain on the system and thus give a false outcome.

4.6. Future perspectives

Is there any potential clinical value of HRV monitoring in patients with RA? There have been reports that patients with low HRV have a weaker response to anti-rheumatic therapies, such as TNF alpha inhibitor therapy (Adlan et al., 2014). Moreover, implantable vagus nerve stimulation has been shown to inhibit TNF and IL-6 production, which in turn could improve RA disease severity (Koopman et al., 2011; Ingegnoli et al., 2020). Thus, HRV could be a useful tool within the field of personalized medicine, with the aim to identify patients that are suitable for different treatments.

5. Conclusions

Investigation of HRV is valuable for revealing possible imbalance in the ANS in patients with RA. In this study we were able to verify that newly diagnosed patients with RA who were followed up after five years, despite medication and a reduced disease activity, have lasting impaired cardiac autonomic function during parasympathetic stimulation with paced deep and normal breathing. Furthermore, the impaired HRV was not correlated with markers of inflammation. Reduced HRV was correlated with higher blood pressure, indicating that HRV could be a valuable risk indicator for development of hypertension in patients with RA.

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CRediT authorship contribution statement

SE: study design, statistical analyses, major contributor in writing manuscript. AS: critical review, study design, contributing to writing manuscript. UW: study design, statistical analyses, contributing to writing manuscript NS: study design, critical review, contributing to writing manuscript. All authors have approved the final manuscript.

Declaration of competing interest

The authors declare no potential conflicts of interest.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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