Original Article

A Study of Autonomic Function in Newly Diagnosed Rheumatoid Arthritis Individuals Using Heart Rate Variability as a Tool

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by synovial inflammation and joint damage. Beyond the joints, RA is associated with significant extra-articular manifestations, including cardiovascular autonomic dysfunction. Heart rate variability (HRV) is a simple, non-invasive, and reliable tool for the assessment of autonomic nervous system function. Most previous studies have focused on patients with established RA, often confounded by long disease duration and medication effects. **Materials and Methods:** A case–control study was conducted involving 42 newly diagnosed (duration <6 months), treatment-naïve RA patients (mean age 45.2 ± 8.1 years; 33 females, 9 males) and 42 healthy controls (mean age 44.8 ± 7.9 years; 33 females, 9 males). A standard 5-min resting electrocardiogram was recorded for all participants. HRV analysis was performed to derive time-domain parameters: Standard deviation of NN intervals (SDNN), root mean square of successive differences (RMSSD), and frequency-domain parameters: Low frequency (LF) power, high frequency (HF) power, and LF/HF ratio. **Results:** The RA group showed a significant reduction in all HRV parameters compared to the control group. SDNN (32.1 ± 8.4 ms vs. 48.9 ± 11.2 ms, $P < 0.001$), RMSSD (21.5 ± 6.8 ms vs. 35.3 ± 9.7 ms, $P < 0.001$), and total power (346 ± 112 $ms^{2\ vs.}$ 782 ± 245 ms^2, $P < 0.001$) were markedly lower in the RA group. In the frequency domain, both LF power (112 ± 45 $ms^{2\ vs.}$ 285 ± 98 ms^2, $P < 0.001$) and HF power (98 ± 41 $ms^{2\ vs.}$ 254 ± 87 ms^2, $P < 0.001$) were significantly reduced. The LF/HF ratio was not significantly different between the two groups (1.18 ± 0.4 vs. 1.12 ± 0.3, $P = 0.45$). **Conclusion:** Newly diagnosed, treatment-naïve RA patients exhibit significantly reduced HRV, indicating global autonomic impairment affecting both sympathetic and parasympathetic branches equally, without a shift in autonomic balance. This suggests that autonomic dysfunction is an early feature of RA, possibly linked to the systemic inflammatory process itself. HRV serves as a valuable tool for its early detection.

Keywords: Autonomic dysfunction, Heart rate variability, Newly diagnosed, Parasympathetic, Rheumatoid arthritis, Sympathetic.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disorder characterized primarily by persistent synovitis of the diarthrodial joints, leading to pain, swelling, stiffness, and progressive joint destruction, often resulting in significant functional disability and reduced quality of life.[1] The pathophysiology of RA is a complex interplay of genetic predisposition (e.g., shared epitope in *HLA-DR* genes), environmental triggers (e.g., smoking, microbial agents), and dysregulated immune responses. This dysregulation leads to the activation of innate and adaptive immune cells, production of autoantibodies (rheumatoid factor and anti-citrullinated protein antibodies), and a cascade of pro-inflammatory cytokines, most notably tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1.[2] This self-perpetuating inflammatory process results in the formation of pannus tissue, cartilage degradation, and bone erosion.

While the articular manifestations define the clinical diagnosis, RA is more accurately described as a systemic disease with profound extra-articular consequences. Among

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these, cardiovascular disease (CVD) stands as the leading cause of premature mortality, accounting for nearly 40–50% of all deaths in the RA population.[3] The risk of myocardial infarction, heart failure, and sudden cardiac death is significantly elevated compared to the general population, a risk comparable to that of patients with type 2 diabetes.[4] This elevated cardiovascular risk is not fully explained by an increased prevalence of traditional risk factors such as hypertension and dyslipidemia alone. Instead, the chronic, systemic inflammatory state inherent to RA is now recognized as a major, independent driver of accelerated atherosclerosis and cardiovascular morbidity.[5] Chronic inflammation promotes endothelial dysfunction, oxidative stress, and a pro-thrombotic state, creating a fertile ground for cardiovascular events.

One critical, yet often subclinical, mechanism linking systemic inflammation to cardiovascular risk is autonomic dysfunction, specifically cardiovascular autonomic dysregulation.[6] The autonomic nervous system (ANS), comprising the sympathetic (SNS) and parasympathetic (PNS) branches, is the primary regulator of cardiovascular homeostasis, controlling heart rate, blood pressure, vascular tone, and cardiac contractility. A delicate balance between the SNS (catabolic, "fight-or-flight") and PNS (anabolic, "rest-and-digest") is essential for maintaining physiological stability. Disruption of this balance, often manifesting as reduced PNS tone and/or SNS overactivity, is associated with increased arrhythmogenesis, endothelial dysfunction, and plaque vulnerability.[7]

Heart rate variability (HRV), defined as the beat-to-beat variation in the heart's R-R intervals, is a simple, non-invasive, and highly reproducible quantitative marker of autonomic heart rate control.[8] The analysis of HRV, through time-domain and frequency-domain parameters, provides a window into the integrity and dynamic interaction of the SNS and PNS. A reduction in overall HRV (e.g., low standard deviation of NN intervals [SDNN]) is a powerful and independent predictor of adverse cardiovascular outcomes and all-cause mortality in various conditions.[9] A decrease in high-frequency (HF) power is a specific indicator of impaired PNS (vagal) activity, whereas the interpretation of low-frequency (LF) power and the LF/HF ratio is more complex, reflecting baroreceptor function and the sympathovagal balance.[8]

A growing body of evidence has documented impaired HRV in patients with established RA, indicating a state of autonomic imbalance, typically characterized by reduced global HRV and suppressed PNS activity.[10,11] However, a significant limitation of most existing studies is their focus on patients with long-standing disease. These findings are potentially confounded by the cumulative effects of chronic pain, joint deformity, physical deconditioning, and, most notably, long-term exposure to medications such as corticosteroids, non-steroidal anti-inflammatory drugs, and disease-modifying anti-rheumatic drugs (DMARDs), all of which can independently influence ANS function.[12] Consequently, it remains unclear whether autonomic dysfunction is a primary feature of RA's pathophysiology or a secondary consequence of the chronic disease state and its treatment.

To address this critical gap in the literature, it is essential to investigate the ANS at the earliest possible stage of the disease. Studying newly diagnosed, treatment-naïve patients provides a unique opportunity to observe the unadulterated impact of RA-associated systemic inflammation on autonomic regulation, free from the confounding effects of long-term therapy and chronic disability. Therefore, this case–control study was designed with the primary objective to comprehensively assess and compare autonomic function, using standardized time-domain and frequency-domain HRV analysis, in a rigorously selected cohort of 42 newly diagnosed, treatment-naïve RA individuals and 42 age- and sex-matched healthy controls. We hypothesize that autonomic dysfunction, evidenced by significantly reduced HRV parameters, is present at the clinical inception of RA, underscoring its role as an early, intrinsic extra-articular manifestation of the disease.

Materials and Methods

Research design, setting, and population

This study employed an analytical, case–control design to compare autonomic function between newly diagnosed RA patients and healthy controls. The study was conducted over 12 months by the Department of Physiology. The target population for the case group consisted of all adults (aged 18–60 years) presenting to the rheumatology outpatient department with a new diagnosis of RA within the preceding 6 months. The target population for the control group consisted of age- and sex-matched healthy individuals with no history of chronic inflammatory or autoimmune disease, recruited from hospital staff, patient attendants, and the local community.

Inclusion and exclusion criteria for sample selection

- Inclusion criteria for RA group (cases):
  1. Fulfillment of the 2010 ACR/EULAR classification criteria for RA
  2. Diagnosis of RA within the last 6 months (≤180 days)
  3. Age between 18 and 60 years
  4. No prior exposure to DMARDs, biologic agents, or corticosteroids.
- Inclusion criteria for control group:
  1. Age and sex-matched to the RA cases
  2. No clinical evidence or history of any chronic inflammatory, autoimmune, or CVD.
- Exclusion criteria (for both groups):
  1. Diagnosis of diabetes mellitus, hypertension, or known CVD (e.g., coronary artery disease, heart failure, and arrhythmia)
  2. Thyroid dysfunction, renal impairment, or hepatic disease
  3. Pregnancy or lactation
  4. Current use of any medication known to affect autonomic tone (e.g., beta-blockers, anticholinergics, and antidepressants)

5. Presence of any condition that could interfere with HRV recording (e.g., atrial fibrillation and excessive ectopy).

Sample size calculation

The sample size was calculated using G*Power software (version 3.1.9.7). Based on a previous similar study by Evrengül *et al*. (2004), an effect size (Cohen's d) of 0.9 for the primary outcome variable, SDNN, was anticipated. To achieve a statistical power (1-β) of 0.95 and a significance level (α) of 0.05 for a two-tailed independent samples t-test, a minimum of 38 participants per group was required. To account for potential dropouts or technical issues with data acquisition, the sample size was rounded up to 42 participants in each group, making a total sample size of 84.

Procedure for data collection

Data collection followed a standardized protocol:

1. Screening and consent: Potentially eligible participants were screened. Those who met the criteria were explained the study's nature and purpose, and written informed consent was obtained.
2. Clinical assessment: All RA patients underwent a detailed clinical evaluation by a rheumatologist, including a 28-joint count for tenderness and swelling to calculate the DAS-28 score.
3. Blood sampling: Fasting venous blood samples were drawn from RA patients for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) analysis.
4. HRV recording
   - Participants were instructed to refrain from smoking, alcohol, caffeine, and heavy meals for 12 h before the test.
   - The test was conducted in the morning (9-11 AM) in a quiet, temperature-controlled laboratory.
   - After a 10-min supine rest to achieve a steady physiological state, a 5-min single-lead electrocardiogram (ECG) was recorded in the supine position using a high-fidelity digital ECG recorder. Participants were instructed to breathe normally but not to fall asleep or speak.

Data analysis

All data were anonymized using a unique identification code for each participant. The data, including demographic details, clinical scores, laboratory results, and derived HRV parameters, were entered into a password-protected Microsoft Excel spreadsheet. To ensure data integrity, a double-data entry and verification process was employed. The final, verified dataset was stored on a secure, encrypted institutional server, accessible only to the principal investigators. Statistical analysis was performed using IBM Statistical Package for Social Sciences Statistics for Windows, Version 26.0.

Results

As detailed in Table 1, the study groups were well-matched for baseline demographics. There was no statistically significant difference in age (45.2 ± 8.1 years vs. 44.8 ± 7.9 years, $P = 0.817$) or sex distribution (78.6% female in both groups) between the RA and control cohorts. The body mass index was also comparable between groups (24.1 ± 3.2 kg/m^2 vs. 23.8 ± 2.9 kg/m^2, $P = 0.654$). As expected, the RA group had a mean disease duration of 3.4 ± 1.5 months and exhibited high disease activity, with a mean DAS-28 score of 5.8 ± 1.1. Crucially, the systemic inflammatory markers were significantly elevated in the RA group, with ESR and CRP levels being substantially higher than in the control group (48.5 ± 16.2 mm/1st h vs. 12.3 ± 5.1 mm/1st h, $P < 0.001$ for ESR; and 28.4 ± 10.7 mg/L vs. 3.1 ± 1.5 mg/L, $P < 0.001$ for CRP), confirming the presence of active systemic inflammation in the patient cohort (Table 1).

The analysis of HRV parameters, presented in Table 2, revealed profound autonomic dysfunction in the RA group. In the time-domain analysis, all measures were significantly reduced in patients compared to controls. The SDNN, a marker of overall HRV, was markedly lower in the RA group (32.1 ± 8.4 ms vs. 48.9 ± 11.2 ms, $P < 0.001$). Similarly, the root mean square of successive differences (RMSSD), a key indicator

Table 1: Baseline demographic and clinical characteristics of the study participants

Characteristic	RA group (*n*=42)	Control group (*n*=42)	*P*-value
Age (years)	45.2±8.1	44.8±7.9	0.817
Sex, *n* (%)			1.000
Female (%)	33 (78.6)	33 (78.6)	
Male (%)	9 (21.4)	9 (21.4)	
Body mass index (kg/m^2)	24.1±3.2	23.8±2.9	0.654
Disease duration (months)	3.4±1.5	-	-
DAS-28 score	5.8±1.1	-	-
ESR (mm/1st h)	48.5±16.2	12.3±5.1	**<0.001**
CRP (mg/L)	28.4±10.7	3.1±1.5	**<0.001**

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, Bold: Highly significant

Table 2: Comparison of heart rate variability parameters between RA patients and healthy controls

HRV parameter	RA group (*n*=42)	Control group (*n*=42)	*P*-value
Time-domain analysis			
Mean NN interval (ms)	752.3±85.6	798.5±92.4	0.021
SDNN (ms)	32.1±8.4	48.9±11.2	**<0.001**
RMSSD (ms)	21.5±6.8	35.3±9.7	**<0.001**
pNN50 (%)	5.2±3.1	12.8±5.5	**<0.001**
Frequency-domain analysis			
Total power (ms^2)	346±112	782±245	**<0.001**
LF power (ms^2)	112±45	285±98	**<0.001**
HF power (ms^2)	98±41	254±87	**<0.001**
LF power (nu)	52.1±8.5	53.8±7.2	0.321
HF power (nu)	47.9±8.5	46.2±7.2	0.321
LF/HF ratio	1.18±0.4	1.12±0.3	0.445

HRV: Heart rate variability, SDNN: Standard deviation of NN intervals, RMSSD: Root mean square of successive differences, LF: Low frequency, HF: High frequency, Bold: Highly significant

of PNS activity, was significantly suppressed in RA patients (21.5 ± 6.8 ms vs. 35.3 ± 9.7 ms, $P < 0.001$). The frequency-domain analysis corroborated these findings. The RA group demonstrated a severe reduction in Total Power (346 ± 112 ms^2 vs. 782 ± 245 ms^2, $P < 0.001$), indicating a global decline in autonomic modulation. Both the LF power (112 ± 45 ms^2 vs. 285 ± 98 ms^2, $P < 0.001$) and HF power (98 ± 41 ms^2 vs. 254 ± 87 ms^2, $P < 0.001$) in absolute units were significantly lower in the RA group. However, when these components were expressed in normalized units, there was no significant difference in LF (nu), HF (nu), or the LF/HF ratio between the groups ($P = 0.321$ and $P = 0.445$, respectively), suggesting a concurrent impairment of both autonomic branches without a shift in the sympathovagal balance (Table 2).

To further investigate the relationship between inflammation and autonomic function, correlation analyses were performed within the RA group, with the results shown in Table 3. Strong, statistically significant negative correlations were observed between all key HRV parameters and the measures of disease activity. Specifically, SDNN, RMSSD, total power, LF power, and HF power all correlated inversely with the DAS-28 score (e.g., SDNN: r = −0.612, $P < 0.01$), ESR (e.g., SDNN: r = −0.548, $P < 0.01$), and CRP (e.g., SDNN: r = −0.589, $P < 0.01$). This indicates that higher disease activity and greater systemic inflammation are directly associated with a more significant reduction in HRV (Table 3).

Discussion

This case–control study was designed to elucidate the state of ANS function at the very inception of RA, free from the confounding influences of chronicity and pharmacotherapy. Our principal finding is that newly diagnosed, treatment-naïve RA patients exhibit a significant and global reduction in HRV compared to their healthy counterparts. This manifests as a concurrent depression of both SNS (LF power) and PNS (RMSSD, HF power) components, indicating widespread autonomic impairment rather than a simple shift in sympathovagal balance, as evidenced by an unaltered LF/HF ratio. Furthermore, the strong inverse correlation between HRV parameters and disease activity markers suggests a direct link between the systemic inflammatory milieu and autonomic dysfunction.

Table 3: Correlation between HRV parameters and disease activity markers in the RA group ($n=42$)

HRV parameter	DAS-28	ESR	CRP
SDNN	−0.612**	−0.548**	−0.589**
RMSSD	−0.598**	−0.531**	−0.572**
Total power	−0.634**	−0.562**	−0.601**
LF power	−0.571**	−0.503**	−0.540**
HF power	−0.554**	−0.488**	−0.525**

**Correlation is significant at the $P<0.01$ level (2-tailed). Calculated using Pearson's correlation coefficient*. HRV: Heart rate variability, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, SDNN: Standard deviation of NN intervals, RMSSD: Root mean square of successive differences, LF: Low frequency, HF: High frequency

The significantly reduced SDNN and total power in our RA cohort point to an overall decline in autonomic modulation, which is a recognized predictor of adverse cardiovascular prognosis.[8] The most striking finding is the pronounced suppression of PNS tone, as unequivocally demonstrated by the markedly lower values of RMSSD and HF power. This finding aligns with the growing understanding of the "cholinergic anti-inflammatory pathway," a neural mechanism through which the vagus nerve suppresses the release of pro-inflammatory cytokines.[13] Our results suggest that this crucial anti-inflammatory pathway may be impaired from the earliest clinical stages of RA. The failure of this homeostatic mechanism could potentially create a vicious cycle, where inflammation damages autonomic control, which in turn permits further unchecked inflammation, thereby contributing to both disease persistence and heightened cardiovascular risk.

Our results find strong support in the literature, yet also highlight the critical importance of studying early disease. A study by Evrengül *et al*. (2004),[9] which included RA patients with a AQ3
mean disease duration of 7 years, also reported significantly reduced time and frequency-domain HRV parameters, including SDNN and HF power, compared to controls. The consistency between their findings in established RA and ours in new-onset disease strongly suggests that the autonomic defect is a fundamental aspect of RA pathophysiology, rather than a late sequelae. However, a key distinction lies in the pattern of sympathovagal balance. Some studies in established RA have reported an elevated LF/HF ratio, implying a relative SNS dominance.[10] In contrast, our treatment-naïve cohort showed no such shift. This divergence suggests that the apparent SNS overactivity observed later in the disease course may be a secondary phenomenon, potentially driven by chronic pain, medication effects, or long-term adaptive mechanisms, rather than a primary event.

The significant reduction in LF power observed in our patients provides a more nuanced view of autonomic involvement. While often interpreted as a marker of SNS activity, LF power is heavily influenced by baroreceptor function and represents a complex interplay between both autonomic branches.[8] Its reduction, in the context of equally suppressed HF power, indicates a state of global autonomic failure. This pattern of combined impairment is corroborated by a study by Stojanovich *et al*. in autoimmune patients, which described a "non-dipper" pattern of blood pressure and autonomic dysfunction, attributing it to the inflammatory process affecting central autonomic networks.[14] Our findings in early RA are consistent with this hypothesis, pointing toward a systemic insult that broadly disrupts autonomic regulation.

The robust negative correlations we observed between HRV indices (SDNN and RMSSD) and inflammatory markers (DAS-28, ESR, and CRP) provide a compelling mechanistic link. Pro-inflammatory cytokines such as TNF-α and IL-6, which are highly elevated in active RA, have been shown to have direct access to the central nervous system, where they can disrupt nuclei responsible for autonomic control.[5,14,15]

Furthermore, inflammation can cause oxidative stress and damage to peripheral nerve fibers and cardiac innervation. Therefore, the autonomic dysfunction we detected via HRV is likely a direct consequence of the systemic inflammatory burden, positioning it as a key intermediary between RA-related inflammation and the accelerated cardiovascular morbidity observed in these patients.

The demonstration of significant autonomic dysfunction at diagnosis has important clinical ramifications. HRV analysis could serve as a simple, non-invasive tool for early cardiovascular risk stratification in RA. Identifying patients with severe autonomic impairment at baseline might allow clinicians to flag them for more aggressive management of both inflammation and traditional cardiovascular risk factors.

Conclusion

This study provides clear evidence that autonomic dysfunction, characterized by a global reduction in HRV affecting both SNS and PNS branches, is present at the clinical onset of RA. This dysfunction is closely correlated with disease activity, implicating systemic inflammation as a primary driver. The use of HRV as a tool offers a valuable window into this subclinical, yet prognostically significant, extra-articular manifestation. Integrating autonomic assessment into the initial evaluation of RA could enhance risk prediction and pave the way for more comprehensive cardiovascular protection strategies from the very start of the disease journey.

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