Elevated sympathetic nervous system activity in patients with recently diagnosed rheumatoid arthritis with active disease

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Abstract

Objective

To investigate sympathetic (SNS) and parasympathetic (PNS) nervous system activity in patients with recently diagnosed rheumatoid arthritis (RA), and to analyze the association between activity of these systems and disease activity, and complaints that frequently occur in RA, viz., pain, fatigue, negative mood, and stiffness.

Methods

To assess sympathetic and parasympathetic nervous activity, the Pre-Ejection-Period (PEP) and Respiratory Sinus arrythmia (RSA) were measured on two consecutive nights in a real-life environment in 25 patients with RA [19 female (f), 6 male (m), mean age 55.2 years) and 28 healthy controls (20f, 8m, mean age 55.8 years].

Results

Patients showed a significantly shorter PEP (reflecting elevated SNS activity) compared to healthy controls, an effect that was most pronounced in those with active disease. RSA and the heart period did not differ between patients and healthy controls. The heart period was significantly associated with stiffness, but neither PEP nor RSAwere associated with pain, fatigue, mood, or stiffness.

Conclusion

Our study showed that cardiac sympathetic nervous system activity is elevated in RA, whereas cardiac parasympathetic activity remains at a normal level. Our results suggest that inflammatory stress rather than the common symptoms of RA challenge the SNS.

Key words

Rheumatoid arthritis, sympathetic, parasympathetic, pre-ejection-period, respiratory sinus arrhythmia.

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease which is characterized by chronic inflammation of the joints. During inflammatory stress, pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor -α (TNF-α) are released from the inflammatory site and stimulate the secretion of corticotropin-releasing-hormone (CRH) (1, 2). CRH in turn activates the sympathetic nervous system and the release of catecholamines (2-5). In addition, afferent vagal input has been suggested to be activated by cytokines (6-9), thereby functioning as a pathway for communication between cytokines and the brain (6-9). Although both the sympathetic and parasympathetic nervous systems are activated by disease activity, the efferent sympathetic part of the autonomic nervous system (ANS) in particular has been suggested to play an important role in inflammation in RA (10-12). Some attention has been drawn to the possibility of efferent vagal modulation of local and systemic inflammation (13-17). In response to inflammation-linked stimuli, parasympathetic outflow was reported to increase.

Experimental studies have reported altered cardiac autonomic nervous responsiveness in RA patients (18, 19). In these studies, standardized autonomic function tests (Valsalva maneuver, deep breathing, orthostatic tests) and mental stress tasks were commonly employed to assess autonomic nervous responsiveness. Most frequently, elevated resting heart rate levels, and diminished autonomic nervous reactivity have been found in RA patients compared to healthy controls (18, 19). The observed altered autonomic nervous reactivity in RAhas been suggested to pertain to both diminished sympathetic (18) and diminished parasympathetic reactivity (19, 20). Although altered autonomic reactivity in RA has been reported to be associated with the severity of pain (18), and with the number of swollen joints (19), in general no associations between autonomic nervous system functioning and disease activity variables or disease duration were observed (18, 19).

To date cardiac autonomic nervous system functioning in RA patients has been assessed in experimental settings in reaction to standardized tasks. However, ANS activity in the natural environment may better reflect the common state than responses to laboratory stressors. Moreover, except for one study (18), autonomic nervous activity was studied in patients with longstanding RA. In such patients ANS function will primarily reflect the long-term consequences of inflammation and other stressors of the disease, while the possible role of the ANS as an antecedent or contributing factor to the disease process will be more clearly manifested in the early phase of RA. In addition, in previous studies the heart rate and blood pressure were included to assess autonomic nervous system activity. These autonomic variables reflect a mixed influence of both the sympathetic and parasympathetic nervous systems. In the present study, we aimed at a more direct assessment of sympathetic and parasympathetic activity in RApatients.

Elevated sympathetic nervous system and increased parasympathetic nervous system activity are expected to occur as a consequence of inflammatory stress. In addition, ANS dysfunction may occur as a result of deconditioning mechanisms and psychological stressors, such as the frequently occurring symptoms of RA – pain, fatigue, and negative mood (21-23). These kinds of associations are likely to be bi-directional. For example, pain as a stressor induces sympathetic activation, whereas sympathetic activation affects pain thresholds and tolerance (24, 25).

The main aim of this study was to investigate whether sympathetic and parasympathetic activity nervous system activity are increased in patients with recently diagnosed RA. In addition, we explored whether the activity of these systems is associated with disease activity and the symptoms of pain, fatigue, negative mood, and stiffness.

Materials and methods

Participants

The participants were 25 recently diagnosed patients with RA (19 women,

mean age 55.2 years, SD 13.0) and 28 healthy controls (20 women, mean age 55.8 years, SD 11.3). Patients had a median erythrocyte sedimentation rate (ESR) of 15.0 mm/first hour (range 3-60), a median Thompson joint score of 31.0 (range 0-465), and a disease duration <2 years. Patients were drawn from a sample of a larger population-based study on the efficacy of 3 medication treatment strategies among outpatients with RAof recent onset (26).

Three patients were taking disease-modifying antirheumatic drugs (DMARDs) alone (1 intramuscular gold, 2 oral methotrexate), and 15 patients were taking non-steroidal antiinflammatory drugs (NSAIDs) in combination with DMARDs (1 intramuscular and 1 oral gold, 1 penicillamine, 1 sulfasalazine, 3 hydroxychloroquine, 8 oral methotrexate). At the time of the study, 5 patients were taking prednisone (5 to 10 mg daily), 2 of them in combination with NSAIDs, 2 in combination with DMARDs, and one in combination with NSAIDs and DMARDs. None of the patients received any corticosteroid joint injection within 3 months prior to the start of the study. Two patients used no medication at all.

Inclusion criteria were: (1) RA according to the American College of Rheumatology (ACR) classification criteria (27), (2) a minimal age of 18 years, and (3) absence of other serious diseases. The healthy controls were recruited via the RA patients and friends and relatives. Exclusion criteria for the healthy controls included the presence of: (1) a chronic disease, (2) chronic pain, (3) heart problems, or (4) hypertension. The recruitment period covered four months. All subjects took part voluntarily and provided written informed consent for their participation in the study. They were paid a small sum for their attendance.

The study was approved by the Medical Ethic Committee of the University Medical Center Utrecht.

Procedure

Assessments were taken in the real-life environment of the subjects on two consecutive days using an identical assessment procedure. On the evening prior to the start of the study, each participant was individually visited at home by a research assistant, who explained the procedure to the subject. At night, subjects were equipped with the ambulatory monitoring device (AMD) (28), which continuously registered cardiac autonomic activity at night. Autonomic activity was assessed during sleep at their home, which has the advantage of minimal influences of postural and physical activity changes, the consumption of caffeine and nicotine, and psychological events.

After explaining the procedure on the evening prior to the start of the study, the subject was attached to the ambulatory recording equipment. Subjects started the recording when going to bed. During the time of the study, a short manual was left at the subject's home, in which he/she could re-read the instructions on how to attach the device and what to do in case it failed to record properly. If the measuring equipment failed to function, and following the instructions did not solve the problem, the subjects could contact one of the research assistants on a mobile phone at any time for help. The next morning, subjects were allowed to detach the measuring device when they got out of bed.

During the day ecological momentary assessment was used (29, 30). Participants were alerted by a beep from a pre-programmed wristwatch (Ironman Triathlon, Timex® Data Link) at 9 fixed time points: on awakening, 15, 30, and 45 minutes later, and at 10:00 am, 12:00 pm, 2:30 pm, 5:00 pm, and 7:30 pm. At each time point, subjects were instructed to collect a saliva sample. Study data on the cortisol concentration in saliva is reported in Dekkers *et al*. (31). Apart from the time of awakening, participants were instructed to answer questions concerning pain, negative mood, and stiffness, recording their responses in a prepared booklet. Half an hour after awakening, participants also rated the quality of their sleep during the past night. Participants were instructed to continue their normal sleep, daily activity and work routines, and to refrain from heavy exercise during the period of the study.

Physiological equipment

Autonomic activity at night was recorded by means of an ambulatory monitoring device (AMD) (28, 32). The AMD simultaneously records electrocardiogram (ECG) and impedance cardiogram (ICG) signals, from which the cardiac parasympathetic and sympathetic activity were derived, respectively. In addition, the AMD records the respiration signal (i.e. inspiration and expiration phases). After the skin was firmly rubbed with alcohol, disposable pre-gelled electrodes (AMI type 1650-005 Medtronic) for the recording of the ECG were placed on the sternum over the first rib, at the apex of the heart over the ninth rib on the left lateral margin of the chest, and a ground electrode above the right iliac crest. The ECG electrode on the sternum over the first rib is a combined ECG/ICG electrode, also designed to measure the ICG signal. The second measuring electrode was placed directly over the tip of the xyphoid process of the sternum. The two ICG current electrodes were placed at the back, at the base of the neck (C3/C4) and over vertebrae T8/T9 (28, 33).

Autonomic activity variables

The period (in milliseconds) between two R-waves of two successive QRS-complexes in the ECG signal is called the inter-beat interval or heart period.

The pre-ejection period (PEP) is defined as the period running from the start of the electromechanical depolarization of the ventricles (Q-point of the ECG) till the actual ejection of blood from the left ventricle (opening of the aortic valve). This point, called the B-point, is identified as a change in the slope of the ascending section of the dZ/Dt waveform, which is often easily recognized in the graphic display of the ICG signal (34). The PEPis an index of cardiac contractility and has been proven to be a useful marker of the sympathetic influence on the heart (34, 35).

ICG values were stored during user defined "beat-to-beat" periods, during which data on all heart periods was stored. In this study, the AMD software was set to start a 10-minute 'beat-to-beat' recording every hour. The ICG

signal was averaged every 30 seconds to obtain averaged PEP values. With the use of AMD software (32), it was possible to visually check the positions at time of the upstroke (B-point), which is used to indicate the onset of left ventricular ejection, and the Dz/ Dt_{min} point in the impedance cardiogram. These points were edited when the algorithm failed to correctly detect them. Next, PEP was computed as the time period (in msec) between the Q-point of the ECG and the B-point of the ICG signal.

Respiratory sinus arrhythmia (RSA) reflects the parasympathetic influence on the heart. RSA is a rhythmical fluctuation in heart periods at the respiratory frequency that is characterized by shortening and lengthening of the heart periods in a phase relationship with inspiration and expiration, respectively (36). The peak-to-trough method is a method that uses the time series of heart periods, which are derived from the ECG signal, in combination with the respiration signal to compute the RSA (33). With this method, the RSA score was computed as the difference between the shortest heart period during heart rate (HR) acceleration in the inspiratory phase and the longest heart period during deceleration in the expiratory phase (28). All signals were visually checked for disturbances in the heart rate and respiration signal that were simultaneously shown.

As the RSA is very sensitive to variations in respiration (37), periods in which respiration was considered to be unreliable were deleted. In fact, the RSA can be interpreted as parasympathetic control of the heart, provided there is stable respiratory behavior (28, 35, 37, 38). Analyses of respiration showed no difference in the respiration rate between groups (data not shown), reflecting that RSA results are not influenced by differences in respiration.

Due to equipment failure, autonomic activity data are not available for 1 patient and 1 healthy control.

Symptom assessment

Assessment of common symptoms in RA, i.e. pain, fatigue, negative mood, and stiffness have been described in detail elsewhere (39). At each signaled time point, participants rated the extent to which they felt each symptom on a 5-point Likert scale. Scales were recoded so that for each symptom the score ranged from 0 (no pain, fatigue, negative mood, stiffness) to 4 (extreme pain, fatigue, negative mood, stiffness). None of the values for pain, fatigue, negative mood, and stiffness were missing.

Half an hour after awakening, participants completed a Dutch questionnaire on sleep quality (GSKL) (40) to assess quantitative and qualitative aspects of their sleep during the past night. The score ranged from 0 (high sleep quality) to 15 (low sleep quality).

Disease activity measures

The ESR (Westergren) of patients was assessed during a routine visit to the hospital, which took place within approximately two weeks after or before their participation in the study. The Thompson joint score (41) was assessed on the evening of the first day at the patient's home by a trained research assistant. Joints that were both painful and swollen were scored. The theoretical range varies from 0 to 534.

Statistical analysis

Disease activity measures (ESR and Thompson joint score) were considered as a dichotomous variable. A median split yielded limits for both the ESR (range 3-60) and the Thompson joint score (range 0-465) which more or less agreed with the cut-off point for active disease. For the joint score, the group without active disease had a Thompson joint score <7 (n =11; range 0-6) and the group with active disease had a Thompson joint score > 30 (n = 13; range 31-465). Similarly, the median split for ESR yielded groups of patients without (ESR < 16 mm/h, n = 13; range 3-15) and with active disease (ESR > 20 mm/h; n=11; range 21-60).

Since the sleep duration varied but all subjects slept at least 6 hours, autonomic activity recording data of the first 6 hours from sleep onset were analyzed. Mean values for sympathetic activity, parasympathetic activity, and the heart period were averaged across each 10-minute beat-to-beat period (per hour) during each night. Mean levels of the symptoms of pain, fatigue, negative mood, and stiffness for each day were averaged across the 8 time points.

In preceding analyses we tested whether the mean levels and trends of the ANS variables differed between the two nights. Neither the levels nor trends differed significantly between the nights, and consequently we used the averaged data of the two nights in further analyses.

Repeated measures analysis of variance was used to examine whether the trends and levels of the ANS variables differed between patients and healthy controls. This method allows one to simultaneously analyze group differences (such as differences between patients and healthy participants) and *within-subject* changes (such as changes in the trend of a variable).

We tested whether the mean levels of the ANS variables (across nights) were different for the patient and healthy control groups (*group effect*), and whether the trends of the ANS variables (across nights) differed between the patients and healthy controls (*time x group interaction*). In cases where significant group differences were found, Student-Newman-Keuls post-hoc comparison tests were used to locate specific pair-wise differences in the level or trend of the ANS variables. T-tests for independent samples were performed to assess differences in symptoms and sleep quality between patients and healthy controls.

All symptoms and autonomic activity variables met the assumption of linearity, expect negative mood. Therefore, Pearson's product moment correlation coefficients were calculated in the patient group to analyze the associations of autonomic activity variables and symptoms (pain, fatigue and stiffness). Spearman's rank order correlation coefficients were calculated in the patient group to analyze associations in which negative mood was involved. Partial correlations to control for age, gender, and disease activity were computed where appropriate.

Results

Sympathetic and parasympathetic activity

Figure 1 shows the levels and trends of the PEP and RSA, reflecting cardiac sympathetic and parasympathetic activity respectively, and of the heart period by group (patients versus healthy controls). A significant group effect for PEP was found ($F_{1.49} = 5.5$, $p = 0.02$), indicating higher mean levels of sympathetic activity in patients than in healthy controls. Mean levels for parasympathetic activity ($F_{1.49} = 1.85$; $p = 0.18$) and the heart rate ($F_{1.49} = 1.7$, $p = 0.20$) did not differ between the two groups.

PEP showed a significant *time x group* interaction ($F_{5.45} = 2.8$, $p = 0.03$), indicating a different trend for the PEP in patients and healthy controls. The PEP in healthy controls steadily increased from the second hour after sleep onset, reflecting a decrease in sympathetic activity, whereas in patients the PEP remained more or less stable (Fig. 1). For RSA($p = 0.58$) and the heart period ($p = 0.61$) the trend did not differ between patients and healthy controls.

To check whether prednisone had influenced SNS activity level because of its mitigating effect on the counter-regulatory loop of the HPA axis, the aforementioned analyses were repeated separately in patients who were and were not taking prednisone. The mean PEP was not significantly different between these two groups ($p = 0.6$), suggesting that prednisone had not affected SNS activity in our patients.

Disease activity

We investigated whether the levels and trends in the PEP, RSAand heart period were different between patients with and without active disease based on their joint score (Fig. 2) and ESR (Fig. 3). The PEP was significantly different between the three groups for the joint score ($F_{2.48} = 3.2$, $p = 0.05$) and for ESR ($F_{2.48} = 3.4$, $p < 0.05$), with the PEP being shortest in patients with active disease, higher in patients without active disease, and highest in healthy controls (Figs. 2 and 3).

Mean levels of RSA were not significantly different between the healthy controls and the patients grouped by joint score ($F_{2.48} = 2.7$, $p = 0.08$) or by ESR ($p = 0.25$). Since healthy controls and patients with active disease based on the joint score showed a similar RSA (Fig. 2), the observed trend was considered to be of no further relevance.

The mean heart period was significantly ($F_{2.48} = 4.2$, $p = 0.02$) different for controls and the patients grouped by joint score; patients with active disease had a significantly shorter heart period, i.e., a higher heart rate, compared to both the patients without active disease and the healthy controls ($p = 0.05$). The mean heart period did not significantly differ between the controls and patients grouped by ESR ($p = 0.33$), but the results pointed in the same direction as observed when considering the joint score. The trends for PEP, RSAand the heart period across the night did not differ between the subgroups (no *time x group* interaction).

Disease-related symptoms, sleep quality, and associations with ANS activity

The time of going to bed ($p = 0.94$), sleep duration ($p = 0.56$), and sleep quality ($p = 0.18$) did not differ between the groups. Sleep quality also did not differ between patients with high and low disease activity ($p = 0.87$).

Neither the PEP nor RSA at night showed associations with any of the symptoms levels (Table I). The heart period was negatively associated with the stiffness level ($r = -0.52$, $p = 0.010$); patients with a shorter heart period (i.e. a higher heart rate) experienced more stiffness during the day. Controlling for gender or disease activity did not affect this association. A trend was observed for a correlation between the heart period and pain ($r = -0.37$, $p = 0.08$), suggesting that patients experiencing more pain during the day had a higher heart rate at night.

None of the autonomic variables (all ps > 0.31) was significantly associated with sleep quality.

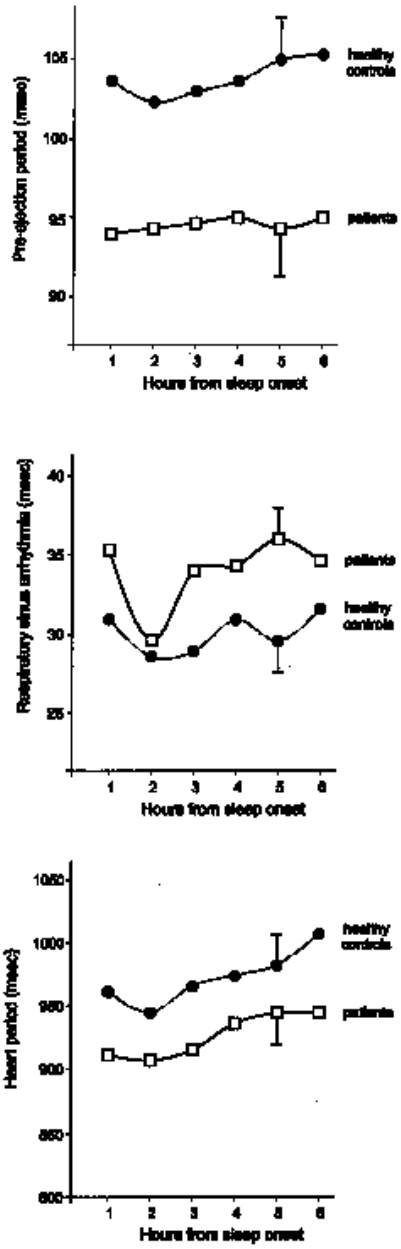

Fig. 1. Mean levels (± SEM) and the change over time in the pre-ejection-period (PEP), respiratory sinus arrythmia (RSA) and heart period in 24 patients with recently diagnosed rheumatoid arthritis and in 27 healthy controls. (For clarity, the error bar is only presented at the 5th hour of sleep).

Discussion

Although the autonomic nervous system has frequently been suggested to be involved in inflammatory processes, only a few physiological studies in RA have addressed this issue. To examine ANS activity in RA, we used methods that enabled us to differentiate between sympathetic and parasympathetic ANS activity in the natural environment of patients recently diagnosed with RA.

Our results suggested elevated sympathetic activity in patients with RA. This

finding is in line with growing evidence pointing to impaired ANS activity in RA (42, 43). Similar hypersympathetic nervous tone has been observed in patients with SLE, Crohn's disease and ulcerative colitis (44), suggesting that increased sympathetic activity may be a common phenomenon in chronic inflammatory diseases.

No difference in RSA between patients and healthy controls was found, suggesting that parasympathetic activity is not affected by chronic inflammation. A similar conclusion was reported in a study of parasympathetic stress responsiveness (45). The normal heart period found in our patients is in line with a previous observation in patients with a recent RA diagnosis (18), but contrasts with the observed elevated heart rate levels in patients with longstanding RA (46, 20).

Therefore our examination of ANS activity suggests that – as expected – SNS activity in particular is elevated in the early phases of RA, and that PNS activity is at a normal level.

We expected disease activity to be involved in altered ANS activity. Elevated sympathetic activity and an increased heart rate in patients was most pronounced in those with active disease, whereas parasympathetic activity was not dependent on disease activity. The elevated sympathetic activity may point to an adaptive reaction to dampen immune and inflammatory responses (47), or to a disadvantageous consequence of CRH stimulation of which the primary functional role is to dampen inflammation via cortisol increase. This finding, combined with the previous observation of elevated cortisol levels in this group with active disease (31) is supportive of our hypothesis that cytokines released by inflammatory tissues activate the SNS (1, 2), through the stimulation of CRH that simultaneously activates cortisol release. This mechanism needs further confirmation.

In addition to inflammatory stress, we explored the associations between ANS activity and experiental stress, i.e. stress experienced as a result of the disease-related symptoms. Sympathetic and parasympathetic activity showed

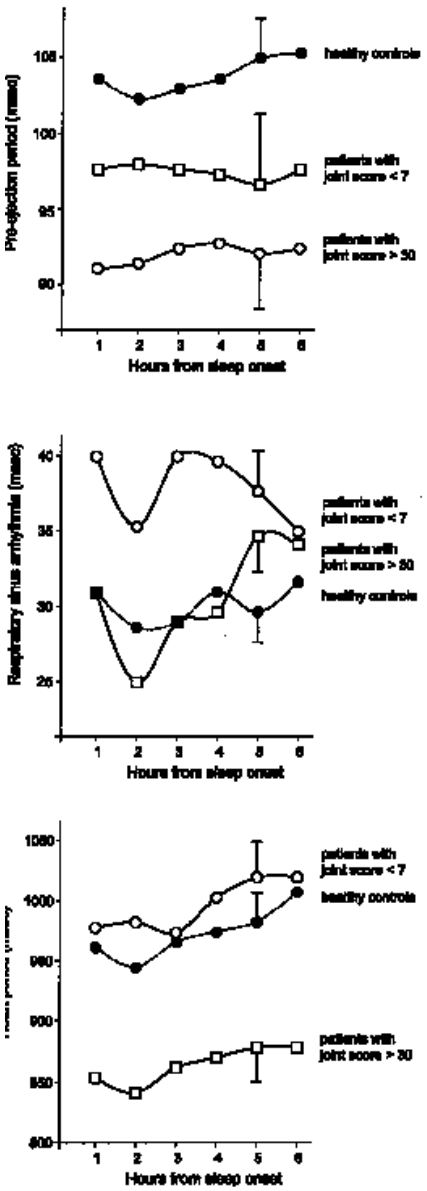

Fig. 2. Mean level (± SEM) and the change over time in the pre-ejection-period (PEP), respiratory sinus arrythmia (RSA) and heart period in 13 patients with high disease activity (Thompson joint score > 30), 11 patients with low disease activity (Thompson joint score < 7), and 27 healthy controls. (For clarity, the error bar is only presented at the 5th hour of sleep)

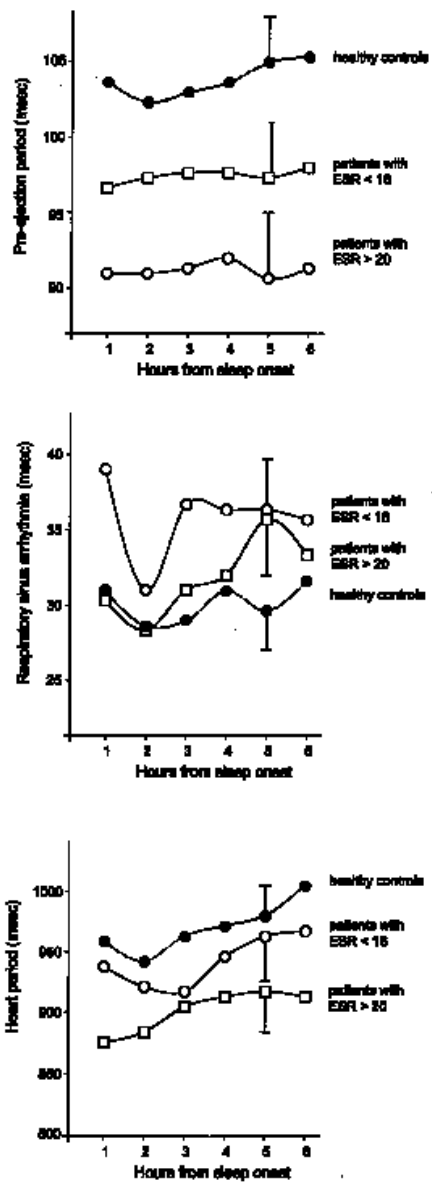

Fig. 3. Mean level (± SEM) and the change over time in the pre-ejection-period (PEP), respiratory sinus arrythmia (RSA) and heart period in 11 patients with active disease (ESR >20 mm/h), 13 patients without active disease (ESR < 16 mm/h), and 27 healthy controls. (For clarity, the error bar is only presented at the 5th hour of sleep)

no association with any of the symptoms, but the heart rate was significantly associated with the level of stiffness and almost significantly with pain. It is possible that the consequences of symptoms are predominantly manifested in the heart rate, but a larger sample size than the one in our study is required to confirm such an impact of multiple stressors on ANS activity.

Several points in our study need comment. First, autonomic activity was quantified by measuring cardiac sympathetic and parasympathetic activity. It has been demonstrated that in healthy persons stress-induced sympathetic activation exerts its influence in parallel on the heart and immune parameters (48-52). However, in patients with RA the SNS may lose control at the level of the immune system (53, 54). As a consequence, it is difficult to infer from

Table I. Correlations of autonomic activity variables with disease-related symptoms in 24 patients with RA.

	Pre-ejection-period	Respiratory sinus arrhythmia	Heart period
Pain	-0.10	-0.34	-0.37
Fatigue	0.20	-0.02	-0.09
Stiffness	-0.02	-0.25	-0.59 †
Negative mood	-0.04	-0.35	-0.12

† $p < 0.01$; coefficients for pain, fatigue and stiffness are Pearson's correlation coefficients, and those for negative mood are Spearman's rank order coefficients.

our data the consequences of elevated SNS activity for synovial tissues at inflammatory sites.

Second, several environmental factors, including the home environment, working routines, caffeine and nicotine (55), and sleep quality (56, 57) could have been responsible for the enhanced sympathetic activity in our patients. In the ambulatory assessment situation, the environment was not standardized. Also, a significantly higher number of patients stayed home from work due to their illness and disability to work (results not shown). Coffee intake and the number of smokers, however, did not differ between patients with or without active disease. Self-reported sleep quality in our patients did not differ from that in healthy participants, but it is possible that sleep measured by electro-encephalography would have revealed disturbed sleep in patients.

Third, medications might conceivably have affected autonomic activity. Because of the relatively small sample sizes of the medication subgroups in this study, we cannot exclude the possibility that medication intake has influenced our results. The possible effect of prednisone on SNS activity level was not confirmed in our group. Cortisol levels in patients using prednisone were lower than in those not taking prednisone (not shown), but the power of the test was too low to demonstrate statistical significance. The possible impact of medication on autonomic nervous system activity needs further confirmation.

Our study shows that in the early phase of RA, cardiac sympathetic activity is elevated, while parasympathetic nervous system activity is normal. Our findings suggest that inflammatory stress, more than the common symptoms of RA, challenges the SNS. Future studies are needed to confirm whether persistent elevated SNS activity compromises the physiological homeostasis of patients with RA.

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