Cardiovascular and pupillary autonomic nervous dysfunction in patients with rheumatoid arthritis – a cross-sectional and longitudinal study

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Abstract

Objectives

Patients with inflammatory diseases often demonstrate autonomic nervous dysfunction. This study was initiated to investigate cardiovascular (CAD) or pupillary autonomic dysfunction (PAD) in patients with rheumatoid arthritis (RA).

Methods

Between 1997 and 1998, 33 RA patients were examined for characteristics, and parameters of CAD and PAD. In a longitudinal part of this study, thirty patients have been re-evaluated 8.3 ± 0.1 yr later (response rate = 91%).

Results

A total of 18 patients (60%) demonstrated either CAD or PAD. The prevalence of CAD was 6/30 (20%) and the prevalence of PAD was 15/30 (50%). Of all cardiovascular tests, the Ewing test demonstrated the worst results (13/30 patients were below the 5th percentile). Similar as in other diseases, several RA patients demonstrated autonomic nervous hyperreflexia with values above the 95th percentile (relative variation coefficient: 7/30; respiratory sinus arrhythmia measure: 12/30; Valsalva measure: 1/30; Ewing measure: 0/30; latency time of pupillary light reflex: 5/30; maximal pupillary area: 0/30). During the 8-year observation period, 4/30 RA patients died. Non-survivors as compared to survivors had increased heart rate variation in the respiratory arrhythmia test (p= 0.038, hyperreflexia) but largely decreased heart rate variation in the Ewing test (p= 0.009, hyporeflexia). Non-survivors as compared to survivors demonstrated more frequent pupillary autonomic dysfunction (100% vs. 42%, p= 0.035).

Conclusions

This study demonstrates that CAD and PAD were frequent in patients with RA. Patients with a poor test result in the Ewing test and PAD might have an increased risk of death. This study in RA patients demonstrates similar results as in patients with diabetes mellitus.

Key words

Rheumatoid arthritis, cardiovascular autonomic dysfunction, pupillary autonomic dysfunction, mortality.

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Introduction

Cardiovascular (CAD) and pupillary autonomic dysfunction (PAD) were reported in patients with rheumatic diseases (1-13). In rheumatic diseases, the general prevalence of CAD is 0-25% and of PAD 15-35% depending on the applied methods (1-13). Previously, we delineated that autonomic nervous function needs to be tested using strict age-dependent criteria in order to avoid false positive diagnosis of CAD and PAD (14), which explains why prevalence depends on diagnostic criteria. It is still unclear whether these abnormalities reflect a structural damage of nerve fibers or whether the tonus of the sympathetic and parasympathetic nervous system has changed due to the chronic inflammatory process. Since circulating proinflammatory cytokines stimulate the hypothalamus and the sympathetic nervous system, an imbalance might be expected. Every imbalance of the two portions of the autonomic nervous system - the sympathetic and the parasympathetic nervous system - leads to visible signs of autonomic nervous function (reviewed in ref. 15). At this point, the question arises as to what happens with the autonomic nervous system in chronic inflammatory diseases.

Some studies indicated that patients with chronic inflammatory diseases have an elevated activity of the sympathetic nervous system (2, 16-21). Such an increased sympathetic tone may be a consequence of hypothalamic changes with an observed shift from CRH to vasopressin, which has been demonstrated in experimental arthritis (22). On the basis of these findings, an imbalance of the sympathetic and the parasympathetic nervous system can be expected. Necessarily, such an imbalance should lead to signs of autonomic nervous dysfunction, which was the subject of this study in patients with rheumatoid arthritis (RA).

A longitudinal aspect of the present work was the documentation of mortality in those RA patients with autonomic nervous dysfunction. A recent meta-analysis of patients with diabetes mellitus demonstrated an increased mortality risk in patients with cardiovascular autonomic dysfunction (CAD) compared to patients without CAD (23). The pooled relative risk of mortality in the presence of CAD was 3.5 (95%, confidence interval 2.7 - 4.5) (23). Increased mortality in these patients was thought to arise from dysfunctional heart rate control and abnormal vascular dynamics leading to arrhythmia and sudden unexpected deaths (23). However, this has never been investigated in patients with RA or other chronic inflammatory diseases.

It was the aim of this study to investigate the prevalence and characteristics of CAD and PAD in patients with RA. In addition, we studied the association between CAD or PAD and mortality 8 years after applying a baseline autonomic function test battery.

Patients and methods

Patients, clinical and laboratory parameters

Thirty-three white patients with diagnosed RA fulfilling the American College of Rheumatology criteria (24) with complete data sets were included in this study. Between 1997 and 1998, 33 RA patients were referred to the Department of Internal Medicine of the University Hospital Regensburg. All patients entered the study consecutively without any selection. At baseline these patients had no co-morbidities or a laboratory constellation, which might have accelerated cardiovascular diseases (Table I). All subjects in this study were fully informed about the purpose of investigations and gave written consent according to the declaration of Helsinki. The study was approved by the Ethics Committee of the University of Regensburg. Patients with other causes of peripheral neuropathy such as diabetes mellitus and alcohol associated neuropathy, genetically determined neuropathy, injected drug or toxin neuropathy were excluded. All patients had a thorough clinical examination by a rheumatologist with a long-term experience in autonomic nervous function testing. Table I gives the clinical parameters of patients at baseline. Erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factor were measured by routine

Table 1. Baseline clinical characteristics of patients with rheumatoid arthritis. Data are given as means SEM, percentages in parentheses, and ranges in brackets.

	All patients	Survivors	Non-survivors
n	30	26	4
Female / male	17 / 13	16 / 10	1 / 3
Age (yr)	52.2 ± 1.9 (37 - 75)	51.6 ± 2.1 (37 - 75)	56.5 ± 2.2 (50 - 59)
Disease duration (yr)	6.7 ± 1.2	6.4 ± 1.3	8.6 ± 4.8
Number of swollen joints	9.0 ± 1.4	8.8 ± 1.6	10.2 ± 1.8
Number of tender joints	8.8 ± 1.2	8.7 ± 1.4	9.5 ± 1.3
Visual analog scale for joint pain (1 to 10)	3.8 ± 0.4	3.6 ± 0.4	4.8 ± 0.8
Global assessment of patients (1 to 10)	4.4 ± 0.4	4.4 ± 0.4	4.8 ± 0.1
Global assessment of physician (1 to 10)	3.7 ± 0.3	3.7 ± 0.3	4.0 ± 0.6
Erythrocyte sedimentation rate (mm)	30.2 ± 4.0	29.6 ± 4.5	35.3 ± 8.2
C-reactive protein (mg/l)	30.9 ± 7.3	31.4 ± 8.3	27.5 ± 12.1
Rheumatoid factor positive	19 (63.3)	16 (61.5)	3 (75.0)
Cardiovascular co-morbidities			
Obesity	0 / 30	0 / 26	0 / 4
Hyperlipidemia	0 / 30	0 / 26	0 / 4
Hypertension	0 / 30	0 / 26	0 / 4
Diabetes mellitus	0 / 30	0 / 26	0 / 4
Ischemic events in the history	0 / 30	0 / 26	0 / 4
Medication			
Prednisolone	18 (60.0)	17 (65.4)	1 (25.0)
Daily prednisolone (mg/d)	6.3 ± 1.3	6.9 ± 1.4	2.5 ± 2.5
Methotrexate	14 (46.7)	12 (46.2)	2 (50.0)
Daily methotrexate (mg/d)	6.8 ± 1.4	7.0 ± 1.6	5.6 ± 3.6
Hydroxychloroquine or chloroquine	2 (6.7)	1 (3.9)	1 (25.0)
Sulfasalazine	6 (20.0)	4 (15.4)	2 (50.0)
Azathioprine	2 (6.7)	1 (3.9)	1 (25.0)
Cyclosporin	2 (6.7)	2 (7.7)	0 (0)
NSAIDs	18 (60.0)	16 (61.5)	2 (50.0)

Survivors and non-survivors were not different in all mentioned parameters. All patients did not receive any medication for the treatment of cardiovascular co-morbidities.

laboratory tests.

After a median of 8.3 yr (range: 7.8 - 8.8 yr), 30 patients were re-investigated using a telephone questionnaire. We carried out a telephone interview with patients or relatives because we focused on mortality, which can be detected by this method. The time-point of re-investigation at 8.3 yr was not chosen with any further intention. Of the 33 patients initially investigated 3 patients or their relatives were not located or did not want to respond, and these patients were excluded from the follow-up analysis (response rate of 91%). The questionnaire addressed symptoms of cardiac arrhythmia, tachycardia or bradycardia, high blood pressure, myocardial infarction, and death, which was the target variable (including the specific question concerning "sudden death"). At baseline and during the follow-up, no major other diseases appeared in these patients that might have accelerated cardiovascular disease or other causes of death.

Autonomic nervous system examination

CAD was assessed using a test battery that included standardized tests validated in 120 normal subjects (25). The inter test reliability has been tested (25). The parameters were given as exact percentile values of each patient using statistical data of an earlier study kindly provided by Ziegler *et al*. (25). Variation coefficient of 150 heart beat intervals in supine position, heart rate variation during 6 deep breaths per one minute known as respiratory sinus arrhythmia test (R-Rmax - R-Rmin or E-I difference), blowing into a mouthpiece of a manometer for 15 s to maintain a pressure of 40 mmHg known as the Valsalva test (R-Rmax/R-Rmin), heart rate response to standing up known as the Ewing test (lying-to-standing test or R-Rmax/R-Rmin), and orthostatic systolic blood pressure fall after 5 min in supine position. A test was abnormal if the result was below the 5th percentile. With respect to orthostatic blood pressure fall, a fall by 25 mmHg was abnormal(25). The diagnosis of overall CAD was made if two or more of the five individual test results were abnormal.

PAD was assessed by the following test battery validated in 103 normal subjects (26). The inter test reliability has been tested (26): We measured the latency time of pupillary light reflex for the parasympathetic portion and the maximal pupillary area in darkness for the sympathetic portion to study the pupillary autonomic reflex loop. Exact percentile values were used for each test (26). A test was abnormal if the result was below the 5th percentile. The diagnosis of overall PAD was made if one or both tests were abnormal (26).

Statistical analysis

Group medians were compared by the Mann-Whitney test using the statistical package SPSS (SPSS, V.12.0, SPSS, Inc. Chicago). Frequencies were compared by Chi-squared test with Yates continuity correction (SPSS). Due to the number of patients included, relative risk factors can not be calculated (huge values for the risk are expected). Values are expressed as mean ± SEM and the significance level is $p < 0.05$.

Results

Prevalence and characteristics of CAD and PAD in patients with RA

A total of 18 patients (60%) demonstrated cardiovascular or pupillary measures below the 5th percentile (Fig. 1A-C). According to the definition of CAD, the prevalence of CAD was 6/30

(20%). The prevalence of PAD was 15/30 (50%). Only 3/30 patients (10%) demonstrated both forms of autonomic dysfunction.

Of all cardiovascular tests, the Ewing test demonstrated the worst results (Fig. 1A). Thirteen patients demonstrated a Ewing value below the 5th percentile (Fig. 1A). For the relative variation coefficient, the respiratory sinus arrhythmia measure, and the Valsalva value, only one patient demonstrated a value below the 5th percentile (Fig. 1A). A total of five patients had orthostatic systolic blood pressure fall below minus 15mmHg, the threshold for the 5th percentile (Fig. 1B). With respect to pupillary function testing, 10 patients demonstrated a latency time below the 5th percentile and 9 patients a maximal pupillary area below the 5th percentile (Fig. 1C).

Similar as in earlier studies several patients demonstrated autonomic nervous hyperreflexia with values above the 95th percentile (relative variation coefficient: 7/30; respiratory sinus arrhythmia measure: 12/30; Valsalva measure: 1/30; Ewing measure: 0/30; latency time of pupillary light reflex: 5/30; maximal pupillary area: 0/30, see also Fig. 1). This indicates that an imbalance between sympathetic and parasympathetic function existed.

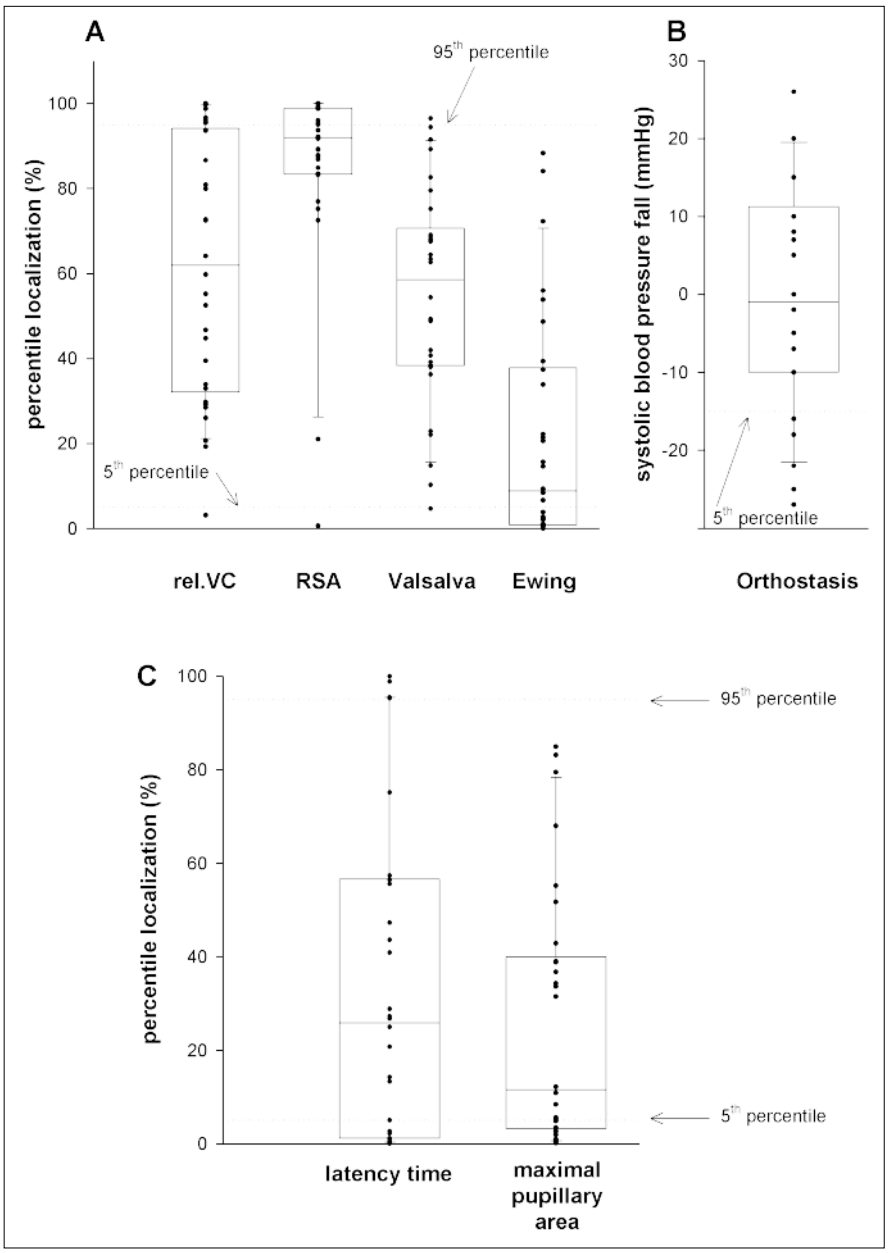

Fig. 1. Characteristics of cardiovascular (A,B) and pupillary autonomic function (C) in patients with rheumatoid arthritis. Individual patients are given as small black circles. Box plots demonstrate the 10th, 25th, 50th (median within the box), 75th, and 90th percentile. The dotted lines indicate the 5th and the 95th percentile of normal subjects.
rel.VC: heart rate variation coefficient; RSA: respiratory sinus arrhythmia test.

Baseline clinical and laboratory parameters in survivors and non-survivors

During the 8-year observation period, 4/30 RA patients died (13%) due to heart failure (n = 1), immunodeficiency / infection (n = 1), and sudden deaths (n = 2). All other patients did not report about cardiac arrhythmia, tachycardia or bradycardia, high blood pressure, myocardial infarction and other sever conditions linked to cardiovascular disease.

At baseline, survivors and non-survivors were not different in age, gender, disease duration, swollen joint score, tender joint score, visual analog scale for pain, global assessment of patient, and global assessment of physician (Table I). Furthermore, survivors and non-survivors had similar medication at baseline (Table I). At baseline, patients did not report on any other co-morbidity except RA. In addition, at baseline, median erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factor status were not different between the two groups (Table I).

Baseline cardiovascular and pupillary autonomic dysfunction in survivors and non-survivors

With respect to the respiratory sinus arrhythmia test, at baseline, survivors had lower percentile values (normal) as compared to non-survivors, which demonstrates hyperreflexia in the latter group (Fig. 2A). At baseline, non-survivors demonstrated markedly lower percentile values in the Ewing test as compared to survivors (Fig. 2A). All non-survivors had Ewing test values below the 5th percentile (Fig. 2A). RA patients had relatively normal percentile values with respect to the heart

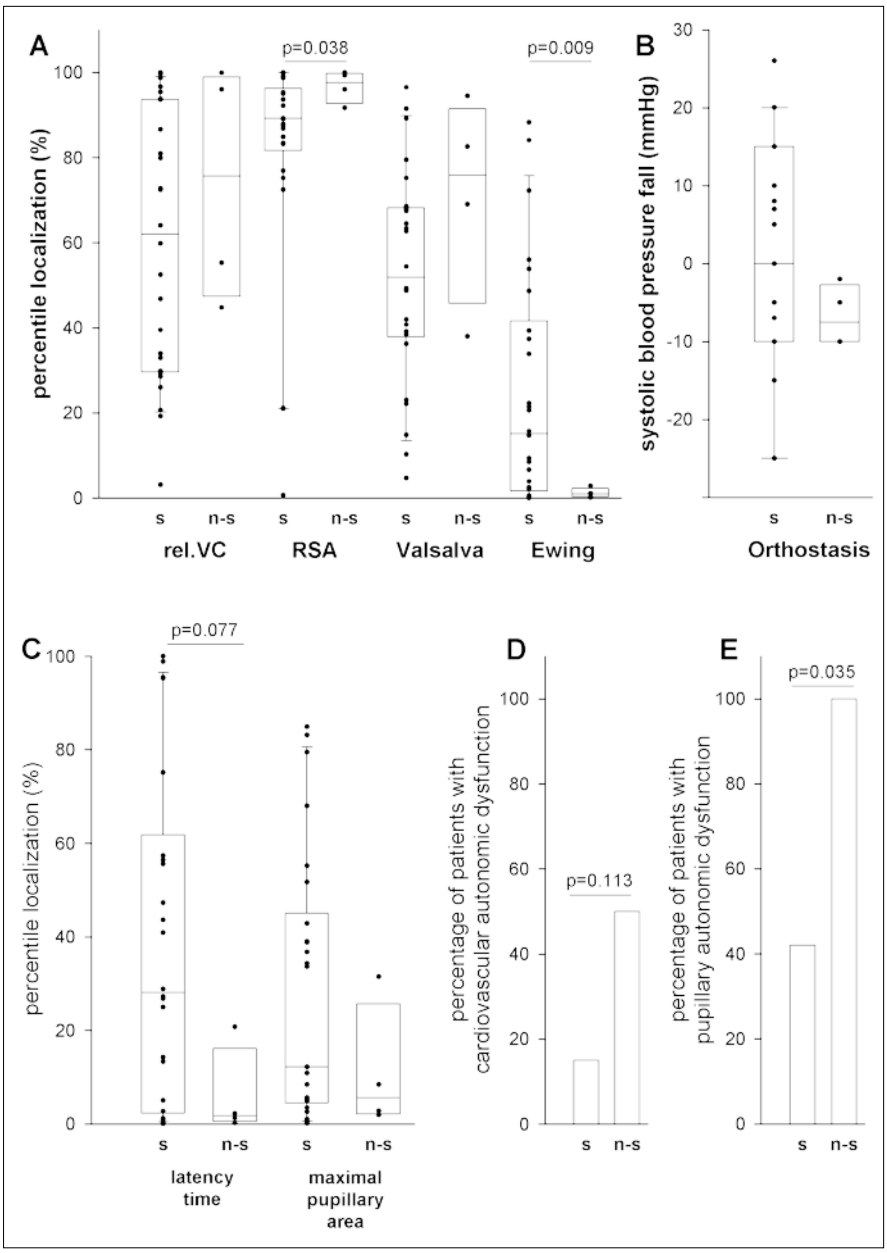

Fig. 2. Characteristics of cardiovascular (A,B) and pupillary autonomic function (C) and frequency of CAD (D) and PAD (E) in survivors and non-survivors with rheumatoid arthritis Explanation of symbols or box plots are given in legend to figure 1.
n-s: non-survivors; rel.VC: heart rate variation coefficient; RSA: respiratory sinus arrhythmia test; s: survivors.

rate variation coefficient and the Valsalva test parameter independent of the survivor status (Fig. 2A). In the orthostasis test, no significant difference was found as well (Fig. 2B). At baseline, six of 30 patients had CAD, and two of these patients died (33%) whereas in the group without CAD only two patients died (33% vs. 8%; Fig. 2D). This difference did not reach the significance level.

At baseline, RA patients who survived as compared to non-survivors tended to have an elevated latency time percentile and maximal pupillary area percentile (Fig. 2C). Only one of 4 non-survivors had a latency time percentile above the 5th percentile (Fig. 2C). The overall percentage of PAD was significantly different in survivors and non-survivors at baseline (Fig. 2E). Fifteen of 30 patients had PAD, and 4 of these patients with PAD died (27%) whereas in the group without PAD not one patient died (27% vs. 0%, p = 0.035; Fig. 2E).

No influence of medication or inflammatory status was observed on readout parameters of CAD and PAD testing (data not shown).

Discussion

The first study in patients with RA on "autonomic neuropathy" with a special focus on sweat abnormalities was published in 1965 (27). A first systematic study in patients with RA was presented in the 1970s (1). The authors concluded: "Significantly more patients with RA had abnormal autonomic function, suggesting that autonomic neuropathy occurs more commonly in RA than hitherto suspected. The existence of an autonomic neuropathy may be an important complicating factor in rheumatoid disease and may lead to increased morbidity and mortality."

In the following years, assessment of autonomic nervous function by standard tests was also applied to other rheumatic diseases such as systemic sclerosis (4, 28), systemic lupus erythematosus (29, 30), primary Sjögren's syndrome (10, 31), fibromyalgia (32), mixed connective tissue disease (12), and familial Mediterranean fever (33). The prevalence rates of CAD is 0-25% and of PAD 15-35% depending on the applied methods (1-13). In our study cohort, prevalence of CAD was 20%, which confirms earlier results. With respect to PAD, which has never been investigated in RA, we observed a prevalence of 50%. This high prevalence is similar as in Type 1 diabetes mellitus.

It is interesting that not only hyporeflexia (below the 5th percentile) but also hyperreflexia (above the 95th percentile) appears in patients with chronic inflammatory diseases (9, 34). This present study confirms hyperreflexia in patients with RA. This was most marked for the respiratory sinus arrhythmia test where 40% of our RA patients demonstrated hyperreflexia. Hyperresponsive results are rare in diabetic patients (R. H. Straub, unpublished). However, in patients with systemic lupus erythematosus and systemic sclerosis hyperreflexia was

found to be common (34). This indicates that the excitability of central autonomic neurons may be increased in patients with chronic inflammatory diseases. In these patients, others have also shown an increased sympathetic tone which might lead to alterations of autonomic nervous function tests (16, 17, 35, 36). In rheumatic diseases, the proinflammatory load may be an important peripheral stimulus to induce autonomic hyperreflexia. Proinflammatory cytokines such as IL-6, IFN-γ, or TNF can stimulate the hypothalamus and may trigger alterations of autonomic centers. This has been demonstrated in fibromyalgia patients after i.v. injection of IL-6 (37).

At this point, the intriguing question arises as to whether autonomic dysfunction is a response to the feedback from the peripheral chronic inflammatory process (e.g., via cytokines acting at the hypothalamus) or whether it is the consequence of pathogenetic factors originating in the CNS that increase disease activity. In other words, is the CNS involved in the progression of rheumatic diseases? Functional imbalance between distinct sympathetic and parasympathetic centers may lead to changes of the set point of activation of autonomic nervous reflex loops in the brain, which are involved in regulation of autonomic reflexes. Patients with long disease duration may have pronounced alterations of the autonomic central nervous outflow. Thus, longer disease duration may lead to more obvious changes of the set point of activation of a given autonomic reflex loop. This may be the reason for the link between disease duration and autonomic hyperreflexia in patients with rheumatic diseases (34). These long-term changes, whether hyporeflexia or hyperreflexia, may continuously impair the cardiovascular system leading to an increased risk of mortality.

However, diagnosis of autonomic neuropathy in connective tissue diseases has never been linked to long-term prognosis. This study in RA patients demonstrates that PAD predicts an increased risk of mortality 8 years after baseline investigation. PAD in contrast to CAD has never been linked to mortality in other studies including those on diabetic patients. In addition, non-survivors demonstrated a markedly disturbed Ewing test and respiratory sinus arrhythmia test indicating autonomic nervous dysfunction. It is thought that autonomic hyporeflexia is an unfavorable factor due to an impairment of important cardiovascular reflex loops, which may predispose do cardiac arrhythmias. We think that the number of non-survivors was too small to draw firm conclusions. Nevertheless, three of our patients died because of heart failure and sudden death, which is most often linked to cardiac rhythm problems. Thus, the results might be compared to the studies in patients with diabetes mellitus (23).

In conclusion, this study describes high prevalence of CAD and PAD in RA patients. In addition, there are indications that disturbed autonomic reflexes might be linked to higher mortality, which needs further confirmation. At the moment, it is unclear whether detection of autonomic dysfunction should lead to more intense programs to reduce additional risk factors as in patients with diabetes mellitus. This must be subject of future longitudinal studies.

Conflict of interest

The authors declare that they have no conflicts of interest.

Key messages

Autonomic nervous dysfunction, whether hyporeflexia or hyperreflexia, is frequent in rheumatoid arthritis. In the longitudinal part of the study, pupillary autonomic dysfunction was more often found in patients who died during the follow-up of 8 years.

References

1. EDMONDS ME, JONES TC, SAUNDERS WA, STURROCK RD: Autonomic neuropathy in rheumatoid arthritis. *Br Med J* 1979; 2:173-5.
2. LEDEN I, ERIKSSON A, LILJA B, STURFELT G, SUNDKVIST G: Autonomic nerve function in rheumatoid arthritis of varying severity. *Scand J Rheumatol* 1983; 12:166-70.
3. HOYLE C, EWING DJ, PARKER AC: Acute autonomic neuropathy in association with systemic lupus erythematosus. *Ann Rheum Dis* 1985; 44:420-4.
4. SONNEX C, PAICE E, WHITE AG: Autonomic neuropathy in systemic sclerosis: a case report and evaluation of six patients. *Ann Rheum Dis* 1986; 45:957-60.
5. KLIMIUK PS, TAYLOR L, BAKER RD, JAYSON MI: Autonomic neuropathy in systemic sclerosis. *Ann Rheum Dis* 1988; 47: 542-5.
6. TAN J, AKIN S, BEYAZOVA M, SEPICI V, TAN E: Sympathetic skin response and R-R interval variation in rheumatoid arthritis. Two simple tests for the assessment of autonomic function. *Am J Phys Med Rehabil* 1993; 72: 196-203.
7. LIOTE F, OSTERLAND CK: Autonomic neuropathy in systemic lupus erythematosus: cardiovascular autonomic function assessment. *Ann Rheum Dis* 1994; 53: 671-4.
8. STRAUB RH, ZEUNER M, LOCK G *et al.*: Autonomic and sensorimotor neuropathy in patients with systemic lupus erythematosus and systemic sclerosis. *J Rheumatol* 1996; 23: 87-92.
9. STRAUB RH, ANTONIOU E, ZEUNER M, GROSS V, SCHÖLMERICH J, ANDUS T: Association of autonomic nervous hyperreflexia and systemic inflammation in patients with Crohn's disease and ulcerative colitis. *J Neuroimmunol* 1997; 80: 149-57.
10. ANDONOPOULOS AP, CHRISTODOULOU J, BALLAS C, BOUNAS A, ALEXOPOULOS D: Autonomic cardiovascular neuropathy in Sjögren's syndrome. A controlled study. *J Rheumatol* 1998; 25: 2385-8.
11. GAMEZ-NAVA JI, GONZALEZ-LOPEZ L, RAMOS-REMUS C, FONSECA-GOMEZ MM, CARDONA-MUNOZ EG, SUAREZ-ALMAZOR ME: Autonomic dysfunction in patients with systemic lupus erythematosus. *J Rheumatol* 1998; 25: 1092-6.
12. STACHER G, MERIO R, BUDKA C, SCHNEIDER C, SMOLEN J, TAPPEINER G: Cardiovascular autonomic function, autoantibodies, and esophageal motor activity in patients with systemic sclerosis and mixed connective tissue disease. *J Rheumatol* 2000; 27: 692-7.
13. DEL ROSSO A, BERTINOTTI L, PIETRINI U *et al.*: Pupillocynetic activity of substance P in systemic sclerosis. *J Rheumatol* 2003; 30:1231-7.
14. STRAUB RH, LANG B, PALITZSCH KD, SCHÖLMERICH J: Estimation of the cut-off value in cardiovascular autonomic nervous function tests: not-age-related criteria or the age-related 5th percentile. *J Diabetes Complications* 1997; 11: 145-50.
15. GENOVELY H, PFEIFER MA: RR-variation: the autonomic test of choice in diabetes. *Diabetes Metab Rev* 1988; 4:255-71.
16. KUIS W, JONG-DE VOS V, SINNEMA G *et al.*: The autonomic nervous system and the immune system in juvenile rheumatoid arthritis. *Brain Behav Immun* 1996; 10:387-98.
17. PERRY F, HELLER PH, KAMIYA J, LEVINE JD: Altered autonomic function in patients with arthritis or with chronic myofascial pain. *Pain* 1989; 39: 77-84.
18. DEKKERS JC: *Psychophysiological responsiveness in recently diagnosed patients with rheumatoid arthritis* (*Thesis*). Dordrecht, Drukkerij Dekkers, 2000:
19. GLÜCK T, OERTEL M, REBER T, ZIETZ B,

SCHÖLMERICH J, STRAUB RH: Altered function of the hypothalamic stress axes in patients with moderately active systemic lupus erythematosus. I. The hypothalamus-autonomic nervous system axis. *J Rheumatol* 2000; 27: 903-10.

20. STRAUB RH, HERFARTH H, FALK W, ANDUS T, SCHÖLMERICH J: Uncoupling of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis in inflammatory bowel disease? *J Neuroimmunol* 2002; 126: 116-25.
21. HÄRLE P, STRAUB RH, WIEST R *et al.*: Increase of sympathetic outflow measured by NPY and decrease of the hypothalamic-pituitary-adrenal axis tone in patients with SLE and RA - Another example of uncoupling of response systems. *Ann Rheum Dis* 2005; 65: 51-6.
22. HARBUZ MS, REES RG, ECKLAND D, JESSOP DS, BREWERTON D, LIGHTMAN SL: Paradoxical responses of hypothalamic corticotropin-releasing factor (CRF) messenger ribonucleic acid (mRNA) and CRF-41 peptide and adenohypophysial proopiomelanocortin mRNA during chronic inflammatory stress. *Endocrinology* 1992; 130: 1394-400.
23. MASER RE, MITCHELL BD, VINIK AI, FREEMAN R: The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care* 2003; 26: 1895-901.
24. ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
25. ZIEGLER D, LAUX G, DANNEHL K *et al.*: Assessment of cardiovascular autonomic function: age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. *Diabet Med* 1992; 9: 166-75.
26. STRAUB RH, THIES U, JERON A, PALITZSCH KD, SCHÖLMERICH J: Valid parameters for investigation of the pupillary light reflex in normal and diabetic subjects shown by factor analysis and partial correlation. *Diabetologia* 1994; 37: 414-9.
27. BENNETT PH, SCOTT JT: Autonomic neuropathy in rheumatoid arthritis. *Ann Rheum Dis* 1965; 24: 161-8.
28. DESSEIN PH, JOFFE BI, METZ RM, MILLAR DL, LAWSON M, STANWIX AE: Autonomic dysfunction in systemic sclerosis: sympathetic overactivity and instability. *Am J Med* 1992; 93: 143-50.
29. MAGARO M, MIRONE L, ALTOMONTE L, ZOLI A, ANGELOSANTE S: Lack of correlation between anticardiolipin antibodies and peripheral autonomic nerve involvement in systemic lupus erythematosus. *Clin Rheumatol* 1992; 11: 231-4.
30. OMDAL R, JORDE R, MELLGREN SI, HUSBY G: Autonomic function in systemic lupus erythematosus. *Lupus* 1994; 3: 413-7.
31. MCCOMBE PA, SHEEAN GL, MCLAUGHLIN DB, PENDER MP: Vestibular and ventilatory dysfunction in sensory and autonomic neuropathy associated with primary Sjorgren's syndrome. *J Neurol Neurosurg Psychiatry* 1992; 55: 211-2.
32. COHEN H, NEUMANN L, SHORE M, AMIR M, CASSUTO Y, BUSKILA D: Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. *Semin Arthritis Rheum* 2000; 29:217-27.
33. ROZENBAUM M, NASCHITZ JE, YUDASHKIN M *et al.*: Cardiovascular autonomic dysfunction in familial Mediterranean fever. *J Rheumatol* 2002; 29:987-9.
34. STRAUB RH, GLÜCK T, ZEUNER M, SCHÖLMERICH J, LANG B: Association of pupillary parasympathetic hyperreflexia and systemic inflammation in patients with systemic lupus erythematosus. *Br J Rheumatol* 1998; 37: 665-70.
35. NAKAJIMA A, SENDO W, TSUTSUMINO M *et al.*: Acute sympathetic hyperfunction in overlapping syndromes of systemic lupus erythematosus and polymyositis. *J Rheumatol* 1998; 25: 1638-41.
36. DEKKERS JC, GEENEN R, GODAERT GL, BIJLSMA JW, DOORNEN LJP: Sympathetic and parasympathetic nervous system activity at night in patients with recently diagnosed rheumatoid arthritis. *In*: DEKKERS JC (Ed.): *Thesis: Psychophysiological responsiveness in recently diagnosed patients with rheumatoid arthritis*. Dordrecht, Dekkers, 2003: 55-74.
37. TORPY DJ, PAPANICOLAOU DA, LOTSIKAS AJ, WILDER RL, CHROUSOS GP, PILLEMER SR: Responses of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis to interleukin-6: a pilot study in fibromyalgia. *Arthritis Rheum* 2000; 43: 872-80.