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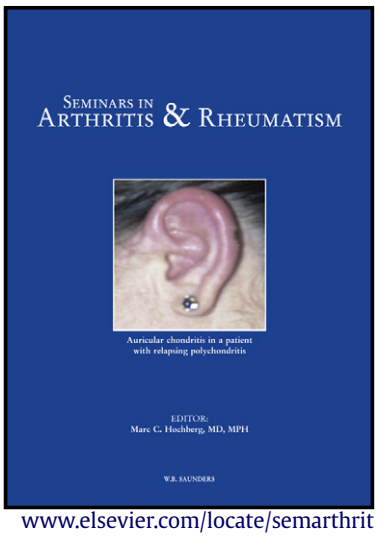
DOI:
10.1016/j.semarthrit.2014.06.003

Document Version
Peer reviewed version

Citation for published version (Harvard):
Adlan, AM, Lip, GYH, Paton, JFR, Kitas, GD & Fisher, JP 2014, 'Autonomic function and rheumatoid arthritis--a systematic review', Seminars in arthritis and rheumatism, vol. 44, no. 3, pp. 283-304. https://doi.org/10.1016/j.semarthrit.2014.06.003



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PII: S0049-0172(14)00159-0
DOI: http://dx.doi.org/10.1016/j.semarthrit.2014.06.003
Reference: YSARH50828

To appear in: *Seminars in Arthritis and Rheumatism*

Cite this article as: Ahmed M. Adlan, Gregory Y.H. Lip, Julian F.R. Paton, George D. Kitas, James P. Fisher, Autonomic Function and Rheumatoid Arthritis - A systematic Review, *Seminars in Arthritis and Rheumatism,* http://dx.doi.org/10.1016/j.semarthrit.2014.06.003

AUTONOMIC FUNCTION AND RHEUMATOID ARTHRITIS - A SYSTEMATIC REVIEW

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Source of support: This work was supported by a grant from Arthritis Research UK (grant number 196633).

Key words: Rheumatoid arthritis; cardiovascular; inflammation; nervous; physiology; systematic review; autonomic; autonomic function

Word count: 4447

ABSTRACT

Objectives Rheumatoid arthritis (RA) is a chronic inflammatory condition with increased all-cause and cardiovascular mortality. Accumulating evidence indicates that the immune and autonomic nervous systems (ANS) are major contributors to the pathogenesis of cardiovascular disease. We performed the first systematic literature review to determine the prevalence and nature of ANS dysfunction in RA and whether there is a causal relationship between inflammation and ANS function.

Methods Electronic databases (Medline, Central and Cochrane Library) were searched for studies of RA patients where autonomic function was assessed.

Results Forty studies in total were included. ANS function was assessed by clinical cardiovascular reflex tests (CCTs)(n=18), heart rate variability (HRV)(n=15), catecholamines (n=5), biomarkers of sympathetic activity (n=5), sympathetic skin responses (n=5), cardiac baroreflex sensitivity (cBRS) (n=2) and pupillary light reflexes (n=2). 9 small studies reported a ~60% (median, range 20-86%) prevalence of ANS dysfunction (defined by abnormal CCTs) in RA. 73% of studies (n=27/37) reported at least one abnormality in ANS function: parasympathetic dysfunction (n=20/26, 77%), sympathetic dysfunction (n=16/30, 53%) or reduced cBRS (n=1/2, 50%). An association between increased inflammation and ANS dysfunction was found (n=7/19, 37%) although causal relationships could not be elucidated from the studies available to date.

Conclusions ANS dysfunction is prevalent in ~60% of RA patients. The main pattern of dysfunction is impairment of cardiovascular reflexes and altered HRV indicative of reduced cardiac parasympathetic (strong evidence) and elevated cardiac sympathetic activity (limited evidence). The literature to date is underpowered to determine causal relationships between inflammation and ANS dysfunction in RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory condition predominantly affecting the synovial joints but leading to extra-articular manifestations. The increased cardiovascular mortality in RA patients (by up to 50%)(1-4) is not fully explained by the presence of traditional risk factors and remains an important research focus.(3, 5-13)

The autonomic nervous system (ANS) plays a critical role in the normal regulation of cardiovascular disease through its effects on the heart, peripheral vasculature and kidneys (Fig. 1).(14) The ANS is broadly comprised of the sympathetic and parasympathetic branches which work independently or in counter-balance to ensure homeostasis is maintained. Accumulating evidence indicates that altered ANS function contributes to the pathogenesis of cardiovascular disease (15, 16) and is an important predictor of cardiovascular mortality.(14, 17-19) Indeed, recent animal studies have demonstrated mechanistic and reciprocating links between inflammation and ANS dysfunction.(20-26) Elevations in circulating pro-inflammatory cytokines increase sympathetic activity (20, 21), reduce cardiovagal baroreflex sensitivity (22) and reduce heart rate variability (HRV) derived indices of cardiac parasympathetic activity (Fig. 1) (26); these are all features of ANS dysfunction associated with cardiovascular disease and increased mortality in humans.(14, 17-19) Therefore, determining ANS function in RA may provide prognostic benefit as well as improve understanding of underlying pathological mechanisms, and hence new improved therapeutic strategies.

Assessing ANS function – an overview

There are various clinical and research techniques that can be used to assess ANS function (Table 1); each with their relative merits and limitations.(27-43)

Clinical cardiovascular reflex tests (e.g. heart rate or blood pressure responses to orthostasis) allow for simple, quick and non-invasive detection of autonomic dysfunction with the additional benefit of grading severity.(28) These reflex tests however are unable to diagnose the cause of autonomic dysfunction, and hence should be interpreted within the clinical context.

HRV is a useful, non-invasive research tool that provides an indirect assessment of cardiac ANS function.(35) Cyclical fluctuations in resting heart rate are caused by cardiac parasympathetic and sympathetic influences and modulated by baroreflex mechanisms. Statistically derived indices of HRV can indicate the contribution of these parasympathetic and sympathetic influences (38, 44), although the physiological interpretation of HRV metrics is an issue of debate.(45) Despite guidelines for HRV assessment and interpretation (Task Force of the European Society and the North American Society of Pacing and Electrophysiology 1996) there is variability in methodology and a lack of normative data;(35) which needs to be considered when comparing results between studies.

Plasma or urinary catecholamines provide an estimate of global sympathetic activity but cannot delineate regional variations in sympathetic activity. Measured levels of catecholamines reflect metabolism and clearance, as well as resting sympathetic tone or release and are affected by numerous confounding factors (including medications, diurnal variation and concomitant diseases) that can make interpretation difficult.(37, 38) Other blood biomarkers of sympathetic activity (e.g. neuropeptide Y) have similar limitations.(30, 41) Norepinephrine spillover studies, unlike plasma or urinary measurement, can assess organ-specific sympathetic activity but are invasive, expensive and technically challenging.(37, 38) Pharmacological agents (e.g. adrenoreceptor antagonists or sympathomimetics) interrogate the ANS system to characterise the precise mechanisms of ANS dysfunction but are invasive and carry inherent risk.(37)

Cardiovascular baroreflex sensitivity assesses cardiovascular control mechanisms that are important for beat-to-beat regulation of blood pressure. Baroreflex assessment involves simultaneous measurement of heart rate (HR) and blood pressure (BP) while subjects are resting quietly (e.g. spontaneous methods), and during perturbations of BP either by non-invasive procedures (e.g. Valsalva's manoeuvre, lower body negative pressure or neck suction pressure) or pharmacological agents (e.g. phenylephrine infusion).(27, 37) The relative strengths and weakness of the methods used for assessing baroreflex function have been reviewed elsewhere.(46)

The microneurography technique uses tungsten microelectrodes to make intra-neural recordings (typically from the peroneal nerve) of sympathetic outflow to the muscle (blood vessel vasoconstrictor impulses) or skin.(37, 38) Muscle sympathetic nerve activity correlates well with cardiac sympathetic activity; is reproducible and well-tolerated in numerous disease populations; and allows quantification of resting activity and response to various stimuli. Its technically challenging nature is the main limitation of this procedure.(38)

Cardiac sympathetic imaging is a minimally invasive research technique that allows for visualisation of various imaging agents (e.g. radio-labelled sympathomimetic amines) using single photon emission computed tomography.(37, 38) This technique has been used in cardiovascular disease and demonstrated prognostic significance; however its use is limited due to expense and lack of availability.(37) Other assessments such as pupillary light reflex responses(34) or sympathetic skin responses(32, 36) can provide an estimation of autonomic dysfunction; however their significance in cardiac autonomic function is not clear.

In this article, we performed the first systematic literature review on ANS function in RA to: i) investigate whether there is sufficient evidence to determine if patients with RA have altered ANS function; ii) determine the prevalence and nature of any autonomic

dysregulation in patients with RA; iii) elucidate whether there is a causal relationship between systemic inflammation (e.g. clinical markers of disease activity, elevated concentrations of specific circulating pro-inflammatory molecules) and ANS dysfunction in RA.

METHODS

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,(47) electronic databases (Medline, Central and Cochrane Library) were searched to identify articles between January 1974 and June 2013, in English. The search term "rheumatoid arthritis" was used in combination with each of the following terms (incorporating common assessments of ANS function, Table 1): "autonomic", "sympathetic", "parasympathetic", "vagal", "heart rate variability", "baroreflex", "catecholamine", "epinephrine", "norepinephrine", "adrenaline", "acetylcholine", "noradrenaline", "cardiovascular battery", "Ewing", "Valsalva", "hand grip", "cold pressor", "orthostasis" and "tilt".

6350 citations were identified and the summaries and/or abstracts were screened for relevance; clinical studies of adults with RA where at least one aspect of ANS function was assessed were deemed relevant. Following removal of duplicate and irrelevant articles 44 full articles were accessed. Irrelevant articles included those that were non-original research (e.g. review articles, editorials, letters etc.), non-RA and animal studies. The following eligibility criteria were applied: articles written in the English language; involving adults with RA; at least one known parameter of ANS function assessed and reported; and an attempt to assess the association between inflammation and ANS function either by inclusion of a non-RA control group, by statistical analysis within a cohort of RA patients, or by intervention with anti-inflammatory therapy. Four articles were excluded as they failed to meet the eligibility

criteria (association between inflammation and ANS function not assessed and did not include a non-RA control group). In total 40 articles were included in the review (Fig. 2).

Data extraction was performed by one of the authors (A.M.A.). A quality assessment was made for each study by adapting a known quality assessment tool (see Appendix 1).(48) The following indices were assessed: study design, inclusion/exclusion criteria, disease characteristics, standardised testing conditions (e.g. time of test, subject position), standardised methodology for autonomic assessment (e.g. adhering to published guidelines), quality of autonomic assessment tool (e.g. more than one technique used), appropriate sample size (e.g. use of power calculations to determine sample size), appropriate statistical tests (e.g. adjustment made for group differences), and associations between ANS function and inflammation tested. Each index was graded between 0-2, and the total points added to give a final score between 0-18. A percentage was calculated to give a Quality Index Score (QIS). The quality assessment was performed by two authors (A.M.A. and J.P.F.) and disagreements were discussed until a consensus was reached. Each study was placed into one (or more) category representing parasympathetic function, sympathetic function and cardiac baroreflex sensitivity and scored as either normal or abnormal. At least one abnormal parameter of autonomic function was required to qualify as an abnormal study (i.e. no studies could be classified as both normal and abnormal in a single domain). Furthermore each study was classified according to the type of autonomic function test performed and placed into one category if comparisons were made between rheumatoid arthritis patients and controls: RA worse than control, no difference or RA better than control. Due to the large heterogeneity in the patient characteristics, tools of ANS assessment employed and parameters reported, no meta-analysis was performed.

RESULTS

Forty articles were included in the review.(49-88) Thirty-six studies were case-control, cross-sectional, observational (Table 2A), of which 3 had an interventional arm (Table 2B); 3 were cohort studies, of which 1 was cross-sectional; and 1 study utilized a randomized, placebo-controlled, single-blind, cross-over design (Table 2B).

In all but six studies the diagnosis of RA was based on the 1987 revised criteria of the American Rheumatism Association.(89) Approximately 80% of patients studied were female with a mean age of ~50 years (estimated calculation from reported values). Mean reported disease duration (from 26 studies) was ~9 years; 4 studies included RA patients diagnosed <2 years. Twenty three (of forty) studies reported RA medications which included disease modified anti-rheumatic drugs of which methotrexate was the most common. Other medications and co-morbidities were only reported in a few studies; but most studies (30 of 40) excluded patients with conditions or medications affecting the ANS (e.g., diabetes mellitus, neurological disease, hypertension, heart failure, vaso-active drugs).

Assessment of ANS Function

Eighteen studies utilized clinical cardiovascular tests (CCTs) of ANS function;(51, 53, 54, 58, 60, 62, 69, 74-83, 85) 15 studies assessed heart rate variability (HRV)(49-51, 55, 57, 59, 61, 65, 68, 71, 73, 77, 86-88) of which 5 assessed HRV in combination with clinical cardiovascular reactivity;(51, 68, 77, 86, 87) and 16 studies used other methods of assessing ANS function including catecholamines (n=5),(66, 67, 84, 86, 87) biomarkers (n=5),(56, 63, 64, 86, 87) sympathetic skin responses (SSR)(n=5),(60, 62, 69, 70, 82) cardiac baroreflex sensitivity (cBRS)(n=2)(50, 51) and pupillary light reflexes (PLR)(n=2).(52, 80) Studies assessed either one (n=30), two (n=8) or three (n=2) parameters of ANS function.

Assessments of ANS function undertaken in RA patients can be broadly categorised into: parasympathetic activity;(27) sympathetic activity;(38) and cBRS.(37) Resting activity was assessed in addition to the response to stimuli. For the purposes of this review ANS dysfunction is defined as either: abnormality in CCTs; impaired HRV and/or disrupted sympatho-vagal balance; reduced cBRS; altered concentrations of catecholamines or biomarkers of sympathetic activity; impairment in SSR; impairment in PLR; abnormalities in the above parameters occurring either at rest or following various stimuli.

Prevalence of ANS dysfunction

73% of studies (n=27/37) reported at least one abnormality in ANS function in RA patients. Nine studies reported the prevalence of ANS dysfunction, determined from abnormal CCTs, in RA patients with varying results (median prevalence 60%, range 33-86%) (see Appendix 2).(51, 54, 58, 60, 62, 77, 80, 81, 83). The wide range in prevalence is reflective of variations in criteria for ANS dysfunction; numbers of patients included in studies (n=10-50); and assessments of ANS function performed. CCTs, unlike many others assessments of ANS function have validated reference values and established criteria for detection of abnormalities and classification of the severity of dysfunction (mild, moderate or severe).(28)

Parasympathetic dysfunction

Parasympathetic activity in RA patients was assessed by 25 case-control, cross-sectional observational studies and 1 cohort study using: CCTs (n=14) with HR responses to deep breathing(51, 53, 58, 62, 74-83) and/or orthostasis(51, 53, 58, 74-81, 83) and/or

Valsalva's manoeuvre)(51, 53, 58, 76, 78-81, 83); HRV (n=13) with time domain(49, 59, 61, 68, 71, 77, 88) and/or frequency domain parameters,(51, 55, 59, 61, 68, 86-88) respiratory sinus arrhythmia (RSA)(57) or heart rate turbulence (HRT)(50); and the PLR (n=2)(52, 80) with constriction and/or maximum velocity latency (Table 2).

Of the 26 cross-sectional studies assessing parasympathetic activity, approximately 77% reported parasympathetic dysfunction (Table 3). The main pattern of parasympathetic dysfunction included impaired clinical cardiovascular reflexes (85%) and abnormal HRV indices (62%)(Table 4). When studies of low quality were excluded (QIS less than 50%) most studies using CCTs found parasympathetic dysfunction (7 of 8) which was supported by abnormal HRV in most studies (7 of 12). Most of the studies that failed to demonstrate an abnormality in parasympathetic function assessed females only (n=5/7) who were relatively young (mean age range 31-56 years); a demographic known to have elevated HRV indices of parasympathetic activity possibly reflecting the effects of oestrogen.(90-93)

For example, Piha et al(78) found a higher resting HR in 43 female RA patients (mean age 49 years) compared to 69 female controls (mean age 43 years) which may suggest reduced resting parasympathetic activity in the RA group. They reported impaired HR (parasympathetic) responses to orthostasis and Valsalva's manoeuvre in RA patients, which was statistically non-significant when age and resting HR were used as co-variates. Although elevations in resting HR may be a result of autonomic dysfunction other factors are known to contribute (e.g. anaemia, infection, anxiety, medications).

Avsar et al(50) reported no difference in HRT in 26 RA patients (18 females, mean age 56 years) compared to 26 well matched healthy controls. HRT assesses the autonomic response to ventricular premature complexes (VPC) (Table 1) and hence there is a selection bias inherent to this technique; the ANS function of subjects without VPCs cannot be

assessed. Secondly, no power calculation was reported and larger studies (>100 patients) were required to predict cardiovascular risk using HRT.(40)

Sympathetic dysfunction

Sympathetic activity in RA patients was assessed by 29 case-control, cross-sectional observational studies and 1 cohort study using CCTs (n=13) with BP responses to orthostasis(51, 53, 54, 74-77, 79-81) and/or handgrip(51, 54, 79, 81) and/or cold pressor tests(54) and/or mental stress(60, 69, 85); HRV (n=10) with frequency domain parameters,(51, 55, 59, 61, 68, 77, 86-88) pre-ejection period (PEP)(57); biomarkers of sympathetic activity (n=5) with plasma neuropeptide Y (NPY)(63, 64, 72, 86), serum chromogranin(56); SSR (n=5)(60, 62, 69, 70, 82); catecholamines (n=4) with plasma(67, 86, 87) or urinary(66) epinephrine (EPI), norepinephrine (NE); PLR (n=1) with maximal area in darkness.(80)

Of the 30 studies assessing sympathetic activity over half reported sympathetic dysfunction (Table 3). The main pattern of sympathetic dysfunction included impaired clinical cardiovascular reflexes (67%), whilst HRV parameters of sympathetic activity were normal in the majority of studies (70%)(Table 4). When studies of low quality were excluded (QIS less than 50%) most studies using CCTs found sympathetic dysfunction (6 of 9) however this was not supported by abnormal HRV in the majority of studies (2 of 10).

The majority of studies that failed to demonstrate sympathetic dysfunction in RA patients were of predominantly pre-menopausal women, which as discussed previously may cause confounding results. Other possible explanations for negative findings include: failure to control for medications that are known to have an effect on the ANS(85); underpowered

studies(63, 75); selection bias when matching controls to RA patients(75); and limitations inherent to ANS assessments for example lack of standardised testing conditions (see introduction).

Baroreflex sensitivity

Of the two cross-sectional, case-control, observational studies(50, 51) assessing cBRS one reported abnormality in RA compared to controls (Tables 3, 4).(51) Aydemir et al(51) reported a lower resting cBRS (using the sequence technique) in 36 RA patients (30 females, mean age 49 years) compared to 40 age and gender matched controls.(51) Avsar et al found no difference in HRT in 26 RA patients (mean age 56±10 years, 18 female) and 26 age and sex matched healthy controls (mean age 55 years, 18 females).(50)

Time course of ANS dysfunction

Three studies assessed patients with early RA (duration<2years); (57, 60, 63) and in 2 studies sympathetic dysfunction was reported (increased resting sympathetic activity and impaired sympathetic responses to mental stress).(57, 60) These few studies suggest that ANS dysfunction in RA may not necessarily be a consequence of long-term disease and inflammatory burden.

Dekkers et al(57) found no difference in respiratory sinus arrhythmia (RSA), a marker of parasympathetic activity in 25 RA patients (19 females, mean age 55 years) compared to well matched healthy controls. RA patients included in this study had a low erythrocyte sedimentation rate (ESR, mean 15 mm/1st hour) and a disease duration <2 years, suggesting that parasympathetic dysfunction may be a late phenomenon. They also reported increased

sympathetic activity (PEP) in RA patients compared to controls suggesting that sympathetic dysfunction may precede parasympathetic dysfunction.

Inflammation and ANS dysfunction

Observational studies

Twenty four studies reported at least one marker of disease severity including ESR (n=19; range 14-61 mm/1st hour)(49, 51, 53, 57, 59, 60, 63, 66, 67, 71, 73, 75, 77, 78, 80-82, 84, 85), CRP (n=12; 5-380 mg/L)(51, 53, 59, 61, 67, 68, 71, 73, 80, 82, 85, 87) and disease activity score (DAS or DAS28; a clinical index comprising of number of swollen and tender joints, acute phase response typically CRP or ESR, and general health)(94)(n=8; 6 moderate and 2 severe)(49, 51, 55, 61, 65, 68, 85, 87). ANS dysfunction was reported more frequently in those studies with higher CRP values (5 v 2; CRP≥14.5 v <14.5 mg/L) and mainly comprised of parasympathetic dysfunction: reduced HRV indices of cardiac parasympathetic control (n=3)(59, 61, 71); and impaired heart rate responses to deep breathing, orthostasis and Valsalva's manoeuvre (n=1)(80).

Approximately one third of studies (n=7/19) reported an association between ANS function and inflammation: CCTs (n=2/9); HRV (n=3/5); biomarkers of sympathetic activity (n=1/2); and PLR (n=1/1) (Table 5). When low quality studies were excluded (QIS less than 50%) only 5 of 14 studies found an association.

In 7 more recent studies (≥1993) using CCTs,(51, 60, 75, 78, 79, 81, 83) no significant correlation was found in RA patients between ANS function and any of the following: ESR, CRP, the Ritchie articular index (assessment of joint tenderness and swelling), the presence of an inflammatory syndrome (not defined), DAS28 (an updated

version of DAS with clinical assessment of 28 joints), disease duration, presence of rheumatoid factor or articular damage on radiograph.

Yadav et al(88) studied 45 RA patients (41 females, mean age 41 years) and found a significant positive correlation between DAS28 and a parasympathetic index of HRV. Anichkov et al(49) also found a correlation between 24-hour HRV parameters of parasympathetic function and markers of disease severity and inflammation such as number of swollen joints, Ritchie articular index, disease activity score and leucocyte count. Dekkers et al(57) (described earlier in review) reported that higher sympathetic activity (determined from PEP) was associated with higher disease activity (ESR and Thompson joint score).

Two studies found no significant correlation between catecholamines and inflammatory indices. Vlcek et al(87) found no significant correlation between plasma catecholamines and inflammation (CRP, DAS28-CRP). Van Middendorp et al(84) found no correlation between 24 hour urinary noradrenaline excretion and markers of inflammation (ESR or interleukin-6) in a cohort of 60 RA patients (38 females, mean age 59 years). Igari et al(66) in a sub-study of 6 RA patients who underwent synovectomy found that 24 hour urinary adrenaline and noradrenaline significantly decreased 2 weeks following synovectomy. Although the investigators did not assess inflammatory markers following synovectomy, it may be assumed that local joint inflammation would have been reduced following synovectomy and hence possibly removing the stimulus for sympathetic activation.

Barendregt et al(52) found that ESR levels were higher in the group with parasympathetic dysfunction (abnormal PLR in the RA group with ocular dryness) compared to those without (although significance values were not reported).

Interventional studies

Two studies investigated HRV in RA patients receiving tumour necrosis factor (TNF) alpha inhibitor therapy.(65, 73) Holman et al(65) studied 33 patients (25 with RA, 8 with psoriatic arthritis) before treatment with TNF-alpha inhibitor therapy and assessed clinical response to treatment (using American College of Rheumatology criteria ACR20/50/70 and DAS28) at various time points up to one year. They found that low HRV indices, reduced parasympathetic and increased sympathetic activity were predictors of poor response to TNF-alpha inhibitor therapy. However the study may have been underpowered as they found no direct correlation between baseline autonomic function and change in DAS28 score following TNF-alpha inhibitor therapy. Despite limitations of the study (one third of patients discontinued therapy by one year; use and dosage of other medications were not controlled; small numbers of RA patients) these results suggest that HRV and sympatho-parasympathetic balance may play an important role in disease activity.

Two studies assessed plasma NPY levels before and after TNF-alpha inhibitor therapy. In a study of 16 female RA patients Kopec-Medrek et al(72) found that infliximab (TNF-alpha inhibitor) significantly reduced inflammation (CRP, ESR) but did not reduce sympathetic activity (plasma NPY). In fact, plasma NPY concentrations rose to a peak after 6 infusions of infliximab and fell to baseline levels 8 weeks after the ninth (final) infusion. The authors did however report a positive correlation between plasma NPY concentrations and CRP (Kendall tau coefficient=0.506, $P<0.006$) and DAS28 (Kendall tau coefficient=0.393, $P<0.033$) at baseline, indicating that plasma NPY may reflect inflammatory status.

Harle et al (64) found that in a cohort of RA patients, adalimumab (TNF-alpha inhibitor) had no effect on serum NPY levels despite good clinical response. They reported

higher plasma NPY concentrations in RA patients with previous prednisolone use only, indicating a possible interaction effect with the hypothalamic-pituitary-adrenal axis.

DISCUSSION

The results of this systematic literature review indicate that ANS dysfunction is prevalent in ~60% (33-86%) of RA patients as determined from observational studies of small sample size (10-50 patients). Stronger evidence (from large prospective cohort studies) is required to confidently determine the true prevalence of autonomic dysfunction in RA. HRV is probably the most feasible ANS assessment in such a large population. Few studies have assessed patients with early RA (duration<2years) but have shown that ANS dysfunction occurs early in RA and is not necessarily an effect of long-term disease and inflammatory burden. More studies of RA patients with early disease are clearly needed and if possible ANS assessment preceding the onset of RA, to determine whether altered ANS function predisposes to developing RA.

Studies using CCTs in RA have shown reduced resting parasympathetic activity and impairment in both sympathetic and parasympathetic reflex responses. Strong evidence from good quality HRV data supports these findings with the majority demonstrating low HRV reflecting reduced resting parasympathetic activity. In addition there is limited evidence for elevated resting sympathetic activity with the majority of good quality HRV data failing to detect abnormal sympathetic function in RA. Studies employing other methods of ANS assessment have shown conflicting results, which may reflect their inherent limitations. There is a lack of evidence from the literature to date to determine causal relationships between systemic inflammation and autonomic dysfunction. The available literature is too small to be clear whether the lack of evidence represents a lack of relationship or simply inadequate power. Only two studies assessed the effects of anti-inflammatory therapy on ANS function

and failed to demonstrate an effect. However, their results suggest that plasma NPY may not be a reliable method of assessing sympathetic activity particularly as the effects of steroids on NPY are not known. Further interventional studies are needed to elucidate causation. The most feasible and ethical study design would be to assess ANS function in RA patients prior to and after anti-inflammatory therapy. This could be achieved for example with HRV assessments using a 24-hour electrocardiograph holter. Although HRV is not routinely used in clinical practice one study suggested a possible clinical role. Holman et al (65) found that low HRV in RA patients predicted a poor response to TNF-alpha inhibitor therapy indicating a possible benefit in determining ANS status prior to initiation of biologic agents. What remains unknown however is whether therapy to improve HRV in these patients would improve their response to anti-inflammatory agents.

Less than half the studies demonstrated an association between increased inflammation and ANS dysfunction (mainly CCTs and HRV), consistent with the results of recent animal studies.(20-22) The lack of associations in the remaining studies may be simply due to a lack of statistical power; the majority of studies in our review did not report a power calculation. Another possible explanation may be the relatively low inflammatory status of patients tested. CRP, ESR and DAS (reported in less than two thirds of studies) were only modestly elevated although it is unclear whether cumulative inflammatory burden can be determined from assessment at a single time point.. Another explanation for a lack of association between inflammation and ANS function in the studies included in our review may be the subtle nature of autonomic dysfunction present in RA or simply the inappropriate choice of immune markers assessed.

The main limitations of this review are the types and number of ANS tests employed in RA patients, with the majority of studies making only one assessment of ANS function. ANS function is complex and multi-faceted and hence a comprehensive assessment is

required in order to fully categorise the presence of dysfunction. Future studies should include a greater variety of tests including arterial baroreflex assessment, with attempts to measure resting ANS function and response to stimuli. Larger sample sizes are required to confirm the prevalence of ANS in RA, and in order to ensure that statistical power is achieved.

Future studies in RA should aim to characterise the inflammatory profile of patients studied so that causal links between inflammation and ANS dysfunction can be determined. The effects of RA medications on ANS function is not fully known and is a difficult confounding factor to control for, especially as RA patients often require medications to induce and maintain remission of disease. One study showed that infliximab infusion (TNF-alpha inhibitor therapy) caused an acute reduction in HRV and sympathetic activity compared to a placebo. The effects of other RA medications on the ANS tests employed to date are unknown although studies of healthy subjects may be the most ethically acceptable way to investigate this.

Another difficulty is discerning between the effects of RA and concomitant co-morbidities or medications on ANS function. Although many studies excluded RA patients with conditions or medications affecting the ANS system, cardiovascular disease (CVD) remains under-diagnosed in this population.(6, 8, 11) Cardiac imaging (e.g. echocardiography or magnetic resonance imaging) to identify such patients and the possible inclusion of a cardiovascular disease control group may help tackle this problem.

In conclusion, the evidence to date supports that ANS dysfunction is a feature of RA although not universally found in all patients. The profile of ANS dysfunction found in RA patients (low HRV, reduced parasympathetic activity and elevated sympathetic activity) is associated with increased cardiovascular and mortality risk and may help to explain the

increased risk in RA patients. Furthermore, this pattern of ANS dysfunction supports the findings from animal studies and may be a consequence of high inflammatory burden. Although associations between inflammation and ANS dysfunction are present in RA patients, the available literature is too small and underpowered to be clear about causality. Further studies are required to: determine the true prevalence of ANS dysfunction in RA, characterise RA patients who have altered ANS function; determine the prognostic role of ANS assessments in predicting cardiovascular and mortality risk; assess the effects of biologic agents on ANS function; consider the role of therapeutic strategies targeting the ANS in RA patients to help control disease activity or improve response to biologic agents.

ACKNOWLEDGEMENTS

None.

TABLES

Table 1. Definition of ANS assessments included in the review

Table 2. Characteristics of studies included in the review

Table 3. Results Summary: Number of studies with abnormal autonomic function in rheumatoid arthritis patients from observational studies

Table 4. Results Summary: Outcome of autonomic assessments from case-control studies

Table 5. Results Summary: Outcome of associations between autonomic function and inflammation in RA

Supplementary data

Appendix 1. Quality index score assessment tool criteria

Appendix 2. Prevalence of autonomic nervous system dysfunction in rheumatoid arthritis

Table 1. Definition of ANS assessments included in the review

Parameter	Definition	Abnormalities
PARASYMPATHETIC FUNCTION		
Clinical Cardiovascular Tests		
Heart rate response to orthostasis(28)	Heart rate response to standing up unaided following a period of lying quietly on a couch. Normal response is an immediate increase in heart rate (around the 15th beat) after standing followed by a nadir in heart rate (around the 30th beat). The 30:15 ratio (of the longest inter-beat (RR) interval around the 30th beat to the shortest RR-interval around the 15th beat) forms part of the Ewing battery of cardiovascular tests.	30:15 ratio ≤1 indicate parasympathetic dysfunction
Heart rate response to Valsalva's manoeuvre(28)	Heart rate response to straining against a closed glottis at a pressure of 40mmHg for 15 seconds. The Valsalva ratio (of the longest RR- interval shortly after the manoeuvre followed by a rebound bradycardia after release) forms part of the Ewing's battery of cardiovascular	Valsalva ratio ≤1.1 indicates parasympathetic dysfunction

	tests.	
Heart rate variation to deep breathing(28)	Heart rate (HR) variation to deep breathing at a rate of 6 breaths per minute. The mean differences between the maximum and minimum heart rates during each breathing cycle forms part of the Ewing's battery of cardiovascular tests.	HR difference ≤10 indicates parasympathetic dysfunction
Strengths: Simple, bedside tests; non-invasive; inexpensive; normative values available; allows grading of severity when tests used in combination.(28) **Weaknesses**: Indirect measures of parasympathetic activity; some parameters also influenced by sympathetic and baroreflex activity (e.g. Valsalva's manoeuvre)(27); relies on experienced practitioners; multiple factors can affect responses to Valsalva's maneouvre (volume and rate of pre-strain breath, strain pressure, depth and duration, standing v supine) and deep breathing (rate and depth of breathing)(37); provides limited information about the mechanism of autonomic dysfunction; single tests are not reliable in detecting autonomic dysfunction as there is a poor correlation between the various indices.(37)		
Heart Rate Variability (HRV)		
rMSSD(35)	Square root of the mean of the sum of the squares of difference between adjacent inter-beat (NN) intervals. Time domain estimate of short-term components of HRV.	Reduced levels indicate low heart rate variability and parasympathetic dysfunction
NN50(35)	Number of pairs of adjacent NN intervals	

	differing by more than 50 milliseconds in the entire recording. Time domain measure.	
pNN50%(35)	NN50 as a percentage of the total number of all NN intervals. Time domain measure.	
SDNN(35)	Standard deviation of all NN intervals. Estimate of overall HRV. Time domain measure.	
SDANN(35)	Standard deviation of the averages of NN intervals in all 5 minute segments of the entire recording. Time domain estimate of long-term components of HRV.	
SDSD(35)	Standard deviation of differences between adjacent NN intervals. Time domain measure.	
HF power(35)	High frequency power of pulse interval in the range 0.15-0.4 Hz. Frequency domain measure.	Reduced levels indicate reduced parasympathetic activity
SD1(39)	Standard deviation of the Poincare plot (non linear technique). Estimate of short term HRV.	Reduced levels indicate reduced heart rate variability
Strengths: Non-invasive; inexpensive; reproducible; automated analysis; resting activity and responses to stimuli can be measured; Task Force guidelines(35) exist for the optimum utility		

of this technique; 24 hour holter monitoring provides a measure of autonomic function in "real life" environment therefore a good clinical technique to monitor responses to interventions. **Weaknesses**: Indirect measure of autonomic activity; no normative values exist; despite the availability of guidelines the variability in methodology makes it difficult to compare values between studies.		
Heart rate turbulence (HRT) – turbulence onset(40)	Early acceleration of the heart rate immediately following a ventricular premature beat is a result of parasympathetic withdrawal.	Impaired HRT represent reduced parasympathetic activity
Strengths: Non-invasive; inexpensive; automated analysis; 24 hour holter monitoring provides a measure of autonomic function in "real life" environment therefore a good clinical technique to monitor responses to interventions. **Weaknesses**: Indirect measure of autonomic activity; no normative values exist; relies on the presence of premature ventricular beats.(40)		
Respiratory sinus arrhythmia(31)	Rhythmical fluctuations in heart rate periods during inspiration (rise) and expiration (fall) represent parasympathetic activity.	Reduced represents reduced parasympathetic activity
Strengths: Non-invasive; inexpensive; selective index of vagal control of the heart.(31) **Weaknesses**: Results can be affected by rate and depth of breathing; provides a measure of resting autonomic activity only.		
Pupillary Light Reflex		
Constriction latency(34)	Measure of the onset of pupillary constriction in response to light stimulus.	A delay can reflect parasympathetic

		dysfunction
Maximum velocity latency(34)	Measure of the maximum constriction velocity in response to light stimulus.	A reduced velocity indicates parasympathetic dysfunction
Strengths: Non-invasive; inexpensive; validated(34); normative values available; allows grading of severity. **Weaknesses**: Provides limited information about the mechanism of autonomic dysfunction; can be confounded by impairments in ocular muscle function and retinopathy.(34)		
SYMPATHETIC FUNCTION **Clinical Cardiovascular Tests**		
Systolic blood pressure response to orthostasis(28)	Systolic blood pressure response to standing up unaided following a period of lying quietly on a couch. The postural drop in systolic blood pressure forms part of the Ewing's battery of cardiovascular tests.	Decrease in systolic blood pressure ≥20 mmHg indicates sympathetic dysfunction
Blood pressure response to sustained handgrip(28)	Blood pressure response to sustained handgrip (30% of the maximum voluntary contraction using a handgrip dynamometer for up to 5 minutes). The difference between diastolic blood pressure before starting and just prior to	Increase in diastolic blood pressure ≤10 mmHg indicates sympathetic dysfunction

	releasing handgrip forms part of the Ewing's battery of cardiovascular tests.	
Blood pressure response to cold pressor test(37)	Blood pressure response to immersion of hand in a container of ice water for 1-3 minutes which results in sympatho-excitation.	Diminished responses indicate sympathetic dysfunction, increased responses indicate exaggerated sympatho-excitation
Blood pressure response to mental stress(37) Heart rate response to mental stress(37)	Blood pressure response to mental stress tasks (such as mental arithmetic or the Stroop colour-word naming test) which results in sympatho-excitation. Heart rate response to mental stress tasks (such as mental arithmetic or the Stroop colour-word naming test) which results in sympatho-excitation.	
Strengths: Non-invasive; inexpensive; normative values available for responses to orthostasis and handgrip(28); allows grading of severity.(28) **Weaknesses**: Relies on experienced practitioners; difficult to standardise muscle effort during sustained handgrip; wide variability in inter-subject responses to cold pressor test and mental stress; provides limited information about the mechanism of autonomic dysfunction; single tests are not reliable in detecting autonomic dysfunction(28); cold pressor, mental stress and handgrip responses have a low sensitivity and specificity for detecting sympathetic dysfunction.(37)		
Heart Rate Variability		
LF power(35)	Low frequency power of pulse interval in the range 0.04-0.15 Hz. Frequency	Increased levels indicate heightened

	domain measure indicating mainly sympathetic activity (but also small parasympathetic component).	sympathetic activity
LF/HF ratio(35)	Ratio of low frequency / high frequency power of pulse intervals. Frequency domain measure of sympatho-parasympathetic balance.	Increased levels indicate predominantly heightened sympathetic activity
Strengths: Non-invasive; cheap; reproducible; automated analysis; resting activity and responses to stimuli can be measured; Task Force guidelines(35) exist for the optimum utility of this technique; 24 hour holter monitoring provides a measure of autonomic function in "real life" environment therefore a good clinical technique to monitor responses to interventions. **Weaknesses**: Indirect measure of autonomic activity; no normative values exist; despite the availability of guidelines the variability in methodology makes it difficult to compare values between studies; LF power has contributions from the parasympathetic nervous system and hence not purely a measure of sympathetic activity.(46)		
Pre-ejection period (PEP)(29, 33)	The interval from the onset of the Q wave (on an ECG) to the left ventricular ejection (detected using impedence cardiography). Pre-ejection period is inversely related to myocardial contractility and can represent sympathetic influences on the heart.	Reduced PEP indicates increased sympathetic activity
Strengths: Non-invasive; provides a reliable measure of systolic time intervals; can provide a		

<table>
<tr><td colspan="3">measure of resting activity and response to stimuli.(33)

Weaknesses: Indirect measure of cardiac autonomic influences; lack of standardised methodology; derived values of stroke volume and cardiac output are less reliable(29); pre-ejection period may be confounded by changes in preload or afterload.(33)</td></tr>
<tr><td colspan="3">Microneurography</td></tr>
<tr><td>Muscle sympathetic nerve activity(37, 38)</td><td>Intra-neural recordings of muscle sympathetic nerve activity (MSNA) using tungsten microelectrodes inserted percutaneous into a peripheral nerve (typically peroneal nerve) allow direct measurement of vasoconstrictor sympathetic outflow.</td><td>Increased levels indicate sympathetic over-activity</td></tr>
<tr><td colspan="3">Strengths: Direct and continuous measure of muscle sympathetic outflow; correlates with cardiac sympathetic activity; reproducible; well tolerated in healthy disease populations; can record for several hours at a time; allows quantification of resting activity as well as response to stimuli.(38)

Weaknesses: Invasive; technically challenging procedure.</td></tr>
<tr><td colspan="3">Catecholamines or Biomarkers of Sympathetic Activity</td></tr>
<tr><td>Catecholamines(37)</td><td>Catecholamines such as epinephrine, norepinephrine and their metabolites detected in the plasma or urine (24 hour collection) may represent sympathetic activity. Confounding factors include medications, diurnal variations and concomitant diseases.</td><td>Increased levels may indicate sympathetic over-activity</td></tr>
</table>

Plasma neuropeptide Y(41)	Peripheral marker peptide released with norepinephrine following sympathetic activation.	
Serum chromogranin A(30)	Acidic, soluble proteins with widespread neuroendocrine distribution in secretory vesicles, co-released with catecholamines by exocytosis from vesicles in adrenal medulla and sympathetic nerve endings.	
Strengths: Minimally invasive; inexpensive; plasma levels allow measurement of resting activity and response to stimuli. **Weaknesses**: Difficult to measure; represents global sympathetic activity and cannot delineate regional variances; plasma levels of catecholamines reflect uptake, release and clearance whilst urinary levels are dependent on renal function; can be confounded by medications, diurnal variations and concomitant diseases.(38)		
Norepinephrine spillover (37, 38)	Regional or organ-specific norepinephrine spillover measurements can characterise regional sympathetic activity.	Increased spillover rates indicate regional sympathetic over-activity
Strengths: Allows direct measurement of organ specific sympathetic activity. **Weaknesses**: Invasive; considerable costs; technically challenging.(38)		
Cardiac sympathetic imaging (37, 38)	Imaging agents (e.g. radio-labelled sympathomimetic amines) can be detected using single photon emission computed tomography, providing visual representation of sympathetic activity.	Provides images showing areas of sympathetic over- or under-activity

	Has been used to demonstrate cardiac sympathetic denervation in cardiovascular disease and has prognostic significance.	
Strengths: Allows direct measurement of organ specific sympathetic activity; provides structural and functional assessment of the sympathetic nervous system; can provide quantification of organ specific noradrenergic uptake.(38) **Weaknesses**: Minimally invasive; considerable costs; limited availability; assessing sympathetic activity in the heart can be technically difficult.(38)		
Other Assessments		
Pupillary light reflex maximal pupillary area in darkness(34)	Measure of maximal pupillary area in response to darkness.	A reduced area indicates sympathetic dysfunction
Strengths: Non-invasive; inexpensive; validated; normative values available; allows grading of severity.(34) **Weaknesses**: Provides limited information about the mechanism of autonomic dysfunction; can be confounded by impairments in ocular muscle function and retinopathy.(34)		
Sympathetic skin responses(32, 36)	Changes in skin electrical conductance in response to various stimuli (such as electrical, acoustic) represent sympathetic cholinergic function.	Absent responses indicates sympathetic dysfunction
Strengths: Non-invasive; simple; fast; inexpensive. **Weaknesses**: Wide intra- and inter-subject variability in sympathetic skin responses due to confounding factors (e.g. ambient temperature, skin temperature, mental or emotional state,		

<table>
<tr><td colspan="3">habituation with repeated stimuli); low sensitivity and specificity; poor correlation with other autonomic assessments (e.g. sudomotor dysfunction).(36)</td></tr>
<tr><td colspan="3">BAROREFLEX SENSITIVITY
Cardiac Baroreflex Sensitivity</td></tr>
<tr><td>Sequence technique(42, 43)</td><td>Spontaneous assessment involving simultaneous recording of blood pressure and RR interval whilst the patient rests quietly. A computer is used to identify sequences of three or more consecutive beats characterised by a progressive increase or decrease in BP which results in lengthening or shortening of the RR interval (consecutively). Regression slope of SBP and RR interval provides a measure of cardiac baroreflex sensitivity</td><td>Reduced slope indicates impaired cardiac baroreflex sensitivity</td></tr>
<tr><td colspan="3">Strengths: Non-invasive; simple; inexpensive; automated analysis; reliable; provides distinct measurements for rising and falling blood pressures.(17, 43)
Weaknesses: No normative values exist; relies on the presence of sequences; marked within subject variation in baroreflex sensitivity (possibly due to haemodynamic, temporal and behavioural factors).(43)</td></tr>
<tr><td>Pharmacological agents(27, 37)</td><td>Phenylephrine (vasoconstrictor) causes increase in blood pressure which results in baroreflex-mediated slowing of the</td><td></td></tr>
</table>

	heart rate. Regression slope of SBP and RR interval or heart rate provides a measure of cardiac baroreflex sensitivity.	
Strengths: Inexpensive; usually produces a high correlation between blood pressure and RR interval suggesting it is a good indicator of arterial baroreflex gain.(37) **Weaknesses**: Invasive; no normative values exist; only assesses the response to rises in blood pressure which may be reduced in subjects with low resting sympathetic outflow (typically young healthy individuals).(37)		
Heart rate turbulence - turbulence slope(40, 95)	Rate of late deceleration (after early acceleration) of the heart rate immediately following a ventricular premature beat represents cardiac baroreflex sensitivity	Reduced turbulence slope indicates impaired cardiac baroreflex sensitivity
Strengths: Non-invasive; inexpensive; automated analysis; 24 hour holter monitoring provides a measure of autonomic function in "real life" environment therefore a good clinical technique to monitor responses to interventions. **Weaknesses**: Indirect measure of autonomic activity; no normative values exist; relies on the presence of premature ventricular beats.(40)		
BP = blood pressure, ECG = electrocardiogram, HR = heart rate, HRV = heart rate variability, NN = inter-beat, RR interval = inter-beat interval, SBP = systolic blood pressure.		

Table 2. Characteristics of studies included in the review

A. Cross-sectional, observational, case-control studies

Study	Year	N	Characteristics	Inclusion Exclusion	Assessment	Key findings	QIS
Clinical cardiovascular tests (n=17)							
Aydemir et al(51)	2010	RA 36 HC 40	30 female, 49 years Disease duration 11.2 years DAS28 4.1 CRP 11mg/L ESR 33 mm/1st hour 31 female, 43 years	I: ARA 1987 criteria E: Condition or medication affecting ANS	Ewing HR variation response to DB, O, VM BP response to HG, O	Abnormal cardiovascular tests in 61-75% of RA patients Impaired sympathetic and parasympathetic responses Higher resting HR in RA patients No association between inflammation (DAS28, CRP, ESR) and ANS function	89%
Bidikar et al(54)	2010	RA 50 HC 50	46 female, 38 years 46 female, 38 years	I: ARA 1987 criteria, age 20-60 yrs E: Condition or medication affecting ANS	Ewing BP response to CP, HG, O	Higher resting HR and SBP in RA patients Abnormal cardiovascular tests in RA Impaired sympathetic responses	56%
Milovanovic et al(77)	2010	RA 38 HC 41	32 female, 56 years 25 RF positive ESR 14.3 mm/1st hour 17 female, 37 years	I: ARA 1987 criteria E: Condition or medication affecting ANS	Ewing HR variation response to DB, O, VM BP response to O	Abnormal cardiovascular tests more prevalent in RA than controls Impaired sympathetic and parasympathetic responses	67%
Stojanovich et al(81)	2007	RA 39	33 female, 58 years Disease duration 9.5years 64% RF positive ESR 14.3 mm/1st hour	I: ARA 1987 criteria E: Condition or medication affecting ANS	Ewing HR variation response to DB, O, VM	Abnormal cardiovascular tests more prevalent in RA Impaired	78%

		HC 35	19 female, 52 years		BP response to HG, O	sympathetic and parasympathetic responses in RA patients No correlation between inflammation (CRP, ESR, Ritchie score) and ANS function	
Veldhuijzen van Zanten et al(85)	2005	RA 21 DC 10	18 females, 57 years Disease duration 12 years CRP 10.4 mg/L ESR 27.5 mm/1st hour DAS28 4.57 6 females, 47 years (osteoarthritis)	I: ARA 1987 criteria, able to stand for 15 minutes E: Previous acute coronary syndrome, diabetes mellitus, serious psychiatric disease	HR and BP (sympathetic) responses to mental stress	Normal sympathetic responses to mental stress seen in RA compared to osteoarthritis controls	61%
Sandhu et al(79)	2004	RA 62 HC 41	39 female, median 63 years Steinbrocker's class 1 or 2 76% RF positive None had evidence of current flare in joint 7 had peripheral nerve damage 21 females, median 50 years	I: ARA 1987 criteria E: Condition or medication affecting ANS	Ewing HR variation response to DB, O, VM BP response to HG, O	Abnormal cardiovascular tests in RA – worse in patients with peripheral neuropathy or RF positive Impaired parasympathetic and sympathetic (only DBP response to HG) responses in RA patients No correlation between inflammation (CRP, ESR) and ANS function	83%
Gozke et al(62)	2003	RA 10 HC 14	10 females, 49 years 14 females, 45 years	I: ARA 1987 criteria E: Symptoms of clinical ANS dysfunction	RR interval variation at rest and in response to DB	Abnormal cardiovascular tests in RA Impaired parasympathetic responses in RA patients	39%
Johannes et al(69)	2003	RA 13	No females, 64 years	I: RA (no criteria), male E: None reported	HR and BP (sympathetic) responses to mental stress	Higher resting HR in RA patients and hypertensive controls, compared to	50%

		HC 30	No females, 39 years			healthy Lower resting DBP in RA patients compared to hypertensive and healthy controls Higher BP (sympathetic) response to mental stress in RA patients compared to hypertensive and healthy controls	
		DC 53	No females, 49 years (Hypertensive)				
Louthrenoo et al(75)	1999	RA 34	30 females, 47 years Disease duration 5.1years 15.5 swollen joints Ritchie articular index 11.6 56% RF positive ESR 35.2 mm/1st hour	I: ARA 1987 criteria E: Condition or medication affecting ANS	Ewing HR variation in response to DB, O SBP response to O	Abnormal cardiovascular tests in RA Parasympathetic dysfunction in RA patients. No correlation between inflammation (ESR, number of swollen joints) and ANS function	61%
		HC 62	50 females, 47 years 34 age and gender match controls used in analysis				
Bekkelund et al(53)	1997	RA 43	43 females, 44 years Disease duration 13.6 years 24.1 arthritic joints Ritchie articular index 22.6 CRP 10.8mg/L ESR 23.2 mm/1st hour	I: ARA 1987 criteria, females, aged 16-55 years E: Known somatic or psychiatric disease, concomitant systemic connective tissue disease or primary neurological disease, alcoholism, atlantodental space>5mm	Ewing HR variation in response to DB, O, VM BP response to O	Normal cardiovascular tests in RA	78%
		HC 61	61 females, 42 years				
Maule et al(76)	1997	RA 17	17 females, 37 years Disease duration 9.3 years	I: ARA 1987 criteria E: Diabetes, obesity, renal failure, chronic liver disease, arrhythmia,	Ewing HR variation in response to DB, O, VM BP response to O	Normal cardiovascular tests in RA	44%
		HC 25	25 females, 32 years				

				anaemia, anti-hypertensive therapy			
Geenen et al(60)	1996	RA 21 HC 20	17 females, 56 years Disease duration 4-12months, VAS pain 26mm ESR 23 mm/1st hour 16 females, 53 years	I: ARA 1987 criteria E: Any other serious disease. Controls were free from chronic pain, cardiovascular complaints or disease.	HR and BP (sympathetic) responses to mental stress	Abnormal cardiovascular tests in RA Impaired HR and BP (sympathetic) responses in RA patients No correlation between inflammation (ESR) and ANS function	67%
Piha et al (78)	1993	RA 34 HC 69 DC 76	34 females, 49 years Disease duration 15 years ARA functional class: I = 6, II = 20, III = 8 28 had arthritis in 3 or more joint areas and positive findings on hand radiographs ESR 23 mm/1st hour 69 females, 43 years 76 females, 43 years (diabetic)	I: ARA 1987 criteria, females E: Condition or medication affecting ANS.	HR variation response to DB, O, VM	Higher resting HR in RA Impaired HR variation (parasympathetic) responses to O and VM (which were statistically insignificant when age and HR used as co-variants) No correlation between inflammation (ESR) and ANS function	78%
Tan et al(82)	1993	RA 30 HC 30	27 females, 51 years Disease duration 90.2months Steinbrocker function class: II = 25, III = 5 CRP 380 mg/L ESR 61 mm/1st hour 26 females, 50 years	I: ARA 1987 criteria E: Control subjects were healthy with no symptoms or signs of neurological disease	RR interval variation at rest and in response to DB	Abnormal cardiovascular tests in 27% of RA patients Impaired parasympathetic activity (RR interval variation in response to DB)	56%
Toussirot et al(83)	1993	RA 50	31 females, 56 years Disease duration 6 years	I: ARA 1987 criteria, patients hospitalized	HR response to DB, O, VM	Abnormal cardiovascular tests in 60% of RA patients	56%

			52% RF positive 52% inflammatory syndrome (not clearly defined) HC 82 53 females, 47 years	with a flare or for therapeutic adjustment E: Condition or medication affecting ANS		Impaired parasympathetic responses (HR response to VM only) in RA patients No correlation between inflammation (inflammatory syndrome, articular damage on radiograph) and ANS function	
Leden et al(74)	1983	RA 17 12 females, 56 years Disease duration 20 years 14 seropositive Steinbrocker's function class: II = 6, III = 8, IV = 2. All had erosions HC 24 8 females, 53 years		I: ARA 1987 criteria admitted for reconstruction joint surgery E: Respiratory disease, abnormal creatinine or proteinuria	BP response to O HR variation response to DB, O	Normal cardiovascular tests in RA patients overall Sub-group showed significant impairment in cardiovascular tests in RA patients with a high v low (7 v 10) disease severity score Impaired parasympathetic (HR variation response to DB and O) and sympathetic responses (BP response to O) found in RA patients with high disease severity score v controls	44%
Edmonds et al(58)	1979	RA 27 55 years HC 13 51 years (old healthy) HC 15 25 years (young healthy) DC 13 54 years (osteoarthritis)		I: Ropes et al 1958 criteria, normotensive E: Cardiac failure, anaemia, medications affecting cardiac rhythm	Ewing HR variation response to DB, O, VM	Higher proportion of abnormal cardiovascular tests in RA Impaired parasympathetic responses in RA patients Mean ESR higher in RA patients with abnormal HR variation response to O	39%

HRV tests (n=13)							
Janse van Rensburg et al(68)	2012	RA 45 HC 39	45 females, 47 years Disease duration 4.3 years DAS28 3.3 CRP 8.6 mg/L 39 females, 45 years	I: ARA 1987 criteria, classification of global functional status = class I or II, female, aged 30-60 years, controlled disease E: Condition or medication affecting ANS.	Short term HRV Parasympathetic (pNN50%, SDNN, rMSSD, HF, SD1), sympathetic (LF, LF/HF ratio) balance at rest and in response to O	Higher resting HR in RA Lower HRV in RA Increased sympathetic tone and decreased parasympathetic activity Reduced response to O in RA	78%
Vlcek et al(87)	2012	RA 22 HC 15	22 females, 31 years Disease duration 7.4 years DAS28-CRP 3.4 CRP 7.5 mg/L 15 females, 30 years	I: ARA 1987 criteria, female, age<40years, normal BMI E: Any disease	Short term HRV Parasympathetic (HF), sympathetic (LF, LF/HF ratio) balance at rest and in response to O	Normal HRV at rest and in response to O in RA	78%
Yadav et al(88)	2012	RA 45 HC 45	39 females, 41 years 39 females, 37 years	I: ARA 1987 criteria E: Condition or medication affecting ANS	Short term HRV Parasympathetic (SDNN, SDSD, rMSSD, NN50, HF), sympathetic (LF, LF/HF) balance	Lower HRV in RA Reduced parasympathetic activity Positive correlation between inflammation (DAS28) and parasympathetic tone (SDSD only)	72%
Avsar et al(50)	2011	RA 26 HC 26	18 females, 56 years 18 females, 55 years	I: ARA 1987 criteria E: Condition or medication affecting ANS	Heart rate turbulence from 24 hour holter ECG monitor at home. Parasympathetic and arterial baroreflex sensitivity	Normal heart rate turbulence (parasympathetic activity and arterial baroreflex sensitivity) in RA patients	56%
Aydemir et al(51)	2010	RA 36	30 females, 49 years	I: ARA 1987 criteria E: Condition	Short term HRV Parasympathetic	Reduced sympathetic activity (LF) in	89%

		HC 40	31 females, 43 years	or medication affecting ANS	(HF), sympathetic (LF, LF/HF ratio) balance at rest and in response to O	RA	
Bruchfeld et al(55)	2010	RA 13	9 females, 52 years Disease duration 13.2years 11 RF positive DAS28-CRP 3.9	I: ARA 1987 criteria E: Smoking, diabetes mellitus	Short term HRV Parasympathetic (HF) and sympathetic (LF, LF/HF ratio) balance	Reduced parasympathetic activity (HF) in RA	61%
		HC 10	3 females, 32 years				
Milovanovic et al(77)	2010	RA 38	32 females, 56 years 25 RF positive ESR 14.3 mm/1st hour	I: ARA 1987 criteria, stable condition E: Condition or medication affecting ANS	Short term HRV Parasympathetic (pNN50%, SDRR, rMSSD, HF), sympathetic (LF, LF/HF ratio) balance Long term HRV Parasympathetic, sympathetic activity	Lower HRV in RA Reduced parasympathetic (SDNN, pNN50%, rMSSD) activity in RA	67%
		HC 41	17 females, 37 years				
Vlcek et al(86)	2008	RA 8	8 females, 31 years	I: ARA 1987 criteria E: None reported	Short term HRV Parasympathetic (HF) and sympathetic (LF, LF/HF) balance at rest and in response to O	Normal HRV at rest and in response to O in RA patients	61%
		HC 8	8 females, 31 years				
Anichkov et al(49)	2007	RA 23	23 females, 48 years Disease duration 4 years 19 RF positive DAS 4.2 ESR 24mm/1st hour Ritchie articular index 16	I: ARA 1987 criteria, female, aged 18-65 yrs, disease duration ≥12 months E: Condition or medication affecting ANS	Long term HRV Parasympathetic (SDNN, SDANN, rMSSD, SD1) activity	Lower HRV in RA patients Reduced parasympathetic activity (SDNN, SDANN, rMSSD, SD1) Negative correlation between inflammation (number of swollen joints, Ritchie articular index, DAS, leucocyte count) and HRV, parasympathetic activity (SDNN, SDANN)	88%
		HC 23	23 females, 47 years				

Goldstein et al (61)	2007	RA 13 HC 11	9 females, median 52 years Disease duration 13 years, 11 RF positive DAS28 4.5 CRP 14.5mg/L 6 females, median 38 years	I: ARA 1987 criteria E: None reported	Short term HRV Parasympathetic (rMSSD, HF) and sympathetic balance (LF, LF/HF ratio)	Lower HRV in RA patients Reduced parasympathetic activity (rMSSD, HF) in RA patients	72%
Kamal(71)	2007	RA 52 HC 51	49 years Disease duration 8.4 years CRP 51.4 mg/L ESR 42.6 mm/1st hour 46 years	I: RA (no criteria) E: Condition or medication affecting ANS	Short term HRV. Parasympathetic activity (SDNN).	Low HRV in RA patients Reduced parasympathetic activity (SDNN) in RA patients	33%
Dekkers et al(57)	2004	RA 25 HC 28	19 females, 55 years Disease duration <2years Thompson joint score 31 ESR 15 mm/1st hour 20 females, 56 years	I: ARA 1987 criteria, minimum age 18 yrs E: Any other serious disease. For healthy controls: chronic disease, chronic pain, hypertension or heart problems	ECG, impedence cardiogram Parasympathetic (respiratory sinus arrhythmia), sympathetic (pre-ejection period) activity.	Lower pre-ejection period found in RA patients (indicating higher sympathetic activity) Normal respiratory sinus arrhythmia (parasympathetic activity) in RA patients Association between inflammation (ESR, Thompson joint score) and increased sympathetic activity	72%
Evrengul et al(59)	2004	RA 42	31 females, 48 years Disease duration 6.5 years 35 RF positive Steinbrocker's function class: I = 16, II = 18, III = 8 CRP 50.3 mg/L ESR 41.7 mm/1st hour	I: ARA 1987 criteria, stages I-IV of Steinbrocker's functional classification E: Condition or medication affecting ANS	Short term HRV Parasympathetic (SDNN, pNN50%, rMSSD, HF), sympathetic (LF, LF/HF ratio) balance	Low HRV in RA patients Reduced parasympathetic activity (SDNN) in RA patients No correlation between inflammation (ESR) and HRV	89%

		HC 44	31 females, 45 years			parameters	
Biomarkers (n=5)							
Kopec-Medrek et al(72)	2012	RA 16	16 females, post-menopausal	I: RA (no criteria) treated with infliximab (TNF alpha inhibitor), post menopausal females, active disease and not received remission after treatment with at least two DMARDs E: HRT, smoking, conditions known to affect ANS	Plasma NPY (sympathetic activity)	Plasma NPY (sympathetic activity) was higher in RA patients Positive correlation between inflammation (CRP, DAS28) and plasma NPY (sympathetic activity)	67%
		HC 16	16 females, post-menopausal Age and BMI matched				
Capellino et al(56)	2008	RA 24	14 females, 58 years	I: ARA 1987 criteria E: None reported	Serum chromogranin A (sympathetic activity)	Serum chromogranin A (sympathetic activity) was higher in RA patients	50%
		HC 37	26 females, 38 years				
Vlcek et al(86)	2008	RA 8	8 females, 31 years	I: ARA 1987 criteria E: None reported	Plasma NPY (sympathetic activity) at rest and in response to O.	Normal plasma NPY (sympathetic activity) in RA patients	61%
		HC 8	8 females, 31 years				
Harle et al(64)	2006	RA 62	52 females, 58 years Disease duration 9.7 years 9 tender joints 7.5 swollen joints ESR 27.7 mm/1st hour.	I: ARA 1987 criteria, fertile women were not taking contraceptives and tested in the early to mid-follicular phase of the menstrual cycle E: None reported	Serum NPY (sympathetic activity)	Higher NPY found only in RA patients with previous prednisolone use	67%
		HC 23	12 females, 52 years				
Grimsholm et al(63)	2005	RA 7	51 years (early RA) Disease duration <1 year	I: ARA 1987 criteria E: None reported	Serum NPY (sympathetic activity)	NPY higher in long-standing RA patients but not statistically significant	28%

	RA 28 HC 11	59 years (long-standing RA) Disease duration >1year 39 years Note: 25/35 female RA patients	NPY in early RA patients comparable to healthy controls

Skin sympathetic responses (n=5)							
Gozke et al(62)	2003	RA 10 HC 14	10 females, 49 years 14 females, 45 years	I: ARA 1987 criteria E: Symptoms of clinical ANS dysfunction	Sympathetic skin responses to nerve stimulation	Normal sympathetic skin responses in RA	39%
Johannes et al(69)	2003	RA 13 HC 30 DC 53	No females, 64 years No females, 39 years No females, 49 years (hypertensive)	I: RA (clinical diagnosis), male E: None reported	Skin temperature and conductance responses to mental stress	Sympathetic skin responses to mental stress higher in RA patients	50%
Geenen et al(60)	1996	RA 21 HC 20	17 females, 56 years Disease duration 4-12months VAS pain 26mm ESR 23 mm/1st hour 16 females, 53 years	I: ARA 1987 criteria E: Any other serious disease. Controls were free from chronic pain, cardiovascular complaints or disease	Sympathetic skin conductance to mental stress	Normal resting skin conductance in RA patients Reduced sympathetic skin responses to mental stress	67%
Jolliffe et al(70)	1995	RA 40 HC 46	57 years 57 years	I: ARA 1987 criteria E: Diabetes mellitus, vasoactive medication, skin conditions affecting the wrist	Sympathetic skin responses to intra-dermal nicotine	Normal sympathetic skin responses in RA patients	44%
Tan et al(82)	1993	RA 30 HC 30	27 females, 51 years Disease duration 90.2months Steinbrocker function class: II = 25, III = 5 ESR 61 mm/1st hour CRP 380 mg/L 26 females, 50 yrs	I: ARA 1987 criteria E: Control subjects were healthy with no symptoms or signs of neurological disease	Sympathetic skin responses to nerve stimulation	Normal sympathetic skin responses in RA	56%
Catecholamines (n=4)							

Vlcek et al(87)	2012	RA 22 HC 15	22 females, 31 years Disease duration 7.4 years DAS28-CRP 3.4 CRP 7.5 mg/L 15 females, 30 years	I: ARA 1987 criteria, female, age<40yrs, normal BMI E: Any disease	Plasma EPI and NE (sympathetic activity) at rest and in response to O	Normal EPI and NE (sympathetic activity) at rest and in response to O in RA	78%
Vlcek et al(86)	2008	RA 8 HC 8	8 females, 31 years 8 females, 31 years	I: ARA 1987 criteria E: None reported	Plasma EPI and NE (sympathetic activity) at rest and in response to O	Baseline plasma NE (sympathetic activity) was higher in RA patients There was a trend for reduced plasma NE (sympathetic activity) in RA patients	61%
Imrich et al(67)	2005	RA 15 HC 14	15 females, 41 years Disease duration 8.2 years CRP 15.4mg/L ESR 20.3 mm/1st hour 14 females, 44 years	I: ARA 1987 criteria, female E: Diabetes, impaired glucose tolerance	Serum EPI and NE (sympathetic activity) at rest and in response to insulin-induced hypoglycaemia	Basal and cumulative levels of EPI were reduced (but not statistically significantly) in RA patients Basal levels of NE were normal in RA patients, but cumulative levels were reduced (reduced basal sympathetic activity). Serum EPI response to insulin-induced hypoglycaemia was normal in RA however serum NE response was reduced in RA (impaired sympathetic response)	67%
Igari et al(66)	1977	RA 22 HC 6	20 females, 45 yrs ESR 44.8mm/1st hr, Steinbrocker class 2.5 2 females, 33 years	I: Ropes et al 1958 criteria for classical or definite RA E: None reported	24 hour urinary adrenaline and noradrenaline (sympathetic activity)	Baseline 24 hour urinary adrenaline was reduced in RA patients	44%

Arterial baroreflex sensitivity (n=2)							
Avsar et al(50)	2011	RA 26 HC 26	18 females, 56 years 18 females, 55 years	I: ARA 1987 criteria E: Condition or medication affecting ANS	Heart rate turbulence from 24 hour holter ECG monitor at home Parasympathetic and arterial baroreflex sensitivity	Normal heart rate turbulence (parasympathetic activity and arterial baroreflex sensitivity) in RA patients	56%
Aydemir et al(51)	2010	RA 36 HC 40	30 females, 49 years 31 females, 43 years	I: ARA 1987 criteria E: Condition or medication affecting ANS	Sequence method (arterial baroreflex sensitivity) at rest and in response to O	Reduced arterial baroreflex sensitivity at rest in RA patients	89%
Pupillary light reflex (n=1)							
Barendregt et al(52)	1996	RA 18 RA 18 HC 33	18 females, 64 years (with ocular dryness) 18 females, 59 years (without ocular dryness) 33 females, 56 years	I: ARA 1987 criteria, with or without dryness of eyes or mouth E: Condition or medication known to affect ANS	Pupillary light reflexes: constriction latency and maximum constriction velocity (parasympathetic activity)	Parasympathetic dysfunction (prolonged constriction latency and elevated maximum constriction velocity) found in RA patients with ocular dryness	61%

Mean values given unless otherwise indicated.
ANS = autonomic nervous system, ARA 1987 criteria = American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis,(89) BP = blood pressure, BMI = body mass index, CP = cold pressor test, CRP = C reactive protein, DAS28 = disease activity score 28, DB = deep breathing, DBP = diastolic blood pressure, DC = disease controls, DMARD = disease modifying anti-rheumatic drug, E = exclusion, ECG = electrocardiogram, EPI = epinephrine, ESR = erythrocyte sedimentation rate, HC = healthy controls, HF = high frequency power in the range 0.15-0.40 Hz, HG = handgrip, HR = heart rate, HRT = hormone replacement therapy, HRV = heart rate variability, I = inclusion, LF = low frequency power in the range 0.04-0.15Hz, LF/HF ratio = low frequency to high frequency ratio, N = number of subjects, NE = norepinephrine, NN = inter-beat interval, NN50 = number of pairs of adjacent NN intervals differing by more than 50 milliseconds in the entire recording, NPY = neuropetide Y, O = orthostasis, pNN50% = NN50 as a percentage of the total number of all NN intervals, QIS = quality index score (%), RA = rheumatoid arthritis, RF = rheumatoid factor antibody, rMSSD = square root of the mean of the sum of the squares of difference between adjacent NN intervals, Ropes et al 1958 criteria = 1958 Revision of diagnostic criteria for rheumatoid arthritis,(96) SBP = systolic blood pressure, SD1 = standard deviation of the Poincare plot, SDANN = standard deviation of the averages of NN intervals in all 5 minute segments of the entire recording, SDNN = standard deviation of all NN intervals, SDSD = standard deviation of differences between adjacent NN intervals, TNF = tumour necrosis factor, VAS = Visual Analogue score, VM = Valsalva's manoeuvre

B. Cohort and interventional studies

Study	Year	N	Characteristics	Inclusion Exclusion	Assessment	Key findings	QIS
Interventional studies (n=3)							
Kopec-Medrek et al(72)	2012	RA 16	16 females, post-menopausal	I: RA (no criteria) treated with infliximab (TNF alpha inhibitor), post menopausal females, active disease and not received remission after treatment with at least two DMARDs E: HRT, smoking, conditions known to affect ANS	Plasma NPY (sympathetic activity) at week 0, 2, 14, 54 and 62.	Plasma NPY (sympathetic activity) was higher in RA patients at baseline and with infliximab infusion. Positive correlation between inflammation (CRP, DAS28) and plasma NPY (sympathetic activity)	67 %
		HC 16	16 females, post-menopausal Age and BMI matched Cross-sectional, case-control, observational study with longitudinal interventional component. Intervention: TNF alpha inhibitor therapy (infliximab) in 16 RA patients. 1 year follow up				
Harle et al(64)	2006	RA 62	52 females, 58 years Disease duration 9.7 years 9 tender joints 7.5 swollen joints ESR 27.7	I: ARA 1987 criteria, fertile women were not taking contraceptives and tested in the early to mid-follicular phase of the menstrual	Serum NPY (sympathetic activity) at week 0 and 12	Higher serum NPY found only in RA patients with previous prednisolone use TNF alpha	67 %

			mm/1st hour	cycle E: None reported		inhibitor therapy had no effect on serum NPY levels, despite a good clinical response	
		HC 23	12 females, 52 years Cross-sectional, case-control, observational study with longitudinal interventional component Intervention: TNF alpha inhibitor therapy (adalimumab) in 32 RA patients Follow up 12 weeks post therapy				
Igari et al(66)	1977	RA 22	20 females, 45 years ESR 44.8 mm/1st hour Steinbrocker class 2.5	I: ARA 1987 criteria for classical or definite RA E: None reported	24 hour urinary adrenaline and noradrenaline (sympathetic activity) before and after synovectomy	Baseline 24 hour urinary adrenaline was reduced in RA patients 24 hour urinary adrenaline and noradrenaline significantly decreased two weeks after synovectomy in RA patients	44 %
		HC 6	2 females, 33 years Cross-sectional, case-control, observational study with longitudinal interventional component Intervention: synovectomy performed in 6 RA patients				
Cohort studies (n=3)							
Holman et al(65)	2008	AL L 33	RA 25, Psoriatic arthritis 8 Disease duration 7.6 years 14 RF positive Baseline DAS28 4.9 Remission	I: Inflammatory arthritis including 25 RA (no criteria) undergoing TNF alpha inhibitor therapy.	Short term HRV. Parasympathetic (HF), sympathetic (LF) and overall HRV (total power).	Low HRV (total power), low parasympathetic (HF) and high sympathetic function (LF) was predictive of poor response to	56 %

			DAS28 2.0			TNF alpha inhibitor therapy. No correlation between baseline autonomic function (HRV parameters) and change in DAS28 score.	
		RA 25	Prospective, double-blind, exploratory study to investigate HRV as a predictor of TNF alpha inhibitor therapy in patients with inflammatory arthritis.				
Schwemmer et al(80)	2006	RA 30	17 females, 52 years Disease duration 6.7 years 9 swollen joints 9 tender joints 63% RF positive CRP 31 mg/L ESR 30.2 mm/1st hour Prospective, cohort study with longitudinal survival Follow-up: 8 years	I: ARA 1987 criteria E: Condition or medication affecting ANS	Clinical cardiovascular tests (Ziegler et al 1992) HR variation at rest and responses to DB, O, VM SBP responses to O Pupillary light reflex: latency time, area in darkness	Cardiac and pupillary ANS dysfunction in 60% of RA patients 3 of 4 deaths were due to cardiac causes Non-survivors had higher HR variation response to DB, but lower HR variation to O	61 %
van Middendorp et al(84)	2005	RA 60	38 females, 59 years Disease duration 13 years Thompson joint score 21 ESR 16 mm/1st hour Cross-sectional, cohort, observational study	I: RA (no criteria) E: Receiving glucocorticoid therapy	24 hour urinary noradrenaline excretion (sympathetic activity)	No correlation found between sympathetic activity and inflammation (ESR or IL-6)	56 %
Other studies (n=1)							

Lazzerini et al(73)	2008	RA 20	Disease duration 10.4 years 16 erosive disease CRP 4.8 mg/L ESR 22.9 mm/1st hour Randomized, placebo-controlled, single-blind cross-over to investigate the arrhythmia risk during acute infliximab therapy in patients with chronic arthritis	I: RA (ARA 1987 criteria) or Spondyloarthritis E: coronary artery disease, no alterations in cardiac enzymes or serum electrolytes, ECG or echocardiographic abnormalities	Short and long term HRV Parasympathetic (rMSSD, pNN50%, SDNN, SDANN, HF power), sympathetic (LF, LF/HF ratio) activity and overall HRV (total power) during infliximab and placebo infusions (2 hour recordings)	TNF alpha inhibitor therapy (infliximab) acutely reduced HRV (total power) and sympathetic activity (LF, LF/HF) Patients who developed new-onset arrhythmia had reduced HRV (total power) and parasympathetic activity (rMSSD, pNN50%, HF), reduced sympathetic activity (LF) and tended to have a higher CRP	61 %

Mean values given unless otherwise indicated.
ANS = autonomic nervous system, ARA 1987 criteria = American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis,(89) BMI = body mass index, CRP = C reactive protein, DAS28 = disease activity score 28, DB = deep breathing, DMARD = disease modifying anti-rheumatic drug, E = exclusion, ESR = erythrocyte sedimentation rate, HC = healthy controls, HF = high frequency power in the range 0.15-0.40 Hz, HR = heart rate, HRT = hormone replacement therapy, HRV = heart rate variability, I = inclusion, IL-6 = interleukin-6, LF = low frequency power in the range 0.04-0.15Hz, LF/HF ratio = low frequency to high frequency ratio, N = number of subjects, NN= inter-beat interval, NPY = neuropetide Y, O = orthostasis, pNN50% = NN50 as a percentage of the total number of all NN intervals, QIS = quality index score (%), RA = rheumatoid arthritis, RF = rheumatoid factor antibody, rMSSD = square root of the mean of the sum of the squares of difference between adjacent NN intervals, SBP = systolic blood pressure, SDANN = standard deviation of the averages of NN intervals in all 5 minute segments of the entire recording, SDNN = standard deviation of all NN intervals, TNF = tumour necrosis factor, VM = Valsalva's manoeuvre

Table 3. Results Summary: Number of studies with abnormal autonomic function in rheumatoid arthritis patients from observational studies

	Abnormal studies		Quality Index Score %; range		
	Number/Total	**%**	**Normal**	**Abnormal**	**Total**
Parasympathetic	20/26	77	65%; 44-78	66%; 33-89	66%; 33-89
Sympathetic	16/30	53	59%; 28-89	67%; 44-89	63%; 28-89
Cardiac baroreflex sensitivity	1/2	50	56%	89%	73%; 56-89

Quality index score % displayed as mean; range.

Table 4. Results Summary: Outcome of autonomic assessments from case-control studies

PARASYMPATHETIC	**RA worse than control** Number (QIS %; range)	**No difference** Number (QIS %; range)	**RA better than control** Number (QIS %; range)
Clinical Cardiovascular Tests			
Total	**11** (63%; 39-89)	**2** (61%; 44-78)	**0** (NA)
Heart rate responses to deep breathing	8 (51, 62, 74, 75, 77, 79, 81, 82)	5 (53, 58, 76, 78, 83)	0
Heart rate responses to orthostasis	7 (51, 58, 74, 77-79, 81)	4 (53, 75, 76, 83)	0
Heart rate responses to Valsalva's Maneouvre	5 (51, 78, 79, 81, 83)	4 (53, 58, 75, 77)	0
Heart rate variability			
Total	**8** (70%; 33-89)	**5** (71%; 56-89)	**0** (NA)
Frequency domain	5 (55, 59, 61, 68, 77)	4* (51, 86-88)	0
Time domain	7	0	0

	(49, 59, 61, 68, 71, 77, 88)		
Heart rate turbulence	0	1 (50)	0
Respiratory sinus arrhythmia	0	1 (57)	0
Pupillary light reflex			
Total	**1** (61%)	**0** (NA)	**0** (NA)
Maximum constriction velocity	1 (52)	0	0
SYMPATHETIC	**RA worse than control**	**No difference**	**RA better than control**
	Number (QIS %; range)	Number (QIS %; range)	Number (QIS %; range)
Clinical Cardiovascular Tests			
Total	**8** (67%; 44-89)	**4 (**61%; 44-78)	**0** (NA)
Blood pressure responses to orthostasis	5 (51, 54, 74, 77, 81)	4 (53, 75, 76, 79)	0
Blood pressure responses to hand grip	4 (51, 54, 79, 81)	0	0
Blood pressure responses to cold pressor test	1 (54)	0	0
Blood pressure responses to mental stress	2 (60, 69)	1 (85)	0
Heart rate variability			
Total	**3** (80%;72-89)	**7** (71%; 61-89)	**0** (NA)
Frequency domain	2 (51, 68)	7 (55, 59, 61, 77, 86-88)	0
Pre-ejection period	1 (57)	0	0
Biomarkers			
Total	**3** (61%; 50-67)	**2** (44%; 28-61)	**0** (NA)
Neuropeptide-Y	2	2	0

	(64, 72)	(63, 86)	
Chromogranin	1 (56)	0	0
Skin sympathetic responses			
Total	**2** (58%; 50-67) (60, 69)	**3** (46%; 39-56) (62, 70, 82)	**0**
Catecholamines			
Total	**2** (64%; 61-67)	**2** (61%; 44-78)	**1**** (63%)
Plasma	2 (67, 86)	1 (87)	1 (67)**
Urinary	0	1 (66)	0
BAROREFLEX SENSITIVITY	**RA worse than control** Number (QIS %; range)	**No difference** Number (QIS %; range)	**RA better than control** Number (QIS %; range)
Cardiac baroreflex sensitivity			
Total	**1** (89%)	**1** (56%)	**0** (NA)
Spontaneous	1 (51)	0	0
Heart rate turbulence	0	1 (50)	0

QIS = quality index score, RA = rheumatoid arthritis.

***** This study (88) is included in two categories as the authors reported abnormal time domain heart rate variability parameters (worse than control) but normal frequency domain (no difference).

** This study (67) is included in two categories as the authors reported lower resting sympathetic activity (better than control) but with an impaired response (worse than control).

Table 5. Results Summary: Outcome of associations between autonomic function and inflammation in RA

	Outcome	
	Association found	**No association**
Clinical cardiovascular tests (n=9)	2 (42%; 39-44)	7 (73%; 56-89)
Heart rate variability (n=5)	3 (77%; 72-88)	2 (72%; 56-89)
Catecholamines (n=2)		2 (67%; 56-78)
Biomarkers (n=2)	1 (67%)	1 (67%)
Pupillary light reflex (n=1)	1 (61%)	
TOTAL	**7 (64%; 39-88)**	**12 (71%; 56-89)**

Values are number of studies (% quality index score; range).

FIGURE LEGENDS

Figure 1. Simplified schematic showing autonomic regulation of the cardiovascular system and the effects of pro-inflammatory cytokines from experimental studies

A Nerve signals from the brain stem are relayed to various organs in the autonomic nervous system. Parasympathetic activation results in slowing of the heart rate, whereas sympathetic activation causes increased ventricular contraction, peripheral and renal vasoconstriction, activation of the renin-angiotensin-aldosterone system, increased sodium retention (kidneys), epinephrine and norepinephrine release (adrenal glands) and increased inflammation (leukocyte activation and increased cytokine production in the spleen). Central and peripheral feedback mechanisms are in place (e.g. arterial and cardiopulmonary baroreceptors, chemoreceptors) to ensure homeostasis is maintained. **B** Experimental studies have shown that pro-inflammatory cytokines (e.g. interleukin 1-Beta, interleukin 6 and tumour necrosis factor alpha) attenuate (-) cardiovagal baroreflex sensitivity and heart rate variability, as well as heighten (+) sympathetic activity.

Figure 2. Flow diagram showing literature search

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ROLE OF THE FUNDING SOURCE

This work was supported by a grant from Arthritis Research UK (grant number 196633).

COMPETING INTERESTS

None

SUPPLEMENTARY DATA

Appendix 1. Quality index score (QIS) assessment tool criteria

Index	**Criteria Assessed**		
	High = 2 points	**Medium = 1 point**	**Low = 0 points**
1. Study Design	Case-control study with appropriate matching (e.g. age, sex, body mass index); and/or interventional with assessment before and after biologic agent	Case-control study but inappropriately matched	Cohort study or other design with inappropriate or no control group
Rationale	A case-control study with appropriate matching is the best study design to answer the principle question of the study – is autonomic dysfunction present in rheumatoid arthritis? An interventional study with assessment before and after biologic agent is the best study design to answer another principle question – is there a link between inflammation and autonomic function in RA?		
2. Inclusion/Exclusion Criteria	Patients included with a formal rheumatoid arthritis diagnosis according to recognised criteria and those with conditions	Patients included with a formal rheumatoid arthritis diagnosis according to recognised criteria but those with conditions	Criteria for rheumatoid arthritis diagnosis not mentioned

	or medications that interfere with autonomic function excluded	or medications that interfere with autonomic function not excluded	
Rationale	In order to establish meaningful conclusions from the study patients included must have the correct diagnosis according to recognised criteria and to prevent confounding factors those with condition or medications affecting autonomic function should be excluded		
3. Disease characteristics	Mentioned in detail (i.e. at least 2): disease duration, inflammatory marker e.g. C-reactive protein or erythrocyte sedimentation rate, swollen or tender joints, medications, functional capacity	Mentioned only 1: disease duration, inflammatory marker e.g. C-reactive protein or erythrocyte sedimentation, swollen or tender joints, medications, functional capacity	Not mentioned
Rationale	Disease characteristics are necessary to determine the inflammatory status of the rheumatoid arthritis patients tested at the time of the study. They allow for meaningful interpretation and comparison between different studies.		
4. Standardised testing condition	Mentioned in detail (i.e. at least 2): e.g.	Mentioned only 1: e.g. testing room	Not mentioned or not

	testing room temperature, time of testing, fasting status, subject position	temperature, time of testing, fasting status, subject position	standardised
Rationale	Testing conditions can affect the results of autonomic function assessments and hence unwanted bias can be avoided by standardising the testing conditions for each subject.		
5. Autonomic assessment – standardised protocol	Mentioned that the study adhered to published guidelines or protocols and comprehensive details provided	Mentioned that the study adhered to published guidelines and protocols but important details missing; or mentioned that study was adapted from guidelines or protocols	No mention of guidelines or protocols
Rationale	Adhering to published guidelines or protocols ensures that testing is performed to the highest standard available and allows for meaningful comparison between different studies.		
6. Autonomic assessment – quality of test	Autonomic function assessed using a recognised and validated tool, and a	Autonomic function assessed using a recognised tool but a basic assessment	Unrecognised tool to measure autonomic function such as

	comprehensive assessment performed (i.e. more than one technique employed) Gold standard or close to gold standard assessment of autonomic function	performed (i.e. only one technique) Reasonable assessment of autonomic function	a novel or non-established method Unknown or poor indicator of autonomic function
Rationale	A comprehensive assessment of autonomic function involves using the best validated tools with numerous aspects of autonomic function tested		
7. Statistics – appropriate sample size	Power calculation performed to determine sample size and sample size achieved	Power calculation performed to determine sample size but sample size not achieved	No mention of power calculation
Rationale	In order to prevent type 2 errors the correct sample size should be calculated in advance and reached.		
8. Statistics – appropriate tests used	Appropriate statistical test applied and comprehensive details mentioned with adjustment made for	Appropriate statistical test applied but lacking details with no adjustment made for co-	Inappropriate statistical test used

	co-variables/confounders when necessary	variables/confounders when necessary	
Rationale	Choosing the most appropriate statistical test ensures accurate results and adjusting for co-variables helps to minimise the bias, allowing meaningful and accurate interpretation and conclusions.		
9. Associations between autonomic function and inflammation made	Associations made (e.g. using regression analysis) and adjustments made for co-variables/confounders (e.g. multiple regression) when necessary	Associations made (e.g. using regression analysis) but no adjustment made for co-variables/confounders when necessary	Not mentioned or no associations made
Rationale	To determine whether links between inflammation and autonomic function in RA exist associations between indices of inflammation and parameters of autonomic function need to be made.		
Each index was graded between 0-2, and the total points added to give a final score between 0-18. If an index was found to be inappropriate (or irrelevant) to a particular study then the index was omitted and the total score reduced to 16. This occurred in studies employing 24 hour home assessments (e.g. 24 hour electrocardiogram monitor or urinary testing) where the index "standardised test conditions" did not apply. For all studies a percentage was calculated			

to give a Quality Index Score (QIS). The quality assessment was performed by two researchers (A.M.A. and J.P.F.) and disagreements were discussed until a consensus was reached.

Appendix 2. Prevalence of autonomic nervous system dysfunction in rheumatoid arthritis

Study	N	Criteria for autonomic nervous system dysfunction	Prevalence (%)
Aydemir et al 2010	36	Ewing test.(28) Two of five abnormal tests from: Heart rate response to Valsalva's manoeuvre (Valsalva ratio≤1.1) Heart rate variation during deep breathing (inter-beat interval maximum-minimum ≤10) Heart rate response to standing (30:15 ratio≤1.0) Blood pressure response to standing (fall in systolic blood pressure≥20) Blood pressure response to handgrip (diastolic blood pressure rise ≤10mmHg)	61
		Modified (by authors) Ewing test.(51) Two abnormal and one borderline from: Ewing test + inspiration/expiration heart rate ratio ≤1 Blood pressure response to orthostasis (fall in diastolic blood pressure≥10mmHg)	75
Bidikar et al 2010	50	Fall in systolic blood pressure in response to orthostasis ≥10mmHg	44
Milovanovic et al 2010	50	Two of three positive tests from: Blood pressure response to orthostasis Heart rate response to deep breathing Heart rate response to orthostasis	86
Stojanovic al 2007	39	Two of three positive tests from:	74

		Blood pressure response to orthostasis Blood pressure response to handgrip Heart rate response to deep breathing Heart rate response to orthostasis Heart rate response to Valsava's manoeuvre Moderate to severe autonomic nervous system (ANS) dysfunction: Ewing score≥4	
Schwemmer et al 2006	30	Ewing test (result below 5th percentile)	43
		Two of five abnormal (below 5th centile from normal healthy control subjects) tests from: RRI variation at rest RRI variation difference between deep breathing and rest RRI variation difference between deep breathing and rest Valsalva's manoeuvre (RRI maximum/RRI minimum) Heart rate response to orthostasis, blood pressure fall ≥25mmHg	20
		One of two abnormal (below 5th centile from normal healthy control subjects) tests from: Latency time of pupillary reflex Maximal pupillary area	50
		Cardiovascular and pupillary dysfunction (both of the above abnormal)	60
Gozke et al 2003	10	Inter-beat interval (RRI) variation difference between DB and rest	50
		RRI variation ratio of deep breathing to rest	80
Geenen et al 1996	13	Lower mean response to cognitive discrimination than the least responding control	38
Tousirrot et al 1993	50	Two of three abnormal tests from: Heart rate response to deep breathing Heart rate response to orthostasis Heart rate response to Valsalva's manoeuvre	60
Edmonds et al 1979	27	Heart rate response to orthostasis, RRI ratio<1	33

N = number of rheumatoid arthritis patients. Prevalence (%) values given are means either quoted or calculated from the study.

Fig 1

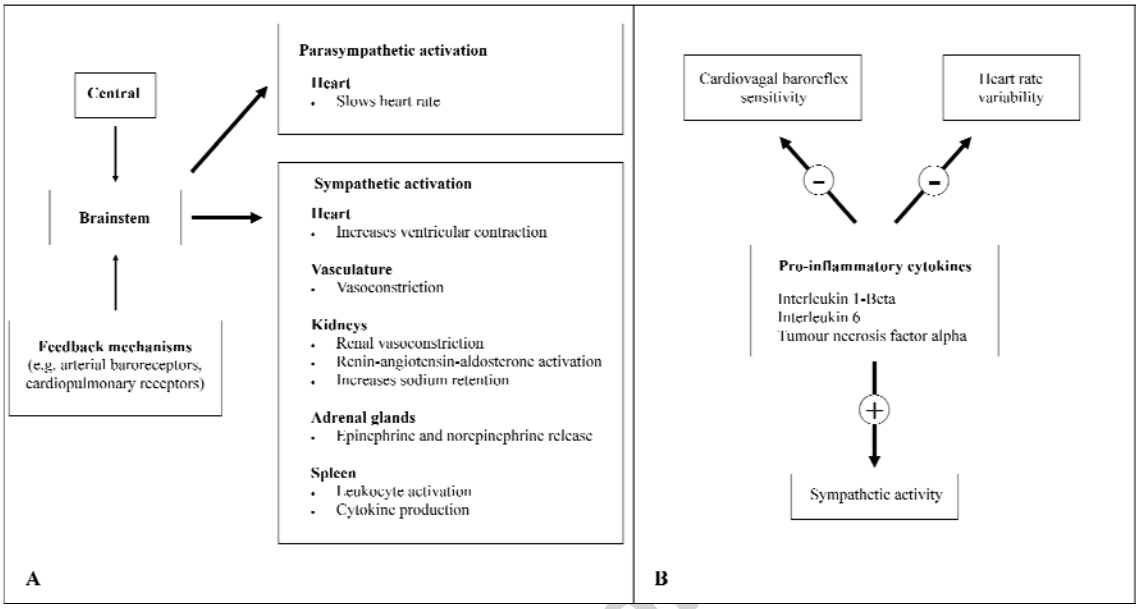

Fig 2