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Cardiovascular autonomic regulation, inflammation and pain in rheumatoid arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory condition characterised by reduced heart rate variability (HRV) of unknown cause. We tested the hypothesis that low HRV, indicative of cardiac autonomic cardiovascular dysfunction, was associated with systemic inflammation and pain. Given the high prevalence of hypertension (HTN) in RA, a condition itself associated with low HRV, we also assessed whether the presence of hypertension further reduced HRV in RA.

Methods: In RA-normotensive (n = 13), RA-HTN (n = 17), normotensive controls (NC; n = 17) and HTN (n = 16) controls, blood pressure and heart rate were recorded. Time and frequency domain measures of HRV along with serological markers of inflammation (high sensitivity C-reactive protein [hs-CRP], tumour necrosis factor-α [TNF-α] and interleukins [IL]) were determined. Reported pain was assessed using a visual analogue scale.

Results: Time (rMSSD, pNN50%) and frequency (high frequency power, low frequency power, total power) domain measures of HRV were lower in the RA, RA-HTN and HTN groups, compared to NC (p = 0.001). However, no significant differences in HRV were noted between the RA, RA-HTN and HTN groups. Inverse associations were found between time and frequency measures of HRV and inflammatory cytokines (IL-6 and IL-10), but were not independent after multivariable analysis. hs-CRP and pain were independently and inversely associated with time domain (rMMSD, pNN50%) parameters of HRV.

Conclusions: These findings suggest that lower HRV is associated with increased inflammation and independently associated with increased reported pain, but not compounded by the presence of HTN in patients with RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory condition associated with substantially increased cardiovascular mortality and risk (Solomon et al., 2003; Pujades-Rodriguez et al., 2016). In a large epidemiological study RA was associated with increased risk of myocardial infarction (adjusted incidence ratio [IRR] = 1.43, 95% confidence interval [CI] 1.21–1.70), heart failure (IRR = 1.61,1.43–1.83), cardiac arrest (IRR = 2.26, 1.69–3.02) and unheralded coronary death (IRR = 1.60, 1.18–2.18) (Pujades-Rodriguez et al., 2016). Low heart rate variability (HRV) indicative of reduced cardiac parasympathetic function predicts mortality risk following myocardial infarction (Bigger et al., 1992; La Rovere et al., 1998) and hence may contribute to the increased cardiovascular risk seen in RA. Studies to date have shown that HRV is reduced in RA, compared to healthy controls (Adlan et al., 2014), although the mechanisms are not known.

Abbreviations: ANOVA, analysis of variance; BP, blood pressure; BMI, body mass index; CI, confidence interval; CPT, cold pressor test; DAS, disease activity score; ECG, electrocardiogram; EDR, ECG-derived respiration; FVC, forearm vascular conductance; HF, high frequency; HR, heart rate; HRV, heart rate variability; hs-CRP, high sensitivity C-reactive protein; HTN, hypertensive; IL, interleukin; IRR, adjusted incidence ratio; LF, low frequency; LSD, least significant difference; LVC, leg vascular conductance; NC, normotensive control; PASAT, paced auditory serial addition test; pNN50%, proportion of RR intervals differing by > 50 ms from previous RR interval; RA, rheumatoid arthritis; RMSSD, square root of the mean of the sum of successive differences; SD, standard deviation; SDNN, standard deviation of all RR [NN] intervals; SPSS, statistical analysis software package; TNF, tumour necrosis factor; TP, total power; VAS, visual analogue scale

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Animal studies have identified direct and reciprocal relationships between parasympathetic activity and inflammatory cytokines (Borovikova et al., 2000; Bernik et al., 2002; Fairchild et al., 2009). Intra-peritoneal administration of the pro-inflammatory cytokine tumour necrosis factor-alpha (TNF-α) in mice, reduced a HRV derived index of parasympathetic activity (Fairchild et al., 2009) while pharmacological (Borovikova et al., 2000; Bernik et al., 2002) and electrical (Borovikova et al., 2000) stimulation of the vagus nerve attenuates the release of inflammatory cytokines. In healthy humans acute inflammation (precipitated by an influenza vaccine) attenuated heart rate recovery following exercise (marker of parasympathetic activity) (Jae et al., 2010). However, studies of RA patients that have examined the associations between inflammation and cardiac parasympathetic activity have been limited (e.g., cytokine concentrations not assessed) and reported equivocal results (Adlan et al., 2014). Another possible explanation for the observed reduction in HRV in RA patients is increased patient-reported pain. Central pain pathways are known to overlap with areas of autonomic control (e.g., nucleus of the solitary tract) (Benarroch, 2006) and in a recent meta-analysis HRV was found to be lower in patients with chronic pain (Tracy et al., 2016). Despite this, the associations between pain and cardiac autonomic function in RA remain unknown. Furthermore, given the high prevalence of hypertension in RA (Panoulas et al., 2007), and that HRV is reduced in hypertension (Singh et al., 1998), it remains to be proven/seen whether the presence of hypertension in RA exacerbates the reductions in HRV. Vasoconstrictor sympathetic nerve activity is elevated in RA patients and associated with pain and inflammation (Adlan et al., 2017). In the absence of direct intraneural recordings of cardiac autonomic activity in humans, HRV analyses have provided a useful indirect surrogate. However, the target-organ specific control of pre-motor and motor neurones (Polson et al., 2007; Simms et al., 2007) along with local modulation of receptor signalling, means that observations from one region (e.g., peripheral vasculature) cannot be generalised to another (e.g., heart). Therefore, important questions remain regarding the consequences of RA to cardiac autonomic regulation as assessed with HRV, and the underlying mechanisms.

The autonomic nervous system plays a key role in orchestrating the cardiovascular response to stressors (Dampney, 1994; Wehrwein and Joyner, 2013). Cardiovascular responses to mental stress (Matthews et al., 2004) or a cold pressor test (CPT; immersion of a limb into cold water) (Treiber et al., 2003) can predict the development of cardiovascular disease. Impaired cardiovascular responses to stressors have been demonstrated in the majority of prior studies in RA patients (e.g., orthostasis, deep-breathing, Valsalva manoeuvre and handgrip) (Adlan et al., 2014). The diastolic blood pressure response to CPT in RA patients has been examined in one study and were reported as being attenuated (Bidikar and Ichaporia, 2010), while the cardiovascular responses to mental stress have been conflicting (Geenen et al., 1996; Veldhuijzen van Zanten et al., 2005; Motivala et al., 2008; Veldhuijzen van Zanten et al., 2008). These conflicting results may reflect opposing effects of inflammatory cytokines on vascular resistance responses to mental stress. Inflammatory cytokines have vasodilatory actions (Takizawa et al., 1997; Clapp et al., 2005), but may also exaggerate vasoconstrictor pathways (Wassmann et al., 2004; Veldhuijzen van Zanten et al., 2008). The vascular responses to mental stress are also regionally differentiated (Folkow et al., 1964), but it is not known how the arm and leg vascular responses to mental stress are affected by RA, and if these responses are related to inflammatory cytokine concentration or patient-reported pain.

In this observational, case-control study of patients with RA and matched-control participants we determined how HRV and cardiovascular responses to CPT and mental stress (paced auditory serial addition test; PASAT) were associated with pain (visual analogue scale, VAS) and baseline serum inflammatory cytokine concentrations. We hypothesised that HRV derived indices of cardiac parasympathetic would be attenuated and cardiovascular reactivity would be greater in individuals with increased inflammatory cytokine concentrations and more reported pain. We further hypothesised that the presence of hypertension in RA would exacerbate the cardiovascular autonomic alterations.

2. Materials and methods

2.1. Participants

The study was approved by the National Research and Ethics Service Committee West Midlands - Edgbaston (11/WM/0298). Written informed consent was obtained from all participants, in accordance with the Declaration of Helsinki (2013). A total of sixty-six participants were recruited, the general and clinical characteristics of which are provided in a previous study testing other hypotheses (Adlan et al., 2017). Thirty patients with a diagnosis of RA (based on the 1987 American College of Rheumatology criteria (Arnett et al., 1988)) were recruited from the rheumatology clinics at Russells Hall Hospital, Dudley, UK and Sandwell General Hospital, West Bromwich, UK including normotensive (RA $n = 13$, mean age ± SD 56 ± 12 yr, 8 women, body mass index [BMI] geometric mean 28, 95% confidence interval 25–30 kg/m^2) and hypertensive (RA-HTN $n = 17$, age 61 ± 10 yr, 12 women, BMI 30, 26–33 kg/m^2). Thirty-three normotensive and hypertensive control participants of a similar age and BMI were recruited from the hospitals and surrounding areas (NC $n = 17$, age 54 ± 13 yr, 10 women, BMI 26, 24–29 kg/m^2; HTN $n = 16$, age 60 ± 10, 11 women, BMI 26, 25–27 kg/m^2). Exclusion criteria included: age < 18 or > 75 years; atrial fibrillation or other heart rhythm disorder, significant valvular disease, coronary artery disease, diabetes, ischemic stroke, chronic renal failure, liver impairment, hormone replacement therapy and those who are pregnant or who might be pregnant. NC participants were free from major illnesses, whilst HTN participants either had a prior diagnosis of hypertension or BP ≥ 140/90 mm Hg.

2.2. Experimental protocol

Following an overnight fast (from food, caffeine and alcohol), participants attended the research laboratory at 09:00 h. Medications were withheld on the morning of testing. A detailed clinical history was taken and physical examination performed in RA patients to count the number of swollen and tender joints in order to determine the disease activity score (DAS28-CRP) (Wells et al., 2009). A visual analogue scale (VAS) was used as a measure of pain (Huskisson, 1974). Height and weight was measured, and BMI was determined (weight/height^2). Subsequent measurements were performed in a temperature-controlled room under uniform conditions with participants resting quietly in the supine position.

2.3. Measurements

HR was continuously recorded using a lead II ECG (BioAmp, ADInstruments, Bella Vista, Australia). Beat-to-beat BP was recorded using finger photoplethysmography (Portapres, Finapres Medical Systems, Amsterdam, The Netherlands) and was calibrated with brachial BP recordings using an automated sphygmomanometer (Omron 705IT, Omron Corporation, Hoopddorp, The Netherlands). Leg blood flow (venous occlusion strain gauge plethysmography, Hokanson EC-6 plethysmograph, D E Hokanson, Bellevue, United States of America, USA) (Joyner et al., 2001) was recorded during rest, test and recovery phases of the CPT and PASAT, as described in detail elsewhere (Adlan et al., 2017). During the PASAT, forearm blood flow was also recorded. Leg and forearm vascular conductance (LVC, FVC) were calculated as Blood flow (ml/100 ml/min)/Mean BP (mm Hg) × 1000. Blood samples for inflammatory markers were centrifuged immediately and plasma stored at − 80 °C. Commercially available ELISA kits were used