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HOW TO CITE THIS ARTICLE
Veldhuijzen van Zanten JJCS, Ring C, Carroll D, et al Increased C-Reactive Protein in Response to Acute Stress in Patients with Rheumatoid Arthritis Ann Rheum Dis Published Online First [date of publication]*. doi: 10.1136/ard.2004.032151

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Increased C-Reactive Protein in Response to Acute Stress in Patients with Rheumatoid Arthritis

Submission for extended report

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Abstract

Objective:
The purpose of the present study was to assess the effects of an acute stress task on inflammatory, haemostatic, rheological, and haemodynamic activity in patients with Rheumatoid Arthritis (RA) compared to Osteoarthritis (OA).

Methods:
21 RA and 10 OA patients underwent a brief mental stress task while standing. Inflammatory, haemostatic, rheological, and haemodynamic variables were measured at baseline, task, and recovery.

Results:
At baseline, erythrocyte sedimentation rate and fibrinogen were higher in RA than OA. White blood cell count, fibrinogen, blood pressure, and pulse rate increased, whereas pro-thrombin time and plasma volume decreased during the task in both patient groups. The stress task increased CRP only in RA patients, and more specifically in those RA patients with high disease activity.

Conclusions:
The increase in the inflammatory marker CRP, which was specific to RA patients, combined with the haemostatic, rheological, and haemodynamic reactions to the stress task, over and above the already high baseline levels, could underlie the increased risk for myocardial infarction in this vulnerable patient group.

Key Words: Cardiovascular diseases, rheumatoid arthritis, c-reactive protein, inflammation, stress
Myocardial infarction (MI) arises from the coincidence of a chronic process, i.e. the gradual building up of an atherosclerotic plaque in the vessel wall, and an acute process, i.e. the rupture of this plaque and formation of a thrombus.\textsuperscript{1} Evidence implicates inflammation in both processes.\textsuperscript{1-4} There is an association between higher levels of inflammatory markers, such as C-reactive protein (CRP), and the prevalence of MI.\textsuperscript{5} The presence of inflammatory molecules (e.g., CRP, cytokines) in plaques renders them more vulnerable to rupture.\textsuperscript{4} It has also been shown that levels of CRP are elevated following MI and that the greater the rise the poorer the prognosis.\textsuperscript{1}

Psychologically stressful events have been considered as precursors of MI.\textsuperscript{6,7} Almost half of surviving patients attributed their MI to an environmental or behavioural trigger, such as episodes of emotional distress or sudden changes in posture.\textsuperscript{8,9} The question arises, however, as to how stress exposures might precipitate MI. Recently, it has been suggested that inflammatory responses to acute mental stress can render the plaque unstable and prone to rupture.\textsuperscript{10} It is well established that acute psychological stress elicits increases in arterial blood pressure and changes in blood rheology, such as decreases in plasma volume and increases in blood viscosity.\textsuperscript{11} The consequent increase in shear stress could lead to plaque disruption.\textsuperscript{2,4} Haemostatic reactions to mental stress, indicating activation of the coagulation cascade, have also been reported.\textsuperscript{12} Thus, if a plaque were to rupture during mental stress and expose its thrombogenic contents to the pro-coagulant milieu, clot formation would be rapidly promoted.\textsuperscript{2,12}

Rheumatoid arthritis (RA) is a chronic inflammatory musculoskeletal disease, with predominant symptoms of pain, stiffness, and swelling of joints.\textsuperscript{13} RA patients have a higher all-cause mortality rate than age- and sex-matched control groups.\textsuperscript{14} It is now recognised that patients with RA are at increased risk for acute cardiovascular events, such as MI, compared to the general population.\textsuperscript{14} Indeed, the most common cause of death in RA is cardiovascular disease, accounting for more than 50% of the mortality.\textsuperscript{15} RA patients also have a higher prevalence of acute cardiovascular events than patients with osteoarthritis (OA), a joint disease not characterised by systemic inflammation.\textsuperscript{15} In addition, RA patients are more likely to experience silent ischaemia during 24-hr Holter recording\textsuperscript{16} and have higher rates of ischaemia measured by myocardial perfusion imaging\textsuperscript{17} than OA patients.

Even though there is convincing evidence that RA is characterised by an increased risk for acute cardiovascular events, the underlying pathways remain to be determined. The most likely explanation is that the inflammation associated with RA has an impact on the vasculature.\textsuperscript{18} Epidemiological studies provide indirect support; there is an association in RA patients between high resting levels of inflammatory markers, such as CRP and erythrocyte sedimentation rate (ESR), and both the incidence of acute cardiovascular events\textsuperscript{19} and the frequency of carotid artery plaques.\textsuperscript{20}

Laboratory stress models have been used to explore mechanisms underlying triggering of MI. Little attention has been paid to the reactions of RA patients to acute stress exposure, although interleukin-6 was found to be elevated in anticipation of a stressful operation in patients with RA but not in patients with OA.\textsuperscript{21} However, there has yet to be a detailed examination of cardiovascular reactions of RA patients to a standard laboratory stress task. Thus, the aim of the present study was to
compare the cardiovascular reactions of RA and OA patients to a combined mental and postural stress task. OA was used as a control group because although it is not characterised by a significant systemic inflammatory component, it has several symptoms in common with RA (e.g., joint pain and stiffness) and may also lead to reduced physical activity, deconditioning, and disability. It was hypothesised that RA patients would have exaggerated inflammatory, haemostatic, rheological, and haemodynamic reactions compared to OA patients.

**METHODS**

**Patients**

Patients were recruited from outpatient rheumatology clinics of the Dudley Group of Hospitals, United Kingdom. Patients had to be able to stand for 15 minutes, but there was no exclusion based on age, sex, medication, disease activity or severity, or comorbidity, other than previously confirmed acute coronary syndrome, diabetes mellitus or serious psychiatric disease. In all, 21 RA patients and 10 OA patients were examined. RA patients met the retrospective application of the 1987 revised criteria of the American College of Rheumatology. Their mean ± SD disease activity score, DAS28, calculated using the number of swollen joints, number of tender joints, ESR, and general health rating, was 4.57 ± 1.11. Patients abstained from caffeine 2 hours and from food and smoking 1 hour prior to stress testing. For ethical reasons, their medication regimens were not interrupted: analgesics (76% RA, 30% OA), disease modifying antirheumatic drugs (DMARDs, 81% RA), non-steroidal anti-inflammatory drugs (14% RA, 10%OA), cyclooxygenase-2 inhibitors (29% RA), anti-TNF (19% RA), steroids (29% RA). All patients gave informed consent and the study was approved by the hospital ethics committee.

**Physiological Measurements**

**Blood Sampling.** A 18-gauge teflon catheter (Venflon™, Becton Dickinson) was introduced into an antecubital vein and connected to a three-way stopcock (Sims Portex). On each draw, the first 3-ml of blood was collected in a syringe and discarded, and then 23-ml of blood was collected in one syringe. After each draw, 3-ml of 0.9% saline (Baxter) was infused to maintain the catheter patent. The drawn blood was immediately transferred into collection tubes. A 4-ml tube containing separation gel (Vacuette, Greiner Bio-One) was used for analysing CRP by immunoturbidity method. A 4-ml tube containing potassium ethylenediaminetetraacetic acid (EDTA K2E, Vacuette, Greiner Bio-One) was used to perform a full blood count using an Advia 120 Hematology system (Bayer), that yielded a white blood cell count (WBC), haematocrit, and haemoglobin. Estimated plasma volume was calculated from haematocrit and haemoglobin using Dill and Costill’s formula. A 5-ml tube containing buffered sodium citrate (Seditainer, Becton Dickinson) was used for ESR measurement. Finally, a 4-ml tube containing sodium citrate (3.2%, Vacuette, Greiner Bio-One) was used to measure fibrinogen and pro-thrombin time using an ACL Futura (Instrumentation Laboratory).

**Haemodynamic Measures.** Systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate were measured using a blood pressure monitor (Omron HEM-705CP), recommended by the British Hypertension Society, and a brachial cuff.
**Stress Task**
The stress task was the paced auditory serial addition test, performed while patients were tilted to a head-up-tilt of 64 degrees. This position elicits 90% of the cardiovascular response while avoiding the discomfort associated with standing upright on a tilt table. For the mental stress task, patients were presented with a series of single digit numbers and required to add each number to the number presented next. Thus, they had to perform simple addition and also remember the latter of two numbers presented for subsequent addition to the next number. Numbers were delivered using an audio tape player and patients had to call out their answers, which were ostentatiously recorded by the experimenter. The task consisted of four consecutive 2-min periods of 30, 34, 40, and 48 numbers at presentation rates of 4.0, 3.5, 3.0, and 2.5 s, respectively. In each block of 10 numbers, patients received an aversive noise burst either following their first incorrect response (a wrong answer, a late response, or no answer), or, if they had not responded incorrectly, at the end of the block. These demands (increasing time pressure, social evaluation, and punishment) have been found to increase the provocativeness of the task. The combination of mental stress and postural stress has been shown to elicit substantial rheological reactions.

**Procedure**
Patients completed one 3-hr session, starting between 9:00 am and 1:00 pm. On arrival, the procedure was explained and demographic information collected. Next, the catheter was inserted and the blood pressure cuff secured. Patients lay semi-recumbent on a bed, and an initial familiarising blood pressure measure was taken. They completed a 20-min formal rest period (baseline) during which they lay semi-recumbent and remained quiet. Patients were then asked to step on the tilt table, which was tilted to 64 degrees. Ten practice trials of the stress task were undertaken, followed by the 8-min task. On task completion, patients again lay semi-recumbent on the bed for a 30-min recovery period.

Blood pressure readings were initiated at the start of mins 14, 16, 18, and 20 of the resting baseline, and mins 2, 4, 6, and 8 of the stress task, as well as mins 24, 26, 28, and 30 of the recovery. Blood was taken immediately after each period: i.e. baseline, task (while on the tilt table), and recovery.

**Data Reduction and Analysis**
SBP, DBP, and pulse rate measurements during baseline, task, and recovery were each averaged to yield a mean baseline, task, and recovery value. Analysis of variance and Chi-square were used to compare the demographic and other characteristics of the two patient groups (Table 1). RA patients were older than OA patients, \( F(1, 29) = 5.63, p < .05, \eta^2 = .162, \) and were less likely to be in paid employment, \( \chi^2 (1) = 11.98, p < .01. \) Given the age difference between the patient groups, 2 group (RA, OA) analyses of covariance (ANCOVA), with age as the covariate, were performed on the baseline physiological data. The effects of the acute stress task were examined using separate group (RA, OA) \( \times \) period (Baseline, Task, Recovery) repeated measures multivariate analysis of covariance (MANCOVA), with age as the covariate. A measure of effect size (eta-squared, \( \eta^2 \)) is reported throughout and, where appropriate, Newman–Keuls post hoc analyses were conducted. Occasional missing data are reflected in variations in the degrees of freedom.
Table 1. Patient characteristics of the rheumatoid arthritis and osteoarthritis patient groups. Values are the means ± SD for continuous variables and percentages for categorical variables.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rheumatoid Arthritis</th>
<th>Osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 11</td>
<td>47 ± 11</td>
</tr>
<tr>
<td>Sex (% women)</td>
<td>86</td>
<td>60</td>
</tr>
<tr>
<td>Married or Co-habiting (%)</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11 ± 2</td>
<td>12 ± 3</td>
</tr>
<tr>
<td>Current or Ex-Smoker (%)</td>
<td>52</td>
<td>80</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>29.0 ± 5.1</td>
<td>25.2 ± 2.6</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>12 ± 11</td>
<td>8 ± 2</td>
</tr>
</tbody>
</table>

RESULTS
Baseline Inflammatory, Haemostatic, Rheological & Haemodynamic Measures
The age-adjusted means of the baseline physiological measures for the two patient groups are summarized in Table 2. ANCOVA revealed that RA patients had higher ESR and fibrinogen compared to OA patients.

Table 2. Mean (SD) age-adjusted baseline measures for rheumatoid arthritis and osteoarthritis patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Rheumatoid Arthritis</th>
<th>Osteoarthritis</th>
<th>F-value</th>
<th>p-value</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/l)</td>
<td>10.4 ± 13.4</td>
<td>5.7 ± 13.9</td>
<td>0.73</td>
<td>.40</td>
<td>.025</td>
</tr>
<tr>
<td>White blood cells (×10⁹/l)</td>
<td>7.7 ± 2.2</td>
<td>6.3 ± 2.2</td>
<td>2.35</td>
<td>.14</td>
<td>.077</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>27.5 ± 16.7</td>
<td>12.8 ± 19.1</td>
<td>4.12</td>
<td>.05</td>
<td>.142</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>4.1 ± 1.0</td>
<td>3.1 ± 1.0</td>
<td>5.64</td>
<td>.03</td>
<td>.173</td>
</tr>
<tr>
<td>Pro-thrombin time (s)</td>
<td>13.4 ± 0.8</td>
<td>13.0 ± 0.8</td>
<td>1.59</td>
<td>.22</td>
<td>.059</td>
</tr>
<tr>
<td>Plasma volume (%)</td>
<td>60.2 ± 4.0</td>
<td>61.9 ± 4.1</td>
<td>1.05</td>
<td>.32</td>
<td>.036</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>137 ± 16.3</td>
<td>129 ± 16.8</td>
<td>1.41</td>
<td>.24</td>
<td>.048</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84 ± 10.4</td>
<td>78 ± 10.8</td>
<td>2.01</td>
<td>.17</td>
<td>.067</td>
</tr>
<tr>
<td>Pulse Rate (bpm)</td>
<td>66 ± 10.4</td>
<td>64 ± 10.7</td>
<td>0.20</td>
<td>.66</td>
<td>.007</td>
</tr>
</tbody>
</table>

Inflammatory Reactions to Stress
Figures 1a and 1b show the baseline, task, and recovery age-adjusted data for the inflammatory measures, CRP and WBC. Group (RA, OA) × period (Baseline, Task, Recovery) MANCOVA, with age as the covariate, revealed no main effects for period or group. However, there was a significant group × period interaction for CRP, $F(2, 21) = 6.69$, $p < .01$, η² = .389. Supplementary analyses confirmed what Figure 1a indicates; CRP increases following the stress task in RA, $F(2, 14) = 10.49$, $p < .01$, η² = .600, but not OA patients. There was a period effect for WBC, $F(2, 24) = 10.10$, $p < .01$, η² = .457; post hoc analyses revealed that in both patient groups WBC increased to the stress task. WBC decreased again during recovery, but still remained
elevated relative to baseline levels. There was no group or group × period interaction effect for WBC. No effects emerged for ESR.

The CRP increase was examined further by allocating the RA patients on the basis of their DAS28 score to a high disease or a low disease activity group. A DAS28 of 4.4 is the average DAS in clinical trials of DMARDS requiring patients with active RA (Professor DPM Symmons, personal communication). Therefore patients with DAS < 4.4 (N = 11) are not in remission and still have some mild to moderate inflammatory activity. Patients with DAS > 4.4 (N = 10) have moderate to severe inflammatory activity. MANCOVA now revealed a period effect for CRP, $F(2, 20) = 4.27, p < .05, \eta^2 = .299$, as well as a group (high disease activity RA, low disease activity RA, OA) × period interaction effect, $F(4, 40) = 4.13, p < .01, \eta^2 = .548$. The summary data are presented in Figure 2. Supplementary analyses indicated that CRP increased significantly in response to the stress task only in the RA patients with high disease activity, $F(2, 5) = 6.44, p < .05, \eta^2 = .720$. Finally, it should be noted that neither baseline CRP nor CRP reactivity were accounted for by differences in medication regimens.

### Haemostatic Reactions to Stress

Figures 1c and 1d display the summary age-adjusted data for fibrinogen and pro-thrombin time. Significant period effects emerged for both fibrinogen, $F(2, 23) = 8.50, p < .01, \eta^2 = .425$, and pro-thrombin time, $F(2, 23) = 36.19, p < .001, \eta^2 = .759$. Post hoc analyses indicated that fibrinogen increased whereas pro-thrombin time shortened in response to the task. Pro-thrombin time lengthened in recovery, while remaining quicker compared to baseline. The overall group effect for fibrinogen intimated in Figure 1c was not statistically significant, $F(1, 23) = 2.77, p = .11, \eta^2 = .107$.

### Rheological Reactions to Stress

Figure 3a presents the summary plasma volume data, adjusted for age. A period effect emerged, $F(2, 24) = 58.22, p < .001, \eta^2 = .829$; post hoc analyses indicated that plasma volume decreased with stress and returned to baseline levels by the end of the recovery. There were neither group nor group × period interaction effects.

### Haemodynamic Reactions to Stress

The summary age-adjusted data for blood pressure and pulse rate are presented in Figures 3b, 3c, and 3d. There were significant period effects for SBP, $F(2, 26) = 11.30, p < .001, \eta^2 = .465$, DBP, $F(2, 26) = 4.89, p < .05, \eta^2 = .273$, and pulse rate, $F(2, 26) = 24.98, p < .001, \eta^2 = .658$. Blood pressure and pulse rate increased from baseline to task and returned to basal levels during recovery. There were no group or group × period interaction effects.

### DISCUSSION

Acute mental combined with postural stress increased CRP only in RA patients and specifically in those RA patients with high disease activity. The observation that CRP did not change with stress in OA patients or RA patients with low disease activity is in agreement with recent findings that CRP was not perturbed by stress in healthy middle aged individuals and students (Ring, PhD, unpublished data, 2002). Thus, stress-induced increases in CRP may be a particular characteristic of RA patients with
high disease activity. CRP is a well-established risk factor for MI. Recently, it has been suggested that CRP is more than merely a risk factor, acting as a causal agent facilitating thrombotic occlusion and atherosclerosis. Thus, the stress-induced increase in CRP in RA patients with high disease activity over and above their high baseline levels could contribute to their increased risk for MI.

The increase in CRP during inflammation is the result of an increase in the number of cells producing CRP, as well as an increase in CRP secretion rate. Not all the CRP produced by the liver is released directly into the blood; small amounts are bound to a hepatic carboxylesterase in the endoplasmatic reticulum. During inflammation, however, this specific binding of CRP is diminished, resulting in more efficient secretion. The RA patients in the present study were characterised by more inflammation, as reflected by higher baseline ESR (+115%) and, although not significant, presumably due to the large inter-individual variability, CRP (+82%) and WBC (+22%), than OA patients. It is possible that due to their higher systemic inflammation, both CRP production and secretion were more efficient, leading to an immediate rise in serum levels with stress in the RA patients with high disease activity.

Although CRP was traditionally thought to be produced exclusively by hepatic cells, there is increasing evidence for other sources of CRP, such as macrophages, lymphocytes, normal vascular tissue, and atherosclerotic plaques. RA patients have increased rates of atherosclerosis; hence, the production of CRP from atherosclerotic plaques can not be disregarded in this patient group. This alternative source of CRP could provide another explanation for the stress-induced CRP increases in RA patients.

There were no group differences in stress response for the other inflammatory markers; ESR did not change in either group, whereas WBC increased similarly in both patient groups, a finding that has been reported previously in both healthy individuals as well as RA patients. However, at baseline, levels of inflammatory markers were higher in RA than OA patients and, consequently, were higher during stress (see Figure 1). The current data show that the stress task elicited an inflammatory response in both patient groups, but also emphasise a degree of specificity in RA patients with high disease activity. Disease activity, as measured by high levels of inflammatory markers, has been associated with an increased risk for cardiovascular events and mortality. Thus, it is possible that RA patients with high disease activity are more vulnerable to cardiac events because of their increased inflammatory activity during rest and stress.

The stress task also produced changes in haemostatic, rheological, and haemodynamic measures, which were similar in RA and OA patients. Collectively, these changes could lead to a hypercoaguable state and an increase in shear stress on the vessel wall, both of which have been implicated as triggers for atherosclerotic plaque rupture. RA patients, however, had higher baseline levels of fibrinogen. Thus, even though the reactions to the stress task were similar in both patient groups, absolute fibrinogen levels were higher during the task in RA patients compared to OA patients. Moreover, categorising the RA patients on the basis of disease activity indicated that RA patients with high disease activity displayed particularly high fibrinogen values. Thus, it is possible that in patients with high disease activity, stress...
serves to elevate the already high fibrinogen values to levels that increase further patients’ susceptibility to thrombogenic events.

An acute cardiovascular event is the result of several mechanisms, such as increased inflammation and coagulation. While many individual risk factors have been recognised, it has been suggested that a cardiovascular risk profile, incorporating several factors, is the best method for characterising risk for acute events. At baseline, RA patients displayed high levels of several individual risk factors, such as ESR and fibrinogen, and a further increase was seen in most measures during stress. Thus, the baseline profile appears to place the RA patients at greater risk than the OA patients, with an even less favourable risk profile evident during stress.

In conclusion, acute stress elicited increases in inflammatory, hemostatic, rheological, and hemodynamic measures in both RA and OA patients. However, there was also a stress-induced increase in CRP, which was specific to RA patients with high disease activity. This inflammatory reaction to stress, which was exacerbated in RA patients, superimposed on their higher baseline levels, could contribute to the increased risk for MI in this susceptible patient group. These findings also imply that effective disease management, in addition to controlling the inflammatory activity, may also need to include training in stress management and coping strategies.
None of the authors have a competing interest to disclose.

The study was approved by the Dudley Research Ethics Committee.

Acknowledgements:
Part of this work was funded by the Dudley Group of Hospitals R & D Directorate
Figure legends

**Figure 1.** Mean age-adjusted (SE) CRP (a), WBC (b), fibrinogen (c), and pro-thrombin time (d) during baseline, stress task, and recovery in RA patients (filled circles) and OA patients (open circles).

**Figure 2.** Mean age-adjusted (SE) CRP during baseline, stress task, and recovery in RA patients with high disease activity (filled circles) and RA patients with low disease activity (open circles).

**Figure 3.** Mean age-adjusted (SE) plasma volume (a), SBP (b), DBP (c), and pulse rate (d) during baseline, stress task, and recovery in RA patients (filled circles) and OA patients (open circles).
References


Figure 2

- RA-high disease activity
- RA-low disease activity

C-Reactive Protein (mg/l)

Baseline Task Recovery
Figure 3

(a) Plasma Volume (%)
(b) Systolic Blood Pressure (mmHg)
(c) Diastolic Blood Pressure (mmHg)
(d) Pulse Rate (bpm)

Baseline | Task | Recovery
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Ann Rheum Dis published online February 11, 2005

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