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Brief report

Increase in systemic vascular resistance during acute mental stress in patients with rheumatoid arthritis with high-grade systemic inflammation

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Abstract

Patients with rheumatoid arthritis are at increased risk for myocardial infarction. It has been hypothesized that mental stress-induced cardiovascular reactions may play a role in the triggering of myocardial infarction. Cardiovascular activity was measured during rest, stress, and recovery in rheumatoid arthritis patients with high systemic inflammation (C-reactive protein > 8 mg/l), rheumatoid arthritis patients with low systemic inflammation (C-reactive protein ≤ 8 mg/l), and osteoarthritis patients. Systemic vascular resistance increased only in rheumatoid arthritis patients with high systemic inflammation. Heart rate and mean arterial pressure increased during the stress task in all groups. Thus, acute cardiovascular events in rheumatoid arthritis patients may be related to stress-induced increases in systemic vascular resistance, particularly in patients with high levels of systemic inflammation.
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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory musculoskeletal disease (Lee and Weinblatt, 2001) associated with increased risk for acute cardiovascular events compared to the general population (Kitas and Erb, 2003) and patients with osteoarthritis (OA), a joint disease that is not characterized by systemic inflammation (DeMaria, 2002). RA patients have an increased risk for myocardial infarction (MI). The most likely explanation is that the inflammation associated with RA has an impact on the vasculature (Bacon and Kitas, 1994; Sattar et al., 2003; Stevens et al., 2005). RA patients have been shown to have a poorer endothelial function compared to healthy individuals (Bergholm et al., 2002; Hurlimann et al., 2002; Van Doornum et al., 2003; Vaudo et al., 2004; Wong et al., 2003), which is associated with the extent of inflammation (Bergholm et al., 2002; Vaudo et al., 2004; Wong et al., 2003). Further, higher incidence of acute cardiovascular events (Wållberg-Jonsson et al., 1999) and a higher frequency of carotid artery plaques (Del Rincòn et al., 2003) have been reported for RA patients with elevated resting levels of inflammatory markers, such as C-reactive protein (CRP).

Anecdotal, epidemiological, and experimental evidence suggests that acute psychological stress may trigger MI (Carroll et al., 2002; Kloner et al., 1997; Strike and Steptoe, 2003; Tofler et al., 1987). Further, acute stress increases blood pressure (Obrist, 1981; Turner, 1994), mediated by either increase in systemic vascular resistance (SVR) or increase in cardiac output (Turner, 1994). The underlying mechanism (i.e., vascular versus cardiac) has clinical importance, with studies showing that stress-induced increases in SVR in coronary artery disease patients were associated with stress-induced myocardial ischemia (Goldberg et al., 1996; Jain et al., 1998).

RA, as an inflammatory disease, provides a good model for exploring the impact of inflammation on cardiovascular reactions to stress, and little is known about stress reactivity in RA patients. Previously we reported an increase in CRP during mental stress in patients with active-RA. This increase

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was not shown in RA patients with inactive disease or in patients with OA (Veldhuijzen van Zanten et al., 2005a). The stress task induced an increase in blood pressure in all patient groups. In the present analyses, we addressed the cardiovascular mechanisms underlying this stress-induced pressor response. Given their increased risk for MI, we hypothesized that patients with active-RA would exhibit larger stress-induced increases in SVR.

2. Methods

2.1. Patients

Patients (21 RA and 10 OA) were recruited from outpatient rheumatology clinics. The exclusion criteria were inability to stand for 15 min, previously confirmed acute coronary syndrome, diabetes mellitus, or serious psychiatric disease. RA patients were grouped according to their baseline resting CRP levels: inactive-RA group with normal CRP (low grade systemic inflammation, CRP $\leq$ 8 mg/l, $N = 12$) or active-RA group with elevated CRP (high-grade systemic inflammation, CRP $>$ 8 mg/l, $N = 9$). This division was based on the laboratory cut-off point (8 mg/l) for normal or abnormal CRP. Patients abstained from caffeine for 2 h and from food and smoking for 1 h before testing. For ethical reasons, their medication regimens were not interrupted: analgesics (89% active-RA, 67% inactive-RA, and 20% OA), disease modifying antirheumatic drugs (DMARDS, 89% active-RA, and 75% inactive-RA), non-steroidal anti-inflammatory drugs (33% active-RA and 10% OA), cyclooxygenase-2 inhibitors (22% active-RA and 17% inactive-RA), anti-TNF (22% active-RA and 17% inactive-RA), and steroids (33% active-RA and 17% inactive-RA). Patients gave informed consent and the study was approved by the hospital ethics committee.

2.2. Physiological measurements

Systolic (SBP), diastolic (DBP), and mean (MAP) blood pressures were measured using an oscillometric blood pressure monitor (Omron HEM-705CP). An ambulatory monitor (VU-AMS) (de Geus et al., 1995; Willemsen et al., 1996) and six Ag/AgCl spot electrodes (Invisatrace, ConMed) recorded electrocardiographic and impedance cardiographic signals continuously (Sherwood et al., 1990). Sixty seconds ensemble averages were used to determine heart rate (HR, bpm), cardiac output (CO, l/min), and SVR (dyne-s/cm^{-5}).

2.3. Stress task

The stress task was the paced auditory serial addition test (Gronwall, 1977), performed while patients were tilted to 64° (see Veldhuijzen van Zanten et al., 2005a). Briefly, patients were presented with a series of single digit numbers and required to add each number to the number presented next under conditions of increasing time pressure, social evaluation, and punishment. The combination of mental stress and postural stress elicits greater hemodynamic reactions than mental stress or postural stress alone (Veldhuijzen van Zanten et al., 2005b).

2.4. Procedure

Patients completed one 3-h session, starting between 9:00 a.m. and 1:00 p.m. Following a 20-min formal rest period (baseline), during which they lay semi-recumbent, patients stepped on the tilt table, and completed the 8-min task. Patients then lay semi-recumbent for 30-min (recovery). Blood pressure readings were initiated at the start of minutes 14, 16, 18, and 20 of baseline, minutes 2, 4, 6, and 8 of stress, and minutes 24, 26, 28, and 30 of recovery. The associated electrocardiographic and impedance cardiographic data were scored for these minutes.

2.5. Data reduction and analysis

Measurements were averaged to yield a mean baseline, stress task, and recovery value. A series of three groups (active-RA, inactive-RA, and OA) analyses of variance (ANOVAs) and Chi-square tests were performed on patient characteristics and baseline cardiovascular variables. Separate 3 × 3 factorial ANOVAs (group × period [Baseline, Task, and Recovery]) were then performed on each cardiovascular variable, with patient group as between-subject factor and period as repeated measures factor. The results of the multivariate solution are reported. Occasional missing data are reflected in variations in the degrees of freedom.

3. Results

3.1. Patient characteristics and baseline cardiovascular measures

The patients' characteristics, demographics, and baseline measures are presented in Table 1. Patients with OA were more likely to be in paid employment compared to the patients with RA.

3.2. Cardiovascular reactions to stress

Fig. 1 presents the cardiovascular activity of the three patient groups during rest, stress, and recovery. A 3 group (active-RA, inactive-RA, and OA) × 3 period (Baseline, Task, and Recovery) ANOVA yielded period, $F(2,22) = 13.67, p < .001, \eta^2 = .55$,

Table 1
Patient characteristics and baseline measures of the rheumatoid arthritis and osteoarthritis patient groups

	RA-high-grade-systemic-inflammation	RA-low-grade-systemic-inflammation	OA	F-value	χ^2-value	p-value
Age (years)	59 ± 12	57 ± 11	47 ± 11	2.82		.08
Sex (% women)	89	83	70		1.17	.56
Married or co-habiting (%)	67	92	100		5.05	.08
Employed (%)	11	33	90		13.01	.01
Education (years)	11 ± 2	11 ± 1	12 ± 3	0.99		.38
Current or ex-smoker (%)	56	55	80		1.80	.41
Body mass index (kg/m^2)	29 ± 6	29 ± 5	25 ± 3	1.93		.17
Disease duration (years)	16 ± 13	9 ± 9	8 ± 2	1.14		.34
Systemic vascular resistance (dyne-s/cm^{-5})	986 ± 438	907 ± 256	823 ± 260	0.59		.56
Mean arterial pressure (mmHg)	102 ± 12	103 ± 12	92 ± 13	2.51		.10
Heart rate (bpm)	68 ± 11	69 ± 10	65 ± 5	0.37		.69
Cardiac output (l/min)	10 ± 4	10 ± 2	10 ± 3	0.04		.96

Values are the means ± S.D. for continuous variables and percentages for categorical variables.

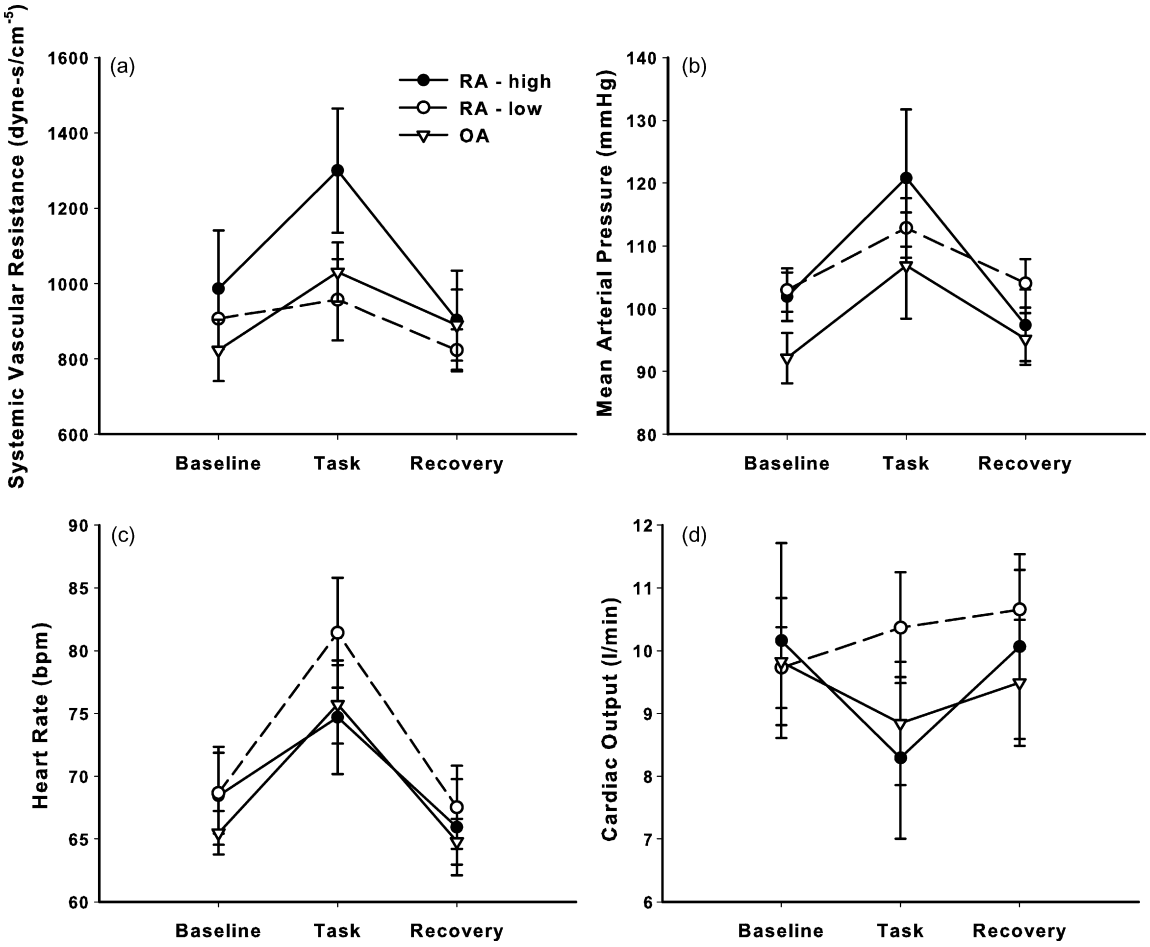

Fig. 1. (a) Mean (SE) systemic vascular resistance, (b) mean arterial pressure, (c) heart rate, and (d) cardiac output during baseline, stress task, and recovery in patients with RA with high-grade systemic inflammation, low grade systemic inflammation, and patients with OA.

and group × period, $F(4,44) = 3.77$, $p = .01$, $\eta^2 = .26$, effects for SVR. Follow-up within-group analyses revealed that SVR increased with stress only for patients with active-RA, $F(2,5) = 9.02$, $p < .05$, $\eta^2 = .78$, but not in patients with inactive-RA or OA patients. The overall group effect for SVR was nonsignificant. ANOVAs yielded period effects for MAP, $F(2,25) = 7.91$, $p < .01$, $\eta^2 = .39$ and HR, $F(2,24) = 55.41$, $p < .001$, $\eta^2 = .82$ but not for cardiac output, $F(2,24) = 1.88$, $p = .18$, $\eta^2 = .14$. Post hoc analyses revealed that MAP and HR were higher during the stress task relative to the baseline and recovery. No group or group × period effects were detected for MAP, HR, or CO.

4. Discussion

The key finding was that SVR increased with stress only in RA patients with high-grade systemic inflammation. In healthy participants, stress-induced increases in SVR were associated with endothelial dysfunction (Sherwood et al., 1999). Previous research has demonstrated that RA patients show endothelial dysfunction, with the poorest function in those patients with the highest levels of inflammation (Bergholm et al., 2002; Vaudo et al., 2004; Wong et al., 2003). Thus, the SVR response to stress may indicate endothelial dysfunction in the patients with active-RA. Endothelial dysfunction is strongly associated with coronary artery disease (CAD) (Lerman and Zeiher, 2005), which is considered as an inflammatory disease (Ross, 1999). Cleland et al. (2000) proposed that inflammation could influence endothelial function in CAD. Similarly, the increased risk for cardiovascular disease in RA patients has been suggested to be explained by the adverse effect of systemic inflammation on the vasculature (Bacon and Kitas, 1994; Sattar et al., 2003; Stevens et al., 2005).

Since peripheral endothelial function is representative of coronary endothelial function (Anderson et al., 1995; Takase et al., 2005), most studies determine endothelial function in the peripheral circulation. Similarly, stress-induced vasoconstriction in the periphery is representative of vascular responses in the coronary arteries of CAD patients, with increases in SVR associated with mental stress-induced ischemia (Goldberg et al., 1996; Jain et al., 1998). Smooth coronary arteries dilate with stress to accommodate the increase in cardiac demand (Dakak et al., 1995; Kop et al., 2001; Yeung et al., 1991), whereas stenosed arteries either fail to dilate (Dakak et al., 1995) or vasoconstrict (Yeung et al., 1991). Thus, the stress-induced increases in SVR in the current study suggest coronary vasoconstriction and ischemia in RA patients with high levels of inflammation. However, without direct measures of ischemia, this inference must remain speculative.

A limitation of the study is that ethical considerations dictated that patients remained medicated. However, patients are at increased risk of cardiac events during treatment, and therefore, examining effects of stress on medicated patients are clinically appropriate. Most patients were treated with multiple anti-rheumatic medications, which combined with low patient numbers, made it impossible to adjust statistically for class of medication. Nevertheless, there was no significant difference in medication use between the two groups with RA. Further, none of the patients were taking beta blockers, angiotensin converting enzyme inhibitors, angiotensin-II receptor blockers, other antihypertensive, or vasoactive medications.

In sum, stress elicited increase in blood pressure and heart rate in patients with RA and OA. An increase in SVR was specific to RA patients with high-grade systemic inflammation, and, given the CO data, it would appear that the increase in blood pressure for active-RA patients is driven solely by the increase in SVR. Thus, the inflammatory status of this patient group influences their vascular reaction to stress. Considered along with the previously reported increase in CRP in response to this stress task (Veldhuijzen van Zanten et al., 2005a), the increase in SVR could contribute to the increased susceptibility for MI in RA patients with high-grade systemic inflammatory activity.

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References

Anderson, T.J., Uehata, A., Gerhard, M.D., Meredith, I.T., Knab, S., Delagrange, D., Lieberman, E.H., Ganz, P., Creager, M.A., Yeung, A.C., 1995. Close relation of endothelial function in the human coronary and peripheral circulations. Journal of the American College of Cardiology 26, 1235–1241.

Bacon, P.A., Kitas, G.D., 1994. The significance of vascular inflammation in rheumatoid arthritis. Annals of the Rheumatic Diseases 53, 621–623.

Bergholm, R., Leirisalo-Repo, M., Vehkavaara, S., Makimattila, S., Taskinen, M.R., Yki-Jarvinen, H., 2002. Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis. Arteriosclerosis, Thrombosis, and Vascular 22, 1637–1641.

Carroll, D., Ebrahim, S., Tilling, K., Macleod, J., Davey Smith, G., 2002. Admissions for myocardial infarction and World Cup football: database survey. British Medical Journal 325, 1439–1442.

Cleland, S.J., Sattar, N., Petrie, J.R., Forouhi, N.G., Elliott, H.L., Connell, J.M., 2000. Endothelial dysfunction as a possible link between C-reactive protein levels and cardiovascular disease. Clinical Science (London, England: 1979) 98, 531–535.

Dakak, N., Quyyumi, A.A., Eisenhofer, G., Goldstein, D.S., Cannon III, R.O., 1995. Sympathetically medicated effects of mental stress on the cardiac microcirculation of patients with coronary artery disease. The American Journal of Cardiology 76, 125–130.

de Geus, E.J.C., Willemsen, G.H.M., Klaver, C.H.A.M., van Doornen, L.J.P., 1995. Ambulatory measurement of respiratory sinus arrhythmia and respiration rate. Biology Psychology 41, 205–227.

Del Rincòn, I., Williams, K., Stern, M.P., Freeman, G.L., O'Leary, D.H., Escalante, A., 2003. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. Arthritis and Rheumatism 48, 1833–1840.

DeMaria, A.N., 2002. Relative risk of cardiovascular events in patients with rheumatoid arthritis. The American Journal of Cardiology 89 (Suppl.), 33D–38D.

Goldberg, A.D., Becker, L.C., Bonsall, R., Cohen, J.D., Ketterer, M.W., Kaufman, P.G., Krantz, D.S., Light, K.C., McMahon, R.P., Noreuil, T., Pepine, C.J., Raczynski, J., Stone, P.H., Strother, D., Taylor, H., Sheps, D.S., 1996. Ischemic, hemodynamic, and neurohormonal responses to mental and exercise stress. Experience from the psychophysiological investigations of myocardial ischemia study (PIMI). Circulation 94, 2402–2409.

Gronwall, D.M., 1977. Paced auditory serial-addition task: a measure of recovery from concussion. Perceptual and Motor Skills 44, 367–373.

Hurlimann, D., Forster, A., Noll, G., Enseleit, F., Chenevard, R., Distler, O., Bechir, M., Spieker, L.E., Neidhart, M., Michel, B.A., Gay, R.E., Luscher, T.F., Gay, S., Ruschitzka, F., 2002. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. Circulation 106, 2184–2187.

Jain, D., Shaker, S.M., Burg, M., Wackers, F.J., Soufer, R., Zaret, B.L., 1998. Effects of mental stress on left ventricular and peripheral vascular performance in patients with coronary artery disease. Journal of the American College of Cardiology 31, 1314–1322.

Kitas, G.D., Erb, N., 2003. Tackling ischaemic heart disease in rheumatoid arthritis. Rheumatology (Oxford, England) 42, 607–613.

Kloner, R.A., Leor, J., Poole, W.K., Perritt, R., 1997. Population-based analysis of the effect of the northridge earthquake on cardiac death in Los Angeles County, California. Journal of American College Cardiology 30, 1174–1180.

Kop, W.J., Krantz, D.S., Howell, R.H., Ferguson, M.A., Papademetriou, V., Lu, D., Popma, J.J., Quigley, J.F., Vernalis, M., Gottdiener, J.S., 2001. Effects of mental stress on coronary epicardial vasomotion and flow velocity in coronary artery disease: relationship with hemodynamic stress responses. Journal of the American College of Cardiology 37, 1359–1366.

Lee, D.M., Weinblatt, M.E., 2001. Rheumatoid arthritis. Lancet 358, 903–911.

Lerman, A., Zeiher, A.M., 2005. Endothelial function: cardiac events. Circulation 111, 363–368.

Obrist, P.A., 1981. Cardiovascular Psychophysiology: A Perspective. Plenum Press, New York.

Ross, R., 1999. Atherosclerosis—an inflammatory disease. The New England Journal of Medicine 340, 115–126.

Sattar, N., McCarey, D.W., Capell, H., McInnes, I.B., 2003. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 108, 2957–2963.

Sherwood, A., Allen, M.T., Fahrenberg, J., Kelsey, R.M., Lovallo, W.R., Van Doornen, L.J.P., 1990. Methodological guidelines for impedance cardiography. Psychophysiology 27, 1–23.

Sherwood, A., Johnson, K., Blumenthal, J.A., Hinderliter, A.L., 1999. Endothelial function and hemodynamic responses during mental stress. Psychosomatic Medicine 61, 365–370.

Stevens, R.J., Douglas, K.M., Saratzis, A.N., Kitas, G.D., 2005. Inflammation and atherosclerosis in rheumatoid arthritis. Expert Reviews in Molecular Medicine [Electronic Resource] 7, 1–24.

Strike, P.C., Steptoe, A., 2003. Systematic review of mental stress-induced myocardial ischaemia. European Heart Journal 24, 690–703.

Takase, B., Hamabe, A., Satomura, K., Akima, T., Uehata, A., Ohsuzu, F., Ishihara, M., Kurita, A., 2005. Close relationship between the vasodilator response to acetylcholine in the brachial and coronary artery in suspected coronary artery disease. International Journal of Cardiology 105, 58–66.

Tofler, G.H., Brezinski, D., Schafer, A.I., Czeisler, C.A., Rutherford, J.D., Willich, S.N., Gleason, R.E., Williams, G.H., Muller, J.E., 1987. Concurrent morning increase in platelet aggregability and the risk of myocardial

infarction and sudden cardiac death. The New England Journal of Medicine 316, 1514–1518.

Turner, J.R., 1994. Cardiovascular Reactivity and Stress. Plenum Press, New York.

Van Doornum, S., McColl, G., Jenkins, A., Green, D.J., Wicks, I.P., 2003. Screening for atherosclerosis in patients with rheumatoid arthritis: comparison of two in vivo tests of vascular function. Arthritis and Rheumatism 48, 72–80.

Vaudo, G., Marchesi, S., Gerli, R., Allegrucci, R., Giordano, A., Siepi, D., Pirro, M., Shoenfeld, Y., Schillaci, G., Mannarino, E., 2004. Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity. Annals of the Rheumatic Diseases 63, 31–35.

Veldhuijzen van Zanten, J.J.C.S., Ring, C., Carroll, D., Kitas, G.D., 2005a. Increased C-reactive protein in response to acute stress in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases 64, 1299–1304.

Veldhuijzen van Zanten, J.J.C.S., Thrall, G., Wasche, D., Carroll, D., Ring, C., 2005b. The influence of hydration status on stress-induced hemoconcentration. Psychophysiology 42, 98–107.

Wållberg-Jonsson, S., Johansson, H., Öhman, M.-L., Rantapää-Dahlqvist, S., 1999. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. The Journal of Rheumatology 26, 2562–2571.

Willemsen, G.H.M., De Geus, E.J.C., Klaver, C.H.A.M., Van Doornen, L.J.P., Carroll, D., 1996. Ambulatory monitoring of the impedance cardiogram. Psychophysiology 33.

Wong, M., Toh, L., Wilson, A., Rowley, K., Karschimkus, C., Prior, D., Romas, E., Clemens, L., Dragicevic, G., Harianto, H., Wicks, I., McColl, G., Best, J., Jenkins, A., 2003. Reduced arterial elasticity in rheumatoid arthritis and the relationship to vascular disease risk factors and inflammation. Arthritis and Rheumatism 48, 81–89.

Yeung, A.C., Vekshtein, V.I., Krantz, D.S., Vita, J.A., Ryan Jr., T.J., Ganz, P., Selwyn, A.P., 1991. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. The New England Journal of Medicine 325, 1551–1556.