Inflammation and Hypertension in Rheumatoid Arthritis

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ABSTRACT. Objective. Hypertension (HTN), a common modifiable cardiovascular risk factor, is more common in patients with rheumatoid arthritis (RA), but the underlying mechanisms are unclear. We examined the hypothesis that mediators of inflammation and markers of cardiovascular risk are associated with HTN in RA.

Methods. We compared measures of inflammation [serum C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), homocysteine, and leptin concentrations] and insulin resistance [homeostasis model assessment index (HOMA)] in RA patients with (n = 90) and without HTN (n = 79). HTN was defined as blood pressure ≥ 140/90 mm Hg or treatment with antihypertensive therapy. The independent association of markers of interest with HTN was examined using multivariable logistic regression.

Results. Patients with HTN were significantly older and had longer disease duration than those without HTN (both p < 0.001). Concentrations of homocysteine [11.1 (8.5–13.5) μmol/l vs 9.3 (7.8–11.0) μmol/l] were significantly higher in patients with HTN (p < 0.001). After adjustment for age, sex, race, smoking, body mass index, and corticosteroid and nonsteroidal antiinflammatory drugs (NSAID) use, increased concentrations of homocysteine (OR 2.9, 95% CI: 1.5–5.5, p = 0.001), and leptin (OR 2.0, 95% CI: 1.0–3.8, p = 0.046) were significantly associated with HTN, but the 28-joint Disease Activity Score, IL-6, CRP, TNF-α, and HOMA index were not (all p > 0.05).

Conclusion. HTN in patients with RA is not associated with generalized systemic inflammation or insulin resistance, but is associated with increasing concentrations of homocysteine and leptin. The pathogenesis of HTN in RA may involve pathways more regularly associated with fat and vascular homeostasis. (First Release Sept 1 2013; J Rheumatol 2013;40:1806–11; doi:10.3899/jrheum.130394)

Key Indexing Terms:

RHEUMATOID ARTHRITIS	INFLAMMATION	HYPERTENSION
BLOOD PRESSURE	HOMOCYSTEINE	LEPTIN

Patients with rheumatoid arthritis (RA) have increased cardiovascular morbidity and mortality[1]. The mechanisms underlying increased cardiovascular risk are unclear, but are likely to include an increased prevalence of some traditional cardiovascular risk factors, as well as additional risk factors specific to RA. Hypertension (HTN) is one of the most common modifiable cardiovascular risk factors in the general population. In patients with RA, HTN may represent a traditional cardiovascular risk factor that is both increased in prevalence and modified by the presence of the disease[2].

Not all studies are concordant, but several, including our own, have found that HTN is more common in patients with RA, particularly in those with longstanding disease, than in the general population[3,4]. As is the case in the general population, HTN in patients with RA is associated with increased atherosclerosis and cardiovascular risk[1,5]. Thus, identifying factors that contribute to HTN in RA is important, particularly where these can be modified and targeted interventions could improve outcomes.

The factors that account for the increased prevalence of HTN in RA are not well defined, but there are several possible contributors: medications, inflammation, oxidative stress, and insulin resistance[4,6]. In addition, concentrations of homocysteine and leptin are increased in patients with RA[7,8], and are associated with HTN in the general population[9,10].

There is limited information about HTN in patients with RA. One study found that HTN was associated with age, body mass index (BMI), and daily prednisolone dose ≥ 7.5 mg and ≤ 30 mg, but not with other medications, inflammation, or insulin sensitivity[11]. We have reported that blood pressure in patients with RA was not associated with the use of medications[12] or insulin resistance[13], and that HTN was associated with osteoprotegerin concentrations[7] but not with oxidative stress[14]. Considering the importance of HTN as a cardiovascular risk factor, and its unexplained increased prevalence in patients with RA, we examined the hypothesis that inflammation, homocysteine, and leptin are independently associated with the presence of HTN.

MATERIALS AND METHODS

Patients. One hundred and sixty-nine patients who are part of a study on cardiovascular risk in RA were recruited, as described[15]. Consecutive eligible patients older than 18 years of age who met the American College of Rheumatology classification criteria for RA[16] and had duration of disease < 5 years or > 10 years were enrolled. Controls did not meet classification criteria for RA or any other inflammatory disease. Control subjects were frequency matched for age, sex, and race with the entire group of patients with RA to ensure that the control group would not differ markedly from either the early or established RA groups in these variables. Patients were recruited from a registry of patients with early RA, local rheumatologists, and by advertisements. Control subjects were recruited from patients' acquaintances, by advertisement, and from a database of volunteers maintained by the General Clinical Research Center. The study was approved by the Institutional Review Board of Vanderbilt University Hospital and all subjects gave written informed consent.

Clinical assessment. Details regarding recruitment and study procedures have been published[15]. Briefly, information was obtained from interviews, review of the medical records, self-report questionnaires, physical examination, and laboratory tests. Blood pressure was measured by a trained study coordinator using an appropriate cuff size and a semiautomated device (DINAMAP PRO Series 200; General Electric Healthcare). Blood pressure was determined as the average of 2 measurements obtained 5 min apart after subjects had rested in the supine position for at least 10 min. HTN was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or currently taking antihypertensive drugs.

Height and weight were measured and BMI calculated by dividing weight (kg) by the square of the height (m^2). RA disease activity was measured using the 28-joint Disease Activity Score (DAS28)[17]. DAS28 is a composite index containing a 28-joint count for tenderness, swelling, erythrocyte sedimentation rate (ESR), and the overall assessment of well-being.

Laboratory tests. Blood was collected after an overnight fast. Glucose, homocysteine, and C-reactive protein (CRP) concentrations and Westergren ESR were measured by the hospital laboratory. Before 2003, the laboratory did not use a high-sensitivity CRP assay, and low concentrations were reported as < 3 mg/l; in 40 patients with RA who had CRP concentrations < 3 mg/l, CRP concentrations were measured by multiplex ELISA. Serum concentrations of tumor necrosis factor (TNF-α), interleukin 6 (IL-6), insulin, and leptin were measured by multiplex ELISA (LincoPlex Multiplex Immunoassay kit; Millipore). Homeostasis model assessment (HOMA) index was calculated using the following formula: [fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5][18].

Statistical analysis. Data are presented as median and interquartile range (IQR). Univariate analyses were performed to compare differences between patients with and without HTN using Pearson's chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

The independent association of each variable with the presence or absence of HTN was assessed using separate multivariable logistic regression models. Covariates for adjustment were chosen *a priori* based on factors known to be associated with blood pressure in RA and non-RA populations[4,19,20] and included age, sex, race, smoking, BMI, and current use of corticosteroids and nonsteroidal antiinflammatory drugs (NSAID). All inflammation measures were natural logarithm-transformed to improve normality. Goodness-of-fit tests for logistic regression models were assessed using Hosmer-Lemeshow tests. Statistical analysis was performed with R 2.9.1 (www.r-project.org), and 2-sided p < 0.05 were considered statistically significant.

RESULTS

The demographic and clinical characteristics of patients with RA, with and without HTN, are summarized in Table 1. HTN was present in 90 patients (53.3%) who were significantly older than those without HTN [n = 79; median (IQR) age 58.5 (51.2–67.0) yrs vs 46.0 (41.0–56.0) yrs; p < 0.001] and had longer duration of RA (p < 0.001). Sex, BMI, smoking history, and serum creatinine did not differ significantly among patients with and without HTN (all p > 0.05). Despite the fact that 64 of the 90 patients with HTN were receiving antihypertensive treatment, their systolic and diastolic blood pressure was significantly higher [145 (136–157) vs 120 (112–130) mm Hg and 78 (71–87) vs 71 (66–78) mm Hg, respectively] than that of patients without HTN (both p < 0.001).

In unadjusted analyses, disease characteristics including DAS28 score (p = 0.04) and ESR (p = 0.02) were higher and methotrexate (MTX) use was less frequent (p = 0.045) in patients with HTN compared to those without, but CRP, TNF-α, IL-6, and HOMA index were not significantly associated with HTN (Table 2). Homocysteine concentrations [11.1 (8.5–13.5) μmol/l vs 9.3 (7.8–11.0) μmol/l] were significantly higher among patients with HTN (p < 0.001), and leptin concentrations were marginally higher [25.7 (11.0–43.8) ng/ml vs 19.5 (5.7–36.9) pg/ml; p = 0.07; Table 2, Figure 1].

After adjustment for age, sex, race, smoking, BMI, and current use of corticosteroids and NSAID, concentrations of homocysteine (OR 2.9, 95% CI: 1.5–5.5; p = 0.001) and leptin (OR 2.0, 95% CI 1.0–3.8; p = 0.046) were statistically significantly associated with HTN. After adjustment for covariates, there were no significant differences in disease duration, DAS28 scores, ESR, and CRP among patients with and without HTN (Table 2). The less frequent current use of MTX in patients with HTN remained statistically significant (p = 0.04) after adjustment (Table 2).

DISCUSSION

The major new finding of our study is that HTN in patients with RA is associated with increased concentrations of homocysteine and leptin, but not with markers of inflammation.

Most studies, including our own[3], have found that the proportion of patients with HTN is higher in RA than in the

Table 1. Clinical characteristics of patients with rheumatoid arthritis (RA) with and without hypertension. Values are the median (interquartile range) unless otherwise indicated.

	Hypertension Present, n = 90	Hypertension Absent, n = 79	p+
Demographics			
Age, yrs	58.5 (51.2–67.0)	46.0 (41.0–56.0)	< 0.001
Sex, % female	73	65	0.22
Race, % white	87	90	0.61
Systolic blood pressure, mm Hg	145 (136–157)	120 (112–130)	< 0.001
Diastolic blood pressure, mm Hg	78 (71–87)	71 (66–78)	< 0.001
Body mass index, kg/m^2	28.4 (24.0–33.4)	27.9 (23.8–32.4)	0.71
Smoking, pack-yrs	0 (0–28)	0 (0–18)	0.63
Serum creatinine, mg/dl	0.8 (0.7–1.0)	0.8 (0.7–0.9)	0.06
Characteristics of RA			
Disease duration of RA, yrs	11.0 (2.0–20.0)	2.0 (1.6–11.5)	< 0.001
Current use of glucocorticoids, %	52	57	0.54
Current use of NSAID, %	58	65	0.37

+ Wilcoxon's rank sum test was used for comparing continuous variables and Pearson's chi-squared test for comparison of categorical variables. NSAID: nonsteroidal antiinflammatory drugs.

Table 2. Disease characteristics and biomarkers in patients with and without hypertension. Values are the median (interquartile range) unless otherwise indicated.

	Hypertension Present, n = 90	Hypertension Absent, n = 79	p*	Adjusted OR (95% CI)**	p**
Disease duration of RA, yrs	11.0 (2.0–20.0)	2.0 (1.6–11.5)	< 0.001	1.3 (0.7–2.4)	0.35
DAS28 scores	4.1 (2.8–5.0)	3.6 (2.4–4.5)	0.04	1.2 (0.7–2.0)	0.45
M-HAQ scores	0.5 (0.1–0.9)	0.4 (0.0–0.8)	0.19	1.3 (0.7–2.5)	0.48
Current methotrexate use†, %	64	78	0.045	0.4 (0.2–1.0)	0.04
Current leflunomide use†, %	20	16	0.55	1.8 (0.7–4.6)	0.25
Current hydroxychloroquine use†, %	21	29	0.23	0.8 (0.3–1.9)	0.59
Current anti-TNF drug use†, %	17	25	0.17	0.5 (0.2–1.3)	0.15
ESR, mm/h	19 (10–39)	11 (5–28)	0.02	1.2 (0.7–2.1)	0.47
CRP, mg/l	4.5 (2.0–11.0)	3.0 (1.0–10.0)	0.16	1.3 (0.7–2.3)	0.42
TNF-α, pg/ml	6.6 (3.2–11.5)	4.8 (2.5–9.6)	0.12	1.2 (0.8–1.8)	0.35
IL-6, pg/ml	16.1 (6.3–38.8)	12.4 (3.5–44.9)	0.13	1.2 (0.7–2.1)	0.56
HOMA index	2.5 (1.1–5.4)	1.9 (1.3–3.5)	0.18	1.1 (0.7–1.7)	0.68
Leptin, ng/ml	25.7 (11.0–43.8)	19.5 (5.7–36.9)	0.07	2.0 (1.0–3.8)	0.046
Homocysteine, μmol/l	11.1 (8.5–13.5)	9.3 (7.8–11.0)	< 0.001	2.9 (1.5–5.5)	0.001

* Wilcoxon rank sum test was used for comparing continuous variables and chi-square test for comparison of categorical variables (unadjusted analyses). ** Separate multivariable logistic regression models adjusted for age, sex, race, BMI, smoking status, current corticosteroid use, and current NSAID were used to estimate the association of each factor with hypertension. Biomarkers were natural log transformed. For continuous variables, the OR with 95% CI is presented per interquartile range increment. † Nonusers represent reference group. DAS28: Disease Activity Score 28-joint assessment; M-HAQ: Modified Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RA: rheumatoid arthritis; TNF: tumor necrosis factor; IL: interleukin; HOMA: homeostasis model assessment index; BMI: body mass index; NSAID: nonsteroidal antiinflammatory drug.

general population. In one of the largest studies involving 28,208 patients with RA and 112,832 control subjects, the prevalence of HTN was 31% in patients with RA compared to 23.4% in controls[21]. In our study, HTN was present in 53.3% (95% CI 45.7–60.6) of patients, and this compares with 71% in a study of 400 patients with RA that was done on an older population (median age 65 years vs 58.5 years in our study)[11]. The high prevalence of HTN reported in patients with RA suggests that factors related to RA or its treatment may play a role in the pathogenesis of HTN. Factors most commonly proposed as risk factors for HTN in RA include medications, inflammation, oxidative stress, and insulin resistance.

Several medications used to treat RA affect blood pressure. For example, corticosteroids, NSAID, and leflunomide[22] can increase blood pressure. However, we have reported that blood pressure did not differ among patients currently taking or not taking these medications[12].
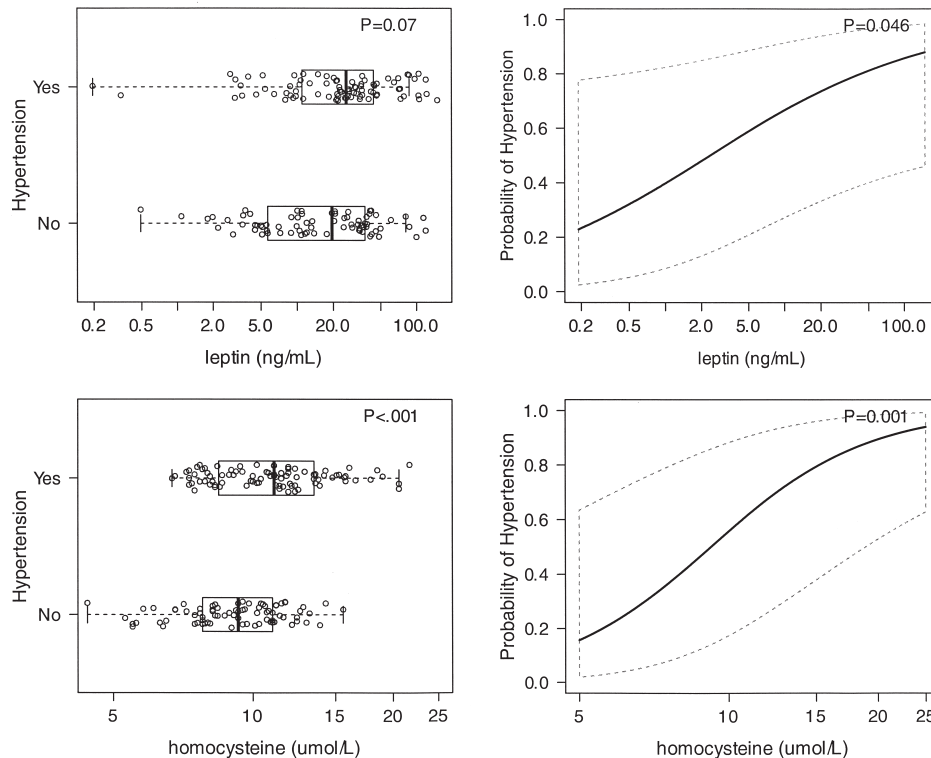
Figure 1. Leptin and homocysteine distribution according to hypertension (HTN) status (left panels) and adjusted probability of hypertension (right panels). In the left panels, the boxes represent the interquartile range (IQR), the lines within boxes represent the median, and the lines outside the boxes represent the lower quartile minus 1.5 × the IQR or the upper quartile plus 1.5 × the IQR. The right panels show the increasing adjusted probability of HTN with increasing concentrations of leptin and homocysteine from separate multivariable logistic regression models adjusted for age, sex, race, body mass index, smoking status, current use of corticosteroid, or nonsteroidal antiinflammatory drugs.

Similarly, in our study we found no association between current use of NSAID, corticosteroids, or leflunomide and HTN. This may be because the changes in blood pressure associated with medications are small and variable, or that physicians avoid prescribing medications that can increase blood pressure to patients at risk of HTN. MTX use was less frequent in patients with HTN. However, another study found no relationship between MTX use and HTN[23], and our findings could be confounded by the selection of patients for MTX therapy if physicians avoided prescribing MTX because of concerns about future renal impairment. Prospective studies to define the effect of MTX on blood pressure will be required to specifically determine whether it protects against HTN. We previously found that both systolic and diastolic blood pressure tended to be lower in patients receiving hydroxychloroquine[12], but in the present study the frequency of hydroxychloroquine use did not differ among patients with and without HTN.

Inflammation, mediated through cytokines, is directly associated with increased arterial stiffness and endothelial dysfunction, and could thus predispose to the development of HTN[24,25]. Inflammation can also result in increased oxidative stress, and thus decreased nitric oxide bioavailability and, consequently, endothelial dysfunction, impaired vasodilation, and increased arterial stiffness[26]. Indeed, in keeping with the theory that inflammation plays a role in the pathogenesis of HTN, increased concentrations of markers of inflammation such as ESR, CRP, TNF-α, and IL-6 were significantly associated with HTN in non-RA populations[27,28,29]. Although concentrations of these inflammatory markers are significantly increased in patients with RA, we found no differences in concentrations among patients with and without HTN. These findings are in accordance with another study that found no significant association between DAS28, CRP, or ESR and HTN in RA[11], and they suggest that generalized systemic inflammation itself may not be the major factor underlying increased risk of HTN in RA.

We have observed that insulin resistance is more common in patients with RA than in controls[3]. Insulin resistance is associated with HTN in the general population and may affect blood pressure through mechanisms that include enhanced renal tubular sodium reabsorption, endothelial dysfunction, and increased sympathetic activity[30]. As was the case in another study[11], we found no

difference in insulin sensitivity in patients with and without HTN. These findings suggest that it is unlikely that insulin resistance is a key factor in the development of HTN in RA.

Higher concentrations of homocysteine are known to be associated with atherosclerosis and thrombosis, but their association with HTN is less widely recognized. Several studies have reported that higher concentrations of homocysteine are associated with increased blood pressure and HTN[31,32]. Additionally, some studies have shown that treatment to lower homocysteine levels can be associated with a reduction in both systolic and diastolic blood pressure[33,34]. Homocysteine is thought to affect blood pressure regulation through several mechanisms including impaired vascular endothelial and smooth muscle cell function, oxidative stress, and increased renal sodium reabsorption[35].

Homocysteine concentrations are elevated in patients with RA compared to control subjects[3], and in our cohort, homocysteine concentrations were not affected by current MTX, perhaps because concurrent folic acid use was almost universal[12]. We found that higher homocysteine concentrations were associated with HTN in RA, but interestingly, we observed that oxidative stress, as determined by urinary F2-isoprostane excretion, was not[14]. This suggests that increased oxidative stress is not the mechanism through which homocysteine contributes to HTN in RA.

It is unclear why homocysteine concentrations are increased or how they might contribute to HTN in RA. There are several possibilities. It is unlikely that altered renal elimination of homocysteine accounts for higher concentrations in RA because we have previously shown in this cohort that creatinine clearance did not differ significantly among RA and control subjects[36]. However, homocysteine production or clearance may be altered because increased homocysteine levels after a methionine load, and an association between homocysteine levels and inflammation, have been observed in RA[37,38]. The adverse effects of homocysteine on endothelial function[39] may be particularly important in RA because endothelial function is often impaired[40].

Leptin is a peptide hormone secreted by adipocytes that suppresses appetite. In addition, there are several mechanisms whereby chronically increased leptin concentrations could increase blood pressure. These include increased sympathetic nervous system activity and impaired natriuresis[41]. Leptin concentrations are strongly associated with obesity, and several studies in the general population have found that higher leptin concentrations are associated with HTN[41]. We have reported that leptin concentrations were higher in patients with RA than control subjects, and that this difference was independent of BMI and correlated with the degree of inflammation[8]. Our finding that leptin concentrations are associated with HTN in RA, independent of BMI and other demographic confounders, raises the possibility that leptin, in addition to a positive association with insulin resistance[42] and a negative association with joint damage[8], may play a direct role in the pathogenesis of HTN in RA.

Our study has a number of limitations; the cross-sectional, observational design can establish association but not causality. Further, we cannot exclude the possibility that factors associated with the early development of HTN may no longer be evident in established HTN. Also, in an observational study it is difficult to define the role of specific medications because they may be differentially prescribed to patients with and without HTN. The number of patients studied, although large for RA studies, is small compared to studies performed in a more general population.

HTN in patients with RA is associated with higher concentrations of homocysteine and leptin, but not with insulin resistance or markers of inflammation. The pathogenesis of HTN in RA may involve pathways more typically associated with the maintenance of fat and vascular homeostasis.

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