Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis

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Objectives. Rheumatoid arthritis (RA) associates with excessive cardiovascular morbidity and mortality. Hypertension (HT) contributes significantly to the development of cardiovascular disease (CVD). Little is known about the factors that influence blood pressure (BP) in patients with RA. In this study, we assessed the prevalence of HT in a secondary care cohort of RA patients, and aimed to identify factors associated with its presence and inadequate control.

Methods. A total of 400 consecutive RA patients were studied. HT was defined as systolic BP $\geq 140$ mmHg and/or diastolic BP $\geq 90$ mmHg or current use of antihypertensive drugs. The association of HT with several demographic and RA-related factors, comorbidities and drugs was evaluated using logistic regression.

Results. HT was present in 282 (70.5%) patients. Of those, 171 (60.6%) received anti-hypertensive therapy, but 111 (39.4%) remained undiagnosed. Of those treated, only 37/171 (21.8%) were optimally controlled. Multivariable logistic regression revealed age (OR = 1.054, CI: 1.02 to 1.07, P = 0.001), body mass index [BMI (OR = 1.06, CI: 1.03–1.121, P = 0.038)] and prednisolone use (OR = 2.39, CI: 1.02–5.6, P = 0.045) to be independently associated with the presence of HT. BMI (OR = 1.11, CI: 1.02–1.21, P = 0.002) and the presence of CVD (OR = 4.01, CI: 1.27–12.68, P = 0.018) associated with uncontrolled HT.

Conclusions. HT is highly prevalent in RA, under-diagnosed particularly in the young, and under-treated particularly in old RA patients with CVD. RA patients receiving steroids should be specifically targeted for screening and treatment; those with any cardiovascular comorbidity may require particularly aggressive monitoring and treatment strategies.

KEY WORDS: Hypertension, Rheumatoid arthritis, Prevalence, Cardiovascular, Control.

Introduction

Rheumatoid arthritis (RA) associates with increased cardiovascular mortality due to increased prevalence of comorbidities such as myocardial infarction (MI), stroke and heart failure (HF) [1, 2]. The adjusted relative risk of MI in women with RA compared to those without RA is estimated to be around 2.0 [2], while acute coronary syndromes may present atypically and recur more frequently in patients with RA [3]. Increased clinical suspicion may aid early identification and appropriate management of risk factors in these patients [1].

HT is quantitatively the most important modifiable risk factor for cardiovascular disease (CVD), being more common than cigarette smoking, dyslipidaemia or diabetes [4]. In the INTERHEART study [5], which included patients from 52 countries, HT accounted for 18% of the population attributable risk of a first MI. HT increases the risk of both coronary artery disease and cerebrovascular disease in the general population [6]. It remains unclear whether HT is commoner in RA [7–9].

Ageing and obesity are known predictors of HT in the general population; smoking cessation and low-grade inflammation may also contribute to the development of HT [10]. In RA, the chronic inflammatory burden may lead to increased arterial stiffness [11], one of the physical causes of raised systolic blood pressure (BP), providing a potential link between inflammation and HT in this disease. Drugs commonly administered to RA patients, such as the non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase II inhibitors (Coxibs) [12], oral steroids [13] and some disease-modifying anti-rheumatic drugs (DMARDs), such as leflunomide [14] and cyclosporin [15], may also cause major or minor increments in BP levels. Comorbidities common in RA, such as insulin resistance [16], dyslipidaemia [17] and renal disease, have also been shown to associate with essential HT in the general population [18, 19]. To date, no studies have investigated the potential association of HT with these factors in patients with RA.

In the present study, we aimed: (i) to identify the overall prevalence of HT in a large secondary care population with RA, and estimate whether undiagnosed and/or sub-optimally controlled HT is a common problem in these patients; and (ii) to identify factors that may associate with the presence and/or insufficient control of HT in RA.

Patients and methods

Four hundred consecutive patients with RA meeting retrospective application of the 1987 revised ACR criteria [20], attending routine out-patient clinics at the Department of Rheumatology of the Dudley Group of Hospitals, Dudley (Black Country), West Midlands, UK, were enrolled in this cross-sectional, one-centre study. The study had local Research Ethics Committee and Research and Development approval and all participants gave their written informed consent according to the Declaration of Helsinki.

Basic demographic and clinical characteristics of the study population are shown in Table 1. All participants underwent a thorough baseline evaluation including a detailed review of their medical history and hospital records, physical examination, and contemporary assessments of height, weight, body mass index (BMI), body composition (using a TANITA Body Composition Analyzer BC-418), current disease activity score (DAS28) [21] and physical function using the Health Assessment Questionnaire (HAQ) [22]. All medications and their exact indication were recorded, including loop and thiazide diuretics, β-blockers, angiotensin-converting enzyme inhibitors (ACE-I) and...
Comorbidities

Dyslipidaemia

Hypercholesterolaemia and non-hypercholesterolaemia calcium channel blockers, a-adrenergic receptor blockers, centrally acting anti-hypertensives, other anti-hypertensives, oral daily prednisolone, paracetamol, NSAIDs, Coxibs and DMARDs. Oral prednisolone dose was defined as low if <7.5 mg/day, medium if ≥7.5 mg/day and high if >30 mg/day [23].

Blood pressure (BP) was the mean of three measurements taken at 5 min intervals on the right arm with the patient in a seated position after at least 5 min rest, using an appropriately sized cuff of the CRITICARE 506DXN machine (Systems Inc). The presence of HT was defined as a systolic BP >130 mmHg and/or diastolic BP >90 mmHg. Number of pack-years of smoking was recorded and never smoked.

Patients were classified as having CVD (RA + CVD) if they had a positive history of any of the following: MI, stroke or transient ischaemic attack (TIA), peripheral vascular disease (PVD), angiplasty, coronary artery bypass grafting (CABG) or if they had a positive Rose questionnaire [25] on assessment. Patients were defined as being diabetic when fasting glucose levels were ≥7 mmol/l and/or oral hypoglycemic medication or insulin was used. Number of pack-years of smoking was recorded and patients were categorised as current smokers, ex-smokers or never smoked.

Venous blood was collected in the fasting state on the same day and a wide range of tests was performed. All biochemical tests were carried out in the Biochemistry Laboratory of Russells Hall Hospital, Dudley Group of Hospitals NHS Trust, UK. Biochemical estimations included: fasting lipids, complete serum biochemical profile, fasting glucose, HbA1c, C-reactive protein, creatinine, urea, electrolytes, ionised calcium, albumin, sodium, potassium, bicarbonate, blood gases, fibrinogen, international normalised ratio, prothrombin time, antithrombin III, D-dimer, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, creatine phosphokinase, troponin I, etc. All tests were done by the same laboratory, in the same time period.
biochemistry, fasting glucose, fasting insulin and C-reactive protein (CRP). Insulin resistance (IR) was evaluated from fasting glucose and insulin using the Homeostasis Model Assessment of IR (HOMA IR) [26] and the Quantitative Insulin sensitivity Check Index (QUICKI) [27], and was defined as the presence of DM or HOMA IR ≥ 2.5 or QUICKI ≤ 0.333. Renal function was assessed by glomerular filtration rate (GFR) estimation using the six-variable modification of diet in renal disease (MDRD) equation [28].

Statistical analysis
The Kolmogorov–Smirnov test was used to evaluate whether each parameter followed a Gaussian distribution. Values were expressed as mean ± standard deviation (s.d.), median (25–75th percentile values) or percentages, as appropriate. Comparisons were performed by Student’s t-test, Mann-Whitney U-test and chi-squared-test for normally distributed, non-normally distributed and categorical variables, respectively.

Binary logistic regression analysis was used to evaluate the independence of the factors associated with HT status and the differences between the ‘controlled HT’ and ‘uncontrolled HT’ groups.

Differences were considered to be significant at a P-value of <0.05 (two-tailed). All analyses were carried out with SPSS 13.0 (SPSS Inc, Chicago, IL, USA).

Results

Descriptive characteristics of the population studied
The cohort consisted almost exclusively (96%) of Caucasians (reflecting the local demographic split) and were predominantly (~73%) females. The mean age (s.d.) was 61.56 ± 12.02 yrs, and the mean ± s.d. systolic and diastolic BP were 142.24 ± 20.74 and 78.85 ± 11.24 mmHg, respectively.

Of the 400 patients, 350 (87.5%) were on DMARDs: 225 (56.3%) on methotrexate, 118 (29.5%) on sulphasalazine, 80 (20%) on hydroxychloroquine, 46 (11.5%) on anti-tumour necrosis factor-α (anti-TNFα) therapy, 16 (4%) on leflunomide, 7 (1.8%) on azathioprine and 2 (0.5%) on cyclosporin; 227 (56.8%) patients were on DMARD monotherapy, while 123 (30.8%) were on combination therapy of two or more DMARDs. One hundred and twenty five patients (31.3%) were taking daily oral prednisolone, [54 (13.4%) low dose, 71 (17.9%) medium dose and 0 (0%) high dose]; 79 (19.8%) NSAIDs and 32 (8%) Coxibs.

There were 118 (29.5%) normotensive and 282 (70.5%) hypertensive patients (male vs female: 79.6% vs 67.1%, P = 0.015). From those with hypertension, 171 (60.6%) had been diagnosed and were on anti-hypertensive medications and 111 (39.4%) had undiagnosed/untreated HT (males vs females: 35.3% vs 41.3, P = 0.637). Undiagnosed/untreated HT was significantly common in the younger age groups (35–44 yrs: 76.2%; 45–54 yrs: 51.6%) than in older age deciles (55–64 yrs: 34.5%; 65–74 yrs: 37.9%; 75+ yrs: 25%) (P = 0.003) (Fig. 1). From the 171 diagnosed hypertensives on treatment, 37 (21.63%) had controlled HT and 134 (78.36%) had uncontrolled HT. Uncontrolled HT was more common in older (P = 0.003, Fig. 1) and overweight/obese patients (P = 0.029, Fig. 2). Average control rate (controlled HT divided by total HT) was 37/282 (13.12%). This was very poor in the younger age group (35–44 yrs: 4.8%) and older age groups (65–74 yrs: 10.7%; 75+ yrs: 7.5%) and poor in the middle-aged patients (45–54 yrs: 19.4%, 55–64 yrs: 19%).

Differences according to hypertensive status
Hypertensive RA patients, when compared to normotensives, were older [65.35 (57.55–71.22) vs 58.86 (46.82–66) yrs, P < 0.001], more often male (30.5% vs 18.6%, P = 0.015), had higher BMI (28.27 ± 4.98 vs 26.42 ± 4.9, P = 0.001), were more often past cigarette smokers (43.5% vs 26.7%, P = 0.005) and users of medium dose prednisolone (21.5% vs 9.3%, P = 0.004), and were more likely to have IR (44.7% vs 22.3%, P < 0.001): diabetes 8.9% vs 2.5%, P = 0.015; HOMA IR 2.06 (1.27–3.52) vs 1.52 (0.93–2.37), P < 0.001; QUICKI 0.34 (0.32–0.37) vs 0.36 (0.33–0.39), P < 0.001. They also had higher lipid levels [TCHOL (5.54 ± 1.16 vs 5.26 ± 1 mmol/l, P = 0.032) and TG 1.3 (1–1.6) vs 1.1 (0.9–1.5) mmol/l, P = 0.013] and worse renal function (79.13 ± 21.63 vs 88.56 ± 18.76 ml/min/1.73 m2, P < 0.001). There were no significant differences between hypertensive and normotensive RA patients in the levels of current inflammation (ESR, CRP, DAS28), physical dysfunction (HAQ) or the use of NSAIDs, Coxibs, leflunomide or other DMARDs.

Patients with controlled HT compared to those with controlled HT were not significantly older (66.22 ± 10.32 vs 62.7 ± 9.28 yrs, P = 0.06), but had significantly higher BMI (28.97 ± 5.12 vs 26.87 ± 4.83, P = 0.03) and prevalence of CVD (36.8% vs 13.5%, P = 0.007). ACE-I/ARBs were used more frequently in the uncontrolled HT group compared to patients with contained HT (63.9% vs 45.9%, P = 0.049); there were no differences in any of the other classes of anti-hypertensive drugs (Table 2).

Multivariable analysis
A logistic regression model including age, sex, BMI, smoking habit, total cholesterol, TG, IR, full MDRD, use of medium dose prednisolone, NSAIDs/Coxibs, leflunomide and statins was utilized in order to evaluate which factors were independently associated with the presence of HT. Variables that retained significance were age (OR = 1.05, CI: 1.02–1.07, P < 0.001),
BMI (OR = 1.06, CI: 1.003–1.121, P = 0.038) and use of medium dose prednisolone (OR = 2.39, CI: 1.02–5.6, P = 0.045).

A similar approach was used to identify factors that may associate with sub-optimal BP control in RA patients. The basic model included age and sex, the factors that were significant in the univariable analysis earlier (BMI and presence of CVD) and the four main classes of anti-hypertensive drugs (thiazide diuretics, β-blockers, ACE-I and dihydropyridine calcium channel blockers). Increasing BMI (OR = 1.11, CI: 1.02–1.21, P = 0.018) and presence of CVD (OR = 4.01, CI: 1.27–12.69, P = 0.018) retained their significant association with sub-optimal BP control, while no other factors transpired as being significant.

### Discussion

The overall prevalence of HT in this secondary care cohort of RA patients with a mean age of 62 yrs was high at 70%; this is higher even than the highest HT prevalence in England, observed in those over 75 yrs of age in the 2003 National Health Survey for England (NHSE) [29], and appears to be present consistently in both male and female RA patients of all age groups. In our study, assessment of BP was based on the mean of three clinic measurements: this may not be as reliable as 24h BP monitoring, which can rule out cases of white-coat HT [30]. However, the NHSE was also based on three BP measurements to define HT, so the increased prevalence observed in our cohort could not be due to such misclassification. The NHSE was community-based, whereas our cohort was exclusively from secondary care, thus the prevalence of HT in the overall population of RA patients may have been overestimated. In addition, our study did not assess local population controls. It is well-established that the prevalence of HT may vary from locality to locality, with northern UK regions having higher HT rates than regions in the South in both sexes after standardization for age [31]. However, a recent survey from the geographically neighbouring (<6 miles) Wolverhampton, also in the Black Country, estimated the overall prevalence of HT in the adult non-diabetic local population at 28%, virtually identical with the national average [32].

A significant proportion of hypertensive RA patients in this cohort (35% of males and 41% of females) were undiagnosed and thus untreated. Again this is higher than the NHSE (males 6.4–33.1%, females 1.7–33.9%) and is quite disappointing, since RA patients are both regular attendees to hospital clinics and frequent users of primary care services [33], so they have ample opportunity to be monitored for their BP. It is particularly alarming that undiagnosed HT was much commoner in the young RA patients, i.e. those who have most to benefit by early identification and treatment. Even in those patients who were diagnosed and treated for HT, the control rate was significantly lower, at 13.2%, than that observed in general population hypertensive males (21.5%) and females (22.8%) [34]. In the younger patients, this poor control rate was predominantly due to the fact that they remained undiagnosed, whereas in the older patients and those with CVD, it was because desirable targets were not met, probably due to either sub-optimal therapy or lack of adherence [35], both of which may result from the polypharmacy that characterizes many patients with RA [36]. We used a stricter definition of optimal control (<140/90 mmHg for patients without DM or CVD, <130/80 mmHg for those with DM or CVD) compared to that used in the NHSE (<140/90 mmHg, regardless of the presence of DM or CVD), but even applying the same definition, the proportion of RA patients with sub-optimal BP control was considerable. Optimal anti-hypertensive therapy has been associated with 40% mean reductions in stroke incidence, 20% in MI and >50% in heart failure [37] in the general population. Such an additional burden of uncontrolled hypertension may lead to additional strokes and MIs and explain part of the increased cardiovascular morbidity and mortality of RA. Similarly increased HT prevalence and poor control was also a characteristic of patients with type 2DM, but the implementation of aggressive, systematic screening and management in this patient group appears to have improved BP control [38] and overall cardiovascular outcomes [39] in the last decade. The parallels between RA and type II DM, in the context of CVD, have been previously drawn [1] with a suggestion that equally aggressive screening and management programs should be established for RA patients. Regular CVD risk assessment has now been formally proposed by the Arthritis and Musculoskeletal Alliance (ARMA) [40] as one of the standards of care for RA patients, but does not appear to have become common practice yet [40], at least in the UK.

One of the main aims of the present study was to identify factors that may associate with HT in RA: this may be useful both for future pathogenic studies and for the identification of patients that may need to be specifically targeted for screening and intervention in the routine clinical setting. Significant univariable associations were found with previous smoking habit and with insulin resistance, mirroring what has previously been described in the general population [10]. However, these associations did not remain robust in multivariable analysis, which suggested that these associations may have been mediated through increasing BMI. This is in agreement with other studies in the general population, which show that overweight and obesity are important mediators of hypertension, in the context of ex-smokers [41] with insulin resistance [42], and associate with current or future HT and relevant end-organ damage in non-RA populations. Indeed, the only demographic/anthropometric characteristics that remained strongly independently associated with HT in this RA cohort were advancing age and increasing obesity. The latter may be particularly important, as it has recently been suggested that the cut-offs for the classification of RA patients into overweight and obese categories should be lowered to a BMI of 23 and 28, respectively, to reflect their altered body composition [43].
Polypharmacy is a characteristic of many patients with RA [36] and many of the drugs used have the potential to cause major or minor increments in BP levels. In the present study, there was no obvious association between HT and the use of either NSAIDs/Coxibs or relevant DMARDs (leflunomide and cyclosporin). The latter may be simply due to the very small number of patients receiving these drugs in the cohort studied. The former is more difficult to explain, as the evidence for their association with HT is compelling [1, 12]. The exact frequency and dosing regimen prescribed was available, but the exact way these drugs were actually used by patients was not investigated or even recorded in detail in this study: it is well known that adherence to therapy may be low in RA in routine clinical practice, in contradistinction to detailed in this study: it is well known that adherence to therapy may be low in RA in routine clinical practice, in contradistinction to randomized controlled trials which usually associate with high(er) adherence rates [35]. However, the most important reason may be the cross-sectional design of this study, which leads to conclusions that can only serve for hypothesis-generation, than provide proof of causality or directionality of any of the associations found.

A good example of this is the significant association found in this cohort between HT and the use of medium dose (≤7.5 mg/day) of oral prednisolone, but not with any of the laboratory or clinical assessments of current inflammation that were used [erythrocyte sedimentation rate (ESR), CRP or DAS28]. This association could be either due to possible hypertensive effects of steroids, or due to the selection of patients with high inflammatory burden who require steroids for disease control. Indeed, there is conflicting evidence for both in the literature. Studies have correlated raised endogenous cortisol levels and high BP [44], though not in patients with RA. In 129 asthmatic and 66 RA patients, it has been suggested that ‘low’ dose prednisolone (defined to be <20 mg/day) cannot cause significant BP increments [13]. The link between steroid exposure and HT is not well understood [44], but increased peripheral vascular sensitivity to adrenergic agonists [45], increased hepatic production of renin substrate (angiotensinogen) and activation of renal tubular type 1 (mineralocorticoid) receptors by cortisol [46] have all been proposed as potential mechanisms. However, increased levels of systemic inflammation have also been associated with HT in the general population. A prospective cohort study [47] has recently demonstrated that CRP levels associate with future development of HT. Increased inflammatory load has been associated with worse overall and CVD outcomes in RA [1, 48], but not directly with HT. We have not collected ‘historical’ data of the extent of systemic inflammation in relation to when HT developed in the RA patients of this cohort, but it would be interesting to study this in prospective cohorts of inflammatory arthritis, such as the Norfolk Arthritis Register (NOAR) [49] or others.

Finally, the present study aimed to identify factors that may associate with sub-optimal BP control in patients with RA. Robust associations were found between uncontrolled BP, increasing BMI and the presence of CVD, the latter because target BP is lower (<130/80) than general (<140/90). This would suggest that older, overweight RA patients with prevalent CVD should be specifically targeted for aggressive monitoring and treatment of their BP. This may be particularly difficult in these patients: none of the anti-hypertensive medications in the present study appeared to be superior to the others and the increased frequency of usage of ACE-I/ARB in uncontrolled hypertensive RA patients may simply mirror the higher rates of prevalent CVD and DM. It is likely that these patients require combination anti-hypertensive therapy, with very close monitoring due to their polypharmacy [36], comorbidities [50] and adherence characteristics [35].

In conclusion, this cross-sectional study suggests an increased prevalence and low control rates of HT in secondary care RA patients compared to the general population of England. This may be of importance in the context of the increased cardiovascular morbidity and mortality of RA. Systems for surveillance, adequate treatment and ongoing monitoring for these patients need to be put in place both in primary and secondary care. The young, and elderly overweight RA patients should be specifically screened for undiagnosed HT, while those with prevalent CVD need aggressive monitoring and treatment strategies to achieve recommended BP targets [51].

Rheumatology key messages

- Hypertension is highly prevalent in RA patients.
- Hypertension is under-diagnosed mainly in young RA patients and under-treated mainly in the older patients with comorbid cardiovascular disease.
- Aggressive strategies for screening, treatment and monitoring of hypertension are required for the RA population.

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