The Relationship Between Cardiac Conduction Times, Cardiovascular Risk Factors, and Inflammation in Patients with Early Arthritis

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ABSTRACT. ***Objective.*** To investigate the prevalence of conduction disorders in patients with early arthritis and the relationship with inflammation and traditional cardiovascular (CV) risk factors.

Methods. Patients with rheumatoid arthritis (RA) have a 2-fold higher risk of sudden cardiac death, possibly owing to conduction disorders. This increased risk might already be present at the clinical onset of arthritis. Therefore, we assessed electrocardiography, blood pressure, 28-joint Disease Activity Score (DAS28), lipid profile, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level in 480 patients with early arthritis at baseline and after 1 year.

Results. The prevalence of conduction disorders was 12.5%. Conduction times at baseline were not associated with DAS28, ESR, or CRP levels and did not change during antirheumatic treatment. Baseline and the improvement in DAS28 (European League Against Rheumatism response), ESR, and CRP were significantly associated with heart rate, lipid profile, and blood pressure. Elevated total cholesterol and blood pressure were associated with an increased QRS time. The change in heart rate differed 7.3 bpm between patients with the least versus largest DAS improvement.

Conclusion. The prevalence of conduction disorders in patients with early arthritis was 12.5%, which is similar to the general population and was not associated with changes in inflammation markers. However, a high cholesterol was associated with a prolonged QRS time. Therefore, the emphasis of CV risk management in arthritis should not be only on treatment of disease activity but also on traditional CV risk factors. The relationship between the improvement in disease activity and heart rate is remarkable because this could imply a 10-year CV mortality risk difference of 24%. (First Release April 1 2017; J Rheumatol 2017;44:580–6; doi:10.3899/jrheum.161184)

Key Indexing Terms:
RHEUMATOID ARTHRITIS HEART RATE CARDIOVASCULAR RISK
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Rheumatoid arthritis (RA) is associated with increased morbidity and mortality, primarily because of cardiovascular (CV) disease[1]. More than 50% of all premature deaths in RA are attributable to CV disease, in particular ischemic events such as myocardial infarction (MI) and stroke[2,3,4]. This increased CV risk is already present at the clinical onset of RA[5,6,7]. Traditional CV risk factors are well described in patients with established RA and some risk factors are shared, including a higher prevalence of smoking, hypertension, dyslipidemia, and a higher body mass index (BMI) compared with the general population[6,8,9]. However, lipid levels are inversely associated with RA disease activity, meaning that higher inflammation levels are associated with lower cholesterol levels. This is paradoxical, because lower cholesterol levels in these patients with active RA disease are associated with an increased CV risk[10].

Further, patients with RA also have a 2-fold increased risk of sudden cardiac death (SCD), mostly due to cardiac arrhythmias[4,8,11]. Structural changes due to ischemic heart disease, congestive heart failure, and systemic inflammation

all promote this arrhythmic risk. Prolongation of the QT time corrected for heart rate (QTc) is another albeit indirect risk factor for arrhythmia in patients with chronic RA[4,8,12,13]. Heart rate is also associated with CV events and premature death. Bemelmans and Visseren found that an increase in heart rate of 10 bpm is related to 10%–30% more chance for CV events and premature death[14]. Hozawa, *et al* showed that an increase of 5 bpm in heart rate was associated with a 17% increase in the risk of CV mortality[15]. Moreover, drugs used in the treatment of RA such as glucocorticoids and nonsteroidal antiinflammatory drugs may also influence arrhythmic risk[16].

The majority of studies that investigated CV disease in patients with arthritis were performed in patients with established disease[1,17]. Because systemic inflammation is already increased years before the clinical onset of arthritis[18], we assessed patients with early arthritis to determine the prevalence of conduction disorders before the start of antiinflammatory treatment and compared this with the general population, in which the prevalence of conduction disorders ranges between 9.1% and 17.3%[19,20,21,22,23,24]. We also studied the effect of inflammation and traditional CV risk factors on conduction times.

MATERIALS AND METHODS

Study population. The study population comprised a cohort of consecutive patients with early arthritis from the Early Arthritis Cohort at Reade in Amsterdam, the Netherlands. This ongoing cohort includes patients aged over 17 years with at least 2 swollen joints, a symptom duration of < 2 years, and no prior treatment with disease-modifying antirheumatic drugs (DMARD). Diagnosis of RA was according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria for RA[25]. Patients were excluded if they had a diagnosis of crystal arthropathy, spondyloarthritis, osteoarthritis, systemic lupus erythematosus, Sjögren syndrome, or infectious arthritis. Data came from patients included between November 2008 and July 2014. Approval was obtained from the local ethics committee (P0120, Ethics Committee of the Slotervaart Hospital and Reade, Amsterdam, the Netherlands), and all participating patients signed written informed consent, according to the Declaration of Helsinki.

Patient characteristics. At baseline, patients were interviewed to record details about symptom history, clinical characteristics, medication use, and demographics, and underwent a physical examination. Followup data were collected after 52 weeks. Disease activity was measured with the Disease Activity Score of 28 joints (DAS28) and the EULAR response was determined[26]. Physical examination included weight, height, blood pressure, ankle brachial index (ABI), and an electrocardiogram (ECG). Blood pressure was measured manually according to the standard hospital procedures. Blood sample measurements included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and lipid profile, consisting of total cholesterol (TChol), triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL).

Treatment. After the baseline visit, treatment could be initiated with methotrexate (MTX), prednisone, hydroxychloroquine (HCQ), sulfasalazine (SSZ), or a combination of these. Patients who used β-blockers or the calcium channel blockers verapamil or diltiazem, antihypertensive drugs, or statins were excluded from analyses that involved conduction times, blood pressure and cholesterol, respectively.

ECG details. A standard resting 12-lead ECG was annually performed with the Mortara Eli 205C. Heart rate in bpm, QRS, QT, QTc, and PQ time in milliseconds was recorded. All baseline ECG were reviewed by a cardiologist (JD) who was unaware of the patient characteristics. These disorders were noted: atrioventricular block (AV), (incomplete) left bundle branch block (LBBB), (incomplete) right bundle branch block (RBBB), left anterior fascicular block (LAFB), left posterior fascicular block, a prolonged QTc time, and other intraventricular conduction disorders. A prolonged QTc time was defined as a QTc time > 450 ms for men and > 460 ms for women.

Statistical analysis. For descriptive purposes, mean (SD), median [interquartile range (IQR)], or percentages were used, where appropriate. Independent Student t test was used for continuous variables with a normal distribution, and the nonparametric Mann-Whitney U test was used for continuous variables that had a skewed distribution. For dichotomous variables, Pearson's chi-square test was used. Fisher's exact test was used with variables in the cross-table smaller than 5. Linear or logistic regression analysis was performed to assess associations between conduction times and clinical and laboratory data. A p value < 0.05 was considered significant. Data were analyzed with SPSS Version 21.0 (SPSS).

RESULTS

Baseline patient data. The study included 480 consecutive patients with early arthritis. Of them, 406 (85%) fulfilled the ACR/EULAR 2010 criteria for RA. The mean age was 53 years and 28% were men. Further descriptive data are in Table 1. At baseline, 63 patients used a statin and 87 patients used 1 or more antihypertensive drugs; of them, 25 used a β-blocker or calcium channel blocker. During the first year, 359 patients started antirheumatic treatment. Eighty patients used monotherapy MTX, 21 HCQ, 4 SSZ, and 5 prednisone. All other patients used a combination of 2 or more of these drugs.

Baseline ECG and heart rhythm. At baseline, 12.5% of all patients with early arthritis had a conduction disorder according to the cardiologist, of which LAFB (27.8%), incomplete RBBB (22.2%), and first-degree AV block (22.2%) were most often diagnosed (Figure 1). A prolonged QTc time was present in 2 patients (0.4%) and in 1 patient with an LBBB. There was no association between ESR, CRP, or DAS28 and the presence of conduction disorders. Patients with a disorder were, however, generally older than those without (56 vs 52 yrs; p = 0.03). Mean (SD) heart rate was 67 (12) bpm; 451 patients had sinus rhythm and 4 had atrial fibrillation. Heart rate was significantly associated with indices of disease activity (Table 2). QT time was significantly associated with DAS28, ESR, and CRP levels; however, QTc time was not significantly associated (Table 2).

CV risk profile. The mean BMI was 26.4 (4.9) kg/m^2, and 32.1% were current smokers. Being overweight (defined as BMI > 25 kg/m^2) or current smoking were not significantly associated with conduction disorders. Mean (SD) systolic blood pressure in patients who did not use antihypertensives was 134 (20) mmHg and diastolic blood pressure was 80 (12) mmHg. A high systolic (> 140 mmHg) or diastolic (> 90 mmHg) blood pressure was found in 118 patients (30.1%). Of these, 14.6% had a conduction disorder versus 11.6% in

Table 1. Demographics. Values are mean (SD) unless otherwise indicated.

Baseline Characteristics, n = 480	Values
Age, yrs	53 (13.3)
Sex, male, n (%)	135 (28.0)
Symptom duration, mos, median (IQR)	6.0 (3.0–17.8)
VAS pain, median (IQR)	52.0 (28.0–70.0)
DAS28	4.8 (1.4)
ESR, mm/h, median (IQR)	20.0 (9.0–38.0)
CRP, mg/l, median (IQR)	7.5 (2.0–20.0)
RF-positive, n (%)	228 (50.9)
ACPA-positive, n (%)	256 (57.3)
TJC 28, median (IQR)	5.0 (2.0–9.0)
SJC 28, median (IQR)	5.0 (3.0–9.0)
Conduction	
Conduction disorder, n (%)	60 (12.5)
HR, bpm*	66.7 (11.5)
QRS, ms*	93.8 (11.7)
QT, ms*	402.6 (30.7)
QTc, ms*	413.0 (17.2)
PQ, ms*	152.1 (23.7)
Cardiovascular risk factors	
Current smoking, n (%)	154 (32.1)
BMI, kg/m^2	26.4 (4.9)
Systolic BP, mmHg†	134.1 (20.4)
Diastolic BP, mmHg†	80.1 (11.8)
ABI†	1.0 (0.1)
TChol, mmol/l ‡	5.1 (1.0)
Triglycerides, mmol/l, median (IQR)	1.1 (0.8–1.5)
LDL, mmol/l ‡	3.2 (0.9)
HDL, mmol/l ‡	1.4 (0.4)
TChol:HDL ratio ‡	4.0 (1.3)

* Patients who did not use β-blockers, n = 455. † Patients who did not use antihypertensive drugs, n = 360. ‡ Patients who did not use statins, n = 417. ABI: ankle brachial index; ACPA: anticitrullinated protein antibodies; BMI: body mass index; CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; BP: blood pressure; ESR: erythrocyte sedimentation rate; HDL: high-density lipoprotein; HR: heart rate; IQR: interquartile range; LDL: low-density lipoprotein; QTc: QT corrected for heart rate; RF: rheumatoid factor; SJC: swollen joint count; TChol: total cholesterol; TJC: tender joint count; VAS: visual analog scale.

the patients with a normal blood pressure (p = 0.34). Prolongation of the QRS time tended to be related to abnormal blood pressure [B: 2.28 (–0.25 to 4.80), p = 0.08]. However, after correction for baseline demographics [DAS28, sex, age, symptom duration, rheumatoid factor (RF) or anticitrullinated protein antibodies (ACPA) positivity, pain visual analog scale (VAS) and BMI], no significant association was found (p = 0.36). The systolic and diastolic blood pressures were associated with DAS28, ESR, and CRP levels (Supplementary Table 1, available with the online version of this article). The mean (SD) ABI was 1.0 (0.1) and 16.0% of the patients had an ABI of < 0.9, and showed no association with conduction disorders.

Of the 417 patients without a statin, 9.1% had TChol of more than 6.5 mmol/l. TChol was not associated with the presence of a conduction disorder. Neither was the TChol:HDL ratio, of which the mean (SD) was 4.0 (1.3). Patients with a high TChol (> 6.5 mmol/l), without statin or β-blocker, showed an association with QRS time. Patients with a high TChol had a mean QRS time of 97.8 (16.9), vs 93.4 (10.9) in the patients with normal cholesterol (p = 0.03). After correction for baseline demographics (DAS28, sex, age, symptom duration, RF, or ACPA positivity, VAS pain, and BMI) the same results were obtained [B 5.38 (0.76–10.00), p = 0.02]. The same results were found when the patients with an RBBB were excluded (p = 0.01). TChol, HDL, and TChol:HDL ratio were significantly associated with disease activity (Supplementary Table 1, available with the online version of this article).

Baseline versus Year 1 disease characteristics. An ECG was done of 244 patients after 1 year. There were 236 patients who did not have a complete visit after 1 year. Reasons were remission (3), the patient moved (8), the patient had a different diagnosis (12), the patient did not want to participate anymore (27), death (2), the patient had a visit without ECG (119), and unknown (65). Baseline characteristics of the 244 patients with 1-year followup data compared with patients who did not have a complete visit after 1 year were comparable except for a small difference in DAS28 (SD) at baseline, 4.9 (1.3) vs 4.6 (1.5).

Of the 244 patients, 39 used a statin at baseline and/or after 1 year, 52 used antihypertensive drugs, and 16 used a β-blocker. After 1 year, DAS28, ESR, and CRP decreased significantly (Table 3). Regarding EULAR response, of the 244 patients, 58.9% had a good response, 24.9% had a moderate one, and 16.2% had none.

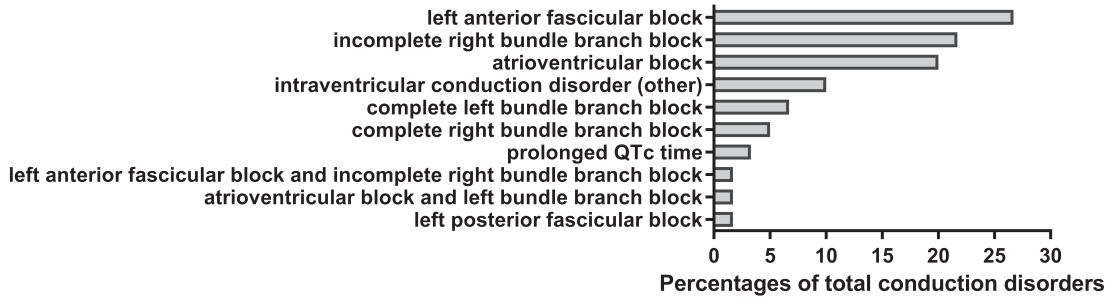

Figure 1. Distribution of total conduction disorders at baseline, n = 60. QTc: QT time corrected for heart rate.

Table 2. Association of heart rate and conduction times with disease activity at baseline in patients who did not use β-blockers (n = 455). All data are corrected for sex, age, symptom duration, RF or ACPA positivity, pain visual analog scale, and body mass index.

	DAS28 Levels		ESR Levels		CRP Levels	
	B (CI)	p	B (CI)	p	B (CI)	p
HR, bpm	2.268 (1.222–3.331)	< 0.001	0.210 (0.151–0.268)	< 0.001	0.207 (0.152–0.261)	< 0.001
QRS, ms	–1.078 (–2.217 to 0.060)	0.063	–0.038 (–0.105 to 0.028)	0.259	–0.028 (–0.091 to 0.036)	0.392
QT, ms	–4.207 (–6.994 to –1.420)	0.003	–0.372 (–0.531 to –0.213)	< 0.001	–0.380 (–0.530 to –0.231)	< 0.001
QTc, ms	0.657 (–0.973 to 2.288)	0.428	0.033 (–0.062 to 0.128)	0.493	–0.007 (–0.097 to 0.084)	0.886
PR, ms	–1.403 (–3.669 to 0.863)	0.224	–0.135 (–0.266 to 0.004)	0.043	–0.117 (–0.242 to 0.009)	0.069

B: beta; CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; HR: heart rate; QTc: QT corrected for heart rate; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies.

Table 3. Change in disease activity and conduction times in patients with 1-year followup data (n = 244). Data are mean (SD) unless otherwise indicated.

Disease Activity	T = 0	T = 1	p
CRP, mg/l, median (IQR)	9.0 (2.0–20.0)	3.0 (1.0–6.0)	< 0.001
ESR, mm/h, median (IQR)	22.0 (10.0–38.0)	10.0 (4.0–19.0)	< 0.001
DAS28	4.9 (1.3)	2.8 (1.2)	< 0.001
TJC 28, median (IQR)	5.0 (3.0–10.0)	1.0 (0.0–3.0)	< 0.001
SJC 28, median (IQR)	6.0 (4.0–9.0)	0.0 (0.0–2.0)	< 0.001
Conduction*			
HR, bpm	66.4 (11.5)	67.0 (10.6)	0.246
QRS, ms	94.2 (10.1)	94.8 (9.8)	0.219
QT, ms	405.2 (30.6)	401.0 (28.9)	0.005
QTc, ms	414.5 (17.6)	414.5 (19.2)	0.732
PQ, ms	149.0 (24.3)	150.0 (23.4)	0.170

* In patients who did not use β-blockers (n = 227). CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; HR: heart rate; IQR: interquartile range; QTc: QT corrected for heart rate; SJC: swollen joint count; TJC: tender joint count.

Year 1 ECG and heart rhythm. Paired t tests showed no significant alterations in conduction times after 1 year of treatment (Table 3). There were no significant differences in conduction times between patients with a good, moderate, or no EULAR response.

A prolonged QTc time was seen in 5 patients (2.0%) and in 1 patient with an intraventricular disorder. Of the 5 patients, 2 were currently using a β-blocker. None of these patients had a prolonged QTc time at baseline. Patients with a prolonged QTc time had a higher mean DAS than patients without prolonged QTc [3.4 (0.6) vs 2.8 (1.2), p = 0.30]. Three patients had a moderate EULAR response, 1 had a good response, and 1 had none.

There was an association between disease improvement and decrease in heart rate. Patients in the quartile with the least DAS improvement or DAS worsening had a mean increase in heart rate over 1 year of 3.8 bpm (p = 0.02). Patients in the quartile with the largest DAS improvement had a decrease in heart rate of –3.5 bpm (p = 0.01). The difference in heart rate change between the 4 groups was statistically significant (p < 0.01; Figure 2A). When patients were divided by EULAR response, patients with a good EULAR response had a mean increase in heart rate of 0.7 bpm, versus a decrease of –1.6 bpm in moderate responders and an increase of 4.9 bpm in those with no response (Figure 2B). The difference of increase in heart rate of 4.2 bpm between the good and nonresponders was significant (p = 0.02). There was no significant difference between good and moderate EULAR responders.

Year 1 CV risk factors. The mean BMI increased to 26.8 (5.1) kg/m^2. Mean (SD) systolic and diastolic blood pressure at the 1-year visit were 132 (16) mmHg and 78 (11) mmHg, respectively. In 13.8%, the blood pressure was elevated. BMI and blood pressure were not associated with conduction times. At 1 year, the mean (SD) TChol increased significantly to 5.4 (1.0) mmol/l, and 8.1% of the patients had a TChol > 6.5. Mean HDL levels increased to 1.6 (0.5) mmol/l. The TChol and HDL increases were associated with improvement in DAS28, ESR, and CRP levels, but not with conduction times. The TChol:HDL ratio decreased from 4.1 (1.2) to 3.6 (1.1); p < 0.01 (Supplementary Table 2, available with the online version of this article).

DISCUSSION

In DMARD-naive patients with early arthritis, the prevalence of conduction disorders was 12.5%, with LAFB, incomplete

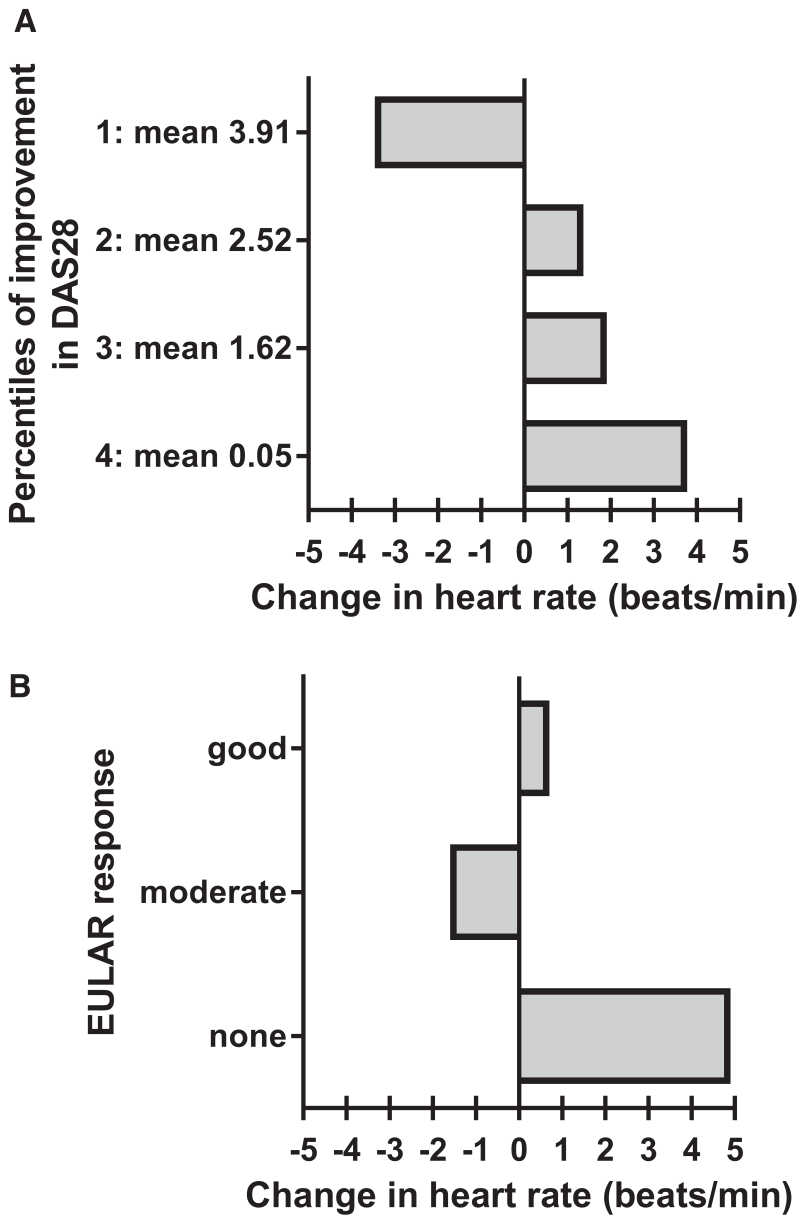

Figure 2. A. Percentiles of improvement in DAS28 and change in bpm, Year 1 minus baseline. B. EULAR response and change in bpm, Year 1 minus baseline. DAS28: 28-joint Disease Activity Score; EULAR: European League Against Rheumatism.

RBBB, and AV block as the most common disorders. This prevalence appears to be similar to the general population, in which the prevalence ranges between 9.1% and 17.3%[19,20,21,22,23,24]. Previous literature showed that patients with RA had a significantly higher risk of both hospitalized and unrecognized MI, prior to the clinical onset of RA. However, the risk of SCD at the time of the clinical onset of RA is not known[27]. The main risk factors for SCD are arrhythmias and QTc interval prolongation. In patients with established arthritis, a prolonged QTc was demonstrated[8,12,13]. In our study, overall there was no increased mean QTc time, and at baseline the QTc time was prolonged in only 0.4% of the patients, a level comparable to the general population[8,19]. Unfortunately, the 2 patients with a prolonged QTc time at baseline did not have an ECG after 1 year of treatment. Five patients (2.0%) developed a prolonged QTc time after 1 year. Of those patients, only 1 reached a good EULAR response.

Multiple factors affect the functioning of ion channels in myocardial cells and therefore conduction times: genetic abnormality, a cardiac disease (such as MI, owing to transmural ischemia), electrolyte levels, and some medications[28]. Another important factor is reactive oxygen species, which affects the ion channels on the cardiac myocytes and is stimu-

lated by cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6)[29]. However, in our study conduction times were not associated with disease and inflammation markers (DAS28, EULAR response, ESR, or CRP levels). Although disease activity improved during 1 year of antiinflammatory treatment, this did not translate into a significant effect on conduction times. Because inflammation is considered the major pathophysiological link between arthritis and conduction disorders, the studied population might explain this difference. Patients with early arthritis have been exposed to inflammatory activity for a shorter period of time, which in our study was a median symptom duration of 6 months, compared with established chronic arthritis. However, it could also be that patients with established RA have prolonged exposure to more traditional CV risk factors, particularly dyslipidemia, which is already present in patients with early arthritis[30,31]. This is important because of the association between traditional CV risk factors and conduction disorders; we found that a high total cholesterol at baseline was associated with a prolonged QRS time. However, this association disappeared after 1 year of treatment. After correction for RBBB, because RBBB can be physiologic, the same results were obtained. However, Kurl, *et al* found that QRS duration is an independent predictor of the risk of SCD, where each 10-ms increase in QRS duration was associated with a 27% higher risk for SCD[32]. In our present study this would mean that the 4.4-ms increased mean in QRS time in the patients with a high TChol resembles a 11.9% higher risk for SCD, compared with the patients with a normal TChol. It has been suggested that TNF-α, interferon-γ, and IL-1 can stimulate the production of ceramide. Ceramide are lipid molecules that partly consist of fatty acids; they downregulate ion channels in cardiac myocytes and can affect conduction times[29]. Therefore, both CV risk management as well as disease control are important and should be performed in all patients with arthritis[33]. Our study strengthens the notion that antiinflammatory treatment, in an early stage of the disease, leads to a significant improvement in several important CV risk factors, including the TChol:HDL ratio and blood pressure[34,35]. Interestingly, patients with early arthritis with lower inflammation markers had a lower heart rate compared with those with high inflammation markers. In the general population, heart rate is positively associated with CRP, as demonstrated by Nanchen, *et al*, who found, in 4084 adults with a known CV risk factor, that an increased heart rate was associated with systemic inflammation[36]. In patients with RA, the association between inflammation and heart rate has not been previously described, particularly not the improvement in inflammation and the change in heart rate. In our study, every 10-point increase in CRP or ESR was associated with an increase in heart rate of 2 bpm, which remained after correction for the VAS pain. This could imply an increased CV mortality of about 7%[14,15]. This relationship between disease activity and heart rate is remarkable because it would imply a 10-year CV risk difference of 24% between no/least improvement and substantial improvement in DAS28 score[14,15]. Patients with higher inflammation markers also had higher blood pressure, of which every 10-point increase in CRP or ESR was associated with an increase in systolic blood pressure of 1.7 mmHg. However, according to Ward, *et al*, this increase in CV risk has less clinical relevance[37].

Our present study shows that patients with early arthritis have the same prevalence of conduction disorders as the general population before antirheumatic treatment. Hence, in this population a mandatory screening ECG appears unnecessary. In contrast, in patients with chronic arthritis a prolonged QTc time is proven, and therefore a standard ECG could be considered in established arthritis[1,4,8,12,13]. For further research it would be interesting to match the patients with a healthy control group and repeat the ECG several years after rheumatic treatment, to investigate whether longer exposure to systemic inflammation increases conduction times and hence, conduction disorders.

Strengths of this study are the large number of consecutive patients and that the population reflects a heterogeneous population from a tertiary center. A limitation is that in addition to β-blockers and calcium channel blockers (verapamil and diltiazem), there are other medications that could affect conduction times (such as antibiotics, antipsychotics, or antidepressants). Unfortunately, no data were available on these medications.

In early arthritis the prevalence of conduction disorders is comparable to the general population. However, the prevalence of traditional CV risk factors was increased in patients with a higher inflammatory load and the factors were associated with an increased QRS time. CV risk factors improved after inflammatory treatment. In particular, the difference in pulse rates between patients with persistent inflammation and patients with low disease activity or remission is remarkable. Therefore, the focus in patients with early arthritis should be on both CV risk management and optimizing antiinflammatory treatment.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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