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Interleukin-17 as a novel predictor of vascular function in rheumatoid arthritis

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Abstract

Objectives—Rheumatoid arthritis (RA) is associated with enhanced cardiovascular (CV) risk and subclinical vascular disease. The proinflammatory milieu has been linked to premature atherosclerosis and endothelial dysfunction in RA. While IL-17 is considered pathogenic in RA, its role in determining vascular dysfunction in this disease has not been systematically assessed. We analyzed candidate variables that could determine endothelial function in various vascular territories in a cohort of RA patients on biologic therapy, with minimal traditional CV risk factors and low disease activity score.

Methods—RA patients (n=51) on stable biologic therapy underwent measurement of conduit artery endothelial function by brachial artery flow-mediated dilatation (FMD); arterial compliance by pulse wave velocity (PWV) assessment; and endothelium-dependent microvascular testing with Endo-PAT2000 device to assess reactive hyperemia index (RHI). IL-17 was quantified by ELISA and disease activity was assessed by DAS-28.

Results—IL-17 and high sensitivity CRP were the main determinants of lower RHI in univariate (p=0.004, <0.001) and multivariate (p=0.004, <0.0001) analysis, respectively. Traditional and non-traditional CV risk variables determined PWV, with a significant positive association with IL-17 in univariate and multivariate analysis (p=0.02, 0.01, respectively). In contrast, conduit endothelial function was mainly determined by rheumatoid factor titers (p=0.003). Anti-CCP titers and disease activity did not determine vascular function.

Conclusion—In RA patients treated with biologics, IL-17 is a main predictor of microvascular function and arterial compliance. This study suggests IL-17 may play a significant role in development of endothelial dysfunction and CVD in RA.

Introduction

The paradigm of chronic inflammation as a driver of atherosclerotic disease is widely accepted[1]. Endothelial damage, vascular noncompliance, and plaque development are observed in chronic inflammatory conditions, predisposing to accelerated vascular disease[2]. Indeed, rheumatoid arthritis (RA) is associated with a 50% higher risk of death from cardiovascular disease (CVD) compared with healthy controls[3]; a risk comparable to that observed in type 2 diabetes mellitus[4]. Furthermore, RA is considered an independent risk

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factor for multi-vessel coronary artery disease[5], and evidence based-guidelines for the amelioration of CV risk in RA have been recently published[6].

In addition to overt CV events, RA patients (particularly those with a positive rheumatoid factor (RF)) display increased prevalence of subclinical atherosclerosis. This has been reported in patients on long term RA treatment[7] and in those with low disease activity and free of traditional CV risk factors[8]. Furthermore, endothelial dysfunction, a phenomenon that predicts future CVD [9], is observed early on during the course of the disease [10, 11].

The striking increases in CVD-associated morbidity and mortality in RA cannot be fully explained by Framingham risk factors. Rather, inflammation and metabolic disturbances present in RA likely contribute to accelerated atherosclerosis. However, it is unclear which factors play primary predisposing roles in RA-associated CVD, and whether the function of the various arterial territories in RA is modulated by the same predisposing factors. Indeed, variations among various vascular territories in their responsiveness to differing stimuli (e.g. shear-stress, agonists including acetylcholine and bradykinin) and their relative dependence on nitric oxide versus other endogenous vasodilators are well known. Therefore, it is conceivable that a conduit vessel such as the brachial artery (3–6 mm) may respond in a differing or discordant fashion to various inflammatory stimuli present in RA, when compared to a resistance arteriole (<400 nm)[12–14].

Proinflammatory mediators such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) are increased in RA, where they play a pathogenic role. These cytokines may promote CV damage in RA, even after controlling for other CV risk factors[15, 16]. While previous evidence supports their role in vascular damage, it is unclear if these cytokines represent the primary vascular dysfunction determinants in RA. Recent interest has focused on the role of interleukin-17 (IL-17) in RA pathogenesis[17], but little is known regarding its role in vascular disease development in this condition. IL-17 may accelerate myocardial fibrosis and promote atherosclerosis in non-RA animal models[18, 19], and elevated circulating IL-17 is detected in patients with acute coronary syndromes[20]. However, association studies between IL-17 levels and vascular function in RA are lacking.

Endothelial dysfunction, manifested as loss of normal vasoreactivity, is an early event in atherogenesis. In the presence of vascular risk factors, endothelial cells undergo phenotypic changes leading to decreased nitric oxide bioactivity, vasoconstriction, inflammation and thrombosis[2]. Individuals with abnormal vasodilator function have increased CV event rates[3]. CV risk can be assessed early on through functional measures of endothelial function, including arterial compliance, flow mediated dilatation (FMD) of large and medium vessels (conduit function), and microvascular endothelial function. These tests, which represent validated surrogate markers of vascular risk in diverse patient populations, are abnormal in RA[3, 8, 21, 22].

In this study, we assessed whether various traditional and nontraditional CV risk factors are associated with microvascular and conduit endothelial function and with arterial compliance in a cohort of RA patients treated with biologic agents, with low disease activity and low burden of traditional CV risk factors. We also examined if various vascular territories differ in the factors that determine their function in RA.

Methods

Subjects

The University of Michigan IRB approved this study, which complied with the Declaration of Helsinki. RA patients who met the 1987 American College of Rheumatology diagnostic

criteria [23] were recruited from University of Michigan Rheumatology Clinic and by advertisement. For inclusion, patients had to be on stable doses of DMARDS and/or biologics for at least 3 months prior to enrollment. Patients were excluded if they were pregnant or breastfeeding, smokers, had diabetes mellitus, a history of congestive heart failure, acute infection, or significant liver or renal disease. Patients on any lipid lowering drugs were required to be on stable doses of the medication for at least 6 months.

Vascular function measurements

Procedures were performed at the University of Michigan Research Vascular Laboratory in a temperature controlled room, after patients fasted and held vasoactive drugs for at least 12 hours.

Pulse Wave Analyses and Arterial Pulse Wave Velocity (PWV)—After subjects rested supine for 10 minutes, applanation tonometry was measured once at the right carotid and femoral arteries for 10 seconds each, following operational guidelines of the Sphygmocor device (Atcor, Itasca, IL). Three-lead ECG recordings were obtained simultaneously with the tonometry to calculate aortic PWV (a direct measure of arterial stiffness). Quality index was 80%.

Concomitant Microvascular and Conduit Brachial Endothelial Function—Simultaneous measurement of conduit artery endothelial-dependent vasodilatation by brachial FMD and of microvascular endothelial-dependent vasodilatation by the EndoPat-2000 device (Itamar, Caesarea, Israel) was performed on the dominant arm as described by us[24]. Ten minutes after PWV determination, patients were connected to the EndoPat-2000 device finger probes and to a 3 lead ECG system to perform ECG-triggered B-mode brachial artery measurements by ultrasound.

Basal resting finger peripheral arterial tonometry (PAT) was recorded by Endopat2000 probes on one finger from each hand. During this period, basal brachial artery diameter was recorded by dominant arm ultrasound for at least 10 seconds for FMD measurement. A dominant arm blood pressure (BP) cuff was inflated to 50 mm Hg above systolic BP for 5 minutes. Upon rapid cuff deflation, reactive hyperemia (RH) was created and RH-PAT recorded in the ipsilateral dominant hand finger for 5 minutes. The device's computer compared 120 seconds of baseline mean PAT to RH-PAT, defined as mean PAT from 60–120 seconds post cuff release on dominant arm. Readings were standardized to contralateral hand PAT during same periods, providing RH-PAT index (RI).

Concomitantly, at 50–90 seconds post BP cuff release during RH, brachial artery diameter (BAD) was recorded to calculate brachial artery FMD, in accord with guidelines[25] and as reported by us[2627]. A Terason2000 ultrasound system (Burlington, MA) with a 10.0 mHz linear array transducer was used. After upper arm cuff was inflated, BAD was imaged longitudinally by B-mode imaging with the transducer 2–10 cm above the antecubital crease on dominant arm. Images were acquired at the end of each R wave on the ECG by a triggered event. Endothelial-dependent FMD was defined as: percent change in BAD from baseline in response to RH (measured from media-adventia line (M-line) to M-line). FMD = [(RH BAD − basal BAD)/basal BAD] × 100 (in %). An image analysis was performed with software from Medical Imaging Applications, Inc (Coralville, IA).

Determination of serum IL-17

High Binding EIA/RIA 96-well plates were coated with anti-human IL-17 in carbonate buffer, incubated at 4° overnight. Standards were prepared from recombinant human IL-17 (Ebioscience). Serum samples and standards were added to wells, incubated for 2 hours at

room temperature, followed by addition of biotinylated anti-IL17 (Ebioscience) and streptavidin HRP (Biolegend) and incubation for 2 hours. After sample color change with TMB reagent (BD Biosciences) addition (BD Biosciences), absorbance was quantified on a microplate reader at 450 nm wavelength.

Other laboratory measurements

Lipid profile, high sensitivity C-reactive protein (hsCRP), insulin and glucose were measured in the Michigan Diabetes Research and Training Center. RF, anti-CCP antibodies, erythrocyte sedimentation rate (ESR) and complete blood count were measured at University of Michigan Central Laboratories.

Insulin resistance assessment

The Homeostatic Model Assessment (HOMA1-IR) was used to assess insulin resistance[28] using the formula: HOMA1-IR = (Fasting plasma Insulin (μU/ml) × fasting plasma glucose mg/dl))/405.

Statistical Analysis

Measures of vascular endothelial function were analyzed as dependent variables. Continuous variables were summarized using means and standard deviations and categorical variables by counts and percentages. A log transformation was applied to variables with highly skewed values (hsCRP, ESR, anti-CCP, IL-17 and RF). For univariate analyses, one-way analysis of variance (ANOVA) or linear regression methods were used to evaluate the effect of each predictor on vascular function. Forward stepwise multivariate regression analyses were performed to identify the effect of predictors in the presence of other factors associated with vascular dysfunction. Variables with $p < 0.15$ in the univariate analyses were included in the multivariate analyses. The above analyses were repeated for the 34 subjects with detectable levels of IL-17. A $p \leq 0.05$ was considered significant. Procedures were done in SAS 9.2.

Results

Demographic and clinical characteristics of RA patients

Fifty-one patients treated with stable doses of biologic medications, with or without concomitant DMARDs, were analyzed. Of these, 3 (5.88%) were treated with abatacept, 15 (29.4%) with adalimumab, 24 (47.1%) with etanercept, 3(5.88%) with infliximab and 6 (11.76%) with rituximab. Thirty-two of these patients (63 %) were also on DMARDs: 4 (12.5%) leflunomide, 26 (81.25%) methotrexate, and 2 (6.25%) sulfasalazine. Patients were on prednisone (%; mean dose(range).

Demographics and information regarding disease duration and activity and autoantibodies is included in Table 1. Clinical characteristics, including traditional CVD risk factors, are shown in Table 2.

Factors associated with vascular function in RA

Table 3 shows the association between vascular measurements and clinical and laboratory features among patients. Patients who were anti-CCP positive vs negative had higher IL-17 levels, (30 vs 19 pg/mL, p=0.01). Males had higher BAD (p=0.003), hematocrit (p=0.003) and diastolic BP (p=0.049) compared to females.

Microvascular endothelial function (RHI) was significantly negatively associated with IL-17 and hsCRP levels in univariate and multivariate analysis (Tables 3 and 4). The negative

association between IL-17 and RHI persisted when only those subjects with detectable IL-17 levels were included in the analysis (n=34, p=0.03). Other variables that negatively associated with RHI were also linked to inflammation and included ESR, triglycerides, white cell count and RF levels, but these associations did not persist in multivariate analysis. There were no associations between traditional CV risk factors and RHI. Patients with undetectable IL-17 levels had a significantly higher RHI than those with measurable IL-17 levels (2.4 vs 2.0, p=0.03). The length of RA disease duration was significantly lower among patients with undetectable IL-17 (10 vs 19 years, p=0.01).

Regarding PWV, univariate analysis showed a positive association with both traditional (age, heart rate, SBP) and nontraditional risk factors (IL-17, ESR and white cell count) (Table 3). In multivariate analysis, heart rate and IL-17 continued to significantly predict PWV (p=0.01, p=0.004 respectively) (Table 4). The positive association between IL-17 and PWV also persisted when only subjects with detectable levels of IL-17 were included in the analysis (n=34, p=.004)

In analysis of conduit FMD, RF levels negatively correlated with FMD in univariate and multivariate analysis (Tables 3 and 4). No other traditional or nontraditional CV risk factors predicted conduit FMD.

No significant associations were observed between the various vascular function tests and DAS-28, HOMA, anti-CCP, insulin levels, RA disease duration, serum lipids, specific DMARDs or biologics or statin therapy (not shown).

Discussion

Increased CVD cause significant excess mortality in RA, and exists independently of traditional Framingham risk factors[29, 30,31]. Increased subclinical atherosclerosis prevalence and severity are found in poorly controlled RA patients[5, 32, 33] but also in those on long-term DMARD treatment[7].

Despite widespread use of biologics alone and in combination with DMARDs, there is no evidence that CV-related morbidity and mortality rates in RA in the United States are decreasing. In fact, the mortality gap between RA and the general population appears to be widening[34,35,36]. While improvements in both endothelial function and PWV, as well as decreases in inflammatory markers and insulin resistance, have been reported in RA patients treated with TNF inhibitors, it is not clear that these benefits are sustained or contribute to significant decreases in CV events and mortality[21, 37–40]. Furthermore, while a link between proinflammatory responses and vascular damage has been proposed, various conflicting results exist with regards to the association between specific inflammatory markers and endothelial dysfunction at various vascular territories, as well as during various stages of the natural history of plaque development and acute coronary syndromes.

In this study of patients on biologic agents with well controlled RA and low Framingham CV risk factors, we investigated the association of inflammatory markers and traditional CV risk factors to FMD, a measure of conduit artery vasodilator function; to RH, a measure of microvascular vasodilator function; and to PWV, a measure of arterial stiffness. Abnormalities in these measures have been linked to enhanced CV risk in various patient populations[41, 42].

Our results demonstrate that IL-17 is independently negatively associated with both microvascular function and large vessel arterial compliance in RA patients treated with biologics, primarily anti-TNF agents. These observations may have clinical relevance because endothelial dysfunction is strongly linked to pathogenesis and clinical expression of

future vascular damage. Further, patients with non-detectable IL-17 had significantly higher microvascular function. In addition, we have reproduced what other groups have observed in other patient populations, with variations in determinants of vascular function in different vascular territories[43]. Indeed, the only determinants of conduit FMD were RF levels, while IL-17 and inflammatory markers associated with lower RHI and higher PWV.

These findings support the hypothesis that systemic inflammation represents a mechanistic link between risk factors and vascular dysfunction in both the microvasculature and large vessel territories. RH is a complex response[44]. and the association we observed between IL-17 and other inflammatory markers with lower RHI may reflect endothelial dysfunction in the microvasculature. Furthermore, reports that changes in the microcirculation may be important predictors of CVD in women[44] can be extrapolated to a disease with female predominance like RA. As such, our results indicate a potentially important role for IL-17 and the inflammatory burden in CV prognosis. RA is associated with impaired large, muscular artery function, resulting in arterial stiffness [45]. The latter correlates with risk of morbidity and mortality due to CVD[46, 47,] While arterial stiffness has been linked to IL-6 and TNF[48], our study is, to our knowledge, the first report of associations between IL-17 with PWV.

While IL-17 may play crucial in RA pathogenesis, its potential role in endothelial dysfunction and increased CVD in this disease remains unclear. Evidence from atherosclerosis animal models supports a role for this cytokine in plaque formation. IL-17A is proatherogenic by promoting monocyte/macrophage recruitment into the aortic wall[49]. There is constitutive expression of IL-17E by resident plaque cells, and IL-17-expressing B cells and neutrophils in advanced and complicated plaques, indicating a potentially complex contribution of IL-17 family cytokines in atherosclerosis [50]. Elevated plasma IL-17 levels in patients with acute myocardial infarction have been observed[51] and IL-17 induces an inflammatory phenotype on vascular smooth muscle cells[52]. IL-17 is also critical for the maintenance of angiotensin II-induced hypertension and vascular dysfunction, adding another link between the inflammatory milieu in RA and traditional CV risk factors [53]. Until more evidence supports a mechanistic link between IL-17 and CVD in RA, however, we cannot exclude that this cytokine could be merely a marker for the presence of other factors that account mechanistically for the observed variation in vascular function. How TNF, IL-6 and IL-17 interact to enhance CV risk in RA also deserves further investigation. Further, as there is evidence that vascular dysfunction in RA may not be improved with short-term treatment with conventional DMARDS[54], it will be interesting to assess how targeted anti-IL-17 therapies modify vascular function.

A proportion of RA patients in this study had undetectable IL-17 levels. This supports previous reports that show undetectable serum IL-17 in a subset of RA patients and healthy controls[55, 56] Undetectable Il-17 in our population could reflect various factors including downregulation secondary to biologics and/or DMARDs or genetic polymorphisms[57]. Whether this subset of patients are relatively protected from vascular dysfunction warrants future investigation.

Importantly, nn this RA cohort with well controlled disease, there were no associations between vascular abnormalities and RA disease activity, supporting previous findings that effective RA treatment may lead to arterial stiffness improvements[21].

The present study has some limitations. While the association between RA-induced systemic inflammation and impaired vascular function remains significant adjusted for other factors, only prospective studies will have the potential to discern a causal relationship. The studied cohort was predominantly white, and findings may not apply to other ethnic groups. Several

of the factors showing correlation may be inter-correlated and finding independent effects can be difficult even after multivariate adjustment. Furthermore, the patient cohort examined in this study represents a subgroup of RA patients treated with biologic agents. The population is therefore not representative of RA patients as a whole, or other RA subgroups such as TNF-naïve patients. Future studies should assess if IL-17 continues to be an important determinant of vascular function in other RA groups including patients with more active disease or those with recent diagnosis.

Finally, we did not observe associations between levels of antibodies to CCP with any of the vascular markers studied, while there was significant negative association between RF and conduit vascular function. This supports evidence from a large population-based study demonstrating association between CVD and the presence of RF but not anti-CCP[59], but does not support the findings of extensive subclinical atherosclerosis observed in anti-CCP-positive vs negative patients with RA[60], or the observed independent association of anti-CCP antibodies with the development of ischemic heart disease[61]. These conflicting results from various studies of autoantibodies and CVD in RA[62, 63] indicate that the exact role played by autoantibodies in accelerated atherosclerosis in RA is still undefined.

Overall, the results of this study suggest that factors predicting conduit vascular function in RA patients differ from those associated with large vessel arterial compliance and microvascular function. Our findings support IL-17 as a potential marker of vascular risk in RA in small and large vascular territories and a causative association between this cytokine and CVD. Furthermore, our results indicate that, even in patients with well controlled RA on stable doses of biologics, factors inherent to the disease including RF, IL-17 and inflammatory markers, continue to be the main determinants of vascular function. Indeed, this study supports growing evidence that, although RA treatment has improved over time, the inflammatory milieu may continue to determine vascular function even in patients with well controlled disease and low traditional CV risk factors. Whether IL-17 represents an attractive therapeutic target for both RA disease manifestations and for possible amelioration of CV risk warrants further examination.

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Table 1

Demographic and clinical features of study participants

	RA cohort N=51
	n(%)
Females	43(84.3)
Race	
Caucasian	45(88.2)
African American	4(7.8)
Asian	2(3.9)
Ethnicity(%Hispanic)	5(9.8)
	Mean(SD)
Age (years)	56.1(10.9)
Anti-CCP (U/mL)	54.5(57.2)
RF (IU/mL)	188.8(420.0)
DAS-28	3.2(1.6)
Years since RA diagnosis	16.1(11.9)
SBP (mmHg)	136.4(17.2)
DBP (mmHg)	81.1(9.8)
BMI	28.9(6.3)

CCP: cyclic citrullinated peptide; RF; rheumatoid factor; SBP; systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; SD: standard deviation

Table 2

Laboratory markers of cardiovascular risk and inflammation

	RA cohort N=51
	Mean(SD)
ESR(mm/hr)	17.0(17.2)
hsCRP(mg/dL)	5.2(6.4)
IL-17 (pg/mL)	2611.0(6007.7)
Total Cholesterol (mg/dL)	190.7(41.4)
Triglycerides (mg/dL)	110.5(62.2)
HDL (mg/dL)	65.6(17.4)
LDL (mg/dL)	111.5(33.9)
Fasting serum insulin(μU/ml)	19.7(11.7)
Fasting glucose(mg/dL)	93.1(10.3)
HOMA1-IR (mg/dl × μU/ml)	4.5(2.6)

ESR: erythrocyte sedimentation rate; hsCRP: high sensitivity CRP; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA: homeostatic model assessment.

Table 3

Univariate analysis of determinants of vascular function in RA

	RHI (β, p)	FMD (β, p)	Aortic PWV (β, p)
RA cohort n=51	ESR(−0.34,0.001) hsCRP(−0.38,<0.0001) IL-17(−0.07,0.004) RF (−0.13,0.03) Trig(0.003,0.04) WBC(−0.1,0.04)	RF(−1.29,0.003)	Age(0.12,<0.0001) ESR(1.13,0.01) HR(0.07,0.01) IL-17(0.24,0.02) SBP(0.07,0.0001) WBC(0.45,0.02)

RHI-reactive hyperemia index; FMD=flow mediated dilatation; PWV=pulse wave velocity; ESR=erythrocyte sedimentation rate; hsCRP=high sensitivity C-reactive protein; RF=rheumatoid factor; Trig=triglycerides; WBC=white cell count; HR=heart rate; SBP=systolic blood pressure

Table 4

Multivariate analysis of determinants of vascular function in RA

	RHI (β, p)	FMD (p,β)	Aortic PWV (p,β)
RA cohort n=51	hsCRP(−0.35,<0.0001) IL-17(−0.06,0.004)	RF(−1.24,0.003)	HR(0.20,0.001) IL-17(0.06,0.01)

RHI-reactive hyperemia index; FMD=flow mediated dilatation; PWV=pulse wave velocity; hsCRP=high sensitivity C-reactive protein; RF=rheumatoid factor; HR=heart rate;