Brachiocephalic Vessel Duplex Sonography in Rheumatoid Arthritis Patients

Evija Stumbra-Stumberga, Helena Mikazane

Rīga Stradiņš University, Department of Internal Medicine, Latvia
evijastumbra@inbox.lv

Abstract

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting 1% of general adult population. The systemic inflammation associated with novel risk factors such as disease activity, and seropositivity could contribute to accelerated atherosclerosis. The latter correlates with a risk of morbidity and mortality due to cardiovascular diseases (CVD).

Therefore, the article reflects on the examination of brachiocephalic vessels of rheumatoid arthritis and control group patients with duplex ultrasound and focuses on the methods that are used for screening subclinical and already proved atherosclerosis. 20 patients with confirmed RA and 27 sex and age matched healthy controls (aged 25–82) were recruited for prognostication and prediction of real cardiovascular risks for these patients. Carotid arteries haemodynamic parameters, elastic properties, IMT (intima media thickness) and plaques were measured using high resolution B-mode, M-mode and Doppler-mode ultrasound to calculate arterial wall distensibility and β stiffness indices, blood flow velocities, maximal IMT, and the size of atherosclerotic plaques. Correlations between brachial arterial blood pressure, carotid haemodynamic, wall elastic indices and patient's age, activity of disease, inflammation markers were calculated separately and in comparison with controls.

Our preliminary observations indicated that IMT dx (dextra) could be a reliable marker correlating with the disease activity of rheumatoid arthritis apart from a patient's age. Duration of the disease did not correlate with IMT, β stiffness parameters and carotid plaques. In our study carotid plaques of ACC (*a. carotis communis*) and ACI (*a. carotis interna*) in control group and RA group were age dependent, except plaques in *a. subclavia dx* that had correlation with seropositivity – ACPA (anti CCP autoantibody).

Keywords: duplex sonography, rheumatoid arthritis, cardiovascular disease.

Introduction

Recent evidence supporting an inflammatory basis for atherosclerosis (Kerekes, 2008) has led many investigators to study relationship between systemic inflammatory conditions such as RA and risk of cardiovascular diseases. Systemic inflammation represents a mechanistic link between risk factors and vascular dysfunction in both microvasculature and large vessel territories. Changes in microcirculation may be important predictors of CVD (cardiovascular disease).

Endothelial dysfunction has been recently described in patients with RA (Kerekes, 2008). Maintenance of vascular homeostasis is largely dependent on endothelial lining of blood vessels. Endothelia cells release vasoactive mediators (e.g., nitric oxide, endothelin-1) and express cell surface

molecules (e.g., leukocyte adhesion molecules) which influence the vascular tone, leukocyte adherence, platelet activation, coagulation, and smooth muscle proliferation (Vaudo, 2004). Altered function of the arterial endothelium is currently considered the earliest stage of development of atherosclerosis, and therefore it is recognised as a promoter of cardiovascular events. As a result, the study of endothelial function in clinical research has emerged as an important end point that complements the imaging techniques for structural arterial diseases burden (such as carotid intima media thickness).

Ultrasound measures the thickness of intimal and media layers combined, the carotid IMT. Measurement of the intima-media thickness (IMT) of the far wall of the common carotid artery by high-resolution ultrasonography has been established as a clinically useful index for identifying early-stage atherosclerosis (Baltgaile, 2012). Commonly used the IMT measurements become the marker of early stage of decreased elasticity or increased stiffness of arterial wall. The IMT and carotid artery stiffness turned out to be useful predictors of risk of cerebrovascular and cardiovascular events (Schachinger, 2000).

Since no precise direct measurement method for the determination of arterial wall elasticity or stiffness has been suggested, several indirect methods such as calculation of arterial compliance, Young's modulus of elasticity, β stiffness index and arterial distensibility are commonly used (Baltgaile, 2012).

Aim

The aim of this study was to investigate the changes in arterial wall elastic properties, β stiffness index, intima-media thickness (IMT) and plaque formation with relation to age, disease duration, disease activity and inflammation markers in patients with RA and control group in order to detect and estimate cardiovascular and cerebrovascular risk factors.

Material and Methods

20 patients with confirmed RA (13 women, 65%, and 7 men, 35%, mean age 50 ± 17 years, range 25–82; all Caucasian) and 27 sex and age matched healthy controls (aged 27–82) were recruited.

RA patients were selected from consecutive patients at the Outpatient Clinic of Rheumatology at Health Centre 4, who had been diagnosed according to the revised criteria 1987 of the American College of Rheumatology (Arnett, 1988).

The control group consisted of patients attending the same out-patient department for vascular ultrasound check-up without clinical symptoms of RA, vascular disease or any other systemic disease.

The demographic data, including sex, age and disease duration were recorded at the time of the study. Comparison between RA patients and controls accounted for CV risk factors through specification of enrolment criteria, matching, or statistical adjustment. For this reason patients with prominent arterial hypertension (> 150/80 mmHg), significantly elevated cholesterol markers – LDH (low density cholesterol) (> 3.5 mmol/l) and Triglyceride (1.5 mmol/l), obesity and any other systemic disease, smokers, patients with previous MI (myocardial infarction) and stroke – were excluded from the analysis. The same exclusion criteria were applied for the control group. Data from 20 patients with RA and 27 sex, age and risk factors matched controls were collected. Correlations between brachial arterial blood pressure, carotid haemodynamic, wall elastic indices and patient's age, activity of rheumatoid arthritis, inflammation markers were calculated separately and compared with controls.

Resting blood pressure in the right arm was measured with sphygmomanometer at the time of ultrasound examination, after at least 15 minutes of supine rest. Three measurements were taken every 5 minutes, and the average result was recorded. Laboratory variables relevant to RA activity as erythrocyte sedimentation rate (ESR), white blood cell count, platelet cell count, C-reactive protein (CRP), rheumatoid factor (RF), anti citrullinated peptide autoantibodies (Anti CCP) as well as serum levels of total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol, LDL cholesterol were measured by routine methods. A written informed consent was obtained from all study participants.

Carotid Ultrasonography. All study participants underwent carotid ultrasonography, which was performed by experienced research sonographers. In brief, the participants were examined in supine position with slight hyperextension of the neck. Both extra cranial carotid arterial systems were extensively scanned in multiple planes to optimise the identification of atherosclerosis, which was defined as discrete plaque protruding into the lumen at least 50% beyond the diameter of the surrounding wall. Intima-media thickness was measured from end-diastolic (minimum dimension) M-mode images of the far wall of the distal common carotid artery. The intima-media thickness was not measured in the location containing plaque. Mean values of right and left intima-media thickness were presented. Reproducibility of intima-media thickness and detection of plaque has been well documented (Kanters, 1997). Brachiocephalic ultrasonography studies were performed in the control group before 2014, whereas the examination of the patients with RA were performed from 2012 to 2014.

Carotid arteries haemodynamic parameters, elastic properties were measured using high resolution B-mode, M-mode and Doppler-mode ultrasound to calculate arterial wall distensibility and stiffness indices, blood flow velocities (Golemati, 2003). Carotid distensibility measured as changes in the arterial diameter or circumferential area in systole and diastole is a reflection of mechanical stress affecting the arterial wall during the cardiac cycle (Baltgaile, 2012).

The distensibility can be calculated as Ds – Dd, where Ds is end-systolic diameter of artery, Dd is the end-diastolic diameter.

$$\text{Distensibility or Wall Strain} = \frac{Ds - Dd}{Dd}$$

Since the distensibility of arterial wall is mainly blood pressure and volume dependent, the systolic and diastolic pressure ratio is included in most calculations of the vessel's elastic properties (Baltgaile, 2012). The wall stress can be defined as the difference in systolic and diastolic blood pressure:

$$\text{Pulse pressure (PP)} = Ps - Pd$$

$$\text{The stiffness index is calculated as } \beta = \ln \frac{Ps}{Pd} \times \text{Strain}$$

Statistical Analysis. Descriptive data of normal variables are expressed as the mean ± SD. Statistical analysis was carried out by independent 2-tailed t-test. Correlations between variables were determined using Pearson correlation analysis for normally distributed values and Spearmen correlation analysis as nonparametric test. R values of these correlations were determined and corresponding p values < 0.05 were considered significant.

Results

Statistically, the control and RA group patients' age did not differ, T test $p = 0.20$, Levene's test $p = 0.13$.

Arterial wall elastic properties, β stiffness index, correlation with seropositivity inflammation markers and duration of RA, disease activity DAS28 (das28).

No statistically proved correlations were found between β stiffness parameters and the duration of disease ($r_s = 0.061$, $p = 0.797$), as well as DAS28, seropositivity and CRP.

There was no statistically significant difference between the control and RA groups for β stiffness parameters.

Arterial wall intima media thickness correlation with age, inflammation markers and duration of RA, disease activity (DAS28).

Patients with RA had mean values of IMT dx higher than the healthy subjects (± SD 1.02 ± 0.21 vs. 0.88 ± 0.22, $t = 2.45$, $p = 0.19$) but between both groups IMT sin had no differences (1.01 ± 0.28 vs. 0.89 ± 0.23, $t = 2.47$, $p = 0.18$).

No statistically proved correlations were found between the IMT and the duration of disease IMT dx (r_s = −0.145, p = 0.541) and IMT sin (r_s = −0.365, p = 0.114). IMT sin had no statistically proved correlations with inflammation markers (CRP) and disease activity (DAS28); however, IMT dx had weak correlation with DAS28 (disease activity) and IMT dx (r_s = 0.467, p = 0.038).

Statistically proved correlation was found between IMT dx et sin of the control group and RA group with age IMT sin (r_s = 0.524, p = 0.018), except IMT dx of RA patient group, which did not correlate with patient's age respectively (r_s = 0.206, p = 0.383).

Atherosclerotic plaques indicate correlation with age, duration of disease, seropositivity, disease activity and inflammation markers.

The presence of carotid plaques correlates with age in both groups, especially the plaques in ACI dx (r_s = 0.852, p < 0.001), ACC dx bifurcation (r_s = 0.706, p = 0.002), ACI sin (r_s = 0.654, p = 0.021) and ACC sin bifurcation (r_s = 0.625, p = 0.010).

No statistically proved correlations were found between the carotid plaques and the duration of disease, CRP and DAS28. Brachiocephalic vessel plaques did not correlate with seropositivity (RF, Anti CCP), except the plaques of arteria Subclavia dx, which had statistically significant correlation with Anti CCP (r_s = 0.715, p = 0.002).

Discussion

In our small patient study we measured the wall elasticity or β stiffness of ACC (*arteria carotis communis*), usually not very frequently done; moreover, it is time consuming as well. We kept in mind that most similar researches of the arterial wall distensibility and elasticity have been performed on brachial arteries, but the recording of pressure ratio during the cardiac cycle in a brachial artery can provide only indirect information on pressure/strain ratio in carotid artery. Calculations of FMD (flow mediated dilatation), PWV (pulse wave velocity), and other stiffness parameters cannot be attributed to carotid artery properties only because brachial, femoral, aortic and internal carotid arterial segments differ in the proportion of elastin-collagen to smooth muscle as well as proportion of endothelium to media layer and neural control (Baltgaile, 2012).

Considering this argument, it seems logical to evaluate the carotid artery wall dynamics by ultrasound measurements of the arterial wall structure and movements in a strictly precised vascular area (Baltgaile, 2012).

A decrease of arterial distensibility (i.e. increase of arterial wall stiffness) seems to be a common pathological mechanism for many factors associated with cerebrovascular and cardiovascular diseases. The factors affecting the arterial wall motions depend mainly on the left ventricle, intra-arterial pressure and blood volume, endothelium function, smooth muscle tone and neural control mechanisms. Good reproducibility of carotid arteries diameters measured by 2D grayscale imaging, M-mode and A-mode (wall tracking) is proved (Baltgaile, 2012). However, it is also mentioned that very small changes in linear measurements of carotid diameters can have big effects.

In our study no statistically proved correlations between β stiffness parameters and duration of disease were found (r_s = 0.061, p = 0.797). Whereas the duration of the disease of RA for young people can be a couple of months to several years and, on the contrary, for older patients for some months. We calculated β stiffness by the formula described above, which includes logarithm of pulse pressure and strain. No statistically proved correlations were detected between β stiffness parameters DAS28, seropositivity and CRP. DAS28 and CRP are dependent on several IL (interleukin) releases that change all the time and are inconstant, as well as the autoantibody production that can be and cannot be present for every RA patient. In the study of Szekanecz et al., anti CCP production showed an insignificant association with more characteristic endothelial dysfunction (Kerekes, 2008).

Furthermore, the stiffness parameters of arterial wall in RA patients did not differ from the same indices of healthy controls. There was no statistically significant difference between control and RA groups for β stiffness parameters. It just means we had quite homogenous groups which did not show much difference in pulse pressure and wall strain on both sides. Another possibility is that β stiffness index is

not a very sensitive marker for small groups to show statistically significant differences for autoimmune and control group patients. Elasticity and β stiffness index mostly depends on the process of aging that impacts the degenerative process of elastic fibres, promoting fibrotic/sclerotic transformation of vessel walls. It approves that our small study group was more age dependent.

Our study is also a subject to potential limitations because of a small number of participants we could analyse, remembering that the decrease of stiffness and elasticity is found to people with atherosclerosis inducing factors (primary arterial hypertension, cholesterol, diabetes mellitus, hypertrophy of left ventricle). Therefore, we could not recruit many control and RA patients, taking into account all the risk factors mentioned above which increase with age and are widespread among people in Latvia. Prolonging the observation time to include more participants would likely increase the statistical power, allowing us to detect weaker associations that did not reach significance in the present analysis.

It is supposed that in rheumatic diseases ccIMT has become the most commonly used indicator of subclinical atherosclerosis. Numerous cross-sectional studies have demonstrated increased ccIMT in patients with RA, indicating accelerated atherosclerosis (Kerekes, 2012). Therefore, early determination of ccIMT in RA patients may be useful to assess patients with high cardiovascular and cerebrovascular risk.

Early carotid arterial wall disease is a useful predictor of risk of both ischemic stroke and coronary heart disease in asymptomatic population as well. However, ultrasound measures the thickness of intimal and media layers combined and the carotid IMT. It is important because the media layer is sensitive to increased pressure in the lumen, responding by hypertrophy (Baltgaile, 2012). Thus, the thickened IMT in the presence of hypertension may not reflect the presence of atheromatous plaque. That reduces the number of patients we could include, keeping in mind that older patients more frequently suffer from arterial hypertension, hypercholesterolemia. Furthermore, inhabitants of Latvia suffer from increased arterial hypertension and hypercholesterolemia.

No statistically proved correlations were found between IMT and duration of disease as well. In the study by Szekanecz et al. ccIMT (common carotid artery IMT) also correlated with age. What is more, in Szekanecz et al., study seropositivity (RF, anti CCP) and inflammatory markers as CRP showed an insignificant association with more pronounced atherosclerosis and endothelial dysfunction (Kerekes, 2008).

Current guidelines recommend the assessment only of the common carotid segment. Moreover, the assessment of ccIMT is considered to be a quantitative approach, but this technique does not allow the fine ultrastructural analysis of the whole extra cranial carotid system (Kerekes, 2012). In a comparative study, the ccIMT was reported to have only a moderate sensitivity in predicting in the future cardiovascular events. The presence of plaque in the carotid system or the determination of total plaque area are considered to be better predictors for future myocardial and cerebrovascular events than ccIMT (Kerekes, 2012).

Therefore, we examined brachiocephalic vessels, not only the branches of arteria carotis, which are mainly investigated with ultrasound and found something unexpected beside the things we could prognosticate like carotid plaque correlation with age. Plaques of *arteria subclavia dx*, had statistically significant correlation with anti CCP ($r_s = 0.715$, $p = 0.002$), with one of autoantibodies which plays a crucial role in the pathogenesis and progression of RA (Kerekes, 2008).

The presence of carotid plaques correlates with age in both groups especially the plaques in ACI dx ($r_s = 0.852$, $p < 0.001$), ACC dx bifurcation ($r_s = 0.706$, $p = 0.002$), ACI sin ($r_s = 0.654$, $p = 0.021$) and ACC sin bifurcation ($r_s = 0.625$, $p = 0.010$).

Statistically unproved correlations were found between carotid plaques and duration of disease, CRP and DAS28. Brachiocephalic vessel plaques did not correlate with seropositivity (RF, anti CCP), except plaques in *a. subclavia dx* that had correlation with seropositivity – ACPA (anti CCP autoantibody).

Conclusion

The past decade has experienced the emergence of two new paradigms in inflammatory disease: first, cardiovascular complications of atherosclerosis have markedly increased in patients with rheumatoid arthritis (RA) and second, inflammatory mechanisms are important in the pathogenesis of atherosclerosis (Shoenfeld, 2005). Therefore, there is a vital necessity to determine atherosclerosis at early

stages (Snow, 2005). Several non-invasive screening methods have been developed as a measurement of intima-media thickness (IMT) and carotid artery stiffness that are thought to be useful predictors of risk of cerebrovascular and cardiovascular events (Kumeda, 2002). The different parameters of carotid artery wall elasticity could be measured by high resolution B-mode and M-mode ultrasound using manual and automatic measurements as well as wall echo-tracking system (Baltgaile, 2012). The development of methods based on ultrasound RF signal, tissue Doppler imaging and other tracking systems help to increase the accuracy of automatic measurement of vascular wall properties such as IMT, arterial stiffness / distensibility and wall compliance, although even these methods are not absolutely perfect (Baltgaile, 2012). Good reproducibility of carotid arteries diameters measured by 2D grayscale imaging, M-mode and A-mode (wall tracking) has been proved. However, it is also mentioned that very small changes in linear measurements of carotid diameters can have big effects on estimates of arterial mechanical properties such as strain and Young's modulus (Baltgaile, 2012).

Our preliminary observations indicate that IMT dx could be a reliable marker correlating with disease activity of rheumatoid arthritis apart from a patient's age. The duration of disease does not correlate with the IMT, β stiffness parameters, and carotid plaques. In our study the carotid plaques of ACC and ACI in the control group and RA group were age dependent, except the plaques in *a. subclavia dx* which had correlation with seropositivity – ACPA (anti CCP autoantibody). In future we should pay attention and examine all brachiocephalic vessels not only the branches of *a. carotis* which are the most investigated ones, to reveal as much as we can about current patients atherosclerosis process. It could give us additional information of the whole atherosclerotic burden.

References

1. Arnett F. C., Edworthy S. M., Bloch D. A., et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*, 1988; 3: 315–324.
2. Baltgaile G. Arterial wall dynamics. New Trends in Neurosonology and Cerebral Hemodynamics – an Update**:** *Perspectives in Medicine*. Ed. by E. Bartels, S. Bartels, H. Poppert. 2012. Pp.146–151.
3. Golemati S., Sassano A., Lever M. J., et al. Carotid artery wall motion estimated from B-mode ultrasound using region tracking and block matching. *Ultrasound Med Biol*, 2003; 29 (3): 387–399.
4. Kanters S. D., Algra A., van Leeuwen M. S. and Banga J. D. Reproducibility of *in vivo* carotid intima-media thickness measurements: a review. *Stroke*, 1997; 28: 665–671.
5. Kerekes G., Szekanecz Z., Der H., et al. Endothelial dysfunction and atherosclerosis in rheumatoid arthritis: a multi-parametric analysis using imaging techniques and laboratory markers of inflammation and autoimmunity. *The Journal of Rheumatology*, 2008; 35: 3.
6. Kerekes G., Soltesz P., Nurmohamed T., et al. Validated methods for assessment of subclinical atherosclerosis in rheumatology. *Nature Reviews*, 2012; 8: 224–229.
7. Kumeda Y., Inaba M., Goto H., et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. *Arthritis Rheum*, 2002; 46: 1489–1497.
8. Schachinger V., Zeiher A. M. Atherosclerosis-associated endothelial dysfunction. *Z Kardiol*, 2000; 89: 70–74.
9. Shoenfeld Y., Gerli R., Doria A., et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. *Circulation*, 2005; 112: 3337–3347.
10. Snow M. H., Mikuls T. R. Rheumatoid arthritis and cardiovascular disease: the role of systemic inflammation and evolving strategies of prevention. *Curr Opin Rheumatol*, 2005; 17: 234–241.
11. Vaudo G., Marchesi S., Gerli R., et al. Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity. *Ann Rheum Dis*, 2004; 63: 31–35.