Indexed, Abstracted and Cited: Index Copernicus International (Poland), ISRA Journal Impact Factor, International Impact Factor Services (IIFS), Directory of Research Journals Indexing (DRJI), International Institute of Organized Research and Scientific Indexing Services, Cosmos Science Foundation (South-East Asia), International Innovative Journal Impact Factor, Einstein Institute for Scientific Information {EISI}, Directory of Open Access Scholarly Resources. Science Indexing Library (UAE), Swedish Scientific Publication (Sweden), citefactor.org journals indexing, Directory Indexing of International Research Journals

World Journal of Biology and Medical Sciences

Published by Society for Advancement of Science®

ISSN 2349-0063 (Online/Electronic)

Volume 4, Issue- 1, 14-22, January to March, 2017

Journal Impact Factor: 4.197

WJBMS 04/01/08/2017

A Double Blind Peer Reviewed / Refereed Journal

www.sasjournals.com

wjbmedsc@gmail.com/wjbms.lko@gmail.com

RESEARCH PAPER

Received: 25/02/2017 Revised: 04/04/2017 Accepted: 05/04/2017

Evaluation of the Endothelial Function in Rheumatoid Arthritis in Black Sub-Saharan African Subjects

Maïmouna TOURE[1], Fatou Bintou SAR[2. 7], Souleymane THIAM[3], Demba DIEDHIOU[4], Moustapha NIASSE[5], Valentin OUEDRAOGO[1], Abdou Khadir SOW[1], Mor DIAW[1], Aïssatou SECK[1], Salimata Diagne HOUNDJO[1], Mamadou SARR[6. 7], Modou Oumy KANE[6], Abdoulaye BA[1.7] and Abdoulaye SAMB[1.7]

1. Laboratory of Physiology and Functional Explorations. FMPO. UCAD. BP 5005. Dakar Fann. Sénégal.
2. Laboratory of Physiology.Faculty of Health Sciences. Thiès.Sénégal.
3. Laboratory of Biochimistry and Molecular Biology. FMPO. UCAD. Dakar. Sénégal.
4. Medical Clinic II.FMPO. UCAD. Dakar. Sénégal.
5. Rheumatology Department of the University Hospital LeDantec. UCAD. Dakar. Sénégal.
6. Laboratory of Physiology Pharmaceutical.Faculty of Medicine. Pharmacy and Dentistry. UCAD. Dakar. Sénégal.
7. UMI 3189.Environnement. Health. Societies. CNRS. CNRST. Bamoko - UCAD University, Dakar, Sénégal.

ABSTRACT

Rheumatoid arthritis is often characterized by fatal cardiovascular events. Endothelial dysfunction would be a predictive marker of the occurrence of such cardiovascular events. Impaired endothelial function is often the initial stage of vascular pathology in rheumatoid arthritis. Thus the aim of our study was to assess endothelial function in black Africans with rheumatoid arthritis by measuring the peripheral arterial tone through an EndoPAT2000. This is a prospective, descriptive and analytical study conducted in the department of Physiology and functional exploration of the Cheikh Anta Diop University of Dakar. Were excluded patients under 18 years and those with rheumatoid arthritis was associated with severe complications or other medical conditions or pregnancy. The study included 19 subjects aged 18 years and older. The post-occlusion induced reactive hyperemia was significantly reduced in more than half of patients (57.89%). A reactive hyperemia index decreased demonstrates impaired endothelial function. Rheumatoid arthritis is the cause of endothelial dysfunction. A positive correlation was found between endothelial dysfunction and systolic blood pressure, mean arterial pressure, CRP and uremia. But after a regression, none of these factors has influenced independently endothelial dysfunction. Endothelial dysfunction is a new concept in rheumatoid arthritis. In the latter, currently considered as a cardiovascular disease, assessment of endothelial dysfunction would predict the risk of cardiovascular events, to assess the degree of vascular and functional impairment and may also have prognostic value.

Keywords: Rheumatoid arthritis, Endothelial Function and Black Africans.

INTRODUCTION

The vascularendotheliumis an anatomicalbarrierbetween the circulating blood and the vascularsmooth muscle cells. Besides, itplays an essential role in many basic physiological vascular regulations. In the normal conditions, blood pressure and blood flow are the major factors that influence biology of the endothelium directly by the blood flow (mechanical stimuli) or indirectly by chemical factors (chemical stimuli) [PratiC. et al., 2014].

Cardiovascular disease is the learding cause of increased mortality in rheumatoid arthritis (RA) [Soubrier M. and Dougados M., 2006]. This chronic inflammatory rheumatism is the most common in adults [NassarK. et al., 2013] and it is generally characterized by a decrease in life expectancy mainly because of cardiovascular events [Avina-Zubieta JA. et al., 2008].

In the prospective study NHS (Nurses health study), it was shown that patients with RA had a risk of vascular accidents more than twice as high compared to patients without RA [Solomon DH. et al., 2003]. These vascular accidents are generally atheromatous [Del Rincon I. et al., 2001] with endothelial dysfunction as the first stage of this atherosclerosis [Hansson GK., 2005 ;Cohn JN. et al., 2004]. Indeed. endothelial dysfunction is a risk factor independent of the occurrence of cardiovascular accidents [Cohn JN. et al., 2004].

The existence of endothelial dysfunction could be constitute a therapeutic target or better a marker of predictive risk of cardiovascular events in patients with RA. Thus the aim of our study was to assess endothelial function of black African subjects with rheumatoid arthritis by the noninvasive measurement of peripheral arterial tone (vasodilator responses to vascular occlusion) using EndoPAT2000 device.

METHODOLOGY

Subjects and protocol

This prospective and experimental study was conducted in the service of human physiology and function explorations in Faculty of Medicine, Pharmacy and Odontology (FMPO) of the cheikh Anta DIOP University (UCAD) from Dakar to Senegal. It was made from April 2016 until January 2017.

The patients were recruited from rheumatology department in the University Hospital Aristide LeDantec of FMPO of Dakar in Senegal.

All the recruited subjects were all informed about the interest of this work and signed an index form of informed consent.

The protocol was create by concordance with the guideline set by the declaration of Helsinki and approved by the Ethics Committee of the FMPO / UCAD.

The study included 19 subjects aged 18 years and older. The parameters for this study were reported in a single medical visit. Were Excluded patients under 18 years and those whose RA was associated with severe complications (ischemia, gangrene) or other conditions (other primary or secondary connective) or pregnancy.

Sociodemographic information and those concerning the history of the disease were collected by questionnaire and medical review.

Evaluation of the anthropometric and cardiovascular parameters

For each patient included.were measured:

-The Weight with a person weighs Secca®,

-The Size with a measuring rod,

-The Waist and hip circumference with rubanmetre

The body mass index (BMI) and heart rate were automatically calculated by the EndoPAT2000.

Systolic blood pressure (SBP) and diastolic blood pressure(DBP) were measured manually with a Spengler® type sphygmomanometer after 10 min of rest. Its were measured before the test with the EndoPAT2000.

Mean blood pressure (MBP) was calculated using the formula of Messaï E. Arnette Ed Blackwell (Paris), 1995: MBP = (SBP+2 DBP) / 3.

The biological parameters were measured in the laboratory of biochemistry of Faculty of Medicine, Pharmacy and Dentistry / UCAD of Dakar / Senegal at 8 am on the day after fasting for 12 hours.

Evaluation of the biological parameters

The biological parameters were measured the same day in the laboratory of biochemistry and molecular biology of the FMPO / UCAD of Dakar / Senegal.

The takings were made at 8 am in the morning after a fast of at least 12 hours (am).

Some venous blood was taken at the level of the fold of the elbow of the not dominant arm.

So on fluoride tube we measured the fasting blood sugar.On heparine tube we measured lipids (Cholesterol Total, HDL-Cholesterol, LDL-Cholesterol and Triglycerides) and the renal function (Creatininemia and Urea).

By enzymatic method, we measured the fasting blood sugar, the Total Cholesterol, the HDL-Cholesterol, the LDL-Cholesterol, the Triglycerides, the Urea and the Creatininemia.

By chemical method, we measured the Calcemia.

Assessment of endothelial function

For the assessment of endothelial function.we used a new device EndoPAT2000 Itamar® brand. It is a device for measuring the peripheral arterial tone by vasodilatory response to 5 min occlusion of the brachial artery vascular flow using an inflatable cuff placed on the arm. Reactive hyperemia in response to the occlusion is calculated automatically by the device and translated into reactive hyperemia index (RHI) and its logarithm (LnRHI). The calculated values are normalized bymeasures on the contralateral arm where the blood flow is not interrupted. The measurement technique was made according to the recommendations of Goor DA. et al [Goor DA. et al., 2004].

After each measurement.the software installed in a PC and connected to the device.directly expresses the results giving RHI and LnRHI whose normal values are respectively (1.67 to 2) and (0.51 to 0.70). A RHI value less than 1.67 or LnRHI value less than 0.51 may be considered as an endothelial dysfunction.

Statistical Analysis

The analyzes were performed using Epi Info 7 and SPSS 16. Data were expressed as mean ± standard deviation, percentages and relative values.Pearson test for correlations then linear and logisticregressions were realized to look for relations between the various variables.

The results of the tests are considered significant when $p<0.05$

RESULTS

Descriptive results

Sociodemographicdata and Characteristics of Rhumatism Arthritis in our study

The meanage of the study population was 42.84 ± 12.80 years. The sex ratio (M/F) was 0.19. We find that 81% of patients had a RA with the presence of rheumatoid factor (FR). The mean dose of corticosteroid was 10 mg / day (Table 1).

Table 1. Characteristics of patients and rheumatoid arthritis

	Women N=16	Men N=3	Total Pop N=19
Background and Cardiovascular Risk Factors			
Family Autoimmunity N (%)	4 (25)	-	4 (21.05)
Hypertension N (%)	3 (18.8)	-	3 (15.79)
Dyslipidemia N (%)	2 (12.5)	-	2 (10.53)
Characteristics of rheumatoid arthritis			
Positive RF (UI/mL) N (%)	13 (81.2)	-	13 (68.42)
Positive Ab anti-PC (UI/mL) N (%)	16 (100)	3 (100)	19 (100)
Disease duration (months) Means ± SD	43.00 ± 41.31	24.33 ± 0.58	40.05 ± 38.36
Corticosteroid Duration (months) Means ± SD	24.25 ± 36.69	25.00 ± 1.0	24.37 ± 33.50
Corticosteroids Dose (mg/day) Means ± SD	9.69 ± 1.25	8.33 ± 2.89	9.47 ± 1.58
Immunosuppressive duration (months) Means ± SD	24.54 ± 41.01	13.50 ± 16.26	23.07 ± 38.42
Immunosuppressive dose (mg/week) Means ± SD	14.23 ± 0.53	15 ± 0.00	14.33 ± 0.45

RF=Rhumatoid Factor, Ab anti-PC= Antibodies antiproteines citrullinated

Anthropometric and clinical characteristics constant

The mean of the clinical parameters were expressed by gender (Table 2)

Table 2. Frequency and means of anthropometric and clinical characteristics of the study population

	Women (N=16) Means ± SD	Men (N= 3) Means ± SD	Total pop (N=19) Means ± SD
Anthropometric characteristics			
BMI (Kg/m²)	25.04 ± 1.22	20.11 ± 2.19	24.26 ± 1.14
Waist size (cm)	81.00 ± 12.75	75.67 ± 7.02	80.16 ± 2.76
Hips circumference (cm)	102.06 ± 10.19	94.00 ± 5.57	100.79 ± 2.28
Clinical constant			
HR (bpm)	82.00 ± 13.43	78.67 ± 21.39	81.47 ± 3.27
SBP (mmHg)	134.75 ± 25.93	133.00 ± 9.85	134.47 ± 5.49
DBP (mmHg)	82.13 ± 13.01	79.00 ± 4.00	81.63 ± 2.76
MAP (mmHg)	99.60± 16.27	97.00 ± 5.90	99.25 ± 3.44

BMI: body mass index, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure,MBP: mean blood pressure

Biological features

The CRP testing showed a higher than normal levels in thirteen patients (13) or 68.42% of the study population, Serum calcium, fasting glucose, lipid profile, kidney function and the rest of the laboratory tests were normal in all subjects (Table 3).

Table 3. Means and standard deviations of the biological parameters

We found that the mean of each of the biological parameters was normal. (Table 3)

parameters	Means ± SD
Total Cholesterol (g/l)	2.15 ± 0.25
HDL-Cholesterol (g/l)	0.63 ± 0.11
LDL-Cholesterol (g/l)	1.23 ± 0.22
Triglycerides (g/l)	0.77 ± 0.28
Fast blood sugar (g/l)	0.89 ± 0.12
Urea (g/l)	0.21 ± 0.07
Creatininemia (mg/l)	6.65 ± 1.38
Calcemia (mg/l)	81.82 ± 17.82

Characteristics of endothelialfunction

We had more than half of our subjects (11 patients or 57.89% of the study population) which had an impaired endothelial function.

Factorsinvolved in endothelial dysfunction in our patients

Afterunivariate,positive correlations with endothelial dysfunction were found with SBP, MBP, CRP and Urea (Table 4).

Table 4. Factors involved in impaired endothelial function.

Only arterial pressure and stigma of renal function were significantly correlated with the existence of endothelial dysfunction. (Table 4)

	LnRHI	
Variables	**p-value**	**correlation coefficient (r)**
BMI (kg/m²)	p=0.733	NS
Hypertension (mmHg)	p=0.102	NS
Physical activity	p=0.999	NS
family rheumatism	p=0.852	NS
Positive RF	p=0.999	NS
DBP	p=0.079	NS
SBP	p<0.0001	r=0.75
MBP	p=0.002	r=0.66
CRP	p=0.035	r=0.49
Urea	p=0.039	r=0.48

BMI: body mass index.RF : Rhumatoid Factor.DBP : diastolic blood pressure. SBP : systolic blood pressure. MBP: mean blood pressure. HR: heart rate. CRP : C-reactive protein

After multiple regression tests (linear and logistic), none of the parameters studied were significantly impacting independently on endothelial dysfunction in RA.

DISCUSSION

Our study shows that the post-occlusion inducedreactivehyperemiawasabnormal in over half of our patients. That decreased RHI (reactivehyperemia Index) demonstrates impaired endothelial function. Thus RA is the cause of a significant endothelial dysfunction.

This prospective, cross-sectional study was conducted to evaluate non invasive endothelial function by a new EndoPAT2000® device from a cohort of African black patients with RA.

This new non invasive methodmaybean earlyclinical screening tool for cardiovascular damage in RA.

This study maybe one of the first that describes endothelial dysfunction through an EndoPAT2000 during RA.

In our patients more than half or 57.89% had endothelial dysfunction and these results are consistent with the literature. Endothelial dysfunction in RA has been described for the first time in 2002 by Bergholm R et al. [Bergholm R. et al., 2002].Whoreported a decrease in the acetylcholine-dependentvasodilation in the brachial artery arthritis patients compared to controls. This finding was confirmed by other studies such [Chatterjee Adhikari M., 2012] who had shown the possibility of a decrease in endothelium-dependentvasodilation. However these results are controversial. In fact other studies have also noted a lack of change in endothelial function in RA [Södergren A. et al., 2010].

It is well established that the endothelium is capable of synthesizing and releasing different mediators. They are likely to have effects on vascular and circulating cells and affect vascular function as vasomotricity[Bunting S. et al., 1976]. Thesemediators are eithervasoconstrictor (endothelin) or vasodilator (NO). Indeed, NO is an important vasoactive factor thatregulates the vasodilation action on smooth muscle cells but also inhibits platelet aggregation and leukocyte adhesion to vascular wall [PratiC. et al., 2014].

Endothelial dysfunction (ED) indicates a secretoryabnormality of one or more of these mediators. Generally ED is considered as an abnormality of endothelial NO bioavailability and thus an impairment of endothelium-dependent vascular dilatation [Soubrier M. and Dougados M., 2006]. ADMA (AsymmetricDiMethyl Arginine) is a potent endogenous inhibitor of NOS (nitric oxidesynthase in blood), the increase in plasma levels reflect an ED. It was evaluated in RA and it seems to be a predictor of the development of a ED in recent RA without disease or cardiovascular risk factor [Spasovski D., 2013].

These results could suggest an impairment of endothelium-dependentarterialvasodilation in RA. However there are other biomarkers of endothelial function (Vascular Cell AdhesionMolecule [VCAM]. Inter Cellular AdhesionMolecule[ICAM-1], Von Willebrand factor, endothelialcells circulating) that deserve to be studied to better elucidate this ED in RA [Prati C. et al, 2014].The increase in these adhesion molecules was observed as well as a strong correlation of plasma concentrations with markers of inflammation in RA compared with a group of healthy controls. Meanwhile other authors suggest the possibility of complex interactions between environmental and genetic determinants affect both the immune system and the vascular system to modify the cardiovascular risk in RA [Prati C. et al., 2014].

In our study.we found a positive correlation of endothelial dysfunction with SBP, MAP, CRP and the rate of blood urea. But after regression, none of these factors has influenced independently ED. However the authors cited other intrinsicfactors to the RA as systemicautoimmuneprocesses, in whichauto-antibodiesmayplay a direct role of endothelialimpairment [Montecucco F.and Mach F., 2009].Similarly, Sandoo et al. Have recently demonstrated a link between ED and the activity of AR [Sandoo A. et al., 2011]. In addition to traditionalrisk factors, chronic systemic inflammation may be incriminated.It is considered as a phenomenthatwouldinduce pro-atherogenic changes including ED [Hermann C. et al., 2000].Besides,Prati C et al.,conclude that the ED seems to get worse with the duration of the disease [Prati C. et al., 2014]. However, these results must be qualified by the lack of control group, the low numbers, time of short evaluation and the lack of evidence on the integrity of smooth muscle cells [Prati C. et al., 2014].The role of ED has been suggested to explain the development of vascularcomplications in RA by Bacon [Bacon PA. et al., 2002].

The EndoPAT2000 is new device thatallows a repetitive, non-invasive and not operatordependentmeasureof endothelialfunction. So it has a diagnostic value and preventing cardiovascular risk factors of patients followed for a RA but it could be used as part of epidemiological studies.

CONCLUSION

The concept of endothelial dysfunction (ED) is a new concept in autoimmune diseases such as RA. It is considered as a subclinical condition which predisposes to the development of atherosclerosis. The endothelial dysfunction is also a risk factor independent of the occurrence of cardiovascular accidents.The evaluation of ED by measuringreactivevasodilation occlusion istherefore part of the recent non-invasive and physical methods that could help predict the risk of cardiovascular events and also assess the degree of damage vascular functional. It may also have prognostic value. In RA, which is currently considered as a cardiovascular disease, the mechanisms generating DE are little studied and theycouldprobablymultifactorial. Thus, larger studies taking into account autoimmune factors are required to sit this DE and more elucidate the factors involved.

Conflict of interest: None

ACKNOWLEDGEMENTS

Personnel of the Laboratory of Human Physiology, Rheumatology Department of Le Dantec University Hospital, The recruited Polyarthritis patients.

REFERENCES

Prati C., Demougeot C., Guillot X., Godfrin-Valnet M. and Wendling D. (2014). Dysfonction endothéliale et rhumatisme. Revue du rhumatisme; 81,362–367.

Soubrier M. and Dougados M. (2016). Athérome et polyarthrite rhumatoïde. La revue de médecine interne; 27, 125–136.

Nassar K.,Janani S., Rachidi W. and Mkinsi O. (2013). L'évaluation de la fonction musculaire et le risque de chute au cours de la polyarthrite rhumatoïde: outils d'évaluation et effets des traitements. Rev Mar Rhum; 25, 20-7.

Avina-Zubieta J.A., Choi H.K., Sadatsafavi M., et al. (2008). Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum; 59,1690–7.

Solomon D.H., Karlson E.W., Rimm E.B., et al. (2003). Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation; 107,1303-7.

Del Rincon. I.,Williams K., Stern M.P., Freeman G.L. and Escalante A. (2001). High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum;44: 2737–45.

Hansson G.K. (2005). Inflammation. atherosclerosis and coronary artery disease. N Engl J Med; 352:1685–95.

Cohn J.N., Quyyumi A.A., Hollenberg N.K. and Jamerson K.A. (2004). Surrogate markers for cardiovascular disease. Functional markers. Circulation;109(Suppl IV):31–46.

Goor D.A., Sheffy J., Schnall R.P. et al. (2004). Peripheral arterial tonometry: a diagnostic method for detection of myocardial ischemia induced during mental stress tests: a pilot study. Clin Cardiol;27:137–141.

Bergholm R., Leirisalo-Repo M., Vehkavaraa S., et al. (2002). Impaired responsiveness toNO in newly diagnosed patients with rheumatoid arthritis. Arterioscler ThrombVasc Biol;1:1637–41.

Chatterjee Adhikari M., Guin A., Chakraborty S., et al. (2012). Subclinical atherosclerosis and endothelial dysfunction in patients with early rheumatoid arthritisas evidenced by measurement of carotid intima-media thickness and flow-mediated vasodilatation: an observational study. Semin Arthritis Rheum;41:669–75.

Södergren A., Karp. K., Boman. K., et al. (2010). Atherosclerosis in early rheumatoid arthritis: very early endothelial activation and rapid progression of intima mediathickness. Arthritis Res Ther;12:R158.

Bunting S., Gryglewski R., Moncada S., et al. (1976). Arterial walls generate from pros-tag land in endoperoxides a substance (prostaglandin X) which relaxes strips of mesenteric and coeliac ateries and inhibits platelet aggregation. Prostaglandins; 12:897–913.

Spasovski D., Latifi A., Osmani B., et al. (2013). Determination of the diagnostic values of asymmetric dimethylarginine as an indicator for evaluation of the endothelial dysfunction in patients with rheumatoid arthritis: 818037. http://dx.doi.org/10.1155/2013/818037.

Montecucco F. and Mach F. (2009). Common inflammatory mediators orchestrate pathophysiological processes in rheumatoid arthritis and atherosclerosis. Rheumatology (Oxford);48:11–22.

Sandoo. A., Veldhuijzen van Zanten J.J., Metsios G.S., et al. (2011). Vascular function and morphology in rheumatoid arthritis: a systematic review. Rheumatology(Oxford);50:2125–39.

Hermann C., Assmus B., Urbich C., et al. (2000). Insulin-mediated stimulation of proteinkinase Akt: a potent survival signaling cascade for endothelial cells. Arterioscler Thromb Vasc Biol;20:402–9.

Bacon P.A., Raza K., Banks M.J., et al. (2002). The role of endothelial cell dysfunction in thecardiovascular mortality of RA. Int Rev Immunol;21:1–17.

Corresponding author: Maïmouna TOURE, Former Hospital Internal,Assistant in Human Physiology.
Email: drmaimounatoure@gmail.com