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Increased Risk of Arterial Stiffness in Rhumatoid Arthritis Patients in a Sub-Saharan African Setting

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Abstract

Background: Analysis of arterial stiffness (AS) is a good marker of early arterial disease and an important determinant of cardiovascular risk, independent of other traditional cardiovascular risk factors. Carotid-femoral pulse wave velocity (CfPWV) is the gold standard to evaluate arterial stiffness. There is evidence that patients with rheumatoid arthritis (RA) have a higher arterial stiffness than their age-matched healthy counterparts and thus have higher cardiovascular (CV) risk. However, data on arterial stiffness in African rheumatoid arthritis patients is scarce. **Objectives:** To determine the patterns of arterial stiffness in rheumatoid arthritis patients in a sub-Saharan African setting, using CfPWV and Augmentation index (AIx). **Method:** We conducted a case-control study, at the Douala general hospital over four months (February to May 2018) on 63 subjects among which 31 RA patients matched for age and sex with 32 healthy subjects. AIx and CfPWV were determined non-invasively by radial pulse wave analysis and carotid femoral wave analysis respectively, using a sphygmocor Atcor device (SphygmoCor, PWV Medical, Sydney, Australia). **Results:** The mean age of RA patients was 47 ± 14 years with most of them being females (n = 26, 83.9%). CfPWV was significantly higher in RA patients compared to the control group (mean: 8.85 ± 2.1 vs 7.45 ± 1.38; p ≤ 0.01) as well as was AIx (Median: 33 [26 - 43] vs 26 [20 - 31]; p = 0.01). RA (OR: 6.105; 95% CI: 1.52 - 24.54; p < 0.01), Diabetes (OR: 1.34; 95% CI: 1.14 - 5.17; p = 0.05), elevated CRP levels (OR: 4.01; 95% CI:

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1.16 - 13.68; p = 0.03) and Hypertension (OR: 5.75; 95% CI: 1.24 - 11.60; p < 0.01) were independent determinants of arterial stiffness. **Conclusion:** Arterial stiffness, a well-recognized marker of cardiovascular risk is increased among patients suffering from rheumatoid arthritis when compared to a healthy control group.

Keywords

Rheumatoid Arthritis, Arterial Stiffness, CfPWV, Augmentation Index

1. Introduction

Rheumatoid Arthritis (RA) is a disabling systemic autoimmune disease that affects 24 per 10.000 people worldwide making it the most frequent chronic inflammatory rheumatic diseases in the general population [1]. In sub-Saharan Africa, recent studies described a prevalence and severity of RA close to that observed in the Caucasian populations contrary to what was described by certain authors who believed it was relatively benign in this setting [2] [3]. Mortality rates are considered to be more than twice higher in patients with RA than in the general population and occur largely as a result of higher rates of cardiovascular disease [4]. RA patients are more likely not only to have silent ischemic heart disease and experience sudden death but also to develop heart failure and die shortly thereafter [5]. Traditional cardiovascular (CV) risk factors such as hypertension, smoking, and diabetes certainly contribute to the increased risk of mortality in RA patients but do not fully explain it [6]. Rather, the high systemic inflammatory burden associated with RA appears to be a key driver of increased CV risk [7]. The heightened inflammatory state in RA is linked to accelerated atherosclerosis, with systemic inflammation exacerbating adverse changes in both established and novel CV risk factors [7] [8]. Increased arterial stiffness (AS) is one of the earliest stages of the atherosclerotic process and an independent predictor of cardiovascular disease and mortality among Caucasians population [9] [10]. Pulse-wave velocity (PWV) is the gold standard measure for AS while augmentation index (Aix) is a surrogate measure and direct index of pressure wave reflections. PWV and AIx are currently considered as independent predictors of major CV events and all-cause mortality thus, these surrogate markers of subclinical atherosclerosis provide important prognostic information over traditional CV risk factors [9] [10] [11] [12]. Though a few studies show similar rates of arterial stiffness in RA patients and healthy individuals, most of the findings in Europe and other developed settings show that RA is associated with an increase in arterial stiffness [13] [14] [15]. In Egypt, Youssef *et al.* described increased rates of arterial stiffness in rheumatoid arthritis patients as compared to healthy individuals [16]. In the sub-Saharan African setting however, data remains sparse on this subject. We therefore sought to describe patterns of arterial stiffness in RA patients as compared to healthy controls in this

sub-Saharan setting, and ascertain its potential determinants.

2. Materials and Methods

Study design and participants

We conducted a case-control study at the Rheumatology Unit of the Douala General Hospital between February to May 2018. Included were patients with RA diagnosed by a rheumatologist fulfilling the ACR/EULAR 2010 classification criteria for RA, aged > 16 years old, who provided informed consent and were attending the rheumatology outpatient clinic [17]. Healthy subjects matched for age and sex with no history of smoking, cardiovascular diseases, diabetes mellitus, cancer, liver disease, thyroid disease and kidney disease, who provided informed consent were recruited.

Sample size and sampling methods

We consecutively and exhaustively enrolled all RA patients, presenting at rheumatology unit of the Douala general hospital, who respected our inclusion criteria. All participants were subjected to a full clinical clerking during which socio-demographic data and past medical history (family history of cardiovascular disease, diabetes or any other chronic illnesses, smoking, alcohol consumption, physical activity, year of diagnosis of RA, Disease Activity Score, current medication of RA) were recorded. The patients; weight, number of tender swollen joints, height and waist circumference was recorded during physical examination. Hemodynamic parameters (blood pressure, heart rate, pulse pressure, PWV [CfPWV and AIx]) and paraclinical investigations (CRP, FBC) were noted.

Data collection

Data was collected by the consulting cardiologist. Socio-demographic data (date of birth, sex, marital status, level of education and monthly income) were collected using a preconceived data abstraction form (see appendix 1), together with clinical histories (family history of cardiovascular disease, diabetes or any other chronic illnesses, smoking, alcohol consumption, physical activity, year of diagnosis of RA, Disease Activity Score (DAS), current medication of RA). Physical examination was done to obtain weight, height, waist circumference. Weight was measured with a calibrated electronic balance and recorded in kilograms (kg). Height was measured with a stadiometer with vertical backboard and a head plate in centimeters (cm). Waist circumference was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest using a tape, and at the end of normal expiration and recorded in cm.

AIx and central hemodynamic parameters

After 10 mins of supine rest, peripheral blood pressure was recorded at the brachial artery using an electronic sphygmomanometer OMRON M3 (OMRON HEALTHCARE Co. Ltd. Kyoto, JAPAN). Blood Pressure values obtained were then recorded in the sphygmocorCvms software. Radial artery waveform was obtained with a hand-held tonometer probe (Millar pressure tonometer, PWV

Medical, Sydney, Australia) from the right wrist and a corresponding central waveform was generated with a validated transfer function (Sphygmocor, AtCor, Sydney). AIx a composite measure of systemic arterial stiffness and wave reflection amplitude, heart rate and central hemodynamic parameters were determined by the integrated software. All measurements were made in duplicates and mean values used for analysis.

PWV measurement

After entering values for mean pressure, diastolic pressure, distal and proximal distances into the software, the CfPWV path length was measured to the nearest millimetre from the right carotid pulse to the suprasternal notch (proximal distance) and from the suprasternal notch to the femoral pulse (distal distance). This distance was multiplied by a factor of 0.8. This was then followed by placing ECG electrodes on the patient's right wrist, left wrist and left foot respectively. An ECG tracing scrolled across the computer monitor with a net positive QRS complex and quality pulse waveforms were obtained from the carotid and femoral pulses. The software displaced the calculated PWV. At least two measurements were made. Arterial stiffness was defined as; an increased aortic PWV (pulse wave velocity ≥ 10 m/s) or as increased aortic AIx (augmentation index: AIx ≥ 30%).

Statistical Analysis

Data analysis was done using SPSS version 21. Group comparisons for categorical variables were done using the chi-squared test or Fisher's exact test where appropriate, while the independent samples t-test was used for comparing group means for normally distributed continuous variables. The level of Statistical significance was set at a p-value ≤ 0.05.

Ethical Considerations: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the faculty of Medicine and biomedical sciences, University of Yaoundé I (reference number 0221/UYI/FMSB/VDRC/DAASR/CSD; 07/05/2018).

3. Results

Socio-demographic parameters of study participants

A total of 63 patients were enrolled, 31 cases (RA patients) and 32 controls (healthy participants). Our study population was predominantly female, (54/63, 84.1%), with a similar sex distribution in case and control groups, (83.9% and 84.4% females predominance in case and control groups respectively). Similarly, the mean ± SD age was matched in both groups, with a mean age of 47 ± 14 years in cases and 44 ± 13 years in the control group, p = 1.01. Table 1 summarizes socio-demographic data of our study population.

Clinical parameters of study participants

Our study participants in the case arm had a mean ± SD disease duration of 9 ± 7 years, with most of them being in moderate disease activity (48.4%). As concerns medication, the most used medications were corticosteroids (70.1%),

Table 1. Socio-demographic characteristics of study population.

Characteristic	RA patients (n, %) N: 31	Healthy subjects (n, %) N: 32	Total (n, %) N: 63
Gender			
Male	5 (16.1)	5 (15.6)	10 (15.9)
female	26 (83.9)	27 (84.4)	53 (84.1)
Marital status			
Married	16 (51.6)	11 (34.4)	27 (42.9)
Single	9 (29.0)	16 (50.0)	25 (39.7)
widow	6 (19.4)	5 (15.6)	11 (17.4)
Occupation			
Student	2 (6.5)	1 (3.1)	3 (4.8)
Unemployed	12 (38.7)	9 (28.1)	21 (33.3)
Self employed	3 (9.7)	8 (25)	11 (17.5)
employed	14 (45.2)	14 (43.8)	28 (44.4)
Level of education			
No education	1 (3.2)	0 (0)	1 (1.6)
Primary	2 (6.5)	0 (0)	2 (3.2)
Secondary	16 (51.6)	13 (40.6)	29 (46.0)
Higher	12 (38.7)	19 (59.4)	31 (49.2)
Income			
<50,000	14 (45.2)	11 (34.4)	25 (39.7)
50,000 - 200,000	14 (45.2)	18 (56.3)	32 (50.8)
200,000 - 500,000	1 (3.2)	1 (3.1)	2 (3.2)
No income	2 (6.4)	2 (6.3)	4 (6.3)

followed by methotrexate (61.3%). Compared to healthy participants, RA patients presented higher rates cardiovascular risk factors such as abdominal obesity (20/31 vs 11/32, $p = 0.04$); body Mass Index (BMI) ≥ 25 kg/m^2 (20/31 vs 11/32, $p = 0.02$) and hypertension (5/31 vs 1/32, $p = 0.02$). As concerns biochemical parameters, the mean fasting Blood Sugar (Mean: 111.58 ± 46.4 vs 87.72 ± 13.86, $p \leq 0.01$) and median CRP (Median: 1 [1 - 2] vs 6 [3 - 11], $p \leq 0.01$) were significantly higher in RA patients as compared to healthy controls. Table 2 summarises relevant clinical data of study participants.

Evaluation of arterial stiffness

As previously described, we used CfPWV and AIx to evaluate arterial stiffness. Overall, the mean ± SD PWV was significantly higher in RA patients (8.85 ± 2.1), as compared to healthy controls (7.5 ± 1.4), $p \leq 0.01$. Similarly, the median [IQR] AIx was significantly higher in RA patients; 33 [26 - 43] as compared to

healthy controls; 26 [20 - 31], p = 0.01. See Table 2.

Using CfPWV to assess for arterial stiffness, 18/31 (58.1%) RA patients had CfPWV > 10 m/s as compared to 07/32 (21.9%) healthy controls; OR: 3.58; p = 0.02; 95% CI: 1.2 - 10.1. Similarly, RA patients had 6 fold increased odds of having AIx ≥ 30% (12/31) as compared to healthy controls (3/32), OR: 6.11; p ≤ 0.01; 95% CI: 1.5 - 24.5. On logistic regression, CRP (p = 0.032), RA (p = 0.021), and hypertension (p = 0.005) were independent determinants of PWV. See Table 3.

Table 2. Clinical data of study population

Parameter	RA Patients	Healthy subjects	p value
Disease Characteristics			
Disease duration, mean ± SD, years	9 ± 7	/	/
Disease activity score, n (%)			
• HAD, n (%)	3 (9.7%)	/	/
• MDA, n (%)	15 (48.4%)	/	/
• LDA, n (%)	5 (26.1%)	/	/
• Remission, n (%)	8 (25.8%)	/	/
Medications			
• Corticosteoid, n (%)	20 (70.9%)	/	/
• Methotrexate, n (%)	19 (61.3%)	/	/
• Hydroxychloroquinone, n (%)	14 (45.2%)	/	/
• NSAID, n (%)	4 (12.9%)	/	/
• Sulfasalazine, n (%)	2 (6.5%)	/	/
• No medications, n (%)	3 (9.7%)	/	/
Anthroprometric parameters			
BMI, mean ± SD, kg/m^2	28.0 ± 4.8	25.2 ± 3.7	p = 0.05
Abdominal circumference, mean ± SD, cm	95.6 ± 10.5	88.6 ± 9.7	p = 0.07
Cardiovascular risk factors			
Smoking, n (%)	0	0	/
Alcohol consumption, n (%)	15 (48.4%)	22 (68.8%)	0.10
Family history of CVD, n (%)	17 (54.4%)	14 (43.8%)	0.40
Abdominal obesity, n (%)	20 (64.5%)	11 (34.4%)	**0.02**
Physical activity, n (%)	10 (32.3%)	17 (53.1%)	0.10
BMI ≥ 25 kg/m^2, n (%)	20 (64.5%)	11 (34.4%)	**0.02**
Hypertension, n (%)	5 (16.1%)	1 (3.1%)	**0.02**
Dyslipidemia, n (%)	0	0	/

Continued

Diabetes, n (%)	2 (6.5%)	0	0.54
Biochemical Profile			
CRP, median [IQR] (mg/l)	5.6 [3.0 - 11.4]	0.2 [0.2 - 0.34]	**<0.0001**
FBS	111.6 ± 46.4	87.7 ± 13.9	**0.001**
• Normal glycemia	20 (62.5%)	32 (100%)	/
• Glucose intolerance	4 (12.9%)	0%	/
• Hyperglycemia	7 (22.6%)	0%	/
Haemodynamic Parameters			
Peripheral			
• SBP	123 ± 16	119 ± 11	0.31
• DBP	81 ± 9	80 ± 7	0.42
• PP	42 ± 10	38 ± 7	0.68
• HR	79 ± 11	73 ± 8	0.05
• PMAP	95 ± 10	93 ± 8	0.06
• Central			
• PWV	8.9 ± 2.1	7.5 ± 1.4	**0.002**
• AIx	28.5 ± 10.7	22.2 ± 9.3	**0.01**
• CSBP	115 ± 15	114 ± 13	0.86
• CDBP	82 ± 9	81.4 ± 8	0.73
• CMAP	96 ± 11	93 ± 9	0.13

Legend: The table summarizes clinical findings of the study population. Significant p values are presented in bold.

4. Discussion

We sought to describe patterns of arterial stiffness in RA patients, as compared to healthy controls, using CfPWV and AIx. We observed a significant difference in mean CfPWV and AIx between RA patients and healthy subjects. As concerns CfPWV, RA patients had a higher mean value of CfPWV (1.40 m/s), as compared to the healthy subjects. This result is similar to findings by other studies, such as Touré *et al.*, who showed similar findings [18]. This might be due to the chronic inflammatory state in RA patients (also indicated my elevated CRP in our population), which impairs endothelial function leading to increase progression of arteriosclerosis and thus arterial stiffness. Similarly, AIx was higher in RA patients when compared to that healthy subjects. This comes in agreement with many other studies who showed that AIx was higher in RA patients in the absence of traditional CV risk factors [19] [20]. As shown by existing literature, increased AIx is a good predictor of future cardiovascular events and mortality and is associated with large artery remodelling in RA patients. As different

Table 3. Multivariate analysis.

Variable	*p* value	Odd ratio (95% CI)
Physical activity	0.662	0.045 (0.001 - 0.342)
Alcohol	0.321	0.284 (0.040 - 1.322)
Arterial pressure	0.052	0.098 (0.403 - 2.301)
Body Mass Index	0.063	
Normal weight versus Obesity		0.210 (0.105 - 7.910)
Overweight versus Obesity		0.420 (−0.741 - 8.525)
Disease duration	0.250	
1 - 5 years versus <1 year		0.724 (0.028 - 0.513)
5 - 10 years versus <1 year		0.632 (0.012 - 0.176)
>10 years versus <1 year		0.523 (−0.421 - 0.320)
CRP	0.001*	0.500 (0.014 - 0.9)
Hypertension	0.015*	0.221 (0.001 - 0.204)
Diabetes	0.051	
Glucose intolerance versus Diabetes		0.601 (0.005 - 8.210)
Normal glycemia versus Diabetes		0.500 (0.041 - 8.17)
CMA	0.524	0.410 (−8.78 - 1.252)
CPULSEPRESSURE	0.422	0.653
CSBP	0.799	0.002
CDBP	0.965	0.065
Age	0.814	
Diagnosed of RA	0.021*	0.036 (0.093 - 0.743)
DAS	0.621	
MDA vs Remission		0.604 (0.125 - 0.910)
LDA vs Remission		0.742 (0.014 - 0.07)
HAD vs Remission		0.254 (0.011 - 0.91)

Legend: The table shows linear regression analysis for factors influencing CfPWV. The asterix (*) indicates significant p values and therefore independently associated factors.

cardiovascular risk factors affect the Aix such as hypertension as described by Kingue *et al.*, it may be seen as a composite measure of deleterious effects on the vascular system [21]. Therefore, measuring the AIx in addition to noting traditional cardiovascular risk factors could be a valuable tool for assessing the risk in a given patient especially in the context of RA.

Chronic inflammation has been suggested to be related to stiffening of arteries with the possible mechanism being vessels wall infiltration by inflammatory cells which promotes increase production of matrix metalloproteinase with subse-

quent degeneration of compliant elastin fibres that, in turn, lead to decreased arterial compliance. C-reactive protein represents the most studied inflammatory biomarker of cardiometabolic disorders so far. CRP was found to be higher in RA patients and independently associated with arterial stiffness in our study population, though epidemiological data on the cross-sectional relationship between CRP and measures of AS from literature are controversial [22] [23]. Remarkably, CRP was shown to a strong predictor of PWV in a prospective setting within longer follow up periods of more than 15 years [24] [25]. Despite the fact that we found CRP levels to be higher in RA patients than controls, the Median CRP in RA patients was quite low (5.6 mg/l) to fully explain arterial stiffness. The current findings therefore suggest that, the increased arterial stiffness in patients under study reflected the cumulative inflammatory disease process rather than the degree of acute systemic inflammation.

Hypertension was independently associated with arterial stiffness in our study population, with diabetic patients showing higher chances of arterial stiffness, though not statistically significant after logistic regression. Hypertension increases pulsatile aortic wall stress which accelerates elastin degradation, leading to arterial stiffness [25]. Kingue *et al.* showed that, arterial compliance decreases with increase severity of hypertension, indicating a higher risk of developing cardiovascular events in severely hypertensive patients [21]. Diabetes causes accelerated arterial ageing, thereby enhancing AS in both type 1 and type 2 Diabetes. Furthermore, the presence of microvascular and macrovascular complications is associated with a further increase in AS [26].

Potential Limitations

Inflammatory markers in particular may not accurately represent concentrations over time and cumulative inflammatory burden. Another limitation could be that the majority of our RA patients were on methotrexate which may be responsible for the insignificant values of some arterial stiffness parameters. A previous study suggested that methotrexate treatment reduces overall cardiovascular mortality in patients with rheumatoid arthritis [27].

5. Conclusion

In this sub-Saharan setting, aortic stiffness is increased in rheumatoid arthritis patients as compared to healthy control subjects, indicating a higher propensity to develop cardiovascular events in this population, especially in those with high CRP values (CRP ≥ 25 mg/l), and those with hypertension. Therefore, RA patients should undergo more meticulous screening for cardiovascular risk factors and more specific cardiovascular prevention strategies, in order to limit future cardiovascular events.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

I. Data Abstraction Form

Last-First names: ……

Identification number: ……

Address: ……

Person/persons to contact: ……

Date of birth:
|__|__|/|__|__|/|__|__||__|__|
DAY/MONTH/YEAR

Age:

Date:
|__|__|/|__|__|/|__|__||__|__|

SECTION 1: SOCIO-DEMOGRAPHIC DATA

101	Gender: 1. Male |__| 2. Female |__|	|__|
102	Marital Status: 1. Married |__| 2. Single |__| 3. Divorced |__| 4. Widowed |__|	|__|
103	Level of education: 1. Primary |__| 2. Secondary |__| 3. University |__| 4. Never been to school |__|	|__|
104	Occupation: 1. Employed |__| 2. Student |__| 3. Unemployed |__| 4. Self-employed |__|	|__|
105	Income: 1. <50,000 |__| 2. 50,000 - 200,000 |__| 3. 200,000 - 500,000 |__| 4. >500,000 |__|	

SECTION 2: CLINICAL DATA

Past Medical History

201	Have you been diagnosed with RA? YES/NO	
202	If yes in which year were you diagnosed of RA/disease duration? <6 Months, 6 Months - 1 year, 1 - 5 years, 5 - 10 years, >10 years	|__ |
203	Hypertension 1. Yes |__| 2. No |__|	|__|
204	Diabetes 1. Yes |__| 2. No |__|	|__|
205	Dyslipidemia 1. Yes |__| 2. No |__|	
	Chronic inflammatory diseases? 1. Yes |__| 2. No |__| If yes, which?	
206	Any other chronic illness 1. Yes |__| 2. No |__| If yes which? ……	|__|
207	Any family History of Cardiovascular Disease? 1. Yes |__| 2. No |__| If yes please state ……..	|__|

Social History

Smoking

208	Do you smoke? 1. Yes |__| 2. No |__|	|__|
209	How long have you been smoking or stopped (if current or ex-smoker)?	|_____|
210	How many of these do you smoke per day?	|_____|
211	Quantity in Pack per year? <5, 5 - 10, 10 - 15, 15 - 20, >20	|_____|

Alcohol Consumption:

212	Do you take any alcoholic drinks like beer, wine, and whisky? 1. Yes |__| 2. No |__|	|__|
213	How often do you take alcoholic drinks? 1. ≥5 days/week |__|; 2. 1 - 4 days a week |__|; 3. 1 - 3 days/month |__|; 4. less than once per month |__|	|__|
214	What quantity do you drink in one week? Number of units	|__|
215	Alcoholic index: <5, 5 - 10, 10 - 15, 15 - 20, >20	

Continued

Physical activity:

301 Do you do physical activities? 1. YES |__| NO|__| |__|
What duration? <30 mins |__| 30 m - 1 h |__| 1 h - 1 h 30 |__| >2 h |__|

302 At what frequency? |__|
1. Once/week|__| 2. Twice/week|__| 3. Trice/week |__| 4. Daily |__|

303 What level of physical activity do you do during your leisure time? |__|
1. Mild |__| 2. Moderate |__| 3. High|__|

Drug history

401 When did you start taking medications for Rheumatoid arthritis?

402 Which of the following medications do you take? |__|
1. Methotrexate |__| 2. Aziathropine |__| 3. Cyclosporine |__| D-Penicillamine |__|
4. Sulfasalazine |__| 5. Hydroxychloroquine |__| 6. Minocycline|__| 7. Leflunomide|__|
8. Infliximab |__| 9. Etanercept |__| 10. Corticosteroid |__| 11. NSAIDs|__|

403 Are there other medications you take routinely? Yes |__| No |__| if yes please state them |__|

Disease Activity Score (DAS) |__|

404 Number of tender joints:
Number of swollen joints:
CRP/ESR:
Patient global health/10

SECTION III: ANTHROPOMETRIC AND BLOOD PRESSURE MEASUREMENTS

501 Weight ……kg; Height……. m|__|
BMI: Underweight, normal, overweight, obese,

502 waist circumference ……cm
abdominal obesity YES/NO

503 Average clinic Systolic Blood pressure……..mmHg

504 Average clinic Diastolic Blood pressure……mmHg

505 Heart rate……..beats/min

506 Pulse pressure

PWA

601 PWV

602 Have arterial stiffness? YES/NO

603 Aix

604 Aix: Normal, increased

605 Central pulse pressure

606 Central blood pressure

SECTION 4: PARA-CLINICAL INVESTIGATIONS

CRP:
701 Range normal/high

702 Fasting Capillary glycemia:
Range hypo, normal, glucose intolerance, hyperglycemia