BLOOD PRESSURE INDICES AND DISEASE SEVERITY IN PATIENTS WITH SICKLE CELL ANAEMIA.

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ABSTRACT

BACKGROUND: Individuals with sickle cell anaemia (SCA) have lower systemic blood pressures compared to individuals with haemoglobin HbAA phenotype.

OBJECTIVE: To evaluate blood pressure indices of individuals with SCA in steady state, in comparison with haematological and clinical markers of disease severity.

METHODOLOGY: Seventy-nine (79) individuals with SCA (subjects) in steady state and 50 age-matched individuals with Hb AA (controls) were prospectively studied. Height, blood pressure (BP), weight, creatinine clearance (by 24-hour urine collection), full blood count (FBC) and reticulocyte count were obtained from all subjects and controls. Body mass index (BMI), corrected reticulocyte count, mean arterial pressure (MAP) and pulse pressure (PP) were calculated using standard protocols.The frequency of vaso-occlusive crises in the last one year and number of blood transfusions in the last two years were obtained from subjects. Data was analyzed using descriptive and inferential statistics and $p \leq 0.05$ was used to define the level of statistical significance.

RESULTS: The systolic (105.52±11.75mmHg and 113.20±7.94mmHg respectively; P = 0.01), diastolic (62.59±9.33mmHg and 75.40±5.70mmHg respectively; P=0.03) and mean arterial pressures (76.90±8.81mmHg and 88.00±5.51mmHg respectively;P =0.04) were significantly lower in subjects when compared with controls. ; pulse pressure (PP) was however significantly higher in subjects than controls (42.92±10.91mmHg and 37.80±7.43mmHg respectively (P = 0.03). In female subjects, the white cell count was negatively correlated with systolic BP (r = -0.39;P = 0.01) and PP (r = -0.33; P = 0.03).

CONCLUSION: Lower systolic and pulse pressures may predict worsening disease severity in individuals with sickle cell anaemia.

KEY WORDS: Sickle cell anaemia, disease severity, blood pressure indices.

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INTRODUCTION

Sickle cell anaemia, SCA, is a genetic disorder that results from a point mutation in the β-globin gene leading the production of haemoglobin S. The disease is prevalent in parts of Africa, the Mediterranean, Southeast Asia and Middle Eastern regions of the world and mirrors the malaria belt.[1]

Considerable variability has been observed in clinical manifestations as well as in laboratory parameters in individuals affected with this disease and this has profound impact on survival.[2] Indeed, these clinical and laboratory parameters are increasingly reported as indices of disease severity. In various studies, the frequency of vaso-occlusive crises,[3] transfusion requirement,[4] platelet[5] and the white cell counts[6] have been documented as markers of disease severity in SCD.

Blood pressure in individuals with SCA has been known to be lower than in controls.[7,8] This has been explained from the standpoint of defective renal concentrating ability with resultant hyposthenuria,[9] lower body mass index (BMI)[10] and reduced arterial wall stiffness[11] found in this disease. Complications such as cerebrovascular accidents have been reported in individuals with SCA who have higher blood pressures.[12] They have also been found to be at

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increased risk of developing ventricular diastolic dysfunction, which is an independent predictor of disease mortality.[12,13] Interestingly, some of these complications were reported to occur at blood pressure ranges considered conventionally normal.[14] These observations have increasingly supported the speculation that hypertension in individuals with SCA may occur at a lower blood pressure than is expected for individuals with Hb AA.[15] The purpose of this study was to evaluate the relationship between blood pressure indices in Nigerians with SCA and some clinical and laboratory parameters that may predict disease severity.

SUBJECTS AND METHODS:

Study subjects:

Seventy-nine (79) known SCA patients that regularly attended the follow–up clinic at the Haematology Out-patient department of our hospital were studied over a 7-month period. They were recruited while in steady state (clinically stable in the preceding three weeks and had not received blood transfusion in the preceding three months),[16] with no clinical features suggestive of congestive heart failure. Controls were 50 apparently healthy Hb AA medical and nursing students, age-matched with study subjects. Ethical approval was obtained from the Ethics and Research Committee of our hospital and all participants gave informed consent.

Clinical and Laboratory Measurements:

The number of major crises episodes in the last one year and the frequency of blood transfusions in the last two years were recorded in a case record form for all subjects. A 24-hour urine collection, for creatinine clearance determination was obtained from subjects and controls. Clinical parameters such as height, weight and blood pressure were measured and recorded for all participants. Sitting blood pressure was obtained at rest, using mercury sphygmomanometer. The systolic and diastolic blood pressures were reported as the first and fifth korotkoff sounds respectively,[17] while the mean arterial blood pressure (MAP) was calculated from the sum of the diastolic blood pressure and one-third of the pulse pressure. Body surface area (BSA) was calculated with the Mostella formula,[18] while body mass index (BMI) was calculated using the formula;

$$\frac{\text{Weight}}{\text{Height}^2}$$

Five milliliter (5mls) of venous blood, anticoagulated in EDTA was obtained from subjects and controls to obtain a full blood count (FBC) using a Sysmex (KN-21) automated analyzer while the reticulocyte count was obtained following standard operating procedures.[19]

The corrected reticulocyte count was calculated using the formula;

$$\frac{\text{Observed Reticulocyte (\%) x Measured Packed Cell Volume (PCV)}}{\text{Appropriate Normal Packed Cell Volume (PCV)}}$$

An addition 5mls of venous blood anticoagulated in lithium heparin was used to obtain serum creatinine levels. A 24hr urine collection was used to estimate urinary creatinine concentrations and together serum and urinary creatinine were used to calculate creatinine clearance for subjects and controls (Jaffe's methodology).[20]

Statistical methods:

Statistical analysis was performed using SPSS version 20 computer software (SPSS Inc.,

Chicago, IL, USA). Data was expressed using descriptive statistics such as percentages, means and standard deviations. The student's t-test was used to examine the relationship between blood pressure indices in SCA subjects and controls. Associations between parameters were tested using Pearson's linear regression for bivariate correlation The level of statistical difference was set at $P \leq 0.05$.

Results:

The mean PCV of subjects in this study was 25.39±6.77L / L, while it was 40.90±4.71L / L in controls. The mean ages of the subjects and controls were 25.39±6.77 years and 25.66±4.77 years, respectively, there was no significant difference between them (P = 0.79; Table 1). The mean crises frequency in subjects was 3.00±1.63 episodes in one year while 29 subjects (37%) were transfused at least once in the 2 years prior to recruitment.

The means of weight, BSA and BMI were lower in subjects than controls (49.39±9.01 kg and 61.04±10.24 kg; 1.45±0.16 and 1.65±0.15; and 18.31±2.48 and 23.27±2.55, respectively. These differences were statistically significant (P = 0.01, respectively; Table 1). There was no significant difference in the height of subjects when compared with controls (1.64±0.01m and 1.62±0.11m respectively; P = 0.25; Table 1).

The means of systolic and diastolic blood pressures in subjects and controls were 105.52±11.75mmHg and 113.20±7.94mmHg; and 62.59±9.33mmHg and 75.40±5.70mmHg respectively (Table 2). There were significant differences in the systolic and diastolic blood pressures of subjects and controls, P =0.01 and 0.03, respectively (Table 2). The means of pulse pressure (PP) and mean arterial pressure (MAP) in subjects and controls were 42.92±10.91mmHg and

37.80±7.43mmHg; and 76.90±8.81mmHg and 88.00±5.51mmHg respectively (Table 2). The differences in the PP and MAP of subjects and controls were significant (P = 0.03 and 0.04 respectively; Table 2).

In male subjects age correlated with systolic and diastolic blood pressures (r = 0.44; P = 0.01 and r = 0.39; P = 0.02 respectively; Table 3) while in female subjects, the white cell count correlated with systolic blood pressure (r = -0.39; P = 0.01) and PP (r = -0.33; P = 0.03; Table 4).

In male controls, the haematocrit was correlated with PP (r = -0.43; P = 0.02) while body mass index correlated with systolic blood pressure (r = 0.39; P = 0.03; Table 5). In female controls the diastolic and mean arterial pressures were positively correlated with age (r = 0.55; P = 0.01 and r = 0.49; P = 0.02, respectively) and negatively corrected with the corrected reticulocyte count (r = -0.61; P = 0.01 and r = -0.62; P = 0.01 respectively), Table 6.

DISCUSSION:

The controls in this study were matched for age with the subjects, as evidenced by the lack of statistical difference in the age distribution of subjects when compared to controls (Table 1).

Historically, individuals with SCA have been characterized by a number of unique physical attributes which have been collectively described as sickle cell habitus or facies, these include some craniofacial features and low BMI.[21,22] The later is said to be as a result of the increased resting energy expenditure caused by exacerbated erythropoietic and cardiac activities.[22] This study corroborated this observation with the weight, BSA and BMI being significantly lower in subjects compared to controls (P = 0.01 respectively; Table 1). On the contrary however, recent studies have reported obesity in individuals with SCD most probably due to better disease management in more developed countries. [24,25]

Sickle cell anaemia is associated with varying degrees of anaemia; this is largely due to chronic red cell haemolysis that occurs, even in the steady state.[26] Anaemia has a profound effect on the cardiovascular system that worsens with increasing severity.[17] In particular, both systolic and diastolic blood pressures have been found to be lower than expected in patients with anaemia.[26] Conversely, individuals with SCA with high PCV have been associated with increased blood viscosity, vascular endothelial dysfunction and hypertension.[27] Even in anaemic patients, the blood pressure has been found to be higher than expected for the severity of anaemia; this has led to the conclusion that individuals with SCA have relative hypertension.[15] A number of earlier studies had documented lower systolic and diastolic blood pressures, including MAP in patients with SCA, compared with controls. [7,10,26,28] Our finding corroborated the above studies; systolic and diastolic blood pressures were significantly lower in individuals with SCA, compared with controls (p values 0.01 and 0.03, respectively, Table 2). In contrast, Oguanobi et al studied 62 individuals with SCA in Enugu, south-east, Nigeria and showed that the systolic blood pressure was not significantly different when compared with controls (119.59±11.70 mmHg and 121.20±8.97 mmHg, respectively, P = 0.60).[29] Similarly, Akinola et al had earlier noted that the mean resting systolic blood pressures in individuals with SCA were within normal limits and were not different from control values.[30] The reasons for this discrepancies were not entirely clear from this study, however we observed that the subjects (particularly) in the Enugu study differed slightly from ours with regards to age, weight and PCV (28.27±5.58 years vs. 25.39±6.77 years, 54.97±10.61kg vs. 49.39±9.01kg and 24.07±3.10L / L vs. 23.90±4.30L / L, respectively). These are indices that are known to have negative and positive influences on the blood pressure.

The pulse pressure was significantly higher and the MAP significantly lower in individuals with SCA when compared with controls, in a similar study in Enugu, Nigeria.[29] This has been attributed to the haemodynamic changes of chronic anaemia, coupled with the increased background inflammatory and oxidative stress associated with the disease.[31] These combine to reduce left ventricular after load as well as blood viscosity, with a resultant decrease in arteriolar tone.[32] The findings of the present study confirmed the above observation (P =0.04, Table 2) when individuals with SCA were compared with controls.

A significant correlation was observed between the age of male individuals with SCA and systolic and diastolic blood pressures (Table 3). The effect of age on blood pressure (and its indices) in SCA has been a subject of diverse opinion. This study agrees with the reports of Rodgers et al,[12] Pegelow et al,[17] and Adams-Campbell et al, [32] while Johnson et al, [7] Grell et al, [28] Oguanobi et al, [29] and Akinola et al [30] did not document any correlation between age and blood pressure and argue that individuals with SCA fail to show the expected rise in blood pressure with age probably because of impaired renal handling of potassium and sodium, which tends to worsen with age.

In female individuals with SCA it was observed that a significant inverse correlation existed between white

blood cell count and systolic and pulse pressures (Table 4). The role of white blood cells in the pathogenesis of SCA, including its usefulness as a marker of disease severity has been variously documented.[6,33] This makes the observation in this study that shows a negative relationship between white cells and systolic blood pressure even more interesting. The earlier report of Desai et al [34] in a cohort of individuals with SCD in the United States is confirmed by this present study. It is believed that the physiologic effects of hypoxia from hypotension (and low haematocrit of SCD) may lead to a number acute anaemic events (AAEs) and acute phase response which could be reflected by an increased WBC and other reactants.[35] In the INTERSALT study, Dyer et al reported that the weight in apparently healthy (non-SCD) individuals correlated significantly with the blood pressure and concluded that weight (adjusted for height) may be a good analysis of the association of adiposity with blood pressure in apparently healthy individuals.[36] This was confirmed in male control in this study where a significant positive correlation between BMI and systolic blood pressure (r = 0.39; p = 0.03; Table 5) was observed. Similarly, male controls showed a significant negative correlation between haematocrit and pulse pressure (r = -0.43; P = 0.02; Table 5). This may be due to the influence of haematocrit on blood viscosity, endothelial function and pulse wave velocity (PWV). Increased PWV has been associated with subclinical organ dysfunction.[37]

The work of Laurent et al noted that progressive arterial wall stiffness was linked to age-dependent vascular damage, in non-SCD subjects, while Demirci et al observed that worsening arterial wall stiffness was most related to high MAP.[38,39] This study recorded a variable relationship between blood pressure indices and age in the non SCD subjects; while it was positively correlated with diastolic and mean arterial pressures in females, (r = 0.55; P = 0.01 and r = 0.49; P =0.02, respectively, Table 6) no similar relationship was observed in males, the reason for this was not apparent from this study.

CONCLUSION

Blood pressure indices varied significantly in individuals with SCA when compared with apparently healthy controls and variations were related with advancing age in males and white cell count in females. Monitoring of the blood pressure in individuals with SCA may thus be useful in determining those with severe disease, particularly among the females.

Table 1: Comparison of Demographic and Anthropometric Data in SCA and Control subjects.

Parameters	HB SS Mean (SD) n = 79	Controls Mean (SD) n = 50	t – Test	*P*-Value
Age (years)	25.39 (6.77)	25.66 (4.77)	-0.26	0.79
Weight (kg)	49.39 (9.01)	61.04 (10.24)	-6.79	*0.01
Height (m)	1.64 (0.01)	1.62 (0.11)	1.16	0.25
Body Surface Area (m^2)	1.45 (0.16)	1.65 (0.15)	-7.00	*0.01
Body Mass Index (kg/m^2)	18.31 (2.48)	23.27 (2.55)	-10.94	* 0.01

*significant p values.

Table 2: Comparison of Blood pressure indices in subjects and controls.

Parameter	Hb SS (79) Mean (SD)	CONTROLS (50) Mean (SD)	t – Test	*P* - Value
Age (in years)	25.39(6.77)	25.66(4.77)	-0.26	0.79
Systolic blood pressure (mmHg)	105.52(11.75)	113.20(7.94)	-4.43	*0.01
Diastolic blood pressure (mmHg)	62.59(9.33)	75.40(5.70)	-9.67	*0.03
Pulse pressure (mmHg)	42.92(10.91)	37.80(7.43)	3.17	*0.03
Mean arterial pressure (mmHg)	76.90(8.81)	88.00(5.51)	-8.80	*0.04

*significant p values.

Table 3: Correlation Analysis for Male subjects; Blood pressure indices with clinical and laboratory parameters.

Parameter	Systolic Blood pressure	Diastolic Blood pressure	Mean arterial pressure.	Pulse pressure
Haematocrit				
r	0.23	-0.15	0.20	0.11
p	0.18	0.41	0.25	0.52
Frequency of crises				
r	-0.09	-0.21	-0.19	0.09
p	0.60	0.24	0.29	0.61
Weight				
r	0.13	0.16	0.17	-0.01
p	0.46	0.38	0.34	0.97
Body Mass Index				
r	0.08	0.17	0.15	-0.07
p	0.66	0.34	0.38	0.68
Body Surface Area				
r	0.14	0.16	0.17	-0.01
p	0.44	0.36	0.32	0.98
Age				
r	0.44	0.39	0.47	0.11
p	*0.01	*0.02	0.14	0.54
History of transfusion				
r	-0.17	-0.32	-0.30	0.12
p	0.34	0.06	0.08	0.50
Corrected reticulocyte count				
r	-0.05	-0.22	-0.18	0.15
p	0.78	0.22	0.31	0.41
White Blood Count				
r	-0.22	-0.26	-0.28	-0.00
p	0.20	0.15	0.11	0.99
Measured Creatinine Clearance				
r	-0.15	0.01	-0.05	0.16
p	0.14	0.96	0.76	0.36

Table 4: Correlation Analysis for Female SCA subjects; Blood pressure indices with clinical and laboratory parameters.

Parameter	Systolic Blood pressure	Diastolic Blood pressure	Mean arterial pressure	Pulse pressure
Hematocrit r p	 0.03 0.83	 -0.01 0.95	 0.01 0.95	 0.04 0.77
Frequency of crises r p	 0.12 0.42	 0.14 0.37	 0.15 0.32	 0.02 0.90
Weight r p	 0.28 0.07	 0.14 0.34	 0.23 0.14	 0.18 0.24
Body Mass Index. r p	 0.14 0.35	 0.06 0.69	 0.11 0.48	 0.11 0.49
Body Surface Area r p	 0.28 0.06	 0.14 0.37	 0.22 0.14	 0.19 0.21
Age r p	 0.28 0.06	 0.13 0.41	 0.22 0.16	 0.20 0.19
History of transfusion. r p	 -0.12 0.45	 0.02 0.90	 -0.04 0.80	 -0.14 0.35
Corrected reticulocyte count. r p	 0.13 0.40	 0.26 0.09	 0.24 0.11	 -0.07 0.63
White Blood Count r p	 -0.39 *0.01	 -0.11 0.47	 -0.26 0.09	 -0.33 *0.03
Measured Creatinine Clearance r p	 -0.08 0.61	 0.14 0.36	 0.06 0.69	 -0.20 0.18

*significant p values.

Table 5: Correlation Analysis for Controls (Male); Blood pressure indices with clinical and laboratory parameters. (N = 29)

Parameter	Systolic Blood pressure	Diastolic Blood pressure	Mean arterial pressure.	Pulse pressure
Hematocrit				
r	-0.31	0.16	-0.04	-0.43
p	0.11	0.42	0.85	*0.02
Weight				
r	0.01	0.12	0.09	-0.08
p	0.98	0.54	0.65	0.67
Body Mass Index.				
r	0.39	0.10	0.26	0.32
p	*0.03	0.60	0.18	0.09
Body Surface Area				
r	0.01	0.11	0.08	0.08
p	0.97	0.57	0.67	0.69
Age				
r	-0.03	-0.25	-0.19	0.16
p	0.87	0.19	0.32	0.42
Corrected reticulocyte count.				
r	-0.07	-0.23	0.20	0.10
p	0.72	0.23	0.31	0.61
White Blood Count				
r	-0.12	0.14	0.04	-0.22
p	0.55	0.48	0.83	0.25
Measured Creatinine Clearance				
r	-0.18	-0.12	-0.17	-0.09
p	0.35	0.54	0.37	0.63

*significant p values.

Table 6: Correlation Analysis for Controls (Female); Blood pressure indices with clinical and laboratory parameters. (N = 21)

Parameter	Systolic Blood pressure	Diastolic Blood pressure	Mean arterial pressure	Pulse pressure
Hematocrit				
r	-0.11	0.25	0.12	-0.27
p	0.65	0.28	0.62	0.25
Weight				
r	-0.06	0.33	0.20	-0.27
p	0.79	0.15	0.39	0.23
Body Mass Index.				
r	0.15	0.26	0.26	-0.02
p	0.52	0.26	0.26	0.93
Body Surface Area				
r	-0.09	0.31	0.17	-0.29
p	0.71	0.17	0.46	0.21
Age				
r	0.20	0.55	0.49	-0.16
p	0.39	*0.01	*0.02	0.50
Corrected reticulocyte count.				
r	-0.37	-0.61	-0.62	0.02
p	0.11	*0.01	*0.01	0.93
White Blood Count				
r	0.05	-0.02	0.02	0.67
p	0.82	0.93	0.95	0.78
Measured Creatinine Clearance				
r	0.20	-0.13	0.02	0.28
p	0.38	0.58	0.94	0.22

*significant p values.

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