

Determinants of Intrarenal Vascular Resistance in Congolese Sickle Cell Patients in Kinshasa: A Hospital-Based Study

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ABSTRACT

Objective: The aim of our study was to detect early changes in renovascular resistance through renal Doppler indexes in sickle cell disease (SCD) patients.

Methods: By a cross-sectional study, two groups were consecutively examined with duplex ultrasound from 1 January to 30 September 2011. One group consisted of patients with SCD attending the sickle cell outpatient clinic, 61 homozygous (SS pattern, mean age 16 years) and 21 heterozygous (AS pattern, mean age 15 years). The other group was a control group consisting of randomly selected patients who were routinely attending the sonography division for non renal abdominal sonography. All control patients were age matched with patient group (within 1 year) to remove the confounding effect of age. The resistive (RIs) and pulsatility (PIs) indices of the main as well as intrarenal arteries were compared among groups.

Results: Homozygous SCD patients had significantly higher RIs and PIs in the intrarenal arteries ($P = 0.001$) compared to controls while there was no significant differences in RIs and PIs between heterozygous SCD patients and controls. Among SCD patients RIs in the intrarenal arteries positively correlated with eGFR ($r = 0.36$; $p = 0.001$), pulse pressure ($r = 0.25$; $p = 0.001$), white blood cell ($r = 0.36$; $p = 0.001$) and negatively correlated with hemoglobin ($r = 0.83$; $p = 0.001$). In multivariate linear regression analysis, the relation persisted only for hemoglobin which explained 61% of the variation of RIs.

Conclusion: The present study documents that there are early intrarenal hemodynamic alterations among SCD patients. This implies that the duplex evaluation of the intrarenal arteries, could be a useful non invasive procedure for monitoring SCD patients and could help detect persons at risk of developing SCD nephropathy.

Key words: renal vascular resistance, determinants, sickle cell disease, black Africans.

INTRODUCTION

Sickle cell disease (SCD) and its complications put an immense amount of social and economic burden on the health infrastructure and resources throughout sub-

Saharan Africa (SSA)¹⁻⁶. Renal complications affect nearly 30-50% of adults with SCD, leading to notable morbidity and mortality^{7,8}. Therefore, early identification and management of SCD

patients at risk of developing sickle cell nephropathy (SCN) appears as a rationale approach to reduce the burden of SCD⁹. Standard renal function tests like serum creatinine, glomerular filtration rate (GFR) and urinary albumin excretion (UAE) become abnormal in this disease only when renal damage has become extensive and largely irreversible¹⁰. Furthermore, the concept of microalbuminuria (MA) as an established hallmark of renal damage and a predictive marker for progressive decline in renal function in disease such as SCD and diabetes has been challenged by the fact that many patients with advanced renal disease never develop MA; in addition, MA in some patients has been reported to regress over a period of time to normoalbuminuria¹¹⁻¹³. This observation highlights the need for identifying other markers that can help predict the early onset and the progression of SCN⁷. Many studies have addressed the biochemical markers but none appear to be specific and/or sensitive enough for clinical use¹⁴. Recently, increased intrarenal vascular resistance (RVR) has been established as a predictor of progressive disease in a number of diseases including SCD¹⁴. Therefore, renovascular changes should be detected at an early stage before irreversible organ damage occurs due to chronic vasculopathy¹⁵. In this regard, Taori et al¹⁴ reported that renal doppler sonography resistive and pulsatility indexes could serve as early radiologic predictors of renovascular changes in sickle cell patients with normal routine urine laboratory tests¹⁴. These indexes can guide clinicians in initiating a more intensive monitoring of laboratory values and a timely treatment¹⁴.

In the Democratic Republic of Congo (DRC), the prevalence of sickle cell disease and of Sickle cell trait is estimated to be at 2% and 20%, respectively¹⁵⁻¹⁷. It has been shown that proteinuria and nephrotic syndrome are commonly seen in sickle cell patients and are associated with poor prognosis in the context of limited access to dialysis¹⁸. Therefore, early detection of patients at high risk of renal damage could

appear as a cost-effective approach to reduce the burden of SCD. Prompted with the above considerations, the present study was undertaken to evaluate the renal vascular resistance (RVR) using Doppler ultrasonography in steady state sickle cell patients attending a sickle cell outpatient clinic in Kinshasa in order to see the contribution of this technique in the management of SCD in the Democratic Republic Of Congo.

MATERIAL AND METHODS

This study was a cross-sectional observational study.

Subjects

In this cross-sectional study, two groups were consecutively examined with duplex ultrasound from 1 January to 30 September 2011. One group consisted of patients with SCD (n=82, range 7-40 years) attending the sickle cell outpatient clinic, 61 homozygous (SS pattern, mean age 16 years) and 21 heterozygous (AS pattern, mean age 15 years). The other group was a control group (n=40) consisting of randomly selected patients who were routinely attending the sonography division for non renal abdominal sonography. All control subjects were age matched with the SCD cases and were in the age group of 7-40 years.

All patients also had non clinical, laboratory, or radiologic evidence of renal disease. Two consecutive clinical contacts were made with the patients and controls, with second contact being a week after the first. For each study participant, a detailed history was obtained including participant's age, gender and relevant medical history of recurrent admissions, blood transfusions and drug use. A thorough physical examination was carried out on each study participant for weight, height, blood pressure (BP) and pulse rate. Weight and height were recorded and body surface area was estimated using standard normogram. The weight of each participant was measured at the nearest 0.1 Kg using a weighing scale made by SECA. The standing height was measured at the

nearest 1 cm using the stadiometer (MALESTI). Body mass index was calculated as weight (Kg)/height (m)². Two consecutive BP readings taken one minute apart were recorded with the subject in sitting position and using an automated device (AND Japan). The mean of two readings was used for statistical analysis. Heart rate was obtained together with BP from the automated device. Mean arterial pressure (MAP) was calculated as diastolic blood pressure (DBP) + [systolic BP (SBP) – DBP/3] and pulse pressure (PP) as SBP-DBP. Early morning urine samples were obtained and tested for albuminuria, using Medi-Test Combi-3 (Germany); in subjects with albuminuria negative samples, a venous blood sample was collected by venepuncture for hematological [hemoglobin, hematocrit, white blood cell (WBC), red blood cell (RBC)] and biochemical (blood glucose and serum creatinine). Haematological and biochemical parameters were determined using the automate Micros Computer 60, (Horiba, Japan) and Visual Biomérieux (France), respectively. Serum creatinine was estimated by picric acid method and patients with normal values (≤ 1 mg/dl) were included. Modified Schwartz formula¹⁹ for participants aged < 21 years and Modified of Diet in Renal Disease (MDRD) equation²⁰ for those aged ≥ 21 years were used for estimating glomerular filtration rate (eGFR).

Doppler Sonography Examination Procedure

Doppler sonography was performed on Prosound 3500 scanner (Aloka) with color flow Doppler facility, using 2.5 to 6 MHz multifrequency sector probe to evaluate renal vascular renal¹⁴. Patients were examined in the supine position: left lateral decubitus for the right kidney and right lateral decubitus for the left kidney. The transducer was placed in the midline with slight inclination to the left to get a coronal section of the aorta. Each renal artery was identified as lying between the superior mesenteric artery and the corresponding renal vein. Doppler

parameters were obtained for main renal, segmental, and interlobar arteries. Two readings from interlobar arteries in the upper pole, interpolar, and lower pole regions were taken and average values of interlobar parameters for each kidney. The mean of the Doppler indices from main renal, segmental, and interlobar arteries of both kidneys of a patient were taken and recorded. The average time taken for Doppler assessment of both kidneys in each subject was 25-30 minutes. For each artery, the resistivity index (RI) and pulsatility index (PI) were measured according to the following formulae: $RI = \frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{peak systolic velocity}}$ $PI = \frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{mean velocity}}$ ¹⁴. Patients who were dyspneic or unable to hold their breath as required were excluded from the study. Those patients with sickle cell crisis, tachycardia, and known hypertensive were excluded from the study.

Statistical analysis

The characteristics of SCD and control subjects were first described and using proportions for categorical variables and mean and standard deviation, for continuous variables.

The characteristics of the subjects of the three groups, i.e. controls, heterozygotes and homozygotes, were first compared globally using chi-square tests for categorical variables and a Kruskal-Wallis, non-parametric ANOVA, for continuous variables. Then, post-hoc Student t-tests were used to compare the groups two by two.

The mean renal RI and PI were used for statistical analysis of differences between groups were first compared globally using a Kruskal-Wallis and then between patients and controls using Student t test;.

The correlation between the duplex indices and clinical and biochemical parameters were assessed using the Pearson's correlation coefficients and then using a partial correlation coefficient to obtain a multivariate analysis. In all the

analyses $p < 0.05$ was considered statistical significant

This study was approved by the institutional review board and informed consent was obtained from all subjects or parent or guardian before enrolment.

RESULTS

General characteristics of the study population are displayed in Table 1 and 2. Compared to controls, homozygous (SS) sickle cell patients had lower IMC (16 ± 4

vs 19 ± 3 Kg/m²; $p = 0.001$), lower ? DBP (58 ± 7 vs 66 ± 7 mm Hg; $p = 0.001$) and higher heart rate (91 ± 12 vs 83 ± 12 b/min; $p = 0.01$). Except for IMC that was lower in heterozygous (AS) sickle cell patients in comparison with controls (17 ± 3 vs 19 ± 3 Kg/m²; $p = 0.05$), there was no differences regarding other variables of interest. As expected, SS patients had also significantly lower hemoglobin (8.15 ± 1.4 vs 13.26 ± 1.4 g/dl; $p = 0.001$), Ht (26 ± 4 vs 42 ± 4 %; $p = 0.001$) compared to AS and controls.

Table 1. General characteristics of the study population by hemoglobin status.

Characteristic	SCD		Controls n = 40	Global Test*	P	
	SS (n = 61)	AS (n = 21)			SS vs AA	AS vs AA
Age, years	16 ± 7	15 ± 7	17 ± 5	0.605	0.441	0.159
Gender: M/F	25/36	10/11	14/26	0.861	0.693	0.495
Weight, Kg	37 ± 13	43 ± 16	48 ± 13	0.001	0.001	0.216
Height, cm	146 ± 19	152 ± 22	156 ± 15	0.010	0.010	0.521
SBP, mm Hg	101 ± 8	104 ± 12	102 ± 10	0.266	0.409	0.587
DBP, mm Hg	58 ± 7	67 ± 8	66 ± 7	0.000	0.001	0.510
MAP, mm Hg	70 ± 6	76 ± 16	78 ± 12	0.000	0.001	0.486
PP, mm Hg	42 ± 10	36 ± 9	36 ± 8	0.003	0.003	0.987
HR, b/min	91 ± 12	76 ± 11	83 ± 13	0.000	0.001	0.707
Hb, g/dl	8.15 ± 1.4	12.95 ± 1.4	13.26 ± 1.4	0.000	0.001	0.432
Ht, %	26.45 ± 4.2	40.84 ± 4.3	41.78 ± 4.5	0.000	0.001	0.393
RBC 10 ⁶ /mm ³	2.62 ± 0.65	4.59 ± 0.58	4.61 ± 0.56	0.000	0.001	0.911
WBC 10 ³ /mm ³	15.6 ± 5.6	5.9 ± 1.4	5.6 ± 1.2	0.000	0.001	0.393
Platelets 10 ⁹ /mm ³	448.6 ± 157.07	238 ± 70.75	266 ± 83.11	0.000	0.001	0.195
Creatinine, mg/dl	0.36 ± 0.17	0.50 ± 0.24	0.64 ± 0.22	0.000	0.001	0.018
eGFR, ml/min/1.73 m ²	251 ± 180.92	129 ± 57.19	139 ± 78.06	0.000	0.001	0.001

Abbreviations: SCD, sickle cell disease SS, homozygous SCD patients AS, heterozygous SCD patients RI, resistive index RA, renal artery ISA, intersegmental artery ILA, interlobar artery.

* Global test for comparison of the three groups, SS, AS and AA: Kruskal-Wallis for continuous variables and Chisquare for categorical variables

Comparative analysis of duplex Doppler in both patients and controls (Table 2) reveals higher RI and PI values in the main renal ($p = 0.001$), the segmental ($p = 0.001$) and the interlobar ($p = 0.001$) arteries in homozygous patients compared to controls; there was no differences between heterozygous and controls regarding RI and PIs values in the intrarenal arteries. RI proved to be a less variable index than PI across the renal vasculature.

Table 2. Renal and intrarenal arteries duplex doppler ultrasound indices in the study population by hemoglobin status.

Parameter	SCD		Controls (AA) n = 40	Global Test*	P	
	SS (n = 61)	AS (n = 21)			SS vs AA	AS vs AA
RI						
-Main RA	0.68 ± 0.05	0.59 ± 0.03	0.57 ± 0.04	0.000	0.001	0.060
-ISA	0.66 ± 0.04	0.58 ± 0.03	0.57 ± 0.04	0.000	0.001	0.535
-ILA	0.66 ± 0.03	0.58 ± 0.04	0.57 ± 0.04	0.000	0.001	0.336
PI						
-Main RA	70 ± 6	76 ± 16	78 ± 12	0.000	0.001	0.486
-ISA	42 ± 10	36 ± 9	36 ± 8	0.000	0.003	0.987
-ILA	91 ± 12	76 ± 11	83 ± 13	0.000	0.001	0.707

Abbreviations: SS, homozygous sickle cell disease patients AS, heterozygous sickle cell disease patients AA, normal hemoglobin patients RI, resistive index RA, renal artery ISA, intersegmental artery ILA, interlobar artery.

* Global test for comparison of the three groups, SS, AS and AA: Kruskal-Wallis for continuous variables and Chisquare for categorical variables

In univariate analysis, there was in SCD patients a negative correlation between RI and hemoglobin ($r = 0.83$, $p = 0.001$), RBC ($r = 0.76$; $p = 0.001$), DBP ($r = -0.44$; $p = 0.001$),

MAP ($r = 0.24$; $p = 0.008$), and a significantly positive correlation what CrCl ($r = 0.36$; $p = 0.001$), PP ($r = 0.25$; $p = 0.001$), WBC ($r = 0.67$; $p = 0.001$), platelet ($r = 0.51$; $p = 0.001$) and pulse rate ($r = 0.26$; $p = 0.005$). In multivariate analysis the strength of the association persisted for only hemoglobin levels and the model explained 61% of the variance of RI; in addition, each one unit hemoglobin level decrease was associated with a correspondent increase in RI values of 0.76.

Using a cutoff of 0.70 and 1.15 for RI and PI, respectively, in SCD patients, 8.5% and 31.7% of homozygous patients had elevated RI and PI, respectively. No heterozygous patient showed elevated RI values; however, only one heterozygous patient had elevated PI values. When considering the 75th percentile as cutoff for RI (0.63) and PI (1.13), respectively, the proportion of patients with elevated RI and PI increased to 29% and 37.8%, respectively.

Table 3. Univariate and multivariate correlates of resistive index (RI) in SCD patients

Variable	Univariate r	P univariate	Multivariate r	P Multivariate*
Hb	0.83	0.001	0.44	<0.001
RBC	0.79	0.001	0.08	0.396
DBP	0.44	0.001	0.17	0.073
MAP	0.24	0.008	0.10	0.301
WBC	0.67	0.001	0.01	0.875
Platelets	0.51	0.001	0.02	0.815
eGFR	0.36	0.001	0.02	0.856
Heart rate	0.26	0.005	0.11	0.229
PP	0.25	0.007	0.05	0.617

Abbreviations: r, correlation coefficient Hb, hemoglobin RBC, red blood cell DBP, diastolic blood pressure MAP, mean arterial blood pressure WBC, white blood cell count eGFR, estimated glomerular filtration rate PP, pulse pressure.

* partial correlations, i.e. correlations adjusted for all other variables of this table

DISCUSSION

The present study reveals a significant increase in the RI and PI in homozygous SCD patients than in controls. Our findings are in agreement with the results of previous studies of renal vascular resistance (RVR) indexes in SCD patients^{14,21,22}. According to Taori et al¹⁴, the observed increase in RVR indexes could be a result of the increased intrarenal vascular tone due to various occlusive mechanisms occurring in SCD that include vascular intimal hyperplasia, thrombosis, altered vascular reactivity, and frank vasospasm. All these mechanisms are the consequence of the abnormal adhesive and procoagulant properties of sickled red blood cell (RBC) and identify the multifactorial nature of the disease other than just microvascular occlusion by sickled RBC¹⁴. However, the interpretation of these findings on RVR should take into consideration the potential influence of non renal factors such as BP, heart rate, the effect of transducer and atherosclerosis affecting the renal wave form²³. To minimize this potential influence of these confounders, patients

with tachycardia or hypertension were excluded, the non compressive sonographic technique was used to avoid an undue increase in RI by diminishing end-diastolic velocity and young patients in the age range 7-30 years were examined. In contrast to Taori et al¹⁴, differences in intrarenal RI and PI values between heterozygous SCD patients and controls did not reach the level of statistical significance. Since hemoglobin appears as the main determinant of RI in the present study as in others¹⁴, this discrepancy could be explained by the similar level of hemoglobin seen in the two groups.

Univariate analysis in SCD patients showed a positive correlation between RI and CrCl, WBC, platelets, PP, heart rate and a negative correlation with hemoglobin, DBP and MAP. However, the strength of the association persisted only for hemoglobin in multivariate analysis. Although many studies showed a negative correlation between RI and CrCl, it has been previously demonstrated in diabetic nephropathy, a condition sharing a similar pathogenesis with SCD nephropathy²⁴ that

the intrarenal arterial resistance correlates with CrCl differently depending upon the stage of the diabetic nephropathy (DN) with a positive correlation in patients with no evidence of clinical renal damage²⁵ and a negative one in those with clinical nephropathy²⁶. This could be the case for our patients without overt clinical nephropathy. Elevated levels of WBC and platelets, as markers of inflammation^{27,28}, have been already related to vascular injury in SCD^{29,30}. Indeed, beyond its role in phagocytizing and killing microorganisms, neutrophil can contribute to the process that impairs vascular integrity and blood flow through its capability to adhere to the endothelium and to generate reactive oxygen species^{29,30}. Correlation between RI and PP as a marker of arterial stiffness as well as heart rate, DBP, MAP has been already reported in other studies on RVR in SCD patients^{14,21,22}. These hemodynamic changes are thought to rely upon increased preload and decreased peripheral vascular resistance with subsequent reduction of afterload³¹. Elevated RI correlated negatively with hemoglobin, therefore implying the necessity for hemoglobin correction to prevent or at least delay the incidence of sickle cell nephropathy³². Anemia with subsequent oxidative stress, low grade inflammation and endothelial dysfunction may contribute to the progressive vascular injury observed in SCD³²⁻³⁶. Therefore, drugs known to reduce oxidative stress, inflammation and endothelial dysfunction such as renin angiotensin system inhibitors and HMG CoA reductase inhibitors or statins could help prevent or delay the renal damage in SCD patients at risk of developing nephropathy³⁷.

One point deserves to mention in the present study is that RI did not show a significant correlation with age. The relationship between RI and age remains a matter of debate. Although many studies³⁸ have reported a statistically significant positive correlation between RI and age,

some authors reported this correlation to be weak and of no clinical importance³⁹.

The findings of the present study are limited by the small sample size and the case-control design. Furthermore, we used updated Schwartz formula and MDRD equation to estimate GFR in SCD; although they correlate well with measured GFR, they were derived for use in subjects with chronic kidney disease and are known to overestimate GFR when compared with gold standard techniques. This positive bias likely is greater in children with SCD because of an above-normal proximal tubular secretion of creatinine and decreased muscle mass⁴⁰.

CONCLUSION

There are early intrarenal hemodynamic alterations in the form of pathologically elevated intrarenal RI in SCD. This implies the usefulness of using the duplex evaluation of the intrarenal arteries, as a non invasive procedure for monitoring SCD patients to identify those at risk of developing the sickle cell nephropathy.

Conflicts of Interest: No conflicts

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Authors' contribution

BJA: collected data and contributed to statistical data analysis and revised the manuscript.

LFB: wrote the protocol, contributed to statistical data analysis and drafted the manuscript

KPK and NAN: conducted statistical data analysis and revised the manuscript

RE: contributed to statistical data analysis and revised the manuscript

MJR: contributed to statistical data analysis and revised the manuscript

SEK: contributed to statistical data analysis and revised the manuscript

TML: contributed to statistical data analysis and revised the manuscript

LBM: contributed to statistical data analysis and revised the manuscript

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