



Research Brief

Impact of relative systemic hypertension on the heart in sickle cell anaemia

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ABSTRACT

Sickle cell anaemia (SCA) is associated with macrovascular complications at relatively normal blood pressures. This has led to the development of the term 'relative systemic hypertension' (RSH). The electrocardiography (ECG) and echocardiography (ECHO) findings in these people has not been well highlighted.

Patients with SCA in steady state were consecutively recruited. History, physical examination, ECG and ECHO information were obtained from all participants after informed consent was obtained. Eighty-three people were recruited in all- 15 of which had RSH, giving a prevalence of 18.1%. Those with RSH had higher packed cell volumes (PCV), smaller right atria area, lower tricuspid regurgitant velocities, lower incidence of early satiety, longer QTc and higher frequency of a history of vaso-occlusive crises. The indices of right and left ventricular function were normal in both groups. Right atrial area was the only significant determinant of RSH in this study.

RSH is associated with higher PCV, longer QTc and smaller right atrial area in SCA patients. More studies to evaluate sympathetic output in SCA with RSH is required.

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1. Introduction

Hypertension is arguably the most important non-communicable cardiovascular risk factor in the world. It prevalence in the general populace ranges between 9.3% and 48.1% in Africa.¹ Target organ damage like coronary artery disease, chronic kidney disease, heart failure and stroke are relatively common among those with uncontrolled hypertension.² And even though about a third of those with hypertension are aware and on orthodox antihypertensives, less than 50% of have their blood pressure within the normal range.¹

As the cardiovascular risk profile of people have been shown to rise once the blood pressure climbs above 115 mmHg systolic and 75 mmHg diastolic, there has been a drive among hypertension specialists, cardiologists and nephrologists to re-define

hypertension-reduce the cut-off points below the JNC VII recommendation of 140 mmHg systolic and 90 mmHg diastolic.^{3,4}

In sickle cell anaemia, target organ damage occurs at blood pressure levels that are significantly less than that of those with Haemoglobin A, with renal dysfunction and pulmonary hypertension found in those followed up.⁵ This has therefore spurred the discussion of strongly re-defining hypertension for this people group. This for now has been arbitrarily put at >120 mmHg systolic and >70 mmHg diastolic in studies.^{6,7} To make comparison with earlier studies easy, we kept to this definition for relative systemic hypertension. The aim of this study was to assess the impact of relative systemic hypertension on the heart using electrocardiography and echocardiography. We compared the clinical, electrocardiographic and echocardiographic characteristics of the patients.

2. Methods

The study was carried out at both the Cardiology and Haematology units of the University College Hospital, Ibadan. The study was descriptive, cross sectional in design.

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2.1. Subjects

The subjects were adult outpatients of the Haematology clinic. The subjects were confirmed as homozygous for haemoglobin S with the aid of haemoglobin electrophoresis. None of the subjects was on any chronic transfusion protocol and they were all indigenous Africans. The subjects were in steady state, as defined by Ballas et al.⁸

Exclusion criteria for subjects include those with hypertension, those in atrial fibrillation, those known with severe lung disease, human immunodeficiency virus infection, rheumatic heart disease, connective tissue disorders, diabetes mellitus and those with poor echocardiographic window. Controls were SCA patients without relative systemic hypertension.

This is a cross-sectional study of the cohorts from right ventricular function in sickle cell anaemia study group.⁹ A convenient sampling method was used for the study. Eligible subjects were consecutively recruited from the haematology clinic, after a written informed consent was obtained. The ethical approval was obtained from the joint University of Ibadan and University College Hospital ethical review board. This research conformed to widely accepted ethical principles as stated at the declaration of Helsinki. Clinical information was obtained from the subjects. A blood sample was collected for the estimation of packed cell volume (PCV). Blood pressure (BP) measurements were obtained according to standard guidelines with the aid of a mercury sphygmomanometer (Accoson, London). Anthropometric measurements were made according to standard recommendations. Body mass index (BMI) was calculated using the formula $BMI = \text{Weight (kg)}/\text{Height (M)}^2$. Body surface area was calculated using the Dubois formula.¹⁰

2.2. Electrocardiogram and echocardiographic evaluation

Twelve-lead resting electrocardiogram was also done for both SCA and HBA, with the paper speed at 25 mm per second and amplitude at 10 mm/mV using commercially available systems (QRS diagnostic® and ECGLAB®). Values were taken from computer-determined analysis of QT interval, heart rate, among other variables, with the QTc generated using a Bazett formula. Echocardiography was done according to standard recommendations.^{10,11} Details of measurements have been earlier described.⁹

2.3. Data management and analysis

All data obtained were entered into a standard proforma. Continuous variables were expressed as mean \pm standard deviation while categorical variables were expressed as count (percentages). Data analysis was done by IBM SPSS Statistics for Windows, Version 20.0.

The Shapiro–Wilks test was used to assess for normality of distribution of variables. The means of continuous variables were compared using the Student's *t*-test for independent groups. For

categorical variables, Chi square and/or Fisher's exact test was applied to test the equality of distributions between the two groups. The clinical, electrocardiographic and echocardiographic (ECHO) differences between those with and without RSH were evaluated as appropriate. Correlational analysis was done between RSH and related variables. A model was created using the significant correlates of RSH to assess for its determinants. A two tailed *p*-value less than 0.05 was considered significant.

3. Results

Eighty-three people with SCA were recruited for this study. Echocardiogram was done for all while Electrocardiogram was done for 41 people with SCA-7 with RSH, 34 without RSH.

Patients with RSH had a tendency to have a higher history of vaso-occlusive crises in the preceding 6 months as compared to those without RSH. However, those without RSH had a significantly higher history of early satiety than those with RSH History of symptoms of cardiovascular dysfunction or other types of crises were not different between both groups. All the patients that had blood transfusion yearly or more frequently had normal (not RSH) BPs (result not shown).

Right atrial area was smaller in those with RSH as compared to those without it. The P wave amplitude in lead II was also significantly smaller. The tricuspid regurgitant jet showed a trend towards being slower in those with RSH and the trans tricuspid late velocity [A] was also slower in them. The corrected QT interval was longer in those with RSH. Details are seen in [Table 1](#).

Packed cell volume and a history of vaso-occlusive crises were the only direct correlates of RSH. QTc interval, right atrial area, trans tricuspid A velocity and history of early satiety all correlated inversely with RSH. Details are seen in [Table 2](#). Right atrial area was however the only significant independent determinant of RSH in this study as seen in [Table 3](#).

4. Discussion

The prevalence of RSH in this study is 18.1%. The right atrial area of people with SCA was smaller in those with RSH than those without it. This may be due to the higher packed cell volume in those with RSH. Reduction in the PCV reduces the viscosity of the blood and reduces the afterload, leading to higher velocity of ejection of blood into the great arteries. This is supported by the finding of higher right ventricular outflow tract velocities in those with RSH.

Vaso-occlusive crises is known to not only cause target-organ damage and dysfunction, but the vessels themselves are also affected. This is supported by observations that the augmentation index and augmentation pressure in those with SCA are increased as compared to HBA controls.^{12,13} It is therefore interesting that

Table 1

Clinical, echocardiographic and electrocardiographic variables of SCA subjects with and without relative systemic hypertension(RSH).

Variables	With RSH (n=15)	Without RSH (n=68)	P value
Packed cell volume (%)	28.3 \pm 4.1	25.2 \pm 5.5	0.084
History of early satiety	2 (13.3%)	30 (44.1%)	0.039
Hx of Vaso-occlusive crises within the past six months	14 (93.3%)	43 (64.2%)	0.031
Left atrial diameter (cm)	3.42 \pm 0.52	3.66 \pm 0.51	0.125
Right atrial area (cm ²)	15.6 \pm 2.9	18.2 \pm 3.7	0.025
Transtricuspid late velocity [A](m/sec)	35.0 \pm 6.1	41.1 \pm 13.0	0.118
Tricuspid regurgitant velocity (m/sec)	176.3 \pm 37.1	212.8 \pm 56.3	0.113
RV outflow tract peak velocity (m/sec)	106.3 \pm 15.5	96.2 \pm 17.9	0.098
P amplitude in lead II (mV)	0.087 \pm 0.05	0.129 \pm 0.045	0.036
QTc interval (msec)	504 \pm 73.4	455.5 \pm 29.6	0.005

Table 2
Correlational analysis of variables with relative systemic hypertension.

Variables	Relative systemic hypertension	P value
Packed cell volume (%)	0.236 ^a	0.040
P amplitude in lead II	−0.288	0.068
QTc interval (msec)	0.399 ^b	0.010
Right atrial area (cm ²)	−0.250 ^a	0.025
Left atrial diameter (cm)	−0.148	0.182
Tricuspid A velocity	−0.268 ^a	0.015
Tricuspid regurgitant velocity (cm/sec)	−0.269	0.113
Sex	−0.088	0.427
History of early satiety	−0.243 ^a	0.027
History of Vaso-occlusive crises	0.245 ^a	0.027

^a Level of significance <0.05.

^b Level of significance <0.01.

Table 3
Determinants of relative systemic hypertension by binary logistic regression.

Variables	Odds ratio	P value	Confidence interval
Packed cell volume (%)	1.422	0.132	0.900–2.249
QTc interval	1.044	0.099	0.992–1.099
Right atrial area (cm ²)	0.354	0.027	0.141–0.891
Vaso-occlusive crises	0.182	0.328	0.006–5.514

R²-0.675(Nagelkerke); 0.401(Cox and Snell)

almost all patients with RSH have a past history of vaso-occlusive crises.

It has been postulated that the increased haemolysis, increased arginase activity, reduced arginine-ornithine ratios¹⁴ with attendant reduced nitric oxide bioavailability leads to increased vasoconstriction and higher blood pressures. This explanation may be sufficient to explain the blood pressure characteristics in those with SCA as compared to those with normal and other haemoglobinopathies. However, it will not explain the findings here, possibly because these were evaluated while in steady state. More plausible explanations include increased bioavailability of nitric oxide in steady state.¹⁵ There are controversies surrounding whether arterial wall stiffness is increased or not in people with SCA in steady state, though studies with larger sample sizes suggest that it is increased.^{12,13,16}

Tricuspid regurgitant velocities were not different between those with RSH and those without it in this study. This is similar to findings by Gordeuk et al.⁵ Increased tricuspid regurgitation velocities (TRV) were found in patients without RSH- all those with RSH had TRV less than 2.5 m/s. Pulmonary hypertension is known to induce both right atrial and right ventricular dilatation from volume overload. This may therefore explain why right atrial area is the only significant determinant of RSH in this study.

Since blood pressure is the product of stroke volume and peripheral vascular resistance, the only assumption left to make is that there is higher sympathetic output to the systemic blood vessels in those with RSH as compared to controls. This is partly supported by the relatively higher heart rate in them. Anaemia also seems to be a stronger factor than blood pressure in determining chamber dimension in people with SCA. This is supported by the fact that those without RSH have larger atria and worse anaemia.

Prolonged QTc has been shown to increase mortality risk in people with SCA.¹⁷ It has also been shown to be related to increased serum aspartate transaminase, increased haemoglobin, tricuspid regurgitation velocity and if the ECG was done as an inpatient.¹⁸ Now, patients with SCA and RSH have been shown to have significantly prolonged QTc as compared to controls in this study.

5. Conclusion

Those with RSH had a tendency to have smaller hearts (smaller atria), higher packed cell volume, prolonged QTc and a history of vaso-occlusive crises in the recent past. Those without RSH had larger atria, lower packed cell volume, shorter QTc interval. They also had more of early satiety and a tendency to have higher tricuspid regurgitant jet velocities. Larger studies designed to evaluate peripheral vascular resistance, sympathetic outflow and the neuro-hormonal axis may be required to properly evaluate this enigma.

Conflicts of interest

All authors have none to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ihj.2020.05.007>.

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