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ORIGINAL RESEARCH

Pulmonary hypertension in Nigerian adults with sickle cell anemia

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Valentine N Amadi[1]
Michael O Balogun[2]
Norah O Akinola[3]
Rasaaq A Adebayo[2]
Anthony O Akintomide[2]

[1]Department of Internal Medicine, Federal Medical Centre, Asaba, Delta State, [2]Cardiac Care Unit, Department of Medicine, [3]Department of Haematology and Blood Transfusion, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Osun State, Nigeria

Background: Sickle cell anemia (SCA) is the commonest hemoglobinopathy and is associated with high morbidity and mortality. Pulmonary hypertension (PH) is reported to play a significant role in this regard. There is very limited literature on PH in SCA in Nigeria.

Objectives: The objectives of this study were to determine the prevalence of Doppler-derived PH in SCA, assess its influence on exercise capacity, and determine the correlates and predictors of measures of estimated pulmonary pressure.

Methods: A total of 92 SCA subjects had echocardiography and 6-minute self-paced walking exercise. PH was diagnosed by Doppler echocardiography on finding a tricuspid regurgitant velocity (TRV) of ≥2.5 m/s. The pulmonary flow profile was also assessed to estimate mean pulmonary arterial pressure (MPAP).

Results: Doppler-derived PH was detected in 23.9% of adults with SCA. The 6-minute walking distance (6MWD) was significantly lower in SCA adults with PH than in those without PH (380.33 ± 63.17 m vs 474.28 ± 76.74 m; $p = 0.014$). TRV and estimated MPAP had a significant inverse correlation with the 6MWD ($r = -0.442$; $p < 0.001$ and $r = -0.571$; $p < 0.001$, respectively).

Conclusion: PH as derived by Doppler is common in Nigerian adults with SCA and has a significantly negative influence on exercise capacity. Screening for PH should be encouraged to optimize management and thus improve their quality of life and life expectancy.

Keywords: pulmonary hypertension, Nigerian adults, sickle cell anemia, doppler-derived

Introduction

Sickle cell anemia (SCA), the commonest hemoglobinopathy worldwide, is associated with reduced life expectancy and early death, and pulmonary hypertension (PH) is reported to play a significant role in this regard.[1,2] PH is increasingly recognized in patients with sickle cell disease (SCD), with a prevalence reported as high as 30% in echocardiography-based studies.[2,3] PH is defined by a mean pulmonary artery pressure >25 mmHg at rest, measured during right heart catheterization.[4,5] There is still insufficient evidence to add exercise criterion to this definition.[4]

In PH, the structural and functional exchanges that constitute remodeling of the vascular walls, principally of the pulmonary artery segment, significantly reduce compliance in the pulmonary circulation. This creates an environment for elevation of pressure values and pulmonary vascular resistance in response to increased cardiac output, such as that occurring on exertion, during controlled exercise or even at rest, being proportional to the degree of remodeling and to the reduction in the functional reserve of the pulmonary circulation.[6]

Correspondence: Valentine N Amadi
Department of Internal Medicine, Federal Medical Centre, 1 Anwai Road, PMB 1033, Asaba, Delta State, Nigeria
Tel +234 80 6262 5318
Email mekuslala@yahoo.com

Classification of PH has evolved over time from a simple classification into "primary and secondary" to that adopted by the World Health Organization (WHO) in Evans, France (1998), where it was classified into four categories, based on similarities in pathophysiology, clinical presentation, and therapeutic options, and to that adopted by the WHO in Venice, Italy (2003), in which a fifth multifactorial category was included.

The etiology of PH in SCA is multifactorial. A close look at the four categories reveals the following observation:

1. Chronic intravascular hemolysis may be associated with endothelial dysfunction, including reduced nitric oxide bioavailability, coagulopathy, and prooxidant and proinflammatory stress, which may contribute to the development of proliferative changes in the pulmonary vasculature, much like those observed in patients with idiopathic pulmonary arterial hypertension (PAH).[7] Cell-free plasma hemoglobin, heme, and arginase-1 released during hemolysis have recently been referred to as erythrocyte damage-associated molecular pattern molecules (eDAMPs).[8]
2. Many patients with SCA have elevated left heart filling pressures as a result of a chronically elevated cardiac output or diastolic dysfunction and would therefore be classified as group 2 or those with pulmonary venous hypertension.[9]
3. Over the course of time, some patients with SCA develop parenchymal lung disease from recurrent acute chest syndrome, putting them at risk for PH (group 3).[9]
4. Finally, patients with SCA are at increased risk for the development of pulmonary thromboembolic disease and, potentially, chronic thromboembolic PH (group 4).[9]

In the recent fifth world symposium held in Nice, France, in 2013, PH due to SCD was categorized into the fifth subgroup, which takes into cognizance the multifactorial nature of its development.[10–12]

Definitive diagnosis of PH requires right heart catheterization; however, transthoracic Doppler echocardiography can aid in the assessment of PH.[5,13] The use of tricuspid regurgitant velocity (TRV) alone does not equate to a clinical definition of PH, but it does define mortality risk and identifies patients at higher risk of PH.[2,3,14]

In Nigeria, studies on PH in SCA are scarce. There is also little information on its relationship with exercise and other clinical and echocardiographic parameters in adult Nigerians with SCA.

This study therefore determined the prevalence of Doppler-derived PH in patients with SCA, evaluated its influence on exercise capacity, and determined the correlates and predictors of measures of pulmonary pressure in these patients seen at the Department of Haematology and Blood Transfusion and Cardiac Care Unit of Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, a tertiary hospital in Southwestern Nigeria. The findings from this study will add more information to the national and global databases.

Methods

A total of 92 homozygous hemoglobin S adults were consecutively recruited from the Haematology Clinic of the OAUTHC. Diagnosis of SCA (HbSS) had been confirmed previously by hemoglobin electrophoresis. The patients were recruited into the study within a 6-month period from January 2012 to June 2012. Patients aged ≥18 years who were in steady state were included in the study. Steady state was defined as being crisis-free for at least 3 weeks since the last clinical event and remaining crisis-free for up to one week after the tests were conducted, as well as not having had a blood transfusion in the preceding 3 months.[15] Patients with severe anemia, ie, hematocrit or packed cell volume (PCV) <18%, abnormal renal function, and coexisting heart diseases such as hypertensive heart disease, valvular heart disease, cardiomyopathies, and congenital heart disease, which could act as confounders, were excluded from the study. Data were obtained using a pro forma that included demographic data, relevant history, and physical examination. Baseline laboratory tests, including hematocrit and renal function test, were carried out to determine suitability for inclusion in the study.

Echocardiography was conducted using the Vivid 7 Pro (General Electric, Boston, MA, USA) model echocardiography machine and involved two-dimensional, M-mode, conventional Doppler (pulsed and continuous wave) and tissue Doppler studies to assess cardiac structure and function and to detect exclusion criteria such as coexisting heart diseases, as mentioned earlier.

The study was conducted using the 5S transthoracic phased array sector probe for adults with transducer frequency of 2.2–5.0 MHz. Measurements were in accordance with the recommendations of the American Society of Echocardiography and involved taking an average of three consecutive cycles.[16]

Left ventricular wall and chamber dimensions, left atrial dimension, and cardiac output were measured using 2D-guided M-mode echocardiography with simultaneous electrocardiographic monitoring of the cardiac cycle. Echocardiographic assessment of PH was obtained using two methods:

1. Determination of peak TRV by continuous wave Doppler by placing the cursor along the tricuspid regurgitant jet in

the apical four chamber view after obtaining a color Doppler display of tricuspid regurgitation jet across the valve.
2. Determination of the right ventricular acceleration time (AT) and the ratio of right ventricular acceleration time to right ventricular ejection time (AT/RVET) from the pulmonary ejection flow jet obtained by continuous wave Doppler with sample volume just proximal to the pulmonary valve in the parasternal short axis view. The acceleration time was taken as the time interval from the onset of right ventricular ejection to peak ejection velocity, while the ejection time was taken as the time interval from the onset to the end of ejection.

An assessment of PH was made on the following finding:

1. a peak TRV of ≥2.5 m/s[3] or
2. an AT <100 ms with an AT/RVET ratio of <0.30.

The use of both a cutoff point of 100 ms and a ratio of AT/RVET is due to the wide variation in cutoff points ranging from 80 to 100 ms in screening for PH reported by different studies.[17,18] The aim of using this combination was to reduce the chances of over- or under inclusion if a single cutoff value of AT alone was used.

Mean pulmonary arterial pressure (MPAP) was estimated using the regression equation developed by Dabestani et al:[18]
MPAP (mmHg) = 90 − (0.62 × AT).

The participants also underwent a 6-minute walking distance (6MWD) test. They were instructed not to participate in strenuous physical activity the day before exercise nor to ingest coffee, drugs, alcohol, or nicotine within 12 hours of exercise testing and to observe a pre-exercise rest period of 10 minutes. The test was performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom used. The length of the corridor was 20 m. The turnaround points were marked with a cone. A starting line was marked on the floor with a bright colored tape to denote the beginning and end of each 40m lap. Volunteers were asked to walk to and fro on this smooth corridor as fast as possible to cover enough ground within 6 minutes. The 6MWD was determined at the end of the exercise.

Data were entered into SPSS version 17.0 computer software package (IBM Corporation, Chicago, IL, USA). Results were presented in tables and graphs. Appropriate descriptive and inferential statistical tests were used to determine relationships between variables. Statistical significance was defined as a p value <0.05.

This study complied with the Declaration of Helsinki. Ethical clearance was obtained from the ethics and research committee of the OAUTHC, Ile-Ife, Nigeria, and informed consent was obtained from the study participants.

Results

A total of 92 SCA patients participated in the study, comprising of 42 males and 50 females. The clinical and demographic parameters are listed in Table 1. The age ranged from 18 to 41 years with a mean age of 25.4 years. The PCV ranged from 20% to 35% with a mean PCV of 26.8%. Other parameters are as shown in the table.

Prevalence of Doppler-derived PH among the study population

The criteria using TRV of 2.5 m/s as a cutoff point yielded a prevalence of 23.9% (22 out of 92), while that using the pulmonary flow jet increased the yield to 38.0% (35 out of 92). All patients who met the first criterion met the second, but the corollary was not true. The sex distribution of PH among patients with SCA showed no statistically significant difference. A total of 15 (35.7%) of the 42 males had PH, while 20 (40%) of the 50 females had PH ($\chi^2 = 0.178$; $p = 0.673$).

Table 2 shows the relationship between Doppler-derived PH and the clinical parameters of the patients. Patients with SCA with PH were older (28.6 ± 5.78 years vs 23.4 ± 3.41 years; $p < 0.001$), had lower PCV (25.6% ± 2.92% vs 27.5% ± 2.35%; $p = 0.001$), and had lower 6-minute walk

Table 1 Clinical and demographic parameters of the study patients

Parameter	Minimum	Maximum	Mean ± SD
Age (years)	18.0	41.0	25.4 ± 5.14
Weight (kg)	29.0	74.0	51.0 ± 7.7
Height (m)	1.30	1.92	1.64 ± 0.08
BMI (kg/m^2)	14.2	24.98	19.0 ± 1.9
BSA (m^2)	1.02	1.99	1.52 ± 0.14
PCV (%)	20.0	35.0	26.7 ± 2.72
Hb Conc (g/dL)	6.67	11.7	8.91 ± 0.91
SBP (mmHg)	80.0	130.0	106.4 ± 10.2
DBP (mmHg)	50.0	86.0	64.5 ± 8.9

Abbreviations: BMI, body mass index; BSA, body surface area; PCV, packed cell volume; Hb Conc, hemoglobin concentration; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2 Relationship between PH and clinical parameters

Parameter	PH	No PH	*p* value
Age (years)	28.6 ± 5.8	23.4 ± 3.4	<0.001*
PCV (%)	25.6 ± 2.9	27.5 ± 2.4	0.001*
HR (beats/min)	84.0 ± 8.2	83.3 ± 3.7	0.616
SBP (mmHg)	107.5 ± 12.1	105.5 ± 8.9	0.264
DBP (mmHg)	64.5 ± 10.2	64.5 ± 8.2	0.987
BMI (kg/m^2)	19.1 ± 2.6	18.9 ± 1.4	0.810
BSA (m^2)	1.50 ± 0.15	1.53 ± 0.14	0.482
6MWD (m)	380.3 ± 63.2	474.3 ± 76.7	0.014*

Note: *Statistically significant.
Abbreviations: PH, pulmonary hypertension; PCV, packed cell volume; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; BSA, body surface area; 6MWD, 6-minute walk distance.

distance (380.3 ± 63.2 m vs 474.3 ± 76.7 m; $p = 0.014$) than those without PH. Other clinical parameters were not significantly different between the two groups ($p > 0.05$).

Table 3 shows the strength of correlation between the echo parameters of PH and 6MWD. Parameters derived from both tricuspid regurgitation and pulmonary flow jets all correlated significantly with the 6MWD. TRV had a negative correlation with 6MWD ($r = -0.442$; $p < 0.001$). The AT and, by extension, the MPAP had the strongest correlation ($r = 0.571$ and $r = -0.571$, respectively; $p < 0.001$).

Table 4A and B shows the relationship between PH and echocardiographic structural and functional parameters, respectively. As shown, SCA subjects with PH had larger left atrial dimensions and index, left ventricular internal diastolic dimension index, end-diastolic volume index, end-systolic volume index, right ventricular wall thickness, right ventricular internal diameter and index, and left ventricular mass index than those without PH ($p < 0.05$). With regard to left ventricular systolic function, subjects with PH had significantly lower ejection fraction ($p = 0.004$), fractional shortening ($p = 0.009$), and tissue Doppler systolic velocity ($p < 0.001$) than those without PH. In terms of left ventricular diastolic function, those with PH had significantly lower early mitral annular tissue diastolic velocity (e') but higher E/e' ratio ($p < 0.001$) than those without PH.

Table 5A lists the statistically significant correlates of TRV. They include age ($r = 0.352$), hematocrit ($r = -0.326$), tissue Doppler systolic velocity ($r = -0.462$), left ventricular internal diastolic dimension index ($r = 0.434$), left atrial dimension index ($r = 0.290$), left ventricular ejection fraction ($r = -0.339$), early mitral annular tissue diastolic velocity ($r = -0.279$), and E/e' ratio ($r = 0.270$). Table 5B lists the independent parameters linked to tricuspid regurgitation velocity, which include left atrial dimension index, tissue Doppler systolic velocity, and hematocrit. Figure 1 shows a scatter plot depicting the correlation between maximum TRV and 6MWD. The higher the maximum TRV, the lower the 6MWD.

Table 3 Correlation strength between parameters of PH and 6MWD

Parameter	Pearson correlation coefficient	*p* value
TRV_{max} (m/s)	–0.442	<0.001*
AT (ms)	0.571	<0.001*
AT/RVET	0.557	<0.001*
MPAP (mmHg)	–0.571	<0.001*

Note: *Statistically significant.
Abbreviations: PH, pulmonary hypertension; 6MWD, 6-minute walk distance; AT, right ventricular acceleration time; AT/RVET, ratio of right ventricular acceleration time to right ventricular ejection time; MPAP, mean pulmonary arterial pressure; TRV_{max}, maximum tricuspid regurgitant velocity.

Table 4 Relationship between PH and echocardiographic (**A**) structural parameters and (**B**) functional parameters

A			
Parameter	**PH present**	**PH absent**	***p* value**
LAD (cm)	3.9 ± 0.4	3.6 ± 0.4	<0.001*
LADi (cm/m²)	2.63 ± 0.35	2.4 ± 0.2	<0.001*
LVIDD (cm)	5.1 ± 0.6	4.9 ± 0.5	0.080
LVIDDi (cm/m²)	3.4 ± 0.5	3.21 ± 0.3	0.010*
EDV (mL)	125.7 ± 36.0	114.1 ± 28.6	0.080
EDVi (mL/m²)	83.8 ± 23.5	74.2 ± 15.1	0.019*
ESV (mL)	42.8 ± 17.8	34.0 ± 11.3	0.080
ESVi (mL/m²)	28.3 ± 11.8	22.0 ± 6.01	0.001*
IVST (cm)	0.90 ± 0.13	0.89 ± 0.14	0.937
LVPWT (cm)	1.08 ± 0.19	1.01 ± 0.17	0.090
RVWT (cm)	0.48 ± 0.07	0.38 ± 0.06	<0.001*
RVIDD (cm)	1.9 ± 0.5	1.6 ± 0.3	0.004*
RVIDDi (cm/m²)	1.3 ± 0.3	1.1 ± 0.2	0.002*
LVMi	124.9 ± 31.4	109.6 ± 27.5	0.016*
RWT	0.39 ± 0.06	0.39 ± 0.05	0.985
B			
Parameter	**PH present**	**PH absent**	***p* value**
LVEF (%)	66.7 ± 7.3	70.4 ± 4.6	0.004*
LVFS (%)	37.4 ± 5.2	40.0 ± 3.9	0.009*
SV (mL)	83.0 ± 23.7	80.0 ± 19.3	0.523
SI (mL/m²)	55.5 ± 15.8	52.2 ± 10.7	0.235
CO (L/min)	6.9 ± 1.9	6.7 ± 1.6	0.467
CI (L/min/m²)	4.6 ± 1.3	4.3 ± 0.9	0.205
E^0 (m/s)	1.1 ± 0.2	1.02 ± 0.1	0.145
E/A	1.5 ± 0.3	1.6 ± 0.2	0.201
TDe′ (cm/s)	11.1 ± 2.0	12.6 ± 1.3	<0.001*
TDs′ (cm/s)	7.3 ± 1.2	8.4 ± 1.0	<0.001*
E/e′	9.8 ± 2.7	8.1 ± 1.0	<0.001*

Notes: *Statistically significant. "i", where seen as suffix, means parameter indexed to body surface area. E^0, transmitral early diastolic velocity; *E/A*, ratio of transmitral early to late diastolic velocity; TDe′, early mitral annular septal tissue diastolic velocity; TDs′,mitral annular septal tissue systolic velocity; *E/e′*, ratio of transmitral early diastolic velocity to early mitral annular septal tissue diastolic velocity.
Abbreviations: PH, pulmonary hypertension; LAD, left atrial dimension; LVIDD, left ventricular internal dimension in diastole; EDV, end-diastolic volume; ESV, end-systolic volume; IVST, interventricular septal thickness; LVPWT, left ventricular posterior wall thickness; RVWT, right ventricular wall thickness; RVIDD, right ventricular internal diameter in diastole; LVM, left ventricular mass; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; SV, stroke volume; SI, stroke index; CO, cardiac output; CI, cardiac index.

Table 6A lists the statistically significant correlates of the estimated MPAP. They include age ($r = 0.467$), hematocrit ($r = -0.467$), 6MWD ($r = -0.571$), left atrial dimension index ($r = 0.397$), and tissue Doppler systolic velocity ($r = -0.387$), all with a p value <0.001. Other significant correlates are the ejection fraction ($r = -0.257$; $p = 0.013$), early mitral annular tissue diastolic velocity e' ($r = -0.322$; $p = 0.002$), E/e' ratio and pulmonary capillary wedge pressure ($r = 0.310$; $p = 0.002$), and right ventricular internal diastolic dimension index ($r = 0.240$; $p = 0.016$). Table 6B lists the independent parameters linked to mean pulmonary artery pressure, which include hematocrit, age, left atrial dimension

Table 5 (**A**) Significant correlates of TRV and (**B**) independent parameters linked to TRV

A

Parameter	Pearson's correlation coefficient	*p* value
Age (years)	0.352	0.001
Hematocrit (%)	−0.326	0.001
6MWD (m)	−0.442	<0.001
LVEF (%)	−0.339	0.001
TDe′ (cm/s)	−0.279	0.007
TDs′ (cm/s)	−0.462	<0.001
E/e′ ratio	0.270	0.009
LADi (cm/m^2)	0.290	0.005
LVIDDi (cm/m^2)	0.434	<0.001

B

Parameter	Unstandardized coefficient	Standardized coefficient	*p* value
LADi (cm/m^2)	−0.880	−0.512	<0.001
TDs (cm/s)	−0.193	−0.428	0.002
Hematocrit (%)	−0.040	−0.203	0.021
Constant	3.411		

Note: TDe′, early mitral annular septal tissue diastolic velocity; TDs′, mitral annular septal tissue systolic velocity; *E*/e′, ratio of early transmitral diastolic flow velocity to early mitral annular septal tissue diastolic velocity.
Abbreviations: TRV, tricuspid regurgitant velocity; 6MWD, 6-minute walk distance; LVEF, left ventricular ejection fraction; LADi, left atrial dimension index; LVIDDi, left ventricular internal diastolic dimension index; TDs, tissue Doppler systolic velocity.

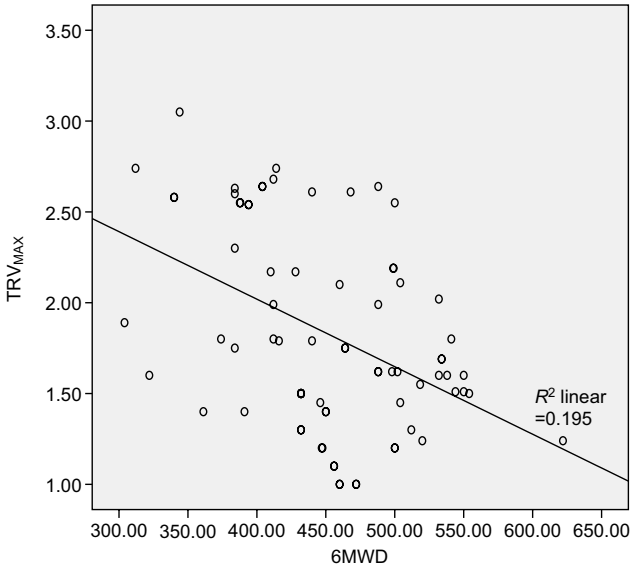

Figure 1 Correlation between TRV_{max} and 6MWD.
Abbreviations: TRV_{max}, maximum tricuspid regurgitant velocity; 6MWD, 6-minute walk distance.

index, and 6MWD. Figure 2 shows a scatter plot depicting the correlation between MPAP and 6MWD. The higher the MPAP, the lower the distance walked in 6 minutes. Table 7 lists the independent parameters linked to 6MWD, which include tissue Doppler systolic velocity, right ventricular diastolic dimension index, mean arterial pulmonary pressure, and hematocrit.

Table 6 (**A**) Significant correlates of estimated MPAP and (**B**) independent parameters linked to mean pulmonary arterial pressure

A

Parameter	Pearson's correlation coefficient	*p* value
Age (years)	0.467	<0.001
Hematocrit (%)	−0.467	<0.001
6MWD (m)	−0.571	<0.001
LADi (cm/m^2)	0.397	<0.001
LVEF (%)	−0.257	0.013
TDe′ (cm/s)	−0.322	0.002
TDs′ (cm/s)	−0.387	<0.001
E/e′ ratio	0.310	0.002
RVIDDi (cm/m^2)	0.249	0.016

B

Parameter	Unstandardized coefficient	Standardized coefficient	*p* value
Hematocrit (%)	−1.105	−0.270	0.003
Age (years)	0.678	0.315	0.004
LADi (cm/m^2)	10.283	0.288	0.004
6MWD (m)	−0.041	−0.231	0.038
Constant	67.237		

Note: TDe′, early mitral annular septal tissue diastolic velocity; TDs′, mitral annular septal tissue systolic velocity; *E*/e′, ratio of early transmitral diastolic flow velocity to early mitral annular septal tissue diastolic velocity.
Abbreviations: MPAP, mean pulmonary arterial pressure; 6MWD, 6-minute walk distance; LADi, left atrial dimension index; LVEF, left ventricular ejection fraction; RVIDDi, right ventricular internal diastolic diameter indexed to body surface area.

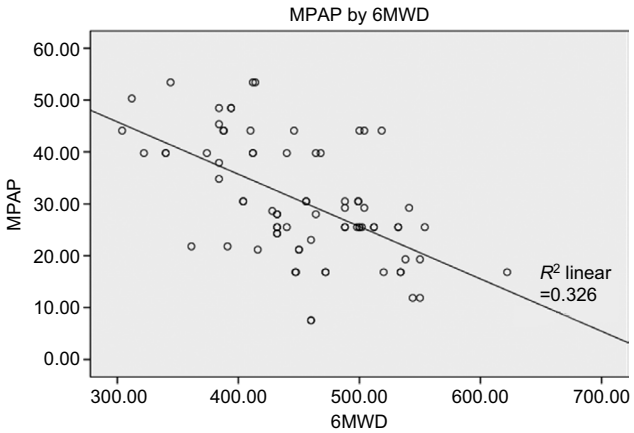

Figure 2 Correlation between MPAP and 6MWD.
Abbreviations: MPAP, mean pulmonary arterial pressure; 6MWD, 6-minute walk distance.

Table 7 Independent parameters linked to 6MWD

Parameter	Unstandardized coefficient	Standardized coefficient	*p* value
TDs (cm/s)	23.522	0.452	0.003
RVIDDi (cm/m^2)	−63.494	−0.298	0.004
MPAP (mmHg)	−2.053	−0.365	0.023
Hematocrit (%)	5.394	0.232	0.024
Constant	278.400		

Abbreviations: 6MWD, 6-minute walk distance; TDs, tissue Doppler systolic velocity; RVIDDi, right ventricular internal diastolic dimension index; MPAP, mean arterial pulmonary pressure.

Discussion

This study showed that the overall prevalence of Doppler-derived PH in SCA was 38%. This is similar to the results of the study by Oguanobi et al[19] in Enugu (Southeastern Nigeria) who reported a prevalence of 41.9%. The slightly lower, although comparable, values may be attributed to the fact that a more stringent criterion was used in the index study that included the AT/RVET ratio rather than an absolute cutoff point. This was to reduce the chances of over- or under inclusion of patients if a single cutoff point of 100 ms was used, given the wide variation in cutoff points of AT between 80 and 100 ms reported by different literature.[17,18]

When peak TRV was used, a total of 22 of the 92 (23.9%) SCA patients had PH. These subjects equally met the second criterion used in the screening for PH. The prevalence of 23.9% seen in this study is comparable to the findings of another study in Zaria (Northern Nigeria) by Aliyu et al[20] who made use of peak TRV of ≥2.5 m/s as a criterion and found a prevalence of 25%. Dosunmu et al[21] in a study in Lagos, Nigeria, got a much lower prevalence of 3.6%. This low prevalence may be possibly due to the lower age group of the study sample compared to the present study. The resolution power of a machine used for the assessment of the tricuspid regurgitant jet may also be a contributory factor. However determined, the limitations of using the TRV were made up for. This is to suggest that echocardiographic assessment of pulmonary flow jet signal improves the yield in screening for PH, given the limitations of the tricuspid regurgitation jet signal.

A significant relationship between Doppler-derived PH and exercise capacity was observed in this study. Those with PH had a significantly lower mean 6MWD during the self-paced walking exercise. Significant correlations were found between the indices of PH and exercise capacity. These findings corroborate those of previous research work done within and outside the country.[20,22,23]

Aliyu et al[20] in Zaria studied 108 patients with SCA and observed that a higher tricuspid regurgitant jet velocity >2.5 m/s was associated with an inability to walk >300 m in 6 minutes ($p = 0.042$).

Machado et al[22] observed that 6MWD correlated inversely with tricuspid regurgitant jet velocity ($r = -0{\cdot}62$; $p = 0{\cdot}0001$) and mean pulmonary artery pressure ($r = -0{\cdot}52$; $p = 0.01$), consistent with the 6MWD test reflecting the functional impairment in patients with SCD and PH.

Anthi et al[23] also observed that patients with SCA with PH exhibited lower 6MWD (320 ± 20 m vs 435 ± 31 m; $p = 0.002$) and oxygen consumption (41 ± 2% vs 50 ± 3% of predicted; $p = 0.02$) than control. They supported the use of 6MWD as an index of PH in patients with SCA.

The results obtained in this study showed that patients with SCA who had Doppler-derived PH were older, had lower hematocrit, and had lower 6MWD than those without PH. The older age of the patients with SCA patients who had PH is probably not unconnected to the longer duration of exposure to the sequelae of chronic anemia, while the association with a lower PCV may be due to the effect of cell-free hemoglobin resulting from chronic hemolysis on nitric oxide bioavailability.[7,8] Corroborating the findings of this study, Dosunmu et al[21] also found a significant negative correlation between hematocrit (PCV) and estimated mean pulmonary artery pressure ($r = -0.3625$; $p = 0.0425$).

Echocardiographic assessment showed that patients with PH had lower ejection fraction and systolic tissue velocity but higher E/e' ratio and larger left atrial and right ventricular sizes than those without PH. Studies assessing the relationship of these parameters with pulmonary arterial pressure are sparse in the SCA population. However, a study by Hammoudi et al[24] examined the relationship between cardiac structural changes and left ventricular diastolic dysfunction in SCA and observed that left atrial enlargement is common in SCA and was independently determined by age, hemoglobin concentration, and left ventricular end-diastolic volume index. Diastolic function as assessed by E/e' was not linked to left atrial size ($p = 0.43$). It was posited that left atrial enlargement may also be due to chronic volume overload.

The prevalence of PH in SCA derived by right heart catheterization ranges from 6% to 10%.[5,25–27] In two separate studies by Parent et al[26] in France and Fonseca et al[27] in Brazil, the prevalence of PH as determined by right heart catheterization was 6.2% and 10%, respectively. However, in these studies, the prerequisite for performing a right heart catheterization (an invasive procedure) was a TRV of ≥2.5 m/s.

Right heart catheterization is usually performed on SCA patients with a TRV of ≥2.5 m/s with or without an N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥160 pg/mL.[5] NT-proBNP, which is a marker for left or right ventricular strain, becomes useful when Doppler echocardiography is unavailable or when there are difficulties with image acquisition.[5]

Fonseca et al[27] reported a trend for worse survival in patients with a TRV of ≥2.5 m/s compared with those who have a TRV of <2.5 m/s

In adults with SCD, an increased TRV >2.5 m/s measured by Doppler echocardiography, an increased serum NT-

proBNP level >160 pg/mL, and PH diagnosed by right heart catheterization are independent risk factors for mortality.[2,5,14]

Recent American Thoracic Society (ATS) guidelines state that patients identified at high risk of death should be screened for comorbid factors that are treatable, including low oxygen tension, iron overload, and thromboembolic disease.[5] The underlying SCD should be treated more aggressively with hydroxyurea therapy or chronic exchange blood transfusion therapy. Patients diagnosed to have PAH should be referred to PAH specialists for Food and Drug Administration-approved PAH therapies.[5,8]

Before any specific treatment for PH is considered, there is need for invasive hemodynamics. Both pre- and post-capillary hemodynamic profiles are found in SCA, stressing the need for a better understanding of the multiple pathophysiological mechanisms involved in the development of PH before considering the patients for targeted therapies.[28]

Conclusion

Doppler-derived PH is a common finding in Nigerian adults with SCA, seen in 23.9% of patients using TRV and 38% of patients using pulmonary flow Doppler. It significantly affects exercise capacity negatively, and has significant relationships with some clinical parameters and echocardiographic indices of cardiac structure and function. Thus, screening for PH is to be encouraged if the quality of life and life expectancy of this group of patients are to be improved upon.

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Disclosure

The authors report no conflicts of interest in this work.

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