

ECHOCARDIOGRAPHIC STUDY OF RIGHT VENTRICULAR ABNORMALITIES IN ADULT PATIENTS OF SICKLE CELL ANAEMIA

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ABSTRACT

BACKGROUND

Sickle Cell Disorder (SCD) is the first diagnosed disease that was linked to the haemoglobin protein. It is an autosomal recessive disorder that occurs throughout the world. The cardiac effects of this chronic illness on the left ventricle have been extensively investigated in adults. However, fewer adult studies and only one study that included adolescents have investigated any aspect of the impact of SCA on the Right Ventricle (RV).

MATERIALS AND METHODS

The study was conducted in the Department of Medicine, Dr. BRAM Hospital, Raipur, among the patients presenting in OPD and admitted in medicine ward. The study comprised of 138 patients with sickle cell anaemia. The age group chosen was between 14 years to 70 yrs.

RESULTS

Out of the total 138 cases, 84 (60.86%) were sickle cell trait (AS) and 54 (39.14%) were sickle cell disease (SS). Right Ventricular End Diastolic Area (RV-EDA), Right Ventricular End Systolic Area (RV-ESA), Right Ventricular Fractional Area Change (RV-FAC), Right Ventricular Free Wall Mass Index (RV-FWMI), Right Ventricular Rate Corrected Ejection Time (RV-Etc) was significantly higher in SS subjects compared to AS subjects. In our study group, 19 out of 58 (35.18%) patients of sickle cell disease had PH as compared to 13 out of 84 (15.47%) patients of sickle cell trait.

CONCLUSION

In our study, we have observed that various parameters which signify right ventricular abnormalities like increased systolic pulmonary pressure (sPAP), right ventricular end diastolic area, right ventricular end systolic area, right ventricular fractional area change, right ventricular free wall mass index and right ventricular ejection time (rate corrected) were found to be significantly higher in sickle cell disease patients (SS genotype) as compared to sickle cell trait patients (AS genotype). Also, the incidence and severity of anaemia was significantly higher in sickle cell disease patients (SS genotype). Moreover, increased incidence and severity of subsequent pulmonary hypertension correlates well with morbidity and mortality in these patients.

KEYWORDS

Echocardiography, Right Ventricle, Sickle Cell Anaemia.

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BACKGROUND

Sickle Cell Disorder (SCD) is the first diagnosed disease that was linked to the haemoglobin protein. It is an autosomal recessive disorder that occurs throughout the world. Chhattisgarh, being a newer state, does not have enough studies and data regarding separate epidemiological and genetic profile of its sickle cell population in spite of it coming under the main sickle cell belt of India. Many epidemiological studies estimated 9% - 15% population having sickle cell genotype in Chhattisgarh. (Paunipagar PV)¹ and (Gupta RB).² Pt. JNM Medical College Hospital, Raipur (CG) is the only

properly functioning apex hospital and Referral centre for sickle cell disorder in the state of Chhattisgarh till date and thus effectively drains the majority of patients across different parts of the state.

The cardiac effects of sickle cell anaemia on the left ventricle have been extensively investigated in adults. (Gerry et al)³ (Covarrubias EA et al)⁴ (Deneberg BS et al)⁵ (Ahmed S et al).⁶

However, fewer adult studies (Ahmed S et al)⁷ (Castro O et al)⁸ (Gladwin MT et al)⁹ (Ataga KI et al),¹⁰ only one study that included adolescents (Cowitz W et al)¹¹ have investigated any aspect of the impact of SCA on the Right Ventricle (RV).

Thus, purpose of the study is to provide a valuable data regarding cardiovascular abnormalities in Sickle Cell Disorder in Chhattisgarh using non-invasive method of two-dimensional colour Doppler Echocardiography.

Aims and Objectives

- To assess the changes in right ventricle in patients of sickle cell anaemia using echocardiographic estimates of systolic function, pressure, size and RV free wall mass.

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- To assess the difference in changes in right ventricular function among sickle cell disease and sickle cell trait patients.
- To assess the effect of the changes in right ventricular function on the development of pulmonary hypertension.

MATERIALS AND METHODS

A total of 138 patients were taken fulfilling the inclusion criteria for the study. Patient’s informed consent was taken. Echocardiography: 3 - 4 cardiac cycles will be analysed to get best phase for better outcome of results. Following parameters will be assessed-

Right Ventricular Fractional Area Change

$$\frac{(RV - EDA) - (RV - ESA)}{(RV - EDA)} \times 100$$

(RV-EDA- Right ventricular end diastolic area, RV-ESA- Right ventricular end systolic area).

Right Ventricular Free Wall Mass Index

5.84 (RV cavity area) (RV free wall thickness) + 1.0

Rate corrected ejection time (ETc)

$$ETc = \frac{ET}{\sqrt{PI}}$$

(ET- Ejection Time, PI- Pulse Interval)

Tricuspid Regurgitation Gradient.

Study Design

Descriptive study.

Statistical Analysis

1. Statistical analysis was done by using description and inferential statistics. All the data were expressed in mean ± standard deviation (SD). The analysis was performed by using Student’s t-test for the difference of means, Chi-square test and correlation.
2. P value < 0.05 was considered as statistically significant.
3. SPSS Software for Windows™ Ver. 17, IBM™ Corp NY and Microsoft Excel™ 2007, Microsoft® Inc USA was used to perform the statistical analysis.

Methodology

Transthoracic echocardiography was performed with the use of the Mindray M7 echocardiography machine. Cardiac measurements were performed according to American Society of Echocardiography guidelines. For all 2-dimensional echocardiographic measurements, maximal and minimal ventricular cavity sizes were used to define end diastole and end systole, respectively. (Helbing et al),¹² (Gutgessel et al),¹³ The apical 4-chamber view was used to measure the RV cavity cross-sectional area by tracing the endocardial border (Joyce et al),^{14,15}

RV free-wall thickness at end-diastole was measured from either the subcostal, coronal or parasternal-axis view, whichever view most clearly illustrated the RV epicardium

and endocardium. RV free-wall mass was calculated using end-diastolic measurements in the following previously validated formula: RV free-wall mass= 5.84 (RV cavity area) (RV free-wall thickness) + 1.0 (Joyce et al).^{14,15}

For comparing echocardiographic measures in subjects of differing body size, these measures were indexed to a power of 0.5 for a linear dimension) and to a power of 1 for area and mass (Gutgessel et al).¹³ RV ejection time was measured from the onset to the termination of the spectral Doppler signal across the pulmonary valve. The pulse interval was determined as the time from the onset of 1 systolic ejection Doppler waveform across the pulmonary valve to the onset of the next such waveform. The rate-corrected ejection time (ETc) was calculated by the equation $ETc = \frac{ET}{\sqrt{PI}}$ where ET is Ejection Time and PI is Pulse Interval expressed in seconds (Joyce et al).¹⁵

The peak instantaneous pressure gradient of Tricuspid Regurgitation (TR) was determined from the maximal continuous-wave Doppler velocity and the simplified Bernoulli equation (Abaci et al).¹⁶

RESULTS

- Out of the total 138 cases, 84 (60.86%) were sickle cell trait (AS) and 54 (39.14%) were sickle cell disease (SS).
- RV-EDA was significantly higher in SS subjects compared to AS subjects (p < 0.0001).

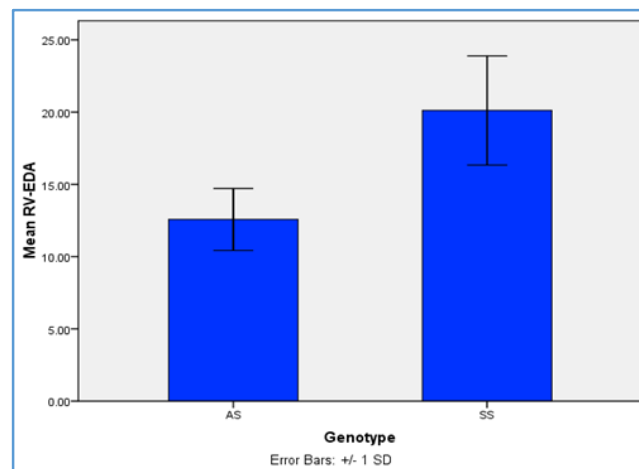


Figure 1. Showing RV EDA in AS and SS Subjects

RV-ESA was significantly higher in SS subjects compared to AS subjects (p < 0.0001).

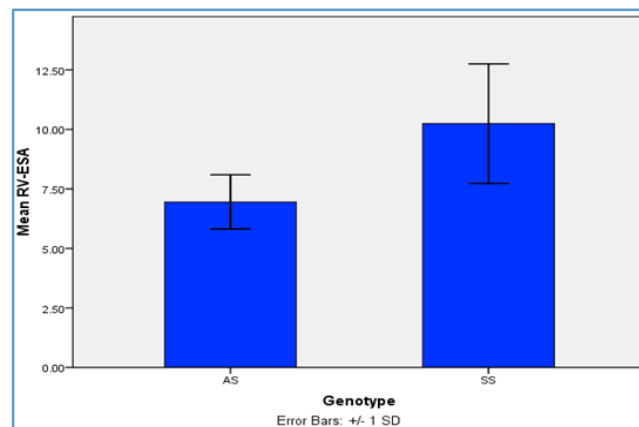


Figure 2. Showing Mean RV ESA in AS and SS Subjects

RV-FAC was significantly higher in SS subjects compared to AS subjects (p= 0.003).

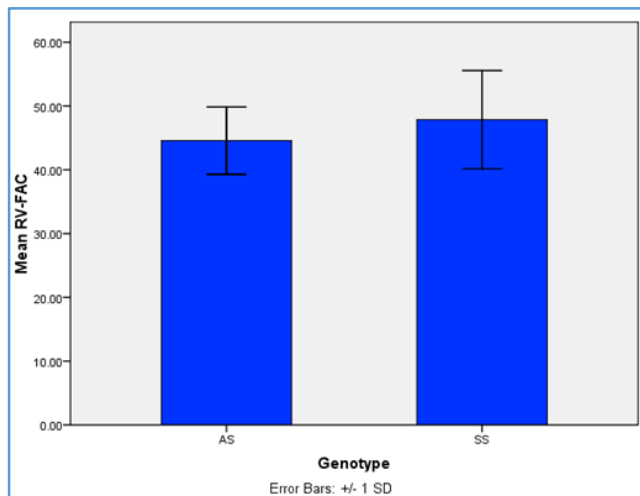


Figure 3. Showing the Mean RV-FAC Values in AS and SS Subjects

RV-FW-MI was significantly higher in SS subjects compared to AS subjects (p < 0.0001).

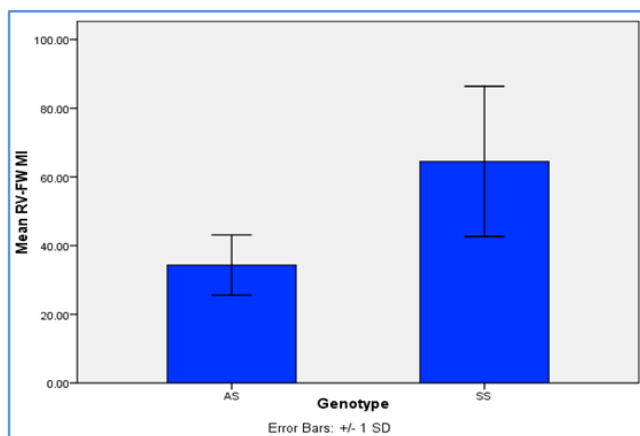


Figure 4. Showing RV-FW-MI Values in AS and SS Subjects

RV-ETc was significantly higher in SS subjects compared to AS subjects (p < .0001).

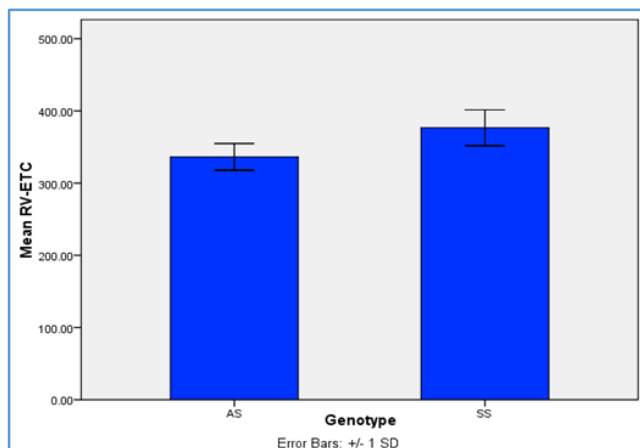


Figure 5. Showing the Mean RV-ETc Values in AS and SS Subjects

In our study, we found that 32 out of 138 (23.18%) sickle cell patients had PH. Out of the 32 patients, 25 (18.1%) had mild, 7 (5.1%) had moderate and 0 patients had severe PH.

In our study group, 19 out of 58 (35.18%) patients of sickle cell disease had PH as compared to 13 out of 84 (15.47%) patients of sickle cell trait.

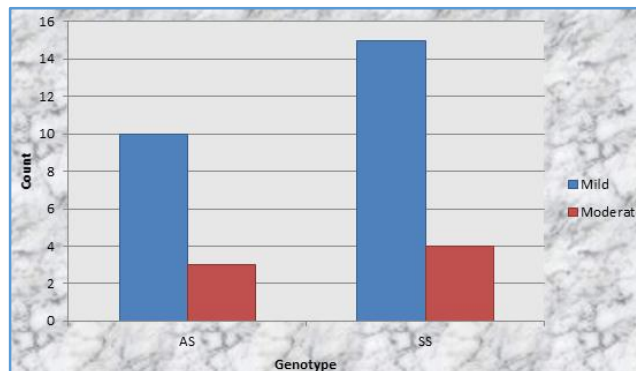


Figure 6. Showing Incidence of Pulmonary Hypertension in AS and SS Subjects

DISCUSSION

Out of the 138 patients included in the study, 84 (60.86%) were sickle cell trait (AS) and 54 (39.14%) were sickle cell disease (SS). The ratio of AS to SS was 1.5:1. The higher incidence of sickle cell trait patients in our study can be explained by the epidemiology of sickle cell anaemia in Chhattisgarh state. Due to a deficiency of the SS phenotype failing to enter the sampled population from either sickness or early death, higher prevalence of sickle cell trait (AS) patients can be found. Similar to our study, Patra et al¹⁷ also found higher incidence of sickle cell trait patients as compared to sickle cell disease patients in their study.

Comparison of RV-EDA between AS and SS subjects was performed using Student’s unpaired “t” test. Mean values in AS subjects was 12.27 ± 2.14 cm² and in SS subjects was 20.11 ± 3.77 cm². Significantly, higher levels of RV-EDA were noted in SS subjects compared to AS subjects (p < 0.0001). RV morphology may serve as a barometer of pulmonary vascular health (much like left ventricular mass does for systemic vascular disease). RV-EDA is an indicator of right ventricular diastolic function. Elevated pulmonary arterial pressure causes right ventricular dilatation resulting in increased RV-EDA. Also, in the setting of chronic anaemia, increased circulating blood volume is documented in sickle cell disease subjects. The larger LA and LV volumes, RA volumes and RV end-diastolic areas in SCD subjects were likely an adaptive response to the increased blood volume (Jessica E. Knight-Perry et al).¹⁸

Comparison of RV-ESA between AS and SS subjects was performed using Student’s unpaired ‘t’ test. Mean values in AS subjects were 6.95 ± 1.13 cm² and in SS subjects was 10.24 ± 2.50 cm². Significantly, higher levels of this parameter were noted in SS subjects compared to AS subjects (p < 0.0001). The effects of pulmonary hypertension and chronic anaemia on the right ventricle lead to its dilatation resulting in higher values of both RV ESA and RV EDA.

Comparison of RV-FAC between AS and SS subjects was performed using Student’s unpaired “t” test. Mean values in AS subjects was 44.56 ± 5.27% and in SS subjects was 47.86 ± 7.69%. Significantly, higher levels of this parameter were

noted in SS subjects compared to AS subjects ($p = 0.003$). Although, higher values of RV-FAC have been found in our study among sickle cell disease subjects as compared to sickle cell trait patients, the RV-FAC values are within the normal range. In the setting of chronic anaemia cardiac output is raised mainly by an increase in stroke volume, which prolongs ETc along with a slight change in heart rate. Moreover, stroke volume is increased principally by raising the diastolic volume with only a minimal change in ejection fraction, which explains why RV-FAC remains in the normal range (Naveen Qureshi et al).¹⁹

Comparison of RV-FW MI between AS and SS subjects was performed using Student's unpaired "t" test. Significantly, higher levels of this parameter were noted in SS subjects compared to AS subjects ($p < 0.0001$). Mean values in AS subjects was 34.34 ± 8.75 gm/m² and in SS subjects was 64.50 ± 21.86 gm/m². RV free wall mass index is calculated using the RV free wall thickness and end diastolic measurements. Years of clinical and subclinical haemolysis and vaso-occlusive episodes in sickle cell anaemia may lead to an obstructive pulmonary vasculopathy with a gradual increase in pulmonary vascular resistance and RV afterload, reflected in a steady increase in RV mass index out of proportion to the chronic anaemia-induced RV preload (Naveen Qureshi et al).¹⁹

Significantly, higher levels of RV-Etc was noted in SS subjects compared to AS subjects ($p < 0.0001$). Mean values in AS subjects was 336.34 ± 18.52 msec and in SS subjects was 376.62 ± 24.89 msec. Chronic anaemia is characterised by a decreased blood oxygen content due to a lower haemoglobin concentration, leading to a compensatory increase in the cardiac output to maintain a normal tissue oxygen supply. In the setting of chronic anaemia cardiac output is raised mainly by an increase in stroke volume, which prolongs ETc along with a slight change in heart rate (Naveen Qureshi et al).¹⁹

In our study, we found that 32 out of 138 sickle cell patients (23.18%) had PH. Out of the 32 patients, 25 (18.1%) had mild, 7 (5.1%) had moderate and 0 patients had severe PH. In our study group, 19 out of 58 (35.18%) patients of sickle cell disease had PH as compared to 13 out of 84 (15.47%) patients of sickle cell trait. Thus, higher prevalence of PH was found in sickle cell disease patients as compared to sickle cell trait patients ($p < 0.0001$). Sickle cell disease is characterised by recurrent episodes of ischaemia-reperfusion injury to multiple vital organ systems and a chronic haemolytic anaemia, both contributing to progressive organ dysfunction. With increased longevity, cardiovascular complications are increasingly evident with the notable development of a progressive proliferative systemic vasculopathy and Pulmonary Hypertension (PH) (Mark T Gladwin et al).²⁰ This correlates with the higher incidence of PH found in sickle cell disease patients in our study.

CONCLUSION

To conclude, very few studies have evaluated the adverse effects of sickle cell anaemia on the right ventricle. In our study, we have observed that various parameters which signify right ventricular abnormalities like increased systolic pulmonary pressure (sPAP), right ventricular end diastolic area, right ventricular end systolic area, right ventricular fractional area change, right ventricular free wall mass index

and right ventricular ejection time (rate corrected) were found to be significantly higher in sickle cell disease patients (SS genotype) as compared to sickle cell trait patients (AS genotype). Also, the incidence and severity of anaemia was significantly higher in sickle cell disease patients (SS genotype).

Moreover, increased incidence and severity of subsequent pulmonary hypertension correlates well with the morbidity and mortality in these patients. Doppler Echocardiography is simple, non-invasive, reproducible, safe and easily available. It identifies large percentage of sickle cell subjects who have asymptomatic pulmonary hypertension and right ventricular dysfunction before they are detected with ECG or by clinical examination. Therefore, early identification of subtle cardiac dysfunction can help predict future cardiopulmonary abnormalities and thereby initiating early treatment to retard the progression of these complications. However, longer-term follow-up studies are essential to accurately rule out detrimental cardiovascular events.

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