*British Journal of Medicine & Medical Research*
*4(26): 4431-4443, 2014*

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# Surrogates of Poor Prognostic Signs in Adult Patients with Homozygous Sickle Cell Disease: An Echocardiographic Study

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author TG designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author AJ performed the statistical analysis and authors ABH and MAA managed the data collection, and authors RS and FQ managed the literature searches. All authors read and approved the final manuscript.*

***Original Research Article***

***Received 13th March 2014***
***Accepted 26th April 2014***
***Published 14th June 2014***

## ABSTRACT

**Background:** Pulmonary Arterial hypertension (PAH) is a late complication in adult patients with homozygous sickle cell Anaemia (SCA). The early identification of PAH may be of paramount importance.
**Aim:** This study is aimed at evaluating the usefulness of NT pro BNP in the assessment of diastolic function of RV in adult patients with sickle cell disease. It is also aimed at the assessment of the predictive risk of serum level of NT pro BNP hormone and ferritin with other pulsed and tissue Doppler indices for the development of pulmonary hypertension in patients with SCA. In addition, we measured the usefulness of tissue Doppler velocity of lateral annulus of tricuspid valve in the assessment of diastolic function of RV in adult patients with SCD.
**Method:** In this cross sectional prospective study, 103 patients with homozygous SCD were studied and compared with age and gender matched healthy control. Every patient had a clinical assessment, pulsed and tissue Doppler evaluation. Blood samples were withdrawn for the level of haemoglobin, ferritin and NT pro BNP hormone. The mean

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difference between the two groups for echo Doppler and biometric variables were assessed. Multiple regression analysis applied for measuring the odds ratio of different biometric and Doppler variables for risk of PAH in SCD.

**Results:** The study group consist of 103 patients with SCA, mean age of 28.52±14.11 year, (range 14-42), with 68 male (66.0%) Patients with SCA compared with control had a significantly low diastolic pressure, lower haemoglobin level but high serum level ferritin and pro BNP hormone. Further, there was a significant increment in the left atrium area (LA), higher right ventricle (RV) wall thickness and diameter. The RV tricuspid annular systolic excursion (TAPSE) was high of 1.42±0.21 vs. 1.11±0.23, P<0.05. RV Pulsed Doppler data showed restrictive filling pattern with significant higher E wave velocity, higher early diastolic filling wave (E)/ atria wave velocity (A) ratio and short Deceleration Time (DT). Further, the ratio of upper pulmonary vein for systolic/diastolic Doppler velocity was significantly lower 1.5±0.12 vs.2.4±0.11, p<0.05. The tissue Doppler of lateral annulus of tricuspid valve in SCA patients showed a significantly lower S wave of 6.7±1.7 vs 11.3±1.9, p<0.01, higher pulsed early velocity( E)/ early Tissue velocity (E-) ratio and lower atria wave velocity (A). The incidence of pulmonary hypertension in SCD patients via tricuspid valve velocity defined as ≥2.5 m/s was 28%. There were positive correlation between the serum level of ferritin, NT pro BNP hormone and tricuspid valve velocity of (r= 0.38) and (r=0.43) respectively. The odds ratio for development of PAH was 3.1 for E/E- ratio ≥13, 2.5 for DT of <160msec, 2.2 for Left ventricle mass Index (LVMI)>121 gm/M2, 1.9 for ferritin ≥600μg/l, 1.6cm for left atrial area ≥20cm, 1.3 for pro- BNP ≥150Pmol/L.

**Conclusion:** Adult patients with SCA have normal Systolic function but increase of LV mass and restrictive diastolic dysfunction. RV has increase wall thickness, systolic and diastolic dysfunction of restrictive pattern. The prevalence of pulmonary hypertension in SCA is 28% with positive correlation between ferritin, pro BNP level and tricuspid valve velocity on echo. The risk of PAH in SCA patients is higher if the patient had on echo DT <160msec, LVMI >121gm/M2, cm, E/E- ratio ≥13 or RV wall thickness >3mm.

*Keywords: Adult sickle anaemia; tissue doppler echocardiogram; pro-BNP; Bahrain.*

## 1. INTRODUCTION

Sickle cell anaemia (SCA) is a form of hereditary haemolytic anaemia characterized by the synthesis of an abnormal haemoglobin S. It is caused by the substitution of amino acid valine for glutamic acid at position six of the globin chain of haemoglobin leading to an abnormal mutant haemoglobin HbS in its homozygous form (HbSS) [1]. Patients usually present with various clinical manifestations such as vaso-occlusive crisis, recurrent haemolytic anaemia with the entrapment of red blood corpuscle in the microvasculature system leading to multi organ infarction that causes an organ dysfunction [2].

The term sickle cell anemia (SCA) denotesa pathological condition that can lead to severe complications or death. Sickle-cell disease occurs more among patients whose ancestors lived in tropical and sub-tropical regions where malaria is common. The incidence of SCA in Saudi Arabian peninsulais in the range of 1.2% to 2.6% [3,4]. SCA patients have a variety of cardiac manifestations depending on the methods of evaluation and the study population according to ethnicity and geographical distribution [5,6]. In homozygous SCA, the earliest marker of cardiac involvement is abnormal diastolic function followed by cardiomegaly and pulmonary hypertension in adulthood with or without heart failure [7,8].

Pulse Doppler echocardiography is commonly used as a non-invasive tool for mitral and tricuspid flow for the pattern of LV diastolic filling [9,10]. The LV diastolic filling pattern on pulsed Doppler has been classified into abnormal relaxation, pseudo-normal and restrictive pattern based on the ratio of early diastolic filling velocity wave E to late filling velocity wave A. [11]. The pattern of abnormal relaxation pattern has low early filling wave (E) , high atrial wave (A) with E/A ratio < 1and prolonged deceleration time of E wave (DT) The constrictive pattern had a high E wave velocity, diminished or absent A wave with E/A ratio > 2 and shortened DT of <160 msec [12,13]. Tissue Doppler velocity of septal mitral annulus as well as pulmonary venous velocities' were validated as extra diagnostic tools for left ventricular diastolic dysfunction [14,15].

Pulmonary Arterial Hypertension (PAH) is a recognized complication in patients with SCD and beta thalassemia major [16,17]. Several studies revealed a prevalence of 20-40% and that the presence of PAH is associated with high risk of mortality [18,19].

The NT-Pro B-type natriuretic peptide (pro BNP) is a 76 amino acid N terminal inactive protein that is cleaved from pro BNP to release brain natriuretic peptide. It is used for screening, diagnosis of congestive cardiac failure and a marker of worse outcome. It is released in response to stretch of myocardial cell. The prognostic value of proBNP has been demonstrated in several cardiovascular disorders [20]. The level of pro BNP has been shown to correlate with the severity of pulmonary hypertension and right ventricle dysfunction [21]. The serum stable and the easily assayed NT-pro BNP have been shown useful in the stratification of pulmonary hypertension [22].

The aims of the study are: Evaluates the usefulness of NT pro BNP in the assessment of diastolic function of RV in adult patients with sickle cell disease. Assess the predictive risk of serum level of NT pro BNP hormone and ferritin with other pulsed and tissue Doppler indices for the development of pulmonary hypertension in patients with SCA Measure the usefulness of tissue Doppler velocity of lateral annulus of tricuspid valve in the assessment of diastolic function of RV in adult patients with SCD.

## 2. MATERIALS AND METHODS

### 2.1 Study Population

One hundred and three patients with sickle cell disease (SCD), with age of 14 to 42 years were enrolled in the study. The study was conducted over 12 months from end of September 2012 to first of October 2013. Patient selection was consecutive from those attending the haematology out patient in Salmaniya Medical Complex (SMC). SMC is the main governmental hospital in the Kingdom of Bahrain with a catchment area of 900,000 populations. The control group was 103 healthy patients matching for age and sex and they were referred to cardiology clinic for echocardiogram evaluation of a murmur or left ventricle function. Patients with sickle cell anaemia SCA and homozygous haemoglobin S (HbSS) were included. The diagnosis was based on haemoglobin electrophoresis and solubility screening test. An informed consent was obtained from the study patients. The study protocol was approved by the institutional committee.

Patients with SCD were excluded if they had haemo-globinopathy, history of blood transfusion within three weeks, adult congenital heart disease, hypertrophic cardiomyopathy, and advanced hepatic or renal failure. Patients' comprehensive history and clinical

examination for blood pressure in mmHg and heart rate per min, presence of raised jugular venous pulse, heart murmur, crackles, S3 gallop, and ankle oedema were recorded. Each patient gave a blood sample for the serum level of NT pro BNP, haemoglobin (HB) and ferritin.

## 2.2 Echocardiographic Evaluation California 92618 USA

Complete echocardiographic pulsed and tissue Doppler assessment was performed by USA manufacture dechomachine, Philips iE33 using 2.5 MHz transducer by the same cardiologist. The measurement of M mode, 2D, pulsed and tissue Doppler echocardiogram was performed by a single technician who is blinded of the clinical status and according to the American Society of Echocardiography guidelines [23]. The LV ejection fraction (EF percent) was assessed using the biplane Simpson methods in the four chamber view [24]. The M-mode guided echo in parasternal view was used to assess the systolic and end diastolic diameter of left ventricle cavity as well as the septum and posterior wall. The LV mass index was calculated as per formula described by Devereux et al. [25] Right ventricle diastolic diameter and thickness of the free wall were measured in the apical view. RV function in systolein apical view was evaluated from the tricuspid annular plane systolic excursion (TAPSE) [26].

Views of echocardiogram were taken at apical view with the sample volume at the tip of the leaflet for pulsed Doppler of both the mitral and tricuspid valve. The early peak velocity (E wave) and the late atrial contraction wave (A wave), E/A ratio and deceleration time of E wave (DT) were measured. The calculation was made as the mean of three beats at end of inspiration and three at the end of expiration. The flow velocity of the upper pulmonary veins in the apical view was obtained in systolic and diastolic for forward flow velocity ratio (S/D). The tissue Doppler of the lateral tricuspid annulus was obtained for systolic velocity (S), late diastolic velocity (A-) and the early filling velocity (E-). All data was taken in the apical four chamber view. Pulmonary hypertension was defined as tricuspid valve velocity on continuous wave of ≥2.5M/S [27].

## 2.3 Statistical Analysis

All data were entered and analysed using the Statistical Package of Social Sciences (SPSS) version 20. Data is presented as mean ± SD. *Student t-test* was used to analyse the differences between the mean variables of M mode for septal wall thickness of LV and RV cavity and wall thickness and LV mass index in the two groups and *Chi-square* analysis for frequency non-continuous data.

Pearson correlation coefficient analysis was used to assess the linear association between concentrations of serum ferritin, pro BNP level and tricuspid valve velocity on CW Doppler. Multiple regression analysis was applied to assess the odds ratio and predictive risk of different variables for the development of pulmonary hypertension in SCD patients. The variables were as follow LV mass index of >121 gm/M2, Left atrial area >20 cm, E/E- ratio of > 13, S wave velocity of tissue Doppler <4 m/s, and DT of E wave <160 msec and the level of serum ferritin >600 ng/l and Pro BNP >150 pmol/L. All reported p-values were two tailed and p-value was regarded as significant at level of <0.05.

## 3. RESULTS

One hundred and three patients with sickle cell disease were enrolled, meanage 28 ± years (range 14-42) and 68 male (66.0%). Table 1 shows the clinical characteristics of patients with SCA and the control group. Patients with SCA compared with the control group had no difference in age, gender, heart rate and systolic blood pressure. Furthermore, haemoglobin level, serum ferritin and pro BNP were significantly different with higher level of ferritin, pro BNP and low haemoglobin and diastolic blood pressure.

**Table 1. Clinical characteristics of the study population, data presented as the mean±SD**

| Characteristics | SCA N=103 | Control N=103 | P value |
|---|---|---|---|
| Age | 28.52±9.11 | 29.74±8.71 | 0.64 |
| Male | 68(66%) | 66(64.0%) | 0.76 |
| Heart rate /min | 72.65±8.23 | 71.42±8.33 | 0.97 |
| SBP mmHg | 128.47±7.92 | 124.58±8.65 | 0.85 |
| DBP mmHg | 67.84±4.55 | 75.25±3.88 | 0.042 |
| Haemoglobin (g/dl) | 9.3±1.2 | 13.2±1.5 | 0.01 |
| Serum ferritin ug/L | 423.25±98.23 | 86.12±16.34 | 0.01 |
| Serum pro BNP pmol/L | 365.76±96.34 | 98.54±19.58 | 0.01 |

*Abbreviations: SBP, systolic blood pressure, DBP diastolic blood pressure, SCA, sicklecell Anemia. Pro BNP, brain natriuretic peptide*

Table 2 displays the echocardiographic measurements of M mode and 2 -D of right and left ventricle. Patients with SCA compared with the control, had a significant increase in right ventricle diameter, wall thickness and left atrial area. The left ventricle mass index was significantly high in SCA patients. There was no significant differences between SCA and the control for LVEF% and LV dimensions in systole and diastole. Tricuspid annular systolic excursion (TAPSE) was significantly higher in SCA patients compared with control suggesting systolic dysfunction.

**Table 2. The M mode and 2 –D echocardiographic data in the study population, the data was presented as mean value ±SD**

| | SCA N=103 | Control N=103 | P value |
|---|---|---|---|
| LA area $(cm)^2$ | 22.21±4.22 | 16.72± 3.90 | 0.042 |
| LVEDD(cm) | 5.51± 0.32 | 4.72±0.35 | 0.361 |
| LVESD(cm) | 3.63±0.24 | 3.12±0.31 | 0.653 |
| LV mass index gm/M2 | 105±10.3 | 83±7.1 | 0.001 |
| RV diameter(cm) | 2.8±0.42 | 2.4±0.31 | 0.043 |
| RV wall thickness (mm) | 0.34±0.06 | 0.28±0.03 | 0.024 |
| LVEF percentage | 58.90±4.7 | 61.22±3.9 | 0.061 |
| RV TAPSE(mm) | 1.42±0.21 | 1.11±0.23 | 0.023 |

*Abbreviations: LA: left Atrium, LVEDD: left ventricle end diastolic dimension, LVESD: left ventricle end systolic dimension, EF%: ejection fraction Percentage, TAPES: tricuspid annulus plane excursions*

Table 3 illustrates both pulsed and tissue Doppler measurements for diastolic filling velocity left ventricles pulsed and CW Doppler of tricuspid valve and ratio systole to diastole velocity in pulmonary vein. SCD patients had a significantly higher left ventricle E/A ratio, lower a wave velocity and shorter deceleration time. Similarly pulsed Wave of RV showed a wave

velocity significantly lower and DT shorter with higher E/A ratio. SCD had a lower acceleration time of <94.24m sec in pulmonary valve velocity suggesting mild degree of pulmonary hypertension. Tissue Doppler of the septal Mitral annulus showed significantly shorter S wave velocity p<0.01, higher E/E- ratio, p<0.05 and lower A- wave, P=0.04. The Ratio of systolic/diastolic velocity of right upper pulmonary vein was significantly lower of, p<0.01. Tricuspid valve on CW Doppler showed significantly higher velocity in the sickle cell disease patients of p<0.01indicating higher pulmonary artery pressure with calculated right ventricle systolic pressure of 38.64 vs. 16.56 mmHg.

**Table 3. Pulsed and tissue Doppler parameters in the study population, data presented as mean ±SD**

| Parameters | Patients with SCA N=103 | Control patients N=103 | P value |
|---|---|---|---|
| LV E wave (mcec) | 85.23±1.92 | 62.43±1.67 | 0.001 |
| LV A wave (msec) | 46.26±4.7 | 56.24±3.2 | 0.032 |
| LV E/A | 1.86±0.01 | 1.10±0.03 | 0.024 |
| LVDT of E wave (msec) | 156.43±23.5 | 189.87±19.5 | 0.031 |
| RV E wave (cm/s0 | 76.65±1.43 | 59.34±1.9 | 0.04 |
| RV A wave (cm/s) | 40.65±3.5 | 49.65±3.4 | 0.043 |
| RV E/A | 1.93±0.03 | 1.20±0.02 | 0.076 |
| RV DT of E wave (msec) | 176.24±21.4 | 210.43±0.24 | 0.012 |
| RV pulmonic vein S/D ratio. | 1.5 ±0.12 | 2.4±0.11 | 0.002 |
| Pulmonary valve acceleration time, msec | 94.24±11.3 | 110.14±14.8 | 0.002 |
| Tricuspid CW velocity (m/s) | 2.9±0.14 | 1.7±0.09 | 0.004 |
| LV Tissue Doppler S wave | 6.7±1.7 | 11.3±1.9 | 0.01 |
| LV TD of E/E - ratio | 12.2±1.2 | 7.2±1.3 | 0.04 |
| LV TD of A – wave | 5.3±1.6 | 7.2±1.2 | 0.02 |

*Abbreviations: SCA: sickle cell Anaemia, LV: left ventricle, RV: right ventricle, E: pulsed Doppler early diastolic filling, A atrial diastolic filling, DT: deceleration time of E wave, E- (tissue Doppler E wave), A- (tissue Doppler of A wave, S/D: systolic /diastolic wave ratio, S: systolic wave*

In SCA patients there were 29/103 (28 %) with tricuspid regurgitation velocity (TVR) of >2.5 m/s, four (4%) of them had velocity >3 m/s and 74/103 (72%) had velocity <2.5 m/s. There was a positive correlation between the serum level of ferritin, pro-BNP and tricuspid valve velocity of (r= 0.38) and (r=0.43) respectively. Fig. 1 shows the percentage of patients in both groups of <2.5 and >2.5 m/s based on TVR on continuous wave Doppler.

Table 4 shows the odds ratio of pulmonary hypertension in SCD patients as follow, 3.1 for E/E- ratio>13, 2.5 for DT of <160 msec, 2.2 for LVMI >121 gm/M2, 1.9 for ferritin >600 ug/L, 1.3 for pro-BNP >150 pmol/L, 1.7 for left atrial area>20cm and 1.4 for right ventricle wall thickness>3 mm.

**Table 4. Odds ratio of multiple regression analysis of different pulsed and tissue Doppler variables in the prediction of pulmonary hypertension in patients with Sickle cell disease with TVR >2.5m/s**

| | Odds ratio | P value |
|---|---|---|
| Pro-BNP>150 pmol /L | 1.3(0.7-1.9) | P=0.01 |
| Ferritin 600 ng /ml | 1.9(1.1-2.7) | P=0.03 |
| E/E- >13 | 3.1(2.5-3.7) | P=0.01 |
| DT<160 msec | 2.5(2.0-3.0) | P=0.01 |
| LV M I>121 gm /M2 | 2.2(1.6-2.8) | P=0.01 |
| Left atrial area >20 cm | 1.7(1.2-2.2) | P=0.01 |
| Right ventricle wall >3 mm | 1.4(1.0-1.8) | 0=0.04 |

*Abbreviations: (DT) deceleration time, (LVMI) left ventricle mass index, ( E/E- ) early filling wave of pulsed Doppler to tissue Doppler E wave, (BNP ) brain natriuretic peptide. (TVR) tricuspid vale regurgitation. (PAH) pulmonary hypertension*

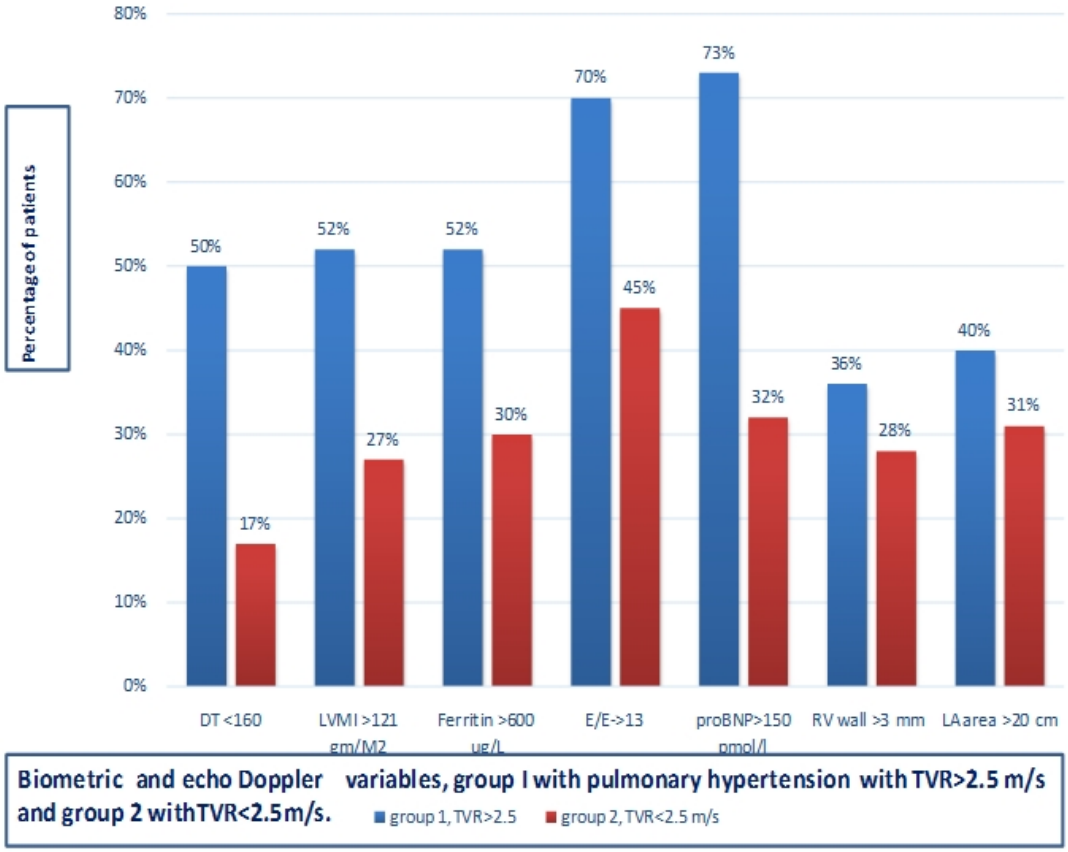


**Fig. 1. The percentage of patients included in each based on results of variables of pulse and tissue Doppler echo, group 1(n=29) with tricuspid valve velocity of ≥2.5 m/s and group 2(n=74) TVR<2.5 m/s**

*Abbreviations: DT: deceleration Time, LVMI: left ventricle mass index, E/E- : Early filling wave on Pulsed Doppler / Tissue Doppler, BNP: brain Natriuretic peptide, TVR: Tricuspid Valve Regurgitation.*

## 4. DISCUSSION

Chronic haemolytic anaemia is accompanied by a state of hyperkinetic circulation with tachycardia [28]. The peripheral resistance is reduced with an dilation of cardiac chambers and hypertrophy [29].

In this study, patients with sickle cell disease had increase of left atrial area and dilation of right ventricle with greater left ventricle mass index than control. The systolic function of left systolic ventricle had no difference compared with control. But the RV systolic function as assessed by tricuspid annular plane systolic excursion (TAPSE) showed significant dysfunction than control. It is possible that LVEF% is insensitive due to its load dependent relationship. It has been observed that patients with SCA had higher preload and lower after load, [30] that cause higher early diastolic LV filling and shorter DT of E which was observed in our patients. The RV systolic and diastolic dysfunction in this study may be due to lung involvement with predominant vaso-occlusive effect and the smaller RV mass than the left ventricle resulting in faster functional derangement.

The diastolic filling pattern for both ventricles was suggestive of restrictive pattern with a significantly high E wave with shortened deceleration time. This is in keeping with one study by Appleton et al. [31] where preload increment is associated with increase of early filling and shortened deceleration time. In two separate studies the diastolic pattern was mainly of abnormal relaxation pattern, [32,33] but the study population in both was a combination of SCA and thalassemia.

The tissue Doppler findings of septal mitral annulus in this study differ from one study that showed patients with SCA had higher tissue Doppler of A- but with higher E/E-[34].

The pulmonary vein systolic /diastolic velocity(S/D) ratio was significantly lower in patients with SCA, this differ compared with Moyssakis et al. [33] where S/D ratio was higher along with prolonged DT but with higher E/A ratio. This difference in results could be due patient's population differences. Patients with SCA had a lower acceleration time of < 94 m sec in pulmonary valve suggesting mild degree of pulmonary arterial hypertension [35]. There were 15/103 (28%) patients in the SCA group with pulmonary hypertension with TR velocity of ≥2.5m/s. The incidence of pulmonary hypertension of 28% in this study was lower than others where the incidences range between 33%-45% [18].

The diastolic function may play a role in the development of pulmonary hypertension. In one study Sachdev et al. [36] observed that diastolic dysfunction and PAH can develop independently in patients with SCA where each contributing to increase mortality alone and patients with both risk factors have a poor prognosis.

The pathogenesis of PAH in patients with SCA is multifactorial and may be due to sickling phenomena, vasoocclusive crises or acute chest syndrome. The repetitive intravascular haemolysis results in the release of haemoglobin that scavenges nitric oxide which finally lead to acute and chronic pulmonary vasoconstrictor [37,38].

The positive correlation between the ferritin, pro -BNP and Tricuspid valve velocity in this study support the notion that iron overload [39] and dilation of the ventricular chambers are implicated in the pathogenesis of pulmonary hypertension [40].

The increase of LV wall thickness due to iron deposit and the high left ventricle end diastolic (LVEDP) pressure evidence by the high E/E – ratio on tissue Doppler with the restrictive pattern of diastolic ventricular filling all contribute to increment of LV wall stiffness which cause left atrial high pressure and dilation.

The stiff myocardium and the increase of left atrial pressure both in addition to other factors invite for the pathogenesis of pulmonary hypertension in patients with SCA.

In one study, SCA patients and beta thalassemia, pulmonary artery pressure was positively correlated with left atrial area, diastolic dysfunction and high serum level of NT pro BNP [41]. In one report by Oguanobi et al. [42] patients with SCD were evaluated clinically with echocardiogram for development of pulmonary arterial hypertension. The ECG variables that are significantly associated with PAH were right ventricle hypertrophy, increased P wave duration and increased QTC dispersion time.

Multiple regression analysis indicated that the most sensitive marker for the development of pulmonary hypertension in SCD is the E/E- ratio>13 with odds ratio of 3.1 followed by DT<160 mse of 2.5, LVMI >121gm/M2 of 2.2, ferritin >600μg/L of 1.9, left atrial area >20 $cm^2$ of 1.7 and pro-BNP >150 pmol/L of 1.3.

In patients with SCA the presence of high E/E- ratio on Tissue Doppler , the shorter Dec elation time of E wave of less than 160 msec both increase the predictive risk of PAH , like wise higher pro BNP level indicates the need for further intensive medication to avoid further future morbidity and mortality.

## 5. CONCLUSION

Adult patients with SCA have normal systolic function but increase of LV mass and restrictive diastolic dysfunction. RV had increase wall thickness, systolic and diastolic dysfunction of restrictive pattern. The prevalence of pulmonary hypertension is 28%. There positive correlation between ferritin, pro BNP level and tricuspid valve velocity on echo. The risk of PAH is higher if the DT of E wave <160 msec, LVMI >121 gm/M2, cm, E/E- ratio ≥ 13 and RV wall thickness >3 mm.

## 6. LIMITATION

This study was conducted on adult patients and some relevant data may be obscured in childhood. Also the pulmonary artery definition was based on tricuspid valve velocity of more than 2.5 m/s where the only reliable method is the invasive RV catheter based study.

## CONSENT AND ETHICAL APPROVAL

Each patient in the study has given an informed consent accepting to give history, be evaluated by echocardiogram and to give blood sample. The study was approved by the institutional committee.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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