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Accuracy of Echocardiographic Measures for Diagnosing Pulmonary Hypertension in Children with Sickle Cell Anaemia

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Abstract

➢ ***Background:***

Echocardiography has evolved to be a non-invasive tool in the assessment of cardiac haemodynamic including pulmonary artery pressures, especially among people at risk of developing pulmonary hypertension. However, concerns were raised over time regarding the contrasting figures of the prevalence of pulmonary hypertension using the conventional peak tricuspid regurgitation jet velocity alone when compared with echo-derived mean pulmonary artery pressure. This analytical cross-sectional study aimed to compare the use of the two measurements in the echocardiographic evaluation of pulmonary artery pressures in children with sickle cell anaemia (SCA).

Three hundred children aged 6 months to 15 years with confirmed diagnosis of SCA in steady state, and age and gender-matched controls were studied. Pulmonary pressure was assessed using Doppler echocardiography from apical 4 chamber RV focused view and parasternal short axis view through Doppler interrogation of the tricuspid regurgitation jet (TRJ). Normal pulmonary artery pressure was defined as tricuspid regurgitation jet velocity (TRV) of less than 2.5 m/s, elevated pulmonary artery pressure (PAP) when the TRV is greater than or equals to 2.5 m/s, and pulmonary hypertension (PH) was defined as a mean pulmonary artery pressure (MPAP) >20 mmHg estimated from mean gradient (MG) derived from the area under the curve of the interrogated TRJ, plus estimated right atrial pressure.

Sixty-four participants with SCA (21.3%) were found to have elevated PAP as against 19 (6.3%) controls. While none of the controls had PH, 17 (5.7%) participants with SCA had MPAP > 20 mmHg diagnostic of pulmonary hypertension. Although there was strong positive correlation between measured peak TRV and MG ($R^2 = 0.801$, $p < 0.001$), quite a number of subjects with elevated PAP were found not to have high MPAP enough to be diagnostic of PH.

Although high peak TRV is a surrogate marker of elevated PAP in children with SCA, it's not diagnostic of PH when compared with estimated MPAP using the mean gradient and estimated RA pressure.

Keywords: *Peak Tricuspid Regurgitation Velocity, Mean Gradient, Pulmonary Hypertension.*

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I. INTRODUCTION

Sickle Cell Anaemia is a non-communicable hereditary disease of public health importance. Approximately 50 million people worldwide have sickle cell anaemia (SCA).[1] In Nigeria, about 25.0% of the population are carriers of sickle cell trait, while the homozygous state is found in about 3.0% of the population.[2] Pulmonary hypertension (PH) is one of the long term complications of SCA characterized by elevated pulmonary artery pressure, leading to significant morbidity and mortality.[2-7] About 20-40% of adult patients with sickle cell anaemia screened with echocardiography have evidence of PH.[3,5] Reported prevalence of PH in children varied from 16-30% in retrospective series,[6-8] to 8.3-33% in recent prospective series.[9-14]

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The flow of blood in the human circulatory system obeys the principles of conservation of mass, energy and momentum, these principles form the basis for the derivation of all the Doppler equations used to determine the severity of cardiac flow abnormalities.[15] By using simplified Bernoulli equation,[15] Doppler echocardiography provides a reliable non-invasive estimation of pulmonary artery pressure from TRJ interrogation.

While echocardiography remains a valuable non-invasive tool in the assessment of pulmonary artery pressure (PAP) especially in resource limited setting where right heart catheterization (RHC) is not readily available, interpreting its findings requires careful consideration. This is important as discrepancies arise between different echocardiographic measures. In recent time, varied opinions emerge regarding the peak tricuspid regurgitation velocity (TRV) cut-off value that is diagnostic of pulmonary hypertension (PH).

For long, peak TRV cut-off of 2.5 m/s has been used to defined elevated pulmonary artery pressure, a marker of PH by two-dimensional echocardiography. [5,6,8,14] Guidelines from the European Society of Cardiology and the European Respiratory Society (ESC/ERS) recommend PH probability to be classified as low (TRV = 2.8 m/s), intermediate (TRV 2.9–3.4 m/s) and high (TRV >3.4 m/s).[16] But most authors have suggested that PH estimation may often be misclassified by traditional thresholds,[17] and that current cut-off points may need to be reconsidered, since small increases in TRV, even at values considered normal, are independently associated with an increased mortality.[18-20] Recently, a value of 2.55 m/s has been favoured to be the more accurate cut-off value indicative of PH.[21]

Additionally, most often the prevalence of PH estimated from peak TRV tends to differ with the prevalence measured using the MPAP. Normal mean pulmonary artery pressure at rest is about 15 mmHg,[9,10] and PH recently defined by a resting MPAP greater than 20 mmHg,[12,21] as against the previous value of greater than or equal to 25 mm Hg using Right Heart Catheterisation (RHC).[9-11] When PAP is assessed from the peak TRV alone to evaluate PH, it reflects the right ventricular systolic pressure which measures systolic rather than MPAP.[22]

This article delves into the disparity often observed in clinical practice, a higher prevalence of elevated PAP based on elevated peak TRV compared to the lower prevalence of PH diagnosed based on the MPAP values measured either through RHC, which is the gold standard or echocardiography derived MG of the TRJ.[7,8]

In an effort to develop standard echocardiographic method of measuring MPAP that is essential for the evaluation of patients with PH, three studies,[22-24] have looked at the possible relationship between the PASP and the MPAP and demonstrated strong correlation among the two pulmonary artery pressure components by RHC. Using linear regression analysis, linear equations relating MPAP and SPAP were derived as follow:

Chemla formula1[23]: MPAP= 0.61 x SPAP +2 mmHg

Syyed formula[22]: MPAP= 0.65 x SPAP +0.55 mmHg

Friedberg formula1[24]: MPAP = 0.69 x SPAP – 0.22 mmHg

From these linear equations MPAP can be derived from echocardiographically determined SPAP.

Acceleration time (AT) across the right ventricular outflow tract (RVOT) can also be used to estimate MPAP,[25] but the major limitation of the AT method is that, in cases where cardiac output is increased as in SCA, AT remains normal in spite of increase in pulmonary artery pressure.[25] Systolic time intervals obtained from spectral Doppler of the pulmonary artery flow have shown that the time to peak pulmonary velocity has a logarithmic relationship with MPAP.[26] But because of the small range of values of the systolic time intervals and their dependence on cardiac output and heart rate, their reproducibility is low and correlation with invasively measured MPAP is suboptimal.[26]

Other method of assessing MPAP by echocardiography is the mean gradient method (MG), developed on the basis of a modification of the traditional echocardiographic method of calculating SPAP.[27] This method involves addition of right atrial pressure to the right ventricular-right atrial mean systolic gradient instead of peak systolic gradient. MG is derived echocardiographically from the area under the curve (AUC) of the tricuspid regurgitation jet Doppler profile.[27]

II. SUBJECTS AND METHODS

The study was a cross-sectional analytical study, carried out at the Department of Paediatrics, Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto. A total of 300 children aged 6 months to 15 years with the diagnosis of SCA in steady state, who were on follow up at the sickle cell clinic of the Department, and 300 age and gender-matched haemoglobin AA controls were recruited in to the study. Participants were selected by simple random sampling using a table of random digits according to the way they were numbered in the outpatient register for the day. Steady state in this study was defined as absence of painful crisis, blood transfusion, acute clinical symptoms or crisis, or febrile illness warranting hospitalisation in the preceding three months.

➢ *Children that Fulfilled the Following Inclusion Criteria were Recruited for the Study:*

- Age 6 months to 15 years.
- Hb Electrophoretic pattern SS
- Absence of crisis, inter current illness such as bronchopneumonia, asthma or any illness that warranted hospitalisation or blood transfusion in the preceding three months.

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For the controls, children on follow up at the paediatric outpatient clinic of the Department and the general out-patient of the Department of family medicine on follow-up for minor ailments, who consented and fulfil the following criteria were recruited.

- Children aged 6 months to 15 years with minor ailments that are not known to affect pulmonary pressure or TRV
- Haemoglobin electrophoretic pattern AA
- Packed cell volume (PCV) of at least 30%

➢ *Children with the Following Conditions were Excluded:*

- Presence of chest wall deformities.
- Patients on therapies known to have effect on pulmonary artery pressure such as anorectic agents, hydroxyurea or chronic transfusion therapy.
- Presence of functional or structural abnormality of the heart or great vessels, like systolic dysfunction, congenital abnormalities of the heart and the great vessels including branch pulmonary stenosis.
- Presence of obvious clinical symptoms of cardiac involvement by infectious, neuromuscular or metabolic disorder; or clinical symptoms of lung disease, asthma, adenoidal hypertrophy, kidney or connective tissue disease and fever.
- Absence of measurable tricuspid regurgitation jet.

Ethical consideration: Ethical approval for the study was obtained from the Ethics Committee of Usmanu Danfodiyo University Teaching Hospital, Sokoto. An informed written consent was obtained from the parent/caregiver of each child with an assent from the older children (7-15 years) after providing adequate explanation about the study.

Standard two-dimensional and Doppler echocardiography was performed in the supine and left lateral decubitus positions using SSI-5000 Sonoscape echocardiography machine (SonoscapeYizhe Building, Yuquan Road, Shenzhen China) with a 3.5–7 MHz transducer. Standard parasternal long and short axes, apical, subcostal, and suprasternal views were used. Screening echocardiography was done first to rule out structural heart abnormalities including right ventricular out flow and branch pulmonary artery obstruction. Left ventricular systolic function was assessed by estimating left ventricular ejection fraction from M-mode using Simpson's rule. Subjects with ejection fraction of 54% - 75% were regarded to have normal left ventricular systolic function.[28]

Colour Doppler interrogation was used to detect tricuspid regurgitation from the apical 4-chamber, RV inflow, parasternal short axis and subcostal views. Tricuspid valve morphology was assessed to ensure normal tricuspid valve morphology. Tricuspid regurgitant jet velocity (TRV) was recorded and the maximum value obtained was taken as the peak velocity. Mean gradient (MG)) was measured by continuous wave Doppler using area under the curve method as shown in the figure below:

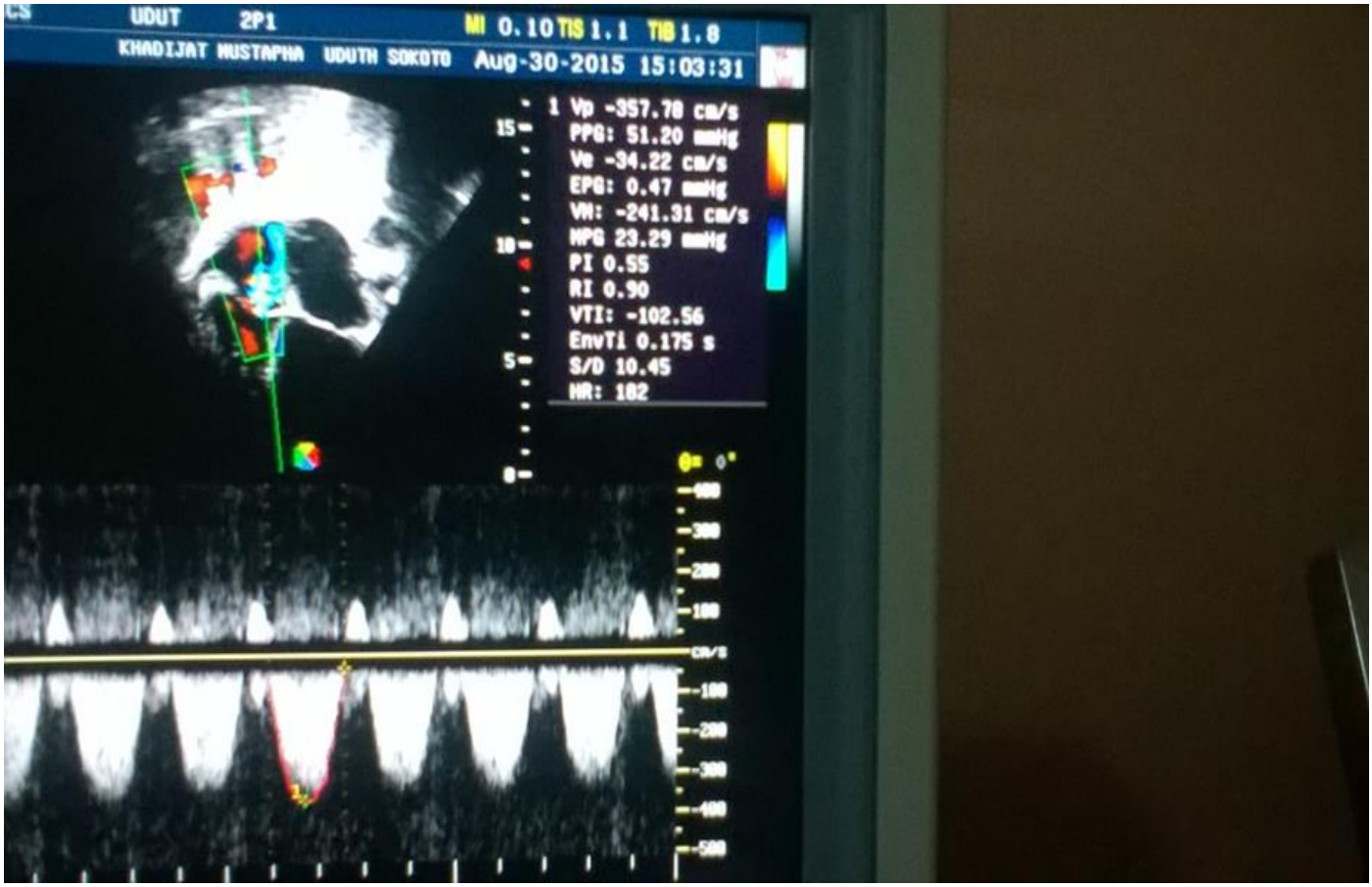

Fig 1 Doppler using area under the Curve Method

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Colour flow Doppler with area under the curve mapping in a 6-year-old girl with SCA and pulmonary hypertension. The peak TRV was 3.6 m/s while the mean gradient (MG) was 23.3 mmHg. Estimated RPA was 5 mmHg (10% of 4TRV2). The MPAP was 28 mmHg (MG + RPA).

Pressure gradient (ΔP) between the right ventricle and the right atrium was calculated using the Bernoulli equation:

$$P1\text{-}P2\ (\Delta P) = 4V^2$$

Where P1 is the right ventricular pressure, P2 is the right atrial pressure and V the peak TR velocity. Ten per cent of ΔP was taken as estimated right atrial pressure.[29] This was added to the mean gradient (MG) derived from the area under the curve to get the MPAP.

$$MPAP = MG + RAP\ (10\%\ of\ 4TRV^2).$$

➢ *PASP was Estimated using Modified Bernoulli Equation as Follow:*

- *Quality Assurance:*

All echocardiographic measurements were done according to the recommendations of the American Society of Echocardiography.[30] The arithmetic mean of three consecutive measurements were used. The TR jet was interrogated from multiple different views (RV inflow, apical four chamber, parasternal short axis and subcostal views) to ensure that the ultrasound beam is parallel to the regurgitant signal, thus allowing optimal Doppler envelope quality and an accurate peak trans tricuspid flow velocity (TTFV).[29,30]

- *Data Analysis:*

Obtained data was analysed using the Statistical Program for Social Science (SPSS) version 23.0 for windows. Measured TRV and MG were compared using pearsean correlation and linear regression models. A p-value < 0.05 was considered statistically significant at 95% CI (two-tailed).

III. RESULT

Six hundred subjects were recruited into the study, comprising 300 SCA participants and 300 Hb AA controls. The age range of all the subjects was 0.5- 15 years, with mean age of 6.5 ± 4.1 years for patients with SCA and 5.9 ± 5.2 years for the controls (p = 0.13) as shown in Table I. One hundred and fifty six of the 300 SCA patients (52.0%) were males and 144 were females with M: F of 1.1:1. In the control group, 138 were males and 168 were females with M: F of 0.9:1.

All echocardiographic variables measured were significantly higher in participants with SCA than the controls as shown in table I. The range of TRV in participants with SCA was 0.9 – 4.2 m/s with mean of 2.0 ± 0.7 m/s, and the range of TRV in the Hb AA controls was 0.8 – 2.6 m/s with mean of 1.6 ± 0.4. The range of MG in participants with SCA was 1.7 – 29.8 mmHg with mean MG of 8.4 ± 4.7 mmHg, while the range of MG in the Hb AA controls was 0.7 – 18.4 mmHg with mean MG of 5.9 ± 3.9 mmHg. The range of MPAP values in patients with SCA was 2.0 – 35.0 with mean MPAP of 10.2 ± 5.8 while the range of MPAP in the Hb AA controls was 1.9 – 21.0 mmHg with mean of 7.8 ± 4.4.

Table 1 Demographic and Echocardiographic Characteristics of the Study Participants.

Variables	SCA patient	Controls	P value
	N= 300	N = 300	
Age (years)	6.5 ± 4.1	5.9 ± 5.2	0.13
M: F	1.1:1	0.9:1	0.14
BMI, (kg/m^2)	14.7 ± 2.9	15.3 ± 1.9	0.002
BSA, (m^2)	0.8 ± 0.3	0.7 ± 0.4	0.09
TRV (m/s)	2.0 ±0.7	1.6 ± 0.4	<0.001
MG (mmHg)	8.4 ± 4.7	5.9 ± 3.9	<0.001
MPAP (mmHg)	10.2 ± 5.8	7.8 ±4.4	<0.001

Sixty four out of the 300 (21.3%) participants with SCA had elevated PAP defined as TRV of > 2.5 m/s; but only 19 (6.3%) out of the 300 Hb AA controls had elevated PAP ($X^2(1) = 45.7$, p = 0.001). Although 21.3% participants with SCA were found to have elevated pulmonary artery pressure (PAP) using cut off point of peak TRV > 2.5 m /s, only 17(5.7%) had mean pulmonary artery pressure (MPAP) ≥ 20 mmHg diagnostic of pulmonary hypertension using the MG, and none of the controls had pulmonary hypertension.

There was strong positive correlation between measured peak TRV and mean gradient (R^2= 0.801, p < 0.001) among the participants with SCA, which was not observed in the controls (R^2 = 0.113).

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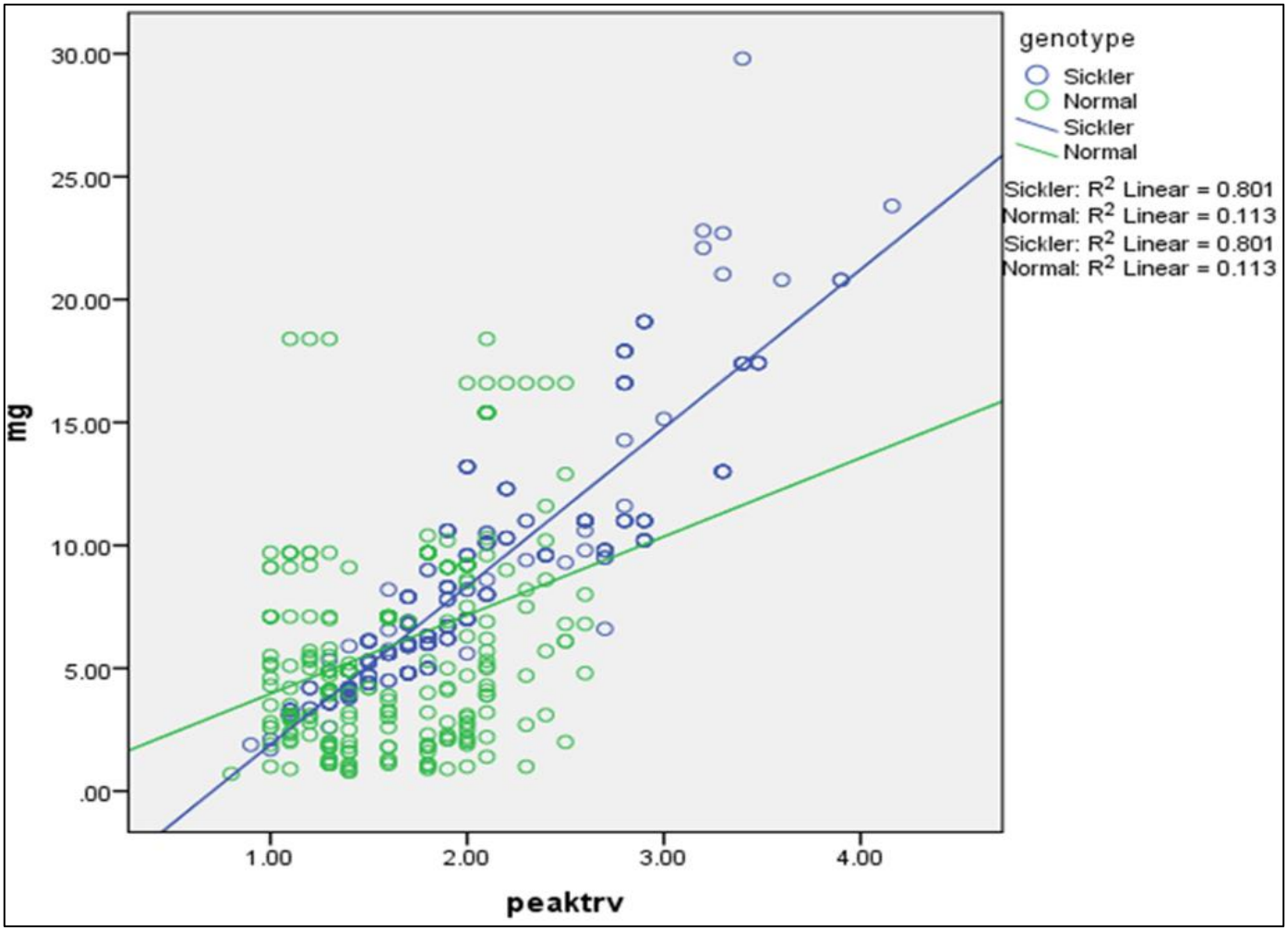

Fig 2 Scatter plot diagram of the linear relationship between TRV and MG

After linear regression analysis, the linear equation relating TRV and MG was found to be:

$$MG = 5.01xTRV-2.0$$

IV. DISCUSSION

Through its ability to quantify blood flow, measure pressure gradients, and estimate intra-cardiac pressures, the role of Doppler echocardiography in the evaluation of people at risk of pulmonary hypertension has been established. Peak TRV, representing the peak velocity of the regurgitant jet across the tricuspid valve, is a readily obtainable echocardiographic measure, and a high TR velocity suggests a significant pressure difference between the right ventricle and right atrium, indirectly indicating elevated PAP.

The finding in this study of a significant difference between the prevalence of elevated PAP using peak TRV value alone and the prevalence of PH defined by the MPAP could be due to the fact that though peak TRV is a marker of elevated PAP, it is only reflective of systolic PAP,[21] telling less of MPAP, which reflects the steady component of flow across the pulmonary artery and the functional status of the restrictive pulmonary vasculature.[31,32]

The difference in the prevalence of elevated PAP (21.3%) and PH (5.7%) observed in this study is significant despite strong positive correlation between TRV and MG measurements. Similar differences were observed in previous studies (40.0% vs 10.0%),[33] (27.0% vs 6.0%)[34] between peak TRV and RHC measured pulmonary pressures. This further support the finding in this study that; elevated TRV though a marker of elevated PAP is not diagnostic of PH.

In this study, PH was defined as MPAP > 20 mmHg based on the recent revised cut-off value for the diagnosis of PH, as against the earlier value of ≥25 mmHg. This is because it has recently been shown that the normal MPAP at rest is 14 + 3 mm Hg with an upper limit of normal of approximately 20 mmHg.[33]

Echocardiographic assessment of PH is better and more reliably done by estimation of MPAP rather than peak TRV alone. The use of MG of the TRJ, developed on the basis of a modification of the traditional echocardiographic method of calculating SPAP is derived from the area under the curve (AUC) of the tricuspid regurgitation jet Doppler profile by Bishop et al at Mayor clinic.[27] It shows satisfactory limits of agreement and correlation between echocardiographically determined MPAP and RHC measured MPAP better than the linear regression derived formulas.[35]

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The earlier formulae relating MPAP with PASP were reviewed for validation. Chemla formula was derived in a prospective study in Paris using small sample size (31 subjects) and only patients with chronic pulmonary hypertension were studied, which can limit its use in acute PH.[23] Syyed formula was derived in Scotland from a small sample size also (65) and both normal subjects as well as subjects with pulmonary hypertension from various aetiologies were used.[22] The low sample size and inappropriate sample collection may hinder the accuracy of these formulas.[35]

Aduen *et al* reported that estimation of MPAP using Chemla and Syyed formulae as well as MG method were reasonably accurate, with a mean difference between calculated MPAP and RHC measured MPAP that was slightly close to 0 for the MG method than for the Chemla and Syyed methods.[35]

Strong correlation between echocardiographically measured TRV and MG demonstrated in this study was only present in participants with SCA, possibly indicating that this relationship could only exist in the presence of elevated PAP. It could further be supported by the fact that, several factors besides elevated PAP can influence TR velocity, including right ventricular function, loading condition, and tricuspid valve morphology and that TRV in the absence of elevated PAP may not demonstrate this correlation with MG.

From the findings in this study, there is need to improve the specificity of echocardiographic assessment for PH by using the MG of the TR jet to estimate the MPAP. The MG, when combined with an estimate of right atrial pressure, allows for a more accurate estimation of MPAP. This approach helps mitigate the influence of transient factors affecting TR velocity and provides a more reliable indicator of sustained pulmonary artery pressure elevation.

The lower MPAP estimated prevalence of PH, despite taking all the necessary measures to address the limitations of accurate TRJ interrogation in this study likely represents a more specific identification of patients with sustained elevation of pulmonary artery pressure meeting the diagnostic threshold for PH.

V. CONCLUSION AND CLINICAL IMPLICATIONS

The discrepancy between TR velocity and MG-based estimations of MPAP in the echocardiographic assessment of PH underscores the importance of a comprehensive approach to echocardiographic evaluation. It is recommended that efforts should be made to use estimated MPAP cut-off value to complement the peak TRV in the assessment of PH during echocardiography.

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