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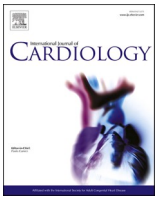

The importance of concomitant mitral regurgitation for estimates of mitral valve area by pressure half time in patients with chronic rheumatic heart disease

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ABSTRACT

Aims: Aim was to study how concomitant mitral regurgitation (MR) assessed by qualitative and quantitative methods influence mitral valve area (MVA) calculations by the pressure half time method (MVA_{PHT}) compared to reference MVA (planimetry) in patients with rheumatic heart disease.

Methods and results: In 72 patients with chronic rheumatic heart disease, MVA_{PHT} was calculated as 220 divided by the pressure half time of the mitral early inflow Doppler spectrum. Direct measurement by planimetry was used as reference MVA and was mean (SD) 0.99 (0.69–1.99) cm^2. Concomitant MR was present in 82%. MR severity was assessed qualitatively in all, semi-quantitatively by measuring the vena contracta width in 58 (81%), and quantitatively by calculation of the regurgitant volume in 28 (39%).

MVA was significantly underestimated by MVA_{PHT}, with increasing MR. In regression analyses MVA_{PHT} underestimated MVA by 0.19 cm^2 per higher grade of MR severity in qualitative assessment, and by 0.12–0.13 cm^2 per mm larger vena contracta width and 10 ml larger regurgitant volume, respectively. The presented associations were more evident when i) MR severity was quantified compared to qualitative assessment and ii) reference measurements were made by three-dimensional transoesophageal recordings compared to transthoracic recordings.

Conclusion: MVA_{PHT} underestimated mitral valve area compared to planimetry in patients with MS and concomitant MR. This study highlights the importance of taking the MR severity into account when evaluating MVA based on the PHT method. Direct measurements should be included in clinical decision making.

1. Introduction

Mitral stenosis (MS) is the most common valvular dysfunction caused by rheumatic heart disease (RHD), a frequent complication of rheumatic fever [1–3]. Even though rare in high income countries its prevalence is estimated to exceed 33 million world-wide [4]. Surgery or interventions is indicated in symptomatic patients with mitral valve area (MVA) ≤1.5 cm^2 [1,5].

With the advent of echo Doppler in the late 70s, non-invasive estimates of MVA replaced the invasive estimation of valve area by the

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Gorlin formula [6]. First MVA was estimated (MVA_{PHT}) by the Doppler pressure half time (PHT), and later by the equation of continuity and by direct measurements using planimetry [7–9]. By development of modern echo machines, planimetry is now the reference measurement for assessment of MVA in MS patients [1,5,10]. However, due to the need of highly trained operators and sometimes poor image quality, the PHT method is still frequently used to diagnose MS world-wide [11]. Known limitations of this method relate to left ventricular (LV) diastolic function, presence of aortic regurgitation and impaired left atrial (LA) and/or LV compliance. Concomitant mitral regurgitation (MR) is frequently seen in patients with chronic MS, but few publications have evaluated the importance of MR when using the MVA_{PHT} method to calculate MVA [12–14]. Of these, one study found concomitant MR to be of importance [14], while the others did not. However, limitations include small sub-populations with concomitant severe MR and only colour Doppler was used for grading of MR severity [12–16].

The aim was to study the importance of concomitant MR, evaluated by qualitative and quantitative methods, for MVA_{PHT} estimations in a population of chronic RHD patients using planimetry as reference measurements. Secondly, we aimed to evaluate if atrial fibrillation (AF), heart rate (HR), aortic regurgitation (AR), systolic pulmonary arterial pressure (SPAP) and indexed left atrial volume (LAVI) influenced the associations. Our hypothesis was that MR above a certain level would lead to an underestimation of MVA by PHT. We expected the association to be most pronounced when grading MR by quantitative methods.

2. Methods

2.1. Study design and population

At Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 101 patients were assessed by a Norwegian Heart team from April 2016 to November 2019. TTE was done in all, and TEE in a subpopulation scheduled for surgery or interventions. In total 25 patients with non-RHD or non-available echocardiograms and four patients with inconclusive planimetric MVA measurements were excluded. The final study group consisted of 72 patients (Fig. 1), whereof 18 patients had 3D (TEE or TTE) planimetric measurement of MVA. This subgroup was included in a sensitivity analysis. The study protocol was approved by the Regional Committee for Health Research Ethics in Norway (ID 7179), and by the local committee for medical research ethics at Addis Ababa University in Ethiopia. The study was registered in the Clinical Trials database (NCT04556188) and conducted in agreement with the Declaration of Helsinki.

2.2. Data collection

Data was collected by the heart team at screening and during the operative or interventional procedures.

Echocardiography was performed by cardiologists experienced in echocardiography. TTE recordings included parasternal long- and short-axis views, standard apical views and sub-costal views in grey scale, colour, and tissue Doppler mode, as well as pulsed-wave and continuous wave blood flow Doppler. TEE included transgastric long- and short-axis view, and TEE standard and non-standardized views of the valves and the ventricles. In sub-populations, 3D full volumes of the different valves for offline analyses were recorded. Further details are included in the Supplementary data file.

2.3. Echocardiographic measurements

The grading of valvular pathology was done according to recent guidelines [1,5]. All echocardiographic recordings were acquired using a GE Vivid E9 or a Vivid *i* ultrasound scanner (GE Ultrasound, Horten, Norway). All echocardiographic analyses were done offline using Echopac SWO; version 201–203 (GE Ultrasound).

MS severity was evaluated by direct tracing of MVA by planimetry and Doppler methods. Planimetric measurements were done in transthoracic and transoesophageal echocardiograms recorded at the tip of the mitral leaflet at mid-diastole. The inner border of the mitral orifice

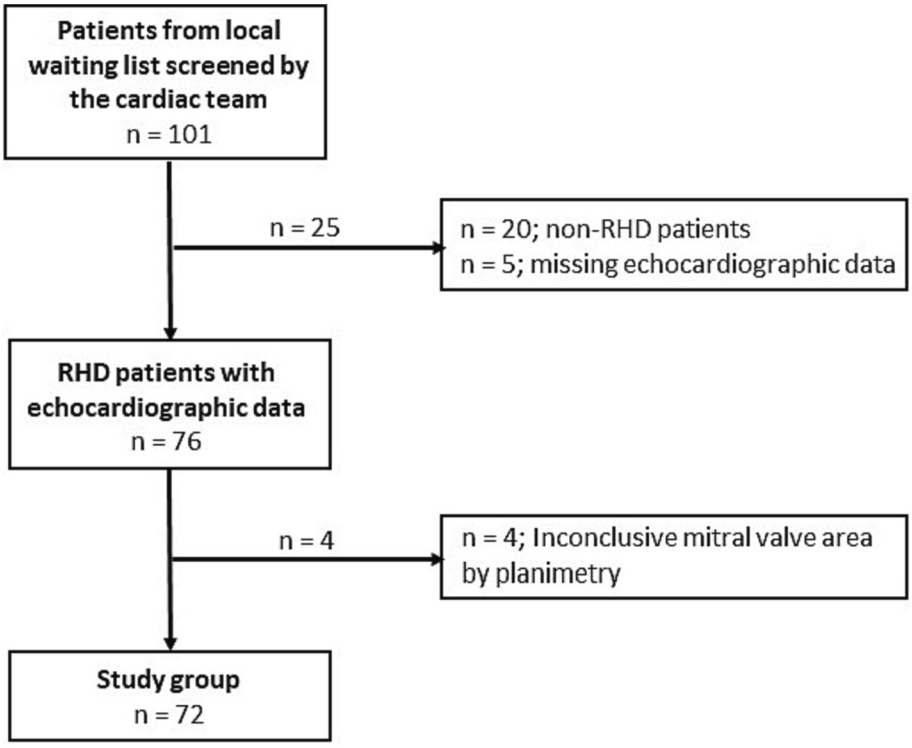

Fig. 1. Flow chart of the study population.
Abbreviations: RHD, rheumatic heart disease.

was traced in short-axis view and the area was calculated (Fig. 2). The best available planimetric measurement was used as reference MVA, with 3D TEE as the preferred assessment, followed by 3D TTE, 2D TEE and 2D TTE. MVA_{PHT} was calculated (in continuous Doppler TTE 4-chamber view recordings with the ultrasound beam aligned to the mitral inflow) using the equation $MVA_{PHT} = 220/PHT$ [17] (Fig. 2). Mitral valve gradients and velocity time integral (VTI) was measured by tracing of the Doppler spectrum.

MR severity was evaluated by three different methods: 1) Qualitative grading based on the experienced echocardiographers expert opinion. 2) The vena contracta width in mm. 3) Quantification of the regurgitant volume (in mL) by the Proximal Isovelocity hemispheric Surface Area (PISA) method. Qualitative grading of the MR was done based on valvular morphology, flow regurgitant colour Doppler signal, the mitral inflow early velocity (E) and presence of systolic pulmonary vein flow reversal. Vena contracta (VC) width was measured at the narrowest point of the colour Doppler signal just downstream of the valvular orifice. Quantitative estimation of the regurgitant volume (RVol) was done by the Proximal Isovelocity hemispheric Surface Area (PISA) method. For PISA measurements the recordings were optimized by narrowing the image field and reducing the Nyquist limit to 30–40 cm/s. The radius of the convergence hemisphere was measured from the mitral orifice at mid-systole using the first aliasing signal. The MR continuous Doppler spectrum was traced with the ultrasound beam aligned to the jet

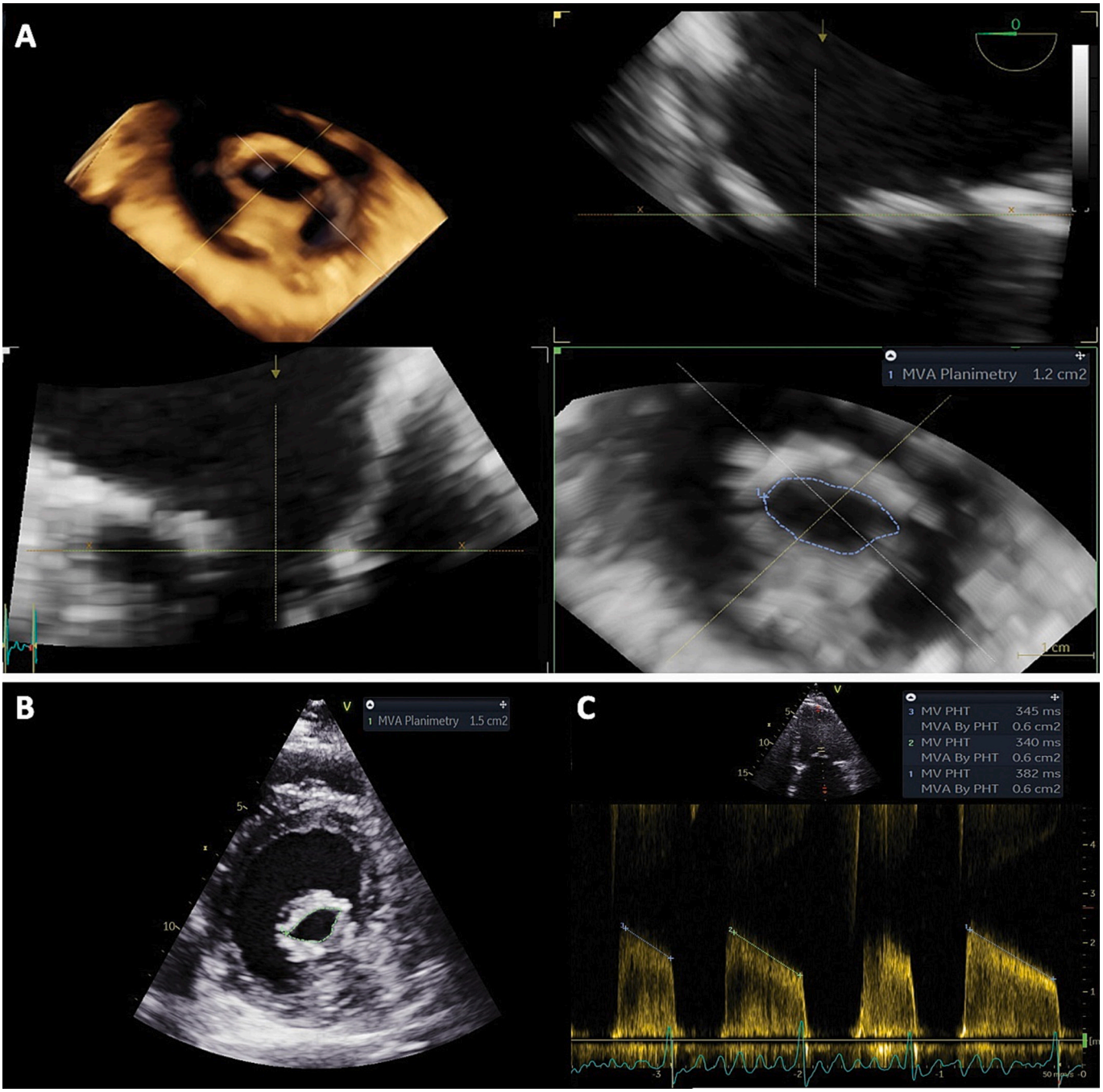

Fig. 2. Methods for measurements of mitral valve area.
Mitral valve area calculations by A) three-dimensional transoesophageal planimetry, B) two-dimensional transthoracic planimetry in parasternal short-axis view and C) pressure half time in mitral inflow Doppler recording.

direction. VC <3 mm, and RVol <30 ml was defined as mild MR, while VC ≥3 mm to <7 mm, and RVol ≥30 ml and < 60 ml was defined as moderate MR, and VC ≥7 mm and RVol ≥60 ml was defined as severe MR. Wilkins score was used to grade the rheumatic affection of the mitral valve [18].

The severity of AR was graded based on valvular morphology, flow regurgitant colour Doppler spectrum, PHT and end-diastolic velocity of the flow reversal in the descending aorta. Further, we measured the VC and quantified the RVol as described above. Further details of echocardiographic measurements are included in the Supplementary data file.

2.4. Statistical methodology

Continuous variables are expressed as mean and standard deviation (SD) or as median and interquartile range (IQR), as appropriate. Normality was evaluated using histograms and normality plots. Categorical variables are presented as frequencies and proportions. The student *t*-test and Wilcoxon test were used for comparisons of groups when appropriate. Proportions were compared using the chi-square test and Fisher exact test.

We subtracted MVA by planimetry from MVA_{PHT} to assess the MVA error (Er_{MVA}). Thus, a negative value of Er_{MVA} was present if the MVA_{PHT} was less than the planimetric MVA. We analysed the associations of Er_{MVA} with MR severity both as categorical variables (no, mild, mild to moderate, moderate, and severe MR) and as scaled variables. We present data from non-transformed linear regression models as they provided superior models compared to transformed models (logarithmic, squared, and radial). We highlighted individuals with concomitant moderate or severe AR for evaluation of relevant interference. A sensitivity analyses was performed restricting the population to patients with planimetric MVA from 3D TEE. Finally, we separately adjusted the regression analyses for heart rate, atrial fibrillation, AR, LAVI, and SPAP, respectively. Due to the modest size of the population, no sex specific analyses with respect to Er_{MVA} was performed. A *p*-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 26.

3. Results

3.1. Population and echocardiographic data

Baseline characteristics of the 72 patients are shown in Table 1 according to sex. More females than men were included (43 (60%) vs.29 (40%)). Atrial fibrillation was present in half of the population and mean heart rate was 84 bpm.

Table 1
Basic characteristics of the study population.

Variables	Women ($n = 43$)	Men ($n = 29$)	Total ($n = 72$)	p-value, sex difference
Age, mean (SD), years	30 (8)	32 (10)	31 (9)	0.59
Height, mean (SD), cm	158 (6)	168 (7)	162 (8)	<0.01
Weight, mean (SD) kg	54 (13)	61 (16)	57 (15)	<0.05
Body mass index, mean (SD), kg/m^2	21.7 (5.3)	21.5 (4.9)	21.6 (5.1)	0.86
Body surface area, mean (SD), m^2	1.5 (0.2)	1.7 (0.2)	1.6 (0.2)	<0.01
Blood pressure systolic, mean (SD), mmHg	111 (18)	116 (21)	112 (19)	0.19
Heart rate, mean (SD), per minute	82 (16)	88 (19)	84 (17)	0.14
NYHA class, median (IQR)	3 (2–3)	2 (2–3)	3 (2–3)	0.13
Atrial fibrillation, n/a (%)	23/43 (54%)	12/29 (42%)	35/72 (49%)	0.31

Abbreviations: n/a, numbers/available; NYHA class, New York Heart failure Association functional class.

Details from baseline echocardiography are summarized in Table 2. Any kind of MS was found in 85% and very severe MS (≤1.0cm^2) in 50%. The majority had concomitant valvular disease. 82% had MR and more than half the population had moderate or severe MR. Aortic- or tricuspid valve regurgitations were each present in ≥65% of the patients.

LV volumes and EF were within normal ranges, but cardiac index and indexed LV stroke volume were low (2.3 L/min/m^2 and 29 mL/m^2, respectively). LAVI was severely dilated, and RV dimensions were above the upper normal reference limit. Further evidence for RV strain is shown by the significantly elevated maximum SPAP (populational mean 59 mmHg).

3.2. Effect of MR by different methods on the difference of MVA by PHT and planimetry

The Graphical abstract and Fig. 3 show the importance of MR severity for Er_{MVA} in the whole population according to the different methods of MR assessment. There was a consistent finding that the PHT method underestimated MVA compared to planimetry in patients with severe MR. The finding was most pronounced when MR was graded by the quantitative PISA method, and more evident when MR severity was evaluated by the vena contracta width than qualitative assessment. Thus, the negative correlation between Er_{MVA} and MR severity by PISA was strongest but there were significant negative correlations between Er_{MVA} and MR severity assessed by all methods, all $p < 0.05$. Moderate or severe AR did not significantly interfere with the results in this population.

Fig. 4 shows the associations of Er_{MVA} with MR severity according to

Table 2
Basic echocardiographic data.

Variable	*N*	Distribution
General measurements		
LV dimension, end-diastolic, mm	72	52 (10)
LV ejection fraction, %	72	53 (9)
Indexed LV stroke volume, median (IQR), ml/m2	55	29 (23–38)
Indexed left atrial volume, ml/m2	71	132 (95)
Right ventricular basal dimension, end-diastolic, mm	70	42 (8)
Tricuspid annular plane systolic excursion, mm	66	19 (5)
Systolic pulmonary arterial pressure, mm Hg	63	59 (23)
Mitral valve (MV)		
MV stenosis, n (%)	72	61 (85)
Severe MV stenosis by planimetry*, n (%)	72	48 (67)
Very severe MV stenosis by planimetry#, n (%)	72	36 (50)
Moderate or severe MV regurgitation, n (%)	72	39 (54)
MV mean gradient, mm Hg	69	12.6 (7)
MV, pressure half-time, ms	66	211 (115)
MV area by planimetry, median (IQR), cm^2	72	0.99 (0.69–1.99)
MV area by pressure half-time, median (IQR), cm^2	66	1.17 (0.79–1.64)
MV regurgitation vena contracta, mm	59	6.4 (2.7)
MV regurgitation volume by PISA, ml	28	59 (39.6)
Wilkins score	72	11.1 (1.7)
Aortic valve (AV)		
AV regurgitation, n (%)	72	47 (65)
Moderate or severe AV regurgitation, n (%)	72	22 (31)
Tricuspid valve (TV)		
TV regurgitation, n (%)	72	62 (86)
Moderate or severe TV regurgitation, n (%)	72	37 (51)
Concomitant valvular dysfunction		
MV combined stenosis and regurgitation, n (%)	61	48 (79)
Combined MV stenosis and AV regurgitation, n (%)	61	41 (67)
Combined MV stenosis and TV regurgitation, n (%)	61	55 (90)
Combined MV stenosis and MV, AV and TV regurgitation, n (%)	61	30 (49)

Values are mean (SD) if not otherwise specified. *Mitral valve area < 1.5 cm^2. #Mitral valve area < 1.0 cm^2. Abbreviations: AV, aortic valve; IQR, interquartile range; LV, Left ventricular; MV, mitral valve; PISA, Proximal Isovelocity Surface Area method; SD, standard deviation; TV, tricuspid valve.

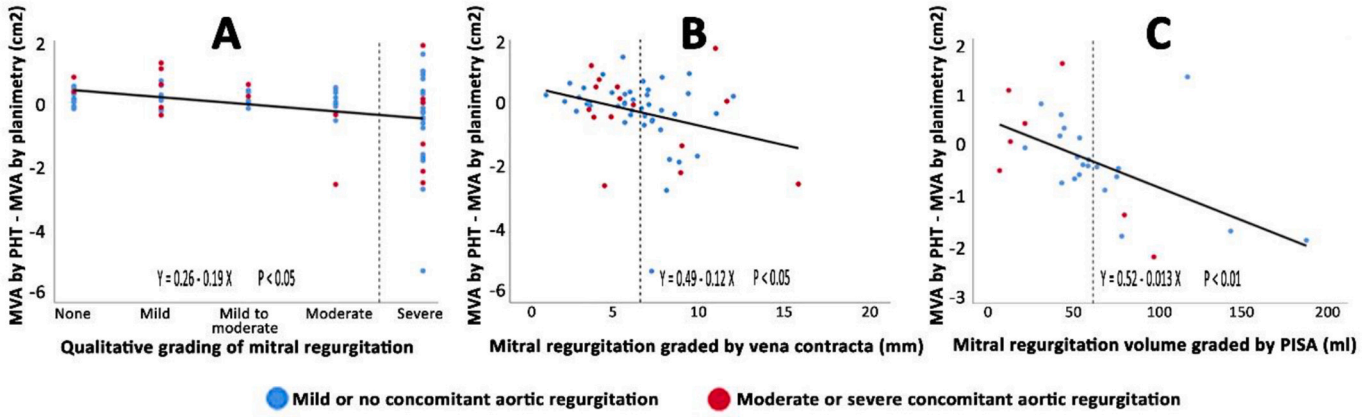

Fig. 3. Mitral valve area errors according to mitral regurgitation severity when estimated by pressure half time compared to planimetry in the whole study population.
Panel A shows the error in mitral valve area calculated as estimate by pressure half-time minus measurement from planimetry according to qualitative grading of mitral regurgitation in the total population. Panel B and C shows the corresponding plots according to vena contracta width and regurgitant volume, respectively. The regression lines are shown as straight lines with corresponding equations and *p*-values.

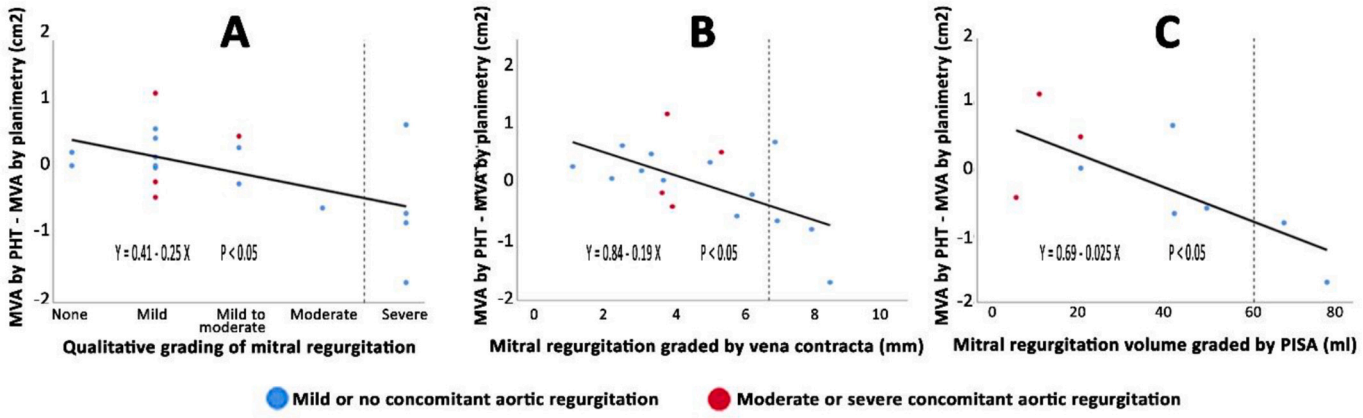

Fig. 4. Mitral valve area errors according to mitral regurgitation severity when estimated by pressure half time compared to planimetry in three-dimensional transoesophageal echocardiograms.
Panel A shows the error in mitral valve area calculated as estimate by pressure half-time minus measurement from planimetry according to qualitative grading of mitral regurgitation in the subpopulation where planimetry performed by three-dimensional transoesophageal echocardiography. Panel B and C shows the corresponding plots according to vena contracta width and regurgitant volume, respectively. The regression lines are shown as straight lines with corresponding equations and *p*-values.

the different methods in patients with available 3D TEE planimetric MVA measurements. In these sensitivity analyses even stronger negative correlations between Er_{MVA} and MR severity were found, all $p < 0.05$. Also in this sub-population the strongest negative correlation of Er_{MVA} with MR severity was found when MR severity was assessed by quantitative assessment. The vertical dotted lines in Figs. 3 and 4 relate to the cut-offs between moderate and severe MR and illustrate less influence when the MR severity was less than moderate. Table 3 displays regression models indicating the underestimation of MVA when estimated by PHT, corresponding to 0.19 cm^2 per grade of MR severity in qualitative assessment, and 0.12–0.13 cm^2 per mm increased VC, and 10 ml increased RVol (by PISA), respectively. In the sensitivity analyses, including only those with 3D TEE planimetry, the corresponding errors were 0.25cm^2 and 0.19–0.25cm^2, respectively. Not surprisingly from a mathematical view, the underestimation of MVA by the PHT method was most pronounced when no severe MS was present. However, the above-mentioned β coefficients relate to the whole population.

Table 4 illustrates that the associations of Er_{MVA} with MR severity were not significantly changed after adjustment for either heart rate, atrial fibrillation, AR, LAVI, or SPAP. In these multivariable analyses atrial fibrillation was an independent predictor for Er_{MVA}, while the others were not.

4. Discussion

The study presents evidence of the impact of concomitant MR when estimating MVA_{PHT} compared to direct measurements. The results showed that in RHD patients, more severe concomitant MR may lead to underestimation of MVA by the PHT method. Mild and moderate mitral regurgitations were of less importance, while when the regurgitation is moderate-severe or severe careful evaluation is needed when grading MS by the PHT method. Importantly, the associations of MR severity with underestimation of MVA by the PHT method was more evident when the MR was graded quantitatively. A similar finding was found when the MVA reference measurements were obtained by 3D TEE. These findings provide further support for the negative influence of concomitant MR for grading of MVA by the PHT method, compared to conflicting results from previous studies.

Table 3
The associations of mitral regurgitation severity on mitral valve area by estimated pressure half time compared to planimetry.

Variable	*N*	Unit	Error MV area,* mean (SD), cm2	p-value
Overall analyses using MV area by planimetry as reference				
MV regurgitation graded qualitatively	71	grade	−0.19 (0.07)	<0.05
MV regurgitation vena contracta	58	mm	−0.12 (0.05)	<0.05
MV regurgitation volume by PISA	28	ml	−0.013 (0.004)	<0.05
Sensitivity analyses using MV area by planimetry in 3D transoesophageal echocardiograms				
MV regurgitation graded qualitatively	18	grade	−0.25 (0.1)	<0.05
MV regurgitation vena contracta	17	mm	−0.19 (0.07)	<0.05
MV regurgitation volume by PISA	9	ml	−0.025 (0.009)	<0.05

* The errors in MV area by PHT compared to reference (planimetry) calculated as MV area by PHT minus MV area by reference method and presented as mean (SD) per specified unit more severe mitral regurgitation. Abbreviations as in Table 2.

Table 4
The associations of mitral regurgitation severity on mitral valve area by estimated pressure half time compared to planimetry after adjustment for relevant covariates.

Variable	*N*	Unit	Error MV area,* mean (SD), cm2	p-value
Adjusted for at least moderate AV regurgitation				
MV regurgitation graded qualitatively	71	Grade	−0.19 (0.08)	<0.05
MV regurgitation vena contracta	58	mm	−0.18 (0.05)	<0.05
MV regurgitation volume by PISA	28	ml	−0.013 (0.004)	<0.01
Adjusted for indexed left atrial volume				
MV regurgitation graded qualitatively	70	Grade	−0.18 (0.08)	<0.05
MV regurgitation vena contracta	57	mm	−0.11 (0.06)#	0.06
MV regurgitation volume by PISA	28	ml	−0.011 (0.05)	<0.05
Adjusted for heart rate				
MV regurgitation graded qualitatively	70	Grade	−0.16 (0.07)	<0.05
MV regurgitation vena contracta	57	mm	−0.11 (0.05)	<0.05
MV regurgitation volume by PISA	28	ml	−0.012 (0.004)	<0.01
Adjusted for present atrial fibrillation				
MV regurgitation graded qualitatively	71	Grade	−0.19 (0.07)	<0.05
MV regurgitation vena contracta	58	mm	−0.11 (0.05)	<0.05
MV regurgitation volume by PISA	28	ml	−0.015 (0.004)	<0.01
Adjusted for maximal systolic pulmonary pressure				
MV regurgitation graded qualitatively	62	Grade	−0.14 (0.07)	0.05
MV regurgitation vena contracta	53	mm	−0.10 (0.04)	<0.05
MV regurgitation volume by PISA	26	ml	−0.014 (0.005)	<0.05

* The errors in MV area by PHT compared to reference (planimetry) per specified unit more severe mitral regurgitation after adjustment for the specified covariates. #$p > 0.05$. Abbreviations as in Table 2.

4.1. Population and echocardiographic data

Most patients had echocardiographic findings of severe MS and/or MR. Compared to previous studies evaluating $MVA_{PHT,}$ both the prevalence and severity of MR was higher in the this study which is an obvious strength compared to previous reports [12,15,19]. The high prevalence of atrial fibrillation (49%), severe dilatation of LA (mean LAVI 132 ml/m^2) and elevated pulmonal artery pressure (mean SPAP 59 mmHg) of the population studied provided substrate for interaction analyses. In adjusted analyses, the associations of MR severity with underestimation of MVA_{PHT} were unchanged, indicating that the importance of MR severity for MVA_{PHT} is causal.

4.2. The importance of the method used for grading MR severity for Er_{MVA}

The finding of a stronger associations with underestimation of MVA_{PHT} when the MR was graded quantitatively is important. These findings are in line with the recommendations that (semi-) quantitative assessment of valvular (mitral) regurgitations is superior to a qualitative assessment [20]. The importance of MR severity quantified by PISA for the assessment of MVA_{PHT} has, to our knowledge, not been evaluated previously. Additionally, in 25% of the present population MVA from 3D TEE planimetry was available for sensitivity analyses. The strong associations of MR severity with Er_{MVA}, when the best possible methods were used to assess both MR severity and MVA, supports the importance of taking MR into account when evaluating MVA by the PHT method.

The finding of underestimated MVA by the PHT method compared to reference planimetry in patients with severe MR is in line with one previous study [14], but is still controversial as other studies did not show significant associations [12,13,15,16,19]. As the PHT method is still frequently used not considering concomitant MR this information is essential. In our results, we found that per 10 ml higher mitral RVol by PISA the PHT method underestimated MVA by 0.13 cm^2. In the sensitivity analyses where the reference measurement was performed by 3D TEE planimetry, the corresponding underestimation was 0.25 cm^2per 10 ml higher mitral RVol. We believe that the reasons why several previous studies did not find MR to be of importance is partly influenced by the limited study samples, as well as the low proportions with moderate or severe concomitant MR. Additionally, uncertainties in grading of MR related to the use of qualitative assessment may be important [12,15,16]. The fact that the strongest association was found between mitral RVol by PISA and Er_{MVA} supports this finding. A probable mechanism of the presented interaction is that the MR influence LV compliance. Whether RHD patients are more sensitive due to relatively small LV volumes is unknown.

We found no clear influence by mild and moderate MR when assessed qualitatively or semi-quantitatively by the vena contracta width. When MR severity was assessed by PISA, we found an underestimation of MVA by the PHT method even with moderate MR. In the presence of concomitant severe MR, the PHT underestimated MVA by all methods used for grading MR. Hence, if the MR is severe by qualitative grading, has VC >7 mm or RVol by PISA >30 ml, MVA_{PHT} may be erroneous and more dedicated methods for MVA estimation should be applied. The fact that underestimation was less when the MVA was very restricted (i.e., severe MS) is not surprising from a mathematical view. This association of Er_{MVA} with MS severity may also explain some of the width in Er_{MVA} as observed by the most severe mitral regurgitations.

4.3. Limitations

The main limitation is the modest study sample, and the fact that MVA by 3D TEE and mitral RVol by PISA was available only in subset of the population. The setting in which the study was conducted, as a part of a clinical educational project aiming to establish governmental cardiac surgery service in Ethiopia, provided some limitations related to

resources, time and data transfer. It would be favourable to have 3D TEE in all patients to add strength to the study, but this was not possible. However, the high proportion of patients with MS and concomitant moderate or severe MR adds valuable new information of the accuracy of estimated MVA_{PHT} for RHD patients. Due to the modest study sample, we were not able to provide more advanced phenotyping information by taking more than two echocardiographic signatures into account in the adjusted analyses, and similarly, we have not performed sex specific subanalyses.

5. Conclusions

In patients with chronic rheumatic heart disease dominated by MS, concomitant MR interfere with calculations of MVA by the PHT method and causes an underestimation of MVA compared to direct measurements by planimetry. The association was stronger when MR grading was done quantitatively and when 3D TEE was used for planimetric reference measurements of MVA. The study highlights the importance of taking the MR severity into account when evaluating MVA in RHD patients based on the PHT method. Lastly, direct measurements should be performed before basing clinical decisions on MVA calculations.

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Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131600.

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