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Reproducibility of reading echocardiographic parameters to assess severity of mitral regurgitation. Insights from a French multicentre study

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Summary

Background. – Poor reproducibility in assessment of mitral regurgitation (MR) has been reported.

Aim. – To investigate the robustness of echocardiographic MR assessment in 2019, based on improvements in technology and the skill of echocardiographers regarding MR quantification.

Methods. – Reproducibility in parameters of MR severity and global rating were tested using transthoracic echocardiography in 25 consecutive patients independently analysed by 16 junior and senior cardiologists specialized in echocardiography (400 analyses per parameter).

Results. – Overall interobserver agreement for mechanism definition, effective regurgitant orifice area (EROA) and regurgitant volume (RVol) was moderate, and was lower in secondary MR. Interobserver agreement was substantial for EROA (0.61, 95% confidence interval [CI] 0.45–0.75) and moderate for RVol with the PISA method (0.50, 95% CI 0.33–0.56) in senior physicians and was fair in junior physicians (0.33, 95% CI 0.19–0.51 and 0.36, 95% CI 0.36–0.43, respectively). Using a multiparametric approach, overall interobserver agreement for grading MR severity was fair (0.30), was slightly better in senior than in junior physicians (0.31 vs 0.28, respectively) with substantial or almost perfect agreement more frequently observed in senior versus junior physicians (52% vs 36%, respectively).

Conclusion. – Reproducible transthoracic echocardiography MR quantification remains challenging in 2019, despite the expected high skills of echocardiographers regarding MR at the time of dedicated percutaneous intervention. The multiparametric approach does not entirely alleviate the substantial dispersion in measurement of MR severity parameters, whereas reader experience seems to partially address the issue. Our study emphasizes the continuing need for multimodality imaging and education in the evaluation of MR among cardiologists.

KEYWORDS

Mitral regurgitation;

Agreement;

Transthoracic echocardiography

Abbreviations: EACVI, European Association of Cardiovascular Imaging; EROA, effective regurgitant orifice area; κ, Kappa; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; PISA, proximal

isovelocity surface area; RVol, regurgitant volume; SPAP, systolic pulmonary artery pressure; TTE, transthoracic echocardiography.

Introduction

Mitral regurgitation (MR) is the most prevalent valvular heart disease in Western countries, with an age-dependant prevalence, affecting up to 10% of people older than 75 years [1,2]. Despite recent progress in MR evaluation by cardiac magnetic resonance imaging, transthoracic echocardiography (TTE) remains the backbone for exploration of both the mechanism of MR and its severity, and thus guides patient management [3]. Several quantitative and semiquantitative parameters are currently recommended for quantifying MR severity [4,5]. Although these methods are routinely used in daily practice worldwide, their reliability was questioned in 2010 [6]. The dynamic nature of MR throughout systole as well as the complexity of MR mechanisms were thought to be partly responsible for the suboptimal interobserver agreement in MR evaluation [6,7]. We hypothesized that the poor reproducibility in MR assessment was related to the poor image quality previously offered by sonographs, alongside insufficient skills of cardiologists in the 2000s, and this issue had to be addressed at the time of mitral-dedicated percutaneous intervention. We thus investigated interobserver agreement in parameters used in daily practice to quantify MR severity within and between junior and senior cardiologists specialized in echocardiography.

Methods

Study population

We prospectively included 25 consecutive patients referred to five tertiary French hospitals (Creteil, Lille, Rennes, Toulouse and Tours) for MR exploration during a 1-month period (May to June 2018). Senior cardiologists specialized in echocardiography at each centre enrolled 4 patients with primary (due to mitral valve prolapse) and 1 patient with secondary MR into the study, according to a standardized acquisition protocol. Thus, 20 primary MRs due to mitral valve prolapse and 5 secondary MRs were included. The distinction between primary and secondary MR was given by the senior cardiologist performing the TTE.

Patients with MR \geq moderate, according to European Association of Cardiovascular Imaging (EACVI) guidelines, were included [4]. Patients with previous mitral surgery, poor echogenicity, another valvular heart disease \geq moderate or a congenital heart disease were excluded.

The local ethics committee approved the protocol and all patients gave informed consent.

Cardiac imaging acquisition and analysis

Two-dimensional TTEs were performed using a commercially available ultrasound machine (Vivid E9 or E95, GE Healthcare, Little Chalfont, UK). Each patient underwent comprehensive TTE according to American Society of Echocardiography (ASE) or EACVI guidelines, with particular attention given to the mitral valve [8,9]. Echocardiographic data were stored for off-line analysis using dedicated software (EchoPAC version 201.0.0; GE Vingmed Ultrasound, Horten, Norway).

Cardiological review

The echocardiographic data were analysed off-line by junior and senior physicians specialized in echocardiography, as follows: quantification of MR severity and evaluation of its mechanisms and consequences were done in eight tertiary public and private hospitals (Amiens, Creteil, Lille, Rennes, Saint Denis, Toulouse and Tours) by one junior and one senior physician in each centre (i.e. 16 physicians). A junior physician was defined as a final-stage cardiology resident and a senior physician as a cardiologist specialized in cardiac imaging, who graduated more than 2 years earlier. All physicians were provided with the entire echocardiographic study, reviewed all images, and were blinded to the patient's medical history, previous MR evaluation, and MR classification (primary or secondary) by the centre that enrolled the patient.

Mitral regurgitation grading

MR severity was graded using effective regurgitant orifice area (EROA) and regurgitant volume (RVol) according to the latest EACVI guidelines [4,9]. Grading was in three categories for primary MR: moderate (RVol between 30 and 44 mL, EROA between 20 and 29 mm²), moderate-to-severe (RVol between 45 and 59 mL, EROA between 30 and 39 mm²) or severe (RVol > 60 mL, EROA > 40 mm²); and in two categories for secondary MR: moderate (RVol < 30 mL, EROA < 20 mm²) or severe (RVol ≥ 30 mL, EROA ≥ 20 mm²). Proximal isovelocity surface area (PISA) radius was classically measured in apical four-chamber view or in parasternal view in case of anterior mitral valve prolapse, as recommended. The area of interest was optimized by lowering imaging depth and reducing the Nyquist limit to 15–40 cm/s. The radius of the PISA was measured at mid-systole using the first aliasing. A multiparametric approach was also performed by each physician using all qualitative, semiquantitative and quantitative parameters available.

Statistical analysis

Continuous variables are presented as means with standard deviations (SD) and qualitative variables as frequencies and percentages. To determine interobserver agreement of binary or ordinal outcome variables, multirater κ statistics were computed using the macro MAGREE with SAS, Version 9.4 (SAS Institute, Cary, North Carolina). This macro implements the methodology of Fleiss et al., measuring the agreement when the number of raters is > 2 [10]. Kappa (κ) values were interpreted according to Landis and Koch, with κ coefficients of 0 = poor; 0.01–0.20 = slight; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = substantial; and 0.81–1.0 = almost-perfect agreement. Multirater κ were calculated for each patient using the online κ calculator developed by Randolph.

To determine the interobserver agreement of continuous outcome variables, intraclass correlations and their 95% confidence intervals (CIs) were calculated using the macro ICC9 with SAS [11]. Intraclass correlation values were interpreted as κ values.

Results

Study population

The characteristics of the patients are summarized in Table 1. Mean age was 62 ± 18 years, 76% were male (76%), and 76% were symptomatic (NYHA \geq II); 1 patient had atrial fibrillation (AF).

Agreement to assess MR mechanism and severity

Overall interobserver agreement to distinguish primary from secondary MR was moderate (0.57 ± 0.03) (Table 2). Interobserver agreement was better in case of posterior versus anterior prolapse, especially for the central segments P2 (substantial, 0.66 ± 0.03) and A2 (moderate, 0.52 ± 0.03). Interobserver agreement was fair or slight to identify a non-central prolapse (A1-P1 or A3-P3). Raw agreement to characterize holo-systolic or end-systolic MR was 0.23 ± 0.03 .

Interobserver agreement to assess MR severity using semiquantitative parameters was fair for vena contracta width, moderate for PISA radius and substantial for peak E wave velocity and time velocity integral (TVI) mitral/TVI aortic ratio (Table 2). Interobserver agreement was moderate for all quantitative parameters (EROA, RVol using PISA method, and RVol using volumetric method).

Interobserver agreement was substantial or almost perfect for assessing MR consequences on left

ventricular and left atrial dilatation and left ventricular function, but only moderate for systolic pulmonary artery pressure (SPAP).

Agreement according to physician experience

Overall interobserver agreement to assess the MR mechanism was better in senior than in junior physicians, especially to identify a P2 prolapse (substantial vs moderate, respectively), a flail leaflet (moderate vs fair) or end-systolic MR (fair vs slight) (Table 2).

Interobserver agreement was also better in senior than in junior physicians for all parameters used to quantify MR severity, i.e. vena contracta width (fair vs slight, respectively), EROA (substantial vs fair), and RVol with the PISA method (moderate vs fair) (Table 2). Interobserver agreement for the RVol calculated using the volumetric method was similar between the two groups, as well as assessment of left ventricular and left atrial consequences, except for SPAP, with better agreement within the senior than the junior group.

Agreement according to the mechanism of MR

Interobserver agreements of parameters used to quantify MR severity were low and were even lower for secondary versus primary MR (i.e. slight vs fair, respectively, for vena contracta width and RVol using the PISA method) (Table 3). EROA for primary MR used by a senior cardiologist appeared to be the most reproducible parameter, with substantial interobserver agreement (0.61, 95% CI 0.43–0.76).

Global MR quantification

Using a multiparametric individual approach, overall distribution of interobserver agreement for grading MR severity was slight or fair in 56% of cases, and substantial and almost perfect in only 36% (Figure 1). Substantial or almost perfect agreement was more frequently observed in the senior than

In the junior group (52% vs 36%, respectively). Overall interobserver agreement for grading MR severity was fair (0.30, 95% CI 0.14–0.44), and was slightly better in the senior group (0.31, 95% CI 0.12–0.42 vs 0.28, 95% CI 0.11–0.40). Of the 400 analyses, discrepancies were apparent between grading from RVol/EROA and the final judgment from the echocardiographer in 78 patients (19.5%), with a tendency to a lower discrepancy in the senior group (17.5% vs 21.5%, respectively; $P = 0.31$).

Discussion

Exploring parameters used in daily practice to assess MR in 25 patients in eight French tertiary public and private hospitals, we found that interobserver agreement for MR mechanism definition and grading with EROA and RVol was only moderate. However, interobserver agreement for the consequences of MR (left ventricular function and left ventricular and left atrial dilatation) was substantial or almost perfect. Interobserver agreement for a single parameter or for a multiparameter quantification was generally better in senior than in junior physicians, and was better for primary than for secondary MR.

Agreement to assess MR mechanism and severity

Surprisingly, the agreement to distinguish primary from secondary MR was only moderate, both in the senior and the junior group. This lack of substantial agreement is an important issue for clinical decision-making regarding corrective surgery, as cut-offs to define severe MR in European guidelines differ according to the mechanism. Of note, this is not an issue in the American guidelines [12,13]. Agreement to define a flail leaflet was only moderate for senior physicians and fair for junior physicians, and was substantial for central prolapse (A2-P2), probably because of its higher prevalence. Conversely, results for medial or lateral prolapse were disappointing in TTE. Overall, the results of the interobserver agreement regarding MR mechanism suggested the importance of transoesophageal echocardiography for a precise analysis of the mechanism to offer the patient the best therapeutic option at the time of development of percutaneous procedures [14,15]. Nevertheless, further studies are needed to analyse interobserver agreement using transoesophageal echocardiography.

Regarding assessment of the severity, our findings highlight the weaknesses of the semiquantitative parameters, especially for vena contracta width, with a very low consistency. Exploring the PISA and vena contracta measurements of 16 patients with MR interpreted by 18 echocardiologists from 11 academic institutions in 2009, Biner et al. found similar results (0.28) [7]. Concerning PISA measurement, the moderate agreement can be explained by the difficulty in measuring the PISA radius. Indeed, agreement was only fair for PISA radius, while it was substantial for other parameters used in the PISA method. This may be explained by several pitfalls linked to this method, i.e. variation during systole, non-holosystolic or eccentric jet and containment [16-18] (Figure

2). Nevertheless, despite these pitfalls, the agreement observed for PISA radius and EROA for primary MR were consistent and acceptable (both substantial) in the senior group in contrast to the junior group, reinforcing the idea of a learning curve for this quantification technique. More strikingly, use of a multiparametric approach to quantify MR severity did not improve the consistency between observers, with only a fair interobserver agreement (0.30), again in perfect agreement with the findings from Biner et al. (0.32).

Conversely, left ventricular and left atrial volumes and function measurements had good interobserver agreement, both for senior and junior physicians, probably reflecting improvements in image quality in recent years. With three-dimensional imaging and automatization of endocardial contouring, the agreement will probably be even better in the near future.

Agreement to assess severity according to physician experience

Our findings clearly show a difference between senior and junior physicians regarding assessment of the mechanism and severity of MR. These results are in line with a recent study from lung et al. [19], which highlighted the importance of the learning curve in the assessment of this valvular heart disease. Of note, EROA agreement within the senior group was better than in the study by Biner et al. (0.61 vs 0.37, respectively) [7].

Agreement in the subgroup of secondary MR

Interobserver agreement of parameters used to quantify MR severity were lower in secondary MR. Evaluation of secondary MR is complex even for senior physicians. Recently, lung et al. found that only 44% of cardiologists evaluated secondary MR appropriately [19]. These difficulties in grading secondary MR may be explained by the non-circular shape of the proximal flow convergence region and the absence of angle correction in the calculation of EROA in secondary MR [20,21]. These concerns should be addressed by an improved learning approach in valvular heart diseases with, for instance, a dedicated level-three teaching plan and use of multimodal imaging.

Study limitations

Despite a limited set of TTE variables, each parameter was assessed 16 times (by eight senior and eight junior physicians) and thus 400 analyses per parameter were obtained. Moreover, all TTE

evaluations were performed by five senior physicians with the same commercially available ultrasound machine to limit variability due to technical/imaging quality. The definition of MR mechanism was left to the discretion of the senior echocardiographer at inclusion, without referring to a gold standard method. The dataset was restricted to two-dimensional imaging, as based on normal clinical routine. Three-dimensional TTE, transoesophageal echocardiography and multimodality imaging would have probably increased the consistency of the reviewers. Finally, we choose to include MR \geq moderate. The interobserver agreement might have been better with the inclusion of mild MR, even if the clinical relevance to quantify mild MR is questionable.

Conclusions

Robust and reproducible TTE MR quantification and mechanism definition remain challenging despite high-quality images echocardiographic and the expected high skills of echocardiographers regarding MR at the time of dedicated percutaneous intervention surge. The multiparametric approach does not entirely alleviate the substantial dispersion in measurement of MR severity parameters, while reader experience seems to partially address the issue, suggesting the continuing need for education in MR evaluation among cardiologists.

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All participants are members of the French Society of Cardiovascular Imaging.

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Table 1 Patient characteristics.

| Variable | (n = 25) |
|-------------------------------------|-----------------|
| Male sex | 19 (76) |
| Age (years) | 62 ± 18 |
| Body surface area (m ²) | 1.86 ± 0.20 |
| Atrial fibrillation | 1 (4) |
| Heart rhythm (bpm) | 71 ± 11 |
| Systolic blood pressure (mmHg) | 135 ± 27 |
| Diastolic blood pressure (mmHg) | 75 ± 16 |
| New York Heart Association class | |
| I | 6 (24) |
| II | 11 (44) |
| III | 6 (24) |
| IV | 2 (8) |
| Secondary mitral regurgitation | 5 (20) |
| Primary mitral regurgitation | 20 (80) |

Data are expressed as mean ± standard deviation or number (%).

Table 2 Interobserver agreement to assess MR mechanism, severity and consequences according to physician experience.

| | Overall | Senior | Junior |
|-------------------------------------|------------------|------------------|------------------|
| MR mechanism | | | |
| Posterior prolapse | | | |
| P1 prolapse | 0.23 ± 0.03 | 0.25 ± 0.04 | 0.20 ± 0.04 |
| P2 prolapse | 0.66 ± 0.03 | 0.76 ± 0.04 | 0.55 ± 0.04 |
| P3 prolapse | 0.17 ± 0.03 | 0.19 ± 0.04 | 0.13 ± 0.04 |
| Anterior prolapse | | | |
| A1 prolapse | 0.12 ± 0.03 | 0.13 ± 0.04 | 0.08 ± 0.04 |
| A2 prolapse | 0.52 ± 0.03 | 0.57 ± 0.04 | 0.47 ± 0.04 |
| A3 prolapse | 0.39 ± 0.03 | 0.51 ± 0.04 | 0.16 ± 0.04 |
| Chordae rupture | 0.35 ± 0.043 | 0.36 ± 0.04 | 0.31 ± 0.04 |
| Flail leaflet | 0.42 ± 0.03 | 0.50 ± 0.04 | 0.32 ± 0.04 |
| MR mechanism (primary vs secondary) | 0.57 ± 0.03 | 0.59 ± 0.04 | 0.55 ± 0.04 |
| Carpentier classification | | | |
| I | 0.06 ± 0.03 | 0.00 ± 0.04 | 0.04 ± 0.04 |
| II | 0.75 ± 0.03 | 0.86 ± 0.04 | 0.66 ± 0.04 |
| III | 0.75 ± 0.03 | 0.87 ± 0.04 | 0.63 ± 0.03 |
| Holo-systolic MR | 0.27 ± 0.03 | 0.39 ± 0.04 | 0.15 ± 0.04 |
| End-systolic MR | 0.25 ± 0.03 | 0.37 ± 0.04 | 0.15 ± 0.04 |
| MR severity | | | |
| E wave velocity (m/s) | 0.80 (0.72–0.86) | 0.74 (0.60–0.84) | 0.87 (0.78–0.92) |
| E/A ratio | 0.87 (0.81–0.91) | 0.90 (0.82–0.94) | 0.83 (0.72–0.90) |
| Vena contracta width (mm) | 0.22 (0.13–0.35) | 0.28 (0.14–0.35) | 0.18 (0.08–0.37) |
| PISA radius (mm) | 0.52 (0.40–0.63) | 0.62 (0.46–0.75) | 0.43 (0.27–0.60) |
| MR peak velocity (m/s) | 0.67 (0.57–0.76) | 0.74 (0.60–0.84) | 0.62 (0.46–0.76) |
| MR TVI (cm/s) | 0.78 (0.70–0.85) | 0.77 (0.65–0.86) | 0.79 (0.67–0.88) |

| | | | |
|-----------------------------------------------|------------------|-------------------|-------------------|
| TVI mitral/TVI aortic ratio | 0.82 (0.75–0.88) | 0.81 (0.69–0.89) | 0.84 (0.73–0.90) |
| EROA (mm ²) | 0.44 (0.33–0.56) | 0.61 (0.45–0.75) | 0.33 (0.19–0.51) |
| RVol (PISA method) (mL) | 0.41 (0.30–0.54) | 0.50 (0.33–0.66) | 0.36 (0.30–0.43) |
| RVol (volume method ^a) (mL) | 0.54 (0.43–0.66) | 0.51 (0.35–0.676) | 0.57 (0.41–0.72) |
| Left ventricular and left atrial consequences | | | |
| SV (Simpson method) (mL) | 0.54 (0.42–0.65) | 0.53 (0.37–0.69) | 0.55 (0.39–0.70) |
| SV (continuity equation) (mL) | 0.71 (0.61–0.79) | 0.76 (0.63–0.85) | 0.65 (0.49–0.78) |
| Left ventricular ejection fraction (%) | 0.76 (0.68–0.83) | 0.77 (0.64–0.86) | 0.76 (0.63–0.85) |
| LVEDD (mm) ^b | 0.84 (0.78–0.89) | 0.83 (0.73, 0.90) | 0.86 (0.77, 0.92) |
| LVESD (mm) ^b | 0.84 (0.73–0.90) | 0.84 (0.73–0.90) | 0.87 (0.78–0.92) |
| LVEDV (mL) | 0.75 (0.66–0.83) | 0.73 (0.60–0.84) | 0.77 (0.65–0.86) |
| LVESV (mL) | 0.81 (0.73–0.87) | 0.78 (0.66–0.87) | 0.84 (0.74–0.90) |
| LAV (mL) | 0.96 (0.94–0.97) | 0.97 (0.94–0.98) | 0.95 (0.92–0.97) |
| SPAP (mmHg) ^c | 0.68 (0.58–0.77) | 0.86 (0.77–0.92) | 0.53 (0.37–0.69) |

k values are given for ordinal outcome variables and intraclass correlations for continuous outcome variables.

EROA, effective regurgitant orifice area; LAV, left atrial volume; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; PISA, proximal isovelocity surface area; RVol, regurgitant volume; SPAP, systolic pulmonary artery pressure; SV, stroke volume; TVI, time velocity integral.

^a RVol (volume method) = stroke volume (Simpson) – stroke volume (left ventricular outflow tract pulsed Doppler).

^b LVEDD and LVESD were measured by two-dimensional left ventricular and left atrial volumes by the Simpson biplane method;

^c Right atrial pressure was estimated using the inferior vena cava diameter and collapsibility [22].

Slight = 0.01–0.20

Fair = 0.21–0.40

Moderate = 0.41–0.60

Substantial = 0.61–0.80

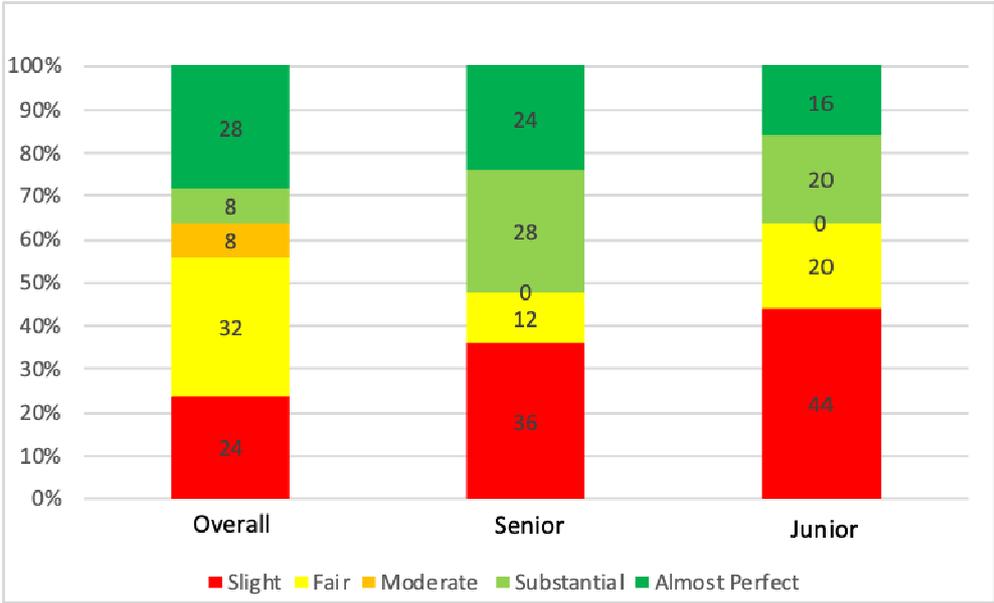
Almost perfect = 0.81–1.

Table 3 Interobserver agreement to assess MR severity according to MR mechanism.

| | Primary | Secondary |
|------------------------------------|------------------|------------------|
| Vena contracta width | | |
| Overall | 0.26 (0.16–0.41) | 0.06 (0.00–0.57) |
| Senior physicians | 0.32 (0.16–0.52) | 0.04 (0.00–0.91) |
| Junior physicians | 0.22 (0.09–0.44) | 0.05 (0.00–0.87) |
| Effective regurgitant orifice area | | |
| Overall | 0.43 (0.30–0.56) | 0.43 (0.20–0.70) |
| Senior physicians | 0.61 (0.43–0.76) | 0.46 (0.15–0.79) |
| Junior physicians | 0.31 (0.16–0.52) | 0.41 (0.41–0.77) |
| Regurgitant volume | | |
| Overall | 0.39 (0.27–0.53) | 0.13 (0.02–0.46) |
| Senior physicians | 0.48 (0.30–0.66) | 0.19 (0.03–0.64) |
| Junior physicians | 0.35 (0.19–0.55) | 0.05 (0.00–0.83) |

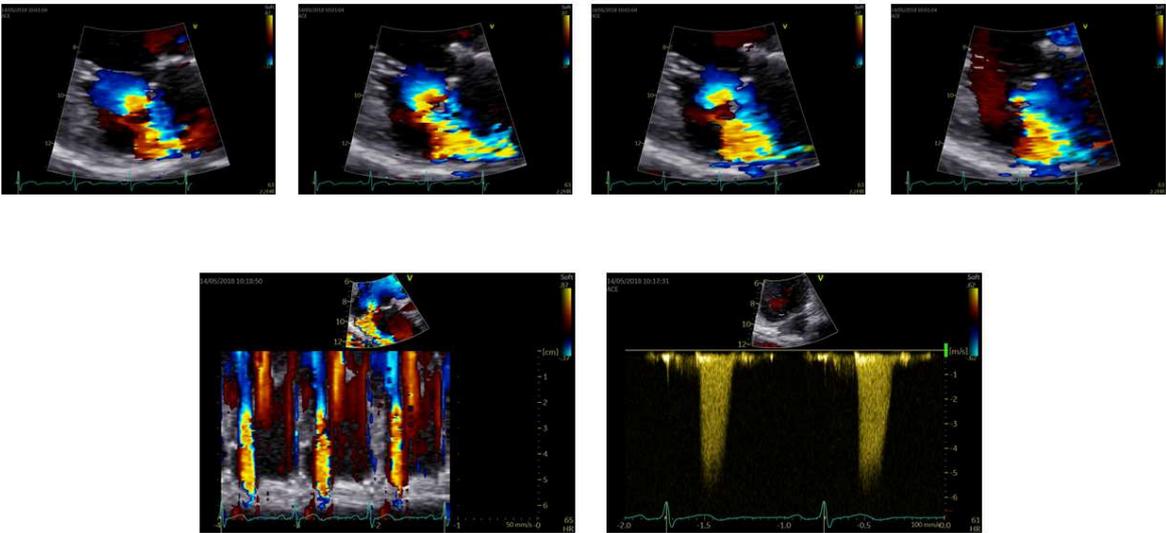
k values are given for ordinal outcomes variables and intraclass correlations for continuous outcome variables.

Figure 1. Distribution of interobserver agreement for grading mitral regurgitation severity using the multiparametric approach.



Figures 2. Examples of pitfalls of the PISA method in our population.

Non-holosystolic mitral regurgitation with variation in effective regurgitant orifice area.



Non-circular effective regurgitant orifice area (A. apical 4-chamber view; B. apical 2-chamber view; C. three-dimensional colour view).

