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RESEARCH ARTICLE

Direct and indirect quantification of mitral regurgitation with cardiovascular magnetic resonance, and the effect of heart rate variability

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Abstract *Object* Quantifying mitral regurgitation with cardiovascular magnetic resonance (CMR) involves indirect calculation, which increases the potential for error. We examined a direct quantification method using velocity mapping across the mitral valve, which may be less susceptible to error, and also examined the effect of heart rate variability on both techniques.

Materials and Methods Fifty-five patients underwent mitral regurgitation quantification with CMR by the direct method and two indirect methods—the standard method subtracting aortic flow (assessed by velocity mapping) from left ventricular stroke volume (assessed by cine imaging) and the 'volumetric' method using the difference between left and right ventricular stroke volumes. The methods were compared using Bland–Altman analyses.

Results Patients with low heart rate variability (beat-to-beat variability <30 bpm; $n = 44$) showed good agreement between direct and indirect methods (95% confidence limits for the difference between measurements ± 16.7 ml/11.8% regurgitant fraction for the standard method; ± 21.7 ml/15.4% for the volumetric method), with no significant offset (mean difference +2.8 ml/+1.9% for standard and +3.1 ml/+2.3% for volumetric methods). Patients with high heart rate variability (>30 bpm; $n = 11$) showed poor agreement between techniques (95% limits ± 80.3 ml/56.0%) and significant offset (mean difference +31.7 ml/+19.5%).

Conclusion Direct quantification of mitral regurgitation with CMR compares well with indirect methods for patients with low heart rate variability, involves fewer calculations and is quick. All CMR measurements that use velocity mapping may be inaccurate, however, in patients with highly irregular rhythms and should be avoided in these patients.

Keywords Mitral regurgitation · Magnetic resonance imaging · Blood flow velocity · Phase-contrast imaging

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Introduction

Mitral regurgitation is common [1] and, with an ageing population, is likely to increase in prevalence. The onset of symptoms is a standard indication for mitral valve surgery [2], but the timing of surgery in asymptomatic patients can be difficult, balancing the need to operate before irreversible left ventricular dysfunction occurs, but without exposing the patient to the risks of premature surgery. There is a trend towards earlier surgery in asymptomatic patients [3,4], and quantifying mitral regurgitation may aid this clinical decision-making. Echocardiography is the clinical standard for assessing mitral regurgitation and is widely available. The assessment of severity, however, is mostly qualitative rather than quantitative [5], and there is significant overlap between moderate and severe regurgitation when compared to quantitative techniques [6]. Semi-quantitative methods exist for echocardiography, by calculating an equivalent regurgitant orifice area using the proximal isovelocity surface area (PISA) technique [7], but this is subject to significant inaccuracies from the assumptions and calculations involved. Despite these limitations, this method has been shown to predict clinical events [8], and recent work using 3D echocardiography shows promise [9], though still

relies on significant assumptions for calculating the quantity of regurgitation.

Cardiovascular magnetic resonance (CMR) can quantify mitral regurgitation [10] and is performed in many cardiovascular CMR centres. It should theoretically improve on the qualitative and semi-quantitative echocardiographic techniques, though the standard CMR method for quantification is indirect. The most commonly used ('standard') CMR method measures mitral regurgitation from a combination of two techniques—phase-contrast imaging ('velocity mapping') to measure aortic flow and multiple left ventricular (LV) short-axis cine images to measure LV stroke volume. Mitral regurgitation is calculated by deducting aortic forward flow from left ventricular stroke volume (the remainder must flow back through the mitral valve, unless there is a ventricular septal defect). The indirect nature of the measurement and use of two different magnetic resonance techniques increase the potential for measurement error, as an error in either would influence the result. Mitral regurgitation can also be assessed with CMR by a 'volumetric' method, comparing the left and right ventricular stroke volumes, which should be equal in the absence of any valve regurgitation or shunt. In the presence of isolated valve regurgitation, the difference between the stroke volumes provides the quantity of regurgitation. The method compares well to the standard indirect method [6], but assumptions involved can limit its usefulness in clinical practice, and the 'standard' technique using aortic flow is most often used.

Direct quantification of mitral regurgitation with CMR is also feasible, by measuring the regurgitant flow across the mitral valve with phase-contrast imaging, and has been shown to be accurate in a phantom model [11], though this study measured flow on the ventricular side of the 'valve' in their model, and the valve was static. The direct flow method has not been widely used, probably because of difficulties identifying a suitable imaging plane with the large, mobile valve and an often eccentric, sometimes mobile, regurgitation jet. The jet is also of high velocity (3–6 m/s), due to the high pressure difference between the left ventricle and atrium, which causes errors in phase-contrast imaging, including spin dephasing, displacement artefact, and intravoxel phase dispersion [12–15]. However, the direct method has the potential advantage of reducing error by requiring only one measurement with a single technique and is quick to apply.

In the present study, we sought to evaluate the direct quantification technique using careful slice positioning in patients with chronic mitral regurgitation and to determine how well it compared to standard indirect quantification techniques. In addition, anecdotal observations have suggested that heart rate variability influences the accuracy of flow measurements and we sought to examine the effect of this on these techniques for quantification of mitral regurgitation.

Materials and methods

Study group

Patients were identified from an observational study of chronic valve disease and were included if they had at least mild (but not trivial) mitral regurgitation on echocardiography. All had isolated mitral regurgitation, without significant other valvular disease and without known coronary disease (on clinical and/or angiographic grounds). Subjects underwent a CMR scan for quantification of mitral regurgitation by two standard indirect techniques and the direct flow quantification method. All subjects gave informed consent to participate in the study, which was approved by the local ethics committee.

CMR scanning

All scans were performed on a Siemens Sonata 1.5 Tesla MR scanner (Siemens Medical Solutions, Erlangen, Germany) with full cardiac hardware and software capabilities. All were prospectively ECG triggered with the acquisition window set to $\sim$ 90% of the R–R interval. For patients with irregular rhythms, the shortest R–R interval was used to determine the window, to avoid over-running into the subsequent cardiac cycle. All images were performed during breath-holding at end-expiration. Care was taken to ensure the mitral valve was positioned at the magnet isocentre to minimise field inhomogeneity. After pilot scans, each patient underwent a multi-slice left and right ventricular function study, as described previously [16]. Briefly, a stack of short axis breath-hold cine images were obtained (steady-state free precession ['TrueFISP'] cine images; temporal resolution 40–55 m/s; TE 1.54 m/s; TR 3.08 m/s; flip angle 50–60°; field of view 380 $\times$ 380 mm; matrix size 256 $\times$ 192 voxels; slice thickness 7 mm) covering the left and right ventricles from base to apex. One image slice was obtained in each expiratory breath-hold. The left and right ventricular endocardial borders in each slice were delineated at end-diastole and end-systole and the area from each slice summed to obtain end-diastolic and end-systolic volumes, according to Simpson's rule. All analyses were performed using a dedicated software package, CMRtools© Imperial College London. The average time taken for a volumetric study was 15 min.

For the standard indirect mitral regurgitation assessment, a single image slice was placed just above the aortic valve, parallel with the annulus. Aortic flow through this slice was quantified using through-plane velocity mapping (scan parameters: temporal resolution 55 m/s; TE 3.2 m/s; TR 7.9 m/s; field of view 380 $\times$ 380 mm; matrix size 256 $\times$ 192 voxels; velocity window 2.0 m/s; slice thickness 5 mm), in a single breath-hold as described previously [17]. To obtain the mitral regurgitant volume, aortic forward flow

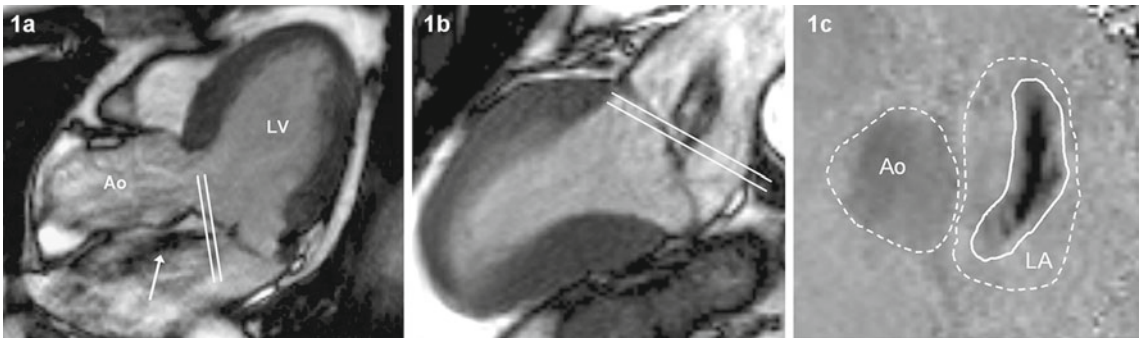

Fig. 1 Direct measurement technique for quantifying mitral regurgitation 3-chamber (**a**) and 2-chamber (**b**) views of the left ventricle in systole showing the mitral regurgitant jet (*arrowed*) and the position of the image slice for direct measurement of mitral regurgitation (*parallel lines*); *LV* left ventricle, *Ao* aorta. **c** Phase-velocity image in systole showing through-plane flow in the image position indicated in (**a**) and (**b**). *Black pixels* indicate high-velocity flow towards the left atrium, with the pixel intensity proportional to the flow velocity; *mid-grey* pixels indicate very low velocities of surrounding tissue/blood. The endocardial borders of the aorta (*Ao*) and left atrium (*LA*) are indicated by the *dashed lines*. *The solid line* outlines the region for assessment of the regurgitant flow jet

was deducted from left ventricular stroke volume obtained from the cine volumetric images above. Assuming no interventricular shunt, the difference between the two provides the mitral regurgitant volume. Mitral regurgitation was also assessed by the 'volumetric' method, comparing left and right ventricular stroke volumes. In the presence of isolated valve regurgitation, the difference between the stroke volumes provides the quantity of regurgitation.

For the direct method, the regurgitant flow jet was imaged on horizontal long axis (4-chamber), vertical long axis (2-chamber) and left ventricular outflow tract (3-chamber) steady-state free precession cine views. These were used to place an image plane just on the atrial side of the mitral valve, *perpendicular to* the predominant direction of the regurgitant flow jet , as close as possible to the valve in peak systole (Fig. 1), but avoiding the very highest flow velocities at the regurgitant orifice to minimise errors. For eccentric jets, this often meant the image plane was significantly different from the plane of the mitral annulus (Fig. 1). In practice, given the saddle-shaped anatomy of the valve and that many of the jets were at least mildly eccentric, the leading edge of the image plane was usually $\sim$ 0.5 cm from the regurgitant orifice. Flow through the image plane was measured with through-plane velocity flow mapping as described above, but with a velocity window set to between 4.0 and 6.0 m/s. If aliasing occurred, the velocity window was increased to accommodate the higher velocity. Each direct flow measurement was acquired during a single breath-hold (10–12 s). The regurgitant flow jet was identified from the velocity (phase) image for each frame of the cardiac cycle and encircled (Fig. 1c). Flow through the region of interest was integrated over the cardiac cycle to obtain the regurgitant volume directly. The corresponding anatomical (magnitude) images were used to ensure the delineated region did not include the aortic outflow tract, particularly for the eccentric anteriorly directed jets.

For all methods, mitral regurgitant fraction was calculated as regurgitant volume/left ventricular stroke volume (measured by cine image stack) $\times$ 100%.

Data handling and statistical calculations

The direct method was compared to both the indirect methods using Bland–Altman plots to determine the difference between the two measures, with 95% confidence intervals indicating the closeness of agreement. Both regurgitant volume and regurgitant fraction were assessed, and scatter plots and correlation between the methods were also generated. To examine the effect of heart rate variability on quantification, we divided the group into those with low heart rate variability (beat-to-beat variability $<$30 bpm)—i.e. those in sinus rhythm or well-controlled atrial fibrillation (AF) and those with high heart rate variability (beat-to-beat variability $\geq$30 bpm)—uncontrolled AF or frequent ectopic beats. The two groups were examined separately, in addition to the whole group analysis. Figures used are mean $\pm$ standard deviation unless otherwise described.

Results

Fifty-five patients were included over a total period of 3 years (42 men; 13 women; mean age 64.1 $\pm$ 13.8 years). Data on the closeness of agreement from the Bland–Altman plots are shown in Tables 1 and 2, with graphs in Fig. 2. Overall, direct mitral regurgitation measurement showed modest agreement when compared to the standard indirect method (95% limits of agreement for regurgitant volume $\pm$44.1 ml; regurgitant fraction $\pm$29.8%; Fig. 2a). There was a small bias towards greater regurgitation with the direct flow method: mean offset +8.5 ml/+5.5%. Similar results were shown for the

Table 1 Comparison of mitral regurgitant volume quantified by direct and indirect methods—Bland–Altman analysis

Regurgitant volume (ml)		Whole group ($n=55$)	Patients with low heart rate variability ($n=44$)	Patients with high heart rate variability ($n=11$)
Direct method versus standard indirect method	95% limits of agreement	±44.1	±16.7	±80.3
	Bias (offset)	+8.5	+2.8	+31.7
Direct method versus volumetric indirect method	95% limits of agreement	±40.8	±21.7	±80.8
	Bias (offset)	+5.4	3.1	+14.8
Standard versus volumetric indirect methods	95% limits of agreement	±30.8	±19.1	±50.6
	Bias (offset)	−3.1	+0.3	−16.9

Table 2 Comparison of mitral regurgitant fraction quantified by direct and indirect methods—Bland–Altman analysis

Regurgitant fraction (%)		Whole group ($n=55$)	Patients with low heart rate variability ($n = 44$)	Patients with high heart rate variability ($n = 11$)
Direct method versus standard indirect method	95% limits of agreement	±29.8	±11.8	±56.0
	Bias (offset)	−5.5	+1.9	+19.5
Direct method versus volumetric indirect method	95% limits of agreement	±28.2	±15.4	±55.9
	Bias (offset)	+3.6	2.3	+8.8
Standard versus volumetric indirect methods	95% limits of agreement	±20.6	±14.0	32.3
	Bias (offset)	−1.9	+0.3	−10.7

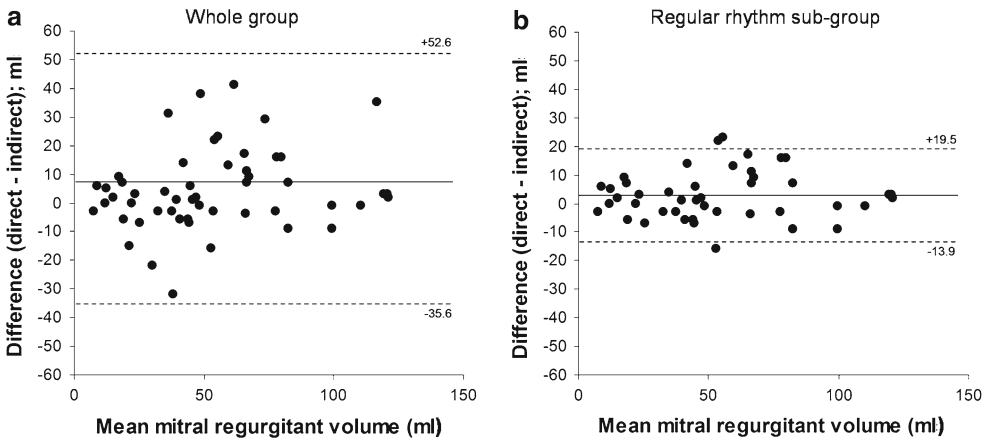

Fig. 2 Comparison of direct and indirect techniques for mitral regurgitation quantification Bland–Altman plots showing the mean difference (*solid line*) and 95% limits of agreement (*dashed line*) for mitral regurgitant volume per cardiac cycle. **a** The whole group ($n=55$); **b** Subjects with low heart rate variability—sinus rhythm or AF with beat-to-beat variability <30 bpm ($n = 44$)

comparison between direct and 'volumetric' indirect methods (95% confidence limits for agreement ± 40.8 ml; 28.2% regurgitant fraction). The scatter plot for direct and standard indirect methods showed a high correlation, as would be expected for two measurements of the same parameter ($r = 0.87$; $P < 0.0001$; Fig. 3).

There was a large difference, however, in the closeness of agreement of the direct method between patients with

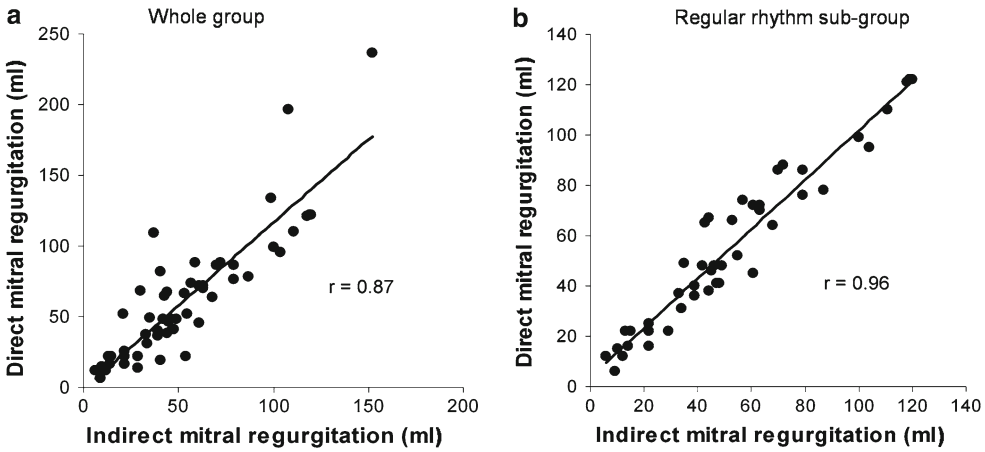

Fig. 3 *Scatter plots* showing regurgitant volume per cardiac cycle by direct and standard indirect techniques, with regression line and correlation coefficient. **a** The whole group ($n = 55$); **b** Subjects with low heart rate variability ($n = 44$)

regular and irregular heart rhythms. Patients with a mostly regular rhythm (beat-to-beat variability <30 bpm; $n = 44$ (38 sinus rhythm; 6 AF with low variability)) showed considerably better agreement between direct and standard indirect methods, with much narrower limits of agreement (approximately 1/3 those of the overall group): ±16.7 ml for regurgitant volume and ±11.8% for regurgitant fraction (Fig. 2b), minimal bias (+2.8ml and +1.9% respectively) and improved correlation ($r = 0.96$; $P < 0.0001$). The results were similar for the comparison between the direct and 'volumetric' indirect methods: 95% confidence limits ±21.7 ml/ ± 15.4%; mean bias +3.1 ml/+2.3% for regurgitant volume and regurgitant fraction respectively.

In contrast, patients with highly irregular rhythms (beat-to-beat variability ≥30 bpm; $n = 11$ (6 AF, 5 frequent ectopic beats)) showed very poor agreement with the standard indirect method, with wide 95% limits of agreement (± 80.3 ml/56.0% regurgitant fraction), and significant bias with a much higher regurgitant volume with direct measurement compared to the standard indirect technique (mean difference +31.7 ml/19.5% regurgitant fraction). A similar pattern was observed when the direct method was compared to the 'volumetric' method : 95% limits of agreement ± 80.8 ml/55.9% regurgitant fraction; mean difference +14.8 ml/8.8% regurgitant fraction.

Discussion

This study suggests that quantification of mitral regurgitation with a direct CMR flow method shows good agreement with indirect CMR quantification for subjects with a regular heart rhythm. Using the direct method involves only a single data acquisition rather than calculation from two differing measurement techniques and may be less prone to measurement error. It also avoids assumptions about other valvular function or cardiac shunting and is faster than measuring LV volumes, though LV volume and functional data are important for the overall assessment of patients with mitral regurgitation. Although the direct quantification method is straightforward, it has not been widely used in CMR units, likely due to the challenges of accurate measurement in high velocity, angulated jets and a highly mobile mitral valve. Our data suggest, however, that despite these difficulties, there is reasonable agreement with indirect techniques. Jet angulation is accommodated with careful placement of the slice *perpendicular to* the predominant direction of the flow jet (rather than parallel to the valve plane) to minimise partial volume and angulation errors [18]. The significant motion of the mitral valve during the cardiac cycle can add to the difficulty in positioning the image slice (which is fixed throughout the cardiac cycle) adjacent to the mitral valve. Moving-slice flow measurements using valve tracking [19] and three-dimensional velocity acquisition [9,20] have been attempted to overcome this, though the technology required for these is complex, and availability of the sequences is extremely limited. In practice, the distance moved by the valve is moderate (∼ 1–1.5 cm), and we sought to examine direct quantification using the more widely available and easy-to-use standard phase-contrast sequence. There remains a potential for error as the valve plane moves away from the imaging slice, but we hypothesise the effects may be mixed: dispersion of the flow jet may reduce the flow quantified in the imaging plane, while entrainment of blood already in the atrium may increase the measured flow. The net effect may thus be small, and our data suggest that the errors are reasonable. The high-velocity jets encountered with mitral regurgitation can be accommodated by selecting an appropriately high-velocity window and a short TE sequence, though the potential errors described in the introduction are minimised rather than removed.

Newer ultra-short TE flow sequences may improve this for all high-velocity flow jets [15].

Patients with highly irregular rhythms (beat-to-beat variability >30 bpm) showed poor agreement between direct and indirect quantification methods. The reasons for this may be partly physiological (left ventricular stroke volume varies with cardiac cycle length due to variable filling of the left ventricle), but there is also a significant effect on phase-contrast imaging. To generate cine flow–encoded images, data are acquired over many cardiac cycles (typically 12–16) during a single breath-hold. Data for each frame of the sequence are collected from *each* of the cardiac cycles, at the same time point after the R-wave. Two data sets are acquired in each sequence, with subtraction of one from the other to obtain the velocity data by cancelling out background phase effects. The temporal separation of these two data sets and the complex image reconstruction require a consistent R–R interval throughout the sequence, so high beat-to-beat variability can result in significant inaccuracies. The flow data from each cardiac cycle is not 'averaged'. The suggestion of inaccurate phase-contrast data with irregular rhythms is supported by a comparison of the two indirect methods for quantification of mitral regurgitation (Table 1), which showed good agreement in patients with a regular rhythm (95% confidence interval ±19.1 ml; mean bias 0.3 ml) but poorer agreement for patients with highly irregular rhythms (95% confidence interval ± 50.6 ml; mean bias −16.9 ml).This suggests that the velocity mapping used in the standard method may affect the accuracy of quantification. The use of a retrospectively gated flow sequence with an arrhythmia rejection algorithm may have improved the selection of cardiac cycles of similar length, but this would require a very long breath-hold, particularly for those with a very irregular heart rate. There would still be some variation in cycle length within the selected R–R interval window, which could introduce an additional error due to the 'stretching' of shorter R–R intervals to the average cardiac cycle length, as occurs with our retrospective gating sequence on the Siemens scanner. Irregular rhythms also degrade the quality of cine imaging (for volumetric assessment), which might underlie part of the error. However, the duration of systole (used for volumetric calculation) remains relatively constant for differing R–R intervals, with the majority of the time difference occurring in diastole. With prospective ECG triggering or appropriate arrhythmia sequences, the effect on cine imaging can be minimised [21]. There remains a physiological variation in stroke volume due to differential filling in diastole, which causes some blurring of endocardial contours, though this is usually mild.

Atrial fibrillation is relatively common in patients with mitral regurgitation, which may limit the utility of quantification using velocity mapping. However, in this study, approximately half the patients in AF were rate controlled with low heart rate variability and good agreement between techniques. Patients with higher degrees of heart rate variability may not be good candidates for quantification of mitral regurgitation by any method using velocity mapping (including both direct and standard indirect methods), unless the variability was controlled pharmacologically. This may limit the usefulness of the technique for these patients, though AF in the context of severe mitral regurgitation is regarded by the American Heart Association as an indication for valve surgery [2], and quantification of regurgitation might therefore be of lower value for clinical decision-making in this group.

The clinical value of quantifying mitral regurgitation has been shown using semi-quantitative measures in echocardiography, with good prediction of survival, cardiac events and requirement for surgery [8]. This underlines the importance of quantitative assessments, and accurate quantification with CMR could be more powerful in predicting prognosis than semi-quantitative echocardiography techniques. Further studies are required to assess this and to determine the cut-off values for regurgitant volume and fraction that are relevant for clinical decision-making.

Limitations

Although we have compared the direct method for quantification of mitral regurgitation to existing indirect methods and demonstrated good agreement between the techniques, it is extremely difficult to obtain satisfactory measures of *accuracy*. There is no ideal 'Gold standard' technique for assessing the quantity of mitral regurgitation, as even phantom models do not involve the appropriate combination of cardiac anatomy and motion of this complex valve, and no technique has been properly assessed for accuracy.

A few patients are unable to tolerate magnetic resonance scanning, due to severe claustrophobia, retained ferrous objects or pacemaker implantation. CMR is also limited in assessing valve morphology, due to lower spatial resolution than trans-oesophageal echocardiography, which remains the best tool for this.

Conclusions

Direct CMR quantification of mitral regurgitation with velocity mapping is feasible and compares well with the standard indirect CMR technique for the majority of patients, though 'gold standard' in-vivo techniques for mitral regurgitation quantification do not exist. Previous echocardiographic studies have suggested that quantification of mitral regurgitation is a powerful predictor of future events, and it should be part of the optimal assessment of patients with this valve lesion. Further studies are needed, however, to refine the clinical utility of CMR quantification. Velocity mapping appears to

be inaccurate for those with highly irregular heart rhythms and should be avoided in this patient group.

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