Background:

Dilated cardiomyopathy (DCM) is the second most common aetiology of heart failure in the general population(1). The hallmark of DCM is enlargement of one or both ventricles with systolic dysfunction. This diagnosis contains a spectrum of primary familial or secondary etiologies, such as infection, inflammatory or toxins affecting the heart. In a contemporary cohort of 250 DCM patients using cardiac magnetic resonance (CMR), Gulati et al. (2) showed that right ventricular ejection fraction (RVEF) ≤45% was an independent predictor of transplant-free overall survival and major heart failure events.

Right ventricular contraction is predominantly driven by longitudinal, followed by radial shortening. In contrast to the LV, twisting and rotational movements do not contribute significantly to RV contraction(3). Strain is a measure of tissue deformation and is defined as percentage of relative shortening of myocardial fibres at end-systole compared with end diastole. As the ventricle contracts, muscle shortens in the longitudinal dimensions and therefore longitudinal strain is a negative number. Conversely, myocardial wall thickens in radial dimensions during systole and therefore radial strain is a positive number. Echocardiography speckle tracking (STE) determined RV longitudinal strain provides prognostic information that is incremental to conventional echo parameters such as TAPSE and S', and is an independent predictor of severe adverse events in patients with pulmonary hypertension (4-6). Strain rate is a measure of the change in strain over time. Strain and strain rate can be measured in different directions, which are radial, longitudinal and circumferential. These directions are demonstrated in figure 1.

The latest 2015 American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines incorporate RV strain in their recommendations regarding ventricular functional assessment(7). Strain

measurement by speckle tracking echocardiography (STE) is based on tracking of characteristic speckle patterns created by interference of ultrasound beams in the myocardium. For CMR, a software called feature/ tissue-tracking (CMR-TT) which is analogous to STE has been developed to determine strain and strain rate measurements derived from steady state free precession cine sequences(8). CMR-TT software works by identifying myocardial features on steady-state free precession cine images and tracking them from frame to frame. Two of its advantages are time-efficiency with no additional sequences being required for analysis. It agrees well with myocardial tagging, which is considered the reference standard for CMR quantitative deformation assessment(8-10).

Left and right ventricular systolic function as determined by cardiac magnetic resonance imaging (CMR) derived ejection fraction is regarded as the gold standard due to its high accuracy and high inter and intra-observer reproducibility. RV analysis in particular due to its geometric complexity can be time consuming and is not routinely performed. Therefore in the context of DCM, where RV ejection fraction (RVEF) provides prognostic information(2), omitting this information removes prognostic information in the final CMR scan report but including this information results in longer post-processing time. Therefore for CMR assessment of DCM, CMR-TT could help identify cases that require contouring to determine RVEF. Due to its time efficiency relative to RV endocardial contouring, it could help streamline cases, which should or should not be contoured.

In this study, we have three aims. Firstly, we want to compare CMR-TT with STE and determine how well CMR-TT and STE correlates with RVEF. Secondly compare CMR-TT and STE against other conventional methods for estimating RV systolic function. Thirdly, determine a cut-off value to determine RV ejection fraction <45% for CMR-TT and how this compares to STE.

Methods:

Institutional research ethics approval was obtained for this prospective study. Patients were recruited from the cardiology clinics of a single centre in Hong Kong (see figure 2) from August 2015 to February 2016. Inclusion criteria were patients with echocardiography reports indicating an LV ejection fraction (LVEF) ≤40% and diagnosis of DCM. Patients with a reported LVEF ≤40% were reviewed. Exclusion criteria were age >85 years, atrial fibrillation, device implantation, metallic implants including prosthetic heart valves, poor mobility, long-term oxygen therapy and claustrophobia. Written consent was obtained from all patients. Echocardiography and CMR were performed within 48 hours of each other.

Echocardiography:

All echocardiograms were performed in the left lateral decubitus position with a commercially available ultrasound system (Vivid 9, General Electric Healthcare, USA) and a 3.5 MHz transducer. In accordance with recommendations from the American Society of Echocardiography, standard views and parameters of the left and right heart were obtained using 2D echocardiography. Conventional apical three-chamber view, apical two-chamber view, apical four-chamber view and RV-focused apical four chamber view images were obtained for speckle tracking. 3 consecutive cardiac cycles of each view were recorded. In particular, while obtaining images intended for speckle tracking analysis, sector widths were optimized to allow complete myocardial visualization while maximizing frame rate to 50-80 frames per sec. Echocardiograms were performed by the same operator who was blinded to the CMR results. Tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode echocardiography with the cursor optimally aligned along the direction of the tricuspid lateral annulus in the apical four-chamber view. It was determined in the M-mode view as the distance between the basal, end diastolic position of the tricuspid

annulus taken at the beginning of the electrocardiogram (ECG) QRS complex and its greatest apical long-axis movement. S' was the peak systolic annular velocities measured by pulsed-tissue wave Doppler imaging (TDI) with the sample volume placed at the level of tricuspid annulus from the apical four chamber view. RV fractional area change (RVFAC) was performed according to American Society of Echocardiography (ASE) guidelines(11).

Speckle-Tracking Echocardiography:

For RV STE, RV-focused apical four chamber view images were analysed off-line by means of commercially available semi-automated 2D strain software (EchoPac BT13, GE Healthcare, USA). For RV STE (see figure 3), the automated function imaging (AFI) technique designated for LV strain measurements in the traditional apical long axis view were similarly employed. RV was divided into six segments (basal free wall, mid free wall, apical free wall, basal septum, mid septum and apical septum). RV endocardial borders of the four-chamber views were then detected and tracked automatically throughout the cardiac cycle. Manual adjustments of the endocardial border contouring and the width of the region of interest were made. The software would then identify timing of aortic closure by ECG (i.e. end systole) which marks the start of the measurement perform the strain analysis. The quality of tracking of each segment would be checked by the software and results of those segments with satisfactory quality would be displayed. RV GLS was obtained by averaging measurements of the strain from the total six segments while RV FWS was obtained by averaging the measurements of strain from the three segments of the RV free wall.

Images were sent to a well experienced echocardiography laboratory(12, 13) in strain analysis for blinded analysis. Inter and intra-observer variability of STE measurements were assessed by using all the cases.

CMR

CMR examination was performed on a 1.5T GE Signa HD scanner within 48 hours from echocardiography was performed. LV 2-chamber cine, 3-chamber cine, 4-chamber cine, RV 2-chamber cine, axial cine stack and short-axis cine stack images was acquired. The cine sequences used a steady-state free-precession sequence and images were acquired in end-expiration with retrospective ECG gating. Imaging parameters were as follows: Echo time (TE) = 1.5msec, repetition time (TR) = 3.4msec, flip angle 45°, temporal resolution was on average 27-30msec, spatial resolution was 1.43mm x 1.43mm, slice thickness was 8mm, and 25 phases were acquired for each cine sequence. Analysis was performed by two readers; a dedicated analyst and a Society of Cardiovascular Magnetic Resonance level 3 radiologist who were blinded to the clinical information. A CMR post processing software (CMR42, Circle Cardiovascular Imaging, Calgary, Canada) was used to outline the left and right ventricular endocardial and epicardial contours on the short axis images and the extent of the LV and RV is determined on the short axis images as well as by cross-referencing with the long axis images. Further checks to ensure the accuracy of the RV measurements were performed by acquiring phase contrast images of main pulmonary artery with a velocity encoding of 150cm/sec to ensure the RV stroke volumes matched the contoured RV stroke volumes unless tricuspid regurgitation was demonstrated. The LV was contoured in order to confirm the accuracy of the RV contouring as stroke volumes should be equal. The short axis contours were used to calculate end-diastolic, end-systolic volumes, stroke volumes and ejection fraction. End-diastolic and end-systolic volumes were corrected using body surface area (Mosteller method).

CMR Tissue Tracking (CMR-TT)

CMR-TT RV strain analysis was performed using CMR42 tissue tracking. Analysis required contouring of the RV endocardial surface as well as the septal wall. Subsequently, the RV epicardial wall was contoured and the tissue tracking tool would track the RV free wall only (see figure 4). This was completed for a single end-diastolic phase image only. The software subsequently identified the myocardial features within the boundaries of the endocardial and epicardial contours and propagated to the other 24 phases. The other phases were quickly assessed to ensure propagation, and assessed to ensure accuracy. This procedure takes less than 1 minute to perform. Inter and intraobserver variability was assessed. All cases were contoured by a first and second observer separately and the cases were re-contoured again by the first observer more than 2 weeks after the initial contouring. CMR TAPSE was performed on 4-chamber cine images by measuring the distance between the RV apex and the lateral aspect of the tricuspid annulus in end-diastole and end-systole. The difference between these two measurements was recorded as the CMR TAPSE. RV corrected TAPSE (Co-TAPSE) is a modified version of TAPSE which involves measuring the distance between the lateral aspect of the tricuspid annulus and the LV apex in end-diastole and end-systole. The difference between these distances is then divided by the length in end-diastole and multiplied by 100(14).

Statistical Analysis:

All continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as a percentage of the total number. For patients with or without decreased RVEF (<45 and >45), continuous variables were compared using 2-tailed unpaired Student T test or Mann-Whitney U test depending on whether the variable was normally distributed or not. Categorical variables were compared using Fisher exact test where appropriate. Correlation with strain and RVEF and correlation between STE and CMR-TT were performed using Pearson correlation analysis. Intra

and inter-observer variability were compared by intra-class correlation coefficient (ICC) using 2-way mixed model of absolute agreement, bias and level of agreement. Receiver operating characteristic (ROC) curve was used to explore cut-off values of STE and CMR-TT for detecting impaired RVEF. Data were analyzed by STATA 14 (StataCorp, Texas, USA). A p-value <0.05 were considered statistically significant.

Results:

Table 1 shows characteristics of the patient cohort divided into two groups based on RVEF≤45% or RVEF>45%. Statistically significant differences between the two groups were seen in the RV parameters only. Age, gender, heart rate and LV parameters were not significantly different.

Correlation of CMR-TT, STE and other RV analysis methods with CMR-derived RVEF:

Table 2 demonstrates the different parameters obtained with CMR-TT and STE and how these correlated with RVEF. The best variables for correlation with CMR derived RVEF was CMR-TT RV free wall longitudinal strain (FLS), STE FLS and STE RV global longitudinal strain (GLS) (r=-0.68, r=-0.79, r=-0.82, p value <0.001 respectively) (see figure 5). CMR-TT RV free wall radial strain (FRS) and radial systolic strain rate showed moderate correlation with RVEF (r=0.66, p<0.01 and r=0.56, p<0.001 respectively). In terms of correlation between STE FLS and CMR-TT FLS, moderate correlation was demonstrated (r=0.56, p=0.002).

Inter-Observer and Intra-Observer Variability:

The inter and intra-observer variability analyses for CMR-TT FRS, CMR-TT FLS, STE FLS and STE GLS are demonstrated in table 3. These parameters show excellent agreement for inter and intra-observer variability. The CMR-TT parameter

with the lowest variability and best agreement was the RV FLS while for STE it was RV GLS.

Comparison of CMR-TT and STE with Other Methods for Estimating RVEF:

The different RV estimation parameters are listed in table 2. STE GLS had a higher correlation with RVEF than S', TAPSE and FAC. CMR-TT FLS showed better correlation than CMR TAPSE and Co-TAPSE. The ROC curves showed that STE GLS had higher accuracy at identifying RVEF<45% than S', TAPSE and FAC. For CMR-TT, the ROC curves also showed superior accuracy at identifying RVEF<45% than CMR TAPSE and Co-TAPSE.

Cut-off value for STE and CMR-TT in detection of RVEF<45%:

For CMR-TT FLS the best cut-off value to provide the highest correctly classified cases with RVEF<45% was ≥-24.4% (AUC=0.87), with 100% sensitivity and 66.7% specificity (see figure 6).

For STE, GLS had the highest AUC closely followed by STE FLS. The cut-off values providing the highest correctly classified results were ≥-20.9% (AUC=0.88), with 100% sensitivity and 60% specificity and ≥-22.0% (AUC=0.87) with 78.6% sensitivity and 80% specificity respectively (see figures 7 & 8).

If the cut-off for STE was set at -20% as per American and European guideline suggestions, FLS would have 57.1% sensitivity and 80.0% specificity with a correctly classified percentage of 69.0%. For GLS, this would be 85.7% sensitivity and 60.0% specificity, with overall a correctly classified percentage of 72.4% of all cases.

Discussion:

Our study aimed to compare the correlation and reproducibility of CMR derived RVEF with CMR-TT and STE as well as explore the cut-off values for determining RVEF≤45%. The CMR-TT and STE parameters which showed the best correlations with CMR derived RVEF were CMR-TT FLS, STE FLS and STE GLS. Compared to previous papers(15-17), STE GLS in our study showed the best correlation with CMR derived RVEF followed by STE FLS, which was only slightly lower but still showed excellent correlation with CMR derived RVEF. In addition, the CMR-TT strain rate parameter was shown to correlate less well than CMR-TT strain, which is in keeping with the known literature(8).

On the ROC curves, CMR-TT FLS, STE FLS and STE GLS (see figures 6-8) showed very good accuracy with AUC of 0.87, 0.87 and 0.88 respectively. These parameters were also highly reproducible with ICC values of >0.9 and in terms of comparison with a previous paper assessing CMR-TT RV global longitudinal strain, that study also obtained an ICC values >0.9 for inter and intra-observer reproducibility(18). The STE FLS and GLS cut-off values of -22.0% and -20.9% were not too different from the recent internationally recommended ≥-20% cut-off(7) in determining RVEF<45%. However, our STE cut-off values were different to a study by Focardi et al(19) which recommended a cut-off value of -17.0% and demonstrated very high accuracy with a 96% sensitivity and 93% specificity (AUC 0.92) to detect an RVEF≤45%. In comparison to our study, the differences could be accounted for by the patient cohorts. The patients used in Focardi et al's study had varied pathologies but were predominantly made up of myocarditis, hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia (ARVD) patients. However, our study looked at DCM patients only and on comparison our cohort had larger biventricular volumes and lower LVEF. These differences could account for the different accuracy of the STE FLS and GLS despite the similar echocardiography equipment and STE software, which were used in both studies.

To the best of our knowledge, setting a cut-off value for CMR-TT FLS to determine RVEF<45% has never been done before and our study has shown that this is feasible with a high degree of accuracy. Further study is warranted to determine if this could be used practically. In situations where the RV is not the chamber of interest, CMR readers typically use several methods including their experience and subjective judgments to determine if RVEF is decreased before committing to formal RVEF quantification. However, there are other semi-quantitative methods, which CMR readers also utilize such as TAPSE(20, 21), RV fractional area change(22) and Co-TAPSE(14), which have been shown to provide faster semi-quantitative assessment to identify RV systolic dysfunction. In our study, we compared the correlation and ability of CMR TAPSE and Co-TAPSE with CMR-TT FLS and showed that CMR-TT FLS had better correlation and was a better tool for identifying RVEF<45%. Interestingly, the paper which studied Co-TAPSE, showed superiority of Co-TAPSE over CMR feature tracking RV GLS as well as CMR TAPSE(14). However this study cannot be directly compared to ours for three reasons. Firstly, our study set out to test whether these different RV parameters could identify an RVEF≤45% whereas the study looking at Co-TAPSE was looking to determine if the different parameters could differentiate normal volunteers from non-ischaemic DCM patients. Secondly, CMR RV global longitudinal strain was used whereas our study used CMR RV free wall strain and did not include the LV septal wall in the analysis so the RV analysed was different between our studies. Lastly, CMR feature tracking was used rather than tissue tracking which are different software tools created by different vendors and have been previously demonstrated to have some differences in strain results(10). We believe that setting the analysis tools to identify an RVEF≤45% would be more clinically useful and as mentioned previously has prognostic implications(2). However, both studies showed that CMR TAPSE was not the most accurate of the various methods tested. This in keeping with another CMR study,

which showed weak correlation between traditional TAPSE and RV systolic function(21). Some echocardiography studies have gone further to show that TAPSE is not predictive of mortality(5, 23). CMR TAPSE is likely less accurate in terms of estimating the RVEF as it is load dependent. Larger RV volumes would require larger displacement of the tricuspid annulus to maintain RVEF since RV systolic function is predominantly determined by longitudinal contraction(24). CMR TAPSE does not account for this and in the context of DCM may explain its reduced accuracy.

In keeping with RV physiology, the CMR-TT free wall radial strain showed lower diagnostic accuracy in identifying RV systolic dysfunction than free wall longitudinal strain but there was still moderate correlation with RVEF. RV radial strain is not a parameter which is commonly assessed with STE(25) but our CMR-TT software including those from different vendors has been able to assess this parameter(26). This allows CMR-TT RV strain to potentially add further information on the RV systolic function and RV longitudinal strain, which is not usually available on echocardiography. However to the best of our knowledge, the evidence for the usefulness of RV radial strain is currently lacking.

Whether the high diagnostic accuracy of CMR-TT identifying RVEF<45% seen in this study can be recreated with other CMR strain analysis software should be investigated. Currently, CMR feature tracking (CMR-FT) software provided by TomTec Imaging systems (TomTec, Unterschleissheim, Germany)(27) has dominated most of the research literature(28) but with the arrival of other software tools created by different vendors, further studies to check the validity of these newer software tools are needed.

CMR-TT remains a relatively new method for assessing RV systolic function. Prior to the development of CMR-TT, other CMR methods such as tagging, strain encoding

(SENC), and displacement encoding with stimulated echoes (DENSE) have been employed to assess strain. Their various strengths and weaknesses have been detailed previously(29). However, one reason for the lack of uptake in the clinical setting of these various techniques has been due to the additional sequences and post-processing required(28, 30, 31). Another method for assessing myocardial function is tissue phase mapping (TPM). This sequence is based on phase contrast imaging with higher temporal resolution and the measurements are in velocities rather than strain or strain rate(32). Like SENC, DENSE and tagging, TPM requires additional sequence acquisitions. A relatively recent development, which uses a similar principal to CMR-TT of making use of the routine cine images, is deformation tracking. This technique has the added advantage of incorporating data from a larger image domain compared to CMR-TT(33), but it is limited to specialist research groups and not widely available unlike CMR-TT which can be purchased. Until recently, a drawback of CMR-TT was the lack of prognostic data in contrast to the well-established prognostic data in STE. However, a recent study of 210 DCM patients has demonstrated that CMR-TT LV strain analysis is predictive of mortality as well as providing incremental risk stratification beyond ejection fraction, biomarkers and clinical information(34). Nonetheless, CMR-TT still has several disadvantages such as the assumption that in-plane displacements or boundaries represent actual deformation or movement of the myocardium. Another issue with CMR-TT is the limitation of cine sequence temporal resolution, which is lower than echocardiography. Our CMR cine sequences had an average temporal resolution of 27-30msec whilst STE typically had temporal resolution of 10-15msec. This could account for the poorer correlation of CMR-TT with RVEF compared to STE but it is probably not the sole issue. While we are not aware of any studies, which correlated RVEF with RV strain, there are several studies comparing LV strain parameters with LVEF. These studies have shown very good or excellent correlation of LV strain parameters and LVEF. In a study by Onishi et al, they demonstrated that LV global

circumferential strain and LV GLS had a correlation of r=0.95 and r=0.88 respectively(35). In another study, Maret et al showed good correlation between LV global longitudinal strain and LVEF (r=0.79) at time when CMR-TT was a new technology(36). One difference with the scanning parameters in these two studies and ours was their cine sequences produced 30 frames per R-R interval whilst ours produced 25 frames per R-R interval. In one study, the temporal resolution was stated to be 26-41msec which is similar or slightly worse than our study. Our group postulates that part of the reduced correlation may again be due to the lower temporal resolution. Since our study's RV longitudinal strain is 50% more than LV longitudinal strain, missing end diastole and end systole by lower temporal resolution would translate into greater variability. Therefore this results in reduced correlation with RVEF.

Study Limitations:

Our study has several limitations. Firstly, the study has a small number of patients despite identifying 299 patients who fitted the inclusion criteria. After consideration of the exclusion criteria, patient consent and removal of suboptimal MR cases, we were left with 29 patients. However despite this, our results have indicated that CMR-TT and STE is a potentially useful and accurate tool in identifying RVEF<45% in DCM patients. Thereby identifying patients with a worse prognosis and may help improve workflow. Secondly, the CMR-TT and STE did not analyse other types of strain such as circumferential strain as this was not available with the current software.

Conclusion:

Of the available strain parameters, STE GLS and CMR-TT FLS show the best correlation with RVEF as well as excellent reproducibility on inter and intra-observer analysis. STE GLS has a higher correlation with RVEF than other standard echocardiography parameters (ie. S', TAPSE and FAC), while CMR-TT FLS shows

363 better correlation than CMR TAPSE and Co-TAPSE. Cut-off values for STE and
364 CMR-TT were recommended and could be a useful tool for fast and accurate echo
365 and CMR analysis of the RV systolic function.
366
367 **List of Abbreviations:**
368 ASE –American Society of Echocardiography
369 AUC –Area under the curve
370 BSA –Body Surface Area
371 CMR –Cardiac magnetic resonance
372 CMR-TT –Cardiac magnetic resonance tissue tracking
373 CMR-FT –Cardiac magnetic resonance feature tracking
374 Co-TAPSE –Corrected tricuspid annular plane systolic excursion
375 DCM –Dilated cardiomyopathy
376 DENSE – Displacement encoding with stimulated echoes
377 ECG -Electrocardiogram
378 FAC –Fractional area change
379 FLS –Free longitudinal strain
380 FRS –Free radial strain
381 GLS –Global longitudinal strain
382 ICC –Intraclass correlation coefficient
383 LV –Left ventricle
384 LVEDV –Left ventricular end-diastolic volume
385 LVESV –Left ventricular end-systolic volume
386 LVEF –Left ventricular ejection fraction
387 ROC –Receiver operating characteristic
388 RV –Right ventricle
389 RVEDV –Right ventricular end-diastolic volume
390 RVESV –Right ventricular end-systolic volume

RVEF –Right ventricular ejection fraction

RVFAC –Right ventricular fractional area change

SENC – Strain encoding

STE –Speckle tracking echocardiography

TAPSE –Tricuspid annular plane systolic excursion

TDI –Tissue doppler imaging

TPM – Tissue phase mapping

Conflicts of interest: None

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Figure 1. Radial (blue arrows), longitudinal (red arrows) and circumferential (orange arrows) directions as demonstrated on a short axis and 4-chamber cine image for the left ventricle and right ventricle.

Figure 2. Flow Chart of Patient Recruitment

Figure 3. Echocardiography speckle-tracking of the right ventricle. The Automated Functional Imaging (AFI) system automatically tracks the endocardial border with appropriate thickness over the region of interest. After manual adjustment, the system will check the quality of tracking of the six segments. After identifying the time of aortic valve closure by ECG, the system will generate the RV global longitudinal strain (GLS) with the average strain values of the six segments. The Quadrupolar plot can be generated showing strain value of individual segments. RV free wall strain (FWS) is provided by averaging the strain value of the three free RV wall segments.

Figure 4. Cardiac magnetic resonance tissue tracking on the 4-chamber view. The yellow line represents the right ventircular endocardial contour whilst the light blue line is the epicardial contour. The orange line which is an upside down T-shape, pinpoints the tricuspid annulus and the RV apex. This allows the software to

566 determine the extent of the right ventricle. The software then identifies the RV free
567 wall throughout the cardiac cycle to obtain the strain measurements.
568
569 **Figure 5.** Scatter plots demonstrating the correlation between STE and CMR-TT with
570 RVEF. Image A shows the scatter plot and correlation between STE RV free wall
571 longitudinal strain and RVEF. Image B shows STE RV global wall longitudinal strain
572 and RVEF. Image C shows CMR-TT RV free wall longitudinal strain compared to
573 RVEF.
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575 **Figure 6.** Receiver Operator Curve of CMR-TT RV FLS to identify an RVEF<45%.
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577 **Figure 7.** Receiver Operator Curve of STE RV FLS to identify an RVEF<45%.
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580 **Figure 8.** Receiver Operator Curve of STE RV GLS to identify an RVEF<45%.
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