

# **The Prevalence and Prognostic Significance of Right Ventricular Systolic Dysfunction in Non-Ischemic Dilated Cardiomyopathy**

*Gulati: RV Dysfunction in Dilated Cardiomyopathy*

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**Word Count:** 7932

**Journal Subject Codes:** [110] Congestive, [30] CT and MRI

## **ABSTRACT**

### **BACKGROUND**

Cardiovascular Magnetic Resonance (CMR) is the gold-standard technique for assessment of ventricular function. Although left ventricular (LV) volumes and ejection fraction are strong predictors of outcome in dilated cardiomyopathy (DCM), there are limited data regarding the prognostic significance of right ventricular (RV) systolic dysfunction (RVSD). We investigated whether CMR assessment of RV function has prognostic value in DCM.

### **METHODS AND RESULTS**

We prospectively studied 250 consecutive DCM patients using CMR. RVSD, defined by RV ejection fraction  $\leq 45\%$ , was present in 86 (34%) patients. During a median follow-up period of 6.8 years, there were 52 deaths and 7 patients underwent cardiac transplantation. The primary end point of all-cause mortality or cardiac transplantation was reached by 42 of 86 patients with RVSD and 17 of 164 patients without RVSD (49% vs. 10%; hazard ratio [HR], 5.90; 95% confidence interval [CI], 3.35 to 10.37;  $P < 0.001$ ). On multivariable analysis, RVSD remained a significant independent predictor of the primary end point (HR, 3.90; 95% CI, 2.16 to 7.04;  $P < 0.001$ ), as well as secondary outcomes of cardiovascular mortality or cardiac transplantation (HR, 3.35; 95% CI, 1.76 to 6.39;  $P < 0.001$ ), and heart failure (HF) death, HF hospitalization or cardiac transplantation (HR, 2.70; 95% CI, 1.32 to 5.51;  $P = 0.006$ ). Assessment of RVSD improved risk stratification for all-cause mortality or cardiac transplantation (net reclassification improvement, 0.31; 95% CI 0.10 to 0.53;  $P = 0.001$ ).

## **CONCLUSIONS**

RVSD is a powerful, independent predictor of transplant-free survival and adverse HF outcomes in DCM.

CMR assessment of RV function is important in the evaluation and risk stratification of DCM patients.

**Key Words:** cardiomyopathy, heart failure, magnetic resonance imaging, prognosis, right ventricular function

## INTRODUCTION

Studies in heart failure (HF) generally focus on functional assessment of the left ventricle. Conversely the right ventricle has received far less attention in the evaluation of HF patients.<sup>1-4</sup> Much of this neglect stems from the fact that the right ventricle has complex structural and physiological properties which pose challenges for assessment of its morphology and function.<sup>2,4,5</sup> However, adverse remodelling of the right ventricle is an important component of the HF syndrome. In particular, previous studies in HF cohorts of mixed etiology have suggested that right ventricular (RV) ejection fraction (RVEF), assessed by radionuclide or thermodilution techniques, may be a major determinant of exercise capacity and outcome.<sup>6-9</sup> Consequently there is growing interest regarding the clinical relevance of RV functional assessment in the HF population.<sup>1,3,4</sup>

Dilated cardiomyopathy (DCM) is the second most common etiology of HF after coronary artery disease,<sup>10</sup> and remains the leading indication for cardiac transplantation.<sup>11</sup> Although the exact prevalence is poorly defined, RV systolic dysfunction (RVSD) has been reported in as many as 65% of DCM patients,<sup>12</sup> suggesting that DCM is frequently a biventricular disease. The potential prognostic impact of RV impairment in DCM has been highlighted by two small studies which suggested that RVSD is an independent predictor of survival.<sup>13,14</sup>

To date, the few studies evaluating RV systolic performance in DCM have either utilised thermodilution or contrast ventriculography to estimate RVEF.<sup>12-14</sup> Such techniques are invasive with the result that their clinical application is limited. In contrast, cardiovascular magnetic resonance (CMR) allows non-invasive measurement of RVEF with high accuracy and reproducibility.<sup>15-19</sup> Despite the fact that CMR is now firmly established as the gold standard for RV assessment,<sup>4,5,20</sup> CMR data regarding the prevalence and prognostic implications of RVSD in DCM is lacking. We therefore sought to prospectively evaluate the prevalence and prognostic significance of RVSD, as assessed by CMR, in a broad spectrum of DCM patients.

## METHODS

### Patients

The study prospectively enrolled 250 consecutive patients with DCM (236 outpatients, 14 inpatients) who were referred for CMR by their treating cardiologist between November 2000 and March 2006. The diagnosis of DCM was made according to World Health Organization/International Society and Federation of Cardiology criteria.<sup>21</sup> All patients had left ventricular (LV) ejection fraction (LVEF) < 50% on transthoracic echocardiography of at least 6 months duration with no evidence of significant coronary artery disease (>50% diameter luminal stenosis in one or more epicardial vessels, history of myocardial infarction or coronary revascularization, or infarct pattern of late gadolinium enhancement). Prior to inclusion the diagnosis of DCM was confirmed by CMR, on the basis of increased LV end-diastolic volume indexed to body surface area (LVEDV index) and reduced LVEF, compared to published reference ranges normalized for age and gender.<sup>22</sup> Patients with a history of chronic lung disease, previous pulmonary embolism or idiopathic pulmonary hypertension were excluded. Additional exclusion criteria were hypertensive heart disease, tachycardia-induced cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, infiltrative cardiomyopathy, hypertrophic cardiomyopathy, athletic heart, significant primary valvular disease, recent myocarditis (<6 months), or congenital heart disease. Significant coronary artery disease was excluded by angiography in 192 (77%) patients, and negative stress imaging studies in 23 (9%) patients. The remaining 35 (14%) patients were younger than 40 years of age, had no history of angina and  $\leq 1$  risk factor for CAD. All patients provided written informed consent. The study was approved by the local institutional ethics committee.

## **CMR**

CMR was performed on a 1.5T scanner (Siemens Sonata or Avanto, Erlangen, Germany). A standardised protocol was employed for all patients. After routine localizer images, cine images were acquired with a balanced steady-state free-precession (SSFP) pulse sequence and retrospective electrocardiographic gating during an end-expiratory breath-hold. Cine imaging was first performed in horizontal and vertical long-axis planes, followed by acquisition of a stack of contiguous short-axis cines at 10 mm intervals (7 mm slice thickness with 3 mm gap) from the atrio-ventricular ring to apex. Typical sequence parameters were as follows: repetition time 3.2 ms, echo time 1.6 ms, in-plane resolution of 2.1 x 1.3 mm, flip angle 60°. Late gadolinium enhancement (LGE) images were acquired 10 to 15 minutes after the intravenous administration of a gadolinium contrast agent (Gd-DTPA/gadobutrol; Schering, Germany; 0.1mmol/kg) using an inversion-recovery gradient echo sequence in identical long-axis and short-axis planes. Inversion times were adjusted to null normal myocardium with images repeated in two separate phase-encoding directions to exclude artifact.

## **CMR analysis**

Cine images were analysed using semi-automated software (CMR Tools, Cardiovascular Imaging Solutions, London) by a single experienced observer who was blinded to all clinical data. Ventricular volumes, ejection fraction and LV mass were measured by standard techniques as previously described.<sup>22</sup> <sup>23</sup> In the case of the right ventricle, this analysis involved 3 principal steps: 1) Delineation of the RV endocardial border at end-diastole and end-systole; 2) semi-automated thresholding of the RV blood pool, with exclusion of papillary muscles and trabeculae, to determine RV end-diastolic volume (RVEDV) and end-systolic volume (RVESV); 3) tracking of the tricuspid valve plane on the horizontal long-axis cine to correct for descent of the atrio-ventricular ring during systole.<sup>23</sup> Ventricular volumes and LV mass were indexed to body surface area. As per recent guidelines, RVSD was defined as  $RVEF \leq 45\%$ .<sup>24</sup> LGE

images were assessed by a second independent blinded observer for the presence of RV or LV myocardial fibrosis. Fibrosis was only deemed to be present when the area of midwall LGE could be identified in both phase-encoding directions and in two orthogonal views.

In order to verify the reproducibility and reliability of RV functional assessment by CMR in our cohort, the intra- and inter-observer variability were calculated for RVEF measurements in 25 randomly selected patients. For intra-observer variability, the RVEF was measured twice by the same observer with a minimum interval of two weeks between serial assessments. The inter-observer variability was assessed using the measurements obtained by a second independent observer blinded to all other analyses.

### **Follow-up and end points**

All end points were adjudicated by the consensus of an independent committee blinded to the CMR findings. Mortality status was checked at 6-monthly intervals using the National Strategic Tracing Service (NSTS), a database for all National Health Service patients in the UK. In the event of death, the underlying cause was established from a combination of death certification, post-mortem data where available, communication with the patients' primary care physicians and cardiologists, and review of medical records for patients who died in hospital.

Patients were contacted every 6 months by telephone interview and/or postal questionnaire to document the occurrence of non-fatal cardiac events over the follow-up period. This information was substantiated by 6-monthly communication with patients' primary care physician and cardiologist to facilitate review of any new correspondence relating to outpatient clinic attendance or hospitalization. Following any hospital stay, the medical records were accessed to verify the cause of hospitalization and inpatient course.

The pre-defined primary end point was a composite of all-cause mortality or cardiac transplantation. Two additional secondary end points were pre-specified: a) Cardiovascular mortality (sudden cardiac death,

HF, stroke or thromboembolic event) or cardiac transplantation; b) A HF composite of HF death, unplanned HF hospitalization or cardiac transplantation. Mode of death was classified according to a modified Hinkle-Thaler system.<sup>25</sup> Sudden cardiac death was defined as unexpected death either within 1 hour of cardiac symptoms in the absence of progressive cardiac deterioration, during sleep or within 24 hours of last being seen alive. HF death was defined as death associated with unstable, progressive deterioration of pump function despite active therapy. HF hospitalization was diagnosed in patients admitted to hospital with signs and symptoms of decompensated HF requiring treatment with intravenous HF medication (diuretics, vasodilators or inotropic agents). Follow-up of patients who underwent cardiac transplantation was censored at the time of procedure. Only the first event in each patient was included in the outcome analysis.

### **Statistical analysis**

Baseline characteristics, stratified by the presence (RVSD+) or absence (RVSD-) of RVSD, are expressed as frequency (%) for categorical data and mean  $\pm$ SD for continuous data. Differences between the two groups were assessed by the chi-square or Fisher's exact tests for categorical variables and unpaired Student's t-test for continuous variables. Linear regression analysis was used to model the relationship between RVEF and LVEF. Intra-observer and inter-observer variability was assessed using the Bland-Altman method,<sup>26</sup> with results presented as mean differences and 95% limits of agreement.

The study population was divided into four subgroups based on RVEF value (>60%, 45-60%, 30-45%, <30%). Kaplan-Meier survival curves were constructed to estimate the cumulative event rate for each end point according to presence or absence of RVSD and RVEF subgroup. Event times were measured from the date of CMR study to the index composite event. The log-rank test was used to compare the Kaplan-Meier survival curves. A univariable Cox proportional-hazards model was employed to analyse the relationship between baseline covariables and end points. Results are reported as hazard ratios (HRs) with



95% confidence intervals (CIs). In order to identify independent predictors of outcome, forward stepwise multivariable Cox regression analysis was performed. Candidate variables with P value < 0.10 on univariable analysis were considered for entry and included in the multivariable model if they improved the likelihood ratio statistic by an amount which corresponded to a P value of <0.05. For each end point, two multivariable models were constructed based on inclusion of either RVSD as a binary categorical variable or RVEF subgroup. Receiver operator characteristic (ROC) curves were used to determine the optimal prognostic RVEF cut-off value (highest sum of sensitivity and specificity) for the primary end point of all cause mortality or cardiac transplantation at 5-years of follow-up. The results for sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) are given with their 95% confidence intervals. The incremental prognostic value of RVSD for the prediction of the primary end point at 5-years, over and above other significant predictors in the multivariable model, was assessed using net reclassification improvement. For each patient, the predicted 5-year risk of death/cardiac transplantation was determined on the basis of a Cox regression model with and without RVSD. Reclassification was examined using 5-year risk thresholds of <5%, 5-10%, 10-20% and  $\geq$ 20%. All analyses were conducted with Stata version 12 (StataCorp, College Station, Texas). A 2-tailed P value of <0.05 was considered statistically significant.

## RESULTS

### Study population

The study cohort comprised of 250 patients whose baseline characteristics are summarised in Table 1. The mean RVEF for the entire cohort was  $48 \pm 13\%$ . A total of 86 (34%) patients had RVSD. Compared to patients without RVSD, patients with RVSD had higher resting heart rate, lower systolic and diastolic blood pressures, more severe New York Heart Association (NYHA) functional class and a lower prevalence of left bundle branch block. There was no significant difference in age or gender between

groups. At enrolment, patients with RVSD were more likely to receive treatment with beta-blockers, angiotensin converting enzyme inhibitors or angiotensin II antagonists, digoxin, loop diuretics and aldosterone antagonists. RVSD was also associated with more severe biventricular adverse remodelling, with higher indexed ventricular volumes and lower LVEF in the RVSD+ group. On LGE-CMR, no patient was observed to have fibrous replacement of the RV free wall. However, LV midwall fibrosis was present in 28% of the cohort and was more prevalent in patients with RVSD. A positive correlation was observed between RVEF and LVEF measurements ( $r=0.58$ ;  $p<0.001$ ) (Figure 1).

### **Intra-observer and inter-observer variability**

Analysis of both the intra-observer and inter-observer variability showed high levels of agreement for the measurement of RVEF. The mean difference (95% limits of agreement) for the intra-observer study was 0.8% (-4.5, 6.0), whilst for inter-observer study this was 0.7% (-6.6, 5.3).

### **Primary end point**

Patients were followed up for a median duration of 6.8 years (interquartile range 5.9 to 8.1 years). Data were collected for a total of 1640 patient-years of follow-up. During follow-up, 52 patients died and an additional 7 patients underwent cardiac transplantation for end-stage heart failure. The primary end point of all-cause mortality or cardiac transplantation therefore occurred in 59 (24%) patients (Table 2).

Figure 2A shows the event-free survival curves of the study population according to the presence or absence of RVSD as defined by an RVEF cut-off of 45%. Patients with RVSD had a significantly higher rate of all-cause mortality or cardiac transplantation ( $P<0.001$ ). Among the 86 patients with RVSD, 42 (49%) patients reached the primary end point, as compared with only 17 (10%) of the 164 patients without RVSD (HR, 5.90; 95% CI, 3.35 to 10.37;  $P<0.001$ ) (Table 2). Additional significant univariable

predictors of the primary end point are listed in table 3. After forward stepwise multivariable analysis, RVSD was the most significant independent predictor of all-cause mortality or cardiac transplantation (HR, 4.24; 95% CI, 2.31 to 7.78;  $P<0.001$ ) (Table 3). Other covariables that were found to be independently associated with transplant-free overall survival in the multivariable model were diastolic blood pressure (HR, 0.97; 95% CI, 0.95 to 1.00;  $P=0.026$ ), NYHA class (HR, 1.70; 95% CI, 1.18 to 2.44;  $P=0.004$ ), LVEDV index (HR per 10 ml/m<sup>2</sup> increment, 1.06; 95% CI, 1.01 to 1.12;  $P=0.018$ ) and midwall fibrosis (HR, 3.27; 95% CI 1.88 to 5.67;  $P<0.001$ ). RVSD remained a significant independent predictor of all-cause mortality alone with patients who underwent cardiac transplantation censored at the time of transplant (HR, 4.20; 95% CI, 2.24 to 7.90;  $P<0.001$ ).

Kaplan-Meier survival analysis also showed a significant association between RVEF subgroup and the primary end point ( $P<0.001$ ) (Figure 3A). In a multivariable Cox regression model, patients with an RVEF<30% (HR, 5.99; 95% CI, 1.33 to 26.95;  $P=0.020$ ) or between 30-45% (HR, 7.75; 95% CI, 1.82 to 33.00;  $P=0.006$ ) had a significantly higher risk of all-cause mortality or cardiac transplantation compared to those with an RVEF>60% (Table 3). There was no difference in outcome between patients in the RVEF 45-60% or RVEF>60% subgroups (HR, 1.85; 95% CI, 0.41 to 8.29;  $P=0.420$ ).

ROC analysis revealed that a cut-off of 45% was the optimal RVEF value for the prediction of all-cause mortality or cardiac transplantation at 5-years (Figure 4). At this cut-off the sensitivity was 71% (95% CI, 56% to 84%), specificity was 74% (95% CI, 67% to 84%), PPV was 37% (95% CI, 27% to 48%) and NPV was 92% (95% CI, 87% to 96%) for the primary end point. The area under the ROC curve was 0.72 (95% CI, 0.65 to 0.80).

Reclassification of patient risk was assessed following the addition of RVSD to a baseline 5-year risk model constructed using the other independent predictors (diastolic blood pressure, NYHA class, LVEDV index and midwall fibrosis) identified on multivariable analysis. The addition of RVSD to the baseline model resulted in 94 correct (down) reclassifications and 30 incorrect (up) reclassifications among the

205 alive/non-transplant patients at 5-years of follow-up (see the online-only Data Supplement). Additionally, 9 correct (up) and 9 incorrect (down) reclassifications occurred among the 45 deceased/transplant patients. The overall net reclassification improvement after adding RVSD to the baseline risk model was 0.31 (95% CI, 0.10 to 0.53,  $P=0.001$ ).

### **Secondary end points**

Among the 52 deaths during the follow-up period, 43 (83%) were cardiovascular in etiology including 21 sudden cardiac death, 20 HF deaths and 2 deaths due to stroke or pulmonary embolism (Table 2). Thirty-nine (16%) patients were hospitalized for the treatment of decompensated HF.

A total of 50 (20%) patients reached the secondary composite end point of cardiovascular mortality or cardiac transplantation (Table 2). The presence of RVSD was associated with significantly worse outcome on Kaplan-Meier analysis ( $P<0.001$ ) (Figure 2B). On multivariable analysis, RVSD was a significant and independent predictor of cardiovascular death or transplantation (HR, 3.77; 95% CI, 1.99 to 7.13;  $P<0.001$ ), together with diastolic blood pressure (HR, 0.97; 95% CI, 0.94 to 1.00;  $P=0.022$ ), NYHA functional class (HR, 1.70; 95% CI, 1.15 to 2.52;  $P=0.008$ ), LVEDV index (HR, 1.08; 95% CI, 1.02 to 1.14;  $P=0.006$ ) and midwall fibrosis (HR, 4.84; 95% CI 2.62 to 8.93;  $P<0.001$ ) (Table 4). Kaplan-Meier estimates of transplant-free cardiovascular survival according to RVEF subgroup are shown in Figure 3B. There was a significant difference in the rate of cardiovascular death or transplantation between RVEF subgroups ( $P<0.001$ ). Analysis between groups in the multivariable model revealed that this difference was primarily driven by the worse outcome observed in the RVEF<30% and RVEF 30-45% subgroups (Table 4).

The secondary HF composite end point of HF death, HF hospitalization or cardiac transplantation occurred in 49 (20%) patients (Table 2). Kaplan-Meier analysis revealed a significantly worse event-free survival rate among patients with RVSD ( $P<0.001$ ) (Figure 2C). The multivariable model identified four

independent predictors of HF outcome: RVSD (HR, 2.85; 95% CI, 1.45 to 5.61; P=0.002), NYHA functional class (HR, 2.49; 95% CI, 1.63 to 3.82; P<0.001), LVESV index (HR per 10ml/m<sup>2</sup>, 1.11; 95% CI, 1.06 to 1.17; P<0.001) and midwall fibrosis (HR, 2.52; 95% CI 1.36 to 4.65; P=0.003) (Table 4). Kaplan-Meier curves by RVEF subgroup demonstrated a stepwise increase in the incidence of the HF composite with decreasing RVEF (P<0.001) (Figure 3C). After multivariable analysis, the adjusted hazard ratios for the HF composite in the RVEF<30%, 30-45% and 45-60% subgroups, as compared with the RVEF>60% subgroup, were 9.37 (95% CI, 1.18 to 74.16; P=0.034), 9.35 (95% CI, 1.22 to 71.40); P=0.031) and 4.03 (95% CI, 0.52 to 31.10; P=0.182) (Table 4).

## DISCUSSION

Risk stratification in DCM is important because of the associated morbidity and mortality due to HF and sudden cardiac death.<sup>27, 28</sup> Although current risk stratification is primarily guided by the degree of adverse LV remodelling, there is increasing appreciation of the potential impact of RVSD on outcome.<sup>1, 3, 4</sup> In this study, we investigated the prevalence and prognostic significance of RVSD, as identified by CMR, in a broad DCM cohort with a wide spectrum of phenotypic severity. Our results indicate that RVSD is present in approximately one third of DCM patients, and represents an independent and incremental marker of adverse prognosis. After adjustment for established prognosticators including LV parameters and NYHA functional class on multivariable analysis, patients with RVSD experienced a four-fold increase in all-cause mortality or cardiac transplantation. RVSD was also an independent predictor of transplant-free cardiovascular survival and HF outcomes. The assessment of RVSD improved risk stratification for transplant-free overall survival. These findings therefore suggest that assessment of RVEF, in addition to LV morphological and functional parameters, may further enhance the prognostic utility of CMR in DCM.

A number of imaging indices are available to evaluate RV systolic function. In addition to RVEF, other commonly used indices in the clinical arena include the tricuspid annular plane systolic excursion (TAPSE), tricuspid annular peak systolic velocity (TAPSV) measured by tissue Doppler imaging, and RV fractional area change. Although TAPSE and TAPSV have been shown to correlate reasonably well with RVEF,<sup>29-31</sup> they are limited to the assessment of longitudinal systolic function,<sup>32</sup> dependent on RV loading conditions,<sup>4</sup> and subject to confounding by significant LV systolic impairment<sup>33, 34</sup> and tricuspid regurgitation.<sup>35</sup> RV fractional area change is derived from a single four-chamber view and may therefore be misleading in patients with regional contractile abnormalities.<sup>5</sup> In contrast RVEF is more representative of global systolic performance. Consequently, although it is itself load-dependent, RVEF represents the most widely accepted and clinically validated index of RV contractility.<sup>2</sup>

Accurate estimation of RVEF has historically been very difficult. Established techniques for RVEF assessment include transthoracic echocardiography (TTE), thermodilution, contrast or radionuclide ventriculography and CMR. Due to its widespread availability, TTE is typically the first line imaging technique for RV functional assessment.<sup>4, 36</sup> However, quantitative assessment of RVEF by TTE is dependent on geometric modelling which is problematic in the case of the right ventricle due to its asymmetric crescentic shape, heavily trabeculated endocardial surface and bellows-like contraction pattern.<sup>2, 20</sup> The substernal location of the right ventricle poses further challenges for imaging by TTE due to inadequate acoustic windows and suboptimal visualisation of its anterior wall.<sup>32, 37</sup> Both thermodilution and contrast ventriculography are invasive, with the latter also limited by the complex RV geometry. The clinical application of these catheterization techniques for RV evaluation is therefore limited. Although non-invasive and independent of geometric modelling, radionuclide imaging requires exposure to ionizing radiation, has low spatial resolution, is susceptible to attenuation artifacts, and does not allow reliable delineation of the RV and right atrial cavities.<sup>31</sup>

CMR offers several advantages with respect to RV assessment. The multiplanar imaging and three-dimensional volume acquisition provided by CMR eliminate the need for geometrical assumptions regarding RV shape.<sup>16, 23</sup> Balanced SSFP cine acquisitions yield high spatial resolution images with excellent discrimination between blood and endocardium.<sup>23</sup> The high accuracy and reproducibility of CMR estimates of RV volumes and EF have been extensively validated, albeit predominantly in healthy individuals.<sup>15-19</sup> Assessment of the inter-observer and intra-observer variability in RVEF measurement in our study population generated comparable reproducibility measures to those reported in normal subjects.<sup>16-19</sup> Our data therefore confirm the utility of CMR for reliable RVEF measurement in DCM, despite the adverse remodelling of the right ventricle which frequently accompanies this condition.

The normal range of RVEF varies depending on the methodology used for assessment. The accepted lower limit of radionuclide-derived RVEF is 40%.<sup>38</sup> Studies that have investigated the prognostic significance of RVEF measured by catheterization techniques most commonly used a cut-off value of

35% to define RVSD.<sup>9, 12, 14</sup> There is currently no international consensus regarding normal values for RVEF assessed by CMR. In a CMR study of 120 healthy subjects, Maceira et al. found that the lower limit of the 95% CI for RVEF varied from 48% to 59 % depending on age and gender.<sup>23</sup> In this study we defined RVSD according to an RVEF  $\leq$ 45%, based on the value proposed by the recent modified Task Force Criteria for the identification of RVSD by CMR in arrhythmogenic right ventricular cardiomyopathy.<sup>24</sup> ROC analysis demonstrated that an RVEF of 45% was also the optimal cut-off value for predicting the primary end-point of all-cause mortality or cardiac transplantation at 5-years in our cohort. Subgroup analysis of patients with RVEF  $>$ 45%, revealed no significant difference in outcome between patients with RVEF 45-60% and those with RVEF $>$ 60% for any of the end-points. An RVEF of 45% would therefore appear to represent a rational threshold for the CMR diagnosis of RVSD, both with respect to DCM phenotypic characterisation and risk stratification.

Although our study did not evaluate the underlying mechanisms of RVSD in DCM, the significant strong correlation observed between LVEF and RVEF is consistent with a pathophysiological link between left and right ventricular systolic function. LV systolic dysfunction may negatively impact upon RV contractility in DCM via multiple mechanisms including increased afterload due to secondary pulmonary hypertension, RV involvement from the LV cardiomyopathic process, ventricular interdependence due to septal dysfunction and myocardial ischemia secondary to reduced coronary perfusion pressure.<sup>1</sup> It has therefore been proposed that RVSD may signify a “common final pathway” in HF progression and provide a sensitive marker of future decompensation and poor prognosis accordingly.<sup>1</sup>

Several previous reports have documented that impaired RVEF is an important prognostic factor in HF.<sup>6-9</sup> However, this observation is based on the study of mixed HF cohorts of ischemic and non-ischemic etiology, in which radionuclide ventriculography or thermodilution were used for RVEF measurement. The prognostic relevance of RVSD may vary according to HF etiology. In 2006, the National Heart, Lung and Blood Institute (NHLBI) identified the study of RV function as a priority in cardiovascular research.<sup>1</sup> CMR represents the current gold standard assessment for RVEF and yet despite the NHLBI’s



recommendations, there are no published CMR data regarding the prognostic implications of RVSD in either DCM or the general HF population. To the best of our knowledge, the present study is therefore the first to show that CMR assessment of RVEF predicts outcome in HF secondary to non-ischemic DCM.

Our findings complement the few other studies to date that have previously examined the prevalence<sup>12</sup> and prognostic significance<sup>13, 14</sup> of RVSD in DCM. La Vecchia et al. found that RVSD was more common in patient with DCM versus those with ischemic HF, despite similar levels of LV impairment in the two groups.<sup>12</sup> In their study, the prevalence of RVSD (defined by an RVEF <35%) in 92 DCM patients was as high as 65%, leading the authors to propose that RVSD may represent a marker for DCM. Whilst our data confirm that RVSD is relatively common in DCM, it was detected in only 34% of the study population. The lower prevalence observed in our cohort, despite using a higher RVEF threshold to define RVSD, may be attributed to differences in selection criteria and EF assessment methodology between the two studies. La Vecchia only enrolled DCM patients with at least moderate LV impairment at baseline (LVEF <45%) and used contrast ventriculography for both LVEF and RVEF measurement. In the present study however, CMR was used to confirm DCM diagnosis at entry and assess RVEF thereafter. The high fidelity of biventricular parameters assessed by CMR not only facilitates more accurate quantification of RVEF, but also allows confident diagnosis of DCM in patients with mild LV dilatation and dysfunction.<sup>39</sup> As a result, our cohort is composed of DCM patients with a wider spectrum of phenotypic severity, including those with mild or early disease.

Only two studies have previously evaluated the prognostic value of RVSD specifically in non-ischemic DCM.<sup>13, 14</sup> Although both these studies also demonstrated that RVSD was associated with transplant-free overall survival, they were performed prior to the widespread incorporation of beta-blockers into standard HF therapy, in small DCM cohorts (62 to 85 patients), in which RVEF was measured by invasive catheterization techniques. Only one study addressed whether RVSD was an independent predictor of outcome using multivariable analysis.<sup>13</sup> However, this study did not include midwall fibrosis, another important prognosticator in DCM,<sup>40-42</sup> in the survival analysis. In contrast we have investigated the

prognostic impact of RVSD in a comparatively large cohort of DCM patients, who were accurately characterised by LGE-CMR and treated with contemporary HF pharmacological therapy, during a longer follow-up. On stepwise multivariable analysis, we have demonstrated that RVSD is not only an important predictor of transplant-free overall survival, but also predicts other hard end points including cardiovascular mortality or cardiac transplantation, and HF death, HF hospitalization or cardiac transplantation. Whilst cardiac transplantation is frequently used as a surrogate for cardiovascular death, analysis of overall survival excluding transplantation yielded similar results. The prognostic significance of RVSD is independent of established prognosticators, including measures of LV size and function, and midwall fibrosis. NRI analysis further revealed that RVSD provided incremental predictive value for transplant-free survival, when compared to other independent risk predictors. Identification of RVSD by CMR therefore improves risk stratification in DCM and may help guide management decisions relating to patient selection and timing for major interventions, such as cardiac transplantation or ventricular assist device implantation.

### **Study Limitations**

The study cohort is selected in that it consists of DCM patients referred for CMR assessment by their treating cardiologists. Whilst this may potentially be subject to referral bias, we studied consecutive patients with a broad range of phenotypic severity. CMR measurement of RVEF from images acquired in the axial orientation may be more reproducible than the short axis orientation used in this study.<sup>16</sup> We deliberately employed the short axis orientation since this is conventionally used in clinical practice due to the fact it allows simultaneous analysis of LV and RV parameters from a single data set. Our results additionally revealed good reproducibility with this method. In this study, RVEF was only measured at rest. Evaluation of RV contractile reserve may offer additive prognostic information. Due to the limited number of events per candidate variable, there is a possibility of overfitting in our multivariate models

and further independent validation is needed. Renal function was not systematically recorded at the time of CMR assessment in all patients and is therefore not included in our analyses. Similarly, the absence of contemporaneous pulmonary arterial pressure measurements means that we were unable to elucidate the contribution of pulmonary arterial hypertension to the development of RVSD or outcome. However, accurate evaluation of pulmonary arterial pressure requires invasive right heart catheterization as estimates derived from Doppler echocardiography are frequently inaccurate.<sup>43</sup> It was not deemed ethical to perform right heart catheterization in all study patients. Whilst CMR itself is unable to assess pulmonary arterial pressure, our study demonstrates that non-invasive assessment of RV function by CMR may additionally serve as an important prognostic marker.

## **Conclusions**

RVSD is common in DCM with a prevalence of 34% in our cohort. Detection of RVSD by CMR represents a powerful independent predictor of transplant-free survival and adverse HF outcomes in DCM. Routine functional evaluation of the right ventricle is therefore warranted in the CMR examination of DCM patients for comprehensive phenotypic characterization and risk stratification. Further study is required to evaluate whether amelioration of RVSD, with treatments that target RV performance, may yet improve prognosis.

## **FUNDING SOURCES**

This work was supported by the National Institute for Health Research Cardiovascular Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London. Dr Gulati receives grant support from CORDA and the Rosetrees Trust. Dr Assomull and Dr Ismail were supported by the British Heart Foundation. Dr Jabbour received funding from the National Health and Medical Research Council of Australia, Victor Chang Cardiac Research Institute, and St Vincent's Clinic Foundation.

## **CONFLICT OF INTEREST DISCLOSURES**

Professor Cook has served as a consultant for GlaxoSmithKline. Professor Pennell has served as a consultant for Siemens and is a director and shareholder of Cardiovascular Imaging Solutions. Dr Prasad has received honoraria from Schering. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## TABLE LEGENDS

### **Table 1. Baseline Characteristics of the Study Group According to the Presence (RVSD+) or Absence (RVSD-) of Right Ventricular Systolic Dysfunction.**

Plus-minus values are means  $\pm$ SD. VF denotes ventricular fibrillation, VT ventricular tachycardia, AF atrial fibrillation, DCM dilated cardiomyopathy, LBBB left bundle branch block, NYHA New York Heart Association, ACE angiotensin-converting enzyme, ARB angiotensin II-receptor blocker, LV left ventricular, RV right ventricular, EDV end-diastolic volume, ESV end-systolic volume, EF ejection fraction.

### **Table 2. Study Outcome Data According to Presence (RVSD+) or Absence (RVSD-) of Right Ventricular Systolic Dysfunction.**

CI denotes confidence interval.

\* The number of patients who experienced an index composite outcome is stated.

### **Table 3. Hazard Ratios for All-Cause Mortality or Cardiac Transplantation in Univariable and Multivariable Analyses**

\* In multivariable model 1, right ventricular systolic dysfunction (presence or absence) was included as a covariable.

† In multivariable model 2, right ventricular ejection fraction subgroup was included as a covariable.



CI denotes confidence interval, VF ventricular fibrillation, VT ventricular tachycardia, AF atrial fibrillation, DCM dilated cardiomyopathy, LBBB left bundle branch block, NYHA New York Heart Association, ACE angiotensin-converting enzyme, ARB angiotensin II-receptor blocker, LV left ventricular, RV right ventricular, EDV end-diastolic volume, ESV end-systolic volume, EF ejection fraction, RVSD right ventricular systolic dysfunction.

**Table 4. Hazard Ratios for Secondary End Points in Multivariable Analysis**

All baseline covariables with a  $P < 0.05$  on univariable analysis were entered into the multivariable model. Only those covariables which were selected as independent predictors of outcome on forward stepwise multivariable analysis are displayed.

\* In multivariable model 1, right ventricular systolic dysfunction (presence or absence) was included as a covariable.

† In multivariable model 2, right ventricular ejection fraction subgroup was included as a covariable.

CI denotes confidence interval, NYHA New York Heart Association, LV left ventricular, EDV end-diastolic volume, ESV end-systolic volume, RVSD right ventricular systolic dysfunction, RVEF ejection fraction, HF heart failure.

## FIGURE LEGENDS

**Figure 1. Relationship between Right Ventricular Ejection Fraction (RVEF) and Left Ventricular Ejection Fraction (LVEF).** The red trace represents the fitted linear regression line.

**Figure 2. Kaplan-Meier Estimates of the Time to All-Cause Mortality or Cardiac Transplantation (Panel A), Cardiovascular Mortality or Cardiac Transplantation (Panel B), and Heart Failure Death, Heart Failure Hospitalization or Cardiac Transplantation (Panel C), According to Presence or Absence of Right Ventricular Systolic Dysfunction.** A right ventricular ejection fraction cut-off value of 45% was used to define right ventricular systolic dysfunction. RVEF denotes right ventricular ejection fraction.

**Figure 3. Kaplan-Meier Estimates of the Time to All-Cause Mortality or Cardiac Transplantation (Panel A), Cardiovascular Mortality or Cardiac Transplantation (Panel B), and Heart Failure Death, Heart Failure Hospitalization or Cardiac Transplantation (Panel C), According to Right Ventricular Ejection Fraction Subgroup.**

**Figure 4. Receiver Operating Characteristic Curve for the Overall Performance of Right Ventricular Ejection Fraction for the Prediction of All-Cause Mortality or Cardiac Transplantation at 5-Years.**

## TABLES

**Table 1.**

Characteristics	All patients (N=250)	RVSD - (N=164)	RVSD + (N=86)	P value
Age - yr	50.8±14.0	51.9±13.5	48.7±14.6	0.081
Male sex (%)	171 (68.4)	108 (65.9)	63 (73.3)	0.232
History of VF or sustained VT (%)	15 (6.0)	9 (5.5)	6 (7.0)	0.638
History of AF (%)	37 (14.8)	20 (12.2)	17 (19.8)	0.109
Diabetes (%)	21 (8.4)	13 (7.9)	8 (9.30)	0.710
Smoker (%)	47 (18.8)	27 (16.5)	20 (23.3)	0.192
History of alcohol excess (%)	32 (12.8)	17 (10.4)	15 (17.4)	0.112
Family history of DCM (%)	18 (7.2)	15 (9.2)	3 (3.5)	0.100
Heart rate - beats/min	75.6±14.9	72.4±13.4	81.9±15.7	<0.001
Systolic blood pressure - mm Hg	119.1±18.9	123.0±17.4	111.6±19.4	<0.001
Diastolic blood pressure - mm Hg	72.6±11.6	73.9±10.9	70.2±12.6	0.017
LBBB (%)	66 (26.4)	51 (31.1)	15 (17.4)	0.020
NYHA functional class (%)				
I	103 (41.2)	84 (51.2)	19 (22.1)	<0.001
II	96 (38.4)	63 (38.4)	33 (38.4)	
III	45 (18.0)	16 (9.8)	29 (33.7)	
IV	6 (2.4)	1 (0.6)	5 (5.8)	
Medications at baseline (%)				
Aspirin	82 (32.8)	58 (35.4)	24 (27.9)	0.233
Warfarin	64 (25.6)	28 (17.1)	36 (41.9)	<0.001
Beta-blocker	162 (64.8)	98 (59.8)	64 (74.4)	0.021
ACE-inhibitor or ARB	231 (92.4)	146 (89.0)	85 (98.8)	0.005
Amiodarone	26 (10.4)	19 (11.6)	7 (8.1)	0.397
Digoxin	42 (16.8)	18 (11.0)	24 (27.9)	0.001
Statin	58 (23.2)	39 (23.8)	19 (22.1)	0.764
Loop diuretic	128 (51.2)	66 (40.2)	62 (72.1)	<0.001
Aldosterone antagonist	82 (32.8)	38 (23.2)	44 (51.2)	<0.001

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Cardiovascular Magnetic Resonance measurements				
LVEDV index - ml/m <sup>2</sup>	132.9±43.7	122.7±36.1	152.3±50.2	<0.001
LVESV index - ml/m <sup>2</sup>	87.2±45.0	73.4±34.7	113.6±50.5	<0.001
LV stroke volume - ml	90.6±29.1	97.5±25.3	77.5±31.5	<0.001
LVEF - %	37.1±13.2	42.2±10.7	27.4±12.1	<0.001
LV mass index - g/m <sup>2</sup>	105.3±31.8	98.8±26.1	117.7±37.7	<0.001
RVEDV index - ml/m <sup>2</sup>	89.8±26.4	80.8±17.1	107.1±32.0	<0.001
RVESV index - ml/m <sup>2</sup>	48.5±25.5	35.4±9.9	73.5±27.6	<0.001
RV stroke volume - ml	82.0±27.5	90.0±24.6	66.8±26.3	<0.001
RVEF - %	48.2±13.9	56.6±7.2	32.3±8.9	<0.001
Midwall fibrosis (%)	71 (28.4)	39 (23.8)	32 (37.2)	0.025
RVEF subgroup (%)				
RVEF>60%	49 (20)			
RVEF 45-60%	115 (46)			
RVEF 30-45%	55 (22)			
RVEF<30%	31 (12)			

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**Table 2.**

<b>Outcome</b>	<b>RVSD - (N=164)</b>	<b>RVSD + (N=86 )</b>	<b>Hazard Ratio (95% CI)</b>	<b>P Value</b>
	no. of patients (%)			
<b>Primary end point</b>				
All-cause mortality or cardiac transplantation	17 (10.4)	42 (48.8)	5.90 (3.35 to 10.37)	<0.001
All-cause mortality	16 (9.8)	36 (41.9)	5.51 (3.06 to 9.94)	<0.001
Cardiac transplantation	1 (0.6)	6 (7.0)	13.01 (1.56 to 108.26)	0.018
<b>Secondary end points</b>				
Cardiovascular mortality or cardiac transplantation	15 (9.2)	35 (40.7)	5.62 (3.07 to 10.30)	<0.001
Cardiovascular mortality	14 (8.5)	29 (33.7)	5.12 (2.70 to 9.70)	<0.001
Heart failure death, heart failure hospitalization or cardiac transplantation*	13 (7.9)	32 (37.2)	6.13 (3.21 to 11.70)	<0.001
Heart failure death	3 (1.8)	17 (19.8)	14.19 (4.15 to 48.45)	<0.001
Heart failure hospitalization	12 (7.3)	27 (31.4)	5.61 (2.84 to 11.10)	<0.001

**Table 3.**

Variable	Univariable Analysis		Multivariable Analysis			
	Unadjusted Hazard		Model 1*		Model 2†	
	Ratio (95% CI)	P value	Adjusted Hazard Ratio (95% CI)	P value	Adjusted Hazard Ratio (95% CI)	P value
Age - yr	1.00 (0.98 to 1.02)	0.753				
Male sex	1.33 (0.74 to 2.40)	0.335				
History of VF or sustained VT	0.83 (0.26 to 2.66)	0.755				
History of AF	0.68 (0.31 to 1.50)	0.338				
Diabetes	0.82 (0.33 to 2.06)	0.679				
Smoker	0.74 (0.36 to 1.50)	0.396				
History of alcohol excess	1.41 (0.73 to 2.71)	0.309				
Family history of DCM	1.18 (0.47 to 2.96)	0.719				
Heart rate - beats/min	1.02 (1.01 to 1.04)	0.003				
Systolic blood pressure - mm Hg	0.97 (0.96 to 0.99)	<0.001				
Diastolic blood pressure - mm Hg	0.95 (0.93 to 0.98)	<0.001	0.97 (0.95 to 1.00)	0.026	0.97 (0.95 to 1.00)	0.027
LBBB	0.79 (0.43 to 1.44)	0.437				
NYHA functional class	2.39 (1.75 to 3.26)	<0.001	1.70 (1.18 to 2.44)	0.004	1.71 (1.20 to 2.44)	0.003
LVEDV index - per 10ml/m <sup>2</sup>	1.13 (1.08 to 1.17)	<0.001	1.06 (1.01 to 1.12)	0.018	1.07 (1.01 to 1.13)	0.013
LVESV index - per 10ml/m <sup>2</sup>	1.14 (1.10 to 1.18)	<0.001				
LV stroke volume - per 10ml	0.88 (0.80 to 0.97)	0.008				

LVEF - %	0.94 (0.92 to 0.96)	<0.001				
LV mass index - per 10g/m <sup>2</sup>	1.14 (1.06 to 1.22)	<0.001				
RVEDV index - per 10ml/m <sup>2</sup>	1.14 (1.05 to 1.25)	0.002				
RVESV index - per 10ml/m <sup>2</sup>	1.22 (1.13 to 1.31)	<0.001				
RV stroke volume - per 10ml	0.84 (0.76 to 0.93)	0.001				
RVEF - %	0.95 (0.93 to 0.97)	<0.001				
Mldwall fibrosis presence	3.29 (1.95 to 5.54)	<0.001	3.27 (1.88 to 5.67)	<0.001	3.20 (1.84 to 5.57)	<0.001
RVSD presence	5.90 (3.35 to 10.37)	<0.001	4.24 (2.31 to 7.78)	<0.001		
RVEF subgroup						
RVEF>60%	1.00				1.00	
RVEF 45-60%	1.84 (0.53 to 6.42)	0.337			1.85 (0.41 to 8.29)	0.420
RVEF 30-45%	8.48 (2.56 to 28.12)	<0.001			7.75 (1.82 to 33.00)	0.006
RVEF<30%	11.39 (3.33 to 38.90)	<0.001			5.99 (1.33 to 26.95)	0.020

**Table 4.**

Secondary End Point	Variable	Multivariable Analysis			
		Model 1*		Model 2†	
		Adjusted Hazard Ratio (95% CI)	P value	Adjusted Hazard Ratio (95% CI)	P value
Cardiovascular Mortality or Cardiac Transplantation	Diastolic blood pressure - mm Hg	0.97 (0.94 to 1.00)	0.022	0.97 (0.94 to 1.00)	0.023
	NYHA functional class	1.70 (1.15 to 2.52)	0.008	1.71 (1.16 to 2.51)	0.005
	LVEDV index - per 10ml/m <sup>2</sup>	1.08 (1.02 to 1.14)	0.006	1.08 (1.02 to 1.14)	0.005
	Mldwall fibrosis presence	4.84 (2.62 to 8.93)	<0.001	4.76 (2.57 to 8.80)	<0.001
	RVSD presence	3.77 (1.99 to 7.13)	<0.001		
	RVEF subgroup				
	RVEF>60%			1.00	
	RVEF 45-60%			1.58 (0.35 to 7.15)	0.551
	RVEF 30-45%			5.99 (1.39 to 25.85)	0.016
RVEF<30%			4.83 (1.07 to 21.90)	0.041	
HF Death, HF Hospitalization or Cardiac Transplantation	NYHA functional class	2.49 (1.63 to 3.82)	<0.001	2.43 (1.59 to 3.72)	<0.001
	LVESV index - per 10ml/m <sup>2</sup>	1.11 (1.06 to 1.17)	<0.001	1.11 (1.05 to 1.17)	<0.001
	Mldwall fibrosis presence	2.52 (1.36 to 4.65)	0.003	2.44 (1.32 to 4.52)	0.004
	RVSD presence	2.85 (1.45 to 5.61)	0.002		
	RVEF subgroup				



RVEF>60%	1.00	
RVEF 45-60%	4.03 (0.52 to 31.10)	0.182
RVEF 30-45%	9.35 (1.22 to 71.40)	0.031
RVEF<30%	9.37 (1.18 to 74.16)	0.034

