ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2020) **21**, 10–21
doi:10.1093/ehjci/jez233

Development and prognostic validation of partition values to grade right ventricular dysfunction severity using 3D echocardiography

Denisa Muraru[1], Luigi P. Badano [2,3]*, Yasufumi Nagata[4], Elena Surkova[1,5], Yosuke Nabeshima[4], Davide Genovese[1], Yutaka Otsuji[4], Valentina Guida[2], Danila Azzolina[1], Chiara Palermo[1], and Masaaki Takeuchi[6]

[1]Department of Cardiac, Thoracic and Vascular Sciences, University of Padua School of Medicine, Via Giustiniani 2, 35128, Padua, Italy; [2]Istituto Auxologico Italiano, IRCCS, Cardiology Unit and Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Piazzale Brescia, 20, 20149 Milan, Italy; [3]Department of Medicine and Surgery, University of Milano-Bicocca, Piazza dell'Ateneo Nuovo 1, 20126, Milan, Italy; [4]Second Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Iseigaoka 1-1, Yahatanishiku, Kitakyushu, 807-8555, Japan; [5]Cardiac Division, Department of Echocardiography, Royal Brompton Hospital, Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, Chelsea, SW3 6NP London, UK; and [6]Department of Laboratory and Transfusion Medicine, School of Medicine, University of Occupational and Environmental Health, Iseigaoka 1-1, Yahatanishiku, Kitakyushu, 807-8555, Japan

Received 22 May 2019; editorial decision 21 August 2019; accepted 23 August 2019; online publish-ahead-of-print 20 September 2019

Aims Transthoracic 3D echocardiography (3DE) has been shown to be feasible and accurate to measure right ventricular (RV) ejection fraction (EF) when compared with cardiac magnetic resonance (CMR). However, RV EF, either measured with CMR or 3DE, has always been reported as normal (RV EF > 45%) or abnormal (RV EF ≤ 45%). We therefore sought to identify the partition values of RV EF to stratify RV dysfunction in mildly, moderately, or severely reduced as we are used to do with the left ventricle.

Methods and results We used 3DE to measure RV EF in 412 consecutive patients (55 ± 18 years, 65% men) with various cardiac conditions who were followed for 3.7 ± 1.4 years to obtain the partition values which defined mild, moderate, and severe reduction of RV EF (derivation cohort). Then, the prognostic value of these partition values was tested in an independent population of 446 patients (67 ± 14 years, 58% men) (validation cohort). During follow-up, we recorded 59 cardiac deaths (14%) in the derivation cohort. Using K-Adaptive partitioning for survival data algorithm we identified four groups of patients with significantly different mortality according to RV EF: very low > 46%, 40.9% < low ≤ 46%, 32.1% < moderate ≤ 40.9%, and high ≤ 32.1%. To make the partition values easier to remember, we approximated them to 45%, 40%, and 30%. During 4.1 ± 1.2 year follow-up, 38 cardiac deaths and 88 major adverse cardiac events (MACE) (cardiac death, non-fatal myocardial infarction, ventricular fibrillation, or admission for heart failure) occurred in the validation cohort. The partition values of RV EF identified in the derivation cohort were able to stratify both the risk of cardiac death (log-rank = 100.1; $P < 0.0001$) and MACEs (log-rank = 117.6; $P < 0.0001$) in the validation cohort too.

Conclusion Our study confirms the independent prognostic value of RV EF in patients with heart diseases, and identifies the partition values of RV EF to stratify the risk of cardiac death and MACE.

Keywords right ventricle • right ventricular ejection fraction • cardiac death • MACE • outcome • 3D echocardiography

* Corresponding author. Tel: +39 02 619112890; Fax: +39 02 619112956. E-mail: lpbadano@gmail.com

Introduction

Right ventricular (RV) ejection fraction (EF) has been reported to have prognostic significance in many conditions, including heart failure,[1] ischaemic and non-ischaemic dilated cardiomyopathy,[2,3] RV myocardial infarction,[4] after coronary artery bypass,[5] pulmonary embolism,[6] pulmonary hypertension,[7] and non-ischaemic cardiomyopathy.[8] Despite the fact that most of the prognostic data about RV EF has been produced using cardiac magnetic resonance (CMR) and CMR is the reference imaging technique to assess RV EF, factors such as availability, costs, portability, time consumption, and contraindications hinder its routine use in every patient who can potentially benefit of RV EF quantitation.

Three-dimensional transthoracic echocardiography (3DE) has been reported to be feasible and accurate to measure RV EF,[9,10] and current guidelines recommend 3DE to assess RV volumes and EF by echocardiography.[11] Moreover, reference values for RV EF by 3DE have been published[12] and Nagata *et al.*[13] have recently shown that 3DE RV EF was predictive of cardiac death and major adverse cardiac events (MACE) in unselected patients with various cardiac conditions. However, previous studies which reported the predictive value of RV EF by 3DE used a dichotomous separation of patients with or without RV dysfunction, as the values for grading the severity of RV dysfunction by 3DE remain to be established.

Accordingly, this study has two specific aims. First, to identify prognostically significant partition values to grade RV systolic dysfunction by 3DE. Second, to validate the partition values identified in the derivation cohort by assessing their ability to predict cardiac death and MACE in an independent cohort of patients with various cardiac conditions.

Methods

Study population

Derivation cohort

To identify prognostically significant partition values to grade RV systolic dysfunction by 3DE, we prospectively analysed 650 retrospectively acquired echocardiographic studies performed from October 2010 to December 2012 at the echocardiography laboratory of the University of Padua. Exclusion criteria were: lack of 3DE acquisitions for RV quantitation, irregular atrial fibrillation preventing the acquisition of non-stitched 3DE data sets of the RV, repeat examinations, poor quality 3DE acquisitions, echocardiographic studies performed for non-clinical indications (driving or working licenses, sport activity screening, etc.), or lack of follow-up data. We finally selected a cohort of 412 patients (65% men; median age 58 years) with various heart diseases (*Figure 1*).

Validation cohort

To validate the partition values identified in the derivation cohort, we screened 842 patients who underwent 3DE at the echocardiographic laboratory of the University of Occupational and Environmental Health in Kitakyushu (Japan) from May 2008 to August 2010. The exclusion criteria included repeat examinations ($n = 161$), healthy volunteers ($n = 201$), aged <18 years ($n = 13$), and patients with poor image quality ($n = 21$). The final validation cohort included 446 patients (58% men, median age 66 years).[13]

Clinical characteristics of study patients, including hypertension, diabetes mellitus, hyperlipidaemia, chronic kidney disease (CKD), valvular heart disease, coronary artery disease, and cardiomyopathy, were evaluated at the time of echocardiography examination based on established criteria. CKD was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2.

The study protocol was approved by the Ethics Committee of the two Universities and the need for informed consent from study participants was waived.

Follow-up

Information concerning survival and adverse cardiac events were obtained at regular intervals via: (i) telephone interview with the patient, or if deceased, with family members; (ii) contact with the patient's physician(s); and (iii) review of electronic medical records of regular outpatient visits and hospital admission records. Mortality status was verified independently through the Social Security Death Index and death certificates. Cause of death was determined based on a review of death certificates, post-mortem exam reports when available, medical records for patients who died while hospitalized, and contact of patient's physician(s), and it was classified as cardiac or non-cardiac death. Assignment of clinical events was performed by physicians unaware of the patient RV EF values. The primary endpoint was cardiac death. The secondary endpoint was MACEs, including cardiac death, nonfatal myocardial infarction, ventricular fibrillation, and heart failure exacerbation requiring hospitalization.

Echocardiography

At the end of a clinically indicated echocardiographic study, 4- to 6-beat full-volume 3D data sets of the four cardiac chambers were obtained during breath-hold using either Vivid E9 (GE Vingmed Ultrasound, Horten, Norway), equipped with 4V probe (University of Padua, Italy), iE33 (Philips Medical Systems, Andover, MA, USA) equipped with X3 transducer (University of Occupational and Environmental Health, Kitakyushu, Japan) from the apical approach.[9,13] The multislice display was used during acquisition to ensure a complete inclusion of the RV in the data set (*Figure 2*). The 3D data sets were exported in DICOM format to a separate workstation equipped with a vendor-independent software packages (4D RV-Function 2.0, TomTec Imaging Systems GmbH, Unterschleissheim, Germany) to measure RV volumes and EF.

3D echocardiography data sets analysis

A detailed description of the quantitative analysis of the 3DE RV data sets performed independently at the two collaborating laboratories has been reported elsewhere.[9,13] Briefly, the image quality of 3D data sets was judged subjectively, considering the signal-to-noise ratio and the completeness of RV endocardium visualization and was categorized on a scale from 1 to 4 (from poor to excellent). Image quality was judged as poor if ultrasound dropout was present in more than one half of the RV free wall in the coronal view.[14]

The 4D RV-Function 2.0 software works in several steps. After having selected the transthoracic approach for the RV 3DE data set acquisition, the operator aligns the 3D data set by setting the left

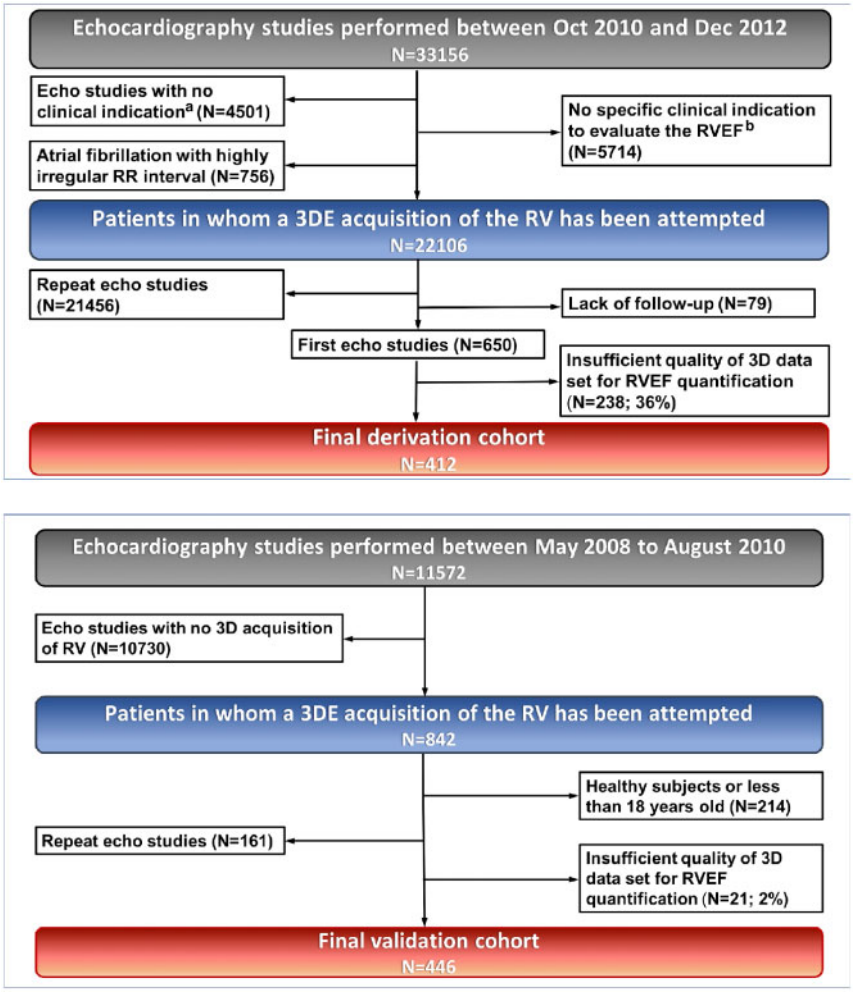


Figure 1 Derivation and validation study population flow charts. The total number of patients who underwent echocardiography at the two study sites is presented in the upper box. Patients in whom a 3DE data set of the right ventricle was not attempted were then excluded. The remaining patients in whom the acquisition of a 3DE data set of the right ventricle was attempted were 22 106 in the derivation cohort (*left panel*) and 842 in the validation cohort (*right panel*), respectively. After removal of patients with repeated echocardiography studies, those younger of 18 years and those lost to follow-up, the derivation and validation cohorts included 650 and 467 patients, respectively. Feasibility was 74% in the derivation cohort and 98% in the validation cohort resulting in a final derivation cohort of 412 patients and a final validation cohort of 446 patients. [a]Echocardiography studies performed to obtain driver or working licenses, to screen athletes, or routinely (i.e. with no cardiological indication) as a screening test before non-cardiac surgery. [b]Echocardiography studies performed in patients admitted to implant a pacemaker, to undergo electrophysiological procedures like ablation of atrial fibrillation or atrial flutter, or to undergo diagnostic coronary angiography with normal echocardiography study.

ventricular (LV) and the RV longitudinal axes in the reference end-diastolic frame (*Figure 3*, left panel, 4Ch (LV), 2Ch (LV), 4Ch (RV), and 2Ch (RV)). On the LV apical long-axis view, the operator sets the landmarks corresponding to the aortic annulus diameter (AV1–AV2, *Figure 3*, left panel, 3Ch (LV)), and on the RV short-axis view, the anterior (AJL) and posterior (PJL) junctions of the RV free wall with the interventricular septum, and the septum-to-RV free wall distance are set (*Figure 3*, left panel, SAX (basal)). The software algorithm analyses ultrasound backscatter intensities and adapts a static RV shape model to all the input data, which can be further optimized by the operator. Then, the RV contours are automatically tracked over the entire cardiac cycle using the speckle-tracking technology, and automated measurements of RV volumes and EF are provided. Manual editing of the automatic endocardial borders was systematically performed on both end-systolic and end-diastolic frames to include the trabecular part of the RV wall, papillary muscles, and moderator band within the RV cavity (*Figure 3*, right panel). RV volumes over time are computed from the dynamic surface model, and maximal and minimal volumes are used to calculate end-diastolic and end-systolic volumes, EF, and stroke volume.

The methodologies for the quantitative volumetric assessment of the LV and the left atrium have been reported elsewhere.[15,16] Patients whose LV EF was lower than 52% were identified as patients with LV dysfunction.[11]

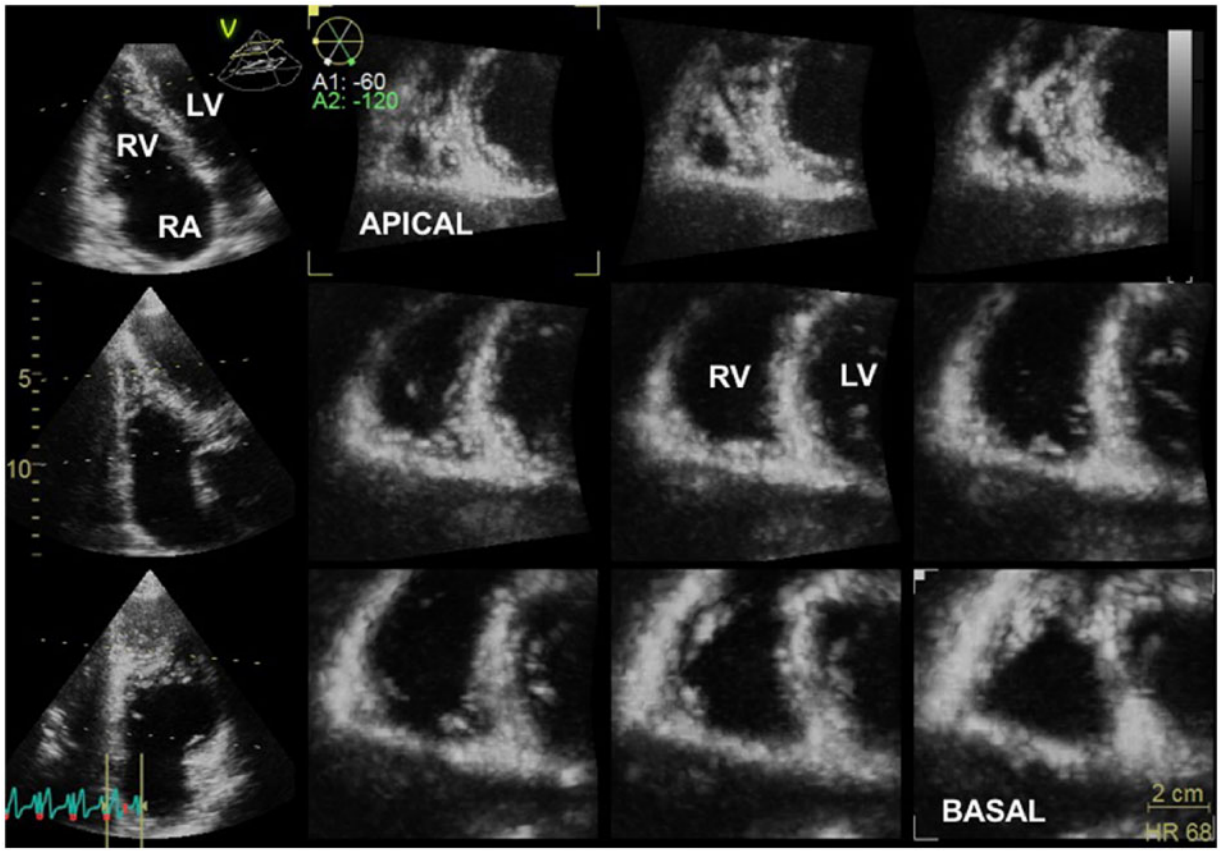


Figure 2 Multislice display used to acquire 3D echocardiography data sets of the right ventricle. The data set was acquired using a right ventricular (RV) focused four-chamber view (reference plane, left upper slice). Then the data set was sliced in two longitudinal planes at 60° and 120° from the reference plane (middle and lower left slices) and nine equidistant transversal planes. The position of the apical and basal slice can be controlled by translating and tilting the dotted lines on the longitudinal planes in order to obtain cut planes perpendicular to the RV length. LV, left ventricle; RA, right atrium; RV, right ventricle.

Statistical analysis

Descriptive statistics of data of the patients enrolled in the derivation and validation cohorts have been performed. Data were reported as median (25 percentile and 75 percentile) for continuous variables, and percentages (absolute numbers), for qualitative variables. Comparison between cohorts were made using Wilcoxon–Kruskal–Wallis test for continuous variables and Pearson χ^2 test for categorical ones.

To test the reproducibility in the measurement of RV volumes and EF, RV endocardial surface detection were repeated in 60 randomly selected patients (25 with atrial fibrillation and 27 with RV EF <45%) by the same observer and by a second independent observer, both blinded to all prior measurements. The inter- and intra-operator variability for RV volume and EF was computed as intraclass correlation (ICC) coefficients.

The pre-specified endpoint in the derivation cohort was cardiac death. Cumulative event rates were calculated according to the Kaplan–Meier method. Differences in event rates between patients with normal or abnormal RV EF[12] were assessed with the log-rank test. Using Cox proportional hazards regression analysis, a multivariable model was developed including the four predictors which were statistically significant at univariable analysis. Relative risks were expressed as hazard ratios (HRs) with associated 95% confidence interval. To test whether RV EF performs better than conventional echocardiography parameters of RV function [i.e. tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change[11]] we used the Harrel C statistics to compare the performance of multivariable models including RV EF, TAPSE, and RV fractional area change, respectively. A K-Adaptive Partitioning algorithm has been run on the derivation cohort to find the partition values to grade the severity of RV dysfunction. It is a multiway partitioning algorithm, which divides the data into K heterogeneous subgroups (in our case $K = 4$) based on the information from a prognostic factor. The resulting subgroups show significant differences in survival. Such a multiway partition was found by maximizing the minimum of the subgroup pairwise test statistics, using 100 bootstrap resampling and 100 permutations.

Kaplan–Meier survival analysis was used to plot cardiac death and MACEs occurred in the validation cohort according to the partition values obtained in the derivation cohort of patients. Differences

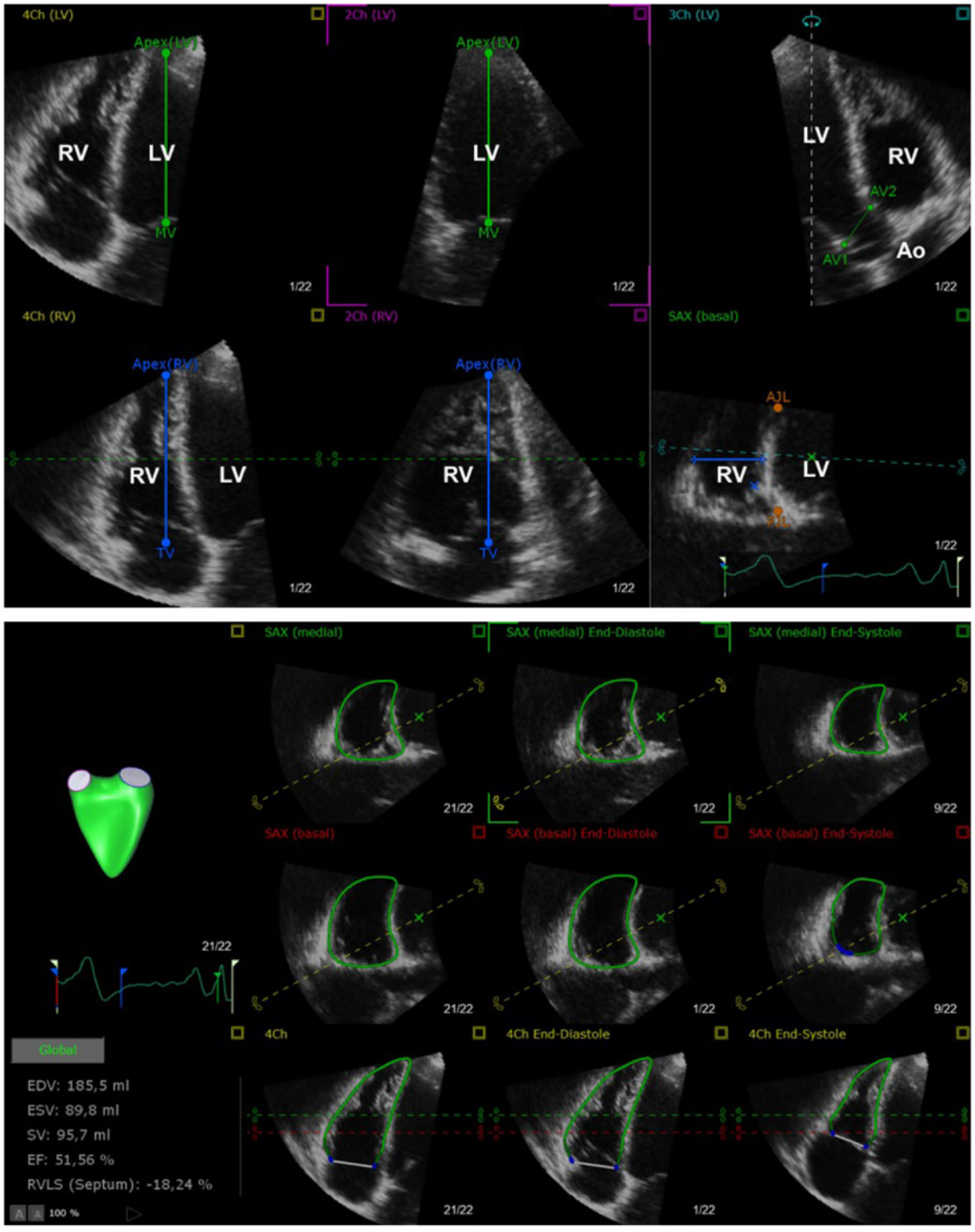


Figure 3 Measurement of right ventricular volumes and ejection fraction. (*Left panel*) Initialization of the 3D echocardiography data set of the right ventricle for the measurement of right ventricular volumes. See text for details. (*Right panel*) After the initialization of the data set a semiautomated endocardial border detection by the algorithm provides a first estimate of the beutel of the right ventricle on the left. The position of endocardial border traced by the algorithm is displayed on mid-cavity (SAX (medial)) and basal (SAX (basal) transversal cut planes, and four-chamber equivalent (4Ch) longitudinal cut plane, both at end-diastole and end-systole, for manual editing. Ao, aorta; AJL, anterior junction of the right ventricular free wall with the interventricular septum; AV, aortic valve; 2Ch, 2-chamber view-equivalent cut plane; 3CH, apical long-axis view-equivalent cut plane; 4Ch, 4-chamber view-equivalent cut plane; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricle; PJL, posterior junction of the right ventricular free wall with the interventricular septum; RV, right ventricle; RVLS, right ventricular longitudinal strain; SAX, short-axis view.

between survival curves were assessed by the log-rank test. Finally, to test if dividing patients into groups according to the severity of RV EF was more clinically meaningful than just separating them in normal or abnormal RV EF, we performed a multivariate analysis comparing HRs of mild, moderate and severe RV dysfunction to the referent group of patients with RV EF> 45%.

Statistical analysis was performed using R (version 3.3.1) and GraphPad Prism (version 7.0a). A *P*-value of <0.05 was considered statistically significant.

Results

We included 858 patients (412 in the derivation cohort and 446 in the validation cohort), whose demographic and clinical characteristics were summarized in *Table 1*. Follow-up duration was significantly shorter in the derivation than in the validation cohort (3.7 ± 1.4 years vs. 4.1 ± 1.2 years; $P < 0.0001$). During follow-up, we recorded 59 cardiac deaths (14%) in the derivation cohort, and 38 cardiac deaths (9%) and 88 MACEs in the validation cohort. Echocardiographic data about RV, LV, and left atrial size and function were summarized in *Table 2*.

Analysis of repeated measurements showed excellent reproducibility of RV volume measurements using 3DE. The ICC values for intra-operator and inter-operator variability of the RV end-diastolic and end-systolic volumes, and EF were 0.87, 0.94, 0.94, and 0.81, 0.84, and 0.89, respectively. The ICC values for RV end-diastolic and end-systolic volumes, and EF were similar in patients with both sinus rhythm and atrial fibrillation (0.89, 0.95, 0.95, and 0.87, 0.92, and 0.93, respectively), and in patients with RV EF both below and above 45% (0.87, 0.93, 0.95, and 0.88, 0.93, and 0.93, respectively).

Demographics and clinical characteristics of the derivation and validation cohorts

Patients enrolled in the validation cohort were older, more frequently women, had a smaller body size and higher systolic blood pressure than patients included in the derivation cohort (*Table 1*). Moreover, patients enrolled in the validation cohort had higher prevalence of systemic hypertension and diabetes than patients included in the derivation cohort. Conversely, both smoking and hypercholesterolaemia were more prevalent in the derivation cohort patients (*Table 1*). Except for coronary artery disease, which was more prevalent in the derivation than in the validation cohort, the prevalence of all other medical conditions were similar between the two cohorts (*Table 1*). Moderate/severe tricuspid regurgitation was detected in 5% of patients in the derivation cohort and 6% of patients in the validation cohort [*P* = not significant (NS)]. Moderate/severe aortic stenosis, mitral regurgitation, and mitral stenosis were detected in 9%, 4%, and 2% of patients in the derivation cohort, and 11%, 6%, and 2% of patients in the validation cohort (*P* = NS).

As expected by ethnical characteristics, the quality of 3DE RV data sets was better in the validation than in the derivation cohort (*Table 2*). Pulmonary systolic pressure was higher in the validation cohort than in the derivation cohort patients (*Table 2*). The RV was larger and the RV EF was lower in the derivation cohort than in the validation cohort patients (*Table 2*). Conversely, the LV was larger and the LV EF was lower in the validation cohort (*Table 2*). Prevalence of LV dysfunction (i.e. 3DE LV EF< 52%) in the derivation cohort was 44%: 100 patients (24%) had mild, 42 patients (10%) moderate, and 41 (10%) severe LV dysfunction. A strain value of -17% or higher was found in 36% of patients in the derivation cohort and 34% of those enrolled in validation cohort which might reflect subclinical LV dysfunction (i.e. peak LV global longitudinal strain >-17% and LV EF > 52%). Prevalence of patients with heart failure and preserved LV EF was similar in the derivation and validation cohorts (28% and 24%, respectively; $P = 0.743$).

Development of partition values to grade the severity of RV dysfunction

The prevalence of RV dysfunction (i.e. RV EF <45%) was similar in the patients included in the derivation ($n = 141$, 34%) and the validation ($n = 129$, 29%) cohorts ($\chi^2 = 2.78$; $P < 0.949$).

Kaplan–Meier analysis showed that patients with reduced RV EF (<45%) had significantly lower probability of survival than patients with RV EF≥ 45% (*Figure 4*).

Cox regression analysis of a model which included age, gender, blood pressure, New York Heart Association (NYHA) class, presence/absence of heart failure with preserved EF, RV volumes and EF, LV volumes and EF, systolic pulmonary artery pressure as covariates, selected age, NYHA class, systolic blood pressure, systolic pulmonary artery pressure, and RV EF as the only independent variables predicting death in the derivation population (*Table 3*, $\chi^2 = 101.51$; $P < 0.0001$). When we used the same Cox regression model to predict MACE instead of death, LV EF was selected in addition to age, NYHA class, systolic blood pressure, systolic pulmonary pressure, and RV EF (*Table 4*, $\chi^2 = 108.37$; $P < 0.0001$). The multivariable model including age, NYHA class, systolic blood pressure, and systolic pulmonary artery pressure as baseline covariates and RV EF categorized in mild, moderate, and severe dysfunction performed better in predicting mortality (Harrel C statistics = 0.85), than the ones using TAPSE (Harrel C statistics = 0.81), or RV fractional area change (Harrel C statistics = 0.81) as measures of RV function ($P = 0.01$ for all).

Independent validation of the partition values to grade the severity of RV dysfunction

Using a multiway partitioning algorithm to divide the derivation cohort into four subgroups based on death incidence, we found that partition values of RV EF equal to 46%, 40.9%, and 32.1% divided our validation cohort in four subgroups with significant difference in survival (*Table 5*). The corresponding partition values of RV EF for MACEs were 46.4%, 40.3%, and 31.7%. To make the partition values easier to remember, we approximated them to 45%, 40%, and 30%. Accordingly, we identified four subgroups of patients with very low risk for mortality (RV EF > 45%), low risk (40% < RV EF ≤ 45%), moderate risk (30% < RV EF ≤ 40%), and high risk (RV EF ≤ 30%) during follow-up.

As expected, the prevalence of patients with LV dysfunction increased by worsening RV EF (*Table 6*). However, the prevalence of patients with LV dysfunction across the various grades of RV

Table 1 Demographic and clinical characteristics of the derivation and validation cohorts

	Derivation cohort ($n = 412$)	Validation cohort ($n = 446$)	*P*-value
Age (years)	58 (43–70)	69 (60–79)	<0.001
Male gender (%)	65	58	0.036
Body surface area (m^2)	1.81 (1.67–1.94)	1.59 (1.5–1.65)	<0.001
Body mass index (kg/m^2)	24.5 (22.1–26.8)	21.5 (19.3–23.5)	<0.001
Heart rate (bpm)	67 (61–74)	65 (60–72)	0.615
Systolic blood pressure (mmHg)	120 (110–135)	139 (119–155)	<0.001
Diastolic blood pressure (mmHg)	70 (70–80)	75 (64–85)	0.602
Cardiovascular risk factors			
Hypertension (%)	49	67	<0.001
Smoking (%)	69	50	<0.001
Diabetes (%)	13	32	<0.001
Hypercholesterolaemia (%)	36	29	0.025
Medical history			
Coronary artery disease (%)	30	43	<0.001
Heart valve disease (%)	22	22	0.991
Dilated cardiomyopathy (%)	11	10	0.783
Hypertrophic cardiomyopathy (%)	7	5	0.452
Pulmonary artery hypertension (%)	4	2	0.754
Congenital heart diseases (%)	12	10	0.512
Others (%)	14	8	0.094

Table 2 Three-dimensional echocardiography

	Derivation cohort ($n = 412$)	Validation cohort ($n = 446$)	*P*-value
3DE RV image quality			0.0054
Poor	0	0	
Fair	56 (14%)	41 (9%)	
Good	304 (74%)	312 (70%)	
Excellent	52 (12%)	93 (21%)	
RV end-diastolic volume (mL/m^2)	82 (68–100)	59 (49–71)	<0.001
RV end-systolic volume (mL/m^2)	42 (33–55)	28 (22–38)	<0.001
RV stroke volume (mL/m^2)	37 (31–46)	29 (25–35)	<0.001
RV ejection fraction (%)	48 (42–52)	52 (43–57)	<0.001
TAPSE (mm)	21 (11–29)	24 (18–26)	<0.001
RV fractional area change (%)	40 (17–53)	45 (19–50)	<0.001
RV free wall strain (%)	-25 (16–34)	-28 (19–35)	<0.001
Systolic pulmonary pressure (mmHg)	29 (22–39)	33 (26–39)	0.047
LV end-diastolic volume (mL/m^2)	68 (56–83)	76 (61–99)	0.918
LV end-systolic volume (mL/m^2)	29 (22–45)	36 (26–55)	0.073
LV stroke volume (mL/m^2)	38 (32–45)	36 (30–43)	0.012
LV ejection fraction (%)	55 (44–62)	51 (40–58)	<0.001
LV global longitudinal strain (%)	-14 (-17 to -10)	-14 (-16 to -10)	0.294
LV global circumferential strain (%)	-14 (-18 to -10)	-25 (-29 to -18)	<0.001
Maximal left atrial volume (mL/m^2)	40 (32–55)	41 (29–56)	<0.001

LV, left ventricular; RV, right ventricular.

dysfunction was similar in the derivation and the validation cohorts (*Table 6*, $\chi^2 = 0.8815$; $P = 0.83$).

During a median of 4.1-year follow-up, 38 cardiac deaths and 88 MACEs occurred in the validation cohort. The partition values of RV EF identified in the derivation cohort were able to stratify the risk of all-cause death (log-rank = 32.93), cardiac death (log-rank = 100.1; $P < 0.0001$), and MACEs (log-rank = 117.6; $P < 0.0001$) in the validation cohort, too (*Figure 5*).

When compared with the reference group of patients with RV EF >45%, patients with mild, moderate, and severe RV dysfunction showed progressive worsening of HRs, both at univariate (HR = 1.722, $P = 0.42$; HR = 8.941; $P < 0.0001$; and HR = 17.681, $P < 0.0001$, respectively) and at multivariate analysis including age, systolic blood pressure, and systolic pulmonary artery pressure as baseline covariates (HR = 1.746, $P = 0.41$; HR = 6.122; $P < 0.0001$; and HR = 13.816, $P < 0.0001$, respectively).

In patients with RV EF< 41%, age and RV EF were the only independent predictors of cardiac death at Cox regression analysis. Conversely, in the same patients, LV EF and age were the independent predictors of MACE.

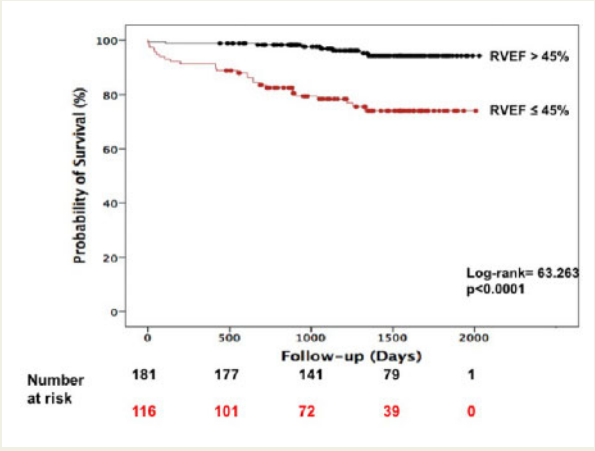


Figure 4 Right ventricular ejection fraction and survival. Kaplan–Meier estimates of survival to cardiac death according to right ventricular ejection fraction in the derivation cohort of patients.

Discussion

To the best of our knowledge, this is the first study reporting the partition values of RV EF obtained with 3DE to stratify RV dysfunction in mild, moderate, or severe based on the associated cardiac mortality risk and occurrence of MACEs. The results of our study can be summarized as: (i) in unselected patients with various cardiac diseases, RV EF confirms to be a strong and independent predictor of cardiac mortality; (ii) RV EF demonstrated higher predictive value for cardiac death and MACE than conventional parameters of RV systolic function (e.g. TAPSE and fractional area change); (iii) RV EF partition values of 45%, 40%, and 30% identify subgroups of patients with incremental and significant differences in all-cause mortality, cardiac mortality, and occurrence of MACEs.

For many years, RV function was largely neglected in the prognostic stratification of patients with cardiac diseases other than congenital heart diseases. However, in the last two decades several studies have reported that RV dysfunction may occur in many cardiac conditions affecting both the right and the left heart, and its presence is a strong and independent predictor of increased morbidity and mortality.[1–8,17,18] One of the reasons why the clinical importance of RV function has been underestimated resides in the difficulty to obtain an accurate quantitative measurement of RV size and function. RV crescentic shape and complex geometry, with inflow and outflow portions in different planes, hindered the use of any tomographic imaging modality, like 2D echocardiography, to obtain reliable measurements, and thus, geometric assumptions were required to calculate RV

Table 3 Predictors of cardiac mortality in the derivation cohort

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	1.05 (1.026–1.075)	<0.0001	1.042 (1.022–1.063)	<0.0001
Male	2.209 (0.82–5.95)	0.117		
Body mass index (kg/m^2)	1.022 (0.925–1.139	0.668		
Systolic blood pressure (mmHg)	0.979 (0.958–1.001)	0.067	0.98 (0.961–1.0)	0.056
RV EDV index (mL/m^2)	1.037 (0.99–1.087)	0.124		
RV ESV index (mL/m^2)	0.957 (0.896–1.023)	0.195		
RV EF (%)	0.896 (0.796–0.949)	0.002	0.915 (0.887–0.944)	<0.0001
RV basal diameter (mm)	0.987 (0.92–1.058)	0.711		
SPAP (mmHg)	1.017 (1.0–1.035)	0.049	1.016 (1.004–1.029)	0.008
LV EDV (mL/m^2)	0.983 (0.94–1028)	0.451		
LV ESV (mL/m^2)	1.031 (0.973–1.091)	0.305		
LV EF (%)	1.047 (0.991–1.1069	0.103		

EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; FAC, fractional area change; LV, left ventricular; RV, right ventricular; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

Table 4 Predictors of major adverse cardiac events (MACE, see text) in the derivation cohort

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	1.15 (1.081–1.213)	<0.0001	1.161 (1.09–1.215)	<0.0001
Male	2.239 (0.89–5.98)	0.127		
Body mass index (kg/m^2)	1.022 (0.925–1.139	0.668		
Systolic blood pressure (mmHg)	0.962 (0.934–0.98)	0.037	0.97 (0.935–0.981)	0.041
RV EDV index (mL/m^2)	1.037 (0.99–1.087)	0.124		
RV ESV index (mL/m^2)	0.957 (0.896–1.023)	0.195		
RV EF (%)	0.912 (0.812–0.961)	0.002	0.913 (0.874–0.93)	<0.0001
RV basal diameter (mm)	0.987 (0.92–1.058)	0.711		
SPAP (mmHg)	1.019 (1.014–1.032)	0.032	1.021 (1.014–1.029)	0.001
LV EDV (mL/m^2)	0.983 (0.94–1.028)	0.451		
LV ESV (mL/m^2)	1.031 (0.973–1.091)	0.305		
LV EF (%)	0.931 (0.813–0.967	0.012	0.94 (0.815–0.963)	0.0021

EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; FAC, fractional area change; LV, left ventricular; RV, right ventricular; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

Table 5 Pairwise comparison of survival in the four subgroups of patients identified using the K-adaptive partitioning algorithm from the derivation cohort

	12.9% ≤ RV EF ≤ 32.1%	32.1% < RV EF ≤ 40.9%	40.9% < RV EF ≤ 46%
32.1% < RV EF ≤ 40.9%	0.0187		
40.9% < RV EF ≤ 46%	<0.0001	0.013	
46% ≤ RV EF ≤ 65.7%	<0.0001	<0.0001	0.0187

EF, ejection fraction; RV, right ventricular.

Table 6 Incidence of patients with left ventricular dysfunction (i.e. left ventricular ejection fraction <52%) according to the different grades of right ventricular dysfuncton

RV ejection fraction	Derivation cohort LV EF <52% (*n* = 183)	Validation cohort LV EF <52% (*n* = 183)
RV EF > 45%	99/273 (36%)	95/268 (35%)
40% < RV EF ≤ 45%	31/52 (60%)	35/75 (47%)
30% < RV EF ≤ 40%	26/57 (46%)	28/72 (39%)
RV EF ≤ 30%	27/32 (84%)	25/31 (81%)

EF, ejection fraction; LV, left ventricular; RV, right ventricular.

volumes. Therefore, it is clear that only an imaging technique which does not rely on geometric assumptions about the shape of the cardiac chamber and takes into account all the components of its pump function can provide accurate assessment of RV geometry and function. Thus, CMR has become the reference imaging modality for RV assessment.[19] However, CMR is quite expensive, time-consuming and of limited availability hindering its routine use in every patient who can potentially benefit from the assessment of RV function.

One possibility to overcome the technical limitations of 2D echocardiography and the limited availability of CMR, is 3DE. Transthoracic 3DE has the advantage of volumetric acquisition of the entire RV, which may overcome the technical and clinical limitations of 2D transthoracic echocardiography.[19,20] The accuracy of transthoracic 3DE-determined RV volumes and RV EF has been validated against CMR in many studies[14,21,22] that consistently showed a slight underestimation of RV volumes by 3DE, but very similar values of RV EF between the two imaging modalities. The reference values of RV volumes and RV EF have been obtained from healthy subjects[12] and, recently, a simpler and more user-friendly software package has been released to measure RV volumes and EF using transthoracic 3DE.[9,10] Finally, current guidelines recommend 3DE to measure RV volumes and EF in laboratories with appropriate 3D platforms and experience.[11]

Availability of accurate imaging modalities to measure RV size and function have prompted researchers to assess its prognostic value showing that RV dysfunction is a powerful and independent predictor of increased morbidity and mortality.[1–8,17,18] Moreover, Surkova *et al.*[23] reported that, in patients undergoing clinically indicated echocardiography, both all-cause mortality and cardiac death in patients with reduced RV EF and normal LV EF were significantly higher than in those with reduced LV EF and normal RV EF ($P = 0.0007$ and $P = 0.0091$, respectively) and they did not differ significantly from patients with reduced EF of both ventricles ($P = 0.2198$ and $P = 0.0846$, respectively). Therefore, it can be hypothesized that due to the accumulating amount of evidences about the prognostic value of RV EF, and the availability of user-friendly software packages that allow either semiautomatic or fully-automated quantitation of 3DE data sets of the RV, measurement of RV EF will progressively become routine (as it is current practice for the LV EF) in the echocardiography laboratory.

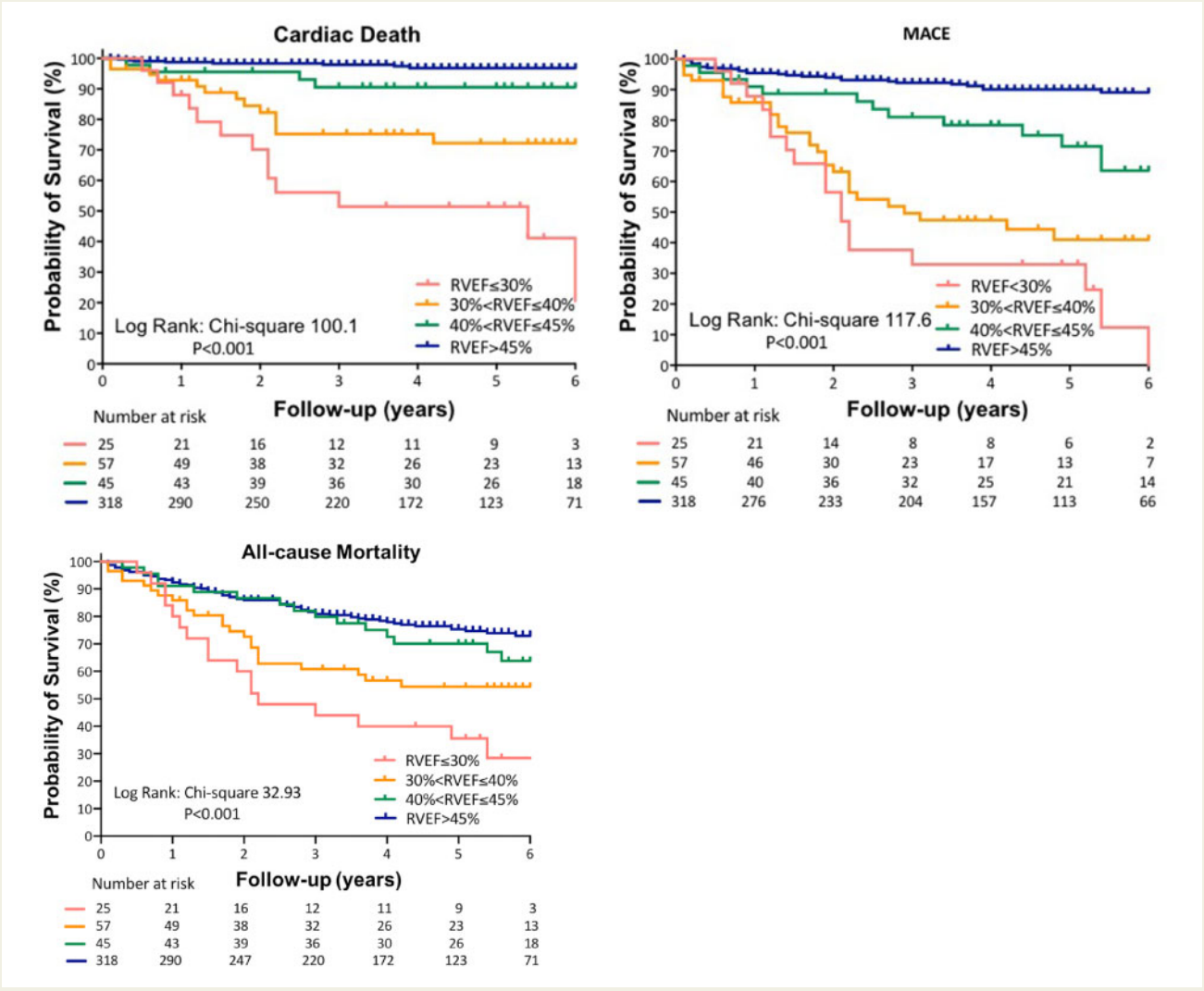


Figure 5 Prognostic validation of partition values to grade right ventricular dysfunction severity. Kaplan–Meier estimates of survival to cardiac death (*right panel*), freedom from MACE (*left panel*), and survival to all-cause mortality (*lower panel*) in the validation cohort using the new partition values to grade the severity of right ventricular dysfunction.

However, RV function has been graded as normal or abnormal, according to RV EF values above or below/equal 45% using both 3DE and CMR,[12,24] without being able to grade the severity of RV dysfunction in order to stratify patient prognosis and tailor treatment, as we are used to do with the LV.[11] Recently, Pueschner *et al.*[8] reported that patients with non-ischaemic cardiomyopathy and RV EF < 35% had significantly higher cardiac mortality than patients with RV EF ≥ 35%. However, their study was not designed to identify partition values to grade RV dysfunction, the accuracy of the selected cut-off value of RV EF was not tested in any validation cohorts of patients and they studied a quite homogeneous cohort of patients with non-ischaemic cardiomyopathy.

Our study is the first specifically designed to identify partition values of RV EF to grade the severity of RV dysfunction in mild, moderate, and severe, based on the associated cardiac mortality risk and occurrence of MACEs in the general population of patients referred for a clinically indicated echocardiographic study. Also, our study validates the partition values identified in an independent population of patients studied by other researchers who used different echocardiographic systems, but the same software package, to measure RV volumes and calculate RV EF by 3DE.[13] The partition values of RV EF that identified subgroups of patients of the derivation cohort with significantly different mortality during follow-up are easy to remember (45%, 40%, and 30%), are consistent with the reference values found in healthy subjects (in whom the lower limit of normality of RV EF was 45%[12,24]) and confirmed their prognostic value in the validation cohort. The latter is even more remarkable since the clinical characteristics of the derivation and validation cohorts were quite different.

Since we know the strong and independent prognostic value of RV EF in many cardiac conditions, the availability of a robust grading of RV dysfunction severity may prompt researchers and clinicians to design specific trials to identify the most effective medical or

device interventions to improve patient prognosis according to the severity of RV functional impairment, as we are used to do for the LV.

Study limitations

The main limitation of this study is the fact that we selected only patients who had a 3DE data set of the RV acquired during their routine echocardiographic studies performed in laboratories with experience in 3DE. This may have created a selection bias in our patients and the results of this study remain to be confirmed in a properly designed multicentre prospective study. Unfortunately, feasibility of 3DE is limited by the patient's acoustic window and the echocardiographer's expertise. Generally, the feasibility of acquiring good enough quality 3DE data sets of the RV in the real world is lower than that of LV (depending on the experience of the operator it may be 75% or less). However, since RV EF value measured in the same patient with 3DE and CMR are very close, a multimodality imaging study could be designed and CMR could be used in patients with suboptimal quality of 3DE data sets of the RV.

Another issue in measuring RV EF is the difficulty to manually trace the endocardium in a very trabeculated cardiac chamber like the RV. However, the advent of artificial intelligence and identification of endocardial borders by pattern recognition techniques may contribute to develop fully automated algorithms to measure RV volumes and EF.

In our study, we sought to identify and validate prognostically significant partition values to grade RV systolic dysfunction by 3DE in the general population of patients undergoing clinically indicated echocardiography. However, it is likely that the prognosis of patients with certain cardiac conditions may be more affected by RV dysfunction than others (e.g. pulmonary hypertension, mitral valve diseases etc.). Unfortunately, our study was not powered to analyse the prognostic value of different degrees of RV dysfunction according to the underlying cardiac condition.

Conclusions

Our results show that 3DE RV EF is a powerful, and incremental risk factor for cardiac mortality and MACEs even in unselected patients undergoing clinically indicated echocardiographic studies. Moreover, we have developed and validated the partition values of RV EF to stratify the severity of RV dysfunction in mild, moderate, and severe. Our findings may be used to design specific trials to identify the most effective medical or device interventions to improve patient prognosis according to the severity of RV functional impairment, as we are used to do for the LV.

Conflict of interest: D.M. has received equipment and research funding from GE Vingmed and equipment grants from TomTec Imaging Systems; L.P.B. has received equipment grants from GE Healthcare and TomTec Imaging systems and is on the Speakers' Bureau of GE Vingmed and Philips Medical Systems; M.T. has received equipment grants from TomTec Imaging Systems. All other authors have declared no conflict of interest.

References

1. Aschauer S, Kammerlander AA, Zotter-Tufaro C, Ristl R, Pfaffenberger S, Bachmann A *et al*. The right heart in heart failure with preserved ejection fraction: insights from cardiac magnetic resonance imaging and invasive haemodynamics. *Eur J Heart Fail* 2016;**18**:71–80.
2. Gulati A, Ismail TF, Jabbour A, Alpendurada F, Guha K, Ismail NA *et al*. The prevalence and prognostic significance of right ventricular systolic dysfunction in nonischemic dilated cardiomyopathy. *Circulation* 2013;**128**:1623–33.
3. Sabe MA, Sabe SA, Kusunose K, Flamm SD, Griffin BP, Kwon DH. Predictors and prognostic significance of right ventricular ejection fraction in patients with ischemic cardiomyopathy. *Circulation* 2016;**134**:656–65.
4. Miszalski-Jamka T, Klimeczek P, Tomala M, Krupiński M, Zawadowski G, Noelting J *et al*. Extent of RV dysfunction and myocardial infarction assessed by CMR are independent outcome predictors early after STEMI treated with primary angioplasty. *JACC Cardiovasc Imaging* 2010;**3**:1237–46.
5. Pouleur AC, Rousseau MF, Ahn SA, Amzulescu M, Demeure F, de Meester C *et al*. Right ventricular systolic dysfunction assessed by cardiac magnetic resonance is a strong predictor of cardiovascular death after coronary bypass grafting. *Ann Thorac Surg* 2016;**101**:2176–84.
6. Vitarelli A, Barilla F, Capotosto L, D'Angeli I, Truscelli G, De Maio M *et al*. Right ventricular function in acute pulmonary embolism: a combined assessment by three-dimensional and speckle-tracking echocardiography. *J Am Soc Echocardiogr* 2014;**27**:329–38.
7. Baggen VJ, Leiner T, Post MC, van Dijk AP, Roos-Hesselink JW, Boersma E *et al*. Cardiac magnetic resonance findings predicting mortality in patients with pulmonary arterial hypertension: a systematic review and meta-analysis. *Eur Radiol* 2016;**26**:3771–80.
8. Pueschner A, Chattranukulchai P, Heitner JF, Shah DJ, Hayes B, Rehwald W *et al*. The prevalence, correlates, and impact on cardiac mortality of right ventricular dysfunction in nonischemic cardiomyopathy. *JACC Cardiovasc Imaging* 2017;**10**(10 Pt B):1225–36.
9. Muraru D, Spadotto V, Cecchetto A, Romeo G, Aruta P, Ermacora D *et al*. New speckle-tracking algorithm for right ventricular volume analysis from three-dimensional echocardiographic data sets: validation with cardiac magnetic resonance and comparison with the previous analysis tool. *Eur Heart J Cardiovasc Imaging* 2016;**17**:1279–89.
10. Medvedofsky D, Addetia K, Patel AR, Sedlmeier A, Baumann R, Mor-Avi V *et al*. Novel approach to three-dimensional echocardiographic quantification of right ventricular volumes and function from focused views. *J Am Soc Echocardiogr* 2015;**28**:1222–31.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–70.
12. Maffessanti F, Muraru D, Esposito R, Gripari P, Ermacora D, Santoro C *et al*. Age-, body size-, and sex-specific reference values for right ventricular volumes and ejection fraction by three-dimensional echocardiography: a multicenter echocardiographic study in 507 healthy volunteers. *Circ Cardiovasc Imaging* 2013;**6**:700–10.
13. Nagata Y, Wu VC, Kado Y, Otani K, Lin FC, Otsuji Y *et al*. Prognostic value of right ventricular ejection fraction assessed by transthoracic 3D echocardiography. *Circ Cardiovasc Imaging* 2017;**10**;doi 10.1161/CIRCIMAGING.116.005384.
14. Sugeng L, Mor-Avi V, Weinert L, Niel J, Ebner C, Steringer-Mascherbauer R *et al*. Multimodality comparison of quantitative volumetric analysis of the right ventricle. *JACC Cardiovasc Imaging* 2010;**3**:10–8.
15. Muraru D, Badano LP, Peluso D, Dal Bianco L, Casablanca S, Kocabay G *et al*. Comprehensive analysis of left ventricular geometry and function by three-dimensional echocardiography in healthy adults. *J Am Soc Echocardiogr* 2013;**26**:618–28.
16. Badano LP, Miglioranza MH, Mihăilă S, Peluso D, Xhaxho J, Marra MP *et al*. Left atrial volumes and function by three-dimensional echocardiography: reference values, accuracy, reproducibility, and comparison with two-dimensional echocardiographic measurements. *Circ Cardiovasc Imaging* 2016;**9**:e004229.
17. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R *et al*. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol* 2001;**37**:183–8.
18. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS *et al*. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the

Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:16–37.
19. Surkova E, Muraru D, Iliceto S, Badano LP. The use of multimodality cardiovascular imaging to assess right ventricular size and function. *Int J Cardiol* 2016;**214**: 54–69.
20. Addetia K, Muraru D, Badano LP, Lang RM. New directions in right ventricular assessment using 3-dimensional echocardiography. *JAMA Cardiol* 2019;doi: 10.1001/jamacardio.2019.2424.
21. Shimada YJ, Shiota M, Siegel RJ, Shiota T. Accuracy of right ventricular volumes and function determined by three-dimensional echocardiography in comparison with magnetic resonance imaging: a meta-analysis study. *J Am Soc Echocardiogr* 2010;**23**:943–53.
22. Grapsa J, O'Regan DP, Pavlopoulos H, Durighel G, Dawson D, Nihoyannopoulos P. Right ventricular remodelling in pulmonary arterial hypertension with three-dimensional echocardiography: comparison with cardiac magnetic resonance imaging. *Eur J Echocardiogr* 2010;**11**:64–73.
23. Surkova E, Muraru D, Genovese D, Aruta P, Palermo C, Badano LP. Relative prognostic importance of left and right ventricular ejection fraction in patients with cardiac diseases. *J Am Soc Echocardiogr* 2019;**32**:doi: 10.1016/j.echo.2019.06.009.
24. Kawut SM, Lima JA, Barr RG, Chahal H, Jain A, Tandri H *et al.* Sex and race differences in right ventricular structure and function: the multi-ethnic study of atherosclerosis-right ventricle study. *Circulation* 2011;**123**: 2542–51.

IMAGE FOCUS

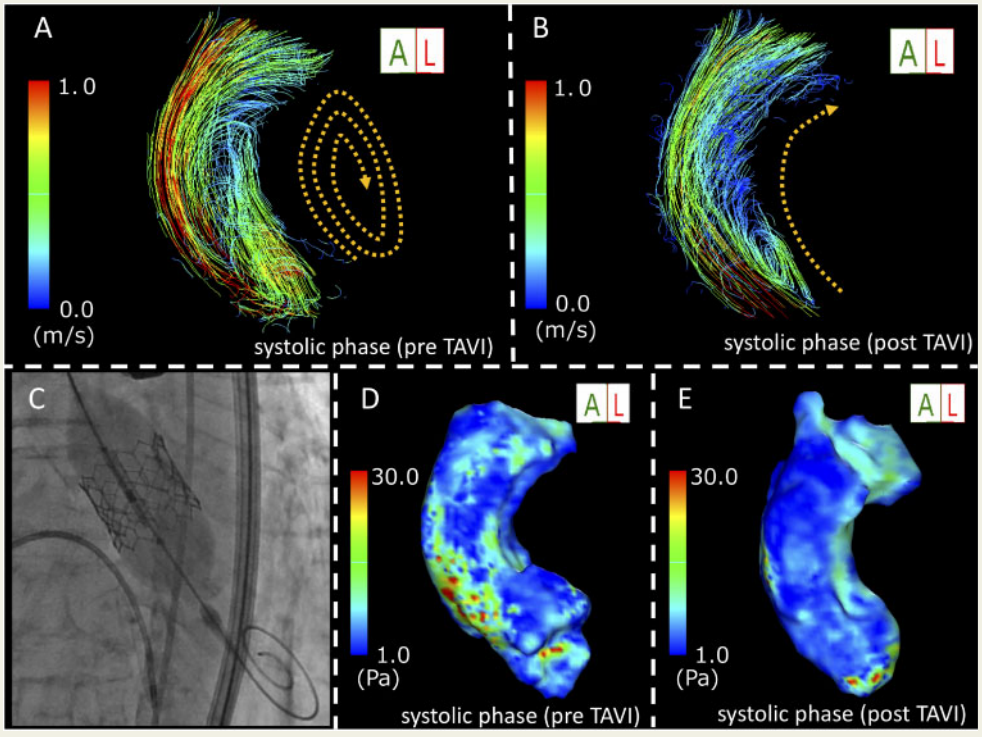
doi:10.1093/ehjci/jez192
Online publish-ahead-of-print 20 July 2019

Four-dimensional flow magnetic resonance imaging visualizes significant changes in flow pattern and wall shear stress in the ascending aorta after transcatheter aortic valve implantation in a patient with severe aortic stenosis

Hirokazu Komoriyama[1], Satonori Tsuneta[2], Noriko Oyama-Manabe[2]*, Kiwamu Kamiya[1], and Toshiyuki Nagai[1]

[1]Department of Cardiovascular Medicine, Hokkaido University Hospital, Kita14, Nishi5, Kita-ku, Sapporo, Hokkaido 0608648, Japan; and [2]Department of Diagnostic and Interventional Radiology, Hokkaido University Hospital, Kita14, Nishi5, Kita-ku, Sapporo, Hokkaido 0608648, Japan

* Corresponding author. Tel: +81 (11) 706 7779; Fax: +81 (11) 706 7408. E-mail: norikooyama@med.hokudai.ac.jp



A female in her 70 s with a contemporary history of severe aortic stenosis (AS) was admitted to our hospital because of oedema and dyspnoea. Echocardiography revealed a markedly calcified tricuspid aortic valve with a transvalvular peak velocity of 4.9 m/s, mean gradient of 48 mmHg, and valve area of 0.80 cm^2. Time-resolved 3D-phase contrast (4D flow) magnetic resonance imaging (MRI) demonstrated a substantial vortex flow (dotted line and curved arrow) with an eccentric accelerated jet flow (red line) in the ascending aorta without the aortic root dilatation during systole (*Panel A* and Supplementary data online, *Movie S1*). She underwent transcatheter aortic valve implantation (TAVI) (*Panel C*) with no severe intraoperative complications. After TAVI, the vortex flow in the ascending aorta was diminished on 4D flow MRI (*Panel B*). In addition, the regional wall shear stress at the ascending aorta was significantly decreased from 19.8 (red colour) to 4.0 Pa (blue colour) after TAVI (*Panels D* and *E*). To the best of our knowledge, this is the first report of visualization of ascending aorta flow changes on 4D flow MRI in a patient with severe AS after successful TAVI.

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.