

ORIGINAL ARTICLE



Added predictive value of right ventricular ejection fraction compared with conventional echocardiographic measurements in patients who underwent diverse cardiovascular procedures

MÁTÉ TOLVAJ¹, MÁRTON TOKODI¹,
BÁLINT KÁROLY LAKATOS¹, ALEXANDRA FÁBIÁN¹,
ADRIENN UJVÁRI¹, FJOLLA ZHUBI BAKIJA^{1,2},
ZSUZSANNA LADÁNYI¹, ZSÓFIA TARCZA¹,
BÉLA MERKELY¹ and ATTILA KOVÁCS^{1*} 

¹ Heart and Vascular Center, Semmelweis University, Budapest, Hungary

² Clinic of Cardiology, University and Clinical Center of Kosovo, Prishtina, Kosovo

Received: May 20, 2021 • Accepted: June 7, 2021

ABSTRACT

Background and aim: Right ventricular (RV) ejection fraction (EF) assessed by 3D echocardiography is a powerful measure to detect RV dysfunction. However, its prognostic value in routine clinical practice has been scarcely explored. Accordingly, we aimed at investigating whether RVEF is associated with 2-year all-cause mortality in patients who underwent diverse cardiovascular procedures and to test whether RVEF can overcome conventional echocardiographic parameters in terms of outcome prediction.

Patients and methods: One hundred and seventy-four patients were retrospectively identified who underwent clinically indicated transthoracic echocardiography comprising 3D acquisitions. The patient population consisted of heart failure with reduced ejection fraction patients (44%), heart transplanted patients (16%), and severe valvular heart disease patients (39%). Beyond conventional echocardiographic measurements, RVEF was quantified by 3D echocardiography. The primary endpoint of our study was all-cause mortality at two years.

Results: Twenty-four patients (14%) met the primary endpoint. Patients with adverse outcomes had significantly lower RVEF (alive vs. dead; 48 ± 9 vs. $42 \pm 9\%$, $P < 0.01$). However, tricuspid annular plane systolic excursion (21 ± 7 vs. 18 ± 4 mm), and RV systolic pressure (36 ± 15 vs. 39 ± 15 mmHg) were similar. By Cox analysis, RVEF was found to be associated with adverse outcomes (HR [95% CI]: 0.945 [0.908–0.984], $P < 0.01$). By receiver-operator characteristic analysis, RVEF exhibited the highest AUC value compared with the other RV functional measures (0.679; 95% CI: 0.566–0.791).

Conclusions: Conventional echocardiographic measurements may be inadequate to support a granular risk stratification in patients who underwent different cardiac procedures. RVEF may be a robust clinical parameter, which is significantly associated with adverse outcomes.

IMAGING 13 (2021) 2, 130–137
DOI: [10.1556/1647.2021.00049](https://doi.org/10.1556/1647.2021.00049)

© 2021 The Author(s)

*Corresponding author. Heart and Vascular Center, Semmelweis University, Városmajor str. 68, Budapest, H-1122, Hungary. Tel.: +36 206663427.
E-mail: attila.kovacs@med.semmelweis-univ.hu

KEYWORDS

3D echocardiography, right ventricle, ejection fraction, mortality

Introduction

The quantification of ventricular performance is a cornerstone of echocardiographic examinations of nearly every indication. The most widely measured parameter of the systolic

function is ejection fraction (EF): robust evidence supports its usefulness because it correlates with clinical signs and symptoms and has established diagnostic and prognostic power in various cardiac diseases [1].

Recently, right ventricular (RV) EF gained particular scientific attention as RVEF seems to have an independent, added prognostic value on top of left ventricular (LV) EF quantification [2]. However, RVEF can be measured only by three-dimensional (3D) imaging methods; there is no appropriate and clinically applied two-dimensional (2D) method that can accurately estimate RV volumes.

Technological advancements in transducer and software technologies allowed RV volume and EF measurement using 3D echocardiography (3DE) with good feasibility and close correlation with gold standard cardiac magnetic resonance imaging [3]. Thus, certain, dominantly tertiary cardiology departments started to apply 3DE-derived RV quantification in their daily routine to harvest its strong potential in pre-operative risk stratification, procedure planning, disease management, and long-term outcome prediction [4].

The aims of our current study were (1) to explore whether RVEF is associated with 2-year all-cause mortality in an aggregate population of patients who underwent diverse cardiovascular procedures in a tertiary care center and (2) to test whether it can overcome conventional echocardiographic parameters in terms of outcome prediction.

Patients and methods

Study design and population

Clinically, hemodynamically stable patients who underwent clinically indicated transthoracic echocardiography at the Semmelweis University Heart and Vascular Center between May 2015 and May 2019 were retrospectively identified. Inclusion criteria were: (1) 18 years of age or older; (2) established left-sided cardiac disease with previous or planned cardiac intervention or surgery with any value of LV and RVEF; (3) 3D images obtained suitable for 3D LV and RV quantification; (4) availability of 2-year follow-up data. Exclusion criteria were: (1) primary RV diseases (primary pulmonary hypertension, arrhythmogenic cardiomyopathy, congenital heart diseases affecting the right heart); (2) acute cardiovascular conditions (acute coronary syndrome, myocarditis, pulmonary embolism, etc.); (3) inadequate echocardiographic image quality. Clinical characteristics, such as demographics, medical history, physical status and vitals, and laboratory parameters were extracted retrospectively from electronic medical records. Our retrospective study is in accordance with the Declaration of Helsinki and was approved by the Regional and Institutional Committee of Science and Research Ethics.

Echocardiographic data acquisition and analysis

Echocardiographic images were acquired using either a Philips EPIQ (equipped with an X5-1 transducer; Philips Medical Systems, Best, the Netherlands) or a GE Vivid E95

(equipped with 4V-D or 4Vc-D transducers; GE Healthcare, Horten, Norway) ultrasound systems. According to current recommendations, a standard acquisition protocol consisting of loops from parasternal, apical, and subxyphoid views was used [1, 5]. RV basal diameter was measured as the end-diastolic dimension in the basal third of the RV inflow from the apical four-chamber view. RV end-diastolic and end-systolic areas and fractional area change (FAC) were measured by manual tracing of the RV endocardial border. M-mode measured tricuspid annular plane systolic excursion (TAPSE) was recorded. RV systolic pressure (RVSP) was calculated from the peak velocity of the tricuspid regurgitation jet. 2D and Doppler measurements referring to LV morphology, systolic and diastolic function, and quantification of valvular heart diseases were performed according to current guidelines [1, 6].

Beyond the routine 2D protocol, ECG-gated full-volume 3D data sets (with or without multi-beat reconstruction) optimized for the right or left ventricle were obtained for offline analysis in accordance with our internal 3D acquisition protocols [4, 7]. Image quality was checked bedside to avoid “stitching” and “dropout” artifacts of the multi-beat 3D data. In case of a single-beat acquisition, a minimum of 15 volumes per second; in case of a multi-beat acquisition, a minimum of 25 volumes per second temporal resolution was targeted. Further measurements were performed on a standalone workstation using dedicated software packages (4D RV-Function 2 and 4D LV-Analysis 3; TomTec Imaging, Unterschleissheim, Germany). The algorithm semi-automatically detects the endocardial surface of the right and left ventricles, and following manual correction, it traces wall motion through the cardiac cycle (Fig. 1). We determined end-diastolic volume index (EDVi), end-systolic volume index (ESVi), and stroke volume index (SVi) normalized to body surface area (BSA), and to characterize global RV and LV functions, EFs were also assessed. We measured LV mass index normalized to BSA by tracing the LV end-diastolic epicardial contour. Moreover, LV GLS (4D LV-Analysis 3) and 2D RV free wall longitudinal strain (4D RV-Function 2) were also calculated.

Study outcomes

Follow-up data [status (dead or alive), date of death] was obtained from Hungary's National Health Insurance Database. The primary endpoint of our study was all-cause mortality at 2 years.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD), whereas categorical variables were reported as frequencies and percentages. After the verification of normal distribution of variables using the Shapiro-Wilk test, the clinical and echocardiographic characteristics were compared with unpaired Student's *t*-test or Mann-Whitney *U* test for continuous variables, and Chi-squared or Fisher's exact test for categorical variables, as appropriate. Cox proportional hazards models were used to compute hazard



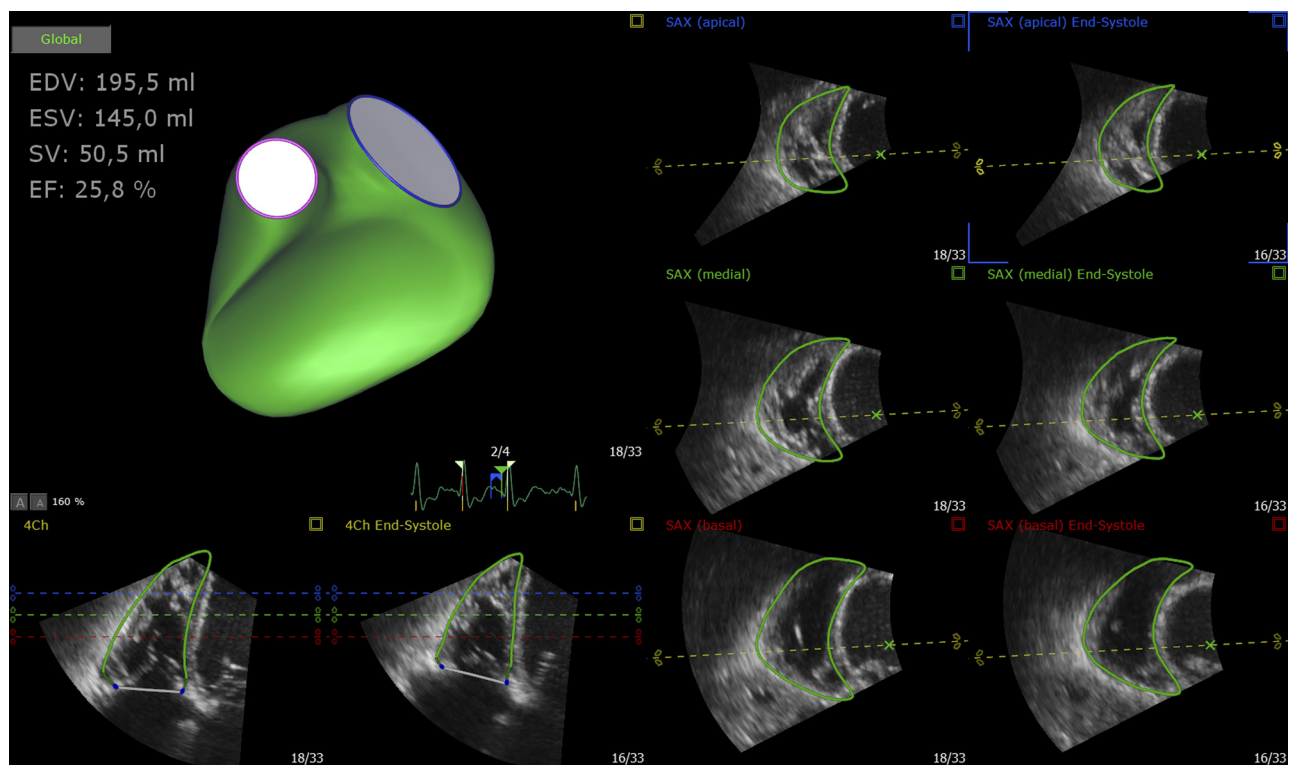


Fig. 1. Representative 3D echocardiographic reconstruction of a heart failure patient's severely dilated and dysfunctional right ventricle (upper left corner). The endocardial borders are semi-automatically identified by the dedicated, commercially available software, which can be manually corrected on multiple short- and long-axis planes to accurately quantify right ventricular volumes. 4Ch: four-chamber view; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; SAX: short axis; SV: stroke volume

ratios (HR) with 95% confidence intervals (95% CI). Receiver-operator characteristic (ROC) curves were generated to assess the discriminatory power of RV systolic functional parameters with regard to the endpoint. Youden's index was used to identify the optimal cut-off points of each parameter; then, these values were used to dichotomize the study population. Outcomes of the dichotomized groups were visualized on Kaplan-Meier curves and compared by log-rank test. A 2-sided *P*-value of 0.05 was considered statistically significant. Analysis was performed in R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

Two hundred and ninety-seven patients with local echocardiography performed were identified and screened for eligibility in our database (Fig. 2). The final study population consisted of 174 patients with an average age of 62 years and a male predominance (72%). Seventy-eight subjects (45%) were heart failure with reduced ejection fraction (HFrEF) patients, of whom 69 patients were referred to our electrophysiology department to assess a potential *de novo* device implantation or upgrade. Later, 14 patients received an implantable cardioverter defibrillator (ICD), while 49 patients underwent cardiac resynchronization therapy (CRT-D) device

implantation during the follow-up period. Nine patients were investigated for candidacy for a long-term LV assist device (LVAD) implantation, and thereafter all of them received such device. Twenty-eight subjects (16%) were heart transplant recipients (HTX) with a median of 96 days after the operation (range from 9 to 515 days). Sixty-eight subjects (39%) were patients with severe primary mitral valve regurgitation (MVR; 29 patients with Barlow's disease, 39 with fibroelastic deficiency) enrolled in a previous prospective study and underwent mitral valve repair or replacement after the echocardiography [8]. In this cohort of 174 patients, coronary artery disease status was previously established (and, if required, treated accordingly). There were also no subjects having moderate or severe stenosis on any valve.

Twenty-four patients met the primary endpoint of all-cause mortality at two years: 16 HFrEF patients (2 with ICD, 10 with CRT-D, 4 with LVAD implanted), 1 HTX patient, and 7 MVR patients. Two patients from the LVAD and two from the MVR cohort died in the early postoperative period.

Patients who met the endpoint were compared to those who did not in Table 1. Patients who died were older (68 ± 10 years) but there was no difference in anthropometric measures, blood pressures and serum creatinine levels (at the time of echocardiographic examination). We did not find a difference in medical history either: prevalence of coronary artery disease, arterial hypertension, diabetes mellitus, and atrial fibrillation was similar in the two groups. Presence of

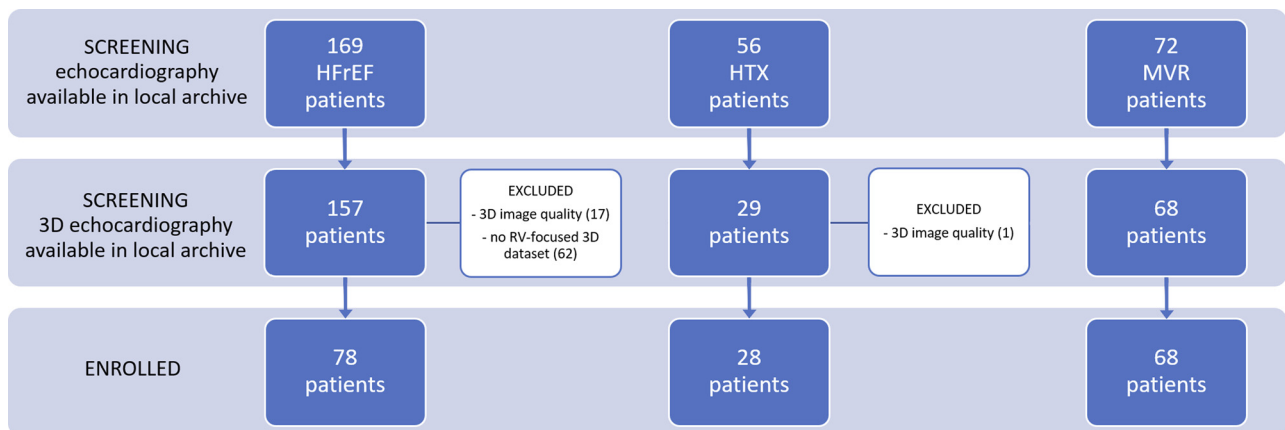


Fig. 2. Patient selection flowchart. Overall, 297 patients were identified with local echocardiography available in our database. 254 had 3D acquisitions available, out of whom 174 patients formed the final study group having appropriate 3D dataset for RV volumetric analysis. Please note that 3D acquisitions (especially RV-focused views) were not part of the routine echocardiographic protocol, which justifies the relatively high drop-out. HFREF: heart failure with reduced ejection fraction; HTX: heart transplantation; MVR: mitral valve regurgitation; RV: right ventricular

significant (defined as moderate or severe) valvular regurgitations was also comparable (Table 1). Concerning conventional and 3D echocardiographic characteristics, patients who died had higher LVESVi, along with a lower LVEF and LV GLS. However, LVEDVi, LVSVi, and LVMi were similar. LV diastolic function measures, including E/A and E/e' ratios, did not differ either. The group with adverse outcome had significantly higher RVEDVi, RVESVi but RVSVi was similar. Among RV functional parameters, RVEF along with FAC and 2D free wall longitudinal strain, was significantly deteriorated in patients who experienced adverse outcomes. Importantly, however, TAPSE and RVSP did not differ.

By univariate Cox analysis, among the left-heart echocardiographic parameters only LVEF (HR [95% CI]: 0.973 [0.950–0.997], $P < 0.05$), and LV GLS (1.075 [1.009–1.146], $P < 0.05$) were significantly associated with the primary endpoint, whereas LV volumes, LVMi, and diastolic function parameters were not. Concerning the metrics of the right heart, beyond RVEDVi, RVESVi, FAC, and 2D free wall longitudinal strain, RVEF (HR [95% CI]: 0.945 [0.908–0.984], $P < 0.01$) was found to be associated with adverse outcomes, while TAPSE and RVSP were not (Table 2).

Using ROC analysis, we have investigated the relative discriminatory power of RV systolic function parameters (TAPSE, FAC, free wall longitudinal strain, RVEF) in predicting the primary endpoint. Among these metrics, RVEF exhibited the highest AUC value (0.679; 95% CI: 0.566–0.791) compared with the other RV functional measures (Table 3). TAPSE and RVEF were directly compared by their ROC curves and by the outcome of the patient subgroups dichotomized at the calculated optimal cut-offs of each parameter on Fig. 3.

Discussion

Using 3DE, we have investigated a diverse patient population with left-sided heart diseases who underwent specific

cardiac interventional or surgical procedures. We found that the conventional echocardiographic measurements may be inadequate to support a granular risk stratification; however, RVEF may be a robust clinical parameter significantly associated with adverse outcomes.

Compared to the relatively simple conical shape of the LV, the RV's morphology and contraction pattern are rather complex [9]. The biplane Simpson's method (by contouring the LV endocardial border in both the apical four- and two-chamber views) provides an easy and relatively accurate quantification of LV volumes and, therefore, widely used in the clinical practice. However, there is no similar, 2D-based approach concerning the right ventricle [5]. Thus, surrogate measures of RV systolic function are applied in the echocardiographic routine having severe shortcomings. TAPSE, s' wave by tissue Doppler imaging and even longitudinal strain by speckle tracking refers only to the longitudinal shortening of the RV in a single apical four-chamber cut and neglects two other "axes" of geometry and function: the radial and the anteroposterior. The radial (inward) motion of the RV free wall results in the so-called "bellows effect", while by the traction of the free wall insertion lines, the LV circumferential contraction also contributes to RV stroke volume (as seen by the anteroposterior shortening of the chamber) [9]. Conventionally, the RV longitudinal shortening was considered the most important determinant of RV global function; therefore, there is a strong clinical belief that TAPSE is the one-stop shop of RV function. However, our research group recently explored in healthy volunteers, that the radial and the anteroposterior motion directions are at least equally important [10]. FAC partly reflects radial direction, but still, this measurement is performed on a single cut of complex 3D structure. Routine 2D echocardiographic measurements entirely neglect anteroposterior motion [11, 12]. Relatively small amounts of inward movement in these directions can produce significant stroke volume due to the massive surface of the RV free wall. These results *per se*

Table 1. Baseline clinical and echocardiographic characteristics of the study population

	All (n = 174)	Alive (n = 150)	Dead (n = 24)	P-value
Demographics, anthropometrics, medical history				
Age, years	62.3 ± 13.5	61.4 ± 13.7	68.1 ± 10.4	0.026
Male, n (%)	126 (72.4)	108 (72)	18 (75)	0.953
Height, cm	173.4 ± 12.2	173.6 ± 12.4	171.9 ± 11.1	0.867
Weight, kg	79.2 ± 15.7	78.8 ± 14.8	82.5 ± 20.7	0.796
Body surface area, m ²	1.9 ± 0.2	1.9 ± 0.2	2 ± 0.3	0.700
Systolic blood pressure, mmHg	126.2 ± 19.7	127.5 ± 18.6	118.9 ± 24.9	0.460
Diastolic blood pressure, mmHg	74.7 ± 16.5	75.3 ± 17.3	71.1 ± 11.5	0.353
Serum creatinine level, μmol/l	97.8 ± 39.3	96.7 ± 39.6	104.5 ± 37.7	0.380
Coronary artery disease, n (%)	38 (22)	33 (22)	5 (21.7)	1.000
Hypertension, n (%)	113 (65.3)	98 (65.3)	15 (65.2)	1.000
Diabetes mellitus, n (%)	39 (22.5)	33 (22)	6 (26.1)	0.866
History or present atrial fibrillation, n (%)	60 (34.7)	52 (34.7)	8 (34.8)	1.000
Moderate or severe mitral regurgitation, n (%)	82 (47.1)	70 (46.7)	12 (50)	0.933
Moderate or severe tricuspid regurgitation, n (%)	21 (12.1)	16 (10.7)	5 (20.8)	0.279
Echocardiographic parameters				
LVEDVi, ml/m ²	94.8 ± 32.6	93.7 ± 32.7	102.6 ± 30.9	0.139
LVESVi, ml/m²	52.3 ± 30.5	50.6 ± 30.3	64 ± 30	0.026
LVSVi, ml/m ²	42.6 ± 19.2	43.1 ± 19.6	38.6 ± 16.3	0.348
LVEF, %	47.5 ± 17.5	48.6 ± 17.4	39.6 ± 16.3	0.009
LVMi, g/m ²	113.8 ± 37	112.9 ± 36.2	119.8 ± 42.3	0.385
LVGLS, %	−15.5 ± 7.4	−16 ± 7.3	−12.1 ± 7.3	0.017
E/A	1.6 ± 0.7	1.6 ± 0.7	1.7 ± 0.8	0.639
Deceleration time, ms	183.1 ± 67.1	182.5 ± 66.4	186.6 ± 72.9	0.998
Mitral lateral annular e', cm/s	10.3 ± 3.5	10.3 ± 3.6	9.9 ± 3.2	0.763
Mitral medial annular e', cm/s	7.2 ± 2.8	7.3 ± 2.8	6.1 ± 2.4	0.091
E/e'	12 ± 5.5	11.8 ± 5.6	13.1 ± 4.8	0.122
RV basal diameter, mm	30.5 ± 8.3	30.1 ± 8.1	32.8 ± 9.5	0.160
RVEDVi, ml/m²	75.5 ± 25	73.8 ± 24	85.8 ± 28.7	0.037
RVESVi, ml/m²	41.1 ± 18.7	39.5 ± 17.3	51.5 ± 24.2	0.009
RVSVi, ml/m ²	34.3 ± 10.8	34.3 ± 11.1	34.4 ± 8.9	0.730
RVEF, %	46.9 ± 9	47.6 ± 8.8	42.2 ± 9.2	0.005
TAPSE, mm	20.2 ± 6.6	20.6 ± 6.8	18 ± 4.2	0.118
FAC, %	41.1 ± 8.7	41.7 ± 8.5	37.6 ± 9.5	0.037
RV free-wall longitudinal strain, %	−23.6 ± 7	−24.1 ± 6.9	−20.5 ± 7.1	0.024
RVSP, mmHg	36.5 ± 14.9	36.1 ± 15	38.7 ± 14.7	0.313

EDVi: end-diastolic volume index; EF: ejection fraction; ESVi: end-systolic volume index; FAC: fractional area change; GLS: global longitudinal strain; LV: left ventricular; Mi: mass index; RV: right ventricular; SP: systolic pressure; SVi: stroke volume index; TAPSE: tricuspid annular systolic excursion.

support the use of 3DE, but the mechanical patterns that evolve in different cardiac diseases are reinforcing it. For example, in pathological states accompanied by RV pressure overload, the radial motion of the RV free wall deteriorates, and longitudinal shortening is maintained long during the disease course [13]. Therefore, TAPSE (and other measures of RV longitudinal contraction) will not be able to capture subtle dysfunction in the early phases and overestimate global function. After cardiac surgeries that apply pericardiotomy, the loss of pericardial constraint results in the loss of longitudinal shortening compensated by radial free wall motion maintaining global RVEF [14, 15]. In these cases, TAPSE will underestimate global function [8]. As the mechanical pattern and thus, the relative usefulness of the

surrogate 2D measures vary, only RVEF by 3DE represents an integrative measure that is robust and informative, independently of the clinical scenario. This feature makes RVEF a good candidate for predicting prognosis even in unselected, diverse patient populations.

Nagata and colleagues published one of the first publications that described the predictive value of RVEF by 3DE [16]. They investigated 446 patients with various cardiovascular diseases and followed them up to record cardiac death and major adverse cardiovascular events (MACE). RVEF was significantly associated with future cardiac death and MACE (similar to E/e' and LVEF) and was significantly related to future cardiac events after adjusting for relevant clinical and echocardiographic parameters. Later, Surkova



Table 2. Univariate Cox proportional hazards models concerning the primary endpoint of 2-year all-cause mortality

	HR [95% CI for HR]	P-value
LVEDVi	1.007 [0.996–1.019]	0.226
LVESVi	1.012 [1–1.023]	0.052
LVSVi	0.987 [0.961–1.013]	0.312
LVEF	0.973 [0.95 – 0.997]	0.026
LVMi	1.005 [0.994–1.015]	0.402
LVGLS	1.075 [1.009 – 1.146]	0.025
E/A	1.136 [0.61–2.113]	0.688
Mitral lateral annular e'	0.968 [0.849–1.104]	0.626
Mitral medial annular e'	0.842 [0.687–1.031]	0.096
E/e'	1.03 [0.966–1.097]	0.367
RVEDVi	1.017 [1.003 – 1.031]	0.020
RVESVi	1.027 [1.01 – 1.045]	0.002
RVSVi	1.002 [0.966–1.039]	0.931
RVEF	0.945 [0.908 – 0.984]	0.006
TAPSE	0.943 [0.884–1.007]	0.078
FAC	0.951 [0.907 – 0.996]	0.032
RV free-wall longitudinal strain	1.071 [1.01 – 1.135]	0.021
RVSP	1.01 [0.986–1.035]	0.418

CI: confidence interval; EDVi: end-diastolic volume index; EF: ejection fraction; ESVi: end-systolic volume index; FAC: fractional area change; GLS: global longitudinal strain; HR: hazard ratio; LV: left ventricular; Mi: mass index; RV: right ventricular; SP: systolic pressure; SVi: stroke volume index; TAPSE: tricuspid annular systolic excursion.

Table 3. Comparison of the discriminatory power by receiver-operator characteristic analysis of right ventricular systolic function parameters concerning the primary endpoint of 2-year all-cause mortality

	AUC [95% CI]	Optimal cut-off	Sensitivity	Specificity
RVEF	0.679 [0.566–0.791]	48.2 %	0.57	0.79
TAPSE	0.600 [0.501–0.698]	24.0 mm	0.35	0.96
FAC	0.630 [0.495–0.766]	34.1 %	0.80	0.52
RV free-wall longitudinal strain	0.643 [0.515–0.771]	–19.4 %	0.57	0.75

AUC: area under the curve; CI: confidence interval; FAC: fractional area change; RV: right ventricular; RVEF: right ventricular ejection fraction; TAPSE: tricuspid annular systolic excursion.

and coworkers confirmed in 394 patients (again with various cardiovascular diseases) that RVEF was associated with all-cause mortality and cardiac death and the impairment of RVEF carried a significantly higher risk of mortality independent of LVEF [2]. The latter two groups also determined those cut-offs of RVEF values that separate the cohorts according to the risk and, therefore, suggested to be applied in the routine clinical practice (45%, 40%, and 30%) [17].

Our results add to this current knowledge by investigating a higher-risk population (dominantly HFrEF patients or patients with severe valvular heart disease) – higher risk, not just in terms of current functional status, but also because of the previous or upcoming invasive procedures and related potential adverse events [8, 18]. Moreover, we compared head-to-head the conventionally used parameters and RVEF and showed the superior discriminatory power of the latter in predicting 2-year all-cause mortality. The optimal cut-off points identified during ROC analysis were close to the ones defined by current recommendations in terms of RVEF, FAC, and 2D free wall longitudinal strain. However, regarding TAPSE, it was 24 mm, which is a clear normal value as RV dysfunction is generally suggested below 17 mm [5]. This

result also highlights that TAPSE cannot be used in general, and the exact clinical scenario has to be taken into consideration. We may hypothesize that mainly the MVR population can bias that value: a dominant (“supernormal”) longitudinal shortening is suggested to be a sign of adverse functional remodeling in patients with severe MVR that is also associated with short-term, perioperative outcomes [8].

Limitations

Several limitations have to be acknowledged. First, the case number is rather limited, and we did not assess long-term outcomes in our current study. We also did not have the power to separately assess the importance of the different etiologies on our results. However, the specific cardiac procedures give a framework to our results that still makes them unique, and the predictive value of RVEF could be established even in the short term. Second, we could not construct multivariate models due to the relatively low event number. Inclusion criteria consist of the availability of 3DE acquisitions suitable for RVEF measurement that may represent a selection bias: patients with poor echo windows



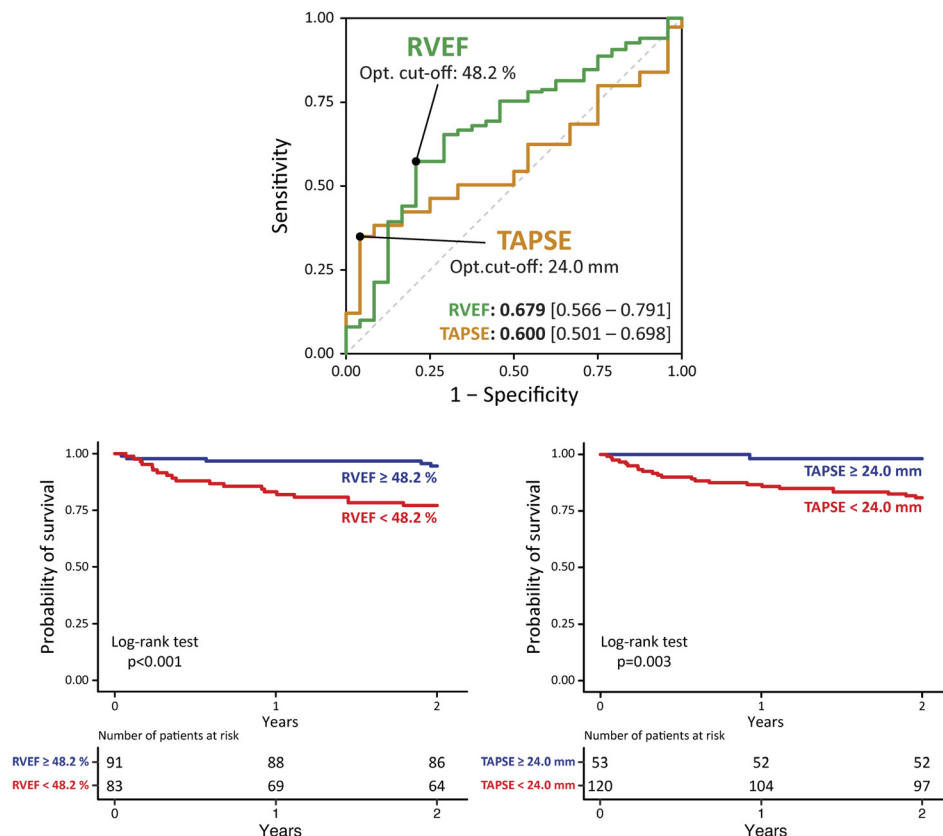


Fig. 3. (Central Illustration). Comparison of the discriminatory power of tricuspid annular plane systolic excursion (TAPSE) versus right ventricular ejection fraction (RVEF) by receiver-operator characteristic analysis concerning the primary endpoint of 2-year all-cause mortality. Outcomes of the patient subgroups dichotomized at the calculated optimal cut-offs of each parameter are visualized on Kaplan-Meier curves

or higher body mass may be underrepresented. The inclusion of the HTX cohort could be a matter of debate. These patients have already undergone surgery and represent a different clinical and hemodynamic scenario than the “standard” left-heart disease populations. It is important to highlight that in the case of the MVR patients, the mechanism of preoperative RV dysfunction is also different from HFrEF, because all of them had maintained LV and RVEF as per the previous prospective study’s exclusion criteria [8]. However, we aimed to capture a more comprehensive cohort with different RV adaptation patterns and show that RVEF is a robust, integrative index of RV function and potential adverse outcomes. RV 2D free wall longitudinal strain was assessed using the 3D dataset and not using the conventional approach (2D speckle tracking on apical four-chamber view); therefore, the clinical value of this measurement could be underestimated. Lastly, patients’ functional status, natriuretic peptide levels, and tricuspid annular velocities by tissue Doppler imaging have not been recorded consistently and therefore, have not been evaluated.

Conclusions

In an aggregate patient population undergoing tertiary cardiology care with various cardiac procedures, we found that

RVEF assessed by 3DE is associated with 2-year all-cause mortality and outperforms conventional measures of RV function in the prediction of adverse outcomes. Our results support the everyday clinical use of 3DE as it provides meaningful additional information for disease diagnosis and prognostication. Further, larger-scale studies involving more specific patient populations are warranted to establish the value of RVEF measurement in predicting different endpoints and long-term outcomes.

Authors’ contribution: Concept and design: MTol, MTok, BM, AK. Echocardiographic examinations and measurements: MTol, MTok, BKL, AF, AU, FZB, LZ, ZT, AK. Statistical analysis: MTok. Figure and Table preparation: MTol, MTok. Manuscript preparation: MTol, AK. Manuscript review: MTok, BKL, AF, AU, FZB, LZ, ZT, BM. Funding: BM. All authors reviewed the final version of the manuscript and agreed to submit it to IMAGING for publication.

Funding sources: This work was supported by the National Research, Development, and Innovation Office of Hungary (NKFI; NVKP_16-1-2016-0017—National Heart Program), the New National Excellence Program (ÚNKP-20-3-II-SE-54, ÚNKP-20-4-II-SE-20, ÚNKP-20-5); the Artificial Intelligence National Laboratory Program, and the Thematic Excellence Program (2020-4.1.1.-TKP2020) of the Ministry



for Innovation and Technology in Hungary, within the framework of the Therapeutic Development and Bioimaging programs of the Semmelweis University. AK was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

Conflict of interests: The authors have no conflict of interest to disclose.

REFERENCES

- [1] 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. *J Am Soc Echocardiogr* 2015; 28: 1–39 e14.
- [2] 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: 1407–15 e1403.
- [3] 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.
- [4] Lakatos BK, Tokodi M, Kispal E, Merkely B, Kovacs A: Morphological and functional assessment of the right ventricle using 3D echocardiography. *J Vis Exp* 2020.
- [5] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al.: Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23: 685–713; quiz 786–688.
- [6] Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al.: Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013; 14: 611–44.
- [7] Ujvari A, Lakatos BK, Tokodi M, Fabian A, Merkely B, Kovacs A: Evaluation of left ventricular structure and function using 3D echocardiography. *J Vis Exp* 2020.
- [8] Tokodi M, Nemeth E, Lakatos BK, Kispal E, Toser Z, Staub L, et al.: Right ventricular mechanical pattern in patients undergoing mitral valve surgery: a predictor of post-operative dysfunction? *ESC Heart Fail* 2020; 7: 1246–56.
- [9] Kovacs A, Lakatos B, Tokodi M, Merkely B: Right ventricular mechanical pattern in health and disease: beyond longitudinal shortening. *Heart Fail Rev* 2019; 24: 511–20.
- [10] Lakatos BK, Nabeshima Y, Tokodi M, Nagata Y, Toser Z, Otani K, et al.: Importance of nonlongitudinal motion components in right ventricular function: three-dimensional echocardiographic study in healthy volunteers. *J Am Soc Echocardiogr* 2020; 33: 995–1005 e1001.
- [11] Tokodi M, Staub L, Budai A, Lakatos BK, Csakvari M, Suhai FI, et al.: Partitioning the right ventricle into 15 segments and decomposing its motion using 3D echocardiography-based models: the updated ReVISION method. *Front Cardiovasc Med* 2021; 8: 622118.
- [12] Surkova E, Kovács A, Lakatos BK, Li W: Anteroposterior contraction of the systemic right ventricle: underrecognized component of the global systolic function. *JACC: Case Reports* 2021; 3.
- [13] Bidviene J, Muraru D, Maffessanti F, Ereminiene E, Kovacs A, Lakatos B, et al.: Regional shape, global function and mechanics in right ventricular volume and pressure overload conditions: a three-dimensional echocardiography study. *Int J Cardiovasc Imaging* 2021; 37: 1289–99.
- [14] Lakatos BK, Tokodi M, Assabiny A, Toser Z, Kosztin A, Doronina A, et al.: Dominance of free wall radial motion in global right ventricular function of heart transplant recipients. *Clin Transplant* 2018; 32: e13192.
- [15] Kovacs A, Lakatos B, Nemeth E, Merkely B: Response to Ivey-Miranda and Farrero-Torres “Is there dominance of free wall radial motion in global right ventricular function in heart transplant recipients or in all heart surgery patients?”. *Clin Transplant* 2018; 32: e13286.
- [16] 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.
- [17] Muraru D, Badano LP, Nagata Y, Surkova E, Nabeshima Y, Genovese D, et al.: Development and prognostic validation of partition values to grade right ventricular dysfunction severity using 3D echocardiography. *Eur Heart J Cardiovasc Imaging* 2020; 21: 10–21.
- [18] Tokodi M, Behon A, Merkel ED, Kovacs A, Toser Z, Sarkany A, et al.: Sex-specific patterns of mortality predictors among patients undergoing cardiac resynchronization therapy: a machine learning approach. *Front Cardiovasc Med* 2021; 8: 611055.

