Forgotten no More – the Role of Right Ventricular Dysfunction in Heart Failure with Reduced Ejection Fraction. An Echocardiographic Perspective

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August 6, 2020

Abstract

While most attention in cardiovascular disease has been traditionally focused on the morphology, function and prognostic role of the left ventricle, during the last decade studies have raised awareness of the crucial role that the right ventricle plays in a variety of cardiovascular settings, including diseases primarily linked to the left ventricle. The assessment of right ventricular performance with conventional echocardiography is challenging. Novel echocardiographic techniques improve the functional assessment of the right ventricle and they showed good correlation with the gold standard represented by cardiovascular magnetic resonance. However, there is no single universally accepted parameter that accurately defines right ventricular function; hence a thorough evaluation of the right ventricle needs an integrative, multi-parametric approach. This review summarizes the traditional and innovative echocardiographic techniques used in the functional assessment of the right ventricle, focusing on the role of right ventricular dysfunction in heart failure with reduced ejection fraction and providing a perspective on recent evidence from literature.

Introduction

Heart failure (HF) remains a rising public health concern, with an estimated prevalence of almost 38 million individuals worldwide [1, 2]. The total percentage of the population with HF is predicted to rise to 2.97% in 2030 [3]. According to the presence or absence of left ventricular (LV) dysfunction, HF can be classified into HF with preserved, mid-range or reduced ejection fraction (EF) [4], the latter being the most extensively studied.

Most of the research focused on the prognostic role of LV dysfunction [5], while the occurrence and significance of right ventricular (RV) dysfunction in HF with reduced EF is less clear. This happened mostly due to the complex three-dimensional shape (3D) of the RV, which makes its echocardiographic assessment challenging [6]; for this reason, the RV used to be called for quite a while "the forgotten chamber" [7]. However, during the last decade, RV dysfunction emerged as a prognostic factor in HF and in pulmonary hypertension [8, 9], thus raising awareness of the importance of accurately evaluating the RV performance. Cardiac magnetic resonance (CMR) imaging remains the gold standard for the assessment of RV size and function [10, 11], but its cost, availability and contraindications make it feasible only in a selected number of patients. By comparison, echocardiography is a bedside, widely available tool, and novel echocardiographic techniques such as myocardial strain imaging and 3D echocardiography have been validated against (CMR) [12, 13], thus allowing an enhanced assessment of RV morphology and function.

The aim of this review is to summarize the role of conventional and novel echocardiographic parameters of RV function in patients with HF and reduced EF, while focusing on the most recent evidence from literature.

The echocardiographic assessment of the RV

The challenges in the echocardiographic evaluation of the RV come from its complex geometry, its position behind the sternum, its trabeculations which make endocardial tracing cumbersome, as well as from its dependence on hemodynamic load and interdependence with the LV. In fact, some authors suggest that up to 20-40% of RV stroke volume result from the contraction of the LV [14]. There is no ideal echocardiographic parameter for quantification of RV performance [15], hence a thorough echocardiographic evaluation needs an integrative, multi-parametric approach from multiple acoustic windows, as suggested by current guidelines [16].

Conventional parameters assessing RV systolic function are tricuspid annular plane systolic excursion (TAPSE), tricuspid lateral annular systolic velocity (S' wave) derived from tissue Doppler imaging (TDI), RV isovolumic acceleration, RV fractional area change (FAC), while RV myocardial performance index (MPI) is a marker of global RV function. Innovative parameters for the assessment of the RV performance are derived from bidimensional (2D) speckle tracking echocardiography (STE) (such as RV global strain and strain rate, as well as RV free wall strain and strain rate), from 3D echocardiography (such as 3D RVEF) and – more recently – from 3D STE.

Tricuspid annular plane systolic excursion (TAPSE)

TAPSE is a highly reproducible, easy obtainable parameter [17] of RV longitudinal function, which is acquired by placing M-mode at the lateral tricuspid annulus in the apical 4-chamber view and by measuring the vertical excursion of the annulus in millimetres (mm). A value of TAPSE $<$ 16 mm reflects RV systolic dysfunction [16, 18]. The main limitations are that TAPSE is angle- and load-dependent [18] and that it only reflects the longitudinal function, neglecting the contribution of the outflow tract to the contraction of the RV [19], potentially leading to an underestimation or overestimation of global RV systolic performance [15].

Ghio et al. showed that TAPSE **[?]** 14 mm is an independent predictor of death or emergency cardiac transplantation in patients with congestive HF [20], while Venner et al. found a TAPSE **[?]** 15 mm to be an independent predictor of major adverse cardiovascular events (MACE) in patients with idiopathic dilated cardiomyopathy (DCM) [21]. Several other studies showed that TAPSE is an independent predictor of all-cause mortality in patients with HF [22-24]. The prognostic ability of TAPSE appears to be improved when combined with the echocardiographic estimation of pulmonary artery systolic pressure (PASP). As shown by Ghio et al. [9], a PASP [?] 40 mm Hg combined with TAPSE **[?]** 14 mm predict unfavourable outcomes in patients with HF, regardless of its aetiology (ischaemic or non-ischaemic).

Tricuspid lateral annular systolic velocity (S' wave)

The systolic velocity of the tricuspid lateral annulus reflects the longitudinal contraction of the RV [18]. S' wave velocity is obtained in the apical 4-chamber view by aligning the ultrasound beam with the longitudinal excursion of the RV and by placing the tissue Doppler marker on the lateral tricuspid annulus [18, 19]. Like TAPSE, it is an easy obtainable parameter, but it is angle-dependent, and it does not reflect the global systolic function of the RV [18, 19]. A S' wave value $<$ 9.5 cm/s reflects RV systolic dysfunction [16, 18].

Studies found that decreased TDI systolic velocity of the tricuspid annulus is an independent predictor of either cardiac death [25] or of cardiovascular death and rehospitalizations for HF [26] in patients with LV systolic dysfunction. Damy et al. showed that S' wave$<$9.5 cm/s is a strong independent predictor of outcomes in patients with LVEF$<$35%, while having superior prognostic value when compared to other RV systolic parameters such as FAC and TAPSE [27]. Similar results were found by de Groote et al. [28], who found no prognostic value for TAPSE in patients with LV systolic dysfunction but found that S' wave$<$9.7 cm/s is an independent predictor of cardiovascular death, with an enhanced prognostic value when combined with RVEF measured by radionuclide angiography. Meluzin et al. showed that the assessment of both TDI systolic and diastolic velocities of the tricuspid annulus provide an enhanced risk stratification in symptomatic HF with reduced EF. The authors found that both TDI systolic and diastolic velocity were independent predictors of survival and of event-free survival, and that patients with combined peak systolic tricuspid annular velocity<10.8 cm/s and peak early diastolic tricuspid annular velocity<8.9 cm/s had the worst prognosis [29].

Right ventricular myocardial performance index (RV MPI)

The index of RV myocardial performance, also known as Tei index, is a marker of both systolic and diastolic RV function and it is calculated by dividing the total isovolumic time (isovolumic contraction plus isovolumic relaxation) to the ejection time [19]. It can be measured using either pulsed-wave Doppler or tissue Doppler, the cut-offs proposed for abnormal RV MPI being >0.43 using pulsed Doppler method and >0.54 using tissue Doppler method [16]. The advantage of RV MPI is that it bypasses the limitations of the complex RV geometry, as it is derived from time intervals only [18]; however, irregular rhythms make MPI difficult to calculate [19].

Vizzardi et al. assessed the prognostic value of RV MPI (calculated with the pulsed Doppler method) in a cohort of patients with HF and reduced LVEF, who were prospectively followed for 5 years for a combined endpoint of cardiac death and readmissions for HF. The authors found that a RV MPI>0.38 was an independent predictor of adverse outcome [30]. In a study by Field et al., each 0.1-unit increase in RV MPI (assessed by pulsed Doppler) was associated with a 16% increased risk of MACE (defined as death, cardiac transplantation or ventricular assist device placement) in patients with advanced HF referred for cardiac resynchronization therapy (CRT) [31]. To our knowledge, no studies evaluated the prognostic role of TDI-derived RV MPI in HF, although some authors suggest that tissue Doppler MPI is superior to pulsed Doppler MPI because it has the advantage of recording all the time intervals in the same cardiac cycle [32].

Right ventricular fractional area change (RV FAC)

FAC is a bidimensional marker of RV systolic function obtained from the apical 4 chamber view by manually tracing the endocardial border of the RV in end-diastole and end-systole, while including the trabeculations in the cavity. It is calculated as: (end-diastolic area – end-systolic area)/ end-diastolic area x 100% [16]. This parameter reflects both the longitudinal and radial contraction of the RV, but it neglects the contraction of the outflow tract [16, 19]. It has shown good correlation with the RV ejection fraction (RVEF) determined by CMR [33], but it is load-dependent and potentially difficult to acquire in case of poor endocardial definition [19, 34]. A RV FAC<35% reflects RV dysfunction [16, 18].

Zornoff et al. found that RV FAC is an independent predictor of total mortality, cardiovascular mortality and development of HF in patients with LV systolic dysfunction following a myocardial infarction (MI), each 5% decrease in FAC being associated with a 16% increase in odds of cardiovascular mortality [35]. Similar findings were reported by Anavekar et al., who found RV FAC to be an independent predictor of all-cause mortality, cardiovascular death, sudden death, HF and stroke in patients with MI and LV dysfunction [36].

A small retrospective study found that RV FAC<26.7% is predictive of death or LV assist device implantation in patients with DCM, providing better prognostic information than other RV functional parameters such as TAPSE and S' wave velocity [37]. Merlo et al. found that RV FAC<35% was an independent predictor of death or heart transplantation in patients with idiopathic DCM; moreover, RV FAC had stronger predictive value than other well-known prognostic factors such as LV dimensions and New York Heart Association (NYHA) functional class [38].

Right ventricular isovolumic acceleration

Myocardial acceleration during isovolumic contraction is usually obtained using TDI at the lateral tricuspid annulus in the apical 4-chamber view. It is calculated as the peak myocardial velocity during isovolumic contraction divided by the time needed to reach this velocity. While it has the advantage of being relatively load-independent [19], it has a large confidence interval around the normal values [18], hence it is not recommended for routine use and no reference value for this parameter has been proposed in the latest guidelines [16]. Consequently, its prognostic utility has not been broadly studied. However, Sciatti et al.

found RV isovolumic acceleration to be a better predictor for cardiac death and rehospitalization in patients with HF and reduced LVEF than traditional parameters of RV systolic function such as TAPSE, RV FAC and S' wave [39].

Right ventricular strain and strain rate derived from bidimensional speckle tracking echocardiography (2D STE)

Speckle tracking echocardiography in a non-invasive, innovative technique that analyses the segmental myocardial deformation along different planes through the displacement of speckles [15]. Originally designed for the assessment of the LV, it is now also being applied for the analysis of RV deformation. Strain represents the percentage change in length of a myocardial segment, while strain rate represents the rate of deformation over time [40]. Both strain and strain rate are indices of myocardial contractility [41]. The measurement of RV longitudinal strain and strain rate is performed in the apical RV-focused 4-chamber view, using software dedicated for the LV assessment. The RV free wall and the interventricular septum (IVS) are each divided into three segments (basal, medial and apical), providing a six-segment model (Figure 1). Global longitudinal strain of the RV is calculated as the average of the six segmental values, while the longitudinal strain of the RV free wall (RVFW) is calculated as the average of the three segmental values of the free wall [42]. The latter is considered to be more specific for the RV [15], since the motion of the IVS contributes to both RV and LV function.

The advantages of bidimensional strain derived from STE are the angle independence, the relative load-independence, the strong correlation with RVEF measured by CMR [43] and the ability of detecting subtle myocardial abnormalities which cannot be determined using conventional parameters [44, 45]. One study showed that RVFW strain had a good correlation with the extent of myocardial fibrosis detected on CMR [46]. However, there is no uniformity in software and no reference range agreement between vendors. Other drawbacks are that strain assessment is dependent on good image quality and it neglects the contribution of the RV outflow tract (RVOT) to the global RV performance. For the longitudinal strain of the RV free wall, a value $>$ -20% is considered abnormal [16].

Martin et al. analysed which RV strain parameter was a better predictor of hospitalizations for HF in patients with left heart disease and found out that the global longitudinal strain of the RV independently predicts readmissions, providing additional prognostic information to that obtained by TAPSE [47]. Similar findings were reported by Motoki et al., who found global RV strain to be an independent predictor of long-term adverse outcomes in patients with LVEF$<$35%, while RVFW strain was not. In their study, a global RV strain $>$ -14.8% independently predicted the primary endpoint of death, cardiac transplantation or hospitalization for HF at 5 year-follow-up [48]. This is contrary to the results of another study, which found that RVFW strain was a better outcome predictor than global RV strain in HF with reduced EF, as it independently predicted total mortality and readmissions for HF even after adjustment for LV dysfunction [49]. Another prospective study showed that a RVFW strain $>$ -21% in patients with HF is an independent predictor for a composite endpoint of death, acute HF, emergency transplantation or left ventricular assist device (LVAD) implantation at 1 year [50].

Carluccio et al. proved the superiority of RV strain over TAPSE, by following 200 patients with HF and reduced EF but preserved TAPSE ($>$16 mm) for a composite endpoint of death and HF rehospitalization. The authors found that the longitudinal strain of the RVFW was an independent predictor of adverse outcome, with a cut-off value for endpoint prediction of -15.3% [51]. In a recent study by Seo et al., 143 patients with DCM were prospectively followed for long-term unfavourable events (defined as all-cause death, cardiac death, aborted sudden cardiac death and HF hospitalization), for a median period of 40 months. The longitudinal strain of the RVFW was the only independent predictor of the primary outcome, with an optimal cut-off value for event prediction of -16.5% [52].

Several studies discovered independent prognostic roles for both global RV strain and RVFW strain in HF with reduced EF. Cameli et al. found that in patients with advanced systolic HF referred for cardiac transplantation, both global and free wall RV strain are independent predictors of an adverse outcome (defined as cardiac death, heart transplantation, LVAD placement, intra-aortic balloon pump implantation or acute HF), with stronger predictive power than other conventional parameters, including parameters of LV function [53]. Iacoviello et al. found that both global RV strain and RVFW strain are independent predictors of all-cause mortality in patients with HF and LVEF<45% [54]. A recent study by Houard et al. evaluated the prognostic value of bidimensional RV strain for survival prediction and compared it with conventional echocardiographic parameters and CMR in 266 patients with HF and reduced EF. The authors found out that both global RV strain and RVFW strain were independent predictors for overall mortality and cardiovascular mortality; moreover, the predictive power of RV strain was higher than that of FAC, TAPSE, CMR-derived RVEF and CMR-derived RV strain [55].

Three-dimensional right ventricular ejection fraction (3D RVEF)

3D echocardiography overcomes the geometric assumptions used in 2D echocardiography, being particularly useful for the evaluation of the RV, which – due to its complex anatomy – cannot be comprehensively assessed with 2D measurements only. 3D echocardiography integrates both the longitudinal and radial components of RV contraction [19] and, unlike bidimensional echocardiography, allows the assessment of the RVOT as well. The images are acquired with a dedicated 3D probe using a full-volume data set from the apical RV-focused view and they are subsequently analysed with dedicated software (Figure 2). The 3D RV volumes and EF have been widely validated against the gold standard represented by CMR [56-58]. The main limitations of 3D RVEF are load-dependency, challenges in correctly tracing the endocardial border, image quality, stitching artefacts in case of arrhythmias, time consumption and limited availability [19]. A 3D RVEF<45% is considered abnormal [16].

In a population-based cohort study which enrolled 1004 elderly people, Nochioka et al. analysed the prevalence and prognostic role of RV dysfunction for HF with 2D and 3D echocardiography. Among patients with no HF at baseline, 3D RVEF proved to be an independent predictor of death or incidence of HF: each 5% decrease in 3D RVEF was associated with a 20% increase in the hazard of death or hospitalization for HF, independent of LVEF [59].

Magunia et al. showed that 3D RVEF is an independent predictor of post-operative RV failure in LVAD recipients [60], which is a well-known, common cause of mortality after LVAD implantation [61]. In a recent study, Nagata et al. investigated the long-term prognostic value of 3D RVEF in 446 patients with various cardiovascular diseases, who were followed during 4.1 years for a primary endpoint of cardiac death and a secondary composite endpoint of cardiac death, ventricular fibrillation, nonfatal myocardial infarction and hospitalization for HF exacerbation. At the end of the follow-up period, 3D RVEF was found to be an independent predictor of both cardiac death and of the secondary endpoint of MACE [62].

A recent retrospective study of Surkova et al. evaluated the relative importance of different combinations of reduced and preserved 3D LVEF and 3D RVEF in predicting mortality in patients with different cardiac diseases. Impaired 3D RVEF, but not LVEF, was a strong and independent predictor of both all-cause mortality and cardiovascular mortality [63]. Moreover, 3D RVEF was superior to conventional echocardiographic parameters of RV performance to predict total mortality. The group of patients with reduced LVEF and reduced RVEF had the highest mortality in the study; interestingly, patients with reduced LVEF and preserved RVEF had significantly better survival than patients with reduced RVEF and preserved LVEF [63]. The results of this study draw the attention to the potential role of therapies targeting RV dysfunction to improve clinical outcome.

Three-dimensional speckle-tracking echocardiography (3D STE)

3D STE is a novel imaging technique that evaluates myocardial deformation using 3D full-volume images. It is limited to research and not available for routine use, but it appears to be a promising tool for the assessment of the complex RV myocardial motion [64]. A study by Field et al. showed favourable results concerning the ability of 3D STE to detect subclinical biventricular dysfunction after anthracycline chemotherapy [31]. Magunia et al. found that 3D strain of the RVFW is a predictor of mortality in LVAD recipients [60]. Smith et al. evaluated the utility of 3D STE for RV assessment in a cohort of patients with pulmonary hypertension of different aetiologies (including left heart disease) and found out that RV area-strain derived from 3D STE correlated well with RVEF and was an independent predictor of mortality [65].

Other parameters of right ventricular function

The interaction between the RV and the pulmonary circulation unit is reflected in the RV–pulmonary artery coupling (RVPAC), which is usually assessed with right heart catheterization. Several echocardiographic studies used the ratio between TAPSE and PASP as a non-invasive surrogate for the RVPAC, as this ratio reflects the interaction between the shortening of the RV fibres and the force generated by the RV [66-69]. TAPSE/PASP ratio was found to be an independent predictor of cardiac mortality [66] and of major events (cardiac death, heart transplant or LVAD implant) [67] in patients with HF. In a recent study, Ghio et al. enrolled 1663 patients with HF (1123 with reduced LVEF, 156 with mid-range LVEF, 384 with preserved LVEF [4]) and showed that TAPSE/PASP is a powerful, independent predictor of all-cause mortality in all HF patients, regardless of the extent of LV dysfunction [68]. Similar results were found by Bosch et al, in a study that assessed the contribution of RV dysfunction in HF with reduced EF (HFrEF) versus HF with preserved EF (HFpEF); they showed that TAPSE/PASP ratio was an independent predictor of all-cause death and HF hospitalization, with no difference between HFrEF and HFpEF and regardless of LVEF [69].

As innovative echocardiographic techniques become part of the comprehensive assessment of RV performance, some researchers used 2D RV longitudinal strain or 3D RVEF for the non-invasive estimation of RVPAC. One recent study found that the ratio between RVFW strain and PASP independently predicted a composite endpoint of all-cause death and rehospitalizations in patients with HF [68]. Similar results were found by Iacoviello et al., who showed that both RVFW strain/PASP ratio and global RV strain/PASP ratio are independent predictors for all-cause mortality in patients with HF and LVEF$<$45% [70]. In another study RVPAC was estimated non-invasively using the ratio between 3D RVEF and PASP; the authors found that each 0.5 units decrease in RVEF/PASP ratio was associated with a 65% increase in the hazard of death or hospitalization for HF [59].

Fractional shortening of the RVOT (RVOT-FS) is an index of RV performance which is obtained using M-mode echocardiography in parasternal short axis window at the level of the aortic root. It is calculated as the percentage change in RVOT diameter at end-systole compared to end-diastole [71]. Several studies showed a good correlation between RVOT-FS and other indices of RV systolic performance [72, 73]. Yamaguchi et al. showed that RVOT-FS is an independent predictor of MACE (defined as cardiac death, heart transplantation or hospitalization for HF) in a cohort of patients with LVEF$<$40%, with a higher rate of adverse outcome in patients with RVOT-FS$<$20% [74].

Cardiac magnetic resonance

In the era of multi-modality imaging, despite the progresses made in innovative echocardiographic techniques, CMR remains the gold standard for the assessment of RV volumes and EF [75, 76]. Several studies have evaluated the prognostic role of CMR-derived RVEF in patients with reduced LVEF. In a prospective study enrolling 250 patients with DCM, Gulati et al. found that RVEF is an independent predictor for transplant-free survival, improving risk stratification for patients with DCM [77]. Mikami et al. showed that in patients with LV systolic dysfunction, RVEF$<$45% is a strong independent predictor of arrhythmic events (sudden cardiac arrest or appropriate implantable cardioverter defibrillator therapy) [78]. In a recent study, Pueschner et al. prospectively evaluated a cohort of patients with non-ischaemic DCM during a median follow-up time of 6.2 years and found that RVEF was a strong independent predictor of cardiac death [79]. All-cause mortality in patients with DCM was independently predicted by RVEF in another study [80]. Interesting results were found by Gill et al., who compared the prognostic role of RVEF in patients with ischaemic and non-ischaemic cardiomyopathy, who were followed for all-cause death and for a composite endpoint of death, acute coronary syndrome, stroke, admission for HF and defibrillator implantation. RVEF proved to be an independent predictor of all-cause death and of MACE in patients with non-ischaemic cardiomyopathy, but not in patients with ischaemic cardiomyopathy [81].

Conclusion

It is widely accepted nowadays that the RV plays a crucial role in various clinical settings. RV dysfunction is a strong independent predictor of mortality and adverse outcomes not only in diseases primarily affecting the right heart or the pulmonary vascular bed, but also in diseases primarily involving the left ventricle, such as congestive HF, dilated cardiomyopathy and ischaemic heart disease. Innovative echocardiographic techniques such as STE and 3D echocardiography overcome the pitfalls and challenges of conventional parameters of RV assessment. While having good correlation with the gold standard of CMR imaging, they have some advantages over CMR, such as less cost and wider availability. Integrating novel techniques in the RV echocardiographic assessment allows a comprehensive evaluation and an enhanced risk stratification for patients with HF, thus improving therapeutic strategies and potentially leading to an improved outcome.

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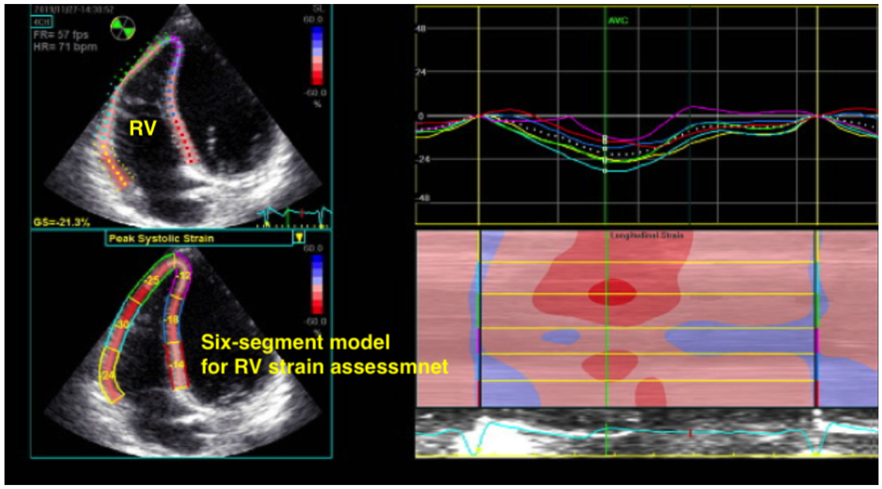
Figure legends:

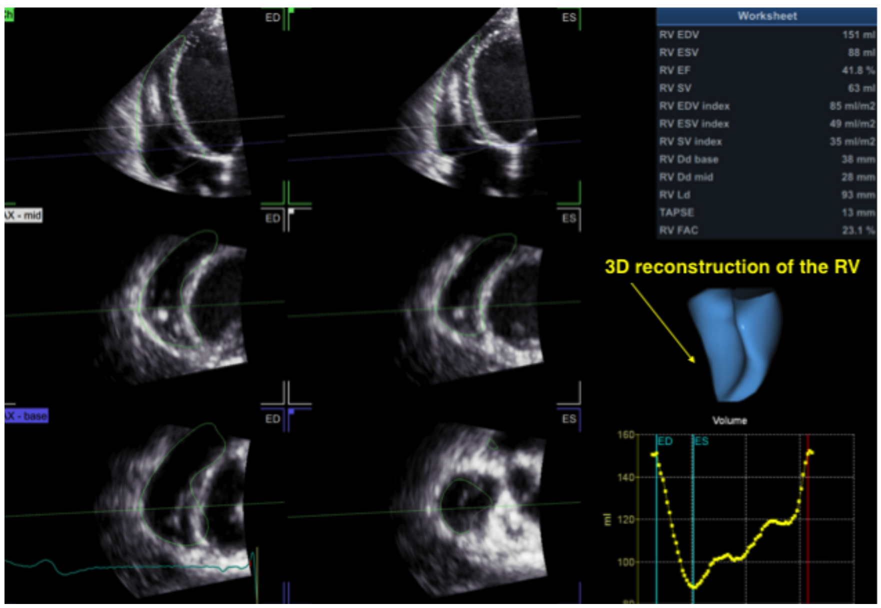
Figure 1. Six-segment model of global longitudinal right ventricular strain using speckle-tracking echocardiography

Abbreviations: RV – right ventricle

Figure 2. Three-dimensional assessment of right ventricular volumes and ejection fraction using dedicated software

Abbreviations: 3D – three dimensional; RV – right ventricle; EDV – end-diastolic volume; ESV – end-systolic volume; EF – ejection fraction; SV – stroke volume


FR= 57 fps
HR= 71 bpm
RV
GS=-21.3%
Peak Systolic Strain
Six-segment model
for RV strain assessmnet
AVC
Longitudinal Strain


ED
ES
Worksheet
RV EDV 151 ml
RV ESV 88 ml
RV EF 41.8 %
RV SV 63 ml
RV EDV index 85 ml/m2
RV ESV index 49 ml/m2
RV SV index 35 ml/m2
RV Dd base 38 mm
RV Dd mid 28 mm
RV Ld 93 mm
TAPSE 13 mm
RV FAC 23.1 %
3D reconstruction of the RV
Volume
ml