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REVIEW

Right Ventricle and Cardiac Resynchronization Therapy. Spectator or Actor?

Silvia DEACONU[1,2], Alexandru DEACONU[1,2], Aura VIJIIAC[1,2], Alexandra ACOSTACHIOAIEI[1,2], Maria DOROBANTU[1,2]

ABSTRACT

Lately, RV dysfunction has emerged as a significant prognostic factor in heart failure with reduced ejection fraction (HFrEF). More so, recent data show a specific pattern of RV contraction in LBBB patients that is corrected by CRT, but not in patients with RV failure. The importance of RV evaluation in CRT patients is still under debate. Establishing the role of RV function in the setting of CRT may help identify patients with high risk of adverse events. Moreover, the changes induced by CRT upon RV may lead to a better understanding of the mechanisms behind CRT effects and may facilitate novel criteria for optimal selection of CRT candidates.

Keywords: right ventricle, cardiac resynchronization therapy, CRT, TAPSE, RV strain.

REZUMAT

În ultima perioadă disfuncția de ventricul drept (VD) s-a dovedit a fi un element de prognostic important la pacienții cu insuficiență cardiacă cu fracție de ejecție redusă. Mai mult, date recente indică un pattern specific de contracție a VD la pacienții cu bloc de ramură stângă major, care este corectat de terapia de resincronizare cardiacă (CRT), nu însă și la pacienții cu disfuncție de VD. Importanța VD la pacienții care efectuează CRT este încă un subiect neclar. Stabilirea rolului VD la pacienții cu CRT ar putea facilita identificarea celor cu risc crescut de evenimente adverse. Mai mult, schimbările induse de CRT asupra VD ar putea duce la o mai bună înțelegere a efectelor tehnicii CRT și la optimizarea selecției pacienților.

Cuvinte cheie: ventriculul drept, terapie de resincronizare cardiacă, CRT, TAPSE, strain VD.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an efficient therapeutic option for patients with HF and reduced ejection fraction (HFrEF). CRT improves clinical status, leads to reverse remodeling of left ventricle (LV), and decreases morbidity and mortality in patients with HFrEF[1,2]. CRT is indicated in patients with symptomatic HFrEF with a QRS duration ≥130ms with LVEF ≤35% despite optimal medical treatment[3]. Restoring LV synchronism and contractility is the rationale behind CRT. The effect of CRT upon RV is less clear and the complex relationship between RV function and CRT has become a subject of intensive research lately.

Furthermore, RV function plays an essential role in end-stage HF patients as a strong prognostic factor[4]. For instance, before left ventricle assist device implantation, RV function evaluation is mandatory.

Cardiac magnetic resonance (CMR) is considered the gold standard technique for evaluation of RV volumes and ejection fraction quantification[5]. Several of the echocardiographic parameters can offer an alternative to CMR in clinical follow up, especially the newer techniques like 3D, speckle tracking echocardiography.

This review's purpose is to summarize the role of RV function using echocardiographic parameters, in the evolution of HF patients undergoing CRT, providing an outlook of recent studies.

[1] „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[2] Department of Cardiology, Emergency Clinical Hospital, Bucharest, Romania

Contact address:
Alexandru DEACONU, „Carol Davila"University of Medicine and Pharmacy, Bucharest, Romania.
E-mail: alexandru.deaconu@umfcd.ro

ECHOCARDIOGRAPHIC EVALUATION OF RV

The position of RV in the thorax, its complex crescent shape and pattern of contraction lead to a challenging evaluation by 2D echocardiography. The RV is the most anteriorly positioned cardiac chamber, located behind the sternum. Due to its shape it requires multiple acoustic windows for evaluation[6].

RV size should be routinely measured using multiple acoustic windows. In general, a diameter above 41 mm at the base and above 35 mm at the midlevel in the RV-focused view indicates RV dilatation[6]. In laboratories with experience in 3D echocardiography RV volumes measurement is recommended[6].

Conventional echocardiographic parameters of the RV systolic function evaluation are: tricuspid annular plane systolic excursion (TAPSE), and RV fractional area change (RV FAC). RV myocardial performance index, or TEI index is a measurement of both systolic and diastolic RV function.

More recent echocardiographic parameters gather: tricuspid S-wave velocity using tissue Doppler imaging (TDI), RV longitudinal strain (RVLS) by speckle tracking echocardiography and three dimensional (3D) echocardiography RV volume evaluation, 3D RV strain.

- TAPSE represents the longitudinal systolic function of RV, assuming that the regional basal segments are representative for the overall RV function. TAPSE is measured by M-mode positioning the cursor at the tricuspid annulus from a standard 4-chamber view and measuring the systolic excursion form baseline to peak (Figure 1, A). A value <17 mm suggests RV systolic dysfunction6. TAPSE correlates well with other methods of investigating RV function[7].
- The systolic velocity of the lateral tricuspid annulus (S') is obtained by tissue Doppler from the apical 4-chamber view, positioning the sample volume at the tricuspid annulus or the basal segment of the RV free wall 8 (Figure 1, B). A peak systolic velocity value (S') less than 11.5 cm/s suggests RV systolic dysfunction, and seems to correlate with RVEF less than 45% at CMR[8]. The cut off value indicating RV systolic dysfunction is under 9.5cm/sec[6].
- The Tei index (the myocardial performance index for the RV) offers a global perspective on RV function, assesssing both diastolic and systolic function. Tei index is calculated as the isovolumic time to ejection time ratio. It can be measured by two methods – pulsed wave Doppler and tissue Doppler. There are different cut-offs for the two, as follows: for pulsed wave Doppler, a value >0.4 indicates RV dysfunction, whereas for tissue Doppler, RV dysfunction is considered at a cut-off of over 0.557. As a pulsed Doppler method, it is less dependent on the quality of the images and on ventricular geometry, and it is relatively independent of the preload, the afterload, and the heart rate[9].
- RV Fractional area change (RV-FAC) is another parameter utilized in assessing the systolic function of the RV by the formula= RV end-diastolic area – RV end-systolic area)/ RV end-diastolic area x100. The cut-off for RV dysfunction is below 35%7. It is measured in the A4C view by tracing the RV endocardium in both systole and diastole (Figure 1 C,D) in RV focused view. The 2D RV-FAC correlates well with the RVEF measured by magnetic resonance imaging[10].
- RV strain can be obtained by TDI or speckle-tracking imaging. The strain expresses the change of an object compared to the initial shape. While TDI is angle dependent, myocardial speckle-tracking is angle-independent and allows studying all components of the regional and global systolic deformation. From 4 chambers apical view focused on the RV, RV longitudinal strain (RV-LS) can be obtained by tracing the endocardial border manually and tracked by the software used (Figure 2). The evaluation includes RV global longitudinal strain (RVGLS) and RV free wall longitudinal strain (RV-fwLS). Both RV-fwLS and RV-GLS showed a stronger correlation with the RVEF, evaluated by CMR[11]. Pooled data (though heavily weighted by a single vendor) suggest that global longitudinal RV free wall strain. Above - 20% is likely abnormal[6].
- 3D echocardiography allows for the direct measurements of RV volumes and RVEF and it is the method that overcomes the complex RV shape (Figure 3). Evaluation of RV volumes and EF has been validated against CMR[12]. RV volumes need to be indexed to body surface area, and the upper limits of normal are gender-specific. End-diastolic volumes >87 mL/m^2 for men and >74 mL/m^2 for women are indicative of RV enlargement[13]. The 3D echocardiography needs special software, and it is not routinely included in everyday

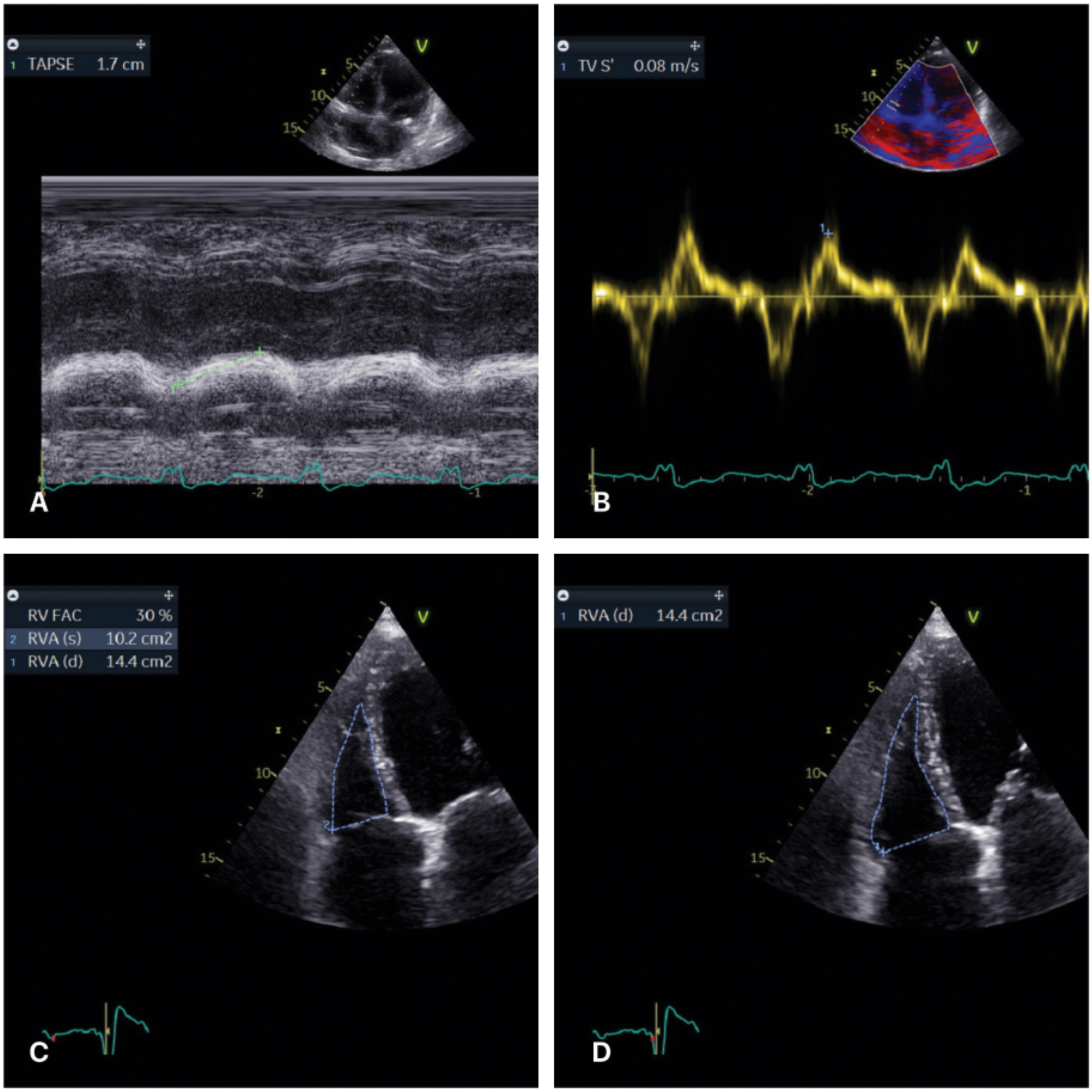

Figure 1. Parameters of RV systolic function. A: Tricuspid annular systolic excursion (TAPSE) measurement. B: Tricuspid S' systolic velocity using tissue doppler imaging. C,D: calculation of RV fractional area change (RV FAC) tracing RV area in systole (C) and diastole (D).

practice, but it is very useful in situations in which a global assessment of RV systolic function is needed.

- RV to pulmonary circulation coupling

The gold standard for evaluation of RV to pulmonary circulation coupling is obtained by invasive measures using pressure-volume loop-derived RV systolic elastance/arterial elastance (Ees/Ea). Lately there are several studies indicating that RV to pulmonary circulation coupling can be also evaluated by echocardiography[14]. Combining parameters of RV systolic function with pulmonary arterial systolic pressure (PASP) seems to be and accurate estimation of RV to pulmonary circulation coupling[15]. A study by Guazzi et al. proposed TAPSE/PASP ratio which was taken as a noninvasive index of RV to pulmonary circulation coupling based on the correlation with invasively evaluated RV systolic elastance/arterial elastance[15]. Another study by Tello at al confirmed that among different parameters of RV function only TAPSE/PASP emerged as an independent predictor of Ees/Ea[14]. In several trials TAPSE/PASP ratio proved to be a predictor of worse prognosis in heart failure patients[15,16] and also in patients undergoing CRT[17]. A group by Iacoviello et al

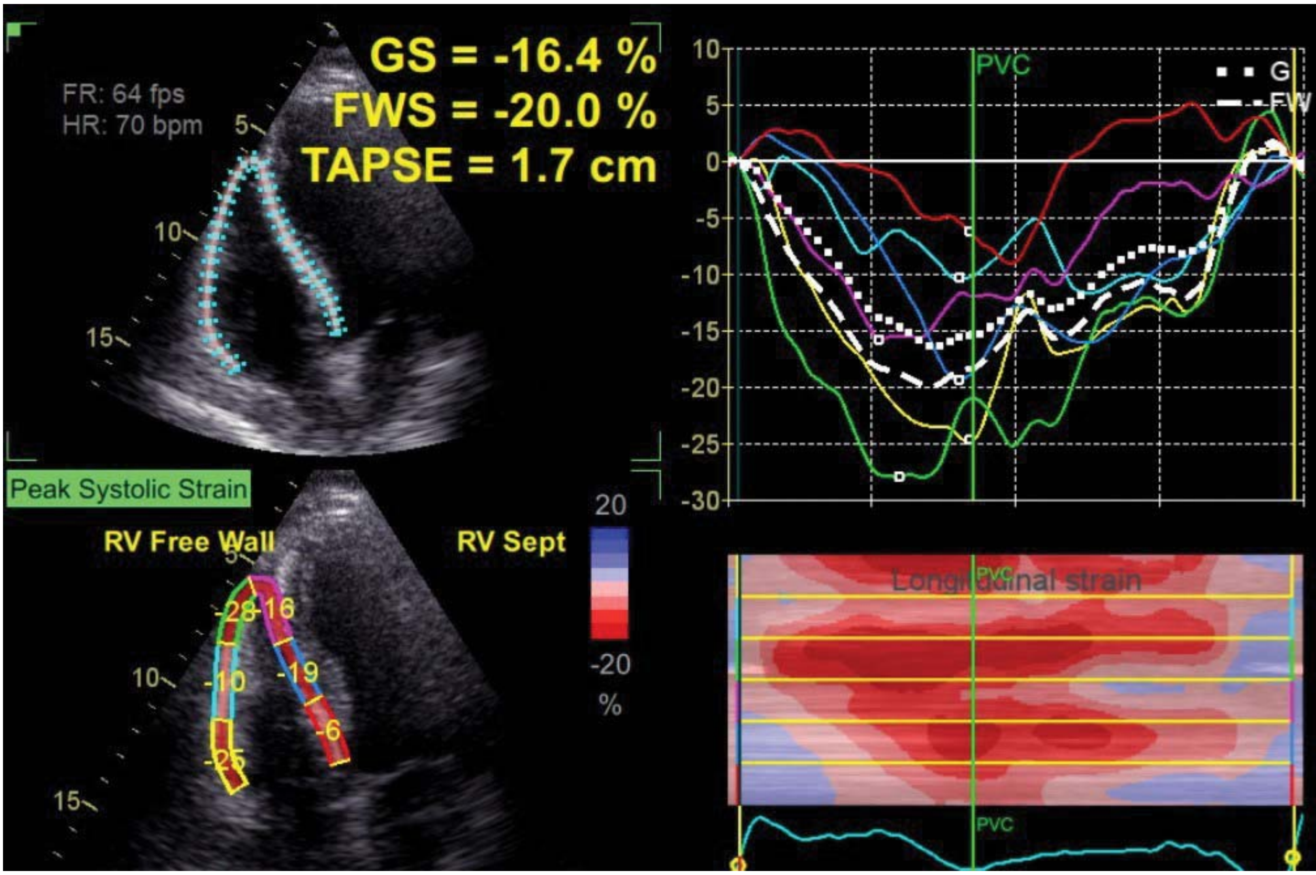

Figure 2. Calculation of RV strain using an automated method performed by specific software, GS: global strain, FwS free wall strain. TAPSE: Tricuspid annular systolic excursion.

proposed a combination of RV longitudinal strain (free wall and global) and PASP that can provide a reliable index of RV pulmonary circulation coupling[18]. This parameter also proved to be independently associated with higher risk of events[18].

RV MECHANICS BEFORE AND AFTER CRT

RV and LV are connected by sharing myocardial fibers within the interventricular septum[19]. The ventricles interact in systole whereas LV contraction increases RV contraction[19] a phenomenon called systolic ventricular interaction[20]. When LV becomes dysfunctional this leads to increased filling pressures and consequently to the elevation of pulmonary artery pressure and the afterload of RV[21]. Along with the deterioration of LVEF, systolic ventricular interaction is also leading to a reduction of RV contractile performance even when the RV is not directly involved in the disease[20]. Next, as the LV becomes more dysfunctional the septal fibres become less oblique, dramatically reducing their mechanical advantage and further impairing RV contractile function[20]. Along with RV failure appears functional tricuspid regurgitation which alters furthermore the RV systolic function.

In patients with LV systolic dysfunction and left bundle branch block (LBBB) there are some others particularities. LBBB leads to an abnormal contraction of the interventricular septum (IVS) with marked early systolic shortening and leftward motion[22]. Because IVS also contributes to RV contraction, this abnormal movement may also affect RV[23].

A very recent study of Storsten et al. investigated how LBBB and CRT modify RV free wall motion. The work gathers animal experimental data with human measurements in patients with non-ischemic cardiomyopathy, LBBB and a normal RV function[23]. The study revealed an abnormal early systolic premature shortening of the RV free wall visible with echocardiographic longitudinal strain analysis. Interestingly, in this study, CRT reduced or abolished this abnormal RV shortening, therefore increasing the RV workload[23].

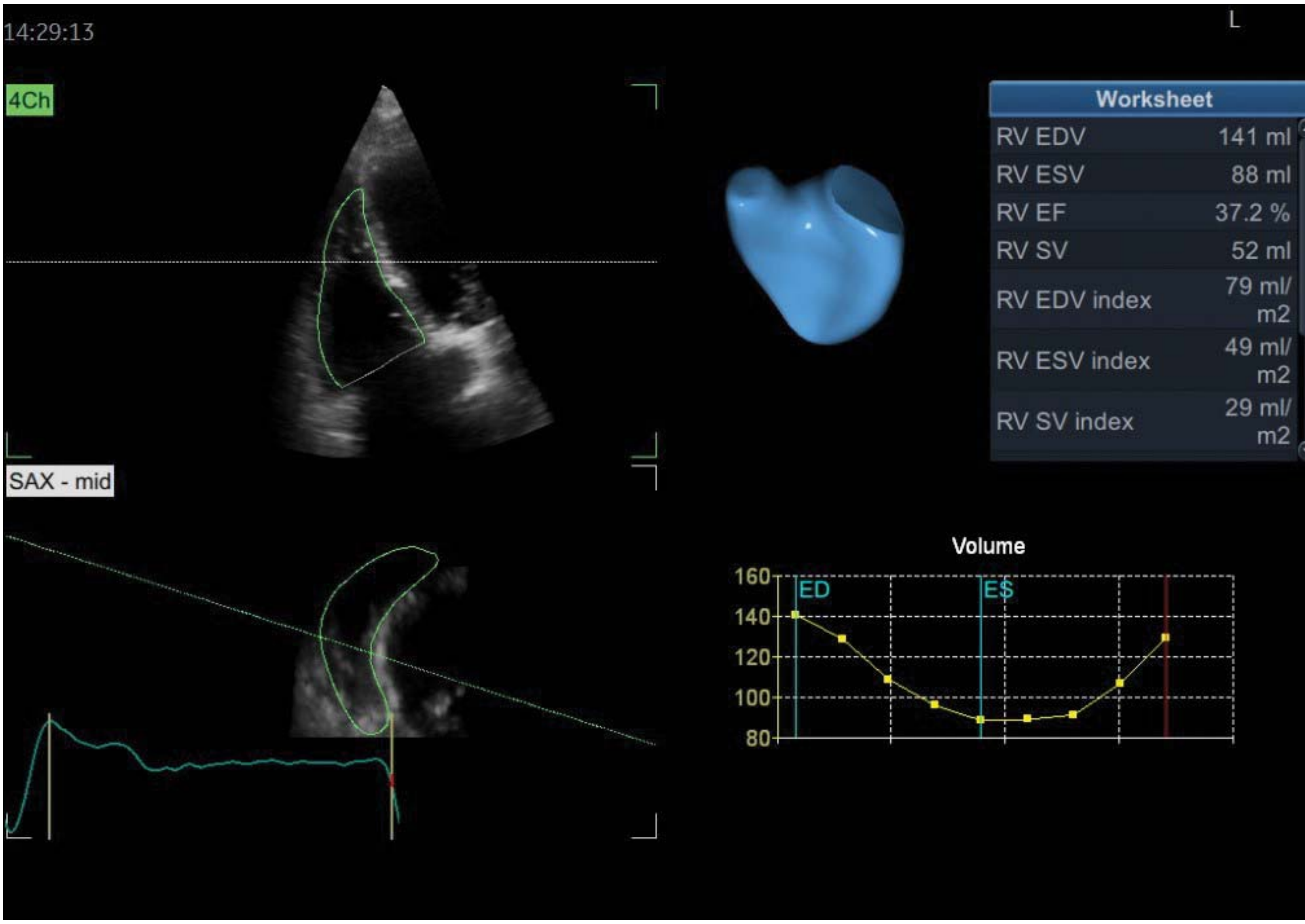

Figure 3. 3V volumes and RV EF calculation using dedicated software.

Next, Lumens et al. tried to prove this hypothesis using computer simulations with models of artificial heart[24] with the purpose of analyzing the mechanics of a failing heart with LBBB and treatment with CRT[24]. They confirmed the early systolic RV shortening in patients with LBBB and the fact that it amenable by CRT. However, CRT did not lead to this mechanical change in the heart with additional RV failure. Both studies support the idea that the presence of the early systolic RV shortening associated with LBBB may have prognostic value and it is modifiable by CRT, and also that a dysfunctional RV leads to less response to CRT.

RV AND RESPONSE TO CRT

The presence of RV systolic dysfunction is associated with a higher risk of adverse cardiovascular events[25] but also less response in CRT patients[26,27]. There is a consensus in literature that RV systolic dysfunction implies a higher risk of cardiovascular events in HFrEF patients, but if it predicts also response to CRT is less clear.

The main parameter used in these trials to assess RV function is TAPSE. A study by Leong et al which included 848 CRT patients show that RV dysfunction (TAPSE <14mm) was associated with a greater incidence of all-cause mortality[25]. Patients with lower TAPSE had a higher mortality, regardless of assigned treatment, in a the study CARE HF (*Cardiac Resynchronization in Heart Failure*) performed over 813 patients[28]. Another analysis of CARE HF study performed by Ghio et al indicate that 18 months after CRT, the decrease in end systolic volume and the increase in EF were less in patients with a TAPSE <14 mm when compared with patients with TAPSE>14 mm[26].

Scuteri et al., use several markers of RV systolic function (TAPSE, PASP, RV end systolic and end diastolic area and RV FAC) and show a negative correlation between baseline RV systolic dysfunction and left ventricular remodeling response to CRT[27].

Interestingly, a very recent work by Patel et al use visual evaluation of RV systolic function done by cardiologists with board certification in echocardiography.

Table 1. Summary of studies analyzing effect of CRT upon RV

Study	Number of patients	Methods	RV markers used	CRT effect on RV	Year
Rajagopalan[34]	35	Echocardiography	TDI S' velocity	Improvement after 3-6 months	2007
Donal et al.[35]	50	Echocardiography	TAPSE TDI S' velocity RV fw S	Improvement after 3 months	2008
Scuteri et al.[27]	44	Echocardiography	RV FAC TAPSE RV EDA, RV ESA	No reduction after 6 months	2009
Burri et al.[36]	44	Radionuclide angiography	RV EF	Slightly improves RVEF after 6 months	2010
Leong et al.[25]	848	Echocardiography	TAPSE	Improvement	2013
Damy et al.[28]	814	Echocardiography	TAPSE	No effect Little interaction with TAPSE	2013
Abdelhamid MA et al.[33]	94	Echocardiography	RV diameters TAPSE RV FAC TDI S' velocity RVGLS	RV reverse remodeling Improves RV systolic function after 6 months (5.9+/-1.2 months)	2017
Storsten et al.[23]	24 /16 dogs	Echocardiography and ultrasonic dimension crystals and micromanometers.	RV strain	Increases workload of RV	2020

RV: right ventricle, TDI: tissue Doppler imaging, TAPSE: tricuspid annular systolic excursion, RV FWS: RV free wall strain, RV FAC: RV fractional area change, RV EF: RV ejection fraction, RV GLS: RV global longitudinal strain

This study shows that CRT response was significantly higher in patients with normal RV compared with patients with dysfunctional RV. Normal RV function was associated with better survival compared with patients with RV dysfunction[29].

Other studies use the composite parameters to evaluate RV to pulmonary circulation coupling and its significance in HF patients with or without CRT. For example, Bracanca et al. evaluated the role of RV-PA coupling estimated by TAPSE/PASP ratio in CRT patients. TAPSE/PASP outperformed PASP and TAPSE in predicting the response to CRT[17].

A low TAPSE/PASP ratio correlated with high risk of cardiovascular events in HF patients with reduced and also with preserved EF[15]. The novel parameter used to estimate RA to pulmonary artery coupling: RV strain/PASP ratio also proved to be associated with an increased mortality risk and worse outcome in HF patients[16].

In contradiction with the data above, Sharma et al conducted systematic search in literature including of 16 studies published between 1966 to 2015 (N =1764), and concluded that baseline RV function as assessed by TAPSE, FAC, RV strain and RVEF does not determine response to CRT as assessed by change in LVEF[30].

Another study by Bernard et al. used systolic peak velocity at the tricuspid annulus (S') to evaluate RV function. Interestingly, RV dysfunction defined by S' velocity <11.5cm/sec was associated with significantly more severe LV longitudinal dyssynchrony. Moreover S' velocity was correlated with LV longitudinal dyssynchrony. However, LV radial contractility and dyssynchrony were not affected by RV function[31].

Very recent work published by Strosten and Lumens with a combination of patient and animal experimental data and computer simulation show that LBBB reduces work upon RV free wall. Conversely CRT induces an increase of work load upon RV that may be supported by only by a functional RV[23,24]. This may explain why a dysfunctional RV may be associated with worse outcome after CRT[24].

EFFECT OF CRT ON RV

RV failure implies a worse prognosis in patients undergoing CRT but the direct effect of CRT upon RV function is still under debate. Table 1 summarizes the main studies that analyzed the effect of CRT upon RV function and structure. Contradictory results may be noticed among the trials.

Leong et al. prove that improvement in RV function after CRT was independent of the improvement in

LV systolic function but significantly associated with the improvement in LV diastolic function[25]. More so, in a study performed using pressure volume loop catheter approach Schmeisser et al. show that the improvement of RV to pulmonary circulation coupling is associated with a greater RV remodeling after CRT[32].

Another study by Abdelhamid et al show that CRT promotes RV reverse remodeling and improves RV systolic function in volumetric CRT responders[33]. The group discusses that this may be a consequence of reducing mitral regurgitation, and the decrease of pulmonary hypertension.

Another study of Burri et al. using radionuclide angiography show that CRT has no acute effect on RVEF, and only slightly improves RVEF at follow-up. Patients with reduced RVEF at baseline were less likely to respond to CRT, indicating that right ventricular systolic dysfunction may play a role in patient selection[36]. Nevertheless, baseline RVEF alone cannot be used to exclude patients from CRT, as 47% of patients with reduced RVEF still showed improvement in NYHA classification[36].

However, in CARE HF trial (*Cardiac Resynchronization in Heart Failure*) CRT improved LV but not RV structure and function with little evidence of an interaction with TAPSE[28]. The recent study of Storsten show an acute increase of the RV free wall workload in hearts with LBBB treated with CRT[23]. This may explain the lack of an obvious improvement of RV function after CRT. Further studies are needed to clearfy how RV function and structure change after CRT and if this change may be related to CRT response.

CONCLUSION

A complete evaluation of RV systolic function and structure needs multiple echocardiographic parameters, by using the conventional and the newest techniques . Echocardiographic evaluation of RV systolic function, in the setting of CRT, may contribute to identify the patients with a higher risk of cardiovascular events. However, currently there are no data indicating that CRT patient selection should be influenced by RV systolic function. Recent data support the idea that there is a specific pattern of RV contraction in LBBB patients which is corrected by CRT with the exception of those with RV failure.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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