

# **Prognostic Significance and Normal Values of 2D Strain to Assess Right Ventricular Systolic Function in Chronic Heart Failure**

## **Short Title: RV dysfunction and prognosis in CHF**

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## **ABSTRACT**

**Aims:** Chronic heart failure (CHF) has a poor prognosis. Our aims were to determine the normal values and prognostic significance in CHF patients of right ventricle (RV)-2D strain, a new echocardiographic parameter.

**Methods and Results:** Between 2005 and 2010, we prospectively enrolled 43 controls and 118 stable CHF patients seen at our CHF clinic. All patients underwent a physical examination, laboratory tests, and echocardiography. Standard echocardiographic variables, tricuspid annular plane systolic excursion, peak systolic velocity of tricuspid annular motion using tissue Doppler imaging, and RV and left ventricle 2D-strain were measured. The primary outcome was death or emergent transplantation or emergent ventricular assist-device implantation or acute heart failure. RV-2D strain was measurable in 39 controls (58±17 years, 50% men), whose median value was -30% (95% confidence interval [95%CI], -39%;-20%); and in 104 CHF patients (80% men, mean age 57±11 years, and mean left ventricular ejection fraction 29%±8%), whose median value was -19% (95%CI, (-34%;-9%). During the mean follow-up of 37±14 months, 44 patients experienced the primary outcome. By Cox proportional hazards multivariate analysis, only RV-2D strain and log-transformed brain natriuretic peptide independently predicted experiencing the primary outcome within the first year. The best RV-2D strain cut-off by ROC analysis was -21%, and patients with values >-21% were at greatest risk ( $\chi^2$ -log-Rank test=14.1,  $p<0.0001$ ).

**Conclusion:** RV-2D strain is a strong independent predictor of severe adverse events in patients with CHF and may be superior over other systolic RV or LV echocardiographic variables.

**Abbreviations:**

ACE: angiotensin-converting enzyme;

AR inhibitors: angiotensin receptor inhibitors.

BNP: brain natriuretic peptide;

CHF: chronic heart failure;

LV: left ventricle

NYHA: New York Heart Association;

RV: right ventricle

## INTRODUCTION

Chronic heart failure (CHF) is an inexorably progressive condition that is ultimately fatal in the absence of cardiac transplantation. The identification of predictors of cardiac events in patients with CHF would help to optimise treatment decisions. Given the increasing prevalence of CHF, a method capable of accurately predicting cardiac events and suitable for use in everyday clinical practice is urgently needed.

The right ventricle (RV) is pivotal in maintaining hemodynamic stability and an adequate cardiac output. Thus, recent studies point to a crucial role for RV systolic function in the course of several cardiovascular diseases.<sup>1,2</sup> Over the last few years, RV systolic function has been proven in many studies to influence the prognosis of patients with CHF.<sup>3-5</sup>

Imaging studies that can be used to assess RV systolic function include echocardiography, angiography, radionuclide ventriculography, and magnetic resonance imaging.<sup>1,2</sup> Among these tools, echocardiography is the most readily available and the most widely used in everyday clinical practice. Consequently, the identification of a simple echocardiographic parameter that reliably predicts outcomes in CHF would be of considerable interest. In several studies, selective systolic motion or contractility of the tricuspid annulus measured by M-mode echocardiography<sup>4,6,7</sup> or tissue Doppler imaging (TDI) were found to hold prognostic significance.<sup>8,9</sup> Recently, 2D imaging of myocardial deformation, or strain, was found useful for assessing left ventricle (LV) function.<sup>10</sup> Angle-independent 2D strain imaging is now available on echocardiography systems and has been shown to reliably reflect RV function. Whether myocardial deformation parameters derived from the RV supply additional information over

standard echocardiography parameters in everyday clinical practice remains unknown.

Furthermore, the normal 2D strain values for the RV have not yet been reported.<sup>11,12</sup>

Here, our objectives were to determine the normal values of RV-2D strain in healthy controls, the prognostic significance of RV-2D strain in patients with CHF, and the best RV-2D strain cut-off for identifying high-risk patients with CHF.

## **METHODS**

### **Study population**

Between 2005 and 2010, we enrolled 118 patients receiving follow-up at our CHF clinics (CHU Henri Mondor, Créteil, France). Inclusion criteria were the use of appropriate medications, a clinically stable condition for at least the past month, and sinus rhythm. We also recruited, through advertising, 43 individuals free of cardiovascular disease and matching on age with the group of the patients, who served as the controls.

The study complied with the Declaration of Helsinki. The local ethics committee approved the research protocol. Informed consent was obtained from each study participant prior to inclusion.

### **Study assessments**

The following were performed in all study participants: medical history, physical examination, blood tests (brain natriuretic peptide [BNP], creatinine, and haemoglobin), and a functional test (6-minute walk test and/or cardiopulmonary testing).

All study participants underwent an echocardiographic examination at rest. The participants were in the left lateral decubitus position. An experienced sonographer performed the examination using a Vivid 7 system (GE Vingmed, Horten, Norway). Standard parasternal views (long and short axis) and four-chamber apical views were obtained. Four-chamber apical 2D grey-scale images were recorded with a frame rate  $\geq 50$  Frames per second (fps). All data were stored digitally for off-line analysis using Echo-PAC software (V7.0.0, GE Vingmed Ultrasound). Standard RV and LV function parameters were determined as recommended by the American Society of Echocardiography,<sup>13</sup> and for each parameter the mean of three consecutive cardiac cycles was recorded. These parameters included the transcuspid annular plane systolic excursion (TAPSE) on the M-mode apical four-chamber view, the tricuspid annular peak velocities using TDI ( $Sa_t$ ,  $Ea_t$ , and  $Aa_t$  waves), LV ejection fraction (LVEF), and LV end-diastolic diameter index to body surface area ( $LVEDD_{ind}$ ). Early ( $E_m$ ) and late ( $A_m$ ) transmitral diastolic peak flow velocities and filling deceleration time (DT) were measured using pulsed-wave Doppler imaging of the mitral valve inflow. Peak accelerations of mitral annular velocity ( $Sa$ ,  $Ea$ , and  $Aa$  waves) were also measured in the lateral and septal positions using TDI. Maximal tricuspid regurgitation velocity was determined.

RV and LV peak systolic longitudinal strain and strain rate were assessed on the apical four-chamber view using speckle tracking analysis. Patients whose RV-2D strain was not measurable were excluded from the analysis. Speckle tracking analyses motion by real-time tracking of the frame-to-frame movements of naturally occurring echo-dense speckles, using Echo-PAC software. The 2D strain and strain rate values can be derived by comparing the displacement of the speckles relative to one another throughout the cardiac cycle. For our study, the endocardial border was drawn manually and the region of interest (ROI) was generated

automatically to include the entire myocardium. ROI position and width were adjusted manually when necessary. Segments with poor-quality tracking were discarded. The software automatically tracked the myocardial movements, dividing the myocardium into six segments. QRS onset is detected from the simultaneous ECG recording to define the time point when strain equals zero. The lateral RV wall and the septal and lateral LV walls were divided into basal, middle, and apical segments for computation of regional strain and strain rate values by the software as means per segment. Global longitudinal strain and global strain rate for the entire traced ventricular contour were computed and expressed as mean $\pm$ SD. The standard echocardiographic measurements, TDI, and offline 2D strain and strain rate measurements were performed by a single sonographer, who was blind to the clinical data and outcome. Inter-observer reproducibility was assessed in a random sample of 30 patients.

### **Outcome measures**

The primary end-point was the occurrence of any of the following: death, emergent cardiac transplantation, emergent implantation of a ventricular assist device, and admission for acute heart failure. In each patient, only the event that occurred first was considered for the analysis, except when acute heart failure resulted during the same hospitalisation in death or emergent surgery for cardiac transplantation or LV assist device implantation, in which case only the death or surgery was recorded. Follow-up information was obtained either from the medical chart or by interviewing the patient. Patients who underwent elective cardiac transplantation or implantation of a ventricular assist device were censored at the time of surgery.

## Statistical analysis

Continuous variables were described as mean $\pm$ SD, except BNP, which was described as median $\pm$ SD (and logarithmically transformed for the other statistical analyses). The two-tailed unpaired Student's test was used to compare means of continuous variables and the chi-square test (or Fisher's test where appropriate) to compare categorical variables. We divided the patients with CHF into two groups based on whether they experienced the primary end-point within 1 year of study inclusion. Patients without the primary end-point who had less than 1 year of follow-up were excluded from the analysis.

We performed a time-to-event analysis using a univariate Cox proportional hazard model. Variables for which *p* values in the univariate analysis were smaller than 0.05 were entered in a multivariate Cox proportional hazard model. Factors independently associated with the primary end-point were identified using backward stepwise selection. We tested three models. The first model included the significant variables measuring RV systolic function and compared the strength of their associations with the primary end-point. The second model included all significant echocardiographic variables and the third model all significant clinical, laboratory, and echocardiographic variables.

The accuracy of RV-2D strain for predicting the occurrence of the primary end-point was assessed by computing the areas under the receiver-operating characteristic (ROC) curves (ROC-AUCs). The Youden test was performed to determine the best RV-2D strain cut-off. Finally, a Kaplan-Meier curve of event-free survival over time was constructed using the RV-2D strain cut-off. Values of *p* smaller than 0.05 were considered significant. Analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).



## **RESULTS**

Figure 1 shows the study participant flow chart. We included 161 individuals, of whom 118 had CHF and 43 were controls. RV-2D strain was measurable in 39 (91%) controls and 104 (88%) CHF patients; only these 143 participants were included in the analysis. RV-2D strain was measurable in most of the lateral wall segments (Figure 1); measurement failures were most common at the basal segment of the RV lateral wall of the controls (Figure 1).

### **Comparison of baseline characteristics between controls and patients**

Table 1 reports the main baseline clinical, laboratory, and treatment characteristics of the controls and CHF patients in whom RV-2D strain was measurable. Table 2 shows the M-mode, transmitral Doppler, and TDI of the LV and RV. The results in the CHF patients indicated severe impairment of RV and LV systolic function and of LV diastolic function.

Table 3 reports the RV and LV 2D strain and strain rate data. For all variables, values were significantly lower in the control group than in the CHF group. Figure 2 shows the distribution of RV-2D strain values. The median RV-2D strain value was -30% (95% confidence interval [95%CI], -39%; -20%) in the controls and -19% (95%CI, -34%; -9%) in the patients with CHF. RV-2D strain correlated strongly with TAPSE and  $S_{at}$ , two echocardiographic variables known to reflect RV systolic function (Figure 3). 2D strain and strain rate values were higher for the RV than for the LV (Table 3).

### **Comparison of patients with CHF who did and did not experience the primary end-point**

At last follow-up, 60 patients, with a mean follow-up of  $33\pm 13$  months, had not experienced the primary end-point and 44 patients had experienced the primary endpoint (acute heart failure episode,  $n=32$ ; and other,  $n=12$ ). Of the 60 patients without the primary end-point, 5 underwent elective heart transplantation and 2 elective implantation of an LV assist device.

After 1 year, 29 CHF patients had experienced the primary outcome and 69 had not. The baseline characteristics of these 97 CHF patients are shown in Tables 1, 2, and 3. The only significant clinical or treatment difference at baseline was a higher prevalence of hypertension in the subgroup with the primary outcome. This subgroup also had worse RV and LV systolic function with higher values for BNP and Em/Am and lower values for LVEF. The subgroup with the primary outcome had higher mean values for LV-2D strain of lateral segments and basal segments and for the mean of these two variables, compared to the CHF subgroup without the primary outcome. Segment-by-segment comparisons showed no significant differences between the two subgroups. The subgroup with the primary outcome within 1 year had significantly higher values for mean septal LV-2D strain rate and mean of the septal- and lateral-segment strain rates. RV-2D strain values for the three RV wall segments were significantly higher in the subgroup with the primary outcome than in the subgroup without the primary outcome after 1 year. In contrast, the two subgroups were not significantly different regarding the RV-2D strain rate values.

### **Prognostic significance of strain and strain rate values**

Tables 4 and 5 show the results of the univariate and multivariate Cox proportional hazard model analyses. RV-2D strain was a better predictor of the primary outcome compared to the other echocardiographic variables measuring RV systolic function (TAPSE and S) or LV

function (LVEF and E/Ea). RV-2D strain remained significantly associated with the primary outcome when all the clinical, laboratory, and echocardiographic variables were added to the model. The best RV-2D strain cut-off for separating CHF patients with and without the primary outcome within 1 year was -21%. Interestingly, 96% of the controls and 56% of the CHF patients had RV strain values below this cut-off.

### **Reproducibility**

Intra-observer reproducibility was 8% for RV global longitudinal strain and 10% for strain rate. Corresponding values for inter-observer reproducibility were 10% and 14%, respectively.

## **DISCUSSION**

We showed that RV-2D strain correlated with standard echocardiographic parameters (TAPSE and peak velocity of tricuspid annular systolic motion by pulsed TDI) used to measure RV contractility. Among our controls, 96% had RV-2D strain values lower than -21%. RV-2D strain was independently associated with the occurrence within 1 year of a composite end-point (death, admission for acute heart failure, emergent cardiac transplantation, or emergent ventricular assist-device implantation). RV-2D strain values greater than -21% (-21% to 0%) were at highest risk for experiencing the primary outcome within the first year.

### **Echocardiographic evaluation of RV systolic function**

The complex shape and marked load dependency of the RV create challenges when assessing RV function.<sup>2</sup> Various echocardiographic surrogates for RV contractility have been

described.<sup>4,9</sup> RV ejection fraction measurement using 2D echocardiography was the first echocardiographic method used to assess RV systolic function<sup>14,15</sup> but required numerous geometric assumptions that diminished the accuracy of the results. Two other parameters were therefore developed, TAPSE<sup>4</sup> and the peak velocity of tricuspid annular systolic motion measured using TDI.<sup>9</sup> These two parameters merely estimate the annular longitudinal function of the RV free wall, based on displacement of the tricuspid ring relative to the transducer. More recently, TDI-based parameters reflecting myocardial deformation, such as strain and strain rate, were shown to be closely related to the intrinsic functional capacity of the RV myocardium and to be more sensitive than previous parameters to subtle changes in contractility.<sup>16,17</sup> However, the angle dependency and absence of automatic measurement methods were major obstacles to the use of RV strain and strain rate. Since then, speckle tracking has been developed to image myocardial deformation imaging as a means of assessing RV systolic function. Speckle tracking provides rapid and simultaneous quantification of both regional and global lateral RV systolic function, as longitudinal lateral (free wall) RV function generates 80% of the RV stroke volume.<sup>18</sup> TDI and 2D strain-derived parameters have been found superior over conventional echocardiographic parameters in identifying patients with regional RV dysfunction.<sup>19</sup> Furthermore, 2D strain is relatively angle-independent and independent of cardiac motion, in contrast to TAPSE.<sup>17</sup> 2D strain is also easily measurable using automatic software.

### **Prognostic significance of RV systolic function in CHF and RV-2D strain**

RV systolic function strongly predicts the occurrence of cardiac events in patients with CHF.<sup>3-5</sup> In keeping with an earlier study in patients with acute myocardial infarction,<sup>20</sup> RV-2D

strain was a strong predictor of our composite primary outcome in CHF patients. A cut-off of -21% was optimal for separating patients with and without the primary outcome after 1 year of follow-up. Similar cut-offs were found using speckle tracking in patients with myocardial infarction (-22.1%)<sup>20</sup> or TDI-derived strain measurement in patients with arrhythmogenic RV cardiopathy (-18.2%).<sup>19</sup> It is worth noting that reported RV cut-offs are higher than the previously reported LV cut-off (-9%).<sup>10</sup>

Longitudinal motion can be quantified using either strain or strain rate. Strain rate is assumed to be load independent and superior over strain in assessing myocardial contractility and prognosis. In our study, however, RV-2D strain performed better than strain rate in predicting the primary outcome. We previously obtained a similar result when assessing the prognostic significance of LV systolic function in patients with unstable CHF.<sup>10</sup> The superiority of 2D strain over strain rate may be related to the smaller amount of noise in the strain data, which facilitates identification of the peak.

### **Limitations of RV-2D strain measurement**

RV-2D strain was not measurable in 18 (11%) of our 161 study participants. The RV basal segment was less often measurable than the apical or middle segment. In the controls, the basal RV segment was difficult to track when motion of this segment was substantial and directed not only anteriorly but also towards the septum. A similar difficulty occurred in CHF patients with major anterior systolic motion of the tricuspid annulus, usually related to elevated pulmonary artery pressure.<sup>11</sup> In our study, we assessed longitudinal RV deformation and not radial RV deformation. When measured accurately, longitudinal deformation reflects global RV

contractile function under baseline conditions and during acute load modulation, whereas circumferential motion is influenced by changes in afterload.<sup>21</sup>

## **Conclusion**

In this study, RV-2D strain reliably reflected RV systolic function. An RV-2D strain cut-off of -21% was best for separating patients with and without the composite primary outcome after 1 year. These results suggest that the use of 2D-strain to assess RV contractility should be encouraged in everyday clinical practice to better evaluate the prognosis of patients with CHF.

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**Conflict of interest**

None of the authors has any conflicts of interest to declare.

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