Original Research

Long-Term Prognostic Value of Longitudinal Strain of Right Ventricle in Patients with Moderate Heart Failure

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Introduction: Right ventricular (RV) systolic dysfunction is a strong prognostic predictor in chronic heart failure (HF). However, assessment of RV function remains difficult. We investigated the prognostic value of different echocardiographic parameters for evaluating RV function in 60 patients with chronic HF and a low left ventricular ejection fraction (<40%) who were on optimal medical treatment.

Methods: RV function was assessed using standard and tissue Doppler echocardiography. The following parameters were measured: tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RVFAC), right myocardial performance index (MPI), tissue Doppler peak myocardial velocity (Sm) and longitudinal strain of the right ventricular wall in the basal and middle segments.

Results: During a mean follow-up of 32 ± 13 months, 6 patients died and 16 were hospitalised for HF. TAPSE, RVFAC, right MPI and Sm did not predict cardiovascular events. The only variable associated with either cardiac death or HF hospitalisation (p=0.002), or HF hospitalisation only (p<0.0001) was systolic longitudinal strain in the basal and middle segments of the RV wall.

Conclusion: Our study demonstrates that longitudinal RV strain is a powerful prognostic variable for the prediction of major cardiac events in patients with chronic HF.

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Right ventricular (RV) systolic dysfunction is a powerful prognostic variable in patients with congestive heart failure (HF).[1] Echocardiography has allowed the rapid and non-invasive assessment of RV systolic function. Initially, RV systolic dysfunction was measured mainly from tricuspid annular displacement.[2,3] The tricuspid annular plane systolic excursion (TAPSE) provides a rough estimate of the longitudinal function of the RV free wall.[3] Another surrogate for RV contractility is RV fractional area change (RVFAC), which has been shown to be a robust tool that shows a good correlation with invasive haemodynamic data.[4]

Recently, the clinical application of Doppler tissue imaging (DTI) and strain imaging has been shown to provide an objective assessment of global and regional RV function. Both methods are relatively easy to apply to the tricuspid annulus and RV free wall. In addition, the myocardial performance index (MPI), or Tei index, can be measured by standard Doppler or DTI and allows the quantitative estimation of right ventricular function. Pulsed-wave DTI is used to measure low-frequency Doppler systolic and diastolic velocities that reflect longitudinal RV myocardial motion; in particular peak tricuspid annular velocity during systolic ejection (Sm) was found to precisely quantify RV systolic function.[5]

More novel tissue Doppler-based echocardiographic parameters of myocardial deformation, such as strain and strain rate have been shown to be closely related to myocardial function.[6] Strain is a measure of deformation in myocardial thickening or shortening and provides additional measurements of myocardial mechanical function, independent of myocardial velocity and right ventricular loading conditions. One-dimensional DTI strain RV is best performed from the apical four-chamber view.

DTI (Sm and strain), TAPSE, right MPI and RVFAC allow an assessment of regional wall motion and myocardial contractility. The prognostic impact of the majority of these RV functional parameters has been assessed mostly in patients with severe HF. However, no study has yet compared the prognostic value of all these parameters of right ventricular function. Thus, the purpose of this study was to determine the prognostic power of multiple parameters for the assessment of RV function in patients with chronic HF.

Methods

We included in our study patients with moderate HF (New York Heart Association, NYHA class II) who were referred to the echocardiography laboratory at the University of Brescia. Only patients with adequate acoustic windows allowing clear visualisation of all cardiac chambers and valves were included in the study.

The criteria for inclusion into the study were: a) NYHA class II; b) stable clinical status and no episode of acute cardiac decompensation for ≥6 months; c) left ventricular ejection fraction (LVEF) <40%; and d) long-term, optimal and stable pharmacological treatment of HF. The exclusion criteria were: a) no prior detailed study of the aetiology of HF; b) history of cardiac surgery; c) haemodynamically significant valvular disease; d) change in drug therapy (particularly diuretic dose) within 6 months before the study; and e) advanced renal or liver insufficiency.

Examinations were performed in accordance with the recommendations of the American Society of Echocardiography.[7] Transthoracic echocardiography was performed using the Vivid 7 ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway).

In each patient we evaluated all right ventricular parameters: TAPSE, RVFAC, right MPI, DTI and strain. TAPSE was measured by M-mode echocardiography at the junction of the tricuspid valve and the RV free wall in the apical four-chamber view. Maximal TAPSE was determined by the total excursion of the tricuspid annulus from its highest position after atrial ascent to the peak descent during ventricular systole. RVFAC was used to evaluate RV systolic function; it was calculated using the following formula:

$$\text{RVFAC} = (\text{RVEDA}-\text{RVESA}) / \text{RVEDA}$$

where RVEDA and RVESA are RV end-diastolic and end-systolic areas, calculated from the apical four-chamber view.

Right MPI was calculated using the formula:

$$\frac{\text{RV isovolumic contraction time} + \text{isovolumic relaxation time}}{\text{pulmonic ejection time}}$$

Pulsed tissue Doppler echocardiography in the apical four-chamber view was performed with the sample volume positioned at the basal and middle RV free wall. The DTI was set to pulsed-wave Doppler mode; filters were set to exclude high-frequency signals and gains were minimised to allow a clear tissue signal. The DTI velocities were obtained from the four-chamber view. A 1-2 mm sample volume was placed in the basal and middle RV free wall in four-chamber view and the resulting velocities were recorded at a sweep speed of 100 mm/s. Systolic peak velocity (Sm) was measured from the myocardial velocity patterns obtained. Colour-coded DTI was obtained from the apical four-chamber view with frame rates exceeding 120 Hz. The colour-coded myocardial velocities were recorded at the base of the RV free wall, below the insertion of the tricuspid valve leaflets. Colour-coded tissue Doppler images of the basal RV wall from the apical four-chamber view were acquired to determine regional strain. Longitudinal strain was analysed in the region of interest, 12 mm in length, positioned in the basal and middle segments of the RV free wall. Peak ejection value was calculated as peak negative strain. The strain on apical RV free wall was not acquired, because of difficulties in accurately obtaining data from the apical segment. Right diastolic function was evaluated through the E and A waves, and the E wave deceleration time of the tricuspid inflow pattern. Finally right atrial area and volume were measured.

All these measurements were made in each patient over three cardiac cycles, and the average was used for statistical analyses. Results are presented as mean ± SD. Unpaired Student's t-tests were used to compare patients with versus without major adverse clinical events (MACE). These included death and rehospitalisation for worsening HF during follow up.

Survival was analysed using Kaplan–Meier cumulative mortality curves. Survival curves were compared using the log-rank test. A p-value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS 16.0 (SPSS Inc., Chicago, IL).

Results

The study group included 60 consecutive ambulatory patients (60.2 ± 10.1 years old; 83% males), with CHF due to left ventricular (LV) systolic dysfunction (LVEF≤40%), who were referred to our Institute from January 2008 to December 2008. Each patient had been on stable beta-blocker therapy for at least 6 months. All the patients had a sufficient acoustic window. At the time of our study all patients were in NYHA functional class II. The mean LVEF was 29.8 ± 8%. Sixteen patients had ischaemic dilated cardiomyopathy and 44 patients an idiopathic aetiology. The patients' characteristics are shown in Table 1.

During a mean follow up of 959 ± 397 days, 6 patients died from cardiovascular events (2 from myocardial infarction, 2 from arrhythmias, and 2 from HF), and 10 were hospitalised for worsening HF. Patients with cardiac events were more likely to be affected by ischaemic dilated cardiomyopathy. Age, sex, and a history of diabetes or hypertension were similar between patients with or without events during follow up.

Table 2 shows the patients' echocardiographic parameters. LVEF was numerically lower, and LV end-diastolic diameter and systolic pulmonary artery pressure were numerically greater in the patients who had a major event during follow up. No differences were observed with respect to the parameters of RV function, except for DTI strain (basal and middle). Parameters of RV diastolic function were also similar between the patients who had and who did not have an event during follow up.

Kaplan–Meyer survival curves of the patients subdivided on the basis of the median value of the basal RV free wall strain are shown in Figure 1 (HF hospitalisation) and Figure 2 (cardiovascular death + HF hospitalisation); the same results was obtained with middle RV free wall strain.

On Cox analysis, no patients with basal and middle RV free wall strain above the median value died or needed cardiovascular hospitalisation, and no other echocardiographic parameters had a prognostic value (Table 3).

Discussion

Our study shows that DTI RV strain, measured at the basal and the middle region, was the only measurement related with outcomes in patients with moderate HF caused by LV systolic dysfunction. None of the other investigated parameters of RV function were related with outcomes.

These findings may appear to conflict with previous studies that showed a prognostic value for the parameters we evaluated.[3,8,9] However, most of those parameters showed prognostic significance in patients with severe congestive heart failure or pulmonary hy-

Table 1. Baseline characteristics of the population.

	General population (n=60)	Idiopathic cardiomyopathy (n=16)	Ischaemic cardiomyopathy (n=44)	p
Male/female n, (%)	50 (83) / 10 (17)	13 (81) / 3 (19)	36 (81) / 8 (19)	NS
Age	60.2 ± 10.1	60.1 ± 10.8	60.3 ± 10.1	NS
Diabetes mellitus n, (%)	27 (45)	7 (43)	18 (40)	NS
Hypertension n, (%)	40 (66)	11 (68)	28 (64)	NS
Hypercholesterolaemia n, (%)	35 (58)	9 (56)	44 (56)	NS
HR (bpm)	68 ± 10	68 ± 11	67 ± 13	NS
SBP (mmHg)	120 ± 12	121 ± 13	120 ± 14	NS
DBP (mmHg)	85 ± 7	86 ± 6	85 ± 9	NS
LVEF (%)	29.8 ± 8.5	30.1 ± 8.5	29.7 ± 8.8	NS
LVEDD (mm)	65.3 ± 4.2	65.1 ± 4.1	65.9 ± 4.1	NS
LVESD (mm)	46.2 ± 5.3	46.2 ± 4.2	46.9 ± 3.1	NS
Beta-blockers/ACE inhibitors/diuretics (%)	90/95/98	91/95/98	90/94/98	NS

HF – heart rate; SBP – systolic blood pressure; DBP diastolic blood pressure; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; ACE – angiotensin-converting enzyme.

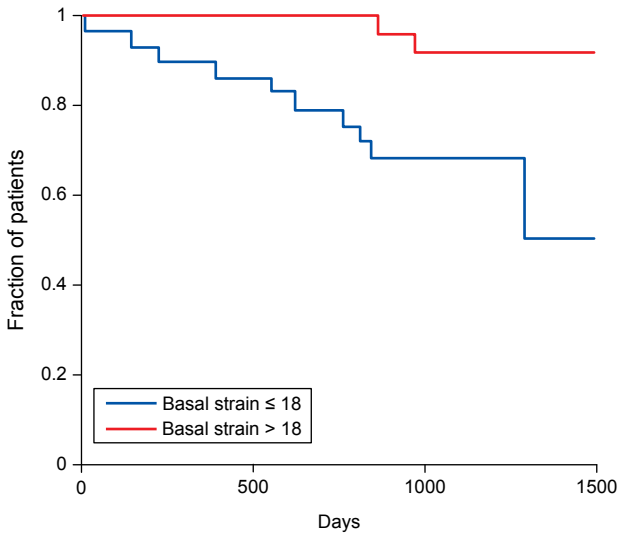

Figure 1. Kaplan–Meier curves for strain of basal right ventricular wall. Event-free from hospitalisation for heart failure in patients with basal strain >18 and ≤18 (median value).

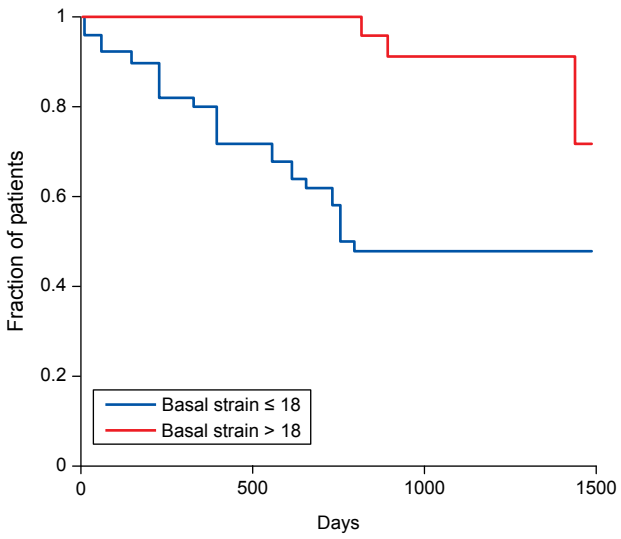

Figure 2. Kaplan–Meier curves for strain of basal right ventricular wall. Event-free from cardiovascular death or hospitalisation.

Table 2. Characteristics of patients with or without events.

	All (n=60)	CV death (n=6)	Alive (n=54)	CV death or HF hosp. (n=22)	HF hosp. (n=16)
LVEF	29.8 ± 8.7	24 ± 8.3	30.5 ± 8.6	28.7 ± 9.5	30.3 ± 8.5
LVEDD	65.8 ± 4.1	68.3 ± 2.9	65.5 ± 4.2	66.5 ± 4.4	65.5 ± 4.0
sPAP	34 ± 9	38 ± 5	33 ± 9	37 ± 9	33 ± 10
TAPSE	17 ± 4	17 ± 5	17 ± 4	17 ± 4	17 ± 4
RVFAC	35.2 ± 13.8	32.8 ± 7.1	35.5 ± 14.4	34.3 ± 13.9	35.6 ± 13.9
Right MPI	0.4 ± 0.3	0.44 ± 0.2	0.38 ± 0.3	0.43 ± 0.4	0.42 ± 0.4
DTI strain (basal)	-19.7 ± 6.2	-12.3 ± 3.3*	-20.5 ± 5.9*	-13.0 ± 3.7†	-22.2 ± 5.1†
DTI strain (middle)	-18.7 ± 5.7	-12.1 ± 3.7*	-19.5 ± 3.9*	-15.0 ± 2.7†	-20.2 ± 4.1†
Sm (basal) m/s	0.12 ± 0.03	0.12 ± 0.04	0.12 ± 0.03	0.11 ± 0.04	0.12 ± 0.03
Sm (middle) m/s	0.12 ± 0.04	0.11 ± 0.05	0.12 ± 0.03	0.11 ± 0.04	0.12 ± 0.03
A wave	0.34 ± 0.13	0.27 ± 0.04	0.35 ± 0.14	0.37 ± 0.16	0.33 ± 0.12
E wave	0.53 ± 0.18	0.56 ± 0.13	0.52 ± 0.18	0.48 ± 0.20	0.54 ± 0.17

* p<0.005, †p<0.0001.
CV – cardiovascular; HF – heart failure; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; sPAP – systolic pulmonary artery pressure; TAPSE – tricuspid annular plane systolic excursion; RVFAC – right ventricular fractional area change; MPI – myocardial performance index; DTI – Doppler tissue imaging.

pertension. Our study examined patients with moderate heart failure. A possible explanation of our results is that the parameters that failed to show any correlation with the prognosis in our study could be less specific and sensitive for RV function itself (contractility) and more influenced by other variables, such as pulmonary hypertension or right ventricular overload, which are less prevalent in NYHA class II patients like those of our study. TAPSE is a widely recognised, clinically useful and feasible marker of RV dysfunction. However it is not specific for RV function, since it has been shown to be strongly influenced by LV systolic function,[10] biventricular dyssynchrony,[11] and loading conditions. Although TAPSE was proven by Ghio et al to have predictive value in patients with HF,[3] it failed to provide prognostic information in our study. It has to be noted that in that earlier study, as well as other studies,[12] TAPSE was measured in a sicker population. We evaluated stable patients with moderate HF in NYHA class II and we believe that, in these patients, TAPSE is less compromised and may lack sufficient sensitivity to achieve clinical significance.

Table 3. Cox multivariate analysis.

	HR (CI)	p
Endpoint: Cardiovascular death		
Covariates:		
Aetiology	0.38 (0.04-3.5)	0.38
LV end-diastolic diameter > median value (66 mm)	4.67 (0.39-55.0)	0.21
LV ejection fraction > median value (30%)	1.62 (0.16-8.24)	0.88
Endpoint: HF hospitalisation		
Covariates:		
Aetiology	0.70 (0.14-3.55)	0.67
LV end-diastolic diameter > median value (66 mm)	0.25 (0.05-1.18)	0.08
LV ejection fraction > median value (30%)	1.16 (0.26-5.24)	0.84
Endpoint: Cardiovascular death + HF hospitalisation		
Covariates:		
Aetiology	0.48 (0.13-1.78)	0.27
LV end-diastolic diameter > median value (66 mm)	0.93 (0.28-3.09)	0.91
LV ejection fraction > median value (30%)	1.40 (0.41-4.72)	0.58

LV – left ventricular; HF – heart failure; HR – hazard ratio; CI – confidence interval.

Because of their rapid acquisition time, reproducibility, and ease of addition to standard transthoracic echocardiographic protocols, right DTI and strain imaging are potentially useful additional measurements for the assessment of RV function.[9]

Peak tricuspid annular velocity during systolic ejection (Sm) was found to quantify RV systolic function,[13] and was demonstrated to be a predictor of outcome among patients with severe HF. However, the Sm value is also significantly afterload-dependent. An inverse relationship between Sm and pulmonary artery pressure was previously described.[13,14] However, pulmonary artery pressure was only moderately increased in our patients, thus limiting the prognostic value of Sm.

Measurement of peak systolic strain in the basal and middle segments of the RV free wall has been used to measure RV performance. The clinical relevance of strain in the assessment of RV performance was first reported in patients with large pulmonary embolisms[15] or repaired congenital heart disease.[16] In fact, RV strain appears to be a more reliable and specific method for evaluating RV performance, since it is less dependent on pulmonary artery pressure and loading conditions.[17] Donal et al recently reported that right systolic strain was a more powerful prognostic index than cardiopulmonary exercise testing and brain natriuretic peptide in severe HF patients with stable disease and an absence of pulmonary hypertension.[18] Our study shows that longitudinal peak systolic strain, unlike other parameters related with RV function, is related with the prognosis of patients who have moderate HF.

We maintain that the prognostic value of longitudinal strain in patients with moderate HF is related to its ability to identify RV contractile dysfunction in the absence of fluid overload. In contrast, RV dysfunction in advanced heart failure and/or with fluid overload and/or pulmonary hypertension can still be accurately assessed by traditional parameters of RV function. It is also possible that new indexes of RV function, such as isovolumic acceleration and isovolumic strain, may allow better prediction of cardiac events.[17,19] They were not, however, assessed in our patients.

The main limitation of our study is the small number of patients studied and the absence of two-dimensional strain parameters. It is likely that some parameters, such as LVEF and end-diastolic diameter, as well as systolic pulmonary artery pressure, would have given different results between patients with and without cardiac events in the follow up, had a larger group of patients been studied. These parameters have been consistently shown to have prognostic significance in patients with heart failure caused by LV systolic dysfunction. On the other hand, apart from DTI systolic strain, the other parameters related to RV function were very similar between patients with and without events in our study group and it is unlikely that a larger study group would have yielded different results.

In conclusion, it is still uncertain which echocardiographic parameter allows a better and more clinically useful assessment of RV function in different populations. Our study suggests that DTI-derived

RV strain, measured at the basal and the middle region, is a major predictor of outcomes in patients with moderate HF caused by LV systolic dysfunction. This finding needs to be confirmed by further studies with larger populations.

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