Original Article

Relationship of soluble ST2 to pulmonary hypertension severity in patients undergoing cardiac resynchronization therapy

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Background: Pulmonary hypertension (PH) is an adverse prognostic marker in patients undergoing cardiac resynchronization therapy (CRT). We sought to determine the relation of biomarkers of fibrosis [soluble ST2 (sST2), galectin-3], wall stretch [amino terminal pro-brain natriuretic peptide (NT-proBNP)], and necrosis [high-sensitivity troponin-I (hsTnI)] to PH severity in CRT patients.

Methods: Biomarkers and right ventricular systolic pressure (RVSP) were measured at CRT implant and 6-month later (n=111). PH was categorized into 3 groups based on RVSP: no (<35 mmHg), mild-moderate (35–60 mmHg), and severe (>60 mmHg). Patients were categorized as progressors (worsened PH), persistent PH (no change) and regressors (improved PH). Endpoints were 6-month CRT response and 2-year major adverse cardiac event (MACE).

Results: RVSP was associated with CRT nonresponse (P=0.02) and MACE (P=0.03). Severe PH patients had 5-fold increase risk for CRT nonresponse (OR 5.0, P=0.04) and MACE (HR 5.7, P=0.04) over non-PH patients. Progressors and persistent PH patients had >2-fold odds for CRT non-response (OR 2.8, P=0.45) and >11-fold increase in MACE compared to no PH patients or regressors (HR 11.6, P=0.02). Only NT-proBNP and sST2 were discernable between PH groups, with graded increase based on PH severity (both P≤0.02), and lower values in regressors versus non-regressors (both P≤0.01). Levels of sST2 decreased at 6 months in regressors (15 ng/mL, P=0.03) and increased slightly (3–8 ng/mL) in non-regressors, without difference for NT-proBNP (P=0.08).

Conclusions: sST2 levels are related with PH severity in CRT patients. Serial sST2 changes after CRT implant suggests potential role to monitor PH after CRT.

Keywords: Pulmonary hypertension (PH); resynchronization therapy; biomarkers; heart failure (HF); echocardiography

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Introduction

Cardiac resynchronization therapy (CRT) is an adjuvant treatment for refractory heart failure (HF) that may reverse left ventricular remodeling, improve symptoms, and reduce mortality (1-3). However, approximately one third of patients fail to show a benefit (4,5). Chronically elevated filling pressure from left HF can induce secondary pulmonary hypertension (PH), leading to increased morbidity and mortality. Identification of PH derived from echocardiography is an adverse prognostic marker in HF and for patients undergoing CRT. Serial assessment of PH after CRT can also be helpful, and improvement of PH after CRT has been identified as an independent positive prognostic marker (6-13). Soluble ST2 (sST2) is an emerging cardiac biomarker, expressed by strained cardiomyocytes, and linked to cardiac fibrosis in HF. Elevated concentrations of sST2 are associated with progressive myocardial remodeling and adverse HF prognosis (14-17). Serial measurements of sST2 provide incremental value to baseline levels, reflecting changes in myocardial remodeling overtime (16). Along with other biomarkers, sST2 concentrations before CRT implantation may help to predict clinical non-response and MACE after CRT (18,19). Besides being associated with left ventricular remodeling, concentrations of sST2 have been linked to pulmonary vascular diseases, including PH. Accordingly in this study, we aim to examine a biomarker panel of myocardial fibrosis (sST2, galectin-3), myocardial wall stretch [amino terminal pro-brain natriuretic peptide (NT-proBNP)], and myocardial necrosis [high-sensitivity troponin-I (hsTnI)] and examine its relationship with PH defined by right ventricular systolic pressure (RVSP) by Echo and changes in the biomarker values to changes in PH status. In a focus analysis with sST2, we hypothesized that baseline and serial sST2 measurements would correlate with PH in patients undergoing CRT and parallel PH changes after CRT. We also hypothesized that sST2 serial variation after CRT will be associated with clinical outcomes.

Methods

Study population and protocol

The "Biomarkers to Predict CRT Response in Patients With HF" (BIOCRT; Clinical Trials.gov # NCT01949246) trial is a prospective observational study of CRT at a single tertiary care center. Study design, inclusion and exclusion criteria were previously reported (20). In brief, eligible patients were CRT candidates ≥18 years old, NYHA functional class II–IV on optimal drug therapy, left ventricular ejection fraction ≤35%, QRS interval ≥120 ms and a HF exacerbation within the past year. Exclusion criteria included life expectancy less than 6 months, severe aortic stenosis, recent cardiac surgery or coronary revascularization, intermittent or continuous intravenous therapy, chronic obstructive pulmonary disease, primary PH and pregnancy.

A total of 111 patients were included in this analysis. Study participants were followed through a time horizon up to 2 years. Thirty two patients did not have RVSP at 6 months (12 participants completed the 6-month office visit, but did not have an echocardiogram, 15 participants had 6-month echocardiography, but RVSP was not measurable, 4 participants had MACE with 3 deaths and 1 hospitalization, 1 participant did not have 6-month follow up, but had follow up later and was noted to be MACE-free and have a positive CRT response), therefore, follow-up echocardiographic data was available in 79 patients. Of the 111 patients included in the study, 88 patients had baseline serum blood samples drawn and 78 patients had plasma samples. For the first 10 patients, we did not have plasma samples as we initially started collecting only serum samples. Some patients had a clinical follow-up but declined the serial blood draws. We had approximately 50% retention rate for follow-up serial samples over 6 months, with resulting 42 patients with serial serum samples and 35 patients with plasma. The institutional review board approved the study protocol and all patients provided written consent prior to study initiation.

Echocardiography

Echocardiographic measurements included end-systolic and end-diastolic volumes by the modified biplane Simpson's method with computation of left ventricle ejection fraction (21,22). Right ventricular size and function were assessed by level 3 readers integrating all available parameters for each exam (RV diameters, tricuspid annular plane excursion, peak tricuspid annular velocity, fractional area change, myocardial performance index) (23). Tricuspid regurgitation was graded using American Society of Echocardiography (ASE) guidelines by level 3 readers, integrating vena contracta,

proximal flow convergence, hepatic vein flow Doppler and jet area (24). RVSP was estimated using simplified Bernoulli equation on peak tricuspid regurgitation jet velocity by continuous wave Doppler (23).

RVSP definitions and serial assessment

PH was defined as RVSP greater than 35 mmHg (25,26). Mild-moderate PH was defined as RVSP >35 and ≤60 mmHg, and severe PH as RVSP greater than 60 mmHg. At 6-months, echocardiography was performed to assess change in RVSP and PH severity. Delta-RVSP classes were defined by change in PH severity class from baseline to 6 months post implantation. Progressors were those whose RVSP worsened by one or more classes from pre-implantation, while regressors are those whose PH severity improved by one or more classes. Persistent PH was defined as those with stable PH severity at 6 months from baseline.

Outcomes

Clinical endpoints included 6-month CRT response and 2-year MACE. CRT response was measured using the Heart Failure Clinical Composite Score (HF CCS). The HF CCS includes subjective metrics like NYHA functional class and global assessment score as well as objective measures of decompensation such as hospitalization and mortality (27). HF CCS scores that were stable or worsened were considered non-responders, while responders improved their HF CCS scores. Major adverse cardiovascular event (MACE) was defined as the composite endpoint of death, cardiac transplant, left ventricular assist device, and HF hospitalization. CRT response and MACE was adjudicated by a committee consisting of 2 cardiologists, blinded to the biomarker and echocardiography results. Disagreement was resolved by consensus with a third cardiologist.

Blood samples

Peripheral venous blood samples were obtained at the time of device implantation and during the 6-month follow up visit. Samples were stored at –80 ℃ and sent to independent laboratories for analysis. The laboratories were blinded to the clinical history and timing of the samples. Plasma sST2 concentrations (Presage ST2; Critical Diagnostics, San Diego, CA, USA) were measured using enzyme-linked immunosorbent assay with an interassay coefficients of variation (CV) <12% and intraassay CV of 2.3%. Plasma gal-3 measurements (BGM Galectin-3, BG Medicine, Inc.) were performed by enzyme linked immunosorbent assay (ELISA), with interassay CV of 2.2%, and intra-assay CV of 3.0%. Serum NT-proBNP measurements (Dimension Vista Flex, Siemens) were performed by a one-step sandwich chemiluminescent immunoassay, with interassay CV of <3% and intra-assay CV of <4%. Serum hs-TnI measurements (Dimension Vista; Siemens) were performed by the one-step sandwich chemiluminescent immunoassay had a total imprecision (CV) of 8.5% at 4.4 pg/mL and 4.6% at 11.8 pg/mL.

Statistical analysis

Descriptive statistics were presented as mean ± standard deviation (SD) for normally distributed variables or as a median with interquartile range for non-normal, continuous variables. Categorical variables were summarized with frequencies and percentages. Wilcoxon-rank-sum tests or t-tests were used to compare continuous variables and Fisher's exact or chi-squared tests were used to compare categorical variables. Kruskal-Wallis test was used for >2 group comparison. Log transformation was applied for non-normally distributed continuous data. Two-year MACE-free survival was analyzed using Kaplan-Meier methodology and comparisons were made using a stratified log-rank test. We used logistic regression to test the association between CRT non-response and baseline log-transformed Echo metrics, 3-caterory PH by RVSP, and progressor categories. We used Cox proportional hazard models to test the association between MACE and baseline log-transformed Echo metrics, 3-caterory PH by RVSP, and progressor categories. A two-tailed P value of <0.05 was considered statistically significant. SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) was utilized for all statistical analyses.

Results

Baseline clinical and echocardiography characteristics are displayed in *Table 1*. Baseline clinical and demographic characteristics did not differ amongst those with and without follow-up 6-month echocardiography (*Table S1*, all P=NS). There were 40 (36%) CRT non-responders and 31 (28%) participants had MACE.

RVSP

Echo-based PH with RVSP >35 mmHg was present in

Table 1 Baseline patient characteristics

Characteristics	All patients (n=111)
Patient characteristics	
Age, years	65 [56–75]
Male, n (%)	85 (77%)
BMI, kg/m^2	27.4 [24.4–32.1]
Diabetes, n (%)	37 (33%)
History of atrial fibrillation, n (%)	38 (34%)
Hypertension, n (%)	66 (59%)
Ischemic cardiomyopathy, n (%)	44 (40%)
Device, n (%)	59 (53%)
PPM	19 (17%)
ICD	44 (40%)
NYHA functional class, n (%)	
I	0 (0%)
II	12 (11%)
III	91 (82%)
IV	8 (7%)
Medications, n (%)	
ACEI/ARB	84 (76%)
BB	93 (84%)
Spironolactone	35 (32%)
Diuretics	87 (78%)
ECG parameters	
QRS duration, ms	162 [146–178]
QRS >150 ms, n (%)	74 (67%)
LBBB, n (%)	59 (53%)
Paced rhythm, n (%)	20/110 (18%)
Echocardiography parameters	
LVEF, %	25 [19–31]
LV dimensions, mm	
End-diastole (EDD)	63±9
End-systole (ESD)	54±9
LV volumes, cm^3	
End-diastole (EDV)	213 [171–254]
End-systole (ESV)	158 [119–209]
RV enlargement, n (%)	26/95 (27%)
RV dysfunction, n (%)	38/94 (40%)
Tricuspid regurgitation (n=96), n (%)	
No	0 (0%)
Trace	25 (26%)
Mild	35 (36%)
Moderate	28 (29%)
Severe	8 (8%)
RVSP, mmHg	42 [35–51]
Laboratory markers	
eGFR (mL/min/1.73 m^2)	62±20

Device indicates presence of ICD and/or PPM at the time of cardiac resynchronization therapy implantation. BMI, body mass index; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitor; ARB, aldosterone receptor blocker; BB, beta blocker; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RV, right ventricular; eGFR, estimated glomerular filtration rate.

89 patients at baseline (80%), with a median RVSP in the study population of 42 mmHg (IQR, 29–60 mmHg). Severe PH with >60 mmHg was present in 13 (15%) patients. Of the baseline Echo parameters, RVSP was the strongest predictor of clinical events, and independently associated in multivariable models (*Table 2*). Compared to those with normal RVSP, severe PH was associated with greater than 5-fold increase risk of CRT non-response and two-year MACE (*Table 3*, *Figure 1*). Mild-moderate PH (RVSP 35–60 mmHg) had a slightly increased risk of CRT non-response and 2-year MACE compared to normal RVSP, but was not statistically significant.

Serial RVSP and clinical outcomes

Table 4 depicts the association of clinical outcomes with changes in PH severity. RVSP progressors (those whose PH severity class worsened) and those with persistent PH had over 2-fold increase odds for being a CRT non-responder at 6 months and over 11-fold increase risk of MACE at 2-year (*Table 4*, *Figure 2*).

Table 2 Echocardiographic variables and relation with clinical endpoints

Variable	Univariate		Multivariable	
	OR/HR (95% CI)	P value	OR/HR (95% CI)	P value
6-month CRT non-response, 40/111 (36%)				
log-RVSP (n=111)	8.2 (1.7–40.5)	0.01	12.0 (1.6–89.1)	0.02
log-LV ESV (n=104)	3.7 (1.3–10.4)	0.01	2.4 (0.47–12.0)	0.29
log-LV EDV (n=104)	3.9 (1.2–13.1)	0.03	–	–
log-LV EF (n=111)	0.22 (0.06–0.82)	0.02	1.3 (0.14–11.2)	0.83
2-year MACE, 31/111 (28%)				
log-RVSP (n=111)	7.7 (2.0–29.9)	0.003	5.6 (1.2–26.9)	0.03
log-LV ESV (n=104)	2.4 (0.97–5.8)	0.06	–	–
log-LV EDV (n=104)	2.4 (0.83–6.9)	0.11	–	–
log-LV EF (n=111)	0.29 (0.09–0.90)	0.03	0.61 (0.17–2.2)	0.45

Multivariable model for 6-month CRT non-response included RVSP, ESV and EF; multivariable model for 2-year MACE included RVSP and EF. ORs (for 6-month CRT non-response) and HRs (for 2-year MACE) listed are per 1-(log-transformed) unit increase. CRT, cardiac resynchronization therapy; OR, odds ratio; CI, confidence interval; RVSP, right ventricular systolic pressure; LV, left ventricular; ESV, end systolic volume; EDV, end diastolic volume; EF, ejection fraction; MACE, major adverse cardiac events; HR, hazard ratio.

Table 3 Association of right ventricular systolic pressure (RVSP) severity to outcomes

Variable	Univariate		Age- and sex-	
	OR/HR (95% CI)	P value	Adjusted OR/HR (95% CI)	P value
CRT non-response, 40/111 (36%)				
No PH: RVSP <35 mmHg (n=22)	1.0 (reference)	–	1.0 (reference)	–
Mild-moderate PH: RVSP 35–60 mmHg (n=76)	2.8 (0.86–9.0)	0.09	2.6 (0.78–8.5)	0.12
Severe PH: RVSP >60 mmHg (n=13)	5.3 (1.1–24.4)	0.03	5.0 (1.1–23.4)	0.04
2-year MACE, 31/111 (28%)				
No PH: RVSP <35 mmHg (n=22)	1.0 (reference)	–	1.0 (reference)	–
Mild-moderate PH: RVSP 35–60 mmHg (n=76)	3.9 (0.93–16.7)	0.06	4.1 (0.96–17.6)	0.06
Severe PH: RVSP >60 mmHg (n=13)	5.5 (1.1–28.6)	0.04	5.7 (1.1–29.4)	0.04

Multivariable models adjusted for age and sex. Reference group are patients with RVSP <35 mmHg. Odds ratio are reported for CRT non-response and hazard ratio for 2-year MACE. CRT, cardiac resynchronization therapy; OR, odds ratio; CI, confidence interval; RVSP, right ventricular systolic pressure; MACE, major adverse cardiac events; HR, hazard ratio; PH, pulmonary hypertension.

PH status by RVSP and biomarker levels

Tables 5-7 show the biomarker panel of myocardial fibrosis (sST2, galectin-3), myocardial wall stretch (NT-proBNP), and myocardial necrosis (hsTnI) and their relationship with PH status by RVSP. Of these biomarkers, only NT-proBNP and sST2 were discernable between groups. Both markers were also associated with right ventricular size/function and TR severity (*Tables S2-S4*).

The baseline median NT-proBNP levels had a graded increase based on PH severity by RVSP (P=0.003) and had lower values in regressors *vs.* non-regressors (P=0.01), there was no significant pattern of NT-proBNP changes at 6 months in those with no PH, regressor, persistent PH, and progressor (P=0.08).

For sST2, there was a graded increase in baseline

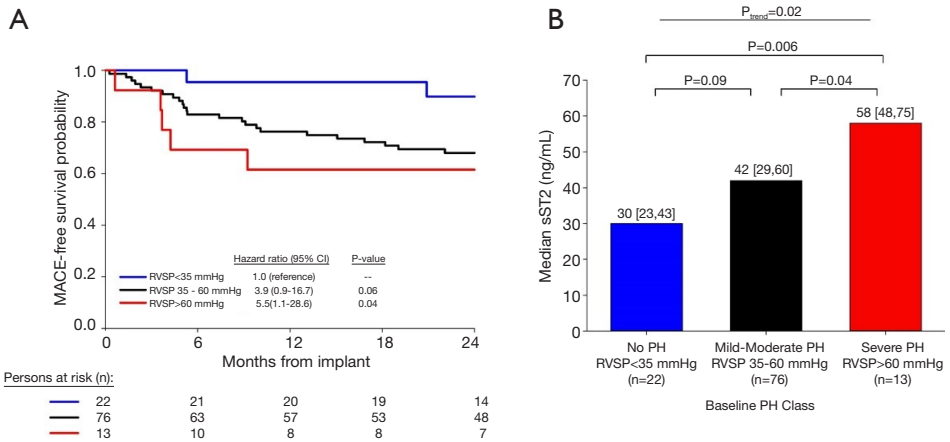

Figure 1 Impact of baseline pulmonary hypertension on clinical events and relation with sST2. (A) MACE-free survival probability according to baseline right ventricle systolic pressure; (B) median sST2 levels according to pulmonary hypertension severity at baseline. MACE, major adverse cardiac event.

Table 4 Progression/regression of right ventricular systolic pressure (RVSP) by 6 month after CRT implant

Variable	Univariate		Age- and Sex-	
	OR/HR (95% CI)	P value	Adjusted OR/HR (95% CI)	P value
CRT non-response, 27/79 (34%)				
No PH and regressors (n=36)	1.0 (reference)	–	1.0 (reference)	–
Persistent PH and progressors (n=43)	2.8 (1.03–7.5)	0.04	2.8 (1.02–7.6)	0.045
2-year MACE, 12/71 (17%)				
No PH and regressors (n=34)	1.0 (reference)	–	1.0 (reference)	–
Persistent PH and progressors (n=37)	11.6 (1.5–89.5)	0.02	11.6 (1.5–89.7)	0.02

Numbers reported are HR for 2 year MACE and OR for CRT non-response. Progressors: RVSP worsened by one or more classes at follow-up *vs.* pre-implantation; regressors: RVSP improved by one or more classes at follow-up *vs.* pre-implantation; persistent PH: RVSP in the same class at follow-up *vs.* baseline; CRT, cardiac resynchronization therapy; OR, odds ratio; CI, confidence interval; RVSP, right ventricular systolic pressure; MACE, major adverse cardiac events; HR, hazard ratio; PH, pulmonary hypertension.

median sST2 levels and PH severity by RVSP (P=0.02). Log-transformed baseline sST2 was associated with CRT non-response [OR 2.9 (1.1–7.6), P=0.03] and for MACE [HR 2.3 (1.02–5.3), P=0.04]. Lastly, when examining serial sST2 concentrations at 6 months, PH regressors had a median reduction in sST2 levels by 15 ng/mL, while non-regressors had increase of 5 ng/mL (P=0.005). Additionally, the sST2 changes at 6 months in those with no PH, persistent PH, progressor increased slightly (3–8 ng/mL) while the regressor group had a reduction in sST2 levels of 15 ng/mL, (P=0.03).

Discussion

In this study, we found that Echo-based RVSP was associated with 6-month CRT nonresponse and 2-year MACE. Severe PH patients were more likely to be CRT non-responder and have 2-year MACE than non-PH patients. Amongst the panel of 4 HF biomarkers of myocardial fibrosis, myocardial wall stretch, and myocardial necrosis, we observed a graded increase in baseline median NT-proBNP and sST2 concentrations with worsening PH severity. Progressors and those with persistent PH were

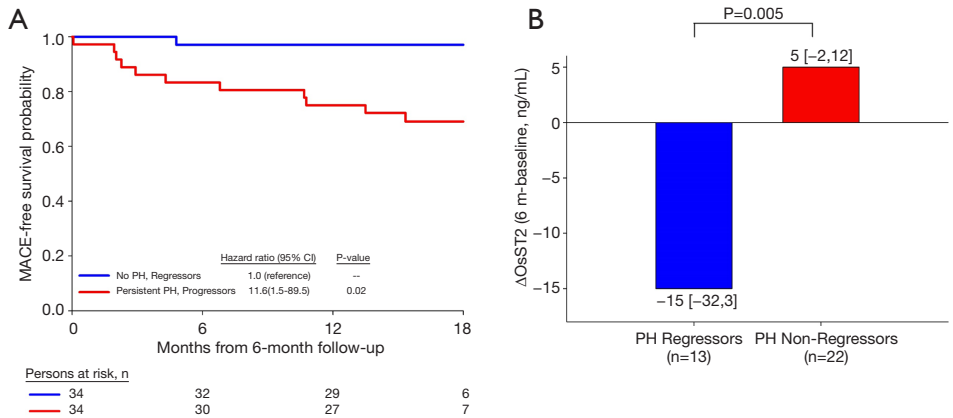

Figure 2 Impact of pulmonary hypertension evolution after CRT on clinical events and relation with sST2. (A) MACE-free survival probability according to pulmonary hypertension (PH) evolution after CRT. PH progression status was determined at 6-month after CRT implantation. (B) Changes in sST2 levels in patients improving *vs.* not improving their pulmonary hypertension severity 6 months after CRT. CRT, cardiac resynchronization therapy.

Table 5 Biomarkers levels and pulmonary hypertension status by RVSP (part I)

Biomarker	No PH	Mild-moderate PH	Severe PH	P value
Myocardial fibrosis				
sST2, ng/mL (n=78)	30 [23–43]	42 [29–60]	58 [48–75]	0.02
Galectin-3, ng/mL (n=76)	16 [11–19]	17 [13–23]	21 [16–24]	0.23
Myocardial wall stretch				
NT-proBNP, pg/mL (n=88)	521 [133–2,784]	1,807 [763–3,455]	3,885 [1,727–20,194]	0.003
Myocardial necrosis				
hsTnI, pg/mL (n=88)	22 [7–38]	19 [10–34]	64 [17–341]	0.07

RVSP, right ventricular systolic pressure; PH, pulmonary hypertension.

Table 6 Biomarkers levels and pulmonary hypertension status by RVSP (part II)

Δ Biomarker	Regressor	Non-regressor	P value
Myocardial fibrosis			
sST2, ng/mL (n=35)	−15 [−32, 3]	5 [−2, 12]	0.005
Galectin-3, ng/mL (n=34)	2 [−0.2, 3]	−1 [−2, 4]	0.29
Myocardial wall stretch			
NT-proBNP, pg/mL (n=42)	−924 [−1,622, −539]	8 [−902, 630]	0.01
Myocardial necrosis			
hsTnI, pg/mL (n=42)	−3 [−13, 0.2]	−1 [−14, 5]	0.22

Regressors: RVSP improved by one or more classes at follow-up *vs.* pre-implantation; non-regressor category includes patients with persistent PH and those with worsened RVSP by one or more classes at vollow-up *vs.* pre-implantation. RVSP, right ventricular systolic pressure; PH, pulmonary hypertension.

Table 7 Biomarkers levels and pulmonary hypertension status by RVSP (part III)

Δ Biomarker	No PH	Regressor	Persistent PH	Progressor	P value
Myocardial Fibrosis					
sST2, ng/mL (n=35)	8 [5–12]	–15 [–32, 3]	3 [–5, 10]	6 [–3, 14]	0.03
Galectin-3, ng/mL (n=34)	1 [–1, 4]	2 [–0.2, 3]	–2 [–3, 3]	16 [–1, 32]	0.30
Myocardial Wall Stretch					
NT-proBNP, pg/mL (n=42)	2 [–121, 81]	–924 [–1,622, –539]	197 [–902, 1,347]	–634 [–1,740, 43,560]	0.08
Myocardial Necrosis					
hsTnI, pg/mL (n=42)	–5 [–26, –1]	–3 [–13, 0.2]	1 [–3, 5]	–14 [–21, 293]	0.20

Progressors: RVSP worsened by one or more classes at follow-up *vs.* pre-implantation; regressors: RVSP improved by one or more classes at follow-up *vs.* pre-implantation; persistent PH: RVSP in the same class at follow-up *vs.* baseline. RVSP, right ventricular systolic pressure; PH, pulmonary hypertension.

more likely to be CRT non-responder at 6 months and have MACE at 2-years when compared to patients with no PH or regressors. Additionally, we found that PH regressors had a reduction in sST2 concentrations while those with no PH, persistent PH, and progressors had a slight increase in sST2 by 6 months. We did not observe this difference for NT-proBNP.

The present study provides further evidence that increased PH is related to morbidity and mortality in patients undergoing CRT (6,13). PH was a common finding in our population, occurring in 80% of our cohort, and was a strong independent predictor of 6-month CRT non-response and two-year MACE. PH in this population is caused by elevated left atrial pressure, which is the result of the variable combination of systolic dysfunction, diastolic dysfunction and/or associated valvular disease. Our finding that that PH (reflecting the global impact of these individual parameters) better predicted clinical outcomes than LVEF or LV size is not surprising. Pre-implantation RVSP measurement serves as a valuable independent prognostic marker beyond the severity of left heart systolic dysfunction.

While the observed relationship between myocardial wall stretch marker of NT-proBNP and RVSP PH severity is known and expected, we also found that sST2 and its serial changes better paralleled PH severity and progression/regression. While both markers can be influenced by volume status, our data suggest that sST2 may be more specific to PH. Interestingly; recent data suggest that extra-myocardial production of sST2 may account for some circulating concentrations of the marker (28). In the BIOCRT study, we found no trans-myocardial gradient when measuring sST2 concentrations in the coronary sinus (20), and other work demonstrated increased sST2 in pulmonary arterial endothelial cells (29), suggesting a potential implication for the pulmonary vasculature in sST2 release. Furthermore in patients with severe pulmonary inflammation, such as those with acute respiratory distress syndrome—a state of severe pulmonary vascular injury and inflammation—some of the highest reported concentrations of sST2 have been reported (30). Taken together, these findings suggest a pulmonary source for sST2 and could explain in part the relationship between serial sST2 and RVSP that we have found.

Study limitations

The study population reflects a small cohort of patients undergoing CRT at a single tertiary care center that may represent selection and treatment bias limiting generalizability. Our study population was predominantly male, had mild-moderate renal insufficiency, and had significant left ventricular systolic dysfunction characterized by primarily NYHA functional class III disease. We do not have inferior vena cava measurements, thus our data on RVSP does not include estimated right atrial pressure from inferior vena cava collapsibility. The small sample size limits the power to examine subgroups and produced large confidence intervals, which limited the number of adjustments in the multivariable model. Follow-up echocardiography and biomarker levels were not available in a proportion of patients at follow-up. Direct invasive measurements would have been interesting; however, this echo-based measure still correlated well with clinical outcomes.

Conclusions

Concentrations of sST2 are associated with PH severity in CRT patients. Reduction in sST2 concentrations is associated with PH regressors in these patients, which suggests its potential role to monitor PH after CRT. Our findings suggest this cardiovascular stress marker may contribute to the understanding of interplay between PH and adverse outcomes in CRT patients.

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Footnote

Conflicts of Interest: Dr. Januzzi is supported in part by the Hutter Family Professorship, receives grant support from Siemens, Singulex, Prevencio, and Roche, and has served as a consultant to Roche Diagnostics, Critical Diagnostics, Abbott, GE, Amgen, and Novartis. Dr. Singh receives grant support from St. Jude Medical, Medtronic Inc., Boston Scientific Corp., Sorin Group, Biotronik, BG Medicine and Siemens. Dr. Truong received grant support from Ziosoft, Inc. (formerly Qi Imaging LLC). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The institutional review board approved the study protocol and all patients provided written consent prior to study initiation.

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Supplementary

Table S1 Baseline patient characteristics of those with and without 6-month follow-up

Characteristics	6-month follow-up (n=79)	No 6-month follow-up (n=32)	P value
Patient characteristics			
Age, years	64 [57–74]	68 [52–76]	0.73
Male, n (%)	60 (76%)	25 (78%)	1.00
BMI, kg/m^2	27.2 [24.4–32.1]	27.5 [24.8–32.9]	0.59
Diabetes, n (%)	26 (33%)	11 (34%)	1.00
History of atrial fibrillation, n (%)	28 (35%)	10 (31%)	0.83
Hypertension, n (%)	50 (63%)	16 (50%)	0.21
Ischemic cardiomyopathy, n (%)	27 (34%)	17 (53%)	0.09
Device, n (%)	43 (54%)	16 (50%)	0.68
PPM	15 (19%)	4 (13%)	0.58
ICD	32 (41%)	12 (38%)	0.83
NYHA functional class, n (%)			0.52
I	0 (0)	0 (0)	
II	9 (11%)	3 (9%)	
III	63 (80%)	28 (88%)	
IV	7 (9%)	1 (3%)	
Medications, n (%)			
ACEI/ARB	62 (78%)	22 (69%)	0.33
BB	67 (85%)	26 (81%)	0.78
Spironolactone	24 (30%)	11 (34%)	0.82
Diuretics, n (%)	59 (75%)	28 (88%)	0.20
ECG parameters			
QRS duration, ms	160 [146–178]	164 [142–186]	0.58
QRS >150 ms, n (%)	53 (67%)	21 (66%)	1.00
LBBB, n (%)	42 (53%)	17 (53%)	1.00
Paced rhythm, n (%)	13/78 (17%)	7 (22%)	0.59
Echocardiography parameters			
LVEF, %	25 [19–30]	25 [21–34]	0.56
LV dimensions, mm			
End-diastole (EDD)	63±9	61±7	0.29
End-systole (ESD)	55±10	53±8	0.21
LV volumes, cm^3			
End-diastole (EDV)	225 [171–274]	204 [166–266]	0.36
End-systole (ESV)	159 [120–214]	154 [105–202]	0.48
RV enlargement, n (%)	19/71 (27%)	7/24 (29%)	0.80
RV dysfunction, n (%)	28/70 (40%)	10/24 (42%)	1.00
Tricuspid regurgitation (n=96), n (%)	n=71	n=25	0.20
Trace	18 (25%)	7 (28%)	
Mild	25 (35%)	10 (40%)	
Moderate	24 (34%)	4 (16%)	
Severe	4 (6%)	4 (16%)	
RVSP, mmHg	42 [35–50]	44 [37–51]	0.58
Laboratory markers			
eGFR (mL/min/1.73 m^2)	62±19	62±20	0.93

Device indicates presence of ICD and/or PPM at the time of cardiac resynchronization therapy implantation. BMI, body mass index; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitor; ARB, aldosterone receptor blocker; BB, beta blocker; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RV, right ventricular; eGFR, estimated glomerular filtration rate.

Table S2 Biomarkers levels and right ventricular size, function, and tricuspid regurgitation (TR) status (part I)

Biomarker	Normal RV size	RV enlargement	P value
Myocardial fibrosis			
sST2, ng/mL (n=77)	37.9 [24.1–56.9]	51.5 [43.1–72.5]	0.005
Galectin-3, ng/mL (n=75)	16 [12–22]	18 [16–28]	0.14
Myocardial wall stretch			
NT-proBNP, pg/mL (n=87)	1,428 [533–2,889]	3,520 [1,657–7,004]	0.001
Myocardial necrosis			
hsTnI, pg/mL (n=87)	19 [9–39]	20 [14–50]	0.32

RV, right ventricle; TR, tricuspid regurgitation.

Table S3 Biomarkers levels and right ventricular size, function, and tricuspid regurgitation (TR) status (part II)

Biomarker	Normal RV function	RV dysfunction	P value
Myocardial fibrosis			
sST2, ng/mL (n=76)	36.1 [23.9–50.7]	55.7 [43.0–75.8]	0.002
Galectin-3, ng/mL (n=74)	16 [13–22]	17 [14–24]	0.50
Myocardial wall stretch			
NT-proBNP, pg/mL (n=86)	1,507 [533–2,665]	2,975 [793–6,834]	0.004
Myocardial necrosis			
hsTnI, pg/mL (n=86)	19 [9–36]	21 [13–63]	0.16

RV, right ventricle; TR, tricuspid regurgitation.

Table S4 Biomarkers levels and right ventricular size, function, and tricuspid regurgitation (TR) status (part III)

Biomarker	Trace TR	Mild TR	Moderate TR	Severe TR	P value
Myocardial fibrosis					
sST2, ng/mL (n=78)	39.6 [30.8–60.0]	31.3 [22.7–46.9]	48.0 [40.2–60.0]	108.8 [36.9–122.7]	0.01
Galectin-3, ng/mL (n=76)	16 [12–23]	16 [13–23]	17 [14–21]	28 [18–35]	0.18
Myocardial wall stretch					
NT-proBNP, pg/mL (n=88)	798 [255–1,727]	1,133 [736–2,786]	2,889 [1,507–4,901]	6,872 [4,316–19,856]	<0.001
Myocardial necrosis					
hsTnI, pg/mL (n=88)	17 [9–25]	20 [11–36]	18 [11–52]	63 [21–437]	0.02

TR, tricuspid regurgitation.