Table 1. Baseline Patient Characteristics in the START Study

Characteristic	All (n=180)	Responder (n=109)	Nonresponder (n=62)	P value*
Age, years	66.3±12.5	66.5±12.0	65.5±13.1	0.61
Male, n (%)	120 (66.7)	69 (63.3)	44 (71.0)	0.57
Ischemic, n (%)	35 (19.4)	18 (16.5)	15 (24.2)	0.23
NYHA class, n (%)				0.98
II	63 (35.0)	40 (36.7)	22 (35.5)	
III	109 (60.6)	64 (58.7)	37 (59.7)	
IV	8 (4.4)	5 (4.6)	3 (4.8)	
Basic rhythm, n (%)				0.49
Sinus	120 (66.6)	71 (64.2)	44 (71.0)	
Pacing (DDD,VDD or VVI mode)	38 (21.1)	27 (24.8)	8 (12.9)	
AF	14 (7.8)	7 (6.4)	5 (8.1)	
Other	8 (4.4)	4 (4.5)	5 (8.1)	
PQ interval, ms	192.2±46.6 (n=155)	182.8±44.5 (n=92)	206.2±48.2 (n=55)	0.003
QRS duration, ms	158.5±30.2	162.7±30.4	151.1±28.7	0.02
Heart rate, beats/min	70.1±14.6	71.1±14.7	68.6±14.1	0.28
Systolic blood pressure, mmHg	106.7±17.9	107.4±17.2	106.0±19.4	0.61
Diastolic blood pressure, mmHg	61.9±11.4	62.1±10.1	61.4±13.3	0.70
Conduction disorder, n (%)				<0.001
LBBB	92 (51.1)	65 (59.6)	21 (33.9)	
Nonspecific	41 (22.8)	17 (15.6)	22 (35.5)	
RBBB	14 (7.8)	4 (3.7)	10 (16.1)	
RV pacing	33 (18.3)	23 (21.1)	9 (14.5)	
Primary ventricular tachyarrhythmia, n (%)				0.34
Nonsustained	63 (35)	33 (30.3)	25 (40.3)	
Sustained	35 (19.4)	20 (18.3)	13 (21.0)	
Ventricular fibrillation	7 (3.9)	5 (4.6)	2 (3.2)	
AF, n (%)				0.14
Paroxysmal AF	25 (13.9)	10 (9.2)	14 (22.6)	
Chronic AF	22 (12.2)	12 (11.1)	8 (12.9)	
Laboratory data				
Hb	12.7±2.2	12.8±2.1	12.6±2.3	0.62
Albumin	3.8±0.5	3.9±0.4	3.8±0.5	0.55
Total cholesterol	177.5±42.5	175.2±39.9	182.1±46.9	0.54
HbA1c	5.8±0.9	5.9±0.8	5.7±1.1	0.47
BUN	27.9±22.8	24.7±14.0	33.6±33.4	0.01
Cre	1.5±1.7	1.3±1.2	1.9±2.4	0.02
Na	138.0±3.7	138.3±3.6	137.6±3.9	0.21
K	4.3±0.5	4.3±0.5	4.3±0.5	0.43
BNP*, pg/ml	576.3±647.9 (n=160)	575.1±721.4 (n=100)	895.6±1,230.9 (n=50)	0.03
Medication, n (%)				
ACEI/ARB	137 (76.1)	82 (75.2)	78 (77.4)	0.74
β-blocker	145 (80.6)	95 (87.2)	43 (69.4)	0.005
Loop diuretics	151 (83.9)	85 (78.0)	57 (91.9)	0.02
Spironolactone	111 (61.7)	67 (61.5)	38 (61.3)	0.98
Amiodarone	60 (33.3)	30 (27.5)	24 (38.7)	0.13
Oral inotropes	20 (11.1)	11 (10.1)	5 (8.1)	0.62
Digitalis	21 (11.7)	13 (11.9)	8 (12.9)	0.91
Statins	46 (25.3)	28 (25.7)	16 (25.8)	0.98
Intravenous inotropes	5 (2.8)	4 (3.7)	1 (1.6)	0.44
hANP	11 (6.1)	6 (5.5)	5 (8.1)	0.51

*Responder vs. nonresponder. ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; Cre, creatinine; hANP, human atrial natriuretic peptide; Hb, hemoglobin; LBBB, left bundle branch block; NYHA, New York Heart Association; RBBB, right bundle branch block; START, Speckle Tracking Imaging for the Assessment of Cardiac Resynchronization Therapy; VT, ventricular tachycardia.

Table 2. Baseline Echocardiographic Parameters in the START Study

Parameter	All (n=180)	Responder (n=109)	Nonresponder (n=62)	P value*
LVEDV, ml	191.7±95.7	180.4±69.9	203.9±116.8	0.10
LVESV, ml	144.1±85.7	135.0±63.4	152.4±104.8	0.18
LVEF, %	26.5±7.0	26.7±6.9	26.7±7.0	0.99
LVDd, mm	63.4±10.0	62.5±8.5	66.6±10.6	0.007
LVDs, mm	54.6±12.2	53.5±9.3	57.7±10.9	0.01
IVSth, mm	9.0±2.6	9.4±2.6	8.7±2.3	0.11
PWth, mm	9.2±2.0	9.1±1.8	9.3±2.2	0.19
E, cm/s	70.1±34.3 (n=174)	68.0±35.5 (n=107)	75.4±32.7 (n=61)	0.18
A, cm/s	65.5±26.4 (n=148)	69.1±26.0 (n=91)	59.6±25.4 (n=50)	0.04
E/A	1.2±1.0 (n=148)	1.1±1.1 (n=91)	1.4±1.0 (n=50)	0.07
DT, ms	203.6±80.4 (n=170)	203.2±71.0 (n=101)	205.0±97.1 (n=59)	0.89
E/E'	16.2±9.7 (n=166)	16.2±10.9 (n=103)	16.0±7.3 (n=55)	0.90
MR index, %	23.7±18.4	21.1±16.7	28.1±21.4	0.02
TR-PG, mmHg	29±12 (n=156)	24.4±11.8 (n=91)	33.2±15.4 (n=52)	0.001
SPWMD, ms	181.6±127.2 (n=178)	199.7±135.4 (n=109)	161.3±110.4 (n=61)	0.06
Ts-SD, ms	49.0±26.4 (n=176)	49.8±27.4 (n=107)	47.0±24.3 (n=58)	0.50
Ts-SL, ms	2.8±83.7 (n=176)	−4.4±84.3 (n=105)	18.6±82.5 (n=57)	0.09
IMD, ms	34.4±43.2 (n=176)	38.4±34.0 (n=109)	20.6±44.2 (n=61)	0.004

*Responder vs. nonresponder. A, peak velocity at atrial contraction of Doppler transmitral flow; DT, deceleration time of E; E, early diastolic peak velocity of Doppler transmitral flow; E/A, ratio of E to A; E/E', ratio of E to E'; E', early diastolic mitral annular velocity; IMD, interventricular mechanical delay; IVSth, interventricular septal thickness; LVDd, left ventricular (LV) dimension at end diastole; LVDs, LV dimension at end systole; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; MR, mitral regurgitation; PWth, posterior wall thickness; SPWMD, septal-to-posterior wall motion delay; TR-PG, pressure gradient of tricuspid regurgitation; Ts-SD, standard deviation (SD) of time from QRS to peak systolic velocity by tissue Doppler imaging in ejection phase for 12 LV segments; Ts-SL, delay between time to peak systolic velocity by tissue Doppler imaging in ejection phase at basal septal and lateral segments. Other abbreviations as in Table 1.

strain (LS) curves were obtained from a total of 18 segments of the 3 apical planes. The maximum peak in each time-strain curve was defined as the peak strain value during the systolic phase and the first half of the diastolic phase. End-systole was defined as timing of the aortic valve closing in the GE system and as timing of the minimum LV area measured by strain analyses in the Toshiba system. In addition, if multiple peaks were present in the time-strain curve, the first peak was also determined (**Figure 2**). Any strain curve with a maximum peak value <3% was excluded for STE analyses because the strain peak could not be distinguished from noise data.

Dyssynchrony Parameters by STE

Time from QRS onset to maximum strain (T_{max}) and to first peak in the multiple strain peaks (T_{first}) were measured in each segment (**Figure 2**).[12] The 3 dyssynchrony parameters in each of T_{max} and T_{first} were calculated as follows: first, standard deviation of T_{max} (T_{max}-SD) and T_{first} (T_{first}-SD) in the 6 segments for RS and CS and the 18 segments for LS; second, time difference (TD) between the smallest T_{max} and largest T_{max} (T_{max}-TD) and between the smallest T_{first} and largest T_{first} (T_{first}-TD) among the 6 segments for RS and CS and the 18 segments for LS; and third, TD between the septum and lateral wall (T_{max}-TD_{SL}, T_{first}-TD_{SL}) for RS, CS, and LS. In the calculations of dyssynchrony parameters with T_{first}, T_{max} was substituted in the segments with a single peak.

Reproducibility

STE measurements were compared among the core laboratories using data sets from 40 randomly selected patients. We investigated data agreement of the diagnosis of dyssynchrony with Cohen's κ coefficients.

Statistical Analysis

Data are presented as mean±standard deviation or percentages. Comparisons between groups were performed with unpaired Student's t-test for continuous variables and χ^2 tests for categorical variables. We assessed the performance of each dyssynchrony parameter to predict responders using the area under the curve (AUC) of the receiver-operating characteristic (ROC) curve. Independent determinants of the volume responders were assessed by multivariate logistic regression analysis adjusted for age and sex using univariate factors with a value of $P<0.05$, which could be assessed in all subjects who were included in the responder study. The risk of clinical endpoints was determined with Cox proportional hazard models. The univariate factors with a value of $P<0.05$ were entered into the multivariable model adjusted for age and sex to assess the effect of the parameters on the endpoints.

In the univariate logistic regression analysis and the univariate Cox proportional hazard models, the best cutoff value for each factor was identified by ROC analysis. The best cutoff value was defined as the point with the highest sum of sensitivity and specificity.

Kaplan-Meier analysis was done to determine the influence of dyssynchrony parameters on the endpoints. $P<0.05$ was considered to indicate statistical significance. Analyses were performed with SPSS version 17.0 (SPSS Inc, Chicago, IL, USA).

Results

Baseline Characteristics

Of the initially enrolled 182 patients, 2 (1.1%) were excluded because of CRT discontinuation immediately after implantation (n=1) or incomplete data (n=1). Ultimately, 180 patients

Table 3. STE Parameters in Volume Responders and Nonresponders and the Ability to Predict Responders in the START Study

Dyssynchrony parameter	All (n=180)	Responder (n=109)	Nonresponder (n=62)	P value*	AUC	P value	Cutoff value	Sensitivity	Specificity	Positive predict value
CS (ms)										
T_{max}-SD	106.1±51.7	114.4±52.8	93.3±46.9	0.01	0.62	0.01	82	0.64	0.53	0.71
T_{max}-TD	236.9±128.4	283.7±131.0	233.1±117.2	0.01	0.61	0.02	216	0.62	0.60	0.73
T_{max}-TD_{SL}	186.8±157.3	208.3±165.3	156.3±129.1	0.02	0.61	0.02	145	0.68	0.52	0.71
T_{first}-SD	133.8±51.8	151.9±45.3	105.3±49.0	<0.001	0.76	<0.001	116	0.82	0.69	0.82
T_{first}-TD	323.8±120.1	360.7±103.1	264.8±121.1	<0.001	0.73	<0.001	283	0.79	0.65	0.80
T_{first}-TD_{SL}	268.0±153.1	317.2±125.8	192.9±148.3	<0.001	0.74	<0.001	208	0.84	0.61	0.79
RS (ms)										
T_{max}-SD	112.7±69.1	122.4±70.4	99.5±66.7	0.04	0.59	0.06	–	–	–	–
T_{max}-TD	235.9±153.7	285.9±154.4	237.8±152.0	0.051	0.59	0.06	–	–	–	–
T_{max}-TD_{SL}	273.7±172.1	197.6±163.0	196.7±149.7	0.97	0.50	0.95	–	–	–	–
T_{first}-SD	142.4±66.9	161.2±61.6	117.9±65.6	<0.001	0.70	<0.001	126	0.76	0.60	0.77
T_{first}-TD	322.9±141.4	366.2±126.9	264.8±136.9	<0.001	0.72	<0.001	283	0.79	0.53	0.75
T_{first}-TD_{SL}	273.7±172.1	320.0±162.5	210.8±167.3	<0.001	0.70	<0.001	265	0.72	0.60	0.76
LS (ms)										
T_{max}-SD	113.0±42.4	118.6±40.8	103.3±43.7	0.02	0.61	0.01	100	0.63	0.57	0.72
T_{max}-TD	368.5±131.7	381.3±122.4	346.1±144.7	0.09	0.58	0.05	–	–	–	–
T_{max}-TD_{SL}	246.0±131.3	260.7±173.1	220.0±135.9	0.11	0.57	0.09	–	–	–	–
T_{first}-SD	128.8±43.6	136.3±42.8	115.2±41.9	0.002	0.63	0.003	129	0.61	0.65	0.75
T_{first}-TD	412.7±121.4	431.7±115.9	379.6±124.6	0.007	0.62	0.01	420	0.64	0.55	0.71
T_{first}-TD_{SL}	318.8±152.0	337.7±156.0	285.5±139.8	0.03	0.61	0.02	248	0.69	0.52	0.71

*Responder vs. nonresponder. AUC, area under the curve; CS, circumferential strain; LS, longitudinal strain; RS, radial strain; STE, speckle tracking echocardiography; T_{first}-SD, SD of time from QRS onset to first peak; T_{first}-TD, time difference between the smallest T_{first} and largest T_{first}; T_{first}-TD_{SL}, T_{first} between the septum and lateral wall; T_{max}-SD, SD of time from QRS onset to maximum strain; T_{max}-TD, time difference between the smallest T_{max} and largest T_{max}; T_{max}-TD_{SL}, TD_{max} between the septum and lateral wall. Other abbreviations as in Tables 1,2.

formed the final study group (Table 1). The number of patients enrolled from each hospital was as follows: Kurashiki Central Hospital 35, Kokura Memorial Hospital 26, University of Tsukuba 21, Hokkaido University 14, Kobe University 13, Tokyo Woman's Hospital 11, Shiga University of Medical Science 10, and other institutes 50. Almost all patients were NYHA class II or III, and the majority had nonischemic heart disease. Based on the guidelines, 38 (21.1%) patients with pacing therapy, the majority of whom depended on RV pacing, had an indication for CRT that was upgraded to biventricular pacing. The images from 135 patients were analyzed on workstations with GE software packages and with Toshiba software package for 45 patients.

Clinical Outcomes

The mean duration of follow-up was 636±284 (range, 4–1,151) days. By the end of the study, 41 patients had reached the endpoint of composite of death from cardiac cause or unplanned hospitalization for heart failure. A total of 20 patients (11.1%) died: 8 from heart failure, 2 from cardiac death (infective endocarditis and ventricular arrhythmia), 5 from sudden death, and 5 from noncardiac death. Unplanned hospitalization for heart failure occurred in 26 (14.4%) patients.

Volume Responder Study

LV volume measurements at 6 months were completed in 171 (95%) of the 180 patients. The 6-month data of the remaining 9 patients could not be assessed they had died: 4 from heart failure, 3 sudden cardiac deaths, and 2 noncardiac deaths. Of the 180 patients, 109 (60.6%) were identified as volume responders to CRT. Baseline patient characteristics of the responder and nonresponder groups are summarized in Table 1. In the responder group, QRS duration was longer and the prevalence of left bundle branch block or RV pacing was greater than in the nonresponder group. Patients in the nonresponder group had significantly higher serum creatinine and B-type natriuretic peptide levels than those in the responder group. The prevalence of patients being administered a β-blocker was higher in the responder group, whereas that of patients being administered loop diuretics was lower in the responder group.

Baseline echocardiographic parameters are presented in Table 2. LV end-diastolic and end-systolic dimensions, mitral regurgitation index, and the pressure gradient of tricuspid regurgitation were significantly higher in the nonresponder group than in the responder group. Of the 4 dyssynchrony parameters, only IMD was significantly higher in the responder group than in the nonresponder group. The AUC to predict volume responders for IMD was 0.61 (P=0.02), with a sensitivity of 0.47, specificity of 0.67, and positive predictive value of 0.72. The cutoff value was 40 ms.

STE dyssynchrony parameters are summarized in Table 3. All dyssynchrony parameters derived from first peak of time-strain curve were significantly higher in the responder group than in the nonresponder group. CS and RS parameters with first peak showed moderate accuracy (AUC ≥0.70), despite the low accuracy in the CS and RS parameters derived from maximum peak. LS parameters derived from both the maximum and first peaks showed low accuracy.

Baseline predictors of volume responders are shown in Table 4. We selected the best first-peak parameter in CS, that in RS and the combined parameter. Three multivariate logistic regression analysis models were assessed using T_{first}-SD of CS

Table 4. Logistic Regression Analysis for Predefined Predictors of Volume Responders in the START Study

Characteristic	Univariate		Multivariate model 1		Multivariate model 2		Multivariate model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age, years	1.01 (0.98–1.03)	0.61						
Sex, male	0.71 (0.36–1.38)	0.31						
LBBB or RV pacing	4.47 (2.24–8.90)	<0.001	5.05 (1.78–14.4)	0.002	4.90 (1.80–13.3)	0.002	4.83 (1.59–14.7)	0.005
Baseline BNP >1,000 pg/ml	0.47 (0.23–0.97)	0.04						
Baseline BUN >30 mg/dl	0.40 (0.20–0.80)	<0.001	0.20 (0.07–0.56)	0.002	0.21 (0.08–0.55)	0.002	0.21 (0.07–0.59)	0.003
Loop diuretics	3.22 (1.16–8.92)	0.03						
β-blocker	3.00 (1.38–6.53)	0.006	7.87 (2.49–24.9)	<0.001	6.67 (2.27–19.6)	0.001	7.08 (2.22–22.4)	0.001
MR index >40%	0.33 (0.15–0.73)	0.006	0.24 (0.07–0.81)	0.02	0.21 (0.07–0.66)	0.007	0.15 (0.04–0.55)	0.004
IMD >40 ms	1.01 (1.00–1.02)	0.005						
CS T_{first}-SD >116 ms	10.0 (4.87–20.8)	<0.001	9.83 (3.78–25.6)	<0.001				
CS T_{first}-TD >283 ms	6.80 (3.40–13.6)	<0.001						
CS T_{first}-TD_{SL} >208 ms	8.57 (4.14–17.7)	<0.001						
RS T_{first}-SD >126 ms	4.72 (2.41–9.25)	<0.001			4.42 (1.81–10.8)	0.001		
RS T_{first}-TD >283 ms	4.26 (2.16–8.38)	<0.001						
RS T_{first}-TD_{SL} >265 ms	3.90 (2.01–7.53)	<0.001						
LS T_{first}-SD >129 ms	2.86 (1.49–5.46)	0.002						
Combined T_{first}-SD	15.3 (6.38–36.8)	<0.001					25.1 (6.04–94.7)	<0.001

CI, confidence interval; Combined T_{first}-SD, combined dyssynchrony criterion that requires at least one of CS T_{first}-SD >116 ms or RS T_{first}-SD >126 ms; T, time. Other abbreviations as in Tables 1–3.

>116 ms, T_{first}-SD of RS >126 ms, and combined T_{first}-SD, which was a combined dyssynchrony criterion that requires at least one of T_{first}-SD of CS >116 ms or T_{first}-SD of RS >125 ms. Each STE dyssynchrony parameter was identified as an independent predictor of a volume responder in addition to the presence of left bundle branch block or RV pacing, serum blood urea nitrogen level >30 mg/dl, administration of β-blocker, and mitral regurgitation index >40%.

Baseline Parameters and Clinical Outcomes

Univariate Cox proportional hazard analyses adjusted for age and sex revealed the relations of 8 predefined parameters with a composite of death from cardiac cause or unplanned hospitalization for heart failure (Table 5). Because 2 dyssynchrony parameters were associated with the endpoint, as well as the multivariate logistic regression analysis, 3 multivariate analysis models were assessed using T_{first}-SD of CS >125 ms, T_{first}-SD of RS >98 ms, and combined T_{first}-SD, which was a combined dyssynchrony criterion that requires at least one of T_{first}-SD of CS >125 ms or T_{first}-SD of RS >98 ms. As shown in the multivariate model 1, T_{first}-SD of CS >125 ms was associated with the endpoints independently of serum creatinine level >1.0 mg/dl and LV end-diastolic volume >250 ml. In contrast, T_{first}-SD of RS >98 ms and combined T_{first}-SD were not identified as independent predictors in multivariate models 2 and 3, respectively.

Outcomes and STE Parameters

Kaplan-Meier estimates of the time to endpoint are shown in Figure 3. There were significantly fewer events in patients with T_{first}-SD of CS >125 ms than in those with T_{first}-SD of CS ≤125 ms (log rank, P<0.001). Of the 13 events in patients with T_{first}-SD of CS >125 ms, heart failure was the cause of death in 3 patients, sudden cardiac death occurred in 2 patients, and unplanned hospitalization occurred in 7 patients. Of the 28 events in patients with T_{first}-SD of CS ≤125 ms, heart failure was the cause of death in 5 patients and of unplanned hospitalization in 19 patients. Sudden cardiac death occurred in 3 patients and noncardiac death occurred in 2 patients. Other cardiovascular events were the cause of death in 1 patient in each arm.

Reproducibility

Interobserver agreement of LV dyssynchrony by STE among the core laboratories was substantial or excellent (Cohen's κ coefficient of T_{max}-SD: RS=0.82, CS=0.80, and LS=0.77; T_{max}-TD: RS=0.79, CS=0.81, LS=0.74; T_{first}-SD: RS=0.81, CS=0.84, and LS=0.78; and T_{first}-TD: RS=0.80, CS=0.81, and LS=0.75).

Table 5. Univariate and Multivariate Predictors of Death From Cardiac Causes or Unplanned Hospitalization for Heart Failure by the Cox Proportional Hazard Model in the START Study

Predictor	Univariate		Multivariate model 1		Multivariate model 2		Multivariate model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, years	1.007 (0.98–1.03)	0.63						
Sex, male	1.23 (0.63–2.34)	0.53						
Ischemic cardiomyopathy	2.02 (1.03–3.99)	0.04						
LBBB or RV pacing	0.50 (0.27–0.93)	0.02			0.49 (0.24–0.99)	0.04		
Loop diuretics	3.41 (1.02–14.1)	0.04						
Amiodarone	0.72 (052–0.98)	0.03						
Cre >1.0 mg/dl	2.98 (1.45–6.11)	0.003	2.51 (1.15–5.45)	0.02	2.70 (1.24–5.89)	0.01	2.67 (1.23–5.86)	0.01
LVEDV >250 ml	3.01 (1.52–6.19)	0.002	5.39 (2.39–12.1)	<0.001	4.74 (2.12–10.6)	<0.001	4.80 (2.16–10.7)	<0.001
CS T_{first}-SD >125 ms	0.31 (0.16–0.61)	0.001	0.35 (0.17–0.73)	0.005				
RS T_{first}-SD >98 ms	0.52 (0.31–0.86)	0.01			0.65 (0.32–1.23)	0.18		
Combined T_{first}-SD	0.50 (0.27–0.94)	0.03					0.62 (0.30–1.27)	0.19

HR, hazard ratio. Other abbreviations as in Tables 1–4.

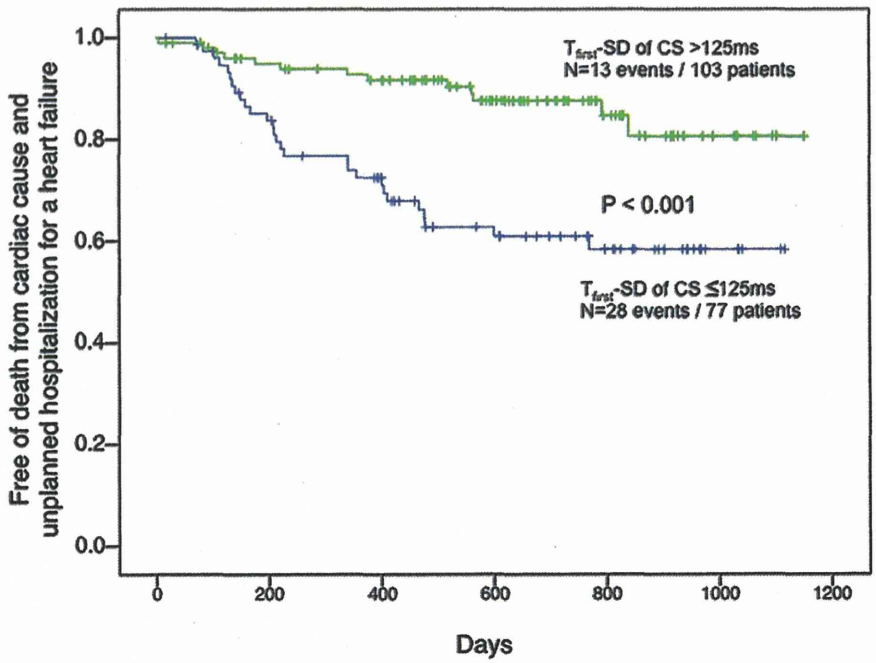

Figure 3. Kaplan-Meier estimates of the probability of freedom of death from cardiac causes and unplanned hospitalization for heart failure. CS, circumferential strain; SD, standard deviation; T_{first}, time to the first peak.

Discussion

This prospective multicenter study revealed strong feasibility of dyssynchrony assessment by STE. In particular, T_{first}-SD of CS was the best dyssynchrony parameter to predict volume responders and T_{first}-SD of RS was second best. Both parameters were also positively associated with clinical endpoints. Moreover, we strictly assessed the objectivity of the data, and the interinstitutional reproducibility was excellent.

Conventional Dyssynchrony Parameters and STE Parameters

Our study reconfirmed the unfeasibility of conventional dyssynchrony parameters obtained from time-to-peak analysis with M-mode, conventional Doppler, or tissue Doppler methods. Because of approximately 30% of patients being nonresponders based on the guidelines,[16] these echocardiographic parameters were developed in single-center studies to improve CRT response.[17] However, these attempts were challenged in prospective multicenter studies because of poor reproducibility, low positive predictive values, and poor accuracy even in healthy control subjects.[4–7,18] Several studies suggested that STE overcame some limitations of tissue velocity imaging and provided a better measurement of mechanical dyssynchrony. The dyssynchrony parameters by STE were proposed as additional indices to predict CRT response in single-center studies or those with small sample sizes.[8–11,19] However, the real clinical effect of STE in identifying CRT responders can be verified only through a well-performed, prospective, and multicenter study. The present study meets these requirements with its study design, good interinstitutional reproducibility, and objectivity of STE data.

First Peak Measurements in Time-Strain Curve

We showed for the first time, to our knowledge, that strain parameters with first peak were superior to maximum peak strain parameters for predicting CRT responders. Moreover, experimental studies suggest that maximum peak strain-derived dyssynchrony indices may exaggerate underlying electrical dyssynchrony, and the parameters do not directly reflect electrical dyssynchrony.[20,21] Abnormal systolic motion of the interventricular septum with electrical dyssynchrony includes multiple phases of myocardial shortening during the pre-ejection and ejection periods. Ventricular contraction abnormalities with electrical dyssynchrony are typically characterized as early septal contraction and lateral stretch, followed by septal stretch and lateral contraction later in systole. Pre-ejection septal shortening reflects active contraction, suggesting that the pre-ejection phase should be included when assessing LV dyssynchrony.[22] Moreover, because of the complex mechanical interactions between different parts of the LV wall, maximum peak measurements by STE mislead by misidentifying apparent dyssynchrony with complete left bundle branch block as no dyssynchrony.[23] Thus, first peak is more related to the electrical activation that can be treated by CRT than mamixum peak.[19–23]

Superiority of CS

In the present study, the first peak of the CS parameter showed the best predictive value as a single parameter approach, and use of combined parameters was superior to that of single parameters. Some researchers reported that global LS decreases firstly in 3 directions and is not associated with LV reverse remodeling or outcomes after CRT, which might be associated with the poor predictive value of LS dyssynchrony parameters in this study.[24,25] In contrast, most researchers have shown the usefulness of RS to predict CRT response.[8–11] The recent randomized, controlled, 2-center trial of the use of RS analysis only to target LV lead placement showed that RS analysis yielded significantly improved response and clinical outcomes.[26] However, a core laboratory was not assigned and reproducibility of strain analysis was not evaluated in that trial. Thus, uncertainty remains as to which approach is best (longitudinal, circumferential, radial, transverse, or combined) to determine dyssynchrony. We believe the evidence from the present study is reliable; however, the difference between CS and RS was small, and further investigations are needed.

Clinical Outcomes

We found that the first peak of the CS parameter was an independent predictor of clinical outcomes. Hara et al[27] showed that patients with dyssynchrony had more favorable long-term survival than those without dyssynchrony after CRT. The important finding was that clinical outcomes of patients with significant dyssynchrony were more favorable than those of patients without dyssynchrony. The present results also support the association of echocardiographic dyssynchrony with patient outcome after CRT.

Objectivity and Reproducibility of the STE Data

Multicenter trials require objective measurements that are accurate and reproducible across enrollment sites. Data from each core laboratory in the present study were registered in a central database via the internet. The PROSPECT study demonstrated poor interinstitutional reproducibility and lower accuracy partly because of differences in methods of data acquisition and analysis.[6] Therefore, we devised standardized data acquisition and analysis protocols to precisely measure first and maximum peak time in the study headquarters and 5 core laboratories. The results show that interobserver agreement of LV dyssynchrony by STE among the core laboratories was substantial or excellent.

Clinical Implications

The clinically important finding was that the first peak and circumferential assessments were found to be superior to other parameters. Some reports have not even defined the position of the first or maximum peak strain. We speculate that clear definition of first-peak measurements makes dyssynchrony assessments more reproducible than maximum peak measurements.[5–7] The evidence from this study is acceptable, and a standardized protocol may improve the ability to predict CRT responders.

Study Limitations

The accuracy of strain parameters in this study was not as good as that previously reported in single-center studies. Recent reports insist on the importance of understanding the complexity and variety of the etiology of cardiac dyssynchrony. We did not take into account lead position or myocardial viability, and the influence of these complex factors cannot be denied. However, we think that the results of this study are more objective than those of previous studies and closer to the true predictive value of time-to-peak strain analysis. Some researchers have advocated new dyssynchrony parameters such as wasted energy or discoordination analysis;[28–30] however, the present prospective study was planned prior to the reporting of these parameters, and we only performed time-to-peak analysis by STE. Results using these new methods could be presented as a subanalysis of the START study.

Conclusions

The START study, a prospective, multicenter study of dyssynchrony assessments, showed for the first time, to our knowledge, that first-peak strain parameters in all 3 directions were superior to maximum peak parameters for predicting CRT responders. In particular, the first peak of the CS parameter showed the best predictive value in a single parameter approach. This study also revealed stong feasibility of dyssynchrony assessments by STE, which may improve the ability to predict CRT responders.

Disclosures

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SHORT COMMUNICATION

Blood Urea Nitrogen/Creatinine Ratio and Response to Tolvaptan in Patients with Decompensated Heart Failure: A Retrospective Analysis

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Abstract

Introduction Arginine vasopressin-stimulated reabsorption of urea occurs in the collecting duct via increased expression of the urea transporter.

Objective The aim of this study was to evaluate whether the blood urea nitrogen/creatinine (BUN/Cr) ratio is useful for predicting tolvaptan response in patients with decompensated heart failure (HF).

Methods Among 71 consecutive patients with HF who received oral tolvaptan between 2010 and 2014, we retrospectively studied 33 patients with decompensated HF without any mechanical circulatory assistance or inotropic support who had already been treated with loop diuretics. A responder to tolvaptan was defined as an individual who experienced a ≥30 % increase in their respective 24-h urine volume.

Results Among the 33 patients, 21 met the criteria of a responder. The area under the receiver operating characteristic curves of BUN/Cr and BUN were 0.790 and 0.714, respectively, and the respective cut-off values for responders to tolvaptan were 23.8 and 49.0. BUN/Cr and BUN retained their significant relationships with the responder status (odds ratio for BUN/Cr >23.8: 20.9; 95 % confidence interval [CI] 2.7–531.1; $p = 0.002$; odds ratio for BUN ≥49: 7.7; 95 % CI 1.4–65.8; $p = 0.02$).

Conclusion Our results suggest that high BUN/Cr may be a predictor of response to tolvaptan in decompensated HF patients. A prospective study with a large sample size is required to confirm this preliminary finding.

Key Points

Arginine vasopressin-stimulated urea reabsorption is increased in excess of the decreased clearance of creatinine in decompensated heart failure (HF) patients; creatinine is filtered by the glomerulus and is secreted in the distal nephron but not reabsorbed.

In decompensated HF patients, baseline blood urea nitrogen/creatinine ratio (BUN/Cr) was higher among tolvaptan responders (defined as having a ≥30 % increase in 24-h urine volume) compared with non-responders.

BUN/Cr is an alternative measure for easily estimating elevated arginine vasopressin levels and may be useful in initiating tolvaptan treatment.

1 Introduction

Patients with acute decompensated heart failure (HF) typically present with signs and symptoms of systemic volume overload and pulmonary congestion [1]. The arginine vasopressin (AVP) concentration is elevated in patients with HF, and AVP activates water reabsorption by means of the V2 receptor in the collecting ducts of the kidneys. Tolvaptan, a selective V2 receptor antagonist, promotes water excretion via the inhibition of water

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reabsorption in the collecting duct. Previous clinical trials have shown that tolvaptan decreases dyspnea frequency, body weight, and edema [2–4]. Tolvaptan is known to increase renal output and improve symptoms of volume overload in patients with decompensated HF. However, in some patients, tolvaptan has no effect on diuresis. It is not yet possible to predict which HF patients will respond to tolvaptan.

AVP-stimulated reabsorption of urea occurs in the collecting duct via increased expression of the urea transporter [5]. Brisco et al. [6] reported that decompensated HF patients with an elevated blood urea nitrogen/creatinine ratio (BUN/Cr), a metric that is used to differentiate between prerenal renal dysfunction and intrinsic renal parenchymal disease, had a significantly greater incidence of improvement in renal function and a greater likelihood of experiencing a return to compensation. The aim of this study was to evaluate whether BUN/Cr is useful for predicting tolvaptan response in patents with decompensated HF.

2 Methods

In this pilot study we reviewed 71 consecutive patients with decompensated HF who were admitted to the Cardiology Department of Tokyo Women's Medical University Hospital and started oral tolvaptan therapy between December 2010 and March 2014. The study's inclusion criteria included symptoms and signs of volume overload, such as peripheral edema, jugular venous distention, hepatomegaly, and pulmonary congestion upon admission, as well as the availability of 24-h urine volume before and after administration of tolvaptan. Patients with septic shock, end-stage renal failure on hemodialysis, or obvious gastrointestinal bleeding, or patients who received any mechanical circulatory assistance and/or inotropic support or who had already received tolvaptan prior to hospitalization were excluded. Ultimately, we retrospectively reviewed 33 decompensated HF patients.

Ischemic heart disease was defined as positive stress test findings, coronary angiography demonstrating at least 75 % stenosis or coronary spastic angina as documented by an acetylcholine provocation test, a history of prior myocardial infarction, or a history of revascularization procedures.

The left ventricular (LV) ejection fraction (LVEF) was calculated by left ventriculography, echocardiography, or radionuclide angiography. Blood pressure and heart rate were measured using a standard cuff mercury sphygmomanometer in the supine position on the morning of the day tolvaptan was first administered (day 1). For all our subjects, serum creatinine, BUN, electrolyte levels, and hemoglobin were measured prior to the administration of tolvaptan on the morning of day 1. B-type natriuretic peptide was obtained within 3 days prior to the administration of tolvaptan. Loop diuretic doses were converted to furosemide equivalents with 8 mg of torasemide = 60 mg of azosemide = 40 mg of furosemide for oral diuretics.

The 24-h urine volume from the medical chart was measured between 0 am and 0 am in our department. Thus, the urine volume on day 1 was not 24-h urine volume after the administration of tolvaptan. We assessed changes in 24-h urine volume on day 2 compared with the corresponding volume prior to tolvaptan treatment (day 0). No clear definitive criteria exist with which to define tolvaptan responders versus non-responders [7, 8]. Among our subjects, the mean percent change in 24-h urine volume on day 2 compared with day 0 was 49.9 % (95 % confidence interval [CI] 27.3–77.0). An increase in urine volume of approximately 30 % seems to be acceptable for diuresis. A responder to tolvaptan was defined as an individual who experienced a $\geq$30 % increase in the respective 24-h urine volume. The protocol was approved by the institutional review board of Tokyo Women's Medical University.

The summary data are presented as either mean ± standard deviation (SD), median (range), or number of patients. The baseline clinical data were compared between the responders and the non-responders using the Mann–Whitney *U* test. Categorical variables were subjected to Fisher's exact test. To assess the predictive value of BUN/Cr or BUN for response to tolvaptan, we performed receiver operating characteristic (ROC) curve analyses and logistic regression analyses. Data analyses were performed with JMP software (version 11.0, SAS Institute, Cary, NC, USA). A p value of <0.05 was considered significant.

3 Results

Among 33 patients, 21 met the criteria of a responder. Clinical characteristics according to response to tolvaptan are shown in Table 1. No significant differences were observed between responders and non-responders aside from the BUN and BUN/Cr ratios. The area under the ROC curves of BUN/Cr and BUN were 0.790 and 0.714, respectively, and the respective cut-off values for responders to tolvaptan were 23.8 and 49.0.

Previous reports have shown that improved outcomes are associated with improvements of hyponatremia in HF patients with hyponatremia [2, 3], as well as with the prerenal flow associated with hypotension, which also indicates that low cardiac output leads to decreased urine output. When both baseline BUN/Cr and BUN were examined together in a regression model adjusted for baseline systolic blood pressure (SBP) >85 mmHg and serum sodium concentration $\leq$135 mEq/L using the cut-off values calculated from the ROC analyses, BUN/Cr and BUN

Table 1 Patient characteristics according to response to tolvaptan

	Responders ($n = 21$)	Non-responders ($n = 12$)	p value
Age (years)	72 ± 12	78 ± 9	0.209
Male	10 (48 %)	10 (83 %)	0.067
Ischemic heart disease	5 (24 %)	5 (42 %)	0.433
Systolic blood pressure (mmHg)	101 ± 19	107 ± 22	0.653
Heart rate (beats per minute)	75 ± 13	71 ± 16	0.561
LVEF (%)	39 ± 12	39 ± 9	0.970
Laboratory value (baseline)			
Blood urea nitrogen (mg/dL)	51.5 ± 20.5	36.2 ± 16.3	0.045
Serum creatinine (mg/dL)	2.01 ± 1.04	2.24 ± 1.40	0.866
BUN/Cr	27.9 ± 10.3	18.7 ± 6.6	0.007
eGFR (mL/min per 1.73 m^2)	32.1 ± 22.7	31.1 ± 18.7	0.940
Serum sodium (mEq/L)	134 ± 6	137 ± 4	0.292
Serum potassium (mEq/L)	4.3 ± 0.6	4.1 ± 0.4	0.310
Hemoglobin (g/dL)	9.8 ± 1.5	10.7 ± 2.1	0.349
B-type natriuretic peptide (pg/mL)	353 (84–3553)	362 (131–1547)	0.750
Medications			
ACE inhibitors/ARBs	14 (67 %)	10 (83 %)	0.429
Beta-blockers	16 (76 %)	6 (50 %)	0.149
Mineralocorticoid antagonists	14 (67 %)	8 (67 %)	1.000
Digitalis	10 (48 %)	3 (25 %)	0.278
Carperitide	6 (29 %)	4 (33 %)	1.000
Nitrate	3 (14 %)	1 (8 %)	1.000
Thiazide diuretics	9 (43 %)	3 (25 %)	0.457
Loop diuretics (oral)	20 (95 %)	9 (75 %)	0.125
Dose	50 (10–100)	40 (20–160)	0.200
Intravenous furosemide	5 (24 %)	3 (25 %)	1.000
Dose	20 (10–60)	20 (20–100)	0.751
Dose of tolvaptan	11 ± 6	7 ± 3	0.053

Data are presented as n (%), mean ± SD, or median (range). Doses are presented as mg daily

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *BUN/Cr* blood urea nitrogen/creatinine ratio, *eGFR* estimated glomerular filtration rate, *LVEF* left ventricular ejection fraction, *SD* standard deviation

retained their significant relationships with the responder status (odds ratio [OR] for BUN/Cr >23.8: 20.9; 95 % CI 2.7–531.1; $p = 0.002$; OR for BUN ≥49: 7.7; 95 % CI 1.4–65.8; $p = 0.02$). These relationships were also significant when a regression model adjusted for baseline SBP >85 mmHg, serum sodium concentration ≤135 mEq/L, and combined use of angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) and beta-blocker (OR for BUN/Cr >23.8: 20.1; 95 % CI 2.7–493.9; $p = 0.002$; OR for BUN ≥49: 8.2; 95 % CI 1.4–76.5; $p = 0.02$).

4 Discussion

Our study showed that (1) baseline BUN/Cr and BUN were higher among tolvaptan responders than among non-responders, and (2) both baseline BUN/Cr and BUN (BUN/Cr to a greater extent than BUN) were independent predictors of responder status in patients with decompensated HF.

Because BUN is affected by protein intake, catabolism, gastrointestinal bleeding, dehydration, and tubular reabsorption of urea, BUN is not as reliable an index of renal function as the glomerular filtration rate (GFR) [9]. Neurohormonal activation enhances proximal and distal tubular reabsorption [9]. In the collecting duct, the reabsorption of urea is facilitated via urea transport by AVP. In patients with HF, AVP levels are elevated, and the incremental increase in AVP is associated with the severity of the HF state [10, 11]. Thus, AVP can rapidly increase urea transport, as well as water transport, in the kidney's inner medullary collecting duct [5]. All of our patients had already received loop diuretics before tolvaptan treatment. Because loop diuretics cause neurohormonal activation [9], our HF patients with higher BUN levels were thought to be