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CME

iCONCEPTS

CONCEPTS ON THE VERGE OF TRANSLATION

CRT Improves LV Filling Dynamics

Insights From Echocardiographic Particle Imaging Velocimetry

Georg Goliasch, MD, PhD,* Kinga Goscinska-Bis, MD,† Giuseppe Caracciolo, MD,* Ayumi Nakabo, MD,* Grzegorz Smolka, MD,† Gianni Pedrizzetti, PhD,*‡ Jagat Narula, MD, PhD,* Partho P. Sengupta, MD*

New York, New York; and Katowice, Poland

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From the *Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; †Department of Cardiology, Medical University of Silesia, Katowice, Poland; and the ‡University of Trieste, Trieste, Italy. Dr. Goliasch was funded by an Erwin Schrödinger Fellowship of the Austrian Science Fund (FWF J 3319-B13). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Leslie A. Saxon, MD, served as Guest Editor for this paper.

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CRT Improves LV Filling Dynamics

Echocardiographic particle imaging velocimetry allows blood flow visualization and characterization of diastolic vortex formation that may play a key role in filling efficiency. We hypothesized that abrupt withdrawal of cardiac resynchronization therapy (CRT) would alter the timing of left ventricular diastolic vortex formation and modify cardiac time intervals. In patients with heart failure (HF) who had chronically implanted CRT devices, the timing of the onset of the diastolic vortex (TDV) from mitral valve opening, transmitral flow, and cardiac time intervals was measured at baseline and after deactivation and reactivation of CRT. Compared with control patients with cardiovascular risk factors but structurally normal hearts, TDV was significantly delayed in patients with HF. Deactivation of CRT resulted in striking delay in TDV due to disorganized flow and reduced flow acceleration, and reactivation reversed these characteristics instantly. In addition, CRT deactivation also prolonged the isovolumic contraction interval, which closely correlated with the changes in the TDV. These data suggest that CRT plays an important role in optimization of left ventricular diastolic filling. (J Am Coll Cardiol Img 2013;6:704–13) © 2013 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) has been used extensively to reverse the progression of advanced heart failure (HF) and contribute to reverse remodeling (1). Response to CRT therapy has been traditionally defined by the survival outcome and the restoration of left ventricular (LV) volumes, and ejection fraction (EF) has been assessed as the surrogate indicators of successful CRT. However, the LV volume and EF may not always correlate with symptomatic improvement in patients with advanced HF. Conversely, clinical improvement in New York Heart Association class and functional capacity may occur despite minimal improvement in left ventricular ejection fraction (LVEF). CRT can also have a stabilizing effect on hemodynamics in the failing heart, and acute decompensation may ensue on discontinuation of CRT.

It is conceivable that the clinical improvement after CRT may at least in part be related to improvement in LV diastolic filling parameters (2). However, the effect of CRT on diastolic function and diastolic filling are not well understood. Although pulsed wave Doppler measurements have demonstrated a significant improvement in transmitral filling velocities after CRT therapy, measurements of global or regional LV relaxation have not been found to be favorably altered. Moreover, the changes in transmitral filling have not been consistently reported and may be partly attributed to the angle dependence and unidimensional acquisition of the conventional Doppler ultrasound imaging (3). The 3-dimensional path assumed by the diastolic ventricular filling may have a wide range of angles and incoherence, particularly in the presence of dyssynchrony and dilated ventricular cavity, and may not be conducive for a single sample volume registration. Moreover, pulsed wave Doppler measurements in CRT patients often display alterations in the flow profile such as the fusion of E and A waves, and may affect the accuracy of Doppler-derived measures.

A crucial component of diastole is the intracavity vortex formation (3), which is further carried from the late diastolic phase into the isovolumic contraction (IC) period. The latter IC vortex persists from mitral valve closure to the opening of the aortic valve and naturally directs the blood flow pattern toward the aortic outflow. This continuation of the diastolic vortex into the IC vortex obviates the need for rapid deceleration and sharp swirls in the blood flow and contributes to energetically favorable intraventricular fluid dynamics. In addition, diastolic vortices may provide a loading mechanism for LV stretching for optimal force generation during LV ejection. Changes in diastolic vortex pattern in various heart ailments and after surgical interventions have been reviewed previously. The diastolic vortex may modulate the intracavity shear stress and provide mechanosensitive feedback to alter cardiomyocyte architecture and diverse cellular processes, including cardiomyocyte proliferation, hypertrophy, and apoptosis involved in cardiac remodeling processes (4). In a normal left ventricle, the intraventricular pressure gradient is aligned in the base-to-apex direction in which the myocardial geometry allows a proper balance of longitudinal

stress. On the contrary, the disharmony of tissue motion may contribute to a chaotic "hammering" of blood and result in progressive modification of LV geometry. Conversely, reduction in incoherent flow and improved timing of filling vortex could induce genomic and proteomic processes, resulting in reversal of LV remodeling. The functional improvement related to CRT has recently been attributed to the reversal of molecular remodeling, with genetic changes governing contractile function and pathological hypertrophy. Thus, the synthesis of data on effects of CRT on diastolic vortices may provide more mechanistic insights into the benefits related to CRT.

Visualization of diastolic vortices has traditionally used magnetic resonance phase contrast velocity mapping. However, magnetic resonance imaging is not feasible in patients with CRT implantation. Echocardiographic particle image velocimetry (echo-PIV) has recently emerged as an alternative technique for 2-dimensional blood flow visualization that combines particle image velocimetry with LV contrast opacification; it has been validated in the in vitro settings and used successfully to characterize intracardiac flow fields at high temporal resolution in experimental and clinical settings (3). Echo-PIV may be more suitable for the assessment of intracavitary dynamics in both diastolic and systolic phases serially during deactivation and reactivation of the CRT device. In this iConcept, we report our pilot data regarding the acute effects of CRT discontinuation on the characteristics of LV diastolic vortex formation by using cardiac time intervals as an endpoint. Prolongation or shortening of the different time intervals and their reproducibility as markers of global cardiac function in HF patients and CRT recipients have been previously validated. We hypothesized that abrupt withdrawal of CRT would alter the timing of LV diastolic vortex formation and therefore modify cardiac time intervals as markers of global cardiac pump efficiency.

ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy
ECG = electrocardiogram
Echo-PIV = echocardiographic particle image velocimetry
EF = ejection fraction
HF = heart failure
IC = isovolumic contraction
IVR = isovolumic relaxation
LV = left ventricular
TDV = timing of onset of diastolic vortex

Echo-PIV and the Diastolic Vortex Characteristics

We studied 11 patients with implanted biventricular pacemakers undergoing a biventricular optimization protocol under echocardiographic guidance. All the patients underwent sensing in the atrium, and the pacing mode at baseline was therefore VDD-BiV (biventricle pacing with atrial tracking) during the study. Response to biventricular pacing was defined as a decrease in the LV end-systolic volume of ≥15% or an absolute increase in LVEF of >5% within 6 months. Of these 11 patients with CRT, 7 (64%) were classified as responders. All patients underwent a complete 2-dimensional B-mode Doppler ultrasound and contrast echocardiography at baseline, 3 min after deactivation of biventricular pacing, and 3 min after reactivation of biventricular pacing. The acquired data were subsequently analyzed offline. Baseline echocardiographic data were compared with that of a control group of 11 patients with cardiovascular risk factors but structurally normal hearts.

Patients underwent a conventional transthoracic echocardiography (Vivid 7, GE Healthcare, Waukesha, Wisconsin). Cardiac time intervals were registered with both Doppler and PIV techniques and were correlated to ensure the accuracy of our data. Sulfur hexafluoride gas-filled, lipid-stabilized microbubbles (SonoVue, Bracco International B.V, Amsterdam, the Netherlands) were used to perform 2-dimensional contrast echocardiography. The contrast agent (0.1 to 0.2 ml of SonoVue) was given as an intravenous bolus injection after being shaken with an agitator for 45 s and was followed by a slow normal saline flush. The intraventricular flow was recorded at a mechanical index of 0.1 to 0.4, with the apical long-axis view.

Echo-PIV is a technique to measure a velocity field by detecting contrast agent microbubbles over subsequent frame pairs. The distance traveled from 1 frame to the next, divided by the time interval, is the local velocity vector. Echo-PIV was performed from an apical 3-chamber view by using prototype software (HyperFlow version 6.2, Advanced Medical Imaging Development SRL, Sulmona, Italy). Echo-PIV is based on tracking of microbubbles that, as with myocardial speckle tracking, uses an interrogation window of finite size (typically 16 × 16 pixels, approximately 4 mm × 4 mm). Once the velocity field inside the left ventricle is estimated, the fluid dynamics of blood motion can be reliably evaluated (3). The inflow velocity time profile is obtained by defining the mitral inflow tract and computing the average velocity across it. The intraventricular vortex is characterized by the amount of vorticity contained therein. Vorticity is defined mathematically as the curl of the velocity, which represents the local rotation of fluid elements; therefore, a compact region of vorticity corresponds to a compactly rotating pattern (i.e., a "vortex"). The vortex is defined by the connected region in which vorticity is >50% of its maximum over the entire heartbeat; the vortex strength curve is then computed by the summation of all vorticity therein

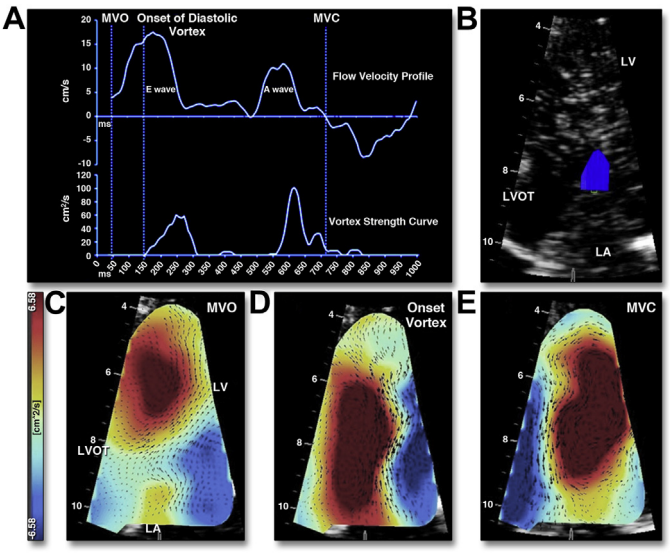

Figure 1. Assessment of Transmitral Velocity Profile and LV Intracavity Vortex Strength in Control

Contrast particle image velocimetry–derived flow velocity and vortex strength curves have been derived simultaneously and displayed together **(A)**. Velocity curve is derived from a region of interest located at the tip of the mitral valve **(B)**, whereas vortex strength is computed for the blood flow within the entire left ventricular (LV) cavity and depicts a transient delay in the timing of onset of diastolic vortex (TDV). Phasic changes in clockwise **(blue)** and counterclockwise **(red)** vortex strength are shown during **(C)** mitral valve opening (MOV), **(D)** onset of vortex, and **(E)** mitral valve closure (MVC). Note that the clockwise **(blue)** and counterclockwise **(red)** vortex during **(D)** early diastolic filling becomes **(E)** unidirectional at end-diastole. See accompanying Online Videos 1 and 2. LA = left atrium; LVOT = left ventricular outflow tract.

Table 1. Baseline Characteristics of the Study Population and Control Patients

	Study Population (n = 11)	Control Patients (n = 11)	p Value
Demographic			
Age, yrs	61 ± 9	61 ± 9	0.87
Male	9 (82)	5 (45)	0.08
Body surface area, m^2	1.96 ± 0.13	1.97 ± 0.33	0.39
Systolic blood pressure, mm Hg	107 ± 12	126 ± 19	**0.02**
Heart rate, beats/min	69 ± 10	67 ± 8	0.70
QRS width, ms	153 ± 17	89 ± 10	**<0.001**
Left bundle branch block	9 (82)	0 (0)	**<0.001**
Risk factors			
Hypertension	5 (45)	4 (36)	0.67
Hyperlipidemia	4 (36)	5 (45)	0.67
Diabetes mellitus	3 (27)	0 (0)	0.06
Medications			
RAAS inhibitor	11 (100)	1 (9)	**<0.001**
Beta-blocker	11 (100)	2 (18)	**<0.001**
Digoxin	4 (36)	0 (0)	0.06
Diuretics	11 (100)	0 (0)	**<0.001**
Statins	6 (55)	3 (27)	0.19

Values are mean ± SD, or n (%). Continuous data were tested for a normal distribution by using the Kolmogorov-Smirnov test and the homogeneity of variance by using the variance ratio test (F-test). The unpaired Student *t* test and chi-square test were used for comparing continuous and categorical variables between the groups, as appropriate. If the variance ratio test was statistically significant, the Mann-Whitney *U* test was used for comparison. Statistical analyses were performed by using MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium). **Boldface** indicates significant p value.

RAAS = renin-angiotensin-aldosterone system.

(or by its average vorticity multiplied by the vortex area). After the vortex extension has been identified, the vortex area is immediately known as its length along the base-to-apex direction. The vortex intensity is then given by the integrated circulation along the identified vortex, which represents a measure of the rotary motion in the vortex. These quantities have been defined in a way to represent overall integral properties of the flow motion such that they provide reproducible estimations of the timings of flow phenomena not influenced by regional fluctuations.

Cardiac time intervals were defined on 2-dimensional echocardiographic images (apical long-axis view) by marking the time points of mitral and aortic valve closure and opening. Further reference points from the surface electrocardiogram were used to define the cardiac time intervals. The pre-ejection period was defined as the duration between the onset of the QRS complex in surface electrocardiography and the opening of the aortic valve. The pre-ejection period included the interval of electromechanical activation, as defined by the appearance of Q waves in the surface electrocardiogram to the opening of the mitral valve. The IC interval was defined as the period between mitral valve closure and aortic valve opening. The ejection period was defined as the duration between aortic valve opening and closing, and the isovolumic relaxation (IVR) period was defined as the duration between aortic valve closing and mitral valve opening. The timing of the onset of the diastolic vortex (TDV) was defined as the interval from mitral valve opening to the appearance of the main diastolic vortex formation (determined from the diastolic ascent of the vortex strength curve), as displayed in Figure 1. In addition, the initial acceleration of LV flow, from mitral valve opening to the onset of vortex formation, was measured as the average slope of transmitral velocity during this period. The acceleration of LV flow was estimated by assuming a constant velocity ramp and was calculated by dividing twice the average velocity with its time duration in milliseconds.

Table 2. Baseline Echocardiographic Characteristics, Time Intervals, and Vortex Parameters

	Study Population (n = 11)	Control Patients (n = 11)	p Value
Echo baseline and flow characteristics			
IVS thickness, mm	11 ± 3	10 ± 1	0.19
End-diastolic volume, ml	258 ± 97	67 ± 9	**<0.001***
End-systolic volume, ml	190 ± 88	31 ± 4	**<0.001***
Ejection fraction, %	25 ± 8	65 ± 3	**<0.001***
E-wave, cm/s	57 ± 16	71 ± 12	**0.04**
A-wave, cm/s	67 ± 27	61 ± 15	0.65*
E/A ratio	1.1 ± 0.3	1.2 ± 0.5	0.34*
E/e' ratio	17.8 ± 3.3	7.7 ± 1.5	**<0.001***
Time intervals			
Cardiac cycle, ms	917 ± 100	948 ± 122	0.54
IC, ms	85 ± 36	61 ± 12	0.053*
Ejection, ms	245 ± 80	293 ± 21	0.07*
IVR, ms	167 ± 52	159 ± 64	0.76
Diastolic filling time, ms	318 ± 109	304 ± 105	0.30
Flow parameters			
Onset of E-wave to peak E, ms	119 ± 51	102 ± 39	0.42
E-wave to vortex formation interval, ms	87 ± 39	31 ± 11	**<0.001***
Early diastolic LV flow acceleration, m/s^2	0.09 ± 0.10	1.13 ± 0.50	**<0.001***
TDV, ms	62 ± 44	21 ± 6	**0.03***
Vortex intensity, % LV vorticity	40 ± 7	49 ± 7	**0.003**
Vortex area, % of LV area	20 ± 2	37 ± 6	**0.001***
Vortex length, % of LV length	50 ± 3	74 ± 14	**<0.001***

Values are mean ± SD. Details of statistical analysis are similar to that presented in Table 1. *p values were determined by using the Mann-Whitney *U* test. **Boldface** indicates significant p value.

E/A = early to late diastolic mitral flow velocity ratio; E/e' = early diastolic flow velocity to mitral annular velocity ratio; IC = isovolumic contraction; IVR = isovolumic relaxation; IVS = interventricular septum; LV = left ventricular; TDV = timing of onset of diastolic vortex formation.

CRT and the Diastolic Vortex

Demographic characteristics of HF patients with CRT and controls are shown in Table 1. Both groups were comparable with regard to age, gender, and risk factors. The median CRT therapy duration was 19 months (interquartile range: 6 to 56). Echocardiographic data displayed significant differences between CRT patients and controls. The data suggested LV remodeling, as seen by differences in volumes and EF (Table 2). Although 2-dimensional echocardiographic features were significantly different between CRT patients and controls, IVR and diastolic filling time did not differ significantly between the 2 groups, whereas IC displayed a trend to be shorter ($p = 0.05$) with a longer duration of ejection ($p = 0.07$) in controls.

Diastolic filling characteristics at baseline. The sequence of LV diastolic filling was studied using echo-PIV. In controls, a counterclockwise vortex formation started immediately after mitral valve opening (Online Video 1) and slowly propagated toward the apex, organizing the flow in the LV apical region (Fig. 1, Online Video 2). In late diastole, although the flow presented some irregularity and fluctuations, the active atrial contraction initiated a

second counterclockwise vortex formation that fused with the primary vortex during IC and produced a coherent circulatory pattern, redirecting the flow toward the outflow tract. In comparison, HF patients at baseline showed a weaker early diastolic counterclockwise vortex formation (Fig. 2, Online Videos 3 and 4) with significantly reduced vortex intensity, vortex area, and vortex length (Table 2).

To establish the validity of the temporal sequence of diastolic filling derived from echo-PIV, we compared the time intervals of diastolic filling obtained from echo-PIV velocity curves with the respective intervals obtained from pulse waved Doppler. The time intervals from R to the onset/peak of the early diastolic filling waves were closely correlated between pulse waved Doppler and contrast PIV ($r = 0.91$; $p < 0.001$) (Figs. 3A and 3B).

TDV and E-wave to diastolic vortex time intervals were significantly delayed in CRT patients at baseline ($p = 0.03$ and $p < 0.001$, respectively) (Table 2). Furthermore, the initial acceleration of the LV inflow was significantly lower in CRT patients compared with controls ($p < 0.001$).

Effects of CRT deactivation. Compared with baseline, CRT deactivation resulted in a significant prolongation of the IC period ($p = 0.007$), which returned to baseline after reactivation of the device ($p = 0.70$ for comparison between baseline and reactivation) (Table 3). This finding is consistent with previous reports in which a change in the IC duration has been used as a noninvasive marker for monitoring the acute response to biventricular pacing (5).

In contrast to IVC, IVR was significantly shortened on deactivation of biventricular pacing compared with baseline ($p = 0.002$) and returned to the baseline value on reactivation of the biventricular pacemaker ($p = 0.44$ for comparison between baseline and reactivation) (Table 3). The observed changes in IVR are also consistent with previous reports (2) of prolonged IVR after CRT activation. Transient CRT deactivation increases the left atrial

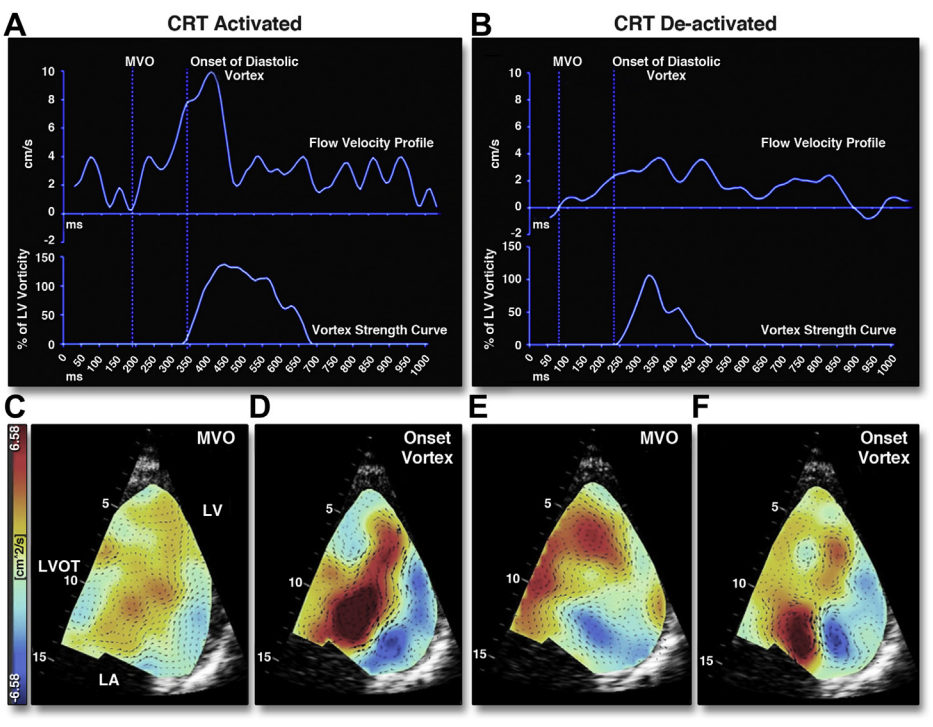

Figure 2. Assessment of Transmitral Velocities and LV Intracavity Vortex Strength During Activated and Deactivated CRT

Contrast particle image velocimetry (PIV)-derived flow velocity and vortex strength curves have been derived simultaneously and displayed side-by-side during **(A)** activation and **(B)** deactivation of cardiac resynchronization therapy (CRT) in the same patient. Phasic changes in clockwise **(blue)** and counterclockwise **(red)** vortex strength are shown with activated CRT device during **(C)** MVO and **(D)** onset of vortex and with deactivated CRT device during **(E)** MVO and **(F)** onset of vortex. Note that the TDV is delayed by 26 ms and the vortex strength is attenuated with deactivation of CRT **(F)**. See accompanying Online Videos 3, 4, 5, and 6. Abbreviations as in Figure 1.

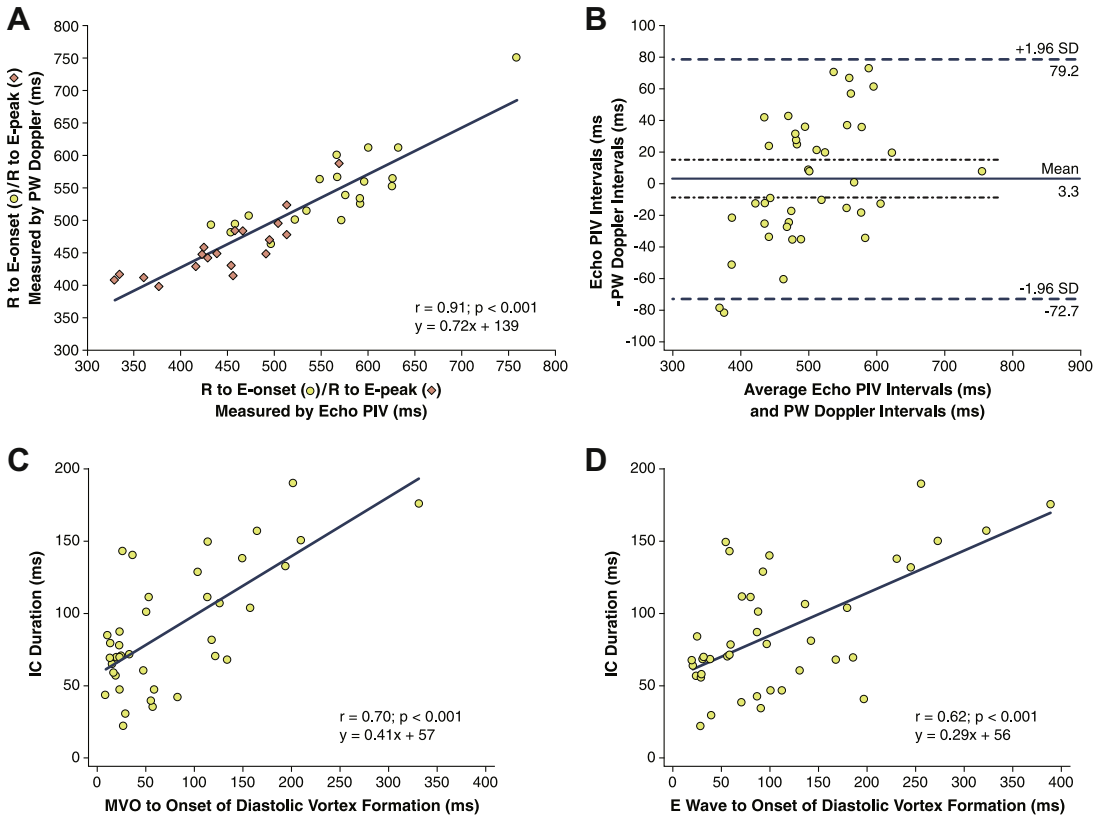

Figure 3. Comparison of Pulsed Wave Doppler and Contrast PIV-Derived Diastolic Velocity Time Intervals

The R wave on the surface electrocardiogram to early diastolic velocity time intervals (E-onset/E-peak) were measured with pulsed wave Doppler obtained at the tip of mitral valve leaflets. The same region of interest was subsequently delineated during echocardiographic particle image velocimetry (echo-PIV) analysis and transmitral long-axis velocity profiles were constructed and correlated **(A)** ($r = 0.91$; $p = 0.001$) along with Bland-Altman analysis **(B)** during baseline examinations performed in CRT patients and controls ($n = 22$). TDV after mitral valve opening (as delineated from mitral valve motion on 2-dimensional images) also was correlated with isovolumic contraction (IC) duration **(C)** ($r = 0.70$; $p < 0.001$) and the onset of E wave to the onset of diastolic vortex formation ($r = 0.62$; $p < 0.001$) **(D)**. Deactivation of CRT delayed the IC interval, which correlated with a delay in the TDV. The correlations between the respective parameters were assessed by using the Pearson correlation coefficient. Abbreviations as in Figures 1 and 2.

Table 3. Time Intervals of the Cardiac Cycle

	Baseline	Deactivated	Reactivated	ANOVA
Cardiac cycle, ms	917 ± 100	921 ± 53	875 ± 121	0.7755
IC, ms	85 ± 36*	121 ± 49	79 ± 39†	**0.0168**
IC, % of cardiac cycle	9 ± 4	13 ± 5	9 ± 4	**0.006**
Ejection, ms	245 ± 80	288 ± 42	250 ± 23	0.7631
Ejection, % of cardiac cycle	27 ± 10	30 ± 7	29 ± 5	0.8017
IVR, ms	167 ± 52*	138 ± 33	168 ± 50†	**0.0079**
IVR, % of cardiac cycle	18 ± 5	14 ± 5	19 ± 4	**0.0139**
Diastolic filling time, ms	318 ± 109	320 ± 61	283 ± 96	0.1869
Diastolic filling time, % of cardiac cycle	34 ± 10	35 ± 9	32 ± 7	0.1977

Values are mean ± SD. Comparison between biventricular pacing at baseline, deactivated biventricular pacing, and reactivated biventricular pacing were performed by using repeated measures analysis of variance (ANOVA) with Greenhouse-Geisser and Huynh-Feldt adjustments for departures from sphericity (MedCalc for Windows, version 9.5.0.0, Mariakerke, Belgium). *$p < 0.05$ comparing the baseline with deactivated pacing (paired Student *t* test). †$p < 0.05$ comparing reactivated and deactivated (paired Student *t* test); ANOVA for repeated measurements. **Boldface** indicates significant p value.

Abbreviations as in Table 2.

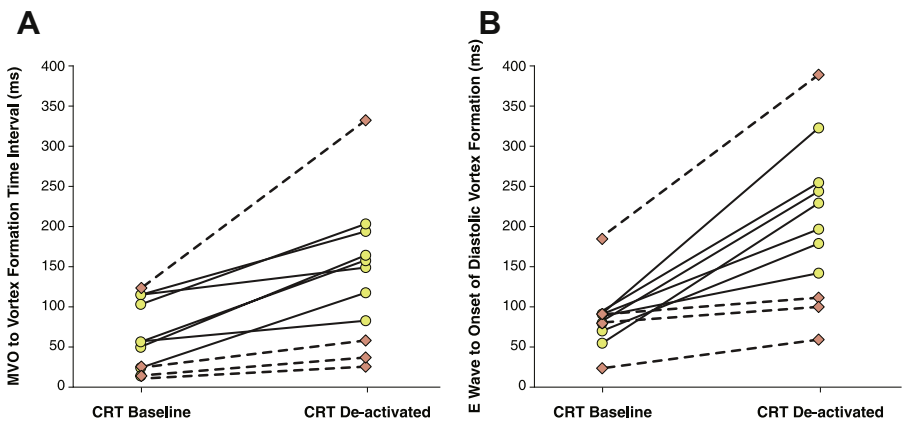

Figure 4. Effect of CRT Deactivation on the TDV and the onset of E wave to the Onset of Diastolic Vortex Formation

Deactivation of CRT therapy resulted in a significant prolongation of TDV **(A)** ($p = 0.001$) and resulted in a significant prolongation of the onset of E wave to the onset of diastolic vortex formation **(B)** ($p < 0.001$). The **dashed lines** indicate CRT nonresponders. Abbreviations as in Figures 1 and 2.

filling pressure, causing early opening of the mitral valve and shortening of the IVR period (2). Conversely, CRT reactivation normalizes the left atrial filling pressure and unmasks the presence of the prolonged IVR period due to the underlying myocardial disease.

In our study, CRT deactivation resulted in delayed development of the early diastolic counterclockwise vortex (Online Videos 5 and 6) compared with the activated CRT device (Fig. 2, Online Videos 3 and 4). This outcome resulted in a significant prolongation of TDV ($p < 0.001$) (Fig. 4), which returned to baseline after reactivation of the device ($p = 0.98$ for comparison between baseline and reactivation) (Table 4). Figure 4 shows the changes in TDV and the delay in the onset of the diastolic vortex formation. This prolonged vortex formation process led to a less mature vortex at the end of early diastole. Therefore, CRT deactivation resulted in a significant decrease in initial LV flow acceleration ($p = 0.02$), which returned to baseline after CRT reactivation ($p = 0.14$ for comparison between baseline and reactivation). The serial changes in the IC duration in patients with CRT showed good correlation with the mitral valve opening–to–vortex formation interval ($r = 0.70$; $p < 0.001$) (Fig. 3C) and the duration from E-wave to diastolic vortex time interval ($r = 0.62$; $p < 0.001$) (Fig. 3D).

All significant parameters demonstrated good reproducibility, with an interclass correlation coefficient >0.95 when tested for interobserver and

Table 4. Flow Parameters: Comparison Between Biventricular Pacing at Baseline, Deactivated Biventricular Pacing, and Reactivated Biventricular Pacing

	Baseline	Deactivated	Reactivated	ANOVA
E/A ratio	1.2 ± 0.5	1.19 ± 0.5	1.0 ± 0.3	0.4544
Onset of E to peak E, ms	102 ± 39	127 ± 47	106 ± 33	0.31
E-wave onset to vortex formation onset interval, ms	87 ± 39*	202 ± 99	102 ± 71†	**0.0026**
Early diastolic LV flow acceleration, m/s^2	0.09 ± 0.10*	0.01 ± 0.03	0.19 ± 0.23†	**0.0059**
TDV, ms	62 ± 44*	137 ± 88	61.0 ± 65.8†	**0.0058**
Vortex intensity, %	40 ± 7	40 ± 4	41 ± 6	0.5388
Vortex area, % of LV area	20 ± 2	20 ± 4	20 ± 2	0.5647
Vortex length, % of LV length	50 ± 3	53 ± 6	51 ± 5	0.1978

Values are mean ± SD. Statistical analysis is similar to that presented in Table 3. *$p < 0.05$ comparing baseline with deactivated pacing (paired Student *t* test). †$p < 0.05$ comparing reactivated and deactivated (paired Student *t* test); ANOVA for repeated measurements. **Boldface** indicates significant p value.
Abbreviations as in Tables 2 and 3.

Table 5. Interobserver and Intraobserver Variability

	Interobserver Variability		Intraobserver Variability	
	ICC	95% CI	ICC	95% CI
IC	0.989	0.967–0.996	0.993	0.979–0.998
IVR	0.973	0.923–0.991	0.977	0.931–0.992
TDV	0.999	0.996–1.000	0.992	0.977–0.997
Early diastolic LV flow acceleration	0.998	0.994–0.999	0.985	0.955–0.995

Intraobserver and interobserver variability were assessed in 5 randomly selected CRT patients during serial reactivation. Interobserver agreement and intraobserver consistency were presented by using interclass correlation coefficients (ICCs) and a 95% confidence interval (95% CI).
Abbreviations as in Table 2.

intraobserver variability. Interclass correlation coefficients are shown in Table 5.

Clinical implications. Our findings suggest that CRT acutely affects diastolic filling, and the change can be measured as change in TDV. LV dyssynchrony produces a disorganized overall LV volume growth in early diastole, which results in a reduced acceleration of mitral flow. The lower acceleration of mitral flow further delays the time to diastolic vortex formation and in turn perpetuates a delay in the IC interval because the formation of an immature diastolic vortex restricts the energy transfer from diastole to systole, impeding the timely opening of the aortic valve. Moreover, our data suggest that LV filling is improved immediately after CRT reactivation due to optimum timing of diastolic vortex formation with shortening of the IC interval. Thus, echo-PIV may be a useful technique for elucidating the acute hemodynamic effects of CRT, particularly in a subset of patients in whom the clinical improvement in symptoms may not coincide with reversal of remodeling or an improvement in LV ejection fraction. The favorable effects of CRT on diastolic filling may also explain why patients with progressive HF become more symptomatic and decompensate if CRT is acutely deactivated (1). This outcome may explain the previously stabilizing effect of CRT therapy on hemodynamics in nonresponders and patients who present with decompensated HF.

Study limitations. A larger sample size with different subgroups of CRT patients will be required for understanding the optimization of the LV flow sequence with different pacemaker settings. We used 2-dimensional apical long-axis views to focus on the inflow and outflow regions of the left ventricle. For assessing the LV flow structure in a dilated heart, a full 3-dimensional structure of flow is desirable; however, this is currently not feasible due to the low temporal resolution of 3-dimensional echocardiographic techniques.

A few other methodologic limitations require consideration. First, we focused on obtaining optimum PIV images at high temporal resolution. Therefore, Doppler measurements and comparisons with contrast PIV were performed only at baseline and not with contrast imaging to avoid contrast destruction and in-homogenous distribution. Moreover, use of contrast imaging at a low mechanical index prohibited simultaneous myocardial strain analysis. Lastly, we did not acquire invasive hemodynamic measurements because image acquisition was performed in outpatient settings. Despite these methodologic limitations, information on the influence of CRT therapy on vortex formation is scarce, and the current investigation therefore provides meaningful data that can be useful for designing future studies.

Conclusions

This pilot investigation presents preliminary data to support the use of echo-PIV for quantifying the effects of CRT on LV diastolic filling and vortex formation. In patients with chronic CRT, acute interruption of the CRT alters LV filling characteristics due to a delay in the onset of the diastolic vortex that prolongs the redirection of blood flow. Acute restoration of LV diastolic vortex formation on CRT reactivation suggests a favorable role played by CRT on optimization of LV diastolic filling. Further studies are needed to elucidate whether optimization of diastolic filling characteristics via variations in the pacemaker settings or lead positioning would be useful for predicting clinical outcomes after CRT.

Reprint requests and correspondence: Dr. Partho P. Sengupta, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, New York 10029. *E-mail: partho.sengupta@mountsinai.org.*

REFERENCES

1. Mullens W, Verga T, Grimm RA, Starling RC, Wilkoff BL, Tang WH. Persistent hemodynamic benefits of cardiac resynchronization therapy with disease progression in advanced heart failure. J Am Coll Cardiol 2009;53:600–7.
2. Waggoner AD, Faddis MN, Gleva MJ, de las Fuentes L, Davila-Roman VG. Improvements in left ventricular diastolic function after cardiac resynchronization therapy are coupled to response in systolic performance. J Am Coll Cardiol 2005;46:2244–9.
3. Sengupta PP, Pedrizzetti G, Kilner PJ, et al. Emerging trends in CV flow visualization. J Am Coll Cardiol Img 2012;5:305–16.
4. Lab MJ. Mechanically Mediated Crosstalk in Heart. In: Kamkin A, Kiseleva I, editors. Mechanosensitivity in Cells and Tissues. Moscow, Russia: Academia, 2005.
5. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002;105:438–45.

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