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Should We Aim for dP/dt_{max} or Stroke Work?

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CME/MOC/ECME Objectives for This Article: Upon completion of this activity, the learner should be able to: 1) discuss invasive methods of hemodynamic testing for CRT optimization; 2) discuss the advantages of stroke volume guided optimization over LV pressure based optimization; and 3) discuss the long-terms benefits of invasive LV optimization.

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Hemodynamic Optimization in Cardiac Resynchronization Therapy

Should We Aim for dP/dt_{max} or Stroke Work?

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ABSTRACT

OBJECTIVES This study evaluated the acute effect of dP/dt_{max}- versus stroke work (SW)-guided cardiac resynchronization therapy (CRT) optimization and the related acute hemodynamic changes to long-term CRT response.

BACKGROUND Hemodynamic optimization may increase benefit from CRT. Typically, maximal left ventricular (LV) pressure rise dP/dt_{max} is used as an index of ventricular performance. Alternatively, SW can be derived from pressure–volume (PV) loops.

METHODS Forty-one patients underwent CRT implantation followed by invasive PV loop measurements. The stimulation protocol included 16 LV pacing configurations using each individual electrode of the quadripolar lead with 4 atrioventricular (AV) delays. Conventional CRT was defined as pacing from the distal electrode with an AV delay of approximately 120 ms.

RESULTS Compared with conventional CRT, dP/dt_{max}-guided optimization resulted in a one-third additional dP/dt_{max} increase ($17 \pm 11\%$ vs. $12 \pm 9\%$; $p < 0.001$). Similarly, SW-guided optimization resulted in a one-third additional SW increase ($80 \pm 55\%$ vs. $53 \pm 48\%$; $p < 0.001$). Comparing both optimization strategies, dP/dt_{max} favored contractility ($8 \pm 12\%$ vs. $5 \pm 10\%$; $p = 0.015$), whereas SW optimization improved ventricular–arterial (VA) coupling (45% vs. 32%; $p < 0.001$). After 6 months, mean LV ejection fraction (LVEF) change was $10 \pm 9\%$ with 23 (56%) patients becoming super-responders to CRT (≥10% LVEF improvement). Although acute changes in SW were predictive for long-term CRT response (area under the curve: 0.78; $p = 0.002$), changes in dP/dt_{max} were not (area under the curve: 0.65; $p = 0.112$).

CONCLUSIONS PV-guided hemodynamic optimization in CRT results in approximately one-third SW improvement on top of conventional CRT, caused by a mechanism of enhanced VA coupling. In contrast, dP/dt_{max} optimization favored LV contractility. Ultimately, acute changes in SW showed larger predictive value for long-term CRT response compared with dP/dt_{max}. (J Am Coll Cardiol EP 2019;5:1013–25) © 2019 by the American College of Cardiology Foundation.

Optimization of cardiac resynchronization therapy (CRT) after implantation includes individualized programming of the atrioventricular (AV) and interventricular delay, selection of the most beneficial left ventricular (LV) pacing electrode, or stimulation by multiple electrodes (i.e., multipoint pacing). Multiple optimization strategies are presently available, and the best method remains to be established. Electrical (e.g., QRS duration/area; Q on surface electrocardiographic [ECG] to LV sensing interval [QLV]) and echocardiographic (e.g., stroke volume; mitral flow) parameters are most widely used in clinical practice, although convincing scientific evidence for these methods is lacking. Alternatively, acute CRT response can be assessed by invasive hemodynamic testing to optimize device settings (1). Typically, the maximum rate of left ventricular pressure rise (dP/dt_{max}) is used as an index of ventricular performance (2). For this purpose, a pressure guidewire is inserted into the LV cavity to perform measurements in a relatively easy and reliable manner. Alternatively, pressure–volume (PV) loops can be obtained using a conductance catheter. A major advantage of the PV approach is that functional measures are provided with information on pre-load, afterload, and contractility, which allows assessment of underlying physiological mechanisms. Stroke work (SW) incorporates all pressure and

volume changes throughout the cardiac cycle and provides a comprehensive appraisal of LV pump function (1,2).

At present, a direct comparison between invasive CRT optimization strategies is lacking. This study aims to: 1) evaluate the acute effect of dP/dt_{max}- versus SW-guided CRT optimization; and 2) relate acute changes in hemodynamic parameters to long-term CRT response.

SEE PAGE 1026

METHODS

STUDY POPULATION. This study is part of the OPTICARE-QLV (Optimization of Cardiac Resynchronization Therapy with a Quadripolar Left Ventricular Lead) study, a multicenter, prospective, observational study. The main aim of the OPTICARE-QLV study was to relate electrical parameters (QLV) to acute hemodynamic response in CRT with quadripolar LV leads, using conductance catheter measurements (3). Inclusion criteria were moderate to severe heart failure (New York Heart Association functional class II or III) despite optimal medical therapy, LV ejection fraction (EF) ≤35%, sinus rhythm, and left bundle branch block (LBBB) according to the Strauss criteria. The study was performed according to the Declaration of Helsinki and in agreement with the local medical ethics committees. All subjects gave written informed consent.

BASELINE PROCEDURES. All patients underwent ECG, echocardiographic, and cardiac magnetic resonance (CMR) examinations before device implantation. CRT implantation was performed under local anesthesia following standard procedures. Right ventricular and right atrial leads were placed at conventional positions. The quadripolar LV lead (Quartet 1458Q, St. Jude Medical, St. Paul, Minnesota) was targeted at an anterolateral, lateral, or posterolateral position using the tributaries of the coronary sinus. After lead placement, fluoroscopy images were made in the left anterior oblique at a 40-degree angle and in the in the right anterior oblique at a 30-degree angle to determine the specific position of each quadripolar LV lead electrode.

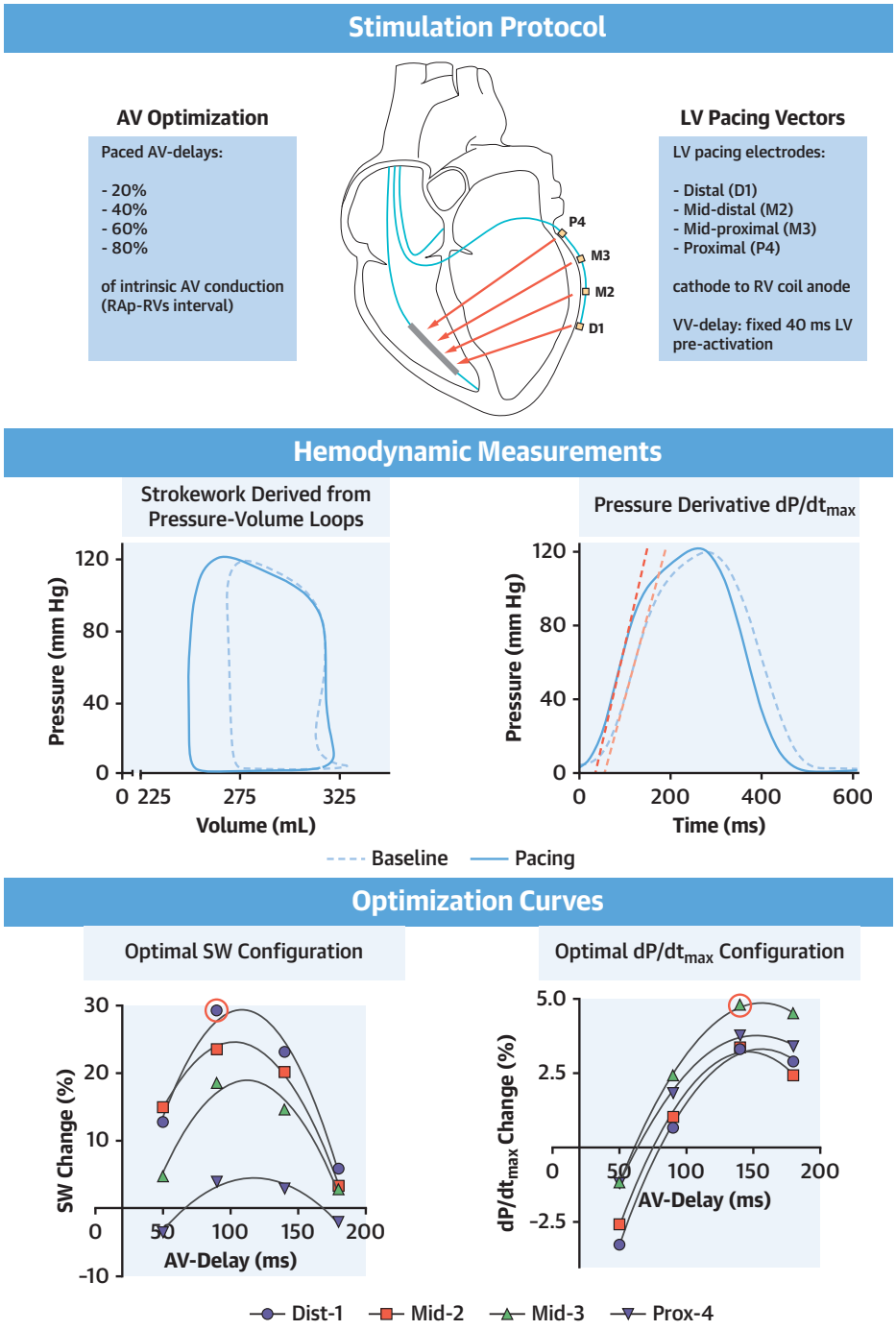
STIMULATION PROTOCOL. Immediately after device implantation, a dedicated 7-F conductance catheter (12 electrodes; 8-, 10-, or 12-mm spacing; CD Leycom, Zoetermeer, the Netherlands) was inserted via the femoral artery and placed in a stable position in the LV apex. PV loops were recorded during each run of biventricular pacing in between baseline recordings with intrinsic conduction (i.e., LBBB). To ensure a stable rhythm, right atrial pacing with 5 to 10 beats/min above the intrinsic heart rate was maintained throughout the stimulation protocol. The stimulation protocol included 4 LV pacing configurations using each individual electrode of the quadripolar lead (i.e., D1: distal electrode; M2: mid-distal electrode; M3: mid-proximal electrode; P4: proximal electrode) as a cathode and the right ventricular shock coil as an anode. Per pacing configuration, 4 AV delays of approximately 80%, 60%, 40%, and 20% of the intrinsic AV conduction (right atrial pacing to right ventricular sensing interval) were programmed, which resulted in a total of 16 pacing runs (**Central Illustration**). The order in which the electrodes were tested was randomized between patients. The interventricular delay was fixed at 40-ms LV pre-activation (4).

HEMODYNAMIC MEASUREMENTS. PV loops were constructed using Conduct NT software version 2.8.1 (CD Leycom, Zoetermeer, the Netherlands). Approximately 60 representative cardiac cycles per pacing run were averaged, disregarding all inappropriate beats. Baseline loops were averaged from 30 beats recorded before and after each pacing run. Subsequently, baseline loops were calibrated by CMR-derived LV volumes. Patients were excluded if the baseline loop showed non-physiological characteristics (volume changes during the isovolumic phases) that resulted in an hourglass-shaped baseline loop, as judged by 2 independent experts. LV pump function was quantified by both SW derived from PV loops and the pressure derivative dP/dt_{max}. To account for baseline drift, the effect of each biventricular pacing setting was calculated as the relative change in LV pump function compared with the mean of the 2 flanking baseline measurements. Optimization curves were used to identify the pacing configurations with the highest increase in SW and dP/dt_{max}, respectively (**Central Illustration**). PV indexes were compared between the optimal SW and dP/dt_{max} configuration, as well as the conventional CRT configuration. Conventional CRT was defined as pacing the distal electrode with an AV delay of approximately 120 ms. dP/dt_{max} was calculated as the maximum rate of LV pressure rise, and SW was directly calculated as the area of the PV loop. In addition, maximal pressure, minimal pressure, pressure rise ($dP_{max-min}$), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and EF were measured. For volumetric measurements, end-diastole was defined at the time of dP/dt_{max}, and end-systole was defined at the time of dP/dt_{min}.

ABBREVIATIONS AND ACRONYMS

AV = atrioventricular
CRT = cardiac resynchronization therapy
dP/dt_{max} = maximum rate of left ventricular pressure rise
E_A = arterial elastance
E_{ES} = end-systolic elastance
ECG = electrocardiography
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
LBBB = left bundle branch block
LV = left ventricular
PV = pressure–volume
QLV = Q on surface electrocardiography to LV sensing interval
SV = stroke volume
SW = stroke work
VA = ventricular–arterial

CENTRAL ILLUSTRATION **Hemodynamic Optimization Protocol**



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The stimulation protocol included 4 left ventricular (LV) pacing configurations using each individual electrode of the quadripolar lead (D1: distal electrode; M2: mid-distal electrode; M3: mid-proximal electrode; P4: proximal electrode). Per electrode, 4 atrioventricular (AV) delays were programmed of approximately 80%, 60%, 40% and 20% of the intrinsic AV conduction resulting in a total of 16 pacing configurations. Per setting, acute response to cardiac resynchronization therapy was measured by change in stroke work (SW) and maximum rate of left ventricular pressure rise (dP/dt_{max}). The pacing configuration with the highest increase in SW and dP/dt_{max} was used for comparison. VV = interventricular.

Effective arterial elastance (E_A) was calculated as end-systolic pressure divided by SV. LV end-systolic elastance (E_{ES}) was estimated by end-systolic pressure divided by ESV (5). The specific end-systolic PV point for these measurements was defined as the maximum ratio of LV pressure to volume. VA coupling was quantified as E_A/E_{ES}, and mechanical efficiency was calculated as the ratio of SW to the PV area, where PV area is the sum of SW and potential energy (6). The setting programmed in the device before discharge was left to the discretion of the operator. Typically, this was the optimal SW electrode with an adequate sensing signal and capture threshold without evidence of phrenic nerve stimulation.

ECHOCARDIOGRAPHY. Echocardiography was performed before and 6 months after CRT implantation. Echocardiographic images were analyzed by a dedicated core laboratory (University Medical Center Utrecht, the Netherlands). LV volumes were measured using the biplane Simpson's method by 2 experienced observers and calculated as averages of multiple (2 to 3) consequent beats. Long-term CRT response was calculated as the absolute percent change in LVEF between baseline and follow-up. Patients with ≥10% increase in LVEF were classified as CRT super-responders.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD in case of normal distribution or as median and interquartile range. Categorical variables were presented as absolute numbers and proportions. Pearson's and Spearman correlations were calculated depending on whether distribution was normal. The paired Student's *t*-test or Wilcoxon's signed rank test was used to compare hemodynamic variables among the optimal SW, optimal dP/dt_{max}, and conventional CRT settings. Cohen's κ coefficient was calculated as the level of agreement between the optimal LV lead pacing electrode and the electrode position among the groups. Receiver-operating characteristics curve analysis was used to determine the predictive value of hemodynamic parameters for long-term CRT response. The commercially available SPSS (IBM SPSS Statistics for Windows, version 22.0, Armonk, New York) was used for statistical analysis. A p value of <0.05 was considered statistically significant.

RESULTS

PATIENT POPULATION. A total of 51 patients were enrolled in the main study, 10 of whom were excluded from this analysis. Nine patients were excluded because of unreliable baseline PV loops, and 1 patient was lost to follow-up due to a psychiatric disorder. Patients with unreliable baseline loops demonstrated larger LVEDVs (396 ± 96 ml vs. 287 ± 82 ms; p = 0.002) and lower LVEFs (16 ± 2% vs. 26 ± 8%; p = 0.001) on CMR compared with patients included in the study. Characteristics of the remaining 41 patients are presented in Table 1.

TABLE 1 Patient Characteristics at Baseline and Echocardiographic Changes After 6 Months

	Total Group (N = 41)	Super-Responders (n = 23)	Others (n = 18)	p Value
Age, yrs	67 ± 9	65 ± 9	69 ± 8	0.184
Male	25 (61)	12 (52)	13 (72)	0.192
Etiology (ICMP)	8 (20)	7 (30)	1 (6)	0.046
NYHA functional class				
II	29 (71)	16 (70)	13 (72)	
III	12 (29)	7 (30)	5 (28)	0.853
Medical history				
Diabetes	5 (12)	1 (4)	4 (22)	0.083
Hypertension	15 (37)	7 (30)	8 (44)	0.355
Atrial fibrillation	4 (10)	2 (9)	2 (11)	0.796
Medication				
Beta-blocker	31 (76)	18 (78)	13 (72)	0.655
Diuretics	29 (71)	16 (70)	13 (72)	0.853
ACE/ATII inhibitors	40 (98)	23 (100)	17 (94)	0.252
Aldosterone antagonist	26 (63)	17 (74)	9 (50)	0.115
Laboratory results				
eGFR, ml/min/1.73 m^2	69 ± 15	73 ± 14	64 ± 16	0.069
NT–pro-BNP, pmol/l	57 (28-134)	51 (28-101)	62 (28-307)	0.511
ECG				
PR duration, ms	179 ± 30	170 ± 20	190 ± 37	0.029
QRS width, ms	167 ± 14	169 ± 15	164 ± 13	0.244
EP: intrinsic AV interval, ms*	271 ± 53	254 ± 36	293 ± 64	0.020
CMR				
LVEDV, ml	286 ± 83	303 ± 75	265 ± 90	0.148
LVESV, ml	216 ± 80	231 ± 66	197 ± 94	0.179
LVEF, %	25 ± 8	24 ± 6	28 ± 10	0.141
Scar on LGE images	7 (18)	2 (9)	5 (31)	0.082
Scar size, % LV mass†	5 (3-16)	2 (1-2)	12 (5-19)	0.095
Echo follow-up				
Change in LVEF after 6 months, %‡	+10 ± 9	+16 ± 6	+2 ± 2	0.001
Change in LVESV after 6 months, %	−33 ± 18	−41 ± 16	−23 ± 15	0.001

Values are mean ± SD or n (%). *Intrinsic AV interval measured as right atrial pacing to right ventricular sensing interval. †Scar size in patients with presence of scar. ‡Absolute changes in LVEF (%).

ACE = angiotensin-converter enzyme; ATII = angiotensin receptor II; AV = atrioventricular; eGFR = estimated glomerular filtration rate; ICMP = ischemic cardiomyopathy; LGE = late gadolinium enhancement; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NT–pro-BNP = N-terminal pro-hormone brain natriuretic peptide; NYHA = New York Heart Association.

ACUTE CHANGES IN HEMODYNAMIC PARAMETERS. During conventional CRT (D1 electrode; AV delay approximately 120 ms), dP/dt_{max} increased by 12 ± 9% and SW improved by 53 ± 48% (Table 2, Figure 1). Compared with conventional CRT, dP/dt_{max}-guided

TABLE 2 Acute Hemodynamic Changes During Conventional CRT and After Hemodynamic Optimization by dP/dt_{max} and SW

				p Value		
	Conventional CRT	dP/dt_{max} Optimization	SW Optimization	Conventional vs. dP/dt_{max}	Conventional vs. SW	dP/dt_{max} vs. SW
$\Delta dP/dt_{max}$	+12 ± 9	+17 ± 11	+12 ± 10	0.001	0.679	0.001
ΔP_{max}	+1 ± 4	+4 ± 4	+1 ± 4	0.001	0.913	0.001
ΔP_{min}	−25 ± 15	−26 ± 38	−25 ± 15	0.901	0.949	0.930
$\Delta dP_{max-min}$	+3 ± 5	+6 ± 4	+3 ± 5	0.001	0.993	0.001
ΔEDV	+3 ± 10	+4 ± 9	+5 ± 9	0.079	0.017	0.159
ΔESV	−10 ± 9	−7 ± 9	−12 ± 10	0.013	0.017	0.001
ΔSV	+52 ± 61	+51 ± 56	+85 ± 70	0.961	0.001	0.001
ΔEF*	+9 ± 8	+8 ± 8	+13 ± 8	0.330	0.001	0.001
ΔSW	+53 ± 48	+52 ± 45	+80 ± 55	0.754	0.001	0.001

Values are mean ± SD. *Absolute changes in EF (%).

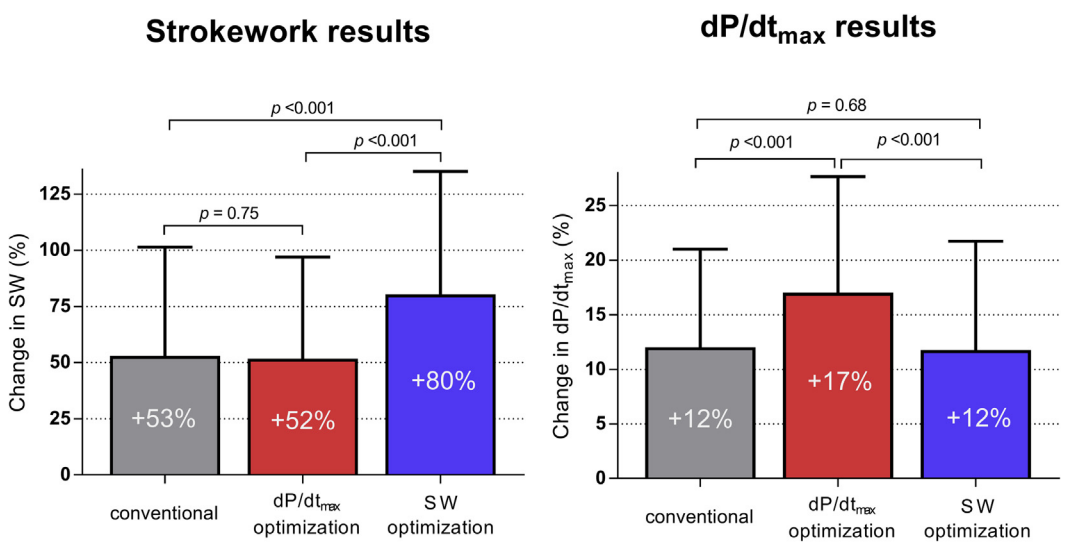
CRT = cardiac resynchronization therapy; $dP_{max-min}$ = pressure rise; dP/dt_{max} = maximum rate of pressure rise; EF = ejection fraction; P_{max} = maximal pressure; P_{min} = minimal pressure; SV = stroke volume; SW = stroke work.

optimization (i.e., the setting that resulted in best dP/dt_{max}) resulted in a one-third additional dP/dt_{max} change (17 ± 11%; $p < 0.001$), but with a similar SW change (52 ± 45%; $p = 0.754$). The highest dP/dt_{max} was achieved with electrode D1 in 12 (29%), M2 in 12 (29%), M3 in 8 (20%), and P4 in 9 (22%) patients (Online Table 1). The AV delay that resulted in optimal dP/dt_{max} was longer compared with conventional CRT (165 ± 41 ms vs. 119 ± 13 ms; $p < 0.001$).

Compared with conventional CRT, SW-guided optimization (i.e., the setting that resulted in best SW) resulted in comparable dP/dt_{max} changes (12 ± 10%; $p = 0.679$), but a one-third additional SW increase (80 ± 55%; $p < 0.001$). The largest SW was achieved with electrode D1 in 22 (54%), M2 in 5 (12%), M3 in 5 (12%), and P4 in 9 (22%) patients. On average, the optimal SW AV delay did not significantly differ from conventional CRT (132 ± 58 ms vs. 119 ± 13 ms; $p = 0.191$).

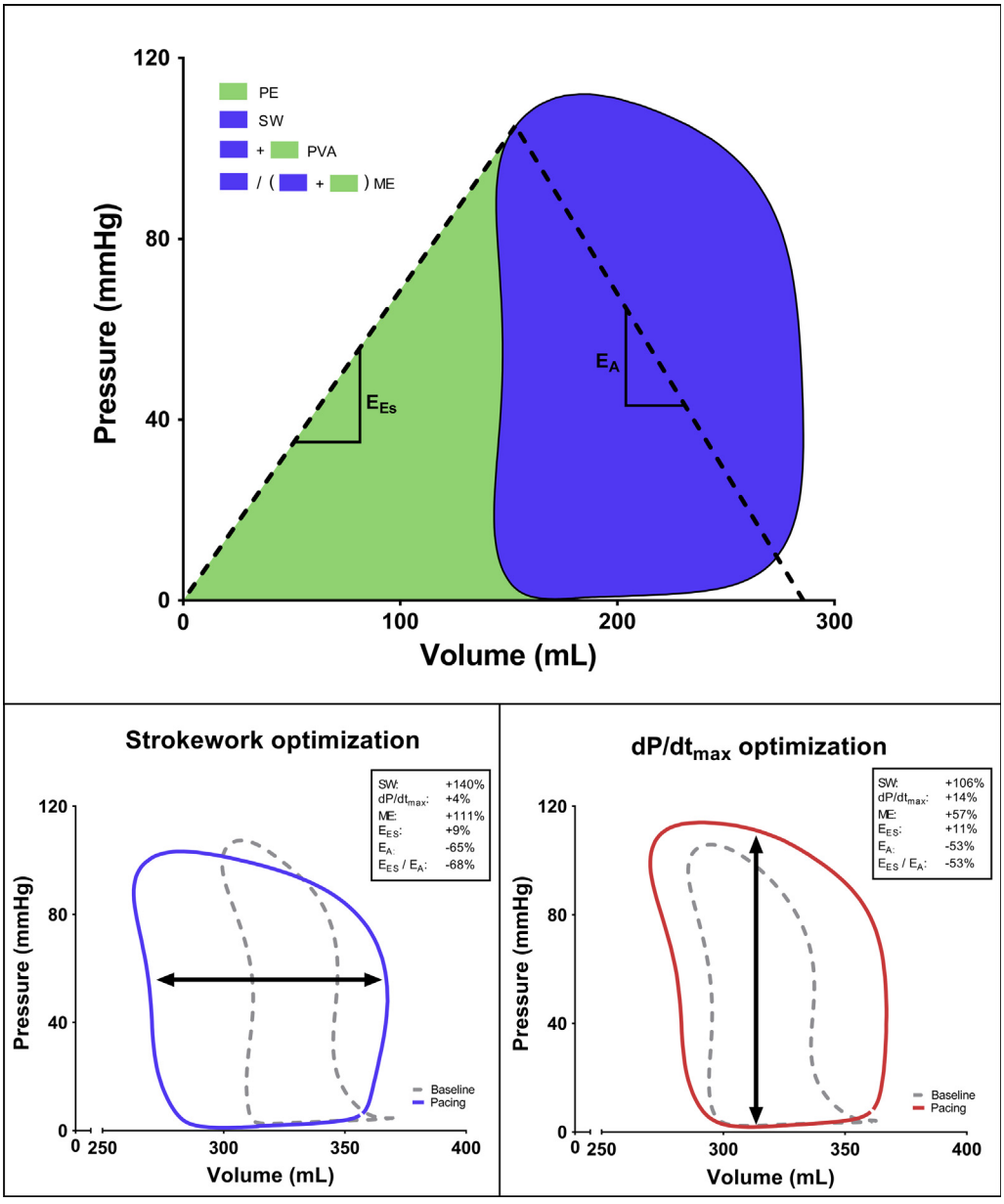
Comparing both optimization strategies, the optimal dP/dt_{max} configuration differed from the optimal SW configurations by a lack of agreement in the pacing electrode (K −0.3) and a significant difference in AV delay (165 ± 41 ms vs. 132 ± 58 ms;

FIGURE 1 Effect of Hemodynamic Optimization on Acute CRT Response



The effect of hemodynamic optimization is illustrated for stroke work (SW) results **(left)** and maximum rate of left ventricular pressure rise (dP/dt_{max}) results **(right)**. SW-guided optimization resulted in one-third additional SW increase compared with conventional CRT without additional dP/dt_{max} changes. dP/dt_{max}-guided optimization resulted in a one-third additional dP/dt_{max} increase without additional SW benefit.

FIGURE 2 VA Coupling Between Optimization Strategies



Schematic illustration of a pressure–volume (PV) loop **(top)**. Typical example of PV loops in a CRT patient that illustrated the effects of SW-guided optimization **(bottom left)** and dP/dt_{max}-guided optimization **(bottom right)**. SW optimization results in widening of the PV loop (i.e., SV augmentation), whereas dP/dt_{max}-guided optimization results in lengthening of the PV loop (i.e., LV pressure rise increase). The optimal dP/dt_{max} configuration demonstrates highest contractility, whereas optimal SW is achieved at a decreased arterial load, resulting in improved ventricular–arterial (VA) coupling and higher mechanical efficiency. Abbreviations as in Figure 1.

$p = 0.001$). When evaluating the relationship between acute changes in SW and dP/dt_{max} for all pacing configurations of the entire population ($n = 635$), a weak correlation was found ($R = 0.24$; $p < 0.001$) (Online Figure 1). Comparing SW and dP/dt_{max} changes in a per-patient analysis, only 9 (22%) patients demonstrated a positive correlation with a correlation coefficient ≥0.50 (Online Figure 2). Comparing changes in hemodynamic parameters between dP/dt_{max}- and SW-guided strategies, the

TABLE 3 Acute Changes in VA Coupling During Conventional CRT and After Hemodynamic Optimization by dP/dt_{max} and SW

	Baseline	Pacing	Δ (%)
Arterial load (E_A)			
Conventional CRT*	2.6 ± 2.0	1.9 ± 1.2	−26 ± 42
dP/dt_{max} optimization†	2.6 ± 1.9	1.9 ± 1.3	−26 ± 35
SW optimization*†	2.7 ± 2.1	1.6 ± 1.1	−44 ± 44
Contractility (E_{ES})			
Conventional CRT‡	0.60 ± 0.25	0.62 ± 0.27	+5 ± 12
dP/dt_{max} optimization†‡	0.60 ± 0.25	0.65 ± 0.28	+8 ± 12
SW optimization†	0.60 ± 0.25	0.63 ± 0.26	+5 ± 10
VA coupling (E_A/E_{ES})			
Conventional CRT*‡	4.6 ± 2.4	3.3 ± 1.9	−28 ± 37
dP/dt_{max} optimization†	4.7 ± 2.4	3.2 ± 1.6	−32 ± 32
SW optimization*†	4.9 ± 2.7	2.7 ± 1.3	−45 ± 39
Mechanical efficiency (SW/PVA)			
Conventional CRT*‡	0.31 ± 0.10	0.40 ± 0.13	+29 ± 26
dP/dt_{max} optimization†‡	0.31 ± 0.10	0.39 ± 0.13	+26 ± 23
SW optimization*†	0.31 ± 0.10	0.42 ± 0.12	+39 ± 23

Values are mean ± SD. *Statistical differences between Conventional CRT vs. SW optimization strategies. †Statistical differences between dP/dt_{max} vs. SW optimization strategies. ‡Significant statistical differences between Conventional CRT vs. dP/dt_{max} optimization strategies.

E_A = arterial elastance; E_{ES} = end-systolic elastance; PVA = pressure-volume area; VA = ventricular-arterial; other abbreviations as in Tables 1 and 2.

former showed a larger pressure increase (6 ± 4% vs. 3 ± 5%; p < 0.001) whereas SW optimization resulted in a larger SV augmentation (85 ± 70% vs. 51 ± 56%; p < 0.001) (Figure 2).

To study interactions between the LV and the arterial system, Table 3 lists changes in VA coupling between optimization strategies. Although dP/dt_{max} optimization was associated with a larger E_{ES} increase compared with SW optimization (8 ± 12% vs. 5 ± 10%; p = 0.015), SW optimization showed a relatively larger reduction in E_A (44 ± 44% vs. 26 ± 35%; p < 0.001). VA coupling at baseline was unbalanced, with E_A/E_{ES} ranging between 4.6 and 4.9. Improvement in E_A/E_{ES} was most pronounced for SW optimization (45 ± 39% vs. 32 ± 32%; p < 0.001). Mechanical efficiency was depressed at baseline (SW/PV area: 0.31), with SW optimization resulting in the highest mechanical efficiency (39 ± 23% vs. 26 ± 23%; p < 0.001) compared with dP/dt_{max} optimization.

TABLE 4 Predictive Value of Hemodynamic Parameters for Long-Term CRT Response

	AUC	p Value	Cutoff (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
$\Delta dP/dt_{max}$	0.65	0.112	≥+9	65	67	71	60
ΔP_{max}	0.60	0.297	≤+1	63	44	64	50
ΔP_{min}	0.69	0.035	≤−26	54	72	72	54
$\Delta dP_{max-min}$	0.58	0.374	≤+3	58	56	64	50
ΔEDV	0.51	0.916	≥+4	63	44	60	47
ΔESV	0.70	0.031	≤−12	58	78	78	58
ΔSV	0.72	0.015	≥+45	83	61	74	73
ΔEF	0.73	0.010	≥+9*	71	61	71	61
ΔSW	0.78	0.002	≥+40	96	50	71	90

*Absolute changes in % EF.

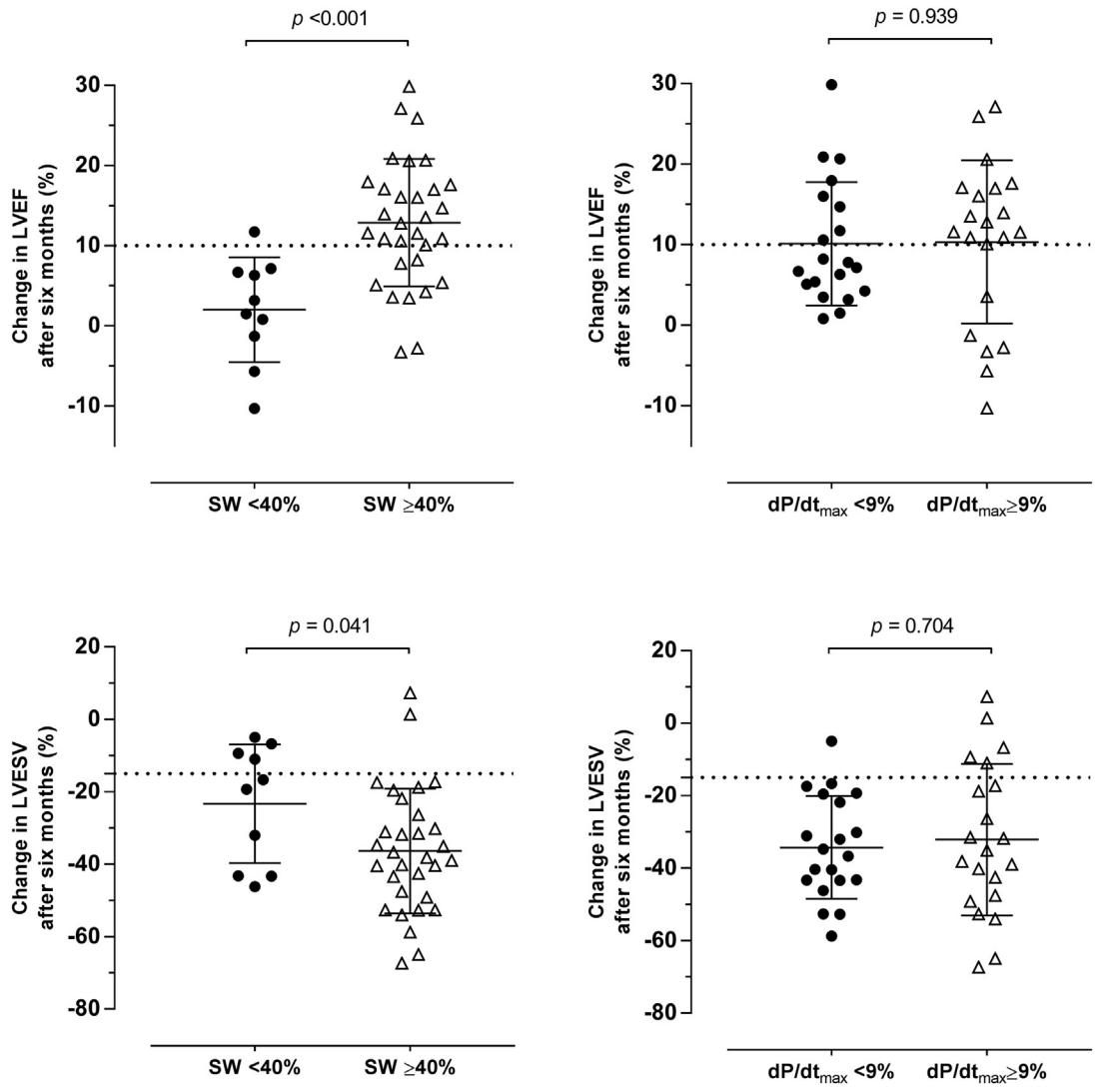
AUC = area under the curve; other abbreviations as in Table 2.

ACUTE CHANGES IN HEMODYNAMIC PARAMETERS IN RELATION TO LONG-TERM CRT RESPONSE. Echocardiographic measurements showed high reproducibility with intraclass correlations values of 0.95 (EDV), 0.96 (ESV), and 0.93 (EF) for intraobserver variability, and intraclass correlations values of 0.92 (EDV), 0.95 (ESV), and 0.91 (EF) for interobserver variability. Absolute LVEF change after 6 months was 10 ± 9%, with 23 (56%) patients showing a ≥10% increase in LVEF (CRT super-responders). For prediction of long-term CRT super-response, change in SW showed an area under the curve (AUC) of 0.78 (p = 0.002), as demonstrated in Table 4 and Online Figure 3, whereas change in dP/dt_{max} revealed a nonsignificant AUC of 0.65 (p = 0.112). To predict long-term CRT super-response, an optimal cutoff value of 40% increase in SW change yielded a sensitivity of 96%, specificity of 50%, and positive and negative predictive values of 71% and 90%, respectively. Using this cutoff value, 31 (76%) patients were categorized as having a ≥40% increase in SW and 10 (24%) patients had a <40% increase, or a decrease in SW. Patients with a ≥40% SW increase showed greater improvement in absolute LVEFs (13 ± 8% vs. 2 ± 7%; p < 0.001) and a larger reduction in LVESV (−36 ± 17% vs. −23 ± 16%; p = 0.041) at follow-up compared with patients without improvement (Figure 3). The optimal cutoff value to predict long-term CRT response by change in dP/dt_{max} was 9%. Twenty-one (51%) patients with ≥9% dP/dt_{max} change were compared with 20 (49%) patients without, but no differences in absolute LVEF change (10 ± 10% vs. 10 ± 8%; p = 0.939) or LVESV change (−32 ± 21% vs. −34 ± 14%; p = 0.704) were found between groups.

DISCUSSION

The present study demonstrated that PV-guided hemodynamic optimization of the LV pacing electrode and AV delay in CRT with quadripolar leads results in approximately one-third additional SW improvement on top of conventional CRT. Hemodynamic optimization by the pressure derivate dP/dt_{max} also showed one-third additional dP/dt_{max} improvement compared with conventional CRT. However, improvement in 1 parameter did not coincide with the other, which indicated 2 different mechanisms.

FIGURE 3 Acute CRT Response and Echocardiographic Changes After 6 Months



Scatter plots illustrating long-term echocardiographic absolute changes in left ventricular ejection fraction (LVEF) **(top)** and LV end-systolic volume (LVESV) **(bottom)** for patient stratification by SW changes **(left)** and dP/dt_{max} changes **(right)**. Abbreviations as in Figure 1.

Although dP/dt_{max} optimization favored LV contractility (expressed as E_{ES}), SW optimization improved VA coupling, which led to higher SV and EF. Acute changes in SW showed higher predictive value for long-term CRT response compared with change in dP/dt_{max}.

HEMODYNAMIC OPTIMIZATION STRATEGIES. Previous studies showed that invasive hemodynamic optimization in CRT could be used to guide LV lead placement (3,7-12), find the optimal AV and interventricular delay (4,13,14), and evaluate benefit from multisite stimulation (12,15-17). However, a standardized approach for invasive optimization was lacking because part of these studies used dP/dt_{max} (4,7,10-14,16), whereas others used SW as an optimization parameter (3,8,9,14-17). Although the 2 strategies have been used interchangeably in the literature, previous work from our group showed a discordant relationship between dP/dt_{max} and SW improvement among CRT candidates (18). Pappone et al. (16) found that even within an individual patient, changes in the 2 parameters were often poorly correlated. The present study confirmed these previous findings and extended them by evaluating the

effect of invasive hemodynamic optimization by dP/dt_{max} versus SW on cardiac performance in CRT with quadripolar LV leads. Each optimization strategy resulted in approximately one-third additional improvement in the parameter used for optimization. However, improvement in 1 parameter did not coincide with the other (**Figure 1**). These findings indicated that although CRT with quadripolar LV leads provided substantial room for hemodynamic optimization, results differed significantly between optimization strategies. Interestingly, dP/dt_{max}-guided optimization resulted in longer AV delays (165 ms; 63% of intrinsic AV interval) compared with SW-guided optimization (132 ms, 49% of intrinsic AV interval). These longer AV delays possibly allowed for fusion of the intrinsic AV conduction and LV capture (i.e., fusion pacing), which was shown to favor dP/dt_{max} (19). Comparing hemodynamic effects, marked differences were observed in LV pressure rise and SV between the optimization strategies. Although dP/dt_{max} optimization favored LV pressure rise (i.e., height increase of the PV loop), SW optimization showed SV augmentation (i.e., widening of the PV loop) (**Figure 2**). Increases in SV involved small changes in EDV and large ESV reductions. These changes could be explained by different interactions between the LV and the arterial system that influenced ventricular performance by alterations in cardiac afterload (i.e., VA coupling). Under normal conditions, the VA system is closely coupled with an E_A/E_{ES} ratio of 0.6 to 1.2 to achieve optimal work and mechanical efficiency (20). However, in chronic heart failure depressed systolic function (low E_{ES}) coupled to a high arterial impedance (high E_A) will result in a state of afterload mismatch with severely elevated E_A/E_{ES} (21). Previous studies showed that CRT improved VA coupling by enhancing LV systolic performance (E_{ES}) and reducing net arterial load (E_A) (22,23). The immediate reduction in afterload was ascribed to acute effects of CRT on sympathetic nerve activity (24,25). Our results were in line with previous findings that demonstrated enhanced VA coupling during biventricular pacing as a result of beneficial changes in both determinants (i.e., E_{ES} increase and E_A reduction). When comparing VA coupling between these optimization strategies, dP/dt_{max} optimization resulted in the highest increase in E_{ES}, whereas SW optimization showed the most reduction in E_A. Net changes in VA coupling were most pronounced for SW optimization, with 45% reduction in E_A/E_{ES}.

LV systolic function is affected by changes in preload, afterload, and contractility. Because additional increases in SW are achieved under conditions of equal contractility (defined as E_{ES}) and comparable pre-load (defined as EDV), enhanced VA coupling may be considered an important mechanism of CRT response (i.e., SW optimization ≈ VA optimization). Interestingly, 1 study described improvements in cardiac function during CRT obtained at diminished energy costs, which indicated enhanced mechanical efficiency (26). Mechanical efficiency can be calculated from the PV loop by the ratio of SW (i.e., external work) to the PV area. The latter reflects the total mechanical energy that is generated by the LV (27). SW optimization demonstrated the highest improvement in mechanical efficiency (39%) relative to dP/dt_{max} optimization (26%) and conventional CRT (29%). These differences might be important because therapeutic interventions that enhance mechanical efficiency were proven to be beneficial with respect to outcomes (28).

ACUTE HEMODYNAMIC CHANGES AND LONG-TERM CRT RESPONSE. Previous studies that examined the predictive value of dP/dt_{max} changes for long-term CRT response yielded conflicting results. Duckett et al. (29) showed that the rise in dP/dt_{max} accurately predicted reverse remodeling after CRT at a cutoff value of 10%. However, their results were not supported by several other studies. Two studies (1 by our group in a different population) found dP/dt_{max} changes to be unrelated to reverse remodeling after CRT (30,31). In addition, 2 more studies found no relationship between acute change in dP/dt_{max} and cardiac morbidity or survival (32,33). Results of the present study added to the accumulating evidence opposing a relationship between acute changes in dP/dt_{max} and long-term CRT outcome. Although the optimal cutoff value we found was similar to the that found by Duckett et al. (29), patients with an acute dP/dt_{max} increase of ≥9% lacked favorable long-term CRT response compared with patients with <9% (**Figure 3**).

In contrast, acute changes in SW accurately predicted long-term CRT response with an optimal cutoff value of 40%. Recently, our group was the first to demonstrate a clear association between acute SW changes and reverse remodeling after 6 months of CRT (30). Acute SW response accurately predicted ≥15% reduction in LVESV at an optimal cutoff value of 20% in a mixed population of patients with wide and narrow QRS complexes. However, the present study included only patients with a strict LBBB (Strauss definition). The presence of favorable patient characteristics associated with a large CRT benefit, combined with the PV-guided hemodynamic optimization protocol, resulted in almost every patient becoming a CRT responder following the ≥15% LVESV reduction definition (6 nonresponders).

Therefore, we used the alternative definition of an ≥10% absolute LVEF increase to identify super-responders, which resulted in a lower response rate (18 nonresponders). The stricter definition of CRT response explained the higher cutoff value of 40% SW change that we found in the present study. Still, acute changes in SW showed high sensitivity for prediction of long-term CRT response, similar to previous findings (30). In other words, patients lacking acute SW response were unlikely to become responders for the long term. This was underlined by 10 SW non-responders, of whom only 1 became a long-term responder (**Figure 3**).

STUDY LIMITATIONS. Due to the invasive nature of the study protocol, the sample size might be considered relatively small. Furthermore, we only included patients with strict LBBB (Strauss criterion), which resulted in a homogenous population that had a low number of ischemic cardiomyopathies and transmural scars. Moreover, a relatively large portion of patients was excluded from the present analysis because of unreliable baseline PV loops. These patients demonstrated severe LV dilation with low EFs on CMR. As a result, electrical conductance was measured in a large blood pool with minimal volume changes throughout the cardiac cycle, resulting in a low signal-to-noise ratio. Baseline PV loops showed large volume changes during the isovolumic phases, which resulted in an hour glass–shaped loop. Underestimation of the baseline loop resulted in excessive SW changes during biventricular pacing and overestimation of LV pump function changes. Although these measurements could still be used to determine the optimal pacing configuration (the patient serves as their own control), absolute changes in SW did not adequately reflect benefit from CRT. Finally, the effect of hemodynamic optimization on long-term CRT response was not investigated in comparison with a control group. Because the optimal SW setting was typically used for programming, this might have introduced bias.

CLINICAL APPLICATION. The development of quadripolar leads offers new possibilities and challenges in the field of CRT. Multiple stimulation sites are now offered from a single lead, increasing opportunities for CRT optimization strategies (34). Hemodynamic optimization was shown to be highly rewarding with an additional one-third increase in acute CRT response. Although noninvasive methods were searched to optimize settings, previous findings of the OPTICARE-QLV demonstrated that: 1) electrical (QLV) parameters were unable to identify the most beneficial pacing electrode of a quadripolar lead (3); 2) optimal AV delays varied substantially between patients (35); and 3) benefit from multipoint pacing was hard to predict from baseline parameters (17). The use of other noninvasive methods such as echocardiography or electrocardiographic markers also need to be proven. For now, invasive hemodynamic optimization strategies might therefore be considered the gold standard approach to optimize benefit from CRT (1). However, the conductance technique is invasive, has limited availability in clinical practice, and is not suitable for all patients. The additional time duration of the stimulation protocol was about 60 min, but because the protocol was performed after wound closure (using the programmer), there was no additional risk of device infection. There was 1 complication of ventricular fibrillation (on entering the LV with the guidewire) that was successfully treated by cardiac defibrillation. No perforation, stroke, or bleeding was observed. Although invasive hemodynamic optimization is not feasible in clinical practice, the concept of volume-based optimization may guide future implementation of noninvasive surrogates of LV volume changes, such as changes in intracardiac impedance or stimulation in the CMR environment. However, it should be noted that noninvasive surrogates do not always translate to direct hemodynamic measurements.

CONCLUSIONS

PV-guided hemodynamic optimization in CRT results in approximately one-third additional SW improvement on top of conventional CRT. Hemodynamic optimization by the pressure derivate dP/dt_{max} showed a similar one-third additional dP/dt_{max} improvement compared with conventional CRT. However, improvement in 1 parameter did not coincide with the other, which indicated different mechanisms. Although dP/dt_{max} optimization favored LV contractility (expressed as E_{ES}), SW optimization improved VA coupling, which led to higher stroke volume and ejection. Ultimately, acute changes in SW showed larger predictive value for long-term CRT response compared with dP/dt_{max}. PV-guided hemodynamic optimization might therefore be considered a potential strategy to use the full potential of CRT with quadripolar leads.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CRT is hampered by one-third of patients becoming nonresponders. Hemodynamic optimization may increase benefit from CRT although a standardized approach is currently lacking. Typically, maximal LV pressure rise dP/dt_{max} is used as an index of ventricular performance. Alternatively, SW can be derived from PV loops. The present study demonstrated that PV-guided optimization in CRT resulted in approximately one-third SW improvement on top of conventional CRT by a mechanism of enhanced VA coupling. In contrast, dP/dt_{max} optimization favored LV contractility. Ultimately, acute changes in SW showed larger predictive value for long-term CRT response compared with dP/dt_{max}. This study provides a method that helps the implanting physician to maximize benefit from CRT implantation in a patient with heart failure and LBBB.

TRANSLATIONAL OUTLOOK: Future studies that investigate the effect of dP/dt_{max}- versus SW-guided CRT optimization in a prospective, randomized controlled trial setting are encouraged.

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KEY WORDS cardiac resynchronization therapy (CRT), dP/dt_{max}, hemodynamic optimization, pressure–volume loops, quadripolar LV leads, stroke work

APPENDIX For supplemental figures and tables, please see the online version of this paper.

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