Impact of synchronous atrioventricular delay optimization on left ventricle flow force angle evaluated by echocardiographic particle image velocimetry

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Abstract

Purpose To evaluate the improvement in electrical synchrony and left ventricle (LV) hemodynamics provided by combining the dynamic atrioventricular delay (AVD) of SyncAV™ CRT and the multiple LV pacing sites of MultiPoint pacing (MPP).

Methods Patients with LBBB and QRS duration (QRSd) > 140 ms implanted with a CRT-D or CRT-P device and quadripolar LV lead were enrolled in this prospective study. During a post-implant follow-up visit, QRSd was measured from 12-lead surface electrograms by experts blinded to pacing configurations. QRSd reduction relative to intrinsic rhythm was evaluated during biventricular pacing (BiV) and MPP for two AVDs: nominal (140/110 ms paced/sensed) and SyncAV (patient-optimized SyncAV offset [10–60 ms] minimizing QRSd). Echocardiography particle imaging velocimetry (Echo-PIV) analysis was performed for each configuration. The resulting hemodynamic force LV flow angle (φ) was analyzed, which ranges from 0° (predominantly base-apex forces) to 90° (predominantly transverse forces). Higher angles indicate more energy dissipation at lateral walls due to transverse flow; lower angles indicate healthier flow aligned with the longitudinal base-apex path of the pressure gradient.

Results Twelve patients (58% male, 17% ischemic, 32±7% ejection fraction, 165 ± 18 ms intrinsic QRSd) completed QRSd and Echo-PIV assessment. Relative to intrinsic rhythm, BiV and MPP with nominal AVD reduced QRSd by 10 ± 9% and 12 ± 9%, respectively. BiV+SyncAV and MPP+SyncAV further reduced QRSd by 19 ± 8%, ($p < 0.05$ vs. BiV with nominal AVD) and 23 ± 9% ($p < 0.05$ vs BiV+SyncAV), respectively. Echo-PIV showed similar sequential hemodynamic improvements. LV flow angular orientation during intrinsic activation (46 ± 3°) reduced with BiV+SyncAV (37 ± 4°, $p < 0.05$ vs intrinsic) and further with MPP+SyncAV (34 ± 4°, $p < 0.05$ vs BiV+SyncAV).

Conclusion These results suggest that SyncAV may improve electrical synchrony and influence LV flow patterns in patients suffering from heart failure compared to conventional CRT with a fixed AVD, with further improvement observed by combining with MPP.

Keywords Cardiac resynchronization therapy · Echocardiography particle imaging velocimetry · Electrical optimization

Abbreviations

AVD	Atrioventricular delay
BiV	Biventricular
CRT	Cardiac resynchronization therapy
HF	Heart failure
GLS	Global longitudinal strain
LV	Left ventricle
LBBB	Left bundle branch block
MPP	MultiPoint pacing
NYHA	New York Heart Association
PIV	Particle imaging velocimetry
QRSd	QRS duration
RA	Right atrium

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RV	Right ventricle
SyncAV^{TM}	Proprietary algorithm for dynamic AVD programming

1 Introduction

Studies have shown the beneficial impact of cardiac resynchronization therapy (CRT) in patients with prolonged QRS duration (QRSd) and reduced ejection fraction (EF) [1]. However, response to CRT remains suboptimal, with up to 40% of patients failing to show clinical or volumetric improvement [2]. Non-response to CRT has been attributed to poor patient selection, left ventricular (LV) lead positioning, and/or device programming. Although strategies in patient sub-selection and LV lead positioning have been established, the benefits of proper device programming are still under debate.

Several methods have been used to guide CRT programming (i.e., echocardiography, invasive hemodynamic measurements, electrical mapping), but these may require costly, time-consuming procedures [3, 4]. On the other hand, using QRSd narrowing to guide programming can be done with a simple 12-lead surface ECG, and has been shown to improve chronic ventricular reverse remodeling [2, 5]. This methodology can be used in clinic after implant and only requires programming several device features, i.e., MultiPoint pacing (MPP) and/or atrioventricular delay (AVD). MPP can deliver stimulation of the LV from two electrodes in the LV lead as cathode. SyncAV^{TM} is a device-based algorithm that dynamically adjusts the AVD shorter than the automatically measured intrinsic AV interval by a programmable "offset" to fuse paced ventricular wave fronts with intrinsic wave fronts. Although acute improvements in electrical synchrony have been demonstrated with SyncAV [6, 7] and MPP [8, 9], their impact on LV flow dynamics has not been evaluated.

Echocardiographic particle imaging velocimetry (Echo-PIV) is an emerging technique that allows to evaluate LV intraventricular fluid motion [10, 11], which plays an important role in cardiac function [12, 13]. Characterization of blood vorticity has potential significance in cardiac physiology [14], in particular to modify adverse clinical outcomes in heart failure patients [15]. The objective of this feasibility study was to evaluate the effect of SyncAV and MPP on electrical synchrony and how this translates to changes in LV flow mechanics.

2 Methods

2.1 Study population

Patients implanted with an Abbott CRT device with quadripolar LV lead (Quartet^{TM} 1458Q) technology according to current guidelines were enrolled during a routine in clinic follow-up visit. Patients at least 18 years of age with a resting heart rate below 100 bpm, preserved atrioventricular conduction (PR < 300 ms), without permanent atrial tachyarrhythmia were enrolled. The study protocol was approved by the local ethics committee of the institution.

2.2 Device programming

CRT devices were programmed to various pacing configurations, during which standard 12-lead ECGs were recorded with patients at rest and in supine position. Table 1 summarizes the CRT settings programmed during the patient follow-up visit. Test settings included intrinsic conduction, BiV pacing with fixed paced/sensed AVD of 140/110 ms (BiV), BiV pacing with SyncAV^{TM} (BiV+SyncAV), MPP with fixed AVD (MPP), and MPP with SyncAV (MPP+SyncAV). SyncAV offsets were varied between 10 and 60 ms for each patient, and the optimal offset was defined as the delay resulting in the narrowest QRSd. Device pacing configurations were performed in a random order for each patient. All settings were performed with simultaneous LV and RV pacing. LV pacing was performed from the cathode with the latest RV-LV activation time for BiV configurations and LV1-LV2 cathodes with the widest anatomical spacing for MPP configurations with no phrenic stimulation. After completion of acute ECG and echocardiography data collection, the device was programmed as selected by physician.

2.3 12-lead ECG recordings

CRT device settings in Table 1 are each programmed for 1 min, and 12-lead surface ECG printouts are collected at 50 mm/s. QRSd measurements were performed manually by an independent observer, blinded to pacing configurations. QRSd was defined as the maximum global duration across all ECG leads, following standard recommendations and ignoring any pre-QRS deflections/pacing spikes [16]. The SyncAV offset (10–60 ms) resulting in the shortest QRSd was selected as the optimal offset, independent for BiV or MPP configurations, for the following echocardiographic evaluations.

2.4 Echocardiography

After ECG SyncAV optimization, patients underwent echocardiographic examination with Siemens SC2000 equipment (Siemens Ultrasound, Mountain View, CA, USA). Echocardiography evaluation was performed by an experienced operator, blinded to device programming configurations. Recordings were collected 5–8 min after device programming to allow mechanical and hemodynamic stabilization. Two-dimensional (2D) B-mode apical two-chamber and

Table 1 Tested device pacing configurations

Setting name	Paced/sensed AVD	Ventricle pacing	SyncAV offset	LV pulse configuration
Intrinsic	Max/Max	-	-	-
BiV	140/110	Simultaneous (LV+RV)	OFF	LV_{late}
BiV+SyncAV	SyncAV	Simultaneous (LV+RV)	10–60 ms	LV_{late}
MPP	140/110	Simultaneous (LV1+LV2+RV)	OFF	$LV1_{max}$-$LV2_{max}$
MPP+SyncAV	SyncAV	Simultaneous (LV1+LV2+RV)	10–60 ms	$LV1_{max}$-$LV2_{max}$

LV_{late} corresponds to the latest activating LV electrode measured from intrinsic sensing in the RV lead. LV_{max} corresponds to the widest cathode separation along the LV lead

four-chamber views were recorded for volume and strain quantification. Volumes were computed by biplane Simpson method. Two-dimensional strain parameters were computed by speckle tracking software included in the echograph (VVI 3.0.1.5 Siemens Ultrasound). Global longitudinal strain (GLS) is reported as the average of the peak strain of the 12 segments to measure systolic function. Mitral inflow E and A wave velocities were measured from apical four-chamber view with pulsed wave Doppler imaging to evaluate velocity of blood inflow. Early to late diastolic inflow velocity ratio (E/A wave ratio) was used as a marker of LV diastolic function.

Two-dimensional B-mode apical three-chamber view with infusion of contrast agent was recorded to evaluate intraventricular blood motion. The ultrasound beam was focused at the LV base to have uniform insonation on the contrast bubble region. The scan field was optimized to contain the entire LV and ensure high frame rates (70–90 Hz) at a mechanical index of approximately 0.4. Three cardiac cycles were digitally acquired for each pacing configuration. The video sequences were recorded during the washout of the contrast agent when the diluted bubbles adequately display the typical swirling motion of the intraventricular blood flow. The clips captured in this phase of the contrast study were processed by particle imaging velocimetry (PIV), a post-processing technique that allows tracking micro bubbles over two subsequent frames: the distance travelled from one frame to the next, divided by the time interval, is collected as the velocity vector [17]. Echo-PIV velocity estimation and post-processing were performed through a dedicated software (Hyperflow ver. 8.2.1.0, AMID SRL, Sulmona, Italy). Dynamic flow properties are assessed by computing the rate of change of flow momentum [18] integrated in the entire LV chamber. This global momentum rate represents the hemodynamic force globally exchanged, at every time instant, between blood and surrounding tissue. The directional distribution of global momentum during the entire cardiac cycle is summarized in terms of a polar histogram. This polar image gives a synthetic picture of the overall hemodynamic velocities associated with intraventricular blood motion, in particular identifying whether they are aligned along the base-apex direction, in compliance with the emptying–filling process, or they deviate by developing non-physiological transversal components. For simple quantification, a single flow angle parameter, φ, indicating the dominant orientation of the hemodynamic velocities throughout a cardiac cycle, was evaluated. This parameter is called the "flow force angle" and ranges from zero, when flow force is predominantly along the base-apex direction, up to 90^{o} when it becomes transversal [18].

Table 2 Baseline patient demographics

Characteristic	All patients
N	12
Age, year	68 ± 9
Male, *n* (%)	7 (58)
Ischemic, *n* (%)	2 (17)
LBBB, *n* (%)	12 (100)
NYHA class, *n* (%)	
II	6 (50)
III	6 (50)
LVEF, %	32 ± 7
PR, ms	183 ± 32
QRSd, ms	165 ± 18
Comorbidities, *n* (%)	
Hypertension	8 (67)
Hypercholesterolemia	6 (50)
Diabetes mellitus	4 (33)
Renal disease	1 (8)
History of smoking	4 (33)

2.5 Statistical analysis

Categorical variables are expressed as number and percentage of patients. Continuous variables are expressed as mean ± standard deviation among patients. Differences in QRS duration, strain, LV inflow, and flow force angle among settings were assessed using Wilcoxon signed-rank test for paired differences. $p < 0.05$ was considered statistically significant. All analyses were performed in MATLAB (Mathworks, Natick, MA).

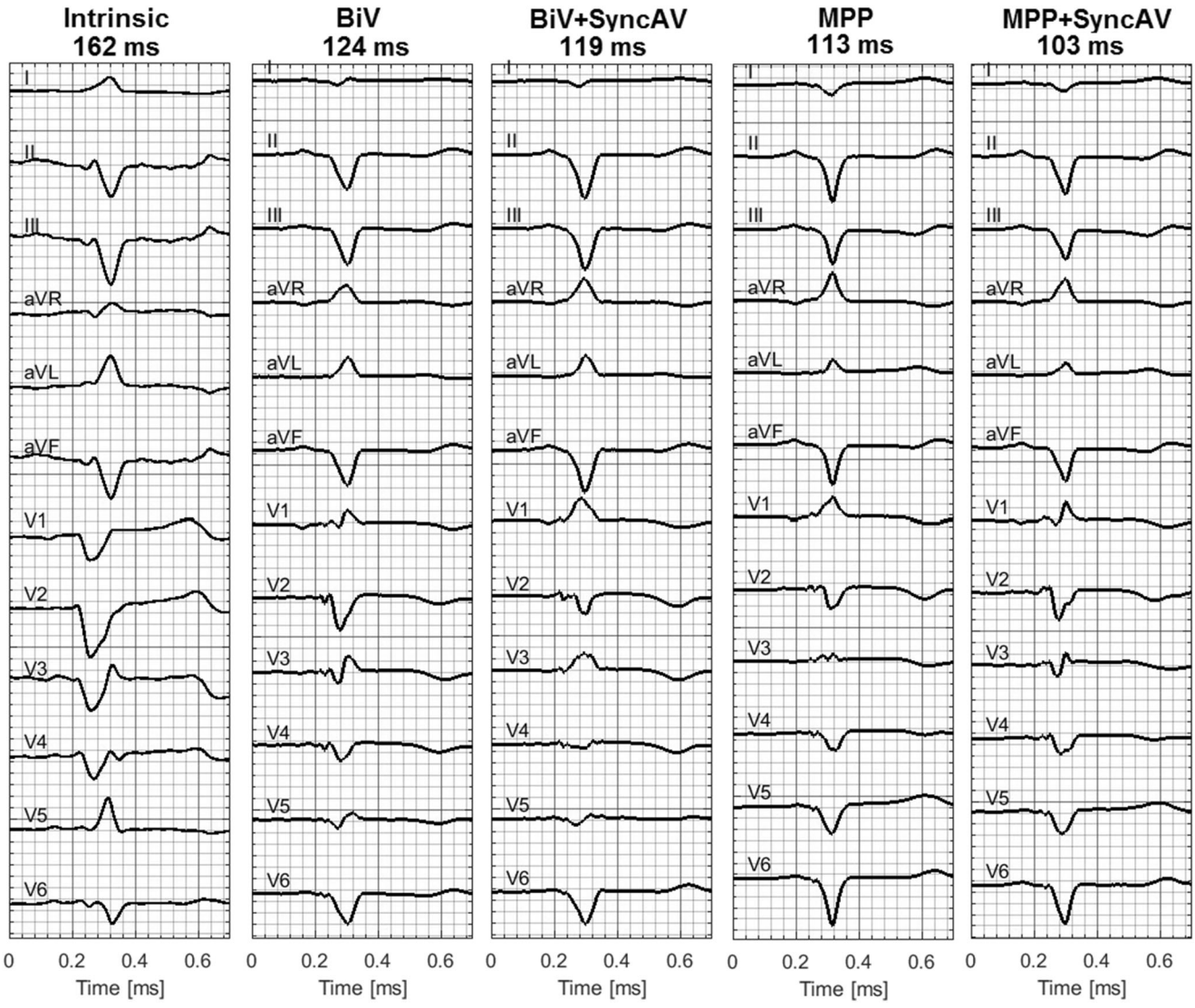

Fig. 1 Sample 12-lead ECG. Example 12-lead ECGs for a patient during intrinsic conduction, BiV, BiV+SyncAV, MPP, and MPP+SyncAV

3 Results

3.1 Patient characteristics

The study included 12 consecutive patients (age: 68 ± 9 years; 58% male; ejection fraction 32 ± 7%; 17% with ischemic cardiomyopathy; PR: 183 ± 32 ms) and were evaluated at a post-implant time of 4.6 ± 5.0 months (range 0.4-14.2 months). Baseline clinical characteristics are listed in Table 2. All patients were in sinus rhythm at the scheduled follow-up visit. The right ventricular (RV) lead was placed in the apex (17%) or septum (mid septum or RV outflow tract, 83%), and the quadripolar LV lead was placed in a lateral (50%), posterolateral (25%), or anterolateral (25%) branch of the coronary sinus. The mean baseline PR interval was 183 ± 32 ms (range 145–246 ms), and mean QRSd during intrinsic conduction was 165 ± 18 ms (range 135–192 ms). Example ECG recordings for the subset of CRT settings evaluated in a single patient are shown in Fig. 1.

3.2 Electrical synchronization

The impact of SyncAV on QRSd is shown in Fig. 2. Relative to intrinsic conduction (165.3 ± 18.0 ms), BiV with nominal AVD reduced QRSd by 10 ± 9% to 149 ± 17 ms ($p < 0.05$ vs. intrinsic). Activating SyncAV with an optimized offset (BiV+SyncAV) reduced QRSd by 19 ± 8% relative to intrinsic ($p < 0.05$ vs. BiV) to 134 ± 14 ms ($p < 0.05$ vs. intrinsic and BiV). With MPP nominal AVD, QRSd was reduced by 12 ± 9% relative to intrinsic, to 144 ± 18 ms ($p < 0.05$ vs intrinsic), and by 23 ± 9% relative to intrinsic, to 126 ± 16 ms ($p < 0.05$ vs BiV+SyncAV), with MPP+SyncAV. The SyncAV offsets resulting in the narrowest QRSd were 40 ± 11 ms and 41 ± 11 ms for BiV and MPP configuration, respectively.

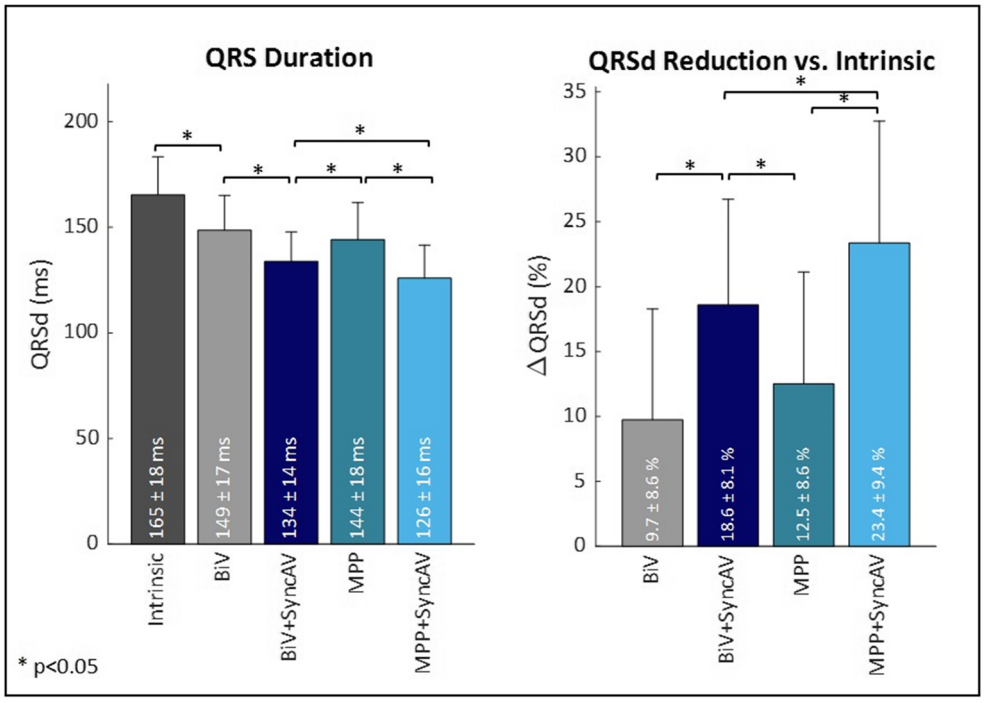

Fig. 2 Impact of SyncAV offset optimization on ECG QRS duration. The impact of SyncAV programming on QRS duration (left) and relative reduction to intrinsic (right) are plotted for all patients

3.3 Left ventricle volume, strain, and mitral inflow evaluation of SyncAV

LV volumes are reported in Table 3 for the various device configurations. In the acute period of device programming, there was no significant modification in end-systolic volume, end diastolic volume, or ejection fraction with the different configurations. LV GLS is evaluated as the 12-segment average for each pacing configuration (Fig. 3 (right)). During intrinsic activation, GLS was – 12 ± 2%. No significant change was observed during BiV (– 12 ± 2%) and BiV+SyncAV (– 12 ± 2%) compared to intrinsic. MPP (– 14 ± 2%) and MPP+SyncAV (– 15 ± 2%) showed significant improvement in GLS compared to intrinsic, BiV, and BiV+SyncAV. However, no significant difference was observed between MPP and MPP+SyncAV.

During intrinsic activation mitral inflow, E/A was 0.77 ± 0.11 and did not show a significant change with BiV pacing (0.78 ± 0.08). Optimization of the AVD with BiV+SyncAV increased the E/A ratio (0.85 ± 0.13) compared to nominal BiV ($p < 0.05$). MPP alone increased E/A to 0.84 ± 0.09 and MPP+SyncAV to 0.88 ± 0.11 ($p < 0.05$ compared to intrinsic and BiV)).

3.4 Echocardiography particle image velocimetry evaluation of SyncAV

A representative case of the LV flow polar histogram, obtained from Echo-PIV during intrinsic activation, BiV, BiV+SyncAV, MPP, and MPP+SyncAV, is illustrated in Fig. 4. Polar distribution of the dominant flow direction is represented for one heart beat during each pacing configuration. The effect of SyncAV on LV flow orientation during the pacing configurations tested is plotted in Fig. 5. Intrinsic activation (CRT device off) resulted in an LV flow angle (φ) of 46 ± 3°. Relative to intrinsic conduction, BiV with a static AVD reduced φ by 7 ± 7° to 39 ± 6° ($p < 0.05$ vs. intrinsic), whereas optimizing AVD during BiV+SyncAV further reduced φ by 9 ± 6° to 37 ± 4° ($p < 0.05$ vs. intrinsic). CRT with two LV electrodes during MPP resulted in a reduction of the LV flow force angle, by 9 ± 6° relative to intrinsic to 37 ± 5° during MPP ($p < 0.05$ vs intrinsic) and by 12 ± 4° to 34 ± 4° during

Table 3 LV volume evaluated during electrical pacing

Characteristic	Intrinsic	BiV	BiV+SyncAV	MPP	MPP+SyncAV
End-systolic volume [mL]	117 ± 30	117 ± 30	118 ± 33	116 ± 32	118 ± 35
End diastolic volume [mL]	172 ± 37	169 ± 36	170 ± 37	168 ± 36	170 ± 38
Ejection fraction (%)	32 ± 7	31 ± 6	31 ± 6	32 ± 8	31 ± 7

No statistical difference was observed between the different configurations

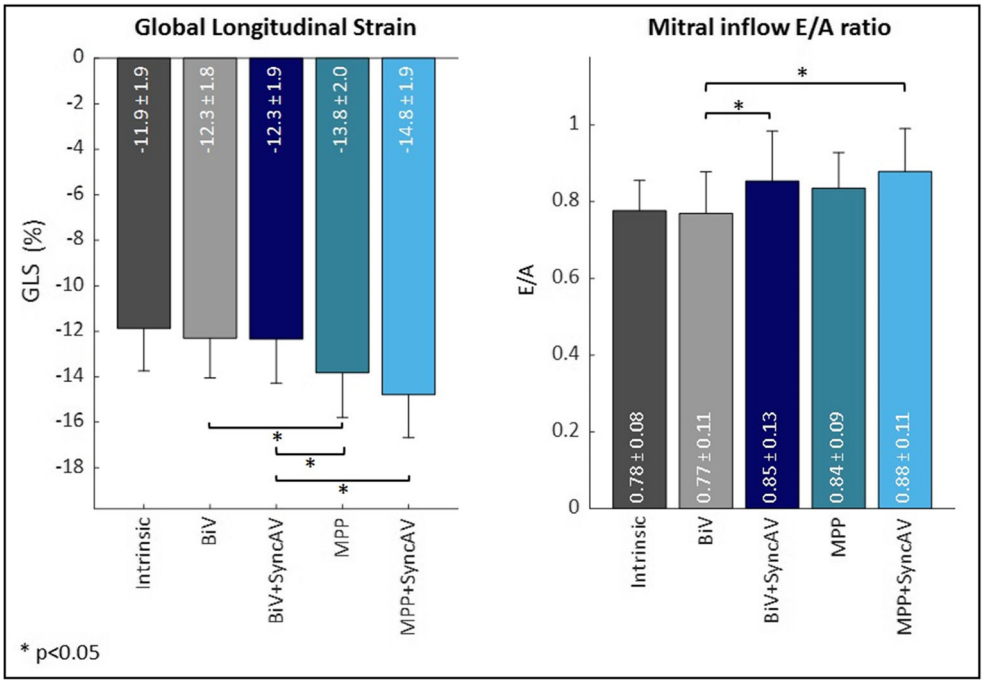

Fig. 3 Impact of SyncAV on LV strain and PW Doppler mitral inflow. The mean 12-segment global longitudinal strain (left) and mitral inflow E/A ratio (right) is plotted for all patients during the various pacing configurations tested

MPP+SyncAV ($p < 0.05$ vs intrinsic, BiV, BiV+SyncAV, and MPP).

4 Discussion

The objective of this feasibility study was to evaluate the impact of SyncAV on acute electrical synchronization and LV fluid mechanics in CRT patients. Enhancements in electrical synchrony have been previously shown with SyncAV [6, 7]. The reduction observed in QRSd relative to intrinsic activation during BiV+SyncAV (19 ± 8%) and MPP+SyncAV (23 ± 9%) was similar to those reported in previous works by Thibault et al. during BiV+SyncAV (20 ± 10%) and O'Donnell et al. during MPP+SyncAV (26±9%) [6, 7]. Acute improvements in electrical synchronization could lead to long-term patient response to CRT [19].

The key outcome of this work was the translated effect of electrical synchrony with SyncAV to the dominant orientation of LV hemodynamic velocities (i.e., flow force angle), evaluated in patients post-CRT implant. Echo-PIV analysis has been recently used as a tool to demonstrate the therapeutic improvement in flow force alignment in patients responding to CRT [10] and could be used to identify appropriate pacing setting during acute echocardiographic optimization of quadripolar CRT [18]. In our work, SyncAV resulted in a reduction in QRSd and improved alignment (base-apex) of the LV flow compared to BiV and MPP with nominal AVD. Acute improvement in the longitudinal alignment of the LV flow angle has been shown, in a small cohort of patients, to identify an association between reverse remodeling during

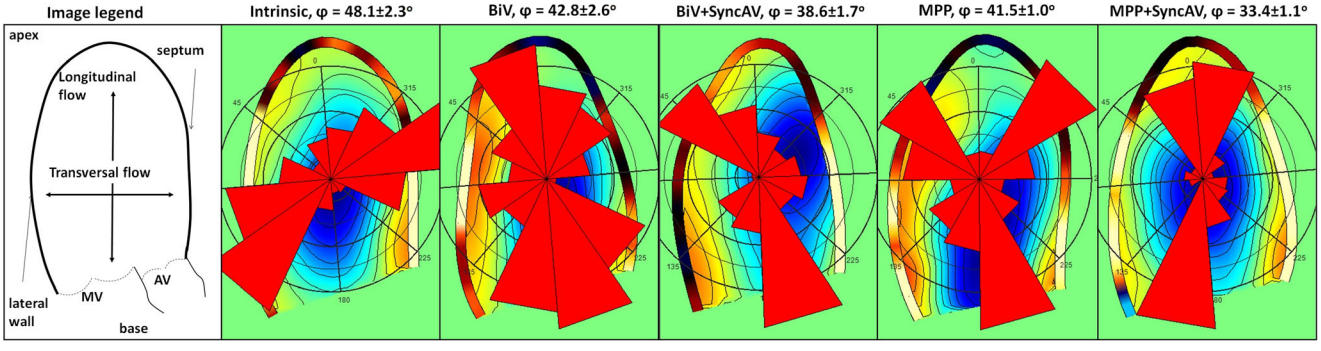

Fig. 4 Case sample Echo-PIV. Example echocardiography particle imaging velocimetry for intrinsic conduction, BiV, BiV+SyncAV, MPP, and MPP+SyncAV. Changes in electrical activation settings modify the orientation (φ) of intraventricular forces during an acute study. The setting (MPP+SyncAV) corresponded to the most aligned (base-apex) intraventricular forces (smallest φ value). MV, mitral valve; AV, aortic valve

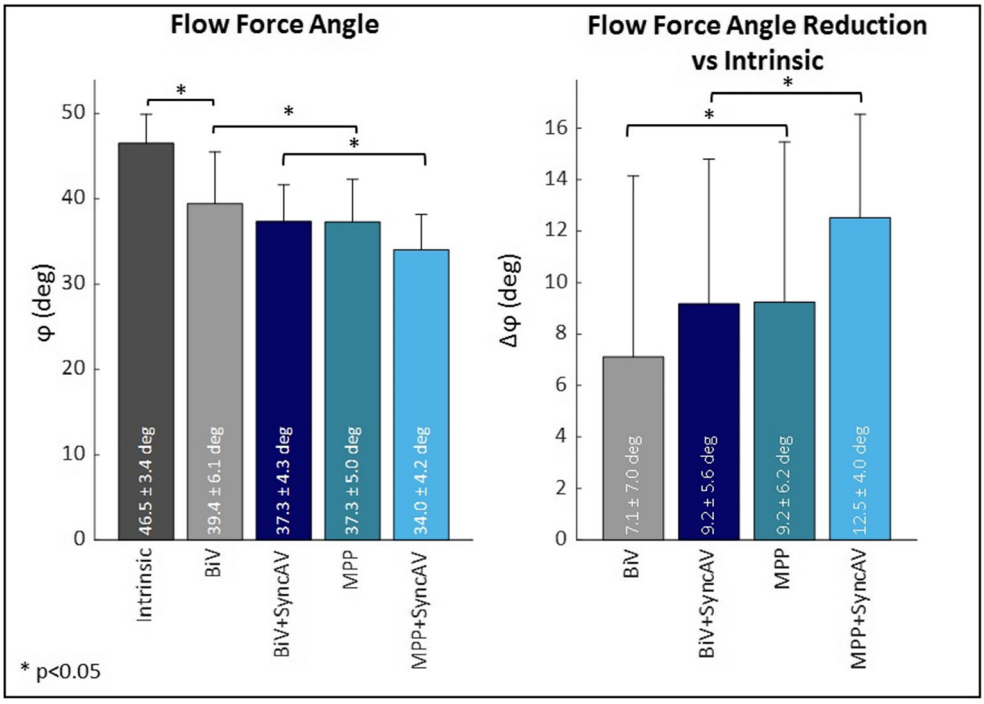

Fig. 5 Impact of SyncAV offset optimization on Echo-PIV flow angular forces. LV flow force angle ,φ, (left) and absolute reduction with respect to intrinsic, Δφ, (right) for all patients

CRT [20]. In a similar manner, acute changes in LV flow angle can be associated to patient response (longitudinal flow) or non-response (transversal flow) to CRT [18, 20]. This preliminary study shows in a small cohort of HF patients with LBBB implanted with a CRT device, the result of electrical synchrony on LV flow forces, which may anticipate long term clinical benefits.

4.1 Clinical implications

As previously demonstrated, SyncAV improves electrical resynchronization beyond conventional BiV pacing [6]. The most important clinical aspect of this work is the effect of SyncAV optimization on the intraventricular LV hemodynamics, assessed in this study by the flow force angle, φ. This study provides additional evidence to previous works [6] that if programmed adequately, SyncAV can improve electrical synchronization by fusing paced activation with the intrinsic activation wave front. This improvement in electrical synchrony can be translated to the intraventricular LV flow mechanics and a correction of the misaligned flow to a more normal base-apex orientation. This improvement in flow may have a potential impact on patient long-term response [18].

4.2 Limitations

The results of this study are limited to acute changes in QRSd and LV flow force angle evaluated by a single observer/center, for which reproducibility and variability of such methodologies have been debated. Data collected in this feasibility study is limited to one post-implant follow-up visit. Chronic evaluation of LV dimensions and tissue mechanics is of utmost importance to correctly evaluate the clinical impact of CRT on LV function and patient response.

Another major limitation in this study is the small number of patients evaluated. Larger studies are needed to characterize LV flow in CRT with the method presented here. Future works should include correlation of QRSd and LV fluid dynamics to invasive hemodynamic measurements as well as long-term clinical outcomes.

5 Conclusion

SyncAV^{TM} optimization resulted in improved acute electrical synchrony, as evaluated by QRS duration reduction. Biventricular and MultiPoint pacing with SyncAV also showed improvements in left ventricle flow force angle measured from echocardiography particle imaging velocimetry. This study showed, in a small patient cohort, that a simple optimization of the AVD can reflect on the orientation of left ventricular blood flow, which may potentially enhance the impact of CRT. However, studies in a larger population with long-term follow-up are needed to confirm if the acute in clinic changes can lead to improved patient outcome.

Compliance with ethical standards

Conflict of interest JM is an employee of Abbott. The other authors declare that they have no conflict of interest.

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