P-wave Morphology Is Associated with Echocardiographic Response to Cardiac Resynchronization Therapy in MADIT-CRT Patients

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Background: In this study we hypothesized that signs of atypical atrial activation would be associated with cardiac resynchronization therapy (CRT) response in patients with mildly symptomatic heart failure (CHF), left ventricular dysfunction, and wide QRS complex.

Methods: Patients included in the CRT-D arm in MADIT-CRT were studied ($n = 892$). Unfiltered signal-averaged P waves were analyzed to determine orthogonal P-wave morphology (typical morphologies were predefined as having positive signals in Leads X and Y and a negative or negative-positive signal in Lead Z. All other patterns were classified as atypical). The association between P-wave morphology and data on echocardiographic response at 1 year was analyzed.

Results: Atypical P-wave morphology was found in 21% ($n = 186$) of the patients at baseline. Patients with atypical P-wave morphology were more often female (31% vs. 24%, $P = 0.025$), had lower BMI (28 ± 5 kg/m² vs. 29 ± 5 kg/m², $P = 0.008$), had more ischemic CHF (60% vs. 52%, $P = 0.026$) and had smaller left atrial volumes (90 ± 20 mL vs. 94 ± 22 mL, $P = 0.034$). Atypical P-wave morphology at baseline was associated with superior response to CRT at 1 year with a larger reduction in left ventricular end-diastolic volume ($-23 \pm 12\%$ vs. $-20 \pm 11\%$, $P = 0.009$), left ventricular end-systolic volume ($-36 \pm 16\%$ vs. $-31 \pm 16\%$, $P = 0.006$), and left atrial volume ($-31 \pm 12\%$ vs. $-27 \pm 12\%$, $P = 0.005$), with a slightly larger absolute increase in left ventricular ejection fraction (LVEF) ($12 \pm 5\%$ vs. $11 \pm 5\%$, $P = 0.009$). These associations were found to be independent of traditional predictors.

Conclusion: The presence of atypical P-wave morphology recorded is independently associated with a favorable echocardiographic cardiac remodeling response to CRT.

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atrial electrophysiology; congestive heart failure; CRT; echocardiography; responders; ECG

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been shown to be associated with reduced mortality and morbidity in patients with advanced congestive

heart failure (CHF) and wide QRS complexes.^{1,2} Recently, these benefits were shown to extend also to the less advanced heart failure population (New York Heart Association [NYHA] class I or II).^{3,4} Although the overall results are positive,

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a substantial proportion of the patients are so called “nonresponders” and have no or negligible effect of CRT.^{5–7} Given the risk of significant complications for the patient and considering the cost for the device it is comprehensible that there is much interest in trying to identify the patients most likely to respond to CRT, but the results so far have been sparse. However, in a recent substudy of the MADIT-CRT population⁴ seven factors were found to be independently associated of CRT response (i.e., female sex, nonischemic origin, left bundle branch block (LBBB), QRS $\geq$ 150 ms, prior hospitalization for heart failure, left ventricular end-diastolic volume (LVEDV) $\geq$ 125 mL/m², and left atrial volume (LAV) $<$ 40 mL/m²) and a scoring system was introduced to help guide the clinical decision of CRT implantation or not.⁸ Left atrial size was found to be among the more powerful predictors.⁸

Detailed analysis of P-wave morphology using unfiltered, signal-averaged P-wave analysis has been shown to reveal information beyond P-wave duration alone.^{9,10} The obtained P-wave morphology has been shown to at least in part depend on interatrial conduction¹¹ and has also been shown to carry prognostic value in patients with ischemic heart disease and CHF.¹⁰ The precise relation between P-wave morphology and atrial volume and changes therein has not yet been established.

In this study, we hypothesized that P-wave morphology, as a marker of atrial activation would be associated with echocardiographic CRT response in patients with mildly symptomatic heart failure, left ventricular dysfunction, and wide QRS complex.

METHODS

Study Population and Clinical Characteristics

The design and results of MADIT-CRT have been reported elsewhere.⁴ Briefly, the study included 1820 patients with documented ischemic cardiomyopathy (NYHA class I or II) or non-ischemic cardiomyopathy (NYHA class II only), sinus rhythm, an ejection fraction of 30% or less, and prolonged intraventricular conduction with a QRS duration of 130 ms or more. Patients were randomized to CRT with an ICD or to only an ICD

in a 3:2 fashion. Patients were followed for a mean of 2.4 years. Exclusion criteria included existing CRT indications, having an implanted pacemaker, ICD or resynchronization device, atrial fibrillation within 1 month before of enrollment, NYHA class III or IV symptoms, myocardial infarction within the past 3 months, coronary revascularization within the past 3 months and other advanced comorbidities. Clinical and demographic data collected at enrollment included information regarding age, gender, race, body mass index, history of myocardial infarction, date of most recent myocardial infarction, hypertension, smoking, diabetes, prior revascularization procedures, and NYHA class. Data regarding medication, ejection fraction, blood pressure, and blood urea nitrogen (BUN) were also obtained at enrolment.

Due to ECG requirement and availability (see below), only patients randomized to CRT-D treatment (n = 1089) were included in this study.

Data Acquisition and Analysis

A 10-minute high-resolution (1 kHz) bipolar ECG recording (Mortara H-12 recorders and H-Scribe scanning system [Mortara Instrument, Inc., Milwaukee, WI, USA]) was obtained per protocol at enrolment and at 1-year follow-up in MADIT-CRT patients included in the CRT-D arm. Data analysis was performed using custom-made software running on MATLAB R2010b for Mac OS X (The MathWorks, Inc., Natick, MA, USA). Unfiltered, signal-averaged P waves were analyzed to determine P-wave morphology.^{12,13} Following high-pass (0.5 Hz) and bandstop (50 Hz) filtering, the QRS complexes were automatically identified and grouped according to similarity (a cross-correlation coefficient, $\rho > 0.9$). P waves were extracted using 250 ms wide signal windows preceding each QRS complex. The signal windows were then shifted in time to estimate the maximal correlation in each lead. P waves with a cross-correlation coefficient of $\rho > 0.9$ (analyzed separately in all leads) were grouped together and averaged. The actual P waves were defined by manual setting of the onset and end. The method used is described in detail elsewhere.^{12,13}

Definitions

The P-wave morphology was classified into one of three predefined classes (Type 1: positive Leads

Table 1. Baseline Clinical Characteristics in the Study Population

MADIT-CRT patients in SR at baseline included in the CRT-D arm		
(n = 895)		
Age	(years)	64 ± 11
Male	(%)	75
Ischemic	(%)	54
History of Atrial Arr	(%)	11
History of Ventricular Arr	(%)	7
Hypertension	(%)	64
Diabetes	(%)	30
BMI	(kg/m ²)	29 ± 5
Systolic BP	(mmHg)	124 ± 17
Diastolic BP	(mmHg)	72 ± 10
BUN	(mg/dL)	21 ± 9
BNP	(pg/mL)	130 ± 169
NYHA (I/II/III/IV)	(%)	(13/87/0/0)
LVEDV	(mL)	246 ± 59
LVESV	(mL)	175 ± 48
RVD	(mL)	28 ± 2
LAV	(mL)	93 ± 22
LVEF	(%)	29 ± 3
Beta-blocker	(%)	94
RAAS	(%)	97
Digitalis	(%)	27
CCB	(%)	7
Amiodarone	(%)	7
LBBB	(%)	71
RBBB	(%)	12
IVCD	(%)	17
Heart rate	(bpm)	67 ± 11
PWD Unfiltered	(ms)	144 ± 17
Type (1/2/3/Atypical)	(%)	(10/69/1/20)

Arr = arrhythmia; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; BNP = brain natriuretic peptide; CCB = calcium channel blockers; LAV = left atrial volume; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PWD = P-wave duration; RAAS = renin angiotensin aldosterone inhibition; RBBB = right bundle branch block; RVD = right ventricular diastolic volume.

X and Y and negative Lead Z, Type 2: positive Leads X and Y and biphasic Lead Z [−/+], and Type 3: positive Lead X and biphasic signals in Leads Y [+/-] and Z [−/+]) using an automatic algorithm.¹³ In previous studies Type 1 P-wave morphology has been found to be more abundant in healthy, younger individuals whereas Type 2 morphology is more common among patients with a history of AF and/or CHF.^{14–16} Type 3 P-wave morphology is primarily seen in patients with concomitant heart disease.¹⁵ P-wave morphologies compatible with block or delayed conduction in more than

one of the interatrial conduction routes (i.e., Type 3 or atypical)¹¹ are collectively denoted "atypical P-wave morphology."

Echocardiographic Studies

Two-dimensional echocardiography was performed at baseline and at 1-year follow-up to assess changes in left ventricular volumes and ejection fraction. The magnitude of echocardiographic response to CRT treatment was estimated as percent reduction in left LVEDV, left ventricular end-systolic volume (LVESV), and LAV between enrolment and 1 year.

Statistics

Data are expressed as mean ± standard deviation. Student's *t*-test or one-way ANOVA was used to analyze unpaired data. The chi-square test was used when analyzing nominal data. Kaplan-Meier curves with log-rank statistics were used to analyze time to endpoint events. Linear regression analysis was performed to estimate the magnitude of the independent effect of parameters. These analyses were adjusted for relevant baseline risk factors. All tests were two-sided and *P* < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 20.0 for Mac OS X (SPSS Inc., Chicago, IL, USA).

RESULTS

Data Availability

At the time of baseline ECG-recording, 1014 (93%) of the 1089 patients were found to be in sinus rhythm, after excluding patients with pacemaker rhythm and atrial fibrillation. Of the 1014 patients in sinus rhythm, 895 (88%) were found to have baseline ECG recordings of sufficient quality for further analysis. The results presented are based on this patient subset. Yet another subset of the patients (*n* = 588, 66%) performed another ECG-recording at 1-year follow-up during sinus rhythm. These patients were included in the P-wave morphology change analyses.

Clinical Characteristics and P-wave Morphology Distribution at Enrolment

Patient characteristics and P-wave parameters at baseline are summarized in Table 1. Notably,

Figure 1. Typical examples of P-wave morphology Type 1, 2 and 3. The atypical example depicts the most commonly seen atypical morphology with exclusively positive signal in Lead Z.

only a small minority of the patients studied was on treatment with antiarrhythmic drugs. P-wave duration was prolonged compared to standard reference values (144 ± 17 ms). Approximately two thirds (69%) of the patients were exhibiting Type 2 P-wave morphology whereas only 10% and 1% of the patients exhibited Type 1 and Type 3, respectively. Twenty percent of the studied subjects had an atypical P-wave morphology. Because of the low number of observed Type 3 morphologies, these were analyzed together with the atypical P-wave morphology for the subsequent analyses, after making sure that no relevant differences in baseline parameters existed between these groups (data not shown). Figure 1 illustrates typical P-wave morphological examples.

Comparison of Baseline Clinical Characteristics and ECG Parameters Based on P-Wave Morphology Classification

Table 2 summarizes the baseline clinical characteristics and ECG parameters based on P-wave morphology classification. Patients with Type 1 P-wave morphology had more often cardiomyopathy of nonischemic origin, had marginally lower diastolic blood pressure and were less likely to be treated with RAAS-inhibiting drugs than patients with other P-wave morphologies. At 12-month follow-up, there were no differences seen in medication in relation to P-wave morphology classification at baseline (data not shown). Patients with Type 2 P-wave morphology were

Table 2. Relation between P-wave morphology and clinical characteristics

		Type 1 (n = 93)	Type 2 (n = 615)	Type 3/Atypical (n = 187)	P =
Age	(years)	63 ± 12	64 ± 11	64 ± 10	0.22
Male	(%)	70	77	69	0.03
Ischemic	(%)	43	54	60	0.02
Hx of Atrial Arr	(%)	8	11	12	0.52
Hx of Vent Arr	(%)	3	8	6	0.13
Hypertension	(%)	55	64	65	0.19
Diabetes	(%)	26	31	29	0.59
BMI	(kg/m ²)	27 ± 4	29 ± 5	28 ± 5	< 0.01
Systolic BP	(mmHg)	121 ± 17	124 ± 18	124 ± 16	0.37
Diastolic BP	(mmHg)	69 ± 10	73 ± 10	72 ± 10	< 0.01
BUN	(mg/dL)	21 ± 8	21 ± 9	21 ± 9	0.65
BNP	(pg/mL)	156 ± 200	124 ± 167	137 ± 157	0.33
NYHA (I/II)	(%)	(8/92)	(14/86)	(14/86)	0.22
LVEDV	(mL)	235 ± 62	249 ± 61	242 ± 52	0.06
LVESV	(mL)	m ± 49	177 ± 49	171 ± 41	0.07
RVD	(mL)	28 ± 2	29 ± 2	28 ± 2	0.01
LAV	(mL)	88 ± 19	95 ± 23	90 ± 20	< 0.01
LVEF	(%)	29 ± 3	29 ± 4	29 ± 3	0.67
Beta-blocker	(%)	95	94	91	0.34
RAAS	(%)	94	98	96	0.03
Digitalis	(%)	28	29	22	0.21
CCB	(%)	2	9	6	0.06
Amiodarone	(%)	3	7	8	0.36
LBBB	(%)	76	70	71	0.52
RBBB	(%)	14	12	11	0.73
IVCD	(%)	10	18	18	0.14
Heart Rate	(bpm)	67 ± 10	67 ± 11	69 ± 10	0.02
QRS duration	(ms)	157 ± 18	158 ± 20	157 ± 18	0.60
PWD unfiltered	(ms)	138 ± 22	145 ± 16	144 ± 18	< 0.01

One-way ANOVA was used to analyze unpaired data. The chi-square test was used when analyzing nominal data. Bold P values indicate $P < 0.05$. Arr = arrhythmia; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; BNP = brain natriuretic peptide; CCB = calcium channel blockers; LAV = left atrial volume; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PWD = P-wave duration; RAAS = renin angiotensin aldosterone inhibition; RBBB = right bundle branch block; RVD = right ventricular diastolic volume.

more often of male gender and had slightly higher BMI whereas patients with atypical P-wave morphology at baseline had significantly higher heart rate than the other patients. Left ventricular dimensions were similar, while patients with Type 2 P-wave morphology had significantly larger right ventricular and left atrial dimensions at baseline. The P-wave duration was significantly shorter in patients with Type 1 P-wave morphology.

P-wave Morphology and CRT Response

Table 3 summarizes the echocardiographic measures of CRT response in relation to P-wave morphology classification at baseline. There was a consistent pattern across the parameters with a more pronounced CRT response in patients with atypical P-wave morphology at baseline. After

adjustment for relevant covariates (i.e., gender, origin of cardiomyopathy, QRS width, bundle branch pattern, prior hospitalization, baseline LVEDV and LAV), atypical P-wave morphology was shown to be an independently associated with favorable echocardiographic cardiac remodeling response to CRT (Table 4). P-wave duration was included in the original model, but was found to be highly insignificant and was therefore excluded from the final model.

P-wave Morphology and Measures of Outcome

Neither baseline P-wave morphology nor P-wave duration was found to be predictive of clinical outcome (i.e., all-cause mortality or nonfatal heart failure, whichever came first, all-cause mortality

Table 3. Relation Between P-Wave Morphology and Echocardiographic Measures of CRT Response

		Type 1 (n = 93)	Type 2 (n = 615)	Type 3/Atypical (n = 187)	P =
LVEDV reduction	(%)	20 ± 11	20 ± 12	23 ± 12	0.03
LVESV reduction	(%)	32 ± 15	32 ± 16	35 ± 16	0.03
LAV reduction	(%)	27 ± 12	27 ± 12	31 ± 12	0.02
LVEF increase	(%)	11 ± 5	11 ± 5	12 ± 5	0.03

One-way ANOVA was used to analyze unpaired data. Bold P values indicate $P < 0.05$. LAV = left atrial volume; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction.

Table 4. Linear Regression Analysis LVEDV Change

	Beta	Std Error	P Value
Intercept	9.4	1.2	<0.01
Female gender	2.6	1.1	0.02
Nonischemic cardiomyopathy	5.1	1.0	<0.01
QRS more than 150 ms	2.9	1.0	<0.01
LBBB	2.8	1.1	0.01
Prior CHF hospitalization	2.0	0.9	0.02
Baseline LVEDV > 125 mL	2.8	1.0	<0.01
Baseline LAV < 40 mL	5.8	1.0	<0.01
Atypical P-wave morphology	2.9	1.0	<0.01

Linear Regression analysis. Bold P values indicate $P < 0.05$. CHF = congestive heart failure; LAV = left atrial volume; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume.

and hospitalization for CHF). This was also true when atypical P-wave morphology was analyzed separately (Figure 2).

LAV and its Relation to P-Wave Morphology and Changes Thereof

At 1-year follow-up a larger proportion of the patients exhibited Type 1 P-wave morphology compared with at baseline (23/55/22% vs. 10/69/21%, $P < 0.001$). Patients with atypical P-wave morphology at baseline tended to change P-wave morphology more often (56%) than patients with Type 2 (35%) or Type 1 P-wave morphology (42%, $P < 0.001$). In patients who exhibited a change in P-wave morphology between baseline and 1-year follow-up a marginally larger change in LAV was seen compared with patients with stable P-wave morphology ($30.3 \pm 11.7\%$ vs. $27.4 \pm 12.9\%$, $P = 0.02$).

Figure 2. No relation between atypical P-wave morphology at baseline and the primary end-point (i.e., all-cause mortality or nonfatal heart failure, whichever came first) was found ($P = 0.526$). This was also true for the secondary outcome measures (all-cause mortality and hospitalisation for CHF).

DISCUSSION

The results of this study indicate that detailed analysis of P-wave morphology in patients with CHF and broad QRS complexes may add value when trying to identify echocardiographic CRT response. Furthermore, the results show that although there is an association between atrial volume and P-wave morphology, at least in the severely dilated state, differences in P-wave morphology are also seen without significant differences in atrial volume. Hence, the atrial conductive properties and sinus impulse propagation route rather than atrial volume are likely to be the major determinants of orthogonal P-wave morphology.

P-wave Morphology and Baseline Characteristics

The observed distribution of P wave morphology at baseline in this study is in keeping with previous studies including similar patient cohorts.¹⁰ The high prevalence of atypical P-waves are well in keeping with the findings in the MADIT II population.¹⁰ Additionally, a similarly high prevalence of atypical P waves was recently reported in patients with arrhythmogenic right ventricular cardiomyopathy.¹⁷ The exact electrophysiological explanation to this atypical activation pattern is not known.

The differences in clinical characteristics between patients with respect to the different P-wave morphologies were generally small and on most instances negligible. However, when present, the observed differences support the assumption that Type 1 P-wave morphology is more commonly seen in patients with less severely diseased atria (e.g, younger age, lower BMI and lower blood pressure and shorter P-wave duration).^{14,15} In this study, patients with Type 2 P-wave morphology were more likely to be of male gender than patients with Type 1 or atypical morphology. In a recent study, male athletes showed a more pronounced atrial remodeling for a comparable amount of training and performance than female athletes.¹⁸ In contrast, another study looking at the basic atrial electrophysiological parameters did not find any gender specific differences.¹⁹ Hence, the reason for the uneven gender distribution between the different P-wave morphologies remains to be explained, but the findings parallels those in previous studies from our group.¹⁴

P-wave Morphology—Volume or Electricity?

There is an association between the P wave as displayed on the ECG and atrial size.²⁰ However, the sensitivity and specificity of these measures to diagnose left atrial enlargement are generally quite low.^{21,22} Little is known about the association between left atrial size and P-wave morphology, but a significant association between P-wave morphology and left atrial size measured using echocardiography has previously been demonstrated.¹⁵ In another study, a clear association between P-wave morphology and left

atrial breakthrough has been shown in patients undergoing left atrial catheterization.^{11,23}

In this study, there were significant differences in left atrial size between patients with different P-wave morphologies at baseline. Moreover, a larger change in LAV was seen on average in patients who changed P-wave morphology between baseline and 1-year follow-up. At follow-up, after significant reductions in left atrial size in most patients, a shift toward a higher prevalence of Type 1 P-wave morphology were seen, again in keeping with the notion of this morphology being the "healthiest."¹⁵ In contrast to these findings indicating a possible role for left atrial size in determining P-wave morphology, no significant differences in the echocardiographic parameters was seen between the different P-wave morphologies at follow-up when the left atrial measures were in part "normalized." To conclude, in patients with CHF, P-wave morphology seems to be influenced by left atrial size. However, the lack of association at 1-year follow-up indicates that this may not hold true in the less diseased heart.

P-wave Morphology and CRT Response—Possible Mechanisms

Atypical P-wave morphology at baseline was found to be associated with favorable echocardiographic cardiac remodeling response to CRT independently of previously described parameters (e.g., QRS duration, LBBB, LVEF, and LAV). As noted previously, atypical P-wave morphology has been shown to be associated with more advanced heart disease as well as with poor clinical outcome.^{10,15} This is well in keeping with other clinical parameters (e.g., NYHA class, QRS width) where the greatest CRT effect is seen in the more diseased individuals. Moreover, as previously mentioned, P-wave morphology has been shown to be related to interatrial conduction.¹¹ One may speculate that the atypical P-wave morphology is produced by abnormal interatrial conduction, which in turn may be a consequence of atrial fibrosis. The atrial wall is thinner than the ventricle wall and therefore potentially more susceptible to fibrotic changes.²⁴ If so, it is rational to assume that changes in atrial electrophysiology (i.e., atypical P-wave morphology) may precede changes in ventricular electrophysiology (e.g., LBBB) in the globally diseased heart. It has also been hypothesized that changes in P-wave morphology

may be related to atrial filling pressure,²⁵²⁵ which also could be part of the explanation to the association between P-wave morphology and favorable echocardiographic cardiac remodeling response to CRT. However, the exact mechanism behind the association cannot be revealed in the present post hoc study, hence further studies are needed to clarify this relationship.

Clinical Implications

Although atypical P-wave morphology was associated with more pronounced echocardiographic response to CRT in this study, the magnitude of the difference was modest. One may argue that the magnitude is similar to those associated with previously suggested predictors,⁸ but it is nevertheless evident that the possible role of P-wave morphology analyses in this setting is as *one component* in a more complex clinical response model.

Study Limitations

This study is lacking a proper control group due to the fact that no digital ECG data was collected from patients in the ICD only arm in MADIT-CRT. Therefore, conclusions regarding changes in P-wave morphology and echocardiographic parameters not associated with the CRT treatment cannot be drawn.

CONCLUSIONS

The presence of atypical P-wave morphology recorded at baseline from orthogonal leads in surface ECG is independently associated with a favorable echocardiographic cardiac remodeling response to CRT. This indicates that detailed analysis of P-wave morphology may add value when trying to identify CRT responders. Furthermore, the results show that although P-wave morphology may in part be influenced by atrial volume, it is unlikely to be the sole determinant of orthogonal P-wave morphology.

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