Interatrial Block Predicts Atrial Fibrillation and Total Mortality in Patients with Cardiac Resynchronization Therapy

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Keywords

Heart failure · Atrial fibrillation · Mortality · Risk stratification · Interatrial block · Abnormal P-wave terminal force in lead V1 · Cardiac resynchronization therapy

Abstract

Background: Interatrial block (IAB) and abnormal P-wave terminal force in lead V₁ (PTFV₁) are electrocardiographic (ECG) abnormalities that have been shown to be associated with new-onset atrial fibrillation (AF) and death. However, their prognostic importance has not been proven in cardiac resynchronization therapy (CRT) recipients. **Objective:** To assess if IAB and abnormal PTFV₁ are associated with new-onset AF or death in CRT recipients. **Methods:** CRT recipients with sinus rhythm ECG at CRT implantation and no AF history were included ($n = 210$). Automated analysis of P-wave duration (PWD) and morphology classified patients as having either no IAB (PWD <120 ms), partial IAB (pIAB: PWD ≥120 ms, positive P waves in leads II and aVF), or advanced IAB (aIAB: PWD ≥120 ms and biphasic or negative P wave in leads II or aVF). PTFV₁ >0.04 mm·s was considered abnormal. Adjusted Cox regression analyses were performed to assess the impact of IAB and abnormal PTFV₁ on the primary endpoint new-onset AF, death, or heart transplant (HTx) and the

secondary endpoint death or HTx at 5 years of follow-up. **Results:** IAB was found in 45% of all patients and independently predicted the primary endpoint with HR 1.9 (95% CI 1.2–2.9, $p = 0.004$) and the secondary endpoint with HR 2.1 (95% CI 1.2–3.4, $p = 0.006$). Abnormal PTFV₁ was not associated with the endpoints. **Conclusions:** IAB is associated with new-onset AF and death in CRT recipients and may be helpful in the risk stratification in the context of heart failure management. Abnormal PTFV₁ did not demonstrate any prognostic value.

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Introduction

In general, patients with cardiac resynchronization therapy (CRT) constitute a cohort of patients affected by many comorbidities. CRT significantly reduces morbidity and mortality [1, 2]; nevertheless, these patients have a relatively short life expectancy [3]. Risk stratification in patients with CRT is difficult and easily available tools for risk stratification are needed.

Interatrial block (IAB) is an electrocardiographic (ECG) sign of an interatrial conduction abnormality de-

Fig. 1. Illustration of the IAB groups.

defined as a P-wave duration (PWD) exceeding 120 ms. If, in addition to P-wave prolongation, biphasic ($\pm$) P waves are found in inferior leads, it is described as an advanced IAB (aIAB).

The association of IAB and atrial arrhythmias such as atrial fibrillation (AF) is well known [4–8], and the first paper that describes the association of IAB and AF was published by Bayés de Luna et al. [9]. The association was later named Bayes syndrome [10, 11]. The ability of IAB to predict total mortality is less established, and few studies have assessed the diagnostic value of IAB in patients with severe heart failure (HF). Yet, IAB has been correlated to non-sudden cardiac death in patients with CRT and mild HF [12] and is predictive of total mortality in primary care patients [4]. aIAB is most often found among the most severely ill patients and has been associated with worse outcomes compared to partial IAB (pIAB) based on the data from mixed or relatively healthy cohorts [4, 13].

Abnormal P-wave terminal force in lead V_1 (PTFV₁), defined as a terminal negative component of the P wave of $>0.04 \text{ mm} \cdot \text{s}$ in lead V_1 , is another established ECG abnormality that also has been shown to be predictive of atrial arrhythmias as well as poor outcomes in patients with stroke, in patients with myocardial infarction and in CRT recipients with mild HF and left bundle branch block (LBBB) [14–17].

To our knowledge, the prognostic importance of IAB and abnormal PTFV₁ has not been studied in CRT recipients with advanced HF.

Objective

The main objective of this study was to analyze the prognostic importance of a preprocedural finding of IAB or abnormal PTFV₁ in a real-life cohort of CRT recipients. Specifically, we sought to evaluate if IAB and abnormal

Fig. 2. Illustration of abnormal PTFV₁.

mal PTFV₁ were associated with a higher risk of new-onset AF or death from any cause during follow-up or total mortality alone during follow-up. A secondary objective was to assess if patients with aIAB had an inferior prognosis compared to patients with pIAB.

Methods

Study Population

We retrospectively included consecutive patients who received a CRT-pacemaker (CRT-P) or CRT-defibrillator (CRT-D) device between the years 1999 and 2012 in Lund, Skåne, Sweden. All CRT implantations were carried out according to contemporary guidelines [3] and only patients with a successfully implanted CRT-device, an ECG available for analysis with proper signal quality and sinus rhythm (SR) within 180 days from the time of CRT implantation and with no preprocedural history of AF were included. Thus, only patients without any documented AF by the time of CRT implantation were included in the study.

For review, the ECG with the shortest time duration from CRT implantation was evaluated. SR was defined as a positive starting component of the P wave in lead II, and all available ECGs were manually reviewed to validate that the ECG signal quality was ac-

Table 1. Baseline characteristics of all patients

Parameter	All patients (n = 210)	No IAB (n = 115; 55%)	pIAB (n = 72; 34%)	aIAB (n = 23; 11%)	Any IAB (n = 95; 45%)
Demographics					
Age, years (IQR)	67 (59–75)	67 (60–74)	67 (58–74)	72 (59–77)	69 (59–75)
Male, %	80	76	89 ^b	74	85
Ischemic heart disease, %	55	55	58	48	56
NYHA Class III or IV, %	70	73	65	70	66
Hypertension, %	31	30	29	42	33
Diabetes, %	32	37	26	25	26
Conventional PM before CRT, %	13	15	13	8	12
Creatinine, $\mu\text{mol/L}$ (IQR)	106 (88–134)	106 (89–135)	110 (85–136)	97 (78–106)	106 (84–133)
Medication at CRT implantation					
Beta-blocker, %	86	83	93	83	91
ACEi or ARB, %	96	94	97	100	98
Loop diuretic, %	92	91	90	100	93
Class I or III antiarrhythmic, %	7	8	7	8	7
Digoxin, %	28	25	33	33	33
Anticoagulant therapy, %	32	28	36	42	37
Cardiac findings at CRT implantation					
QRS duration, ms (SD)	170 (26)	170 (25)	168 (31)	179 (21)	174 (28)
LVEF, % (IQR)	25 (20–27)	25 (20–26)	25 (20–30)	25 (22–31)	25 (20–30)
LBBB, %	80	85	72 ^b	78	74 ^b
PWD, ms (IQR)	116 (102–130)	104 (86–112)	132 (125–142) ^b	130 (126–140) ^b	130 (126–142) ^b
Abnormal PTFV ₁ , %	28	17	42 ^b	39 ^b	41 ^b
Time from analyzed ECG to CRT implant, median (IQR), days	14 (1–58)	15 (1–58)	16 (1–70)	1 (0–49)	12 (1–51)
Time from first available ECG to CRT implant, median (IQR), years	10.7 (4.6–15.4)	11.6 (4.8–16.0)	9.6 (4.4–13.5)	11.9 (4.3–16.0)	9.7 (4.4–13.6)
Number of available ECGs before CRT implant, median (IQR)	20 (13–28)	20 (13–28)	19 (13–29)	19 (10–27)	19 (12–28)
Follow-up characteristics					
CRT-P implanted, n (%)	107 (51)	66 (57)	27 (38) ^b	16 (70)	43 (45)
Potential median follow-up, years (IQR) ^a	8.4 (6.3–12.1)	8.3 (6.2–12.3)	7.6 (6.2–12.1)	10.4 (6.8–12.5)	8.6 (6.3–12.1)

^a Time from CRT implantation to September 15, 2017. ^b Significantly different ($p < 0.05$) from no IAB group.

ceptable and that no patient was included if the ECG showed atrial pacing or AF or if an analysis of the P wave was not possible. A figure of the full inclusion process is available in online supplementary Figure 1 (see www.karger.com/doi/10.1159/000509916 for all online suppl. material).

Baseline ECG Assessment and Definitions of IAB and Abnormal PTFV₁

All available preprocedural ECGs as well as ECGs within 180 days after CRT implantation were extracted from the regional electronic database (MUSE Cardiology Information System version 9, GE Healthcare, Chicago, IL, and Infinity Megacare ECG management system, Dräger, Houston, TX, USA) and processed offline. Using the fully automatic Glasgow algorithm [18], an automated analysis of the PWD and the morphology of the P waves in leads V₁, II, and aVF was performed. The automatic algorithm allows identification of the P-wave morphology as positive (+1), negative (–1), or biphasic with polarity of the initial deflection defined as positive (+2) or negative (–2).

Patients were classified as having either no IAB (PWD <120 ms), pIAB (PWD $\geq$ 120 ms, positive P waves in leads II and aVF)

or aIAB (PWD 120 ms and biphasic [$\pm$] or negative P waves in leads II or aVF). The definition [13] was established on the notion that aIAB diagnosis should primarily be based on leads II and aVF and that isolated abnormal morphologies in lead III are not sufficiently specific for aIAB [19]. Illustrations of the different IAB types are found in Figure 1. PTFV₁ >0.04 mm•s was considered abnormal [20]. An illustration of an ECG with abnormal PTFV₁ is found in Figure 2.

Assessment of AF before and after CRT Implantation

A preprocedural history of AF was evaluated from a manual review of medical records and from the Swedish National Patient Registry (SNPR). The SNPR is administered by the Swedish National Board of Health and Welfare and includes data, starting in the year 1987 on main and secondary diagnoses at discharge from all public hospitals in Sweden. Information about outpatient visits to hospitals is also included. The register uses International Classification of Disease (ICD) codes, with the 9th edition (ICD-9) used between 1987 and 1996, and the 10th edition (ICD-10) used from 1997. AF was defined as the presence of any of the following ICD codes: 427D for ICD-9 and I48 for ICD-10.

Table 2. Outcome in 5 years of follow-up

Outcome	All patients (<i>n</i> = 210)	No IAB (<i>n</i> = 115; 55%)	pIAB (<i>n</i> = 72; 34%)	aIAB (<i>n</i> = 23; 11%)	Any IAB (<i>n</i> = 95; 45%)
Reached primary endpoint	105 (50)	48 (42)	45 (63) ^a	12 (52)	57 (60)
Reached secondary endpoint	75 (36)	34 (30)	32 (44) ^a	9 (39)	41 (43) ^a
Type of endpoint in 5 years					
Death	56 (27)	27 (24)	23 (32)	6 (26)	29 (31)
New-onset AF	46 (22)	20 (17)	20 (28)	6 (26)	26 (27)
HTx	3 (1)	1 (1)	2 (3)	0 (0)	2 (2)

^a Significantly different (*p* < 0.05) from no IAB group.

To study if there were any additional AF cases not reflected in the SNPR or medical records, all available digital pre- and postprocedural ECGs were assessed regarding the occurrence of AF. ECGs were obtained from the regional electronic ECG database which contains all ECGs taken in the hospital catchment area, including primary care facilities, starting from the year 1988. If the automated analysis decoded a rhythm on digital ECG as AF, that specific ECG was manually reviewed by a trained physician (J.J.) to evaluate if the automated analysis was appropriate or not. In cases of doubt, a senior cardiologist (P.G.P.) was consulted. If AF was confirmed, the patient was given a diagnosis of AF before or after CRT implantation. If AF was found before CRT implantation, that patient was consequently excluded from the study. Data regarding AF during CRT follow-up was also achieved from the SNPR and the date of the first time when ECG-documented AF was diagnosed at admission to hospital, or at specialized cardiology in- and outpatient visits, was noted.

Study Endpoint

Information about study endpoints was collected during the period from the time of CRT implantation until September 15, 2017, when data was retrieved from the SNPR. The primary endpoint was a combined endpoint of new-onset AF, death, or heart transplantation (HTx), and the secondary endpoint was death or HTx.

Statistics

Histograms were used to evaluate if continuous data were normally distributed or not. Non-continuous and continuous variables not normally distributed were reported as median (interquartile range). Continuous, normally distributed variables were reported as mean ± SD. Baseline clinical characteristics were compared between patients with no IAB and other groups (no IAB vs. pIAB, no IAB vs. aIAB, and no IAB vs. IAB). The *t* test was used to analyze differences among normally distributed samples, the Mann-Whitney U test to analyze differences among not normally distributed samples, and the Pearson χ^2 test to compare categorical variables.

Separate Kaplan-Meier plots with log-rank tests were used to compare 5-year survival with regard to the study endpoints between the groups depending on the presence of IAB and its types and normal versus abnormal PTFV₁. Multivariable Cox regression analyses adjusted for age, NYHA class, ischemic HF etiology, left

ventricular ejection fraction (LVEF), LBBB, and CRT-P versus CRT-D were performed to assess the impact of IAB and abnormal PTFV₁ on the risk of primary and secondary endpoints at 5 years after CRT implantation. SPSS Statistics for Macintosh, version 25.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

Study Population

In total, 210 patients were included in the study, and the baseline characteristics of all patients are illustrated in Table 1. The median age was 67 years, 80% were male, 70% had New York Heart Association (NYHA) Class III or IV, 55% had ischemic etiology of HF, 51% received a CRT-P device, and 80% had LBBB. Patients with IAB were less likely to have LBBB and more often had abnormal PTFV₁, but no other clinically relevant significant differences regarding baseline characteristics were seen when comparing patients with or without IAB. The median time from CRT implantation to the reviewed ECG was 14 days, and the median number of available preprocedural ECGs were 20 per patient, and the median time from the first available ECG to CRT implant was 10.7 years with no significant differences observed between groups. The shortest follow-up time was 4.7 years, and the median follow-up time was 8.4 years with no statistically significant differences observed between the IAB groups.

Clinical Outcome

In 5 years from CRT implantation, 72 patients (34%) died, 47 patients (22%) had new-onset AF, and 3 patients (1%) underwent HTx. Of the 47 patients with new-onset AF, 16 patients died, and 0 patients were HTx after the AF episode was observed. One patient had new-onset AF after HTx but no patient died after HTx. The outcomes of all patients are found in Table 2.

Fig. 3. Kaplan-Meier plot comparing patients with no IAB to patients with IAB. Endpoint: new-onset AF, death, or heart transplant. log-rank $p = 0.004$.

Fig. 4. Kaplan-Meier plot comparing patients with no IAB, to patients with either pIAB or aIAB. Endpoint: new-onset AF, death, or heart transplant. log-rank $p = 0.013$.

Interatrial Block

In the survival analysis, IAB was associated with a higher risk of the primary endpoint, but patients with aIAB did not have an inferior prognosis compared to patients with pIAB (Fig. 3, 4). IAB was also associated with a higher risk of death from any cause or HTx but aIAB patients did not have an inferior prognosis compared to pIAB patients (see online suppl. Fig. 2 and 3).

In adjusted analysis, IAB was significantly associated with the risk of the primary as well as the secondary endpoint (Table 3). Both pIAB and aIAB were associated with the primary and the secondary endpoints in the univariable and adjusted analyses when compared with the no IAB group (Table 3). No significant outcome differences were observed when comparing patients with pIAB and aIAB (Table 3).

Abnormal PTFV₁

Abnormal PTFV₁ was not associated with any of the endpoints (Fig. 5; Table 3; online suppl. Fig. 4). A forest plot of the adjusted multivariate analysis to the primary and secondary endpoint is presented in Figure 6.

Discussion

In patients with HF and CRT, IAB and abnormal PTFV₁ are common findings. IAB but not abnormal PTFV₁ was associated with the risk of new-onset AF and total mortality independently from other clinical risk factors in our real-life cohort of CRT recipients with severe HF disease. Pa-

Fig. 5. Kaplan-Meier plot comparing patients with normal PTFV₁ to patients with abnormal PTFV₁. Endpoint: new-onset AF, death, or heart transplant. log-rank $p = 0.869$.

tients with aIAB do not seem to have a worse prognosis than patients with pIAB, and the previously recognized dose-response IAB severity appears to have limited applicable value in patients with advanced severe HF, such as those included in our analysis. We were not able to reproduce previous findings of the association between abnormal PTFV₁ and worse outcome. Our results imply that a finding of abnormal PTFV₁ may have limited prognostic usefulness in CRT recipients with severe HF.

Fig. 6. Forest plot of the adjusted multivariate analysis found in Table 3.

Table 3. Multivariable Cox regression analyses.

Parameter	Endpoint death/HTx/AF			Endpoint death/HTx		
	adjusted HR ^a	95% CI	p value	adjusted HR ^a	95% CI	p value
IAB vs. no IAB (<i>n</i> = 182)	1.88	1.22–2.89	0.004	2.05	1.23–3.41	0.006
pIAB vs. no IAB (<i>n</i> = 163)	1.86	1.16–2.97	0.010	1.88	1.08–3.27	0.026
aIAB vs. no IAB (<i>n</i> = 122)	2.39	1.16–4.92	0.018	2.44	1.08–5.52	0.032
aIAB vs. pIAB (<i>n</i> = 79)	0.91	0.43–1.94	0.804	1.07	0.45–2.52	0.878
Abnormal PTFV ₁ vs. normal PTFV ₁ (<i>n</i> = 182)	1.09	0.69–1.73	0.707	1.16	0.67–1.99	0.598

Time from CRT implantation. Follow-up is 5 years. The reference variables are no IAB and normal PTFV₁. ^a Adjusted for age, NYHA Class, ischemic etiology of HF, LBBB, LVEF, CRT-P vs. CRT-D.

Study Population and Data Availability

We aimed to study the association between ECG markers of abnormal atrial function with new-onset AF, which requires a reliable identification of patients with preprocedural AF history. Given the paroxysmal nature of the arrhythmia and commonly observed non-specific symptoms, there is always a risk that patients with preexisting AF may have been included as AF-naïve. However, we aimed to overcome this by combining screening of multiple preprocedural ECGs along with a meticulous review of medical records cross-linked with the SNPR and therefore believe that our study group represents a reasonable approximation of an AF-free cohort of patients with HF.

In this study, we decided not to include data regarding device-detected episodes of AF as atrial high rate episodes by being surrogate markers of AF may not represent true AF episodes [21–23]. Due to the well-acknowledged uncertainties regarding the clinical meaning of short episodes of device-detected AF [24–27], we believe that new-onset AF based only on a ECG-documented clinical AF diagnosis makes the study more robust. Furthermore, as all our patients had regular follow-up through device clinics, patients would receive AF diagnosis code whenever clinical diagnosis of AF was made. Moreover, the

SNPR has been found to be a reliable source of information regarding AF and was validated previously [28, 29], and as a manual review of all available postoperative ECGs added another source of AF, we believe that underdiagnosis of AF was unlikely.

As all included patients received their device according to the guidelines at hand, the population should represent a CRT cohort with advanced HF, and clinicians ought to be able to apply the study's results to most CRT recipients. Thus, we believe that the findings of the study are clinically applicable.

The Prevalence of IAB in Different Populations

Previous studies reported that the prevalence of IAB is higher among older patients with advanced comorbidities and that it is associated with a more severe underlying heart disease. In hospitalized patients, IAB is common, and several studies have reported an IAB prevalence of over 40% [30, 31]. Among healthy young men, however, IAB was present in only 9% of those younger than 35 years and in 5% of those under 20 years [32]. In patients over 100 years though, IAB was found in 46% of subjects. aIAB is far less common than pIAB [13, 33], and the prevalence of aIAB varies greatly depending on the clinical

context. It has been reported in around 1% of patients with mitral valve disease [34], in 14% of patients undergoing coronary bypass graft surgery [35], in 17% of patients admitted with HF [36], and in 17% of ischemic stroke survivors [37].

Prolonged PWD (pIAB) as well as morphological abnormalities in inferior ECG leads (aIAB) are associated with structural abnormalities of the atrial wall such as fibrosis due to ageing and cardiovascular comorbidities [38–40]. One would therefore expect a high prevalence of IAB in CRT recipients. In our study, the prevalence of aIAB (11%) differed greatly from the findings of Sadiq et al. [6], who reported aIAB prevalence among CRT recipients of as high as 38%. The reasons for this discrepancy are unclear given the fact that Sadiq et al. [6] used a “narrower” definition of aIAB (biphasic morphology of the P wave in all inferior ECG leads assessed using manual ECG review), while the patient characteristics of their study otherwise were similar to ours.

The methodology of P-wave processing may have contributed to the observed differences in findings. While manual and automatic approaches have their strengths and weaknesses, we have chosen fully automatic P-wave processing in order to eliminate the risk of subjectivity in assessment of PWD and, perhaps more importantly, its morphology and identification of terminal-negative component in the inferior leads and lead V1. As we have shown previously [41], the use of signal amplification may consistently result in longer PWD values, thus contributing to a greater prevalence of IAB in some studies that used manual measurements [6, 36] but not fully explaining the greater prevalence of biphasic P-wave morphology in inferior leads required for aIAB definition. By adhering to the commercially available automatic ECG processing software, we also aimed to obtain results that can be reproduced by others and applied on a large scale [4].

To summarize, the prevalence of IAB varies significantly in different populations. But, as definitions and assessments of aIAB (e.g., manual reviews of ECG vs. digital analyses) have varied between studies, comparisons and conclusions are difficult to make.

The Prognostic Value of IAB

CRT recipients represent a cohort with advanced structural heart disease and a high number of comorbidities [3]. Moreover, CRT is a therapy that potentially alters hemodynamics and induces reverse remodeling of the left ventricle with ensuing reduced left atrial pressure [42], so patients with CRT constitute a very special population. Thus, classical predictors of mortality and AF in

the general population may not have a similar prognostic value in a subset of patients with HF and CRT. We found that preprocedural IAB could add predictive value to other clinical parameters associated with CRT outcome. Derived from a 12-lead surface ECG, IAB is an easily available non-invasive method that could be helpful in the CRT risk stratification process. A finding of preprocedural IAB should not be ignored, and vigilant monitoring among these patients should be provided as our results indicate that these patients may have a higher risk of death or new-onset AF.

The association of IAB and AF is well known and has been observed in a number of different patient categories [4–7]. Concerning the prognostic influence of IAB in CRT recipients, however, few studies are available. Yet, associations between IAB and new-onset AF have been found before. In the MADIT-CRT cohort, IAB has been found to be predictive of AF [7, 12]. One should bear in mind though that the MADIT-CRT cohort is represented only by patients in NYHA Class I or II with far less comorbidities compared to our real-life CRT population [42]. Also, the study by Holmqvist et al. [12] used orthogonal ECGs, and the definition of IAB differed therefore from ours. Moreover, the association between IAB and AF has recently been evaluated in CRT recipients by Sadiq et al. [6], who found that aIAB was a predictor of new-onset device-detected AF. Yet, the incidence of new-onset AF was higher compared to our cohort as 30% of all patients had AF over a mean follow-up of 32 months. This may be due to the fact that their study included device-detected AF cases, but as it did not include any preprocedural review of ECGs, the number of new-onset AF cases may have been overestimated. However, Sadiq’s cohort constituted a real-life CRT population and was not very different from ours, and the relationship between IAB and new-onset AF seems to be true among CRT recipients as well.

To our knowledge, only one study has evaluated the impact of IAB on mortality in CRT recipients. The study by Holmqvist et al. [12] found that IAB on orthogonal ECGs was predictive of non-sudden cardiac death but not all-cause mortality in the MADIT-CRT cohort. In the general population, more studies are available. Magnani et al. [43] found that IAB was predictive of cardiovascular and all-cause mortality in a representative US sample of patients with mean age of 60 years, and in a recent large Danish study of around 150,000 primary care patients aged 50–90 years, aIAB was found to be predictive of all-cause mortality [4]. The vast number of patients included in the study allowed the authors to find a dose-response relationship between the number of inferior ECG leads with abnormal

morphology and the outcome. The prevalence of aIAB (defined as at least one inferior lead with biphasic morphology) was noted among 10% of patients; 7.8, 1.6, and 0.5% with 1, 2, and 3 inferior leads with biphasic morphologies, respectively. All 3 types of aIAB were predictive of AF, but only aIAB with all 3 inferior leads with biphasic morphology was found to be predictive of all-cause mortality. Also, the more inferior leads affected by abnormal P-wave morphologies, the higher were the hazard ratios for AF. In ischemic stroke survivors, aIAB have recently been found to be a predictor of all-cause mortality, but it was an independent predictor only among patients without advanced cardiovascular morbidities (no diabetes, vascular disease, hypertension, or cardiac failure), which supports our observation of diminished prognostic value of ECG markers in patients with advanced disease [37].

The results from the above-mentioned studies along with our findings suggests that IAB have a prognostic value in CRT recipients too, mainly with regard to a higher risk of AF-development. Considering mortality prediction, the value of IAB and especially aIAB seems to be higher among healthier subjects such as a cohort of primary care patients, in whom aIAB serves as an indicator of more severely affected patients with worse prognosis. In patients with an advanced cardiovascular disease though, other comorbidities probably play a more prominent role resulting in a clinical limited applicability of aIAB P-wave pattern. Yet, our study may have involved too few patients to clearly nuance the previously observed IAB severity differences.

The Prognostic Value of Abnormal PTFV₁

We were not able to reproduce previous findings regarding the correlation between abnormal PTFV₁ and worse outcomes [14–16]. In our study, PTFV₁ did not correlate with the endpoints in patients with LBBB either (see online suppl. Fig. 5, 6), as in Baturova's study of MA-DIT-CRT patients [17]. Baturova's cohort was very different from ours with younger patients in NYHA Class I or II, and the conflicting results may be explained by the obvious differences between the 2 populations. Alternatively, our study may have been underpowered to find any prognostic significance of abnormal PTFV₁. However, given the lack of survival difference between patients with and without abnormal PTFV₁, it is unlikely that the abnormal PTFV₁ bears clinically significant meaning with regard to prognosis for patients with severe HF treated with CRT, and from our findings it seems as if abnormal PTFV₁ has limited applicable value in this very sick population in line with previous studies that have shown limitations of abnormal PTFV₁ in different study popula-

tions [44, 45]. Our results need to be confirmed in future studies before any conclusions can be made.

Strengths and Limitations

Our study included patients with CRT and available preprocedural medical history. A long-term follow-up was available, and no patient was lost to follow-up during the 5-year follow-up period. All devices were implanted according to current ESC CRT guidelines at the time of CRT implantation, and thus our cohort represents a real-life CRT population. All patients had an available ECG within reasonable time from CRT implantation. We believe that a great majority of AF during follow-up represents new-onset AF partly because we used a number of different reliable sources to collect data regarding preprocedural AF history. During follow-up, we may have missed some cases of new-onset AF as no device-detected data regarding AF was included in the study. The study included a limited number of patients, and only a few more events, especially in the aIAB group, potentially could change the results significantly.

Conclusions

IAB is an independent predictor of new-onset AF and death in CRT recipients with severe HF. As a non-invasive, easily available method, IAB adds prognostic value and may be helpful in risk stratification in the context of HF management. Abnormal PTFV₁ did not demonstrate any prognostic value in patients with advanced HF disease.

Statement of Ethics

The study was approved by the local Ethics Committee.

Conflict of Interest Statement

R.B. received lecture fees from Medtronic and Abbot. The other authors declare that they have no conflicts of interest or financial ties to disclose.

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