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ORIGINAL ARTICLE

Inter-atrial block as a predictor of adverse outcomes in patients with HFpEF

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Abstract

Aims Inter-atrial block (IAB), a marker of electrical atrial dysfunction, is associated with an increased risk of atrial fibrillation (AF) and adverse events in various populations. The prognostic impact of IAB in heart failure (HF) with preserved ejection fraction (HFpEF) remains unknown. The aim of this study is to determine the prevalence of IAB and the association of IAB and AF with adverse events in HFpEF across different healthcare settings.

Methods and results To identify electrical atrial dysfunction, baseline ECG's and medical history were analysed in HFpEF patients in an ambulatory setting and after recent HF hospitalisation. Patients were categorised into (i) $HFpEF_{No\ IAB}$, (ii) $HFpEF_{IAB}$, or (iii) $HFpEF_{AF}$. Adverse events included HF hospitalisation, cardiac/sudden death and a composite of both. The ambulatory cohort included 372 patients [mean age 75 ± 7 years, 252 (68%) females]. The recently hospitalised cohort included 132 patients [mean age 81 ± 10 years, 80 (61%) females]. Ambulatory patients included 17 (4%) $HFpEF_{noIAB}$, 114 (31%) $HFpEF_{IAB}$ and 241 (65%) $HFpEF_{AF}$, while recently hospitalised patients included 31 (23%), 73 (55%) and 28 (21%), respectively. After 33 months of follow-up of ambulatory patients, composite endpoints occurred in 0 (0%) $HFpEF_{noIAB}$, 12 (11%) $HFpEF_{IAB}$ [HR 4.1 (95% CI 0.5–522.6)] and 59 (24%) $HFpEF_{AF}$ patients [HR 10.1 (95% CI 1.5–1270.4), $P < 0.001$]. Recently hospitalised patients showed a similar trend, with composite endpoints in 10 (32%) $HFpEF_{noIAB}$, 31 (42%) $HFpEF_{IAB}$ (HR 1.5 [95% CI 0.7–3.1]) and 22 (79%) $HFpEF_{AF}$ (HR 3.8 [95% CI 1.8–8.1], $P < 0.001$).

Conclusions Progressive stages of electrical atrial dysfunction appeared to be prognostic markers of adverse outcomes in ambulatory and recently hospitalised patients with HFpEF. Ambulatory patients with HFpEF and no early stages of electrical atrial dysfunction showed to be at very low risk for adverse outcomes. Whether such patients benefit less strict management remains to be investigated.

Keywords Atrial dysfunction; Atrial fibrillation; Electrocardiography; Heart atria; Heart failure with preserved ejection fraction; Prognosis

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Introduction

Half of all heart failure (HF) patients suffer from HF with preserved ejection fraction (HFpEF).[1] HFpEF is associated with a high comorbidity burden and decreased quality of life.[2] Despite recent treatment advances, the prognosis for HFpEF patients remains poor.[3,4]

Atrial fibrillation (AF) commonly co-exists with HFpEF and may even share part of the underlying pathophysiological mechanisms. Left atrial (LA) dilation and dysfunction are well-established factors present in both AF and HFpEF, which negatively affect disease progression in both conditions.[5–9]

Interatrial block (IAB), characterised by a prolonged P-wave on a 12-lead electrocardiogram (ECG), is a marker of

electrical atrial dysfunction and is associated with LA structural and functional remodelling.[10–12] IAB is relatively common in the general population and among patients with cardiovascular disease, with prevalence estimates ranging from 10% to 60%, increasing drastically with age.[11,13–15] IAB is linked to an increased risk of AF or stroke in the general population and in patients with HF with reduced ejection fraction (HFrEF).[11,16,17] In patients with HFpEF, a prolonged P-wave duration has been proposed as a predictor of new-onset AF.[18] However, additional prognostic effects of IAB in HFpEF remain largely unknown.

Improved risk prediction can help to identify patients with high or very low risk for adverse events and may be used to guide follow-up and implement more optimised management strategies. The primary aim of this study is to evaluate the prevalence of IAB and the prognostic association of electrical atrial dysfunction severity (no IAB, IAB and AF) in patients with HFpEF in different healthcare settings (stable ambulatory and recently hospitalised).

Methods

Study population

The study consisted of two separate HFpEF cohorts.

Ambulatory cohort (Maastricht, Netherlands)

The ambulatory cohort of this study consisted of HFpEF patients prospectively enrolled in the Maastricht HFpEF cohort between January 2015 and June 2021.[19] Detailed information regarding the diagnostic process for HFpEF in this cohort has been reported previously.[20] In short, patients underwent a diagnostic work-up including consultation with a HF-cardiologist, echocardiography and blood tests. Each patient case was discussed within the institutional HF team. HFpEF was diagnosed based on expert consensus of at least two HF-cardiologists according to the ESC 2016 guidelines for HF.[21] Exclusion criteria for this study were (1) HF was ruled out during diagnostic work-up; (2) cardiac valvular interventions prior to or within 1 year after the baseline assessment or valvular heart disease requiring interventions; (3) lack of retrievable 12-lead ECG recordings at baseline; (4) ECG of insufficient quality to assess rhythm or perform ECG analysis as described below; and (5) presence of a paced rhythm on the 12-lead ECG at baseline.

Recently HF hospitalised cohort (Badalona, Spain)

The recently HF hospitalised cohort served as a validation cohort, to validate our findings from the ambulatory cohort. This cohort derives from the STOP-HF clinic (Structured multidisciplinary outpatient clinic for Old and frail Post-discharge patients hospitalised for HF) at the Germans Trias i Pujol hospital in Badalona, Spain. This outpatient clinic was created in 2014 to reduce early readmission rates and facilitate the transition to primary care among vulnerable patients with HF. Patients are seen within 1 week after hospitalisation for decompensated HFpEF and are followed with a structured and multidisciplinary approach. The first outpatient visit following a HF hospitalisation was defined as baseline visit. Detailed information regarding the multifactorial intervention has been reported previously.[22] The same exclusion criteria as the ambulatory cohort were applied to this cohort. Patients with an AF history or AF on the baseline ECG were only included if follow-up data was already collected during a predefined one-year assessment for study feasibility reasons, in which follow-up was updated until the last outpatient visit. Clinical and echocardiographic data were obtained during the first outpatient visit after HF hospitalisation.

Both cohort studies comply with the Declaration of Helsinki, were approved by the local ethics committee (Medical Ethics Committee University Hospital Maastricht/Maastricht University METC 21-017, Research Ethics Committee Germans Trias I Pujol University Hospital PI-18-037) and obtained written informed consent from all participants.

Electrical atrial dysfunction assessment

All 12-lead ECG recordings (speed 25 mm/s, 10 s recording) clinically obtained during baseline visit were exported as PDF files from clinical electronic ECG reading systems. Baseline visit was defined as the first ever visit at the HFpEF outpatient clinic for the ambulatory cohort (Maastricht), and the first outpatient clinic visit after HF hospitalisation for the recently hospitalised cohort (Barcelona). AF was diagnosed based on ECG by an analysing physician (J.W., S.M. or H.L.M.), or based on the medical history. When categorising patients into no IAB, IAB and AF, all patients with a medical history of AF (paroxysmal, persistent of permanent) were categorised as 'AF' irrespective of the baseline ECG rhythm. Subsequently, sinus rhythm ECGs from all patients without AF in the medical history were assessed for IAB presence using AutoCAD software, blinded to clinical data. P-wave onset and end were delimitated with vertical ledger lines across all ECG leads to most accurately determine the overall P-wave duration. Partial IAB was defined as P-wave duration $\geq$ 120 ms, and advanced IAB as P-wave duration $\geq$ 120 ms along with biphasic P-wave morphology in at least two inferior leads (III and aVF) (*Figure* S1)[23] The three analysing physicians underwent training for P-wave duration and morphology assessments to harmonise the measurements. The final training set included 11 randomly selected sinus rhythm ECGs to assess interobserver variability of P-wave duration results. In case of uncertainty about the rhythm or final diagnosis (IAB or no IAB), the ECG was reassessed by at least one of the other physicians to reach consensus.

Outcome measures and follow-up

The primary endpoints of the study included all-cause mortality, cardiac or sudden death, HF hospitalisation, or a composite of HF hospitalisation (HFH) and cardiac/sudden death. Sudden death was defined as a non-traumatic, unexpected fatal event occurring within 1 h of the onset of symptoms (or within 24 h if not witnessed). Details of endpoints during follow-up were mainly collected from the hospital electronic health records (EHR), with general practitioner contact in case the cause of death was unclear. The follow-up time was defined as the number of days between the baseline visit at the HFpEF outpatient clinic of both cohorts and the occurrence of a primary endpoint event. If no study endpoint occurred, patients were censored on 1 October 2022 (ambulatory cohort) and 1 May 2023 (recently hospitalised cohort).

Statistical analysis

Descriptive data were reported as mean ± SD, median (interquartile range), or counts (percentages), as appropriate. Baseline differences between groups (no IAB, IAB and AF) for continuous variables were assessed by one-way ANOVA or Kruskal–Wallis test depending on the distribution of data tested by the D'Agostino skewness test.[24] The chi-square test or Fisher–Freeman–Halton exact test were employed for categorical variables, respectively. Baseline analyses comparing two groups for continuous variables were performed by independent *t*-test or Mann–Whitney *U* test and for categorical variables by chi-square or Fisher's exact. The same principles were applied to evaluate baseline differences in the recently hospitalised cohort. Survival analyses for clinical outcome differences between groups were visualised using Kaplan–Meier curves and tested by Cox regression with Firth's penalised maximum likelihood bias reduction (FLR) due to zero events in the no IAB group.[25] Regular Cox regression analysis was done in the recently hospitalised cohort between no IAB and IAB. Given the small group of no IAB and the absence of relevant clinical differences at baseline, multivariable Cox regression analyses were only performed with interaction for sex in both cohorts to explore sex-dependency of the combined outcome. Inter-observer variability of P-wave duration assessment (J.W., S.M. and H.L.M) was evaluated (n = 11) by intraclass correlation coefficient (ICC) estimates using a single-rating, absolute-agreement, two-way mixed-effects model. In addition, P-wave measurement bias between observers was evaluated by Bland–Altman analyses and corresponding plots.[26] The ICC estimate was excellent [0.92 (95% CI 0.82–0.97)], and the mean bias between observers was low (0.9–4.1 ms) (*Figure* S2). A two-sided *P*-value of <0.05 was considered significant. All analyses were performed with R version 4.1.2 (R Foundation for Statistical Computing).

Results

Clinical characteristics in the ambulatory cohort

In total, 372 ambulatory patients were included in this study (*Figure 1*). The median age was 75 years and approximately two-thirds was female (*Table 1*). A high prevalence of comorbidities such as AF, hypertension and renal dysfunction was observed among these patients with HFpEF.

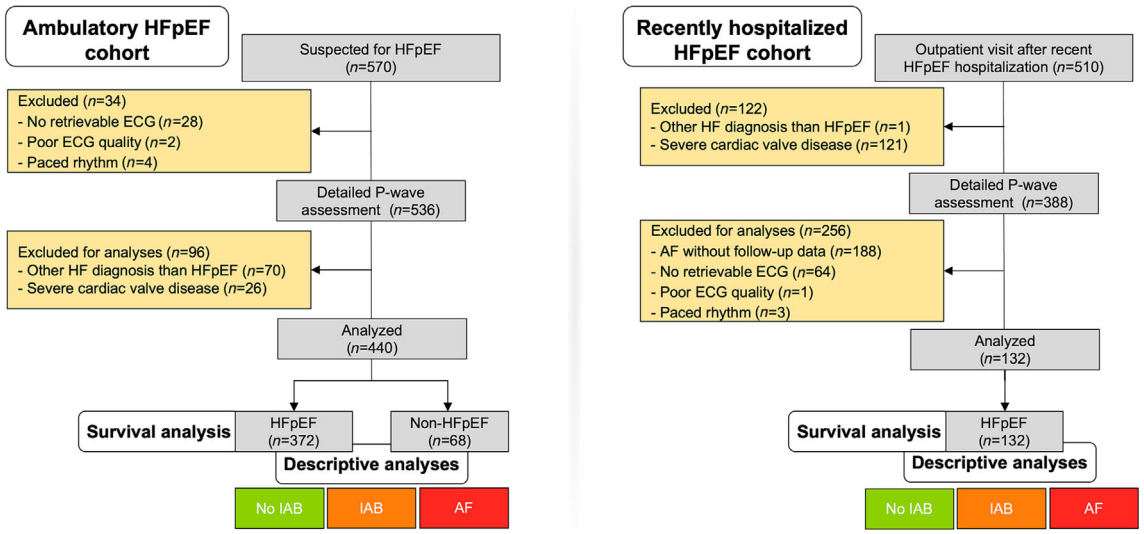
Prevalence of electrical atrial dysfunction in the ambulatory cohort

Electrical atrial dysfunction emerged as a prominent feature in the ambulatory cohort with 241 (64.8%) cases of AF, 114 (30.6%) cases of IAB, and only 17 (4.6%) without IAB. The prevalence of comorbidities was comparable among these three groups (*Table 1*). The IAB group consisted of 76 patients (67%) with partial IAB and 38 (33%) with advanced IAB. Notably, none of the patients without IAB had experienced any prior HFH at baseline. HFpEF patients with IAB appeared to have more left ventricular (LV) hypertrophy compared to those without IAB, while patients with AF had higher New York Heart Association (NYHA) class, N-terminal pro B-type natriuretic peptide (NT-proBNP) values, LA volumes, and estimated right ventricular pressures, along with lower LV and LA strain values.

Outcome of no IAB, IAB and AF in the ambulatory cohort

During the median follow-up of 33 (18–49) months, 71 patients (19%) reached the composite endpoint of HFH or cardiac mortality. Remarkably, the no IAB group exhibited zero events during the observation period. The IAB group and AF group exhibited 12 (11%) and 59 (24%) events respectively. The survival analysis indicated distinct survival trends across the three patient groups. Specifically, a gradient of declining survival was observed from the no IAB group to the IAB group, with the poorest survival outcomes recorded in the AF group [hazard ratio IAB 4.1 (95% CI 0.5–522.6) and AF 10.1 (95% CI 1.5–1270.4), $P < 0.001$] (*Figure 2*). No clear effect of sex was observed for these results ($P_{\text{interaction}} \geq 0.619$). For HFH this trend was seen after approximately 1 year of follow-up, whereas for cardiac mortality the survival difference became evident after 2 to 3 years. Differences in all-cause mortality between patient groups were less apparent (P = 0.273, *Figure* S3), although no events were observed before 3 years follow-up in patients without IAB. Excluding patients with a previous HF hospitalisation up until 6 months prior to baseline (n = 5 with IAB, n = 16 with AF) showed similar results (*Figure* S4). Among the patients without prior

Figure 1 Study flow diagram. Study flow for the ambulatory cohort and the recently hospitalised cohort. AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; IAB, inter-atrial block.



history of stroke, nine patients experienced incident stroke during follow up. One patient was in the no IAB group (8%), two in the IAB group (2%), and six were in the AF group (3%) (P = 0.414).

Findings in recently hospitalised patients

In our recently hospitalised cohort, 132 patients were included. Clinical characteristics during the first outpatient visit are summarised in *Table 2*. This cohort had a median age of 84 years, which is 9 years older than the ambulatory cohort. The sex distribution was comparable between the ambulatory and recently hospitalised cohorts. This cohort included 28 patients (21%) with AF, which were selected based on available follow-up data and do not allow for relative prevalence comparisons with IAB status. In patients in SR, electrical atrial dysfunction was also highly prevalent in the recently hospitalised cohort entailing 73 patients (70%) with IAB and 31 patients (30%) without IAB. The IAB group consisted of 40 patients (55%) with partial IAB and 33 (45%) with advanced IAB. Compared with patients without IAB, patients with IAB had more often NYHA class ≥3, and patients with AF had more often NYHA class ≥3, signs of congestion and higher NT-proBNP values.

During the median follow-up of 15[6–34] months, 62 patients (47%) reached the composite endpoint of HFH or cardiac death. The survival analysis revealed a consistent trend of increasing event rates from patients without IAB, to those with IAB, and peaking in patients with AF [hazard ratio IAB 1.5 (95% CI 0.7–3.1) and AF 3.8 (95% CI 1.8–8.1), $P < 0.001$] (*Figure 2*). This result was not sex-dependent ($P_{interaction} \geq 0.364$). All-cause mortality was similar among patients regardless of the presence of IAB or AF (*Figure* S3).

Discussion

The present study reveals a high prevalence of electrical atrial dysfunction in patients diagnosed with HFpEF. In ambulatory patients with HFpEF, a gradual risk emerged for HFH or cardiac mortality, from patients without IAB, to patients with IAB, and peaking among patients with AF. This gradual prognostic effect was comparable but less pronounced in patients with HFpEF after recent HFH (Graphical abstract), as the latter group had higher event rates in all patient categories.

Previous findings of prognostic effect of IAB

The prognostic implications of electrical atrial dysfunction have been investigated in diverse patient populations, using varying P-wave indices and yielding inconsistent results. A prospective observational registry focusing on elderly patients with structural heart disease did not find a significant association between IAB and mortality. However, P-wave duration was associated with all-cause mortality (HR 1.04 per millisecond of P-wave duration).[27] In a general study population of over 6000 individuals, IAB was not associated with all-cause mortality.[11] Nevertheless, P-wave duration emerged as a potential mortality predictor in this demographic as well.[28] In line herewith, the association between IAB and all-cause mortality in our ambulatory and recently hospitalised cohort was confined. Additionally, a previous retrospective study in more than 1 million individuals without

Table 1 Baseline characteristics of HFpEF patients according to electrical atrial dysfunction group in ambulatory cohort

	Total (n = 372)	No IAB (n = 17)	IAB (n = 114)	AF (n = 241)	P-value$_{trend}$	P-value$_{no\ IAB}$ vs. P_{IAB}	P-value$_{IAB}$ vs. P_{AF}
Age, years	75 ± 7	70 (67, 81)	76 (70, 81)	76 (72, 80)	0.141	0.239	0.309
Female sex	252 (68)	14 (82)	93 (82)	145 (60)	<0.001	1	<0.001
Caucasian	371 (100%)	17 (100%)	114 (100%)	240 (100%)	1.000	1.000	1.000
Medical history							
Atrial fibrillation	237 (64)	0 (0)	0 (0)	237 (98)	<0.001	1	<0.001
Atrial fibrillation ablation	56 (15)	0 (0)	0 (0)	56 (23)	<0.001	1	0.014
CHA_2DS_2-VASc score	5 (4, 5.25)	5 (4, 5)	5 (4, 6)	5 (4, 5)	0.851	0.674	0.617
Significant CAD	59 (16)	2 (12)	20 (18)	37 (15)	0.818	0.736	0.711
Stroke	67 (18)	5 (29)	19 (17)	43 (18)	0.421	0.309	0.889
COPD	67 (18)	6 (35)	18 (16)	43 (18)	0.169	0.086	0.743
Sleep apnoea	74 (20)	4 (24)	22 (19)	48 (20)	0.896	0.745	0.976
Diabetes mellitus	104 (28)	2 (12)	32 (28)	70 (29)	0.332	0.236	0.949
Chronic kidney disease	110 (30)	6 (35)	28 (25)	76 (32)	0.352	0.379	0.221
Hypertension	313 (84)	16 (94)	99 (87)	198 (82)	0.338	0.693	0.337
Hypercholesterolemia	175 (47)	10 (59)	56 (49)	109 (45)	0.481	0.627	0.567
Prior HF hospitalisation	61 (16)	0 (0)	13 (11)	48 (20)	0.018	0.216	0.067
Clinical presentation							
NYHA class ≥3	128 (35)	4 (24)	31 (27)	93 (39)	0.055	1	0.039
Body mass index, kg/m^2	29.4 (26.0, 33.2)	28.9 (25.1, 31.2)	29.0 (26.3, 32.8)	29.8 (25.9, 33.7)	0.781	0.895	0.566
Signs of congestion	127 (39)	3 (18)	33 (33)	91 (43)	0.046	0.325	0.122
Medication							
Beta-blocker	225 (65)	14 (82)	63 (60)	148 (65)	0.183	0.133	0.399
Calcium channel blocker	154 (44)	7 (41)	52 (50)	95 (42)	0.428	0.706	0.247
ACEi/ARB	240 (69)	13 (76)	68 (65)	159 (70)	0.468	0.502	0.372
MRA	63 (18)	1 (6)	12 (11)	50 (22)	0.021	0.691	0.028
SGLT2i	0 (0)	0 (0)	0 (0)	0 (0)	1	1	1
Anticoagulants	222 (65)	0 (0)	10 (9)	212 (95)	<0.001	0.604	<0.001
Digoxin/amiodarone	57 (17)	0 (0)	0 (0)	57 (25)	<0.001	1	<0.001
Laboratory							
NT-proBNP, pg/mL	580 (271, 1376)	295 (215, 560)	272 (169, 499)	956 (449, 1632)	<0.001	0.704	<0.001
eGFR (CKD-EPI), mL/min/1.73 m^2	55 ± 18	61 (50, 69)	61 (45, 73)	53 (40, 69)	0.299	0.883	0.167
Echocardiography							
LV ejection fraction, %	60 ± 5	60 (58, 64)	61 (57, 64)	60 (57, 64)	0.489	0.849	0.237
LV mass index, g/m^2	78 ± 20	67 (59, 89)	79 (67, 89)	78 (63, 95)	0.274	0.092	0.792
Relative wall thickness	0.38 (0.35, 0.42)	0.35 (0.32, 0.39)	0.37 (0.35, 0.42)	0.38 (0.35, 0.43)	0.068	0.038	0.46
LA volume index, mL/m^2	45 (38, 58)	42 (35, 53)	37 (33, 44)	51 (42, 65)	<0.001	0.192	<0.001
Estimated RV pressure, mmHg	32 (26, 41)	28 (24, 30)	29 (24, 37)	34 (28, 44)	<0.001	0.517	<0.001
E/e' average	11.0 (8.7, 14.0)	11.8 (8.4, 14.8)	10.9 (8.8, 13.8)	11.0 (8.7, 13.8)	0.952	0.824	0.924
LV GLS, %	−17.6 (−20.7, −12.5)	−20.5 (−22.6, −17.5)	−19.6 (−21.9, −15.8)	−15.5 (−19.1, −9.8)	<0.001	0.55	<0.001
LA reservoir strain, %	24 ± 12	38 (28, 45)	31 (25, 39)	16 (11, 25)	<0.001	0.122	<0.001
RV FWS, %	−21.3 ± 7.2	−22.9 ± 8.3	−21.8 ± 7.9	−20.7 ± 6.6	0.587	0.71	0.469
Electrocardiography							
P-wave duration, ms	136 (124, 152)	112 (104, 116)	140 (128, 148)	-	-	<0.001	-
QRS-interval duration, ms	112 (104, 120)	108 (100, 112)	112 (104, 118)	112 (104, 124)	0.093	0.036	0.539
QTc-interval duration, ms	449 ± 27	444 (432, 453)	444 (427, 459)	456 (436, 477)	0.02	0.322	0.015
Heart rate, b.p.m.	65 ± 18	73 (68, 77)	66 (60, 78)	63 (55, 69)	<0.001	0.201	0.001

Note: Data presented as count (percentage), median (IQR), or mean ± standard deviation, as appropriate.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR (CKD-EPI), estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration equation; FWS, free wall strain; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; QTc, QT-interval corrected with the Bazett formula; RV, right ventricle; SGLT2i, sodium-glucose co-transporter-2 inhibitors.

Figure 2 Survival curves of ambulatory and recently hospitalised patients with HFpEF. For the ambulatory cohort, panel (A) displays the composite endpoint of cardiac/sudden death or heart failure hospitalisation (HFH) for each stage of electrical atrial dysfunction (no IAB, IAB and AF), panel (B) displays cardiac/sudden death, and panel (C) displays HFH. For the recently hospitalised cohort these survival curves are shown in panels (D), (E) and (F) respectively. Follow up for recently hospitalised patients with AF was recorded up till 1 year after initial outpatient visit. AF, atrial fibrillation; FLR, Firth's penalised maximum likelihood bias reduction; IAB; inter-atrial block.

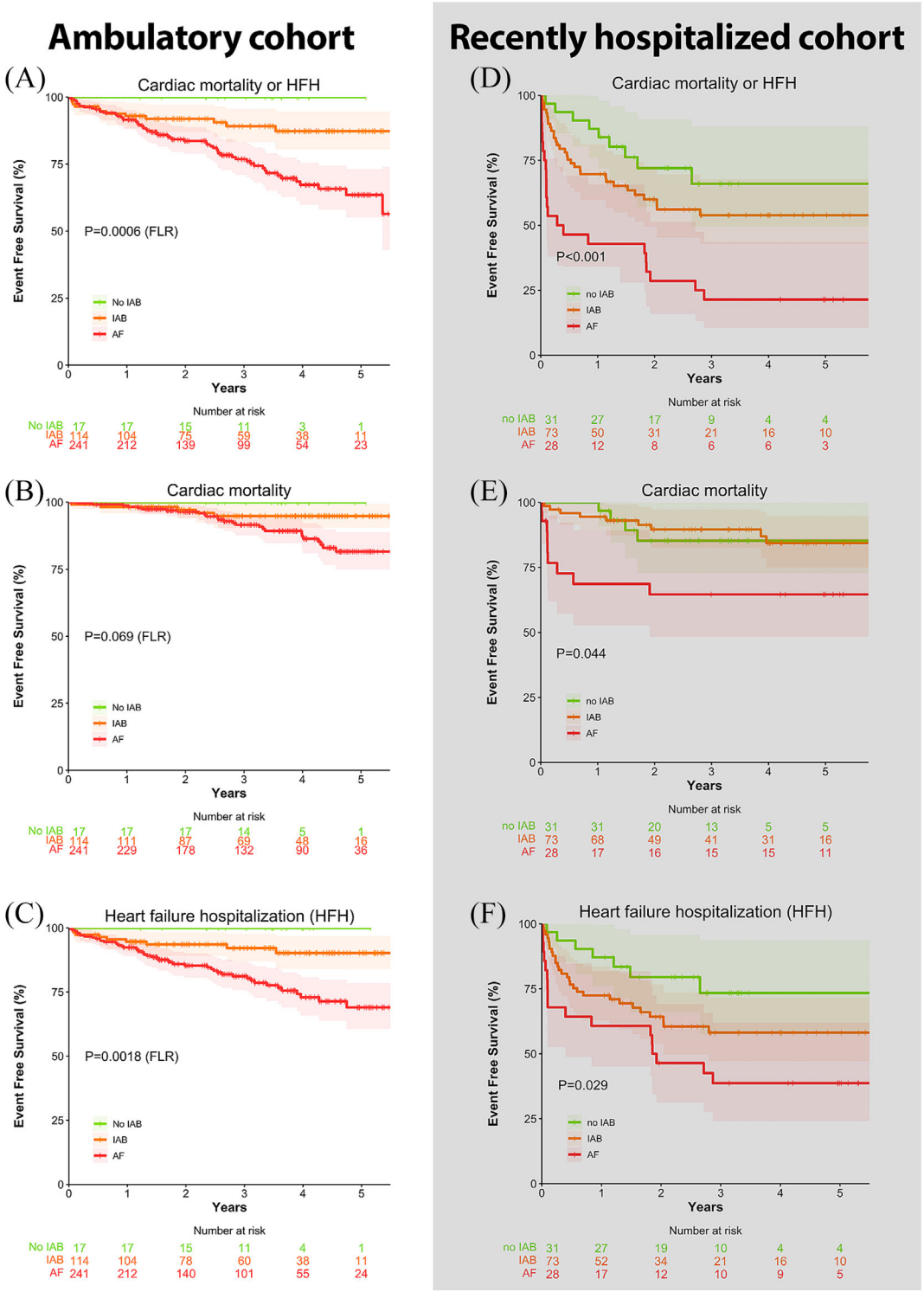


Table 2 Baseline characteristics of recently hospitalised HFpEF cohort according to electrical atrial dysfunction group

	HFpEF						
	Total (n = 132)	No IAB (n = 31)	IAB (n = 73)	AF (n = 28)	P-value$_{trend}$	P-value$_{no\ IAB\ vs.\ IAB}$	P-value$_{IAB\ vs.\ AF}$
Age, years	83 (75, 88)	82 (74, 86)	83 (74, 88)	86 (78, 89)	0.236	0.314	0.339
Female sex	80 (61)	20 (65)	43 (59)	17 (61)	0.866	0.752	1
Caucasian	131 (99%)	31 (100%)	73 (100%)	27 (96%)	0.218	1	0.277
Medical history							
Atrial fibrillation	28 (21)	0 (0)	0 (0)	28 (100)	<0.001	1	<0.001
CHA_2DS_2-VASc score	5 (5, 6)	5 (5, 6)	5 (5, 6)	5 (4.75, 6)	0.921	0.728	0.773
Significant CAD	41 (31)	9 (29)	25 (34)	7 (25)	0.642	0.772	0.512
Stroke	15 (11)	2 (6)	13 (18)	0 (0)	0.018	0.221	0.017
COPD	34 (26)	6 (19)	19 (26)	9 (32)	0.531	0.633	0.714
Sleep apnoea	18 (14)	1 (3)	13 (18)	4 (14)	0.145	0.060	0.774
Diabetes mellitus	63 (48)	14 (45)	34 (47)	15 (54)	0.777	0.487	0.697
Chronic kidney disease	56 (42)	10 (32)	31 (42)	15 (54)	0.255	0.450	0.435
Hypertension	120 (91)	30 (97)	65 (89)	25 (89)	0.445	0.274	1
Hypercholesterolemia	86 (65)	25 (81)	45 (62)	16 (57)	0.107	0.097	0.852
Prior HF hospitalisation	100 (100)	100 (100)	100 (100)	100 (100)	1	1	1
Clinical presentation							
NYHA class ≥3	80 (62)	9 (30)	50 (69)	21 (75)	<0.001	<0.001	0.761
Body mass index, kg/m^2	29.1 (25.3, 33.8)	27.7 (24.0, 32.0)	30.3 (26.4, 35.4)	28.8 (24.8, 32.4)	0.260	0.108	0.463
Signs of congestion	53 (40)	9 (29)	27 (37)	17 (61)	0.033	0.579	0.054
Medication							
Beta-blocker	59 (45)	13 (42)	31 (42)	15 (54)	0.567	1	0.435
Calcium channel blocker	47 (36)	12 (39)	29 (40)	6 (21)	0.210	1	0.135
ACEi/ARB	78 (59)	21 (68)	37 (51)	20 (71)	0.088	0.166	0.097
MRA	13 (10)	2 (6)	7 (10)	4 (14)	0.555	0.721	0.492
SGLT2i	0 (0)	0 (0)	0 (0)	0 (0)	1	1	1
Anticoagulants	35 (27)	2 (6)	7 (10)	26 (93)	<0.001	0.721	<0.001
Digoxin/amiodarone	8 (6)	2 (6)[a]	0 (0)	6 (21)	<0.001	0.087	<0.001
Laboratory							
NT-proBNP, pg/mL	1667 (524, 3965)	1764 (579, 5576)	765 (421, 2549)	3630 (2346, 7944)	<0.001	0.122	<0.001
eGFR (CKD-EPI), mL/min/1.73 m^2	47 (31, 67)	47 (31, 70)	47 (34, 72)	38 (28, 57)	0.199	0.949	0.076
Echocardiography							
LV ejection fraction, %	62 ± 8	62 ± 8	63 ± 8	59 ± 9	0.189	0.220	0.087
Estimated RV pressure, mmHg	47 (38, 56)	50 (38, 60)	49 (38, 56)	46 (36, 54)	0.620	0.795	0.420
LA volume index, mL/m^2	45 ± 8	44 ± 6	44 ± 8	47 ± 8	0.122	0.740	0.054
Electrocardiography							
P-wave duration, ms	129 (118, 140)	114 (110, 116)	134 (128, 145)	-	<0.001	<0.001	-
Heart rate, b.p.m.	70 (65, 80)	74 (65, 85)	69 (65, 76)	78 (67, 80)	0.163	0.220	0.075

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LV, left ventricle; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; RV, right ventricle; SGLT2i, sodium-glucose co-transporter-2 inhibitors.

[a]One patient without IAB but with antiarrhythmic drugs may have had atrial fibrillation, although no medical record or ECG findings indicated atrial fibrillation. However, the survival analyses after excluding this patient remained the same (log-rank P-value <0.001).

previous history of AF or atrial flutter has shown that IAB is associated with stroke, even after adjusting for incident AF and CHA2DS2-VASc score.[29] Due to the limited number of incident stroke events in our study population (n = 2 in the IAB group), this association could not be verified in our cohort.

IAB is a marker for advanced disease

The impact of IAB on HFH seems to be present in other HF phenotypes as well. Similar to our findings, a single-centre observational study conducted in an outpatient cohort of 110 patients with HFrEF found an elevated HF hospitalisation rate in patients with IAB compared to without IAB (62% vs. 38%, P = 0.019) after 1 year of follow up.[30] Interestingly, both IAB and non-IAB groups in their study manifested significantly higher hospitalisation rates compared to our cohorts, likely attributable to a higher NYHA class and a higher HF hospitalisation risk in HFrEF versus HFpEF.[2]

IAB may be a marker of advanced stage of HF, regardless of phenotype, although different underlying mechanisms lead to different clinical manifestations of advanced disease. IAB has previously been identified as a predictor for severe arrhythmias in dilated cardiomyopathy patients.[31] Notably, previous research has shown a low incidence of ventricular tachyarrhythmias in HFpEF.[32] This distinction suggests that for patients with HFpEF, the manifestation of advanced disease is not primarily severe arrhythmias but rather HFH. Consequently, in our HFpEF cohort, IAB may stand out predominantly as a prognostic marker for HFH rather than cardiac mortality.

Potential mechanisms of IAB in HFpEF

Leading drivers for the high IAB prevalence are suggested to be advancing age, hypertension and coronary artery disease,[15] of which the first two factors were applicable in most patients with HFpEF in our study. Previous studies have shown a significant delay in LA conduction in the presence of IAB, subsequently impacting LA contraction and ejection fraction.[12,33] The structural and functional atrial abnormalities associated with IAB may serve as precursors to AF, and they may worsen prognosis even in the absence of AF, possibly through pro-thromboembolic effects.[34] The relevance of atrial function and failure has been extensively investigated, and both structural and functional atrial dysfunction are also thought to aggravate the HF syndrome.[35] A small cross-sectional echocardiographic study found poor LA contractility, lower LA stroke volume and LA ejection fraction in 24 ambulatory patients with various cardiac diagnoses and with IAB, compared with 16 controls without IAB.[36] Yet we did not observe larger left atrial volumes in HFpEF patients with IAB compared with those without, but LA reservoir strain was numerically lower in patients with IAB (respectively 30.9% vs. 38.5%, P = 0.122). However, we did find more LV hypertrophy in HFpEF patients with IAB than no IAB, which has been reported before to be associated with declining LA reservoir strain in HFpEF.[37] Although merged data is scarce,[15,38,39] we postulate underlying increased fibrosis cooccurring in the LV and LA may partially explain the correlations between both cardiac chambers. A previous study in 100 patients at high risk for AF, predominantly without HF, found a significant association between the presence of advanced IAB and LA reservoir strain $<$26%, suggesting a potential link between LA electrical dysfunction and impaired LA reservoir function.[9]

The precise correlation between LA electrical dysfunction in the context of IAB and worsening HFpEF remains an area warranting more investigation. A case study showed atrial emptying against an already closed mitral valve in patients with IAB.[40] If occurring, this may lead to increased LA afterload and decreased LV filling, eventually worsening the HFpEF syndrome because of increased pulmonary capillary pressures and decreased cardiac output in conjunction with the existing increased myocardial stiffness in HFpEF.[41]

Clinical relevance

The finding of the current study may help to identify ambulatory patients with HFpEF but without IAB as a very low risk population. Considering the high prevalence of HFpEF, the low proportion of ambulatory HFpEF patients without IAB still accounts for a high absolute number of patients. Further research is needed to explore whether patients without IAB might benefit from a less strict and more personalised management strategy, considering that the absence of IAB is associated with a notably low risk of HFH or death. As such, we speculate that especially those patients without IAB would be manageable in a primary care setting after a relevant HF diagnostic work-up has been performed and treatments initiated, aiming to decrease the currently high healthcare consumption and costs, and alleviate the burden on patients by circumventing the necessity for hospital visits.[2,42] The inherent higher risk for readmission or death associated with the period immediately following a HFH[43–45] does not support the use of IAB to risk-stratify patients at very low-risk for adverse outcomes during the post-HFH period. IAB is easy to asses using a standard 12-lead ECG, making it accessible during outpatient visits.

Limitations

Certain limitations should be taken into account. First, the study's retrospective design, conducted in two tertiary hospitals, might introduce a selection bias. Second, the low incidence of no IAB precluded the possibility of a multivariable

analysis or adequate power for pairwise analysis, and may contribute to an overestimation of the survival time of patients without IAB compared to the IAB and AF groups. For example, LV hypertrophy was an independent predictor for worse outcome in previous HFpEF research, and our ambulatory patients without IAB had less signs of LV hypertrophy compared with those with IAB.[37] Furthermore, patients in the recently hospitalised cohort may have had not only recent, but also multiple prior hospitalisations, increasing cohort heterogeneity. In addition, the study population was without background SGLT2i therapy, which may reverse atrial remodelling and decrease adverse outcomes.[46,47] Finally, because ECGs were only available at baseline, the progression of electrical atrial dysfunction could not be tracked, such as from no IAB to IAB, or IAB to AF, leaving the temporal impact on prognosis unclear.

Conclusions

Progressive stages of electrical atrial dysfunction appeared to be prognostic markers of adverse outcome in ambulatory patients with HFpEF as well as in patients with a recent HFH. Ambulatory patients with HFpEF and no early stages of electrical atrial dysfunction, although with low incidence, showed to be at very low risk for adverse outcomes after 3 years of follow-up. This underscores the potential clinical utility of assessing electrical atrial dysfunction as a prognostic marker in ambulatory patients with HFpEF.

Conflict of interest

None declared.

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Data availability statement

All relevant data are within the paper and the supporting information. The data underlying this article may be shared on a reasonable request to the corresponding authors.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Baseline 12-lead electrocardiogram p-wave analysis. Examples are shown for no inter-atrial block (IAB) (p-wave $<$120 ms), partial IAB (p-wave $>$ 120 ms) and advanced IAB (p-wave $>$120 ms and biphasic p-wave morphology in at least two inferior leads). Blue vertical ledger lines delimitate the p-wave onset and end across the 12 ECG leads.
Figure S2. Bland–Altman plot showing the measurement bias of P-wave duration between the independent physician observers.
Figure S3. Survival curves for all-cause mortality in patients with HFpEF in different healthcare settings. Panel A shows patients with HFpEF in an ambulatory setting and panel B patients recently hospitalised for HFpEF. Follow-up of patients with AF was recorded up till one year after initial outpatient visit. AF, atrial fibrillation; IAB, inter-atrial block.
Figure S4. Excluding patients with a previous heart failure hospitalisation (HFH) up until 6 months prior to baseline (n = 5 with inter-atrial block (IAB), n = 16 with atrial fibrillation (AF)) showed similar results as the entire ambulatory HFpEF cohort. AF, atrial fibrillation; FLR, Firth's penalised maximum likelihood bias reduction; IAB, inter-atrial block.

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