Journal of Electrocardiology 73 (2022) 12–20

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

Interatrial block and P terminal force in the general population – Longitudinal changes, risk factors and prognosis

Tiia Istolahti, MD [a,b,*], Antti Eranti, MD, PhD [c], Heini Huhtala, MSc [d], Juho Tynkkynen, MD, PhD [e], Leo-Pekka Lyytikäinen, MD [a,f,g], Mika Kähönen, MD, PhD [a,h], Terho Lehtimäki, MD, PhD [a,g], Markku Eskola, MD, PhD [a,f], Ismo Anttila, MD, PhD [i], Antti Jula, MD, PhD [j], Kjell Nikus, MD, PhD [a,f], Jussi Hernesniemi, MD, PhD [a,f]

[a] Faculty of Medicine and Health Technology, Tampere University, Finnish Cardiovascular Research Center, Tampere, Finland
[b] Department of Cardiology, Vaasa Central Hospital, Vaasa, Finland
[c] Heart Center, Central Hospital of North Karelia, Joensuu, Finland
[d] Faculty of Social Sciences, Tampere University, Tampere, Finland
[e] Department of Radiology, Tampere University Hospital, Tampere, Finland
[f] Tays Heart Hospital, Department of Cardiology, Tampere University Hospital, Tampere, Finland
[g] Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland
[h] Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland
[i] Department of Internal Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland
[j] National Institute for Health and Welfare, Helsinki, Finland

ARTICLE INFO

Keywords:
Interatrial block
P terminal force
P wave
Atrial fibrillation
ECG

ABSTRACT

Background: Partial and advanced interatrial block (IAB) and P terminal force (PTF) in lead V1 are markers of atrial remodeling and risk factors for atrial fibrillation (AF). There is a lack of information about constancy and possible factors influencing the development of these P-wave abnormalities.
Methods: The study sample consisted of 6058 Finnish participants (mean age 52.16 ± 14.60 years, 45.0% male) from the general population with an ECG taken in a health examination, and from 3224 of these participants, who had a re-examination 11 years later. Risk factors for incident partial and advanced IAB and PTF were studied using binomial logistic regression analysis, and the prognostic significance of these ECG changes for new AF was studied using time-varying Cox regression analysis.
Results: The rate of reversal to normal of the studied ECG parameters were 47.4% for partial IAB, 40.0% for advanced IAB and 79.3% for PTF. Age, male sex, hypertension, higher BMI, higher LDL cholesterol, ECG left ventricular hypertrophy, use of beta blocker, and use of angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist were independently associated with a risk to develop incident P-wave abnormality. Partial IAB was independently associated with increased AF risk (HR 1.28 [95% CI 1.04–1.58]), as was also advanced IAB (HR 1.72 [95% CI 1.07–2.75]).
Conclusion: Traditional cardiovascular risk factors increase the risk of a new P-wave abnormality. Partial and advanced IAB are associated with increased AF risk. Surprisingly, P-wave abnormalities are often reversible during long-term follow-up in the general population.

Background

Partial and advanced interatrial block (IAB) and biphasic P wave with a deep negative terminal deflection in lead V1 (P terminal force, PTF [1]) in the standard 12-lead ECG have been associated with increased risk of atrial fibrillation (AF) in the general population [2–4]. Previous studies have shown a strong association between AF and atrial fibrosis [5], and structural and electrophysiological remodeling are important background factors for AF. Atrial injury and atrial wall stretch lead to activation of fibroblasts and formation of fibrotic atrial cardiomyopathy. IAB and PTF are markers of atrial remodeling. Disrupted interatrial conduction through the atrial septal wall leads to a

* Corresponding author at: Department of Cardiology, Vaasa Central Hospital, Hietalahdenkatu 2-4, 65100 Vaasa, Finland.
E-mail address: tiia.istolahti@tuni.fi (T. Istolahti).

https://doi.org/10.1016/j.jelectrocard.2022.04.006

Available online 27 April 2022

prolongation of the P wave in the surface ECG [6]. In partial IAB, the length of the P wave exceeds 120 ms, and in the advanced form, in addition to P-wave prolongation, the P waves in the inferior leads (II, III and aVF) are biphasic as a result of caudocranial activation of the left atrium [7].

A previous study showed that P-wave abnormalities in the general population can be highly reversible [8]. This raises the question about the clinical significance of reversible P-wave abnormalities and options for therapeutic interventions to prevent atriopathy. In previous studies, the risk factors for P-wave abnormalities have been similar to those linked to AF [8,9], even though there is scarcity of study data. Wider understanding of the factors associated with the development of IAB and PTF could also help to understand mechanisms leading to AF and enable more targeted preventive interventions.

The aims of this study were to examine longitudinal changes and risk factors for P-wave abnormalities, to re-evaluate earlier findings about the associated risks of partial and advanced IAB to develop AF using ECGs from two different time points, as well as to study the associated risk of PTF for AF development with similar methods.

Methods

Study population

This study is based on the Health 2000 and Health 2011 surveys that were carried out in the years 2000–2001 and 2011–2012 in Finland. The Health 2000 population was designed to cover a nationally representative population sample of the Finnish population and consisted of 8028 individuals aged 30+, of whom 79% (6354 individuals) participated in the health examination. The health examination included a structured examination by a physician, health interviews and series of laboratory tests, including ECG recordings. Participants aged 80+ were oversampled with a double sampling fraction.

All participants of the Health 2000 Survey sample, who were alive, living in Finland on July 6th, 2011, had contact details available and had not refused to participate in further surveys, were invited to take part in the Health 2011 Survey. Of the invited subjects, 73.5% (n = 5903) participated in the study, and 59.0% (n = 4729) participated in the 2011 health examination. To ensure the comparability of the two studies, the aim was to use the same study methodologies in the Health 2011 survey as in the Health 2000 survey, always when possible. More detailed descriptions of the methods of the Health 2000 and 2011 surveys have been published previously [10,11]. Ethical approval for the Health 2000 and 2011 surveys were obtained from the ethical committee at the Hospital District of Helsinki and Uusimaa (HUS).

ECG registration and analysis

During the health examinations, a standard 12-lead resting ECG in supine position was recorded from each subject with GE MAC 5000 or MAC 5500 electrocardiographs (Freiburg, Germany and Milwaukee, WI, USA) at paper speed of 50 mm/s and calibration of 10 mm/mV. The ECG data were sent for further analysis to the Social Insurance Institution's research center in Turku, where the ECGs were analyzed with Magellan software (Marquette Electronics Inc., Milwaukee, WI, USA). The Marquette 12SL algorithm uses median complexes of the 10-s ECG tracing and the onset of QRS is used as the isoelectric line. P-wave durations and amplitudes of different parts of the P wave were automatically measured, the measurement points were checked and corrected if needed. A wave crossing the baseline level constituting an area of ≥160 μVms represented a separate wave. The P-wave duration was measured from the earliest onset in any lead to the latest offset in any lead. Two investigators at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, blinded to the clinical data performed the Minnesota coding [12] for the Health 2000 ECGs. The repeatability of the Minnesota Code was ascertained by a repeat analysis of 200 ECGs.

Definition of P-wave abnormalities

We defined biphasic morphology in the inferior leads (II, III and aVF) as follows: the amplitude of the initial part of the P wave ≥20uV and the amplitude of the terminal part ≤ -20uV. We chose a cut-off of 20 mV, because changes below this magnitude were not recognized in a reproducible manner on enlarged conventional ECG recordings [13]. We defined advanced IAB as P-wave duration ≥120 ms combined with biphasic P waves in at least two inferior leads and partial IAB as P-wave duration ≥120 ms with maximum one biphasic inferior lead. For the purpose of IAB analysis, ECGs with a P-wave duration <120 ms were classified as normal. The validity of the definition was checked and published before [2].

We defined PTF as the area (amplitude x length) of the negative biphasic end of the P wave in lead V1 ≥6 mV x ms as was done in a previous study [4].

In order to validate the definition of PTF, we manually reviewed and measured 25 randomly selected ECGs with PTF and 50 ECGs without, blinded to the clinical data and PTF status. For this purpose, digitalized ECGs with a zoom of 20 mm/mV and 100 mm/s were used. In 72/75 (96.0%) ECGs the manual classification matched the computerized one. In three ECGs with computer-calculated PTF, the area of the negative distal part of the P wave in lead V1 was measured as <6 mV x ms with manual analysis, and therefore the ECG was classified as normal. However, in all of those cases, the P wave was defined as biphasic both in manual and computerized analysis.

Study covariates

Trained study personnel performed the health interview, and they followed a structural detailed written instruction to gather information about pre-existent diseases. Examining physicians performed another structured interview and physical examination in the year 2000. We included data on prevalent diseases from the Care Register for Health Care (CRHC) maintained by the National Institute for Health and Welfare. CRHC contains data of all inpatient episodes in Finland at the individual level since 1969 and on outpatients since 1998. The accuracy of the register has been validated previously [14]. Information about medication was gathered by trained interviewers and in addition, data on drug purchases since 1995 and special drug reimbursements since 1964 were gathered from a separate registry (Statistics on reimbursements for prescription of medicines: The Social Insurance Institution of Finland).

High-density lipoprotein (HDL) cholesterol and plasma glucose concentrations were determined from venous blood samples with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. The diagnosis of diabetes mellitus (DM) included fasting serum glucose (fS-Gluc) ≥7 or a history of use of oral glucose lowering agents or insulin injections [15]. Height and weight were measured, and body mass index (BMI) was calculated. Blood pressure was measured from the right arm with a standard mercury manometer (Mercuro 300; Speidel & Keller, Jungingen, Germany). An average of two measurements was used, of which the first one was measured after rest for at least 5 min in sitting position. Arterial hypertension (HTA) was defined as blood pressure ≥140/90, a previous diagnosis of HTA in the CRHC (ICD-10 I10, ICD-9/8 401) or right for special drug reimbursements for HTA. Smoking was determined as a daily use of cigarettes at the time of the interview. Left ventricular hypertrophy in the ECG (ECG-LVH) was defined by Minnesota code criteria 3.1, 3.3 or 3.4 or Cornell voltage criteria calculated from ECG measurements. Wide QRS was defined a QRS-duration ≥120 ms. Intraventricular conduction disorder (IVCD) was defined by Minnesota code criteria 7.1–8. Classification of CHD required at least one of the following: diagnosed percutaneous coronary intervention (PCI) or bypass surgery in the health interview, ICD-codes I20–25 (ICD-10) or 410–14 (ICD8/9) in the

CRHC, the right for drug reimbursements for CHD, interventional code for coronary artery revascularization in the CRHC or diagnosed angina pectoris, myocardial infarction, percutaneous coronary intervention (PCI) or bypass surgery, stated by examining physician.

Follow-up and definition of AF

The data for mortality and causes of death were gathered from the Causes of Death register maintained by Statistics Finland. It contains 100% of deaths of Finnish citizens in Finland and almost 100% abroad. Information on the incident diseases were obtained from the CRHC and information on new drug reimbursements were obtained from The Social Insurance Institution of Finland's separate registry. Databases were linked using a personal identity code.

The endpoint of the study was new-onset AF. We defined AF based on the Minnesota code criteria 8.3 in the ECG at the baseline (year 2000), ICD-codes I48 (version 10), 4273 (9) or 42792 (8) in the CRHC and Causes of Death register, right for drug reimbursement for dronedarone or direct oral anticoagulants with diagnose-code (ICD-10) I48 or right for special drug reimbursements for AF. The follow-up lasted until the end of the year 2015.

Exclusion criteria

From those 6354 participants, who participated in the health examination in the year 2000, we excluded subjects with missing ECG data ($n = 55$). Of them, the recording was not successful in 36 participants, while in 19 subjects, the ECGs were lost during the further process. We excluded subjects with prevalent AF or atrial flutter diagnosed from study ECGs or registries as defined previously ($n = 204$), ectopic atrial rhythm defined as totally negative P waves in the inferior leads (II, III and aVF) in computer analysis in both ECGs (years 2000 and 2011) ($n = 31$) and those with a heart rate over 120 bpm ($n = 6$) in both ECGs leaving 6058 participants. In the analyses, where we studied the association between different clinical variables and incident P-wave abnormalities, we included only participants with ECGs available at both time points and no incident AF before the year 2011 ($n = 3224$) (Fig. 1.). From these analyses we also excluded participants with any P-wave abnormality (pIAB, aIAB or PTF) at baseline ($N = 494$) and any other P-wave abnormality than the studied one in 2011. In the analysis of factors associated with temporal change of P-wave abnormalities, we included only participants with IAB ($n = 958$) or PTF ($n = 131$) in either of the study ECGs.

Statistical analyses

Comparisons of baseline variables was performed with one-way ANOVA, unpaired *t*-test, Chi-square or Fisher's exact test as appropriate. Lost to follow-up analysis between participants, who participated in the re-examination versus those who did not, was calculated with unpaired t-test or Chi-square test. The associations between clinical factors and incident P-wave abnormalities were analyzed using binomial logistic regression adjusted by age and multivariate adjustment comparing subjects who developed new P-wave abnormality to those who did not develop P-wave abnormality (=reference). To study the risk factors for temporal change of P-wave abnormalities, binomial logistic regression was used among participants with IAB (partial and advanced) and PTF in either ECGs. In these analyses, participants with retained/worsened P-wave abnormalities were compared to participants with improvement of the P-wave abnormality (=reference). Multivariate-adjusted models included all the studied parameters as covariates. To study the prognostic significance of IAB and PTF for the development of new AF in the follow-up period, we used Cox regression analysis with time-varying covariates at the two different time points (2000 and 2011). We tested the proportional hazard assumption with Schoenfeld residuals, and no violation of the assumption was observed. In these analyses we used the following parameters from the year 2000 for multivariate adjustment: age, sex, BMI, HDL cholesterol, LDL cholesterol, HTA, DM, CHD, smoking and ECG-LVH. Analyses were performed with SPSS (versions 25 and 27) and R 4.0.3. Statistical significance was based on two-sided $p < 0.05$.

Results

Study sample

The mean age of the included Health 2000 participants with ECGs available at both study time points was 47.86 years (standard deviation [SD] 11.12 years) at baseline. Table 1 shows the baseline characteristics of these participants divided by P-wave pathology. Participants with P-wave abnormalities were significantly older than those without. They were also more likely to have higher BMI, HTA, higher LDL cholesterol, ECG-LVH, IVCD and beta blocker in use. Participants with IAB were also more likely to be men, have DM, CHD, lower HDL cholesterol and wide

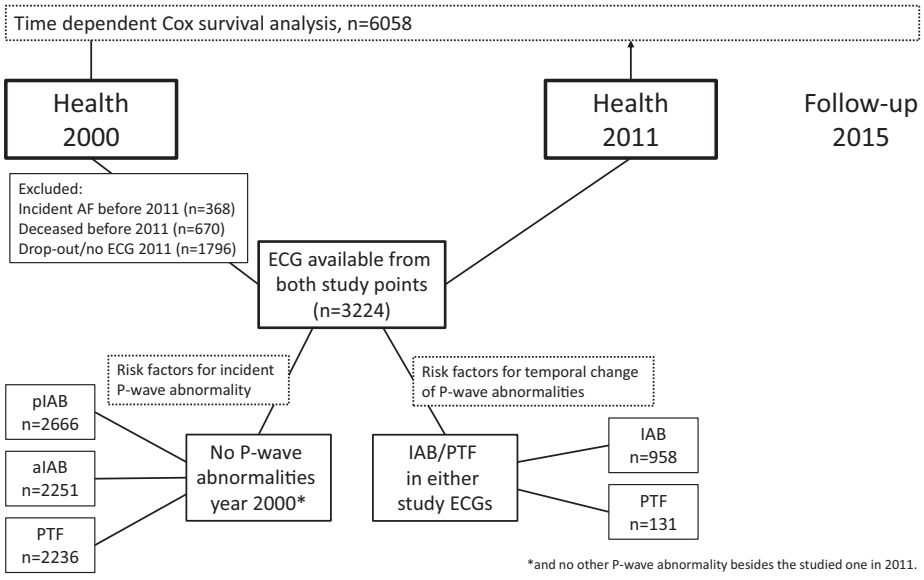

Fig. 1.. There were 6058 eligible Health 2000 participants who were followed until the end of 2015 and new diagnoses of atrial fibrillation were observed. In the analyses, where we studied the association between different clinical variables and incident P-wave abnormalities, we included only participants with ECGs available at both time points. In the analysis of factors associated with temporal change of P-wave abnormalities, we included only participants with IAB or PTF in either of the study ECGs. n=Number of Participants in The Analysis, (n)=Number of Participants per Group, AF=Atrial Fibrillation, pIAB=Partial Interatrial Block, aIAB=Advanced Interatrial Block, IAB=Interatrial Block, PTF=P Terminal Force.

Table 1
Baseline characteristics of the included Health 2000 and 2011 Survey participants ($n = 3224$).

	P wave <120 ms		Partial IAB		Advanced IAB			No PTF		PTF		
	n/mean	%/(SD)	n/mean	%/(SD)	n/mean	%/(SD)	*p* value	n/mean	%/(SD)	n/mean	%/(SD)	p value
N	2778	86.2	426	13.2	20	0.6		3132	97.1	92	2.9	
Age	47.30	(10.95)	51.18	(11.52)	56.20	(10.51)	<0.001	47.61	(10.99)	56.43	(12.10)	<0.001
Men	1151	41.4	244	57.3	16	80.0	<0.001	1368	43.7	43	46.7	0.560
BMI (kg/m^2)	26.30	(4.30)	27.49	(4.42)	29.83	(5.06)	<0.001	26.44	(4.33)	27.52	(4.56)	0.019
Smoking	525	19.0	83	19.5	6	30.0	0.446	592	19.0	22	23.9	0.235
Hypertension	959	34.6	186	43.7	11	55.0	<0.001	1101	35.2	55	59.8	<0.001
Diabetes	77	2.8	18	4.2	3	15.0	0.009	93	3.0	5	5.4	0.202
CHD	81	2.9	21	4.9	3	15.0	0.004	100	3.2	5	5.4	0.224
HDL (mmol/L)	1.37	(0.37)	1.31	(0.34)	1.16	(0.29)	0.001	1.36	(0.37)	1.37	(0.39)	0.735
LDL (mmol/L)	3.76	(1.12)	3.95	(1.07)	3.49	(1.41)	0.003	3.77	(1.11)	4.16	(1.26)	0.001
ECG-LVH	464	16.7	91	21.4	5	25.0	0.041	526	16.8	34	37.0	<0.001
Wide QRS	46	1.7	23	5.4	1	5.0	<0.001	66	2.1	4	4.3	0.138
IVCD	175	6.3	55	12.9	3	15.0	<0.001	217	6.9	16	17.4	<0.001
Beta blocker	201	7.2	63	14.8	5	25.0	<0.001	252	8.0	17	18.5	<0.001
ACEI/ARB	144	5.2	24	5.6	2	10.0	0.592	166	5.3	4	4.3	1.000

BMI = Body Mass Index, CHD = Coronary Heart Disease, HDL = High-density Lipoprotein, LDL = Low-density Lipoprotein, SD = Standard Deviation, n = Number, ECG-LVH = Left Ventricular Hypertrophy in ECG (Minnesota 3.1, 3, 4 and Cornell voltage criteria), IVCD = Intraventricular Conduction Delay, ACEI = Angiotensin-converting Enzyme Inhibitor, ARB = Angiotensin II Receptor Antagonist.

QRS in the ECG. The prevalence of co-morbidities was higher among participants with advanced IAB compared to participants with partial IAB and normal P-wave duration.

Compared with the subjects, who participated in both the Health 2000 study and the re-examination in 2011, the non-participants of the re-examination, were more likely male, were older, had higher BMI, lower HDL cholesterol, more often HTA, DM, CHD, ECG-LVH, IVCD and QRS $\geq$ 120 ms, used beta blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARB) and were active smokers (Appendix, Table 1). Reasons for non-participation were death between the study time points ($n = 670$), and decision not to attend the re-examination ($n = 836$); in addition, no ECG was available for 960 subjects from the follow-up study — of these 879 did not attend the health examination and 81 had no ECG recording for unknown reasons.

Among those who developed new AF between 2000 and 2011 ($n = 368$), the prevalence of P-wave abnormalities in 2000 was 4.6% for advanced IAB, 24.7% for partial IAB and 6.8% for PTF, and among those who died 2.4%, 16.4% and 7.4%, respectively. The proportions of all included Health 2000 participants divided by the outcome year 2011 are presented in the Appendix (Tables 2 and 3).

The prevalence of P-wave abnormalities

Among participants attending both surveys ($n = 3224$), the prevalence of partial and advanced IAB in the baseline ECG was 13.2% ($n = 426$) and 0.6% ($n = 20$). The prevalence of IAB increased during follow-up and in 2011 the corresponding percentages were 21.6% ($n = 697$) and 1.6% ($n = 51$). P-wave duration was normal (< 120 ms) in both ECGs in 70.3% ($n = 2266$) of the participants; 6.6% ($n = 213$) had partial IAB and 0.2% (n = 5) had advanced IAB in both ECGs. In 16.2% ($n = 523$) of the population interatrial conductivity worsened and in 6.7% ($n = 217$) conductivity improved (Fig. 2).

The prevalence of PTF in the baseline ECG was 2.9% ($n = 92$) and in the 2011 ECG 1.8% ($n = 58$). In total 95.9% ($n = 3093$) of the subjects did not have PTF in either ECGs, 0.6% ($n = 19$) had PTF in both ECGs, and 79.3% ($n = 73$) of those who had PTF at baseline, had normal P waves in 2011. New PTF in the 2011 ECG was detected in 1.2% ($n = 39$) of the subjects. The prevalence and proportions of changed IAB and PTF groups within the population are shown in Figs. 2 and 3.

Risk factors for incident P-wave abnormalities and temporal change of P-wave morphology

Age, male sex, higher BMI, HTA and medication with beta blockers or ACEI/ARB were associated with increased risk to develop new partial IAB during the 11-year follow-up, while higher HDL cholesterol was associated with lower risk (Table 2). Of these, age, sex, higher BMI and use of beta blockers were independent risk factors in multivariable adjusted analyses. The risk factors for the development of new advanced IAB were age, LDL cholesterol, ECG-LVH and the use of ACEI/ARB, and all of these were also independent risk factors after multivariate adjustment. Only age and prolonged QRS over 120 ms were associated with increased risk to develop new PTF and in the multivariate adjusted model only age reached statistical significance.

Among participants with partial or advanced IAB in either ECGs (2000/2011), higher BMI and HTA were associated with the risk for worsened or persistent IAB status after multivariate adjustment (Table 3), while higher HDL cholesterol and CHD were associated with improved IAB status. Among participants with PTF, only age was associated with the risk to have persistent/evolving PTF.

Prognostic significance of IAB and PTF

There were 6058 eligible participants in the year 2000 with a mean age of 52.16 years (SD 14.60 years), and 45.0% were male. Table 4 shows the hazard ratios (HR) and their 95% CIs for the risk of subjects with IAB and PTF to develop new AF. There were 536 subjects with a new AF diagnosis during the follow-up. Both partial and advanced IAB associated with increased risk to develop AF in age adjusted (HR 1.42 [1.16–1.73, $p = 0.001$] for partial IAB and HR 1.96 [1.23–3.11, $p = 0.004$] for advanced IAB) and multivariate adjusted models (HR 1.28 [1.04–1.58, $p = 0.020$] and 1.72 [1.07–2.75, $p = 0.024$]), respectively. PTF was not associated with AF in either analysis (HR 1.06 [0.74–1.53, $p = 0.740$] and HR 1.06 [0.73–1.54, $p = 0.747$]).

Discussion

This prospective, population-based study with long-term follow-up showed that P-wave abnormalities in the 12-lead ECG are often reversible; the rate of normalization of partial or even advanced IAB was surprisingly high. On the other hand, progression from partial to advanced IAB was rare. We could also corroborate previous study findings regarding the increased risk for new AF in subjects with partial or advanced IAB. We also gained new insights into the risk factors for the

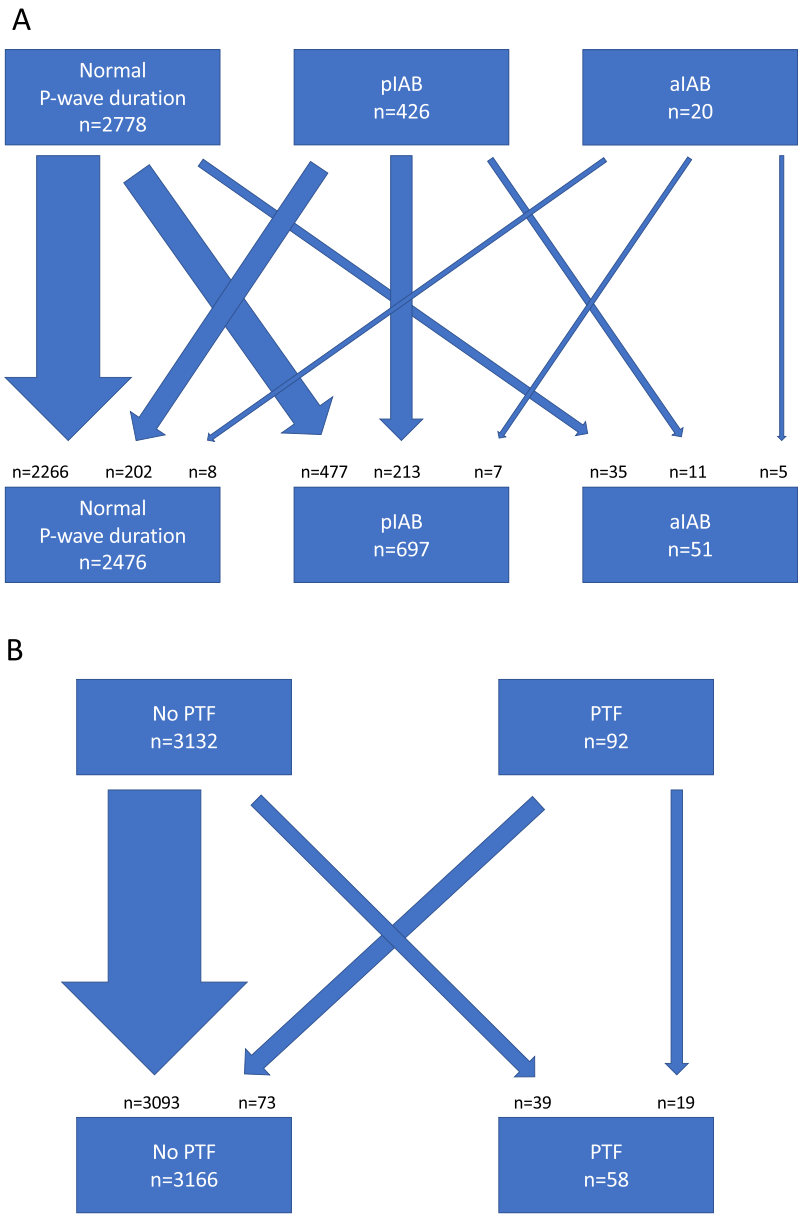

Fig. 2. The prevalence of interatrial block (A) and P-terminal force (B) in 2000 and 2011 and temporal changes within the population. n=Number of participants, pIAB=partial interatrial block, aIAB=advanced interatrial block, PTF=P-terminal force

development of P-wave abnormalities with time.

The reversible nature of P-wave abnormalities

In the present study, nearly half (47.4%) of those, who had partial IAB at baseline, had a normal P-wave duration 11 years later, and 75% of those, who had advanced IAB at baseline, had partial IAB or normal P-wave duration at follow-up. Furthermore, 79.3% of participants with PTF at baseline did no longer have this P-wave abnormality 11 years later. We conclude that IAB and PTF seem to be labile ECG manifestations during long-term follow-up. Similar conclusions were drawn from a previous study, where Lehtonen et al. (2017) [8] studied P-wave duration, PTF ($\geq$ 4 mV x ms) and P-wave axis in the same population. Apart from these studies, the labile nature of P-wave abnormalities has not been well documented in the general population. In hypertensive patients, treatment shortened the maximal P-wave duration [16]. It is not known whether this seemingly favorable change reduces the risk of AF as well. A previous study also showed that in acutely ill cardiac patients (acute myocardial infarction in the majority), there was an association between left ventricular filling pressures and PTF; when pressures dropped to normal, the ECG change returned to normal as well [17]. In the present study, the number of subjects with prevalent P-wave abnormalities was too low to enable analysis of the prognostic significance of the normalization of P-wave pathologies.

It is possible that part of the fluctuation is explained by the change of categories of participants with borderline P-wave abnormalities. It has also been demonstrated that misplacement of the ECG electrode V1 may result in a false ECG diagnosis of PTF based on an increase of the terminal negative area of the biphasic P wave [18]. However, we consider this as a rather unlikely confounding factor in this prospective study with trained study personnel. Also, this analysis included only participants with EGCs available in both study points 11 years apart and no prior AF. It is probable that participants with most advanced atriopathy at baseline developed AF or died during the follow-up and were thus excluded from the analysis.

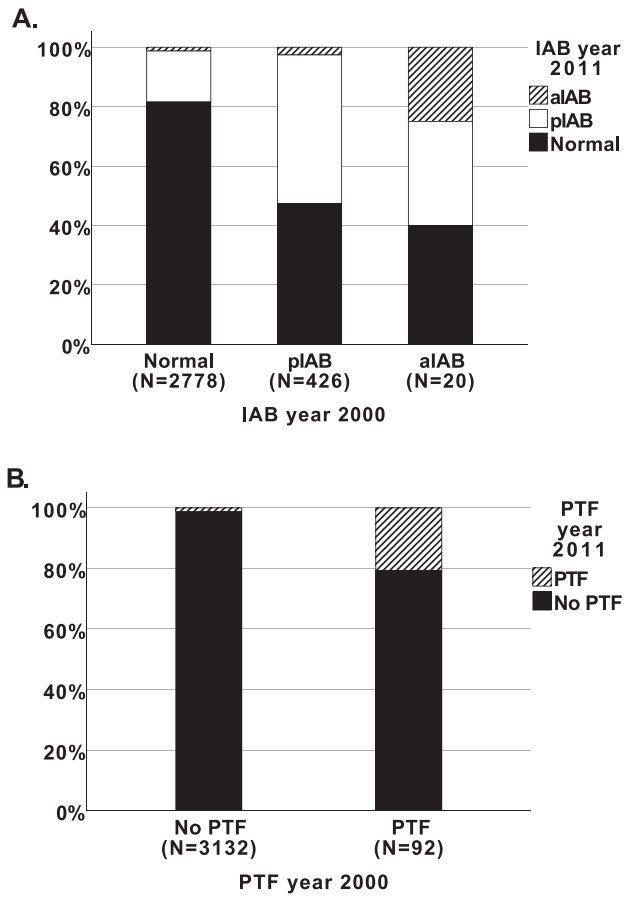

Fig. 3. The rate of changes of the P-wave morphology, (A) IAB and (B) PTF, in % between the baseline (year 2000) and the follow-up ECG (year 2011). N = Number of participants/group.

Risk factors to develop new or altered P-wave abnormality

We found that age was a major contributing factor to develop any P-wave abnormality. The development of new partial IAB was associated with traditional cardiovascular risk factors such as male sex, higher BMI, HTA and low HDL cholesterol, as well as use of beta blockers or ACEI/ARB medication. An earlier study, which included patients from a general hospital, showed similar results: participants with prolonged P-wave duration ≥110 ms were more likely to have HTA, DM, CHD or hypercholesterolemia [19]. In our study, higher BMI and HTA also associated with worsened IAB status, while higher HDL cholesterol and CHD seemed to be associated with improved IAB status. The observation of the possible association with CHD is rather unexpected. Possible explanations for this borderline significant observation could be a type II error or better treatment of other cardiovascular risk factors thanks to the diagnosis. Another potential explanation is survival bias since the prevalence of CHD at baseline was higher among participants with partial and advanced IAB, which could result in higher mortality and a higher dropout rate between the study points of these subjects. On the contrary, the association between worsened or persistent IAB status and HTA or higher BMI is not surprising. Hypertension may increase left atrial pressure and volume by elevating the left ventricular end-diastolic pressure and has been linked to atrial interstitial fibrosis and conduction disturbances [20]. Obesity leads to left atrial remodeling, including increased atrial fibrosis, fatty infiltration and conduction slowing. Mechanisms behind these changes include hemodynamics, cardiometabolic abnormalities, hormones and inflammatory processes. [21]

In contrast to partial IAB, we found that risk factors to develop new

Table 2
Risk factors to develop new P-wave abnormality. Year 2000 clinical variables and binary logistic regression to develop incident P-wave abnormality year 2011.

	pIAB (Odds Ratio [95% CI]) $n = 448$				aIAB (Odds Ratio [95% CI]) $n = 33$				PTF (Odds Ratio [95% CI]) $n = 18$			
	Adjusted with age	*p*-value	Multivariate adjusted	p-value	Adjusted with age	p-value	Multivariate adjusted	p-value	Adjusted with age	p-value	Multivariate adjusted	p-value
Age	1.03 (1.02–1.04) unadjusted	<0.001	1.02 (1.01–1.03)	<0.001	1.10 (1.07–1.13) unadjusted	0.001	1.08 (1.04–1.12)	<0.001	1.08 (1.04–1.13) unadjusted	<0.001	1.07 (1.02–1.13)	0.008
Male sex	1.91 (1.55–2.34)	<0.001	1.94 (1.54–2.45)	<0.001	1.71 (0.85–3.44)	0.133	1.76 (0.82–3.81)	0.149	0.45 (0.15–1.37)	0.159	0.39 (0.11–1.32)	0.130
BMI (kg/m^2)	1.10 (1.08–1.13)	<0.001	1.10 (1.07–1.13)	<0.001	1.05 (0.97–1.14)	0.260	1.04 (0.94–1.14)	0.484	0.95 (0.84–1.08)	0.416	0.970 (0.85–1.11)	0.662
Smoking	0.87 (0.66–1.15)	0.342	0.89 (0.67–1.19)	0.430	0.43 (0.10–1.84)	0.255	0.41 (0.10–1.80)	0.239	2.45 (0.83–7.21)	0.105	2.95 (0.96–9.08)	0.060
Hypertension	1.60 (1.28–2.00)	<0.001	1.08 (0.84–1.38)	0.559	1.77 (0.81–3.87)	0.150	1.17 (0.50–2.71)	0.723	1.10 (0.40–3.04)	0.853	1.26 (0.39–4.02)	0.698
Diabetes	1.36 (0.79–2.36)	0.268	0.89 (0.50–1.58)	0.687	0.82 (0.11–6.19)	0.845	0.64 (0.08–5.17)	0.673	1.63 (0.21–12.65)	0.640	3.51 (0.39–31.51)	0.262
CHD	0.81 (0.45–1.47)	0.493	0.61 (0.32–1.16)	0.130	0.72 (0.16–3.22)	0.671	1.05 (0.21–5.25)	0.955	0.79 (0.10–6.28)	0.820	0.84 (0.09–8.09)	0.882
HDL (mmol/L)	0.55 (0.41–0.73)	<0.001	1.07 (0.77–1.49)	0.699	0.62 (0.23–1.66)	0.339	0.83 (0.27–2.53)	0.741	2.53 (0.85–7.54)	0.097	2.14 (0.59–7.72)	0.245
LDL (mmol/L)	1.00 (0.91–1.10)	0.971	0.98 (0.89–1.07)	0.645	1.56 (1.14–2.15)	0.006	1.52 (1.10–2.11)	0.012	1.06 (0.68–1.64)	0.794	1.04 (0.65–1.67)	0.867
ECG-LVH	1.20 (0.92–1.57)	0.174	1.16 (0.88–1.53)	0.279	2.39 (1.15–4.98)	0.020	2.31 (1.09–4.91)	0.030	1.48 (0.51–4.31)	0.468	1.50 (0.49–4.66)	0.481
Wide QRS	1.66 (0.81–3.39)	0.164	1.18 (0.53–2.64)	0.685	1.25 (0.15–10.21)	0.835	0.39 (0.03–4.88)	0.465	5.81 (1.21–28.83)	0.028	5.85 (0.67–51.24)	0.111
IVCD	1.34 (0.91–1.99)	0.143	1.27 (0.81–1.99)	0.294	1.67 (0.55–5.04)	0.365	2.32 (0.65–8.26)	0.195	2.75 (0.77–9.83)	0.119	1.64 (0.30–9.06)	0.569
Beta blocker	1.57 (1.10–2.22)	0.012	1.48 (1.00–2.18)	0.049	0.46 (0.11–1.98)	0.295	0.38 (0.08–1.84)	0.229	1.65 (0.45–5.98)	0.448	2.30 (0.56–9.50)	0.250
ACEI/ARB	1.63 (1.09–2.44)	0.017	1.32 (0.85–2.03)	0.213	3.11 (1.23–7.87)	0.017	2.97 (1.08–8.18)	0.035	No events		No events	

pIAB = Partial Interatrial Block, aIAB = Advanced Interatrial Block, PTF=P Terminal Force, CI=Confidence Interval, BMI=Body Mass Index, CHD=Coronary Heart Disease, HDL = High-density Lipoprotein, LDL = Low-density Lipoprotein, ECG-LVH = Left Ventricular Hypertrophy in ECG (Minnesota 3.1, 3, 4 and Cornell voltage criteria), IVCD=Intraventricular Conduction Delay, ACEI = Angiotensin-converting Enzyme Inhibitor, ARB = Angiotensin II Receptor Antagonist. Multivariate adjusted models included all the listed parameters as covariates.

Table 3
Risk factors for temporal change of P-wave abnormalities. Risk factors for year 2000 detected P-wave abnormalities (IAB and PTF) to persist or progress year 2011. Binomial logistic regression. Number of participants in the analysis was 958 for IAB and 131 for PTF.

	IAB (Odds Ratio [95% CI])				PTF (Odds Ratio [95% CI])			
	Adjusted with age	p-value	Multivariate adjusted	p-value	Adjusted with age	p-value	Multivariate adjusted	p-value
Age (unadjusted)	1.01 (1.00–1.03)	0.092	1.01 (0.99–1.02)	0.352	1.04 (1.01–1.08)	0.012	1.04 (1.00–1.09)	0.036
Male sex	0.87 (0.64–1.19)	0.384	0.93 (0.66–1.32)	0.698	1.30 (0.64–2.67)	0.469	1.31 (0.57–2.98)	0.526
BMI (kg/m^2)	1.08 (1.04–1.12)	<0.001	1.07 (1.02–1.12)	0.002	0.98 (0.90–1.07)	0.708	0.97 (0.87–1.07)	0.511
Smoking	1.44 (0.99–2.11)	0.060	0.69 (0.47–1.03)	0.070	1.11 (0.47–2.61)	0.821	1.27 (0.50–3.26)	0.619
Hypertension	1.81 (1.30–2.51)	<0.001	1.47 (1.02–2.11)	0.037	1.16 (0.56–2.39)	0.698	1.35 (0.57–3.20)	0.501
Diabetes	0.73 (0.36–1.49)	0.387	0.58 (0.27–1.22)	0.148	0.44 (0.08–2.47)	0.349	0.31 (0.04–2.61)	0.281
CHD	0.47 (0.24–0.94)	0.032	0.47 (0.22–1.01)	0.053	3.42 (0.66–17.83)	0.144	2.65 (0.32–21.74)	0.364
HDL (mmol/L)	0.63 (0.41–0.98)	0.040	0.82 (0.49–1.38)	0.454	0.83 (0.34–1.99)	0.674	0.83 (0.28–2.47)	0.740
LDL (mmol/L)	1.04 (0.90–1.19)	0.629	0.97 (0.84–1.12)	0.684	0.90 (0.66–1.23)	0.509	0.92 (0.65–1.30	0.644
ECG-LVH	1.46 (0.98–2.18)	0.061	1.45 (0.96–2.19)	0.081	0.59 (0.28–1.28)	0.182	0.46 (0.19–1.14)	0.093
Wide QRS	0.79 (0.38–1.66)	0.538	0.87 (0.37–2.09)	0.761	0.55 (0.11–2.73)	0.467	0.79 (0.12–5.36)	0.806
IVCD	0.85 (0.53–1.38)	0.522	0.88 (0.50–1.53)	0.639	0.62 (0.23–1.70)	0.351	0.68 (0.20–2.29)	0.537
Beta blocker	0.93 (0.59–1.48)	0.764	0.90 (0.52–1.53)	0.691	1.82 (0.73–4.55)	0.201	1.50 (0.44–5.10)	0.517
ACEI/ARB	1.27 (0.68–2.38)	0.452	1.04 (0.54–2.02)	0.906	No events		No events	

IAB = Interatrial Block, PTF = P Terminal Force, CI = Confidence Interval, BMI = Body Mass Index, CHD = Coronary Heart Disease, HDL = High-density Lipoprotein, LDL = Low-density Lipoprotein, ECG-LVH = Left Ventricular Hypertrophy in ECG (Minnesota 3.1, 3, 4 and Cornell voltage criteria), IVCD=Intraventricular Conduction Delay, ACEI = Angiotensin-converting Enzyme Inhibitor, ARB = Angiotensin II Receptor Antagonist. Multivariate-adjusted models included all the listed parameters as covariates.

Table 4
Prognostic significance of IAB and PTF to develop new AF during the follow up period. The Cox regression analysis with time varying covariates at two different time points years 2000 and 2011, with the follow up lasting until 2015.

			Hazard ratio (95% CI)			
	AF diagnoses/participants	%	Adjusted with age	p value	Multivariate adjusted	p value
Normal (P wave <120 ms)	388/5132	7.6	1		1	
Partial IAB	129/862	15.0	1.42 (1.16–1.73)	0.001	1.28 (1.04–1.58)	0.020
Advanced IAB	19/64	29.7	1.96 (1.23–3.11)	0.004	1.72 (1.07–2.75)	0.024
No PTF	502/5827	8.6	1		1	
PTF	34/231	14.7	1.06 (0.74–1.53)	0.740	1.06 (0.73–1.54)	0.747

IAB = Interatrial Block, PTF = P Terminal Force, CI = Confidence Interval, AF = atrial fibrillation. Parameters used in multivariate adjustment: Age, Sex, High-density Lipoprotein Cholesterol, Low-density Lipoprotein cholesterol, Body Mass Index, Hypertension, Diabetes Mellitus, Coronary Heart Disease, Smoking and Left Ventricular Hypertrophy in ECG.

advanced IAB included, in addition to age, ECG-LVH, higher LDL cholesterol and use of ACEI/ARB medication. The association with ACEI/ARB is interesting as they are potential preventive medications for IAB, at least based on results from AF patients [22]. Furthermore, antihypertensive treatment with losartan was effective in reducing left ventricular mass according to ECG-LVH [23]. The most probable explanation for the association may be that the use of these medications generally reflects more severe overall cardiovascular risk. However, there is a lack of prospective studies about the effects of medical therapy to prevent or reverse IAB. Only higher age and wide QRS complex were associated with increased risk to develop new PTF, and only higher age associated with increased risk of new PTF or persistence of the ECG parameter.

Surprisingly, the associations with cardiovascular risk factors and the development of P-wave abnormalities were not particularly strong. Thus, it is likely that there are additional, yet unknown, factors leading to the development of P-wave abnormalities, which also explain part of the AF burden in the population. For example, multiple genetic loci have been associated with prolonged P-wave duration. Furthermore, adding complexity, some of the genetic loci associated with increased P-wave duration have been associated with reduced risk of AF [24]. In addition, the susceptibility to inflammation and fibrosis in the atria may differ markedly between subjects, and diet may also play a role [25,26]. Thus, future effort should be directed to identifying and understanding yet unknown risk factors of atrial cardiomyopathy.

Prognostic significance of IAB and PTF

Like in our earlier study about IAB and its subgroups in the general population [2], we found that partial and advanced IAB were associated with increased risk of AF during long-term follow-up. Many previous studies in the general population [3,27], as well as in many different clinical situations [28], have come to the same conclusion. In our study, the HRs were higher among participants with advanced than with partial IAB; this was also shown in a large population study in which the risk seemed to increase with the number of affected biphasic inferior leads [3].

We did not find any increased risk of AF among participants with PTF. Previous studies also have shown conflicting results regarding the association between PTF and AF [29]. A recent study [30] showed that apart from the classical advanced IAB morphology with conduction disturbances through the Bachmann's bundle, additional conduction disturbance in the posterior left atrium led to development of a severely prolonged amplified P wave, lacking the biphasic morphology in the inferior leads. Our study did not include amplified P waves, and it is possible that some cases with further atrial damage presenting with a short positive initial part and a long low-amplitude terminal part of the P wave were classified as having normal P waves.

A well-grounded hypothesis has been presented suggesting that subjects at high risk of stroke with advanced IAB might benefit of early anticoagulation therapy already before an AF diagnosis [28,31]. Even though we found an association between IAB and increased risk of AF, this study revealed that P-wave abnormalities were highly labile during 11 years follow up. This finding seems to complicate the issue of

therapeutic measures in IAB patients, although the prognostic significance of reversal of P-wave abnormalities remains unknown.

Study limitations and strengths

This was a large population study with 6058 participants at baseline. Nevertheless, some of the groups studied remained small-sized. The study protocol with ECGs 11 years apart is a strength of our study. However, we have to consider the possibility that the participants with the most severe P-wave changes did not attend the follow-up survey, because of death or study exclusion due to AF between the study time points. We used the PTF definition of $\geq$6 mV x ms instead of the more often used $\geq$4 mV x ms, which reduces the risk of PTF overestimation due to misplaced V1 electrodes [18]. However, the possible misplacement of the electrode V1 is a limitation in PTF studies even though we consider it less likely to happen in research circumstances than in clinical practice. We used computer-based measurements of the ECG, as manual analysis of the P-wave morphology may be difficult because of the small P-wave amplitudes, disturbing artefacts and because it may be difficult to get a reliable detection of the end of the P wave. Automatic measurements may help to correct for these factors and the repeatability of automated measurements is excellent. To study the prognostic significance of P-wave abnormalities we used time-varying Cox regression, which allowed us to consider timely changes in the studied ECG variables.

Data of prevalent and incident AF were mainly collected from national registers, but it is possible that some AF paroxysms diagnosed in primary care were not included in our analysis. It is also possible that subclinical paroxysmal AF, which was not possible to control for in the study population, may have influenced the results. Also, as in most studies from the general population, we could not correlate our study results with echocardiographic or other imaging data.

Finally, apart from IAB and PTF, our study did not explore the significance of other P-wave abnormalities, such as P-wave area [32], P-wave axis [33], P-wave voltage [34] and P-wave dispersion [35].

Conclusion

Partial and advanced IAB are risk factors for AF development. The risk factors for new P-wave abnormalities include traditional cardiovascular risk factors such as HTA, higher BMI and higher LDL cholesterol. According to our study results, P-wave abnormalities are highly labile during long-term follow-up in the general population. Therefore, we think that the prognostic significance of normalization of P-wave abnormalities needs to be explored before considering therapeutic interventions based on IAB or PTF.

Funding

The study was financially supported by the Maire Taponen's Foundation; the Ida Montin's Foundation and the Doctoral Programme in Medicine and Life Sciences, Faculty of Medicine and Health Technology, Tampere University (for T.I.); and Competitive Research Funding of the Tampere University Hospital [grant numbers 9M048 and 9N035]; the Finnish Cultural Foundation; the Finnish Foundation for Cardiovascular Research; the Emil Aaltonen Foundation; the Tampere Tuberculosis Foundation; EU Horizon 2020 [grant number 755320 for TAXINOMISIS and grant number 848146 for To Aition], and the Academy of Finland [grant number 322098] (for T.L.).

CRediT authorship contribution statement

Tiia Istolahti: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Antti Eranti:** Conceptualization, Methodology, Writing – review & editing. **Heini Huhtala:** Methodology, Formal analysis. **Juho Tynkkynen:** Methodology, Formal analysis, Writing – review & editing. **Leo-Pekka Lyytikäinen:** Software, Writing – review & editing. **Mika Kähönen:** Writing – review & editing, Supervision. **Terho Lehtimäki:** Writing – review & editing. **Markku Eskola:** Writing – review & editing. **Ismo Anttila:** Writing – review & editing. **Antti Jula:** Data curation, Writing – review & editing. **Kjell Nikus:** Conceptualization, Methodology, Writing – original draft, Supervision, Project administration. **Jussi Hernesniemi:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision.

Declaration of Competing Interest

None.

Acknowledgements

We thank the investigators, staff, and participants of the Health 2000 and 2011 surveys, and A. S. Havulinna, V. Salomaa, and the Finnish Institute of Health and Welfare for their work on coding endpoints.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2022.04.006.

References

[1] Morris JJ, Estes EH, Whalen RE, Thompson HK, Mcintosh HD. P-wave analysis in Valvular heart disease. Circulation 1964;29:242–52. https://doi.org/10.1161/01.CIR.29.2.242.
[2] Istolahti T, Eranti A, Huhtala H, Lyytikäinen L-P, Kähönen M, Lehtimäki T, et al. The prevalence and prognostic significance of interatrial block in the general population. Ann Med 2020:1–11. https://doi.org/10.1080/07853890.2020.1731759.
[3] Skov MW, Ghouse J, Kühl JT, Platonov PG, Graff C, Fuchs A, et al. Risk prediction of atrial fibrillation based on electrocardiographic interatrial block. J Am Heart Assoc 2018;7:e008247. https://doi.org/10.1161/JAHA.117.008247.
[4] Eranti A, Aro AL, Kerola T, Anttonen O, Rissanen HA, Tikkanen JT, et al. Prevalence and prognostic significance of abnormal P terminal force in Lead V_1 of the ECG in the general population. Circ Arrhythm Electrophysiol 2014;7:1116–21. https://doi.org/10.1161/CIRCEP.114.001557.
[5] Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. J Am Coll Cardiol 2015;65:2239–51. https://doi.org/10.1016/j.jacc.2015.03.557.
[6] Bayés de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. J Electrocardiol 2012;45:445–51. https://doi.org/10.1016/j.jelectrocard.2012.06.029.
[7] Bayés de Luna A, Baranchuk A, Alberto Escobar Robledo L, Massó van Roessel A, Martínez-Sellés M. Diagnosis of interatrial block. J Geriatr Cardiol JGC 2017;14:161–5. https://doi.org/10.11909/j.issn.1671-5411.2017.03.007.
[8] Lehtonen AO, Langén VL, Puukka PJ, Kähönen M, Nieminen MS, Jula AM, et al. Incidence rates, correlates, and prognosis of electrocardiographic P-wave abnormalities – a nationwide population-based study. J Electrocardiol 2017;50:925–32. https://doi.org/10.1016/j.jelectrocard.2017.07.004.
[9] Benjamin EJ, Chen P-S, Bild DE, Mascette AM, Albert CM, Alonso A, et al. Prevention of atrial fibrillation: report from a National Heart, Lung, and Blood Institute workshop. Circulation 2009;119:606–18. https://doi.org/10.1161/CIRCULATIONAHA.108.825380.
[10] Heistaro S. Methodology report: health 2000 surveyB26. Helsinki, Finland: Publications of the National Public Health Institute; 2008. Available from, http://urn.fi/URN:NBN:fi-fe201204193320.
[11] Lundqvist A, Mäki-Opas T. Health 2011 survey – methods [cited 2021 Jul 1]; Available from: https://www.julkari.fi/bitstream/handle/10024/130780/URN_ISBN_978-952-302-669-8.pdf?sequence=1&isAllowed=y; 2016.
[12] Prineas RJ, Crow RS, Blackburn HW. The Minnesota Code Manual of Electrocardiographic Findings. June, 1982. Littleton, MA: John Wright-PSG, Inc.; 1982.
[13] Recommendations for Measurement Standards in Quantitative Electrocardiography. The CSE working party. Eur Heart J 1985;6:815–25.
[14] Sund R. Quality of the Finnish hospital discharge register: a systematic review. Scand J Public Health 2012;40:505–15. https://doi.org/10.1177/1403494812456637.
[15] World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. Available from, http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/; 2006.

[16] Aizawa Y, Sato T, Akazawa K. Prevalence, significance and reversal of abnormal P-wave indices in hypertension: a review and meta-analysis. J Electrocardiol 2019; 53:13–7. https://doi.org/10.1016/j.jelectrocard.2018.12.008.
[17] Heikkila J, Hugenholtz PG, Tabakin BS. Prediction of left heart filling pressure and its sequential change in acute myocardial infarction from the terminal force of the P wave. Heart 1973;35:142–51. https://doi.org/10.1136/hrt.35.2.142.
[18] Rasmussen MU, Fabricius-Bjerre A, Kumarathurai P, Larsen BS, Domínguez H, Kanters JK, et al. Common source of miscalculation and misclassification of P-wave negativity and P-wave terminal force in lead V1. J Electrocardiol 2019;53:85–8. https://doi.org/10.1016/j.jelectrocard.2019.01.088.
[19] Ariyarajah V, Apiyasawat S, Moorthi R, Spodick DH. Potential clinical correlates and risk factors for interatrial block. Cardiology 2006;105:213–8. https://doi.org/10.1159/000091642.
[20] Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. Circ Res 2017;120:1501–17. https://doi.org/10.1161/CIRCRESAHA.117.309732.
[21] Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis. J Am Coll Cardiol 2017;70:2022–35. https://doi.org/10.1016/j.jacc.2017.09.002.
[22] Chhabra L, Devadoss R, Chaubey VK, Spodick DH. Interatrial block in the modern era. Curr Cardiol Rev 2014;10:181–9. https://doi.org/10.2174/1573403X10666140514101748.
[23] Wachtell K, Okin PM, Olsen MH, Dahlöf B, Devereux RB, Ibsen H, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: the LIFE study. Circulation 2007; 116:700–5. https://doi.org/10.1161/CIRCULATIONAHA.106.666594.
[24] Weng L-C, Hall AW, Choi SH, Jurgens SJ, Haessler J, Bihlmeyer NA, et al. Genetic determinants of electrocardiographic P-wave duration and relation to atrial fibrillation. Circ Genomic Precis Med 2020;13:387–95. https://doi.org/10.1161/CIRCGEN.119.002874.
[25] Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of high-dose Omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA 2020;324:2268. https://doi.org/10.1001/jama.2020.22258.
[26] Pääkkö TJW, Perkiömäki JS, Silaste M-L, Bloigu R, Huikuri HV, Antero Kesäniemi Y, et al. Dietary sodium intake is associated with long-term risk of new-onset atrial fibrillation. Ann Med 2018;50:694–703. https://doi.org/10.1080/07853890.2018.1546054.
[27] O'Neal WT, Zhang Z-M, Loehr LR, Chen LY, Alonso A, Soliman EZ. Electrocardiographic advanced interatrial block and atrial fibrillation risk in the general population. Am J Cardiol 2016;117:1755–9. https://doi.org/10.1016/j.amjcard.2016.03.013.
[28] Baranchuk A, Alexander B, Cinier G, Martinez-Selles M, Tekkesin AI, Elousa R, et al. Bayés' syndrome: time to consider early anticoagulation? North Clin Istanb 2018;5:370–8. https://doi.org/10.14744/nci.2017.60251.
[29] Huang Z, Zheng Z, Wu B, Tang L, Xie X, Dong R, et al. Predictive value of P wave terminal force in lead V1 for atrial fibrillation: a meta-analysis. Ann Noninvasive Electrocardiol 2020;25. https://doi.org/10.1111/anec.12739.
[30] Müller-Edenborn B, Chen J, Allgeier J, Didenko M, Moreno-Weidmann Z, Neumann F-J, et al. Amplified sinus-P-wave reveals localization and extent of left atrial low-voltage substrate: implications for arrhythmia freedom following pulmonary vein isolation. EP Eur 2020;22:240–9. https://doi.org/10.1093/europace/euz297.
[31] Bayés de Luna A, Baranchuk A, Martínez-Sellés M, Platonov PG. Anticoagulation in patients at high risk of stroke without documented atrial fibrillation. Time for a paradigm shift? Ann Noninvasive Electrocardiol 2017;22:e12417. https://doi.org/10.1111/anec.12417.
[32] Chen LY, Ribeiro ALP, Platonov PG, Cygankiewicz I, Soliman EZ, Gorenek B, et al. P-wave parameters and indices: a critical appraisal of clinical utility, challenges, and future research—a consensus document endorsed by the International Society of Electrocardiology and the international society for Holter and noninvasive Electrocardiology. Circ Arrhythm Electrophysiol 2022;15:e010435. https://doi.org/10.1161/CIRCEP.121.010435.
[33] Maheshwari A, Norby FL, Soliman EZ, Koene R, Rooney M, O'Neal WT, et al. Refining prediction of atrial fibrillation risk in the general population with analysis of P-wave Axis (from the atherosclerosis risk in communities study). Am J Cardiol 2017;120:1980–4. https://doi.org/10.1016/j.amjcard.2017.08.015.
[34] Park J-K, Park J, Uhm J-S, Joung B, Lee M-H, Pak H-N. Low P-wave amplitude (<0.1 mV) in lead I is associated with displaced inter-atrial conduction and clinical recurrence of paroxysmal atrial fibrillation after radiofrequency catheter ablation. Europace 2016;18:384–91. https://doi.org/10.1093/europace/euv028.
[35] Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J 1998;135:733–8. https://doi.org/10.1016/S0002-8703(98)70030-4.