IJC Heart & Vasculature 31 (2020) 100639

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Relation of intraventricular conduction delay to risk of new-onset heart failure and structural heart disease in the general population

Jani Rankinen [a,*,1], Petri Haataja [b], Leo-Pekka Lyytikäinen [a,b,c], Heini Huhtala [d], Terho Lehtimäki [a,c], Mika Kähönen [a,e], Markku Eskola [a,b], Andrés Ricardo Pérez-Riera [f], Antti Jula [g], Teemu Niiranen [g], Kjell Nikus [a,b], Jussi Hernesniemi [a,b]

[a] Faculty of Medicine and Health Technology, Tampere University, and Finnish Cardiovascular Research Center, Tampere, Finland
[b] Heart Center, Department of Cardiology, Tampere University Hospital, Tampere, Finland
[c] Department of Clinical Chemistry, Tampere University Hospital, and Fimlab Laboratories, Tampere, Finland
[d] Faculty of Social Sciences, Tampere University, Tampere, Finland
[e] Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland
[f] Design of Studies and Scientific Writing Laboratory, ABC School of Medicine, Santo André, São Paulo, Brazil
[g] The Finnish Institute for Health and Welfare, Helsinki/Turku, Finland

ARTICLE INFO

Article history:
Received 2 August 2020
Received in revised form 7 September 2020
Accepted 10 September 2020
Available online 25 September 2020

Keywords:
Bundle branch block
ECG
Population study
Intraventricular conduction delay
Heart failure
Structural heart disease

ABSTRACT

Background: Intraventricular conduction delays (IVCDs) are hallmarks of heart failure (HF) and structural heart disease (SHD) but their prognostic value for HF and SHD is unclear.
Methods: Relation of eight IVCDs and the incidence of first-time HF or SHD was studied in a nationally representative random sample of 6080 Finnish subjects aged ≥ 30 years (mean age 52.1, SD 14.5 years) who participated in the health examination including 12-lead ECG.
Results: During 16.5 years' follow up, half of the subjects with left bundle branch block (LBBB) and one third of the subjects with non-specific IVCD developed HF. After controlling for known clinical risk factors the hazard ratio (HR) for new-onset HF for LBBB was 3.29 (95% confidence interval 1.93–5.63, P < 0.001) and 3.53 for non-specific IVCD (1.65–7.55, P = 0.001). In corresponding analysis, LBBB predicted SHD with HR 2.60 (1.21–5.62, P = 0.015). Excluding subjects with history of heart disease, including coronary heart disease, did not have impact on results. Right bundle branch block and other IVCDs displayed no relation to endpoints.
Conclusion: LBBB and non-specific IVCD were associated with more than three-fold risk of new-onset HF. Furthermore, LBBB was associated with novel SHD. Their presence should alert clinician even in subjects free from any known heart disease.

1. Introduction

Intraventricular conduction delays (IVCDs) have been associated with impaired prognosis in patients with known cardiac disease. Left bundle branch block (LBBB), right bundle branch block (RBBB), and non-specific IVCD were associated with increased mortality especially in patients with myocardial infarction (MI) [1–3] and heart failure (HF) [4–7]. Mortality rates remain high in symptomatic patients with advanced HF and reduced ejection fraction in spite of improvements in medical therapy and effective utilization of cardiac resynchronization therapy. For timely initiation of therapy, subjects with high-risk of developing HF ought to be identified. Literature assessing the role of IVCDs as risk markers for the development of HF is scarce and has presented conflicting results, and has evaluated only selected bundle branch block categories [8–11].

IVCDs are frequent in patients with structural heart disease (SHD) [12], including valvular heart diseases and cardiomyopathies, but no prior prospective population studies have related IVCDs to novel SHD in subjects without known heart disease. Studies conducted in recent years have evaluated the role of LBBB in inducing left ventricular systolic decline [13,14], while RBBB should play no significant negative role in this aspect [15]. Non-specific IVCD has previously been associated with cardiovascular (CV) mortality [16] and sudden cardiac death [17,18], but the pro-

* Corresponding author at: TAYS Sydänkeskus Oy (Tampere University Hospital Heart Center Co.), P.O Box 2000, 33521 Tampere, Finland.
E-mail address: jani.rankinen@tuni.fi (J. Rankinen).
[1] Visiting address: Elämänaukio 1, 33520 Tampere, Finland.

https://doi.org/10.1016/j.ijcha.2020.100639
2352-9067/

gression to HF has not been extensively studied in patients without overt cardiac disease. Study data regarding the prognostic implications of fascicular blocks, incomplete bundle branch blocks and the R-R' pattern in either of the leads V1 or V2 to predict HF is practically non-existent.

The aim of this study was to explore the association between IVCDs and new-onset HF and SHD in an unbiased random sample of predominantly Caucasian general population during 16.5 years of total follow-up.

2. Methods

2.1. Study population

The Health 2000 is a major Finnish health examination survey. The survey was carried out in 2000–2001, and a representative stratified random cluster sample of the Finnish population was examined. The purpose of the survey was to provide an up-to-date epidemiological data of major public health problems in Finland, their causes and treatment. In brief, a representative stratified random cluster sample of the Finnish population was examined. The sampling included both largest cities and smaller regions and suburbs. For the population aged $\geq$ 80 years, the sampling probability was twice as high as among those <80 years. The implementation of the survey is described in detail elsewhere [19]. The Health 2000 sample comprised 8 028 individuals (3 637 men and 4 391 women) aged 30 or older, of whom 79% (6 354 individuals; 2 876 men and 3 478 women) participated in the health examination. The health examination was performed on each participant 1–6 weeks later at a local health center by centrally trained professional doctors and nurses. After a home interview a comprehensive health examination including questionnaires, measurements (e.g. blood pressure, resting electrocardiogram (ECG)) and physician's physical examination was performed. The National Care Register for Health Care and the national register on rights to reimbursements for medication costs were linked to the Health 2000 Survey data.

We excluded subjects with prevalent HF and SHD from the study (Fig. 1). Thus, the analysis was performed with 6080 subjects: 3298 women and 2 782 men (mean age 52.1, SD 14.5 years). The study protocol of the Health 2000 Survey was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. The participants in the survey signed an informed consent both before the health interview and at the beginning of the health examination.

2.2. ECG analysis and registration

The main exposure variables were IVCDs - for their identification, both Minnesota codes and measurements based on the Magellan software program were used. Four of the conduction delays were classified according to the respective Minnesota classes: RBBB (code 7–2), incomplete RBBB (iRBBB) (code 7–3), the R-R' pattern in either of leads V1 and V2 with R' amplitude $\leq$ R (R-R′ pattern) (code 7–5), and incomplete LBBB (iLBBB) (code 7–6) [20]. LBBB was defined by the Strauss definition [21]. Nonspecific IVCD was defined as QRS duration $\geq$ 120 ms not meeting RBBB or LBBB criteria (Fig. 2). For left anterior fascicular block we used the following definition: frontal QRS axis between −30° and −90°, rS configuration in II, III, and aVF, and qR configuration in aVL, with a QRS duration less than 120 ms. Left posterior fascicular block was defined as frontal QRS axis >120°, lead I rS configuration, leads II, III, and aVF qR configuration, and no pathological Q waves in leads II, III, aVF. The accuracy of the Minnesota coding and IVCD classification was checked by manual ECG analysis by three of the authors (JR, PH, and KN), blinded to the clinical outcome of the subject.

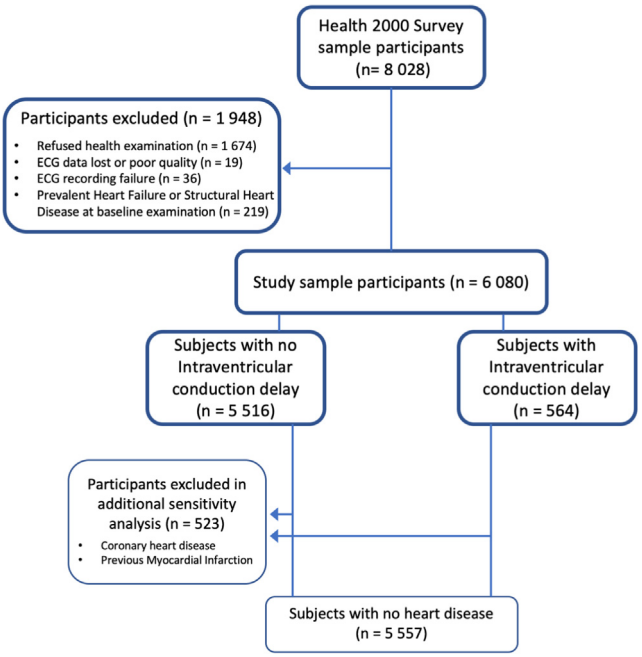

Fig. 1. Flow chart of the Health 2000 study population.

Standard 12-lead ECGs were recorded in the resting supine position by MAC 5000 recorders (Marquette Hellige, Freiburg, Germany and Milwaukee, WI, USA) and stored as digital data on a Marquette MUSE CV 5B system (Marquette Hellige, Milwaukee, WI). All ECGs were read, and the computerized diagnoses and measurements corrected if needed, by a physician experienced with ECG before being stored in the database. ECG was recorded and printed using a paper speed of 50 mm/s. The maximal filter setting of the system (150 Hz) was used. The Minnesota coding was performed at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, by two investigators who were blinded to the clinical data of the patient. ECGs were obtained successfully in 6 318 individuals (99%) who attended the health examination. Nineteen ECGs were rejected owing to data lost in further processes. Abnormalities identified visually in the ECG strips were coded in accordance with the Minnesota coding scheme [22]. The electrical recordings were analyzed by means of Magellan software program (Marquette Electronics Inc., Milwaukee, WI, USA).

2.3. Classification of prevalent conditions and other measurements

Classification as coronary heart disease (CHD) required at least one of the following: diagnosis of MI and/or angina pectoris during the field health examination by a physician, large Q waves in the resting ECG, hospitalization for CHD (International Classification of Diseases [ICD]-8 or ICD-9 codes 410–414 or ICD-10 codes I20–I25), a history of coronary revascularization procedure, the right to drug reimbursements for CHD, or the use of nitroglycerine combined with an anticoagulant, acetyl salicylic acid, or beta-blocker. The Finnish Care Register for Health Care has been shown to be valid in identifying major CHD events [23].

Classification for MI required either a clinical diagnosis of old MI by the examining physician, large Q waves in the resting ECG, or a previous discharge diagnosis of MI (ICD-8 or ICD-9 code 410 or ICD-10 codes I21–I22). Old MI was defined as a positive history of the condition in the medical records or old MI on ECG, or typical

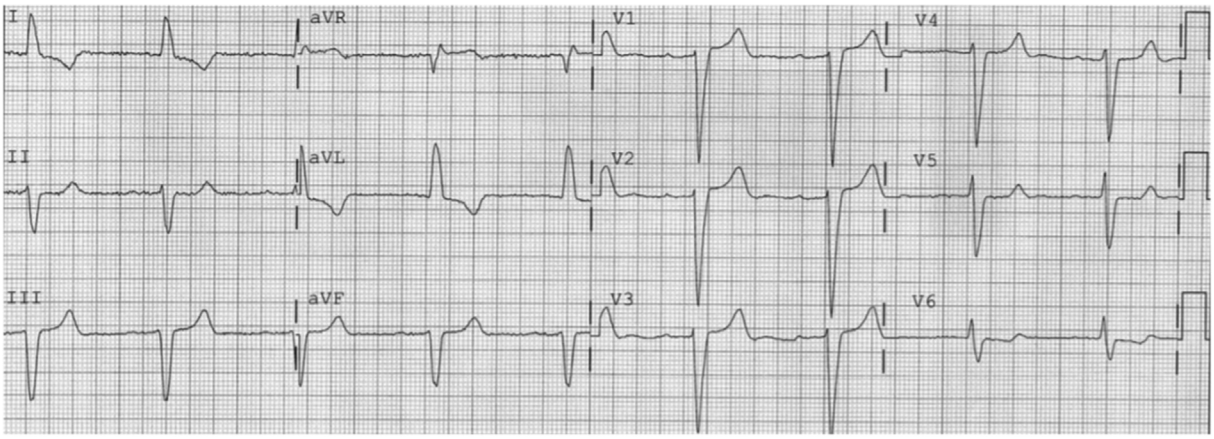

Fig. 2. The 12-lead ECG of a healthy subject with non-specific IVCD. The criteria for left bundle branch block are not fulfilled: QRS duration is 122 ms without notching or slurring in at least two contiguous leads [21]. The subject developed heart failure during the study follow-up.

self-reported history of MI treated in a hospital. Large Q waves indicating probable previous MI included Minnesota codes 1.1–1.3.

HF classification required a clinical diagnosis by the examining physician and either a previous discharge diagnosis of HF (ICD-8 code 4270, ICD-9 code 428, or ICD-10 code I50) or the right to drug reimbursements for HF. The classification for SHD required a previous diagnosis of SHD (ICD-9 codes 39, 425, 746, or ICD-10 codes I34–I37, I39, or I42). The classification for stroke required one or more discharge diagnoses of stroke (ICD-8 codes 430–431, 433–434, ICD-9 codes 430–434, or ICD-10 codes I60, I61, I63). Classification for peripheral arterial disease (PAD) required a clinical diagnosis by the examining physician or previous hospitalization for PAD.

The health examination included measurements of height, weight, body mass index (BMI), and waist circumference. Blood pressure (BP) was measured three times with a mercury sphygmomanometer (Mercuro 300, Speidel & Keller, Juningen, Germany) from the right arm. Hypertension was defined as a clinic average BP $\geq$ 140/90 mmHg or right to drug reimbursements for hypertension. Diabetes mellitus was defined as a serum glucose level of 7.0 mmol/L or greater or a history of the use of oral hypoglycemic agents or insulin therapy. Heart murmur was defined as a systolic or diastolic murmur heard at physician's physical examination. Smoking was defined as daily use of tobacco products. Laboratory tests included measurements for high-density lipoprotein cholesterol, total cholesterol, triglyceride, and serum glucose. Low-density lipoprotein cholesterol was calculated with the Friedewald formula.

2.4. Follow-up

From the baseline examination between 2000 and 2001, the participants were followed up for the main study endpoints until the end of 2015 (total follow-up time 16.5 years, median 15.9 years). Two study endpoints were used: new-onset HF and SHD. New-onset HF was defined as a hospitalization with the pre-described ICD-codes for HF from the Care Register for Health Care, new right to drug reimbursements for HF, or pre-described ICD-codes for HF as the primary underlying or immediate cause of death from the Causes of Death Register. New-onset SHD required a new diagnosis of SHD with the pre-described ICD-codes for SHD from the Care Register for Health Care, or pre-described ICD-codes for SHD as the primary underlying cause of death from the Causes of Death Register. Only the first event was included in the analyses. The follow-up information was gathered by linking the personal identity code from the Health 2000 Survey database to the Care Register for Health Care and the Causes of Death register, maintained by Statistic Finland, which records 100% of deaths of Finnish citizens in Finland and nearly 100% abroad. Diagnoses are registered in these registers by the treating physicians with codes defined in ICD-10. The follow-up information was available for all subjects. The Finnish Care Register for Health Care has been shown to be valid in identifying HF diagnoses and can be reliably used for research purposes [24].

2.5. Statistical analyses

In the Health 2000 Survey, proportions were compared with the chi-square test or Fisher's exact test. Data were categorized into nine groups according to the presence and type of IVCD. The complex sampling design was taken into account by correcting for the oversampling of subjects over 80 years of age. Unadjusted survival to each endpoint was assessed using the Kaplan–Meier method comparing differences between the reference population and subjects with IVCDs at baseline. Adjusted Hazard ratios (HR) were calculated by univariate and multivariate proportional Cox regression model analysis. Multivariate analysis included the following parameters: age, sex, CHD, MI, hypertension, diabetes mellitus, smoking, body mass index and low-density lipoprotein cholesterol. Additional sensitivity analyses were performed excluding subjects with history of heart disease (CHD, previous MI, including Q waves in the resting ECG) and subjects with heart murmurs. All analyses were performed with the SPSS release 25.0 for Windows (IBM Corp, Armonk, NY). A P-value of less than 0.05 was considered to be statistically significant.

3. Results

The prevalence of IVCDs in the general population without HF or SHD was 9,3% (n = 564), with a rather infrequent prevalence of conduction blocks with broad (>120 ms) QRS (LBBB, RBBB or non-specific IVCD) of 2,2% (n = 136). The clinical characteristics of the study population are presented in Table 1. Subjects with LBBB, non-specific IVCD, RBBB and LAFB were older and more often had prevalent CHD, while LBBB and non-specific IVCD were associated with previous MI. Subjects with LAFB presented higher levels of low-density lipoprotein cholesterol. Heart murmurs were more often heard in subjects with RBBB, non-specific IVCD and LBBB.

Table 1
Clinical characteristics and morbidity of the study population according to presence of intraventricular conduction delay.

	No IVCD (n = 5516)	LBBB (n = 37)	RBBB (n = 61)	Non-specific IVCD (n = 38)	LAFB (n = 58)	LPFB (n = 8)	iLBBB (n = 61)	iRBBB (n = 59)	R-R' pattern (n = 242)
	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)
Sex (male, %)	44.2	45.9	63.9	81.6	56.1	75.0	77.2	54.2	48.8
Age (years)	51.5 ± 14.2	70.4 ± 11.6*	68.0 ± 14.7*	57.9 ± 16.6*	64.0 ± 14.2*	38.8 ± 12.2*	52.6 ± 16.3	58.2 ± 14.8*	53.6 ± 14.7
Smoking (current)	1512 (27.6)	7 (18.9)	14 (23.0)	5 (13.2)*	8 (14.0)*	1 (12.5)	18 (31.6)	12 (20.3)	69 (28.5)
LDL cholesterol (mmol/L)	3.7 ± 1.1	3.9 ± 1.1	3.8 ± 1.0	3.6 ± 0.8	4.3 ± 1.4*	3.6 ± 1.0	3.8 ± 0.9	3.8 ± 1.2	3.8 ± 1.1
BMI (kg/m^2)	26.9 ± 4.6	27.4 ± 4.2	26.9 ± 3.8	27.3 ± 3.9	26.7 ± 4.8	23.1 ± 1.6*	28.9 ± 3.7*	26.1 ± 4.1	26.0 ± 4.5*
QRS duration (ms)	90.6 ± 11.7	154.8 ± 16.7*	136.8 ± 11.5*	125.3 ± 7.8*	94.9 ± 10.7*	103.0 ± 8.2*	107.3 ± 5.6*	94.8 ± 10.7*	91.1 ± 10.6*
Hypertension	2525 (46.2)	30 (81.1)*	40 (65.6)*	28 (73.7)*	42 (73.7)*	1 (12.5)	32 (56.1)	31 (52.5)*	112 (46.3)
Diabetes mellitus	282 (5.1)	5 (13.5)*	4 (6.6)	3 (7.9)	4 (7.0)	0	3 (5.3)	5 (8.5)	7 (2.9)
Heart murmur	466 (8.5)	7 (18.9)*	13 (21.3)*	8 (21.1)*	7 (12.3)	0	7 (12.3)	5 (8.5)	19 (7.9)
Coronary heart disease	431 (7.9)	17 (45.9)*	17 (27.9)*	11 (28.9)*	10 (17.5)*	0	4 (7.0)	9 (15.3)	17 (7.0)
Myocardial infarction	149 (2.7)	8 (21.6)*	4 (6.6)	10 (26.3)*	3 (5.3)	0	2 (3.5)	3 (5.1)	8 (3.3)
Stroke	179 (3.3)	3 (8.1)	4 (6.6)	5 (13.2)*	4 (7.0)	0	0	4 (6.8)	12 (5.0)
Peripheral artery disease	71 (1.3)	2 (5.4)	2 (3.3)	5 (13.2)*	2 (3.5)	0	1 (1.8)	1 (1.7)	4 (1.7)
Medication									
ACI/ARB	396 (7.2)	8 (21.6)*	4 (6.6)	7 (18.4)*	4 (7.0)	0	4 (7.0)	8 (13.6)	16 (6.6)
Beta adrenergic blockers	704 (12.8)	16 (43.2)*	15 (24.6)*	12 (31.6)*	9 (15.8)	1 (12.5)	4 (7.0)	14 (23.7)*	35 (14.5)
Calcium channel blockers	287 (5.2)	4 (10.8)	8 (13.1)*	8 (21.1)*	4 (7.0)	0	0	4 (6.8)	18 (7.4)
Antithrombotics	421 (7.7)	8 (21.6)*	13 (21.3)*	11 (28.9)*	11 (19.3)*	0	7 (12.3)	12 (20.3)*	22 (9.1)
Diuretics	302 (5.5)	5 (13.5)	9 (14.8)*	7 (18.4)*	4 (7.0)	0	6 (10.5)	5 (8.5)	12 (5.0)
Statin	318 (343)	4 (10.8)	4 (6.6)	6 (15.8)*	2 (3.5)	0	3 (5.3)	5 (8.5)	11 (4.5)
Study primary enpoints									
Heart failure	347 (6.3)	18 (48.6)*	14 (23.0)*	12 (31.6)*	10 (17.5)*	0	7 (12.3)	8 (13.6)	24 (9.9)
Structural heart disease	241 (4.4)	8 (21.6)*	6 (9.8)	2 (5.3)	7 (12.3)*	0	5 (8.8)	3 (5.1)	13 (5.4)

ACI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor antagonist; BMI = body mass index; iLBBB = incomplete left bundle branch block; iRBBB = incomplete right bundle branch block; IVCD = intraventricular conduction delay; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LDL = low density lipoprotein; LPFB = left posterior fascicular block; RBBB = right bundle branch block. *P < 0.05

3.1. Outcome

During 16.5 years' follow up, 440 subjects developed new-onset HF and 285 subjects had a diagnosis of SHD. Table 1 also shows the rate of new HF and SHD during the follow up within the different IVCD categories. Subjects with LBBB, non-specific IVCD, RBBB, and LAFB had the highest rates of new-onset HF, while for SHD, the highest rates were found in the LBBB and LAFB categories.

In the age- and sex-adjusted Cox regression analysis (Table 2), HR for new-onset HF for LBBB was 3.61 (95% confidence interval [CI] 2.14–6.08, P < 0.001), and for non-specific IVCD 4.05 (95% CI 2.00–8.20, P < 0.001). In the multivariate adjusted Cox model, HR for new-onset HF for LBBB was 3.29 (95% CI 1.93–5.63, P < 0.001), and for non-specific IVCD 3.53 (95% CI 1.65–7.55, P = 0.001). RBBB and the other conduction blocks were not associated with the incidence of HF after adjustments for age and sex.

In the age- and sex-adjusted Cox regression analysis, the HR for SHD in subjects with LBBB was 3.18 (95% CI 1.56–6.47, P = 0.001). The corresponding HR in the multivariate adjusted Cox model was 2.60 (95% CI 1.21–5.62, P = 0.015). Non-specific IVCD and other conduction blocks were not associated with SHD during follow up either in the age- and sex-adjusted or the multivariate adjusted model.

In the Cox regression analysis of subjects (remaining subpopulation n = 5 557) with no history of heart disease, after adjustment for age and sex, the HR for new-onset HF in the subjects with LBBB and non-specific IVCD was 3.58 (95% CI 1.59–8.07, P = 0.002) and 5.14 (95% CI 2.26–11.66, P < 0.001), respectively. In corresponding analysis, HR for SHD for LBBB was 4.65 (95% CI 1.09–11.34, P = 0.001). When the subjects with heart murmurs were removed from analysis (n = 5 097), the HR for new-onset HF was 4.82 (95% CI 1.98–11.72, P = 0.001) for LBBB and 3.63 (95% CI 1.50–11.47,

Table 2
Adjusted Cox proportional hazard analysis for study endpoints according to intraventricular conduction delay.

Variable	New-onset heart failure			Structural heart disease		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age- and sex-adjusted						
LBBB (n = 37)	3.61	2.14–6.08	<0.001	3.18	1.56–6.47	0.001
RBBB (n = 61)	1.12	0.61–2.05	0.717	1.17	0.52–2.64	0.715
Non-specific IVCD (n = 38)	4.05	2.00–8.20	<0.001	1.10	0.27–4.44	0.892
LAFB (n = 58)	1.13	0.93–2.19	0.728	1.73	0.82–3.69	0.153
LPFB (n = 8)	no events			no events		
iLBBB (n = 61)	1.82	0.81–4.08	0.148	2.05	0.91–4.62	0.083
iRBBB (n = 59)	0.44	0.11–1.75	0.242	0.97	0.31–3.02	0.953
R-R' pattern (n = 242)	1.38	0.89–2.15	0.153	1.07	0.61–1.86	0.820
Multivariate[a]-adjusted						
LBBB	3.29	1.93–5.63	<0.001	2.60	1.21–5.62	0.015
Non-specific IVCD	3.53	1.65–7.55	0.001			

CI = confidence interval; iLBBB = incomplete LBBB; iRBBB = incomplete RBBB; IVCD = intraventricular conduction delay; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LPFB = left posterior fascicular block; RBBB = right bundle branch block. [a]Adjusted for age, sex, coronary heart disease, myocardial infarction, hypertension, diabetes mellitus, smoking, body mass index and low-density lipoprotein cholesterol.

P = 0.028) for non-specific IVCD, respectively. Regarding SHD, the HR in subjects with LBBB was 5.90 (95% CI 2.17–16.03, P = 0.001).

4. Discussion

Our study showed clinically important prognostic differences between the categories of IVCDs. We showed that both non-specific IVCD and LBBB are associated with new-onset HF, and LBBB is associated with novel SHD during long-term follow-up in a nationally representative population cohort. During the follow-up, half of the subjects with LBBB and one third of the subjects with non-specific IVCD developed HF. Novel SHD was found in one fifth of the subjects with LBBB. While RBBB and LAFB displayed higher rates of new-onset HF and SHD, neither of them alongside other conduction blocks were associated with novel HF or SHD after adjustments for age and sex.

A few previous prospective studies have addressed the relation of bundle branch blocks and HF. In a study of men born in 1913[25] (n = 855), a diagnosis of HF during follow-up was significantly more common among those with bundle branch block. In the Framingham Heart Study (n = 1759) [26], participants with LBBB (n = 26) but not those with RBBB (n = 59) were more likely to develop HF than those with a QRS duration < 100 ms. Similarly, in the Copenhagen City Heart Study (n = 18 441) [15], RBBB (n = 166) was not associated with increased risk of HF. In the Women's Health Initiative Study (n = 65 975) [10], LBBB (n = 680) and the combination of RBBB and LAFB (n = 139), but not isolated RBBB (n = 740), were predictors of incident HF. The current study corroborates previous study findings that RBBB is not associated with new-onset HF. In addition, our study results add information about the association of this conduction disorder and novel SHD - subjects with RBBB have no excess risk of developing SHD during long-term follow-up. No previous prospective population studies have investigated the possible association between IVCDs and SHD.

Similar to the results the Framingham Heart and Women's Health Initiative Studies, a 40-year follow up of 17 361 subjects in Hiroshima and Nagasaki [27], showed that LBBB (n = 110) was associated with mortality from HF. In the Primary Prevention Study in Gothenburg (n = 7 392) [9], LBBB (n = 46), but not RBBB (n = 70), was associated with increased risk of CHD death and HF in men without angina or dyspnea at baseline. The risk for developing HF was almost fourfold in men with LBBB, close to one observed in the present study.

The presence of LBBB in previous longitudinal studies was also significantly related to underlying cardiac comorbidities also linked to risk of HF. In the present study were able to exclude subjects with either previously known or symptomatic HF and excluding subjects with apparent heart disease at the baseline health examination did not have any significant impact on the results. However, the possibility of underlying silent cardiac conditions, such as reduced left ventricular function without symptomatic heart failure, cannot be excluded. Nevertheless, in a previous retrospective study of patients with LBBB (n = 94) and preserved ejection fraction [13], functional decline measured by change of left ventricular ejection fraction in transthoracic echocardiogram was found in over one third of the patients. Our results are similar demonstrating that approximately half of all subjects with LBBB but without symptomatic prevalent HF at baseline develop symptomatic HF over a long period of time.

One of the most likely causes of left ventricular functional decline in left bundle branch block is the associated mechanical dyssynchrony [14]. This is supported by the fact that biventricular pacing, which corrects dyssynchrony, is associated with a reverse in the LV mechanical decline as well as with better outcomes in patients with symptomatic HF and LBBB [14,28,29]. In an animal model [30], LBBB induced unfavorable ventricular dilation, remodeling and asymmetric hypertrophy in normal hearts. In addition, LBBB induces and aggravates mitral regurgitation by several mechanisms, which prevent normal coaptation of the valve leaflets [31]. These previously referred studies and the results of the current study strongly suggest LBBB alone has a causal role in the development of HF.

Past epidemiological data from 1950s to 1970s [32,33] and clinical experience has shown that isolated LBBB is not necessarily hazardous in younger population as a result of possible age interactions modulating the association between LBBB and novel HF, as younger hearts be capable to compensate the potential loss of ventricular function. This was shown in a large retrospective cohort study of primary care patients referred for ECG [34], where the risk chart depicting 10-year absolute risk of HF revealed the risk significantly increasing with age in subjects with LBBB. Unfortunately, due to limited number of subjects with LBBB in our study population, we are unable to present reliable estimates of this statement.

Previous research on the prognosis of non-specific IVCD has mainly focused on patients with prevalent HF [4,5,35], but the progression to novel HF has not been extensively studied. In contrast to LBBB, subjects with non-specific IVCD show less, but more heterogenous, dyssynchrony [36] and considerable variation in the location of the latest activated site of the left ventricle [37]. In the current study, subjects with non-specific IVCD carried the highest risk of developing HF. In the Women's Health Initiative Study [10], after excluding participants with HF (self-reported), non-specific IVCD (n = 117) was a predictor of incident HF in women. In the Framingham Heart Study population [26], after excluding individuals with prevalent HF or MI, non-specific IVCD (n = 28) was associated with a two-fold risk of HF in the subjects with this conduction disorder in the baseline (n = 1759) ECG in 1949. These findings support the results of the current study.

In the Cardiovascular Health Study (n = 1664) [11], which comprised individuals aged 65 or older, LAFB (n = 39) predicted HF in the absence of overt CV disease. The findings are opposite to the findings from our study, which displayed no relation between LAFB and HF after adjustments for age and sex. While the differences in studied populations might explain the divergence of the result, LAFB is generally considered as a benign ECG finding. Study data on the relation between LPFB and HF is scarce, as LPFB is an extremely rare finding both in the general population and in specific patient groups. As an entity, LPFB may occur in infiltrative cardiomyopathies [38], and LPFB with or without RBBB may be found in cases with Chagas disease [39], which is an important cause of cardiomyopathy in Latin America. No increased risk of HF or SHD was found in subjects with LPFB in this study but the low number of subjects prohibit any definitive conclusions to be drawn.

Incomplete bundle branch blocks and the R-R' pattern were not associated with increased risk of HF or SHD in the present study. The result are is in line with the Copenhagen City Heart Study [15], which showed no relation between iRBBB (n = 624) and HF. On the contrary, the prognostic implications of iLBBB and the R-R' pattern is poorly investigated, and therefore remain largely unknown. Our study results indicate that iLBBB and the R-R' pattern are neither precursors of HF nor SHD.

Several study limitations need to be pointed out. First of all, absence of imaging data is a study limitation typical of a population study, yet the purpose of this study was to evaluate the prognostic implications of IVCDs in the general population using the same information that is normally available in general practice. We also lack data related to possible changes in medication during

follow-up. We think that the large study population representing a wide age range from both genders, well-defined baseline characteristics, and long follow-up gives strength to our study findings.

5. Conclusions

In a population study of individuals aged 30 or older with long-term follow-up, LBBB and non-specific IVCD, independently of several baseline variables, were associated with a more than three-fold risk of new-onset HF. Furthermore, LBBB was associated with novel SHD. The presence of these ECG abnormalities should alert physicians for careful cardiac evaluation even in absence of cardiovascular symptoms. Future clinical studies should focus on whether clinical or imaging follow-up, such as a routine echocardiographic control, is prudent and cost-effective for early prevention and identification of HF in these patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the personnel in the field, support organizations and participants of the Health 2000 Survey for their contributions.

Sources of funding

This study was supported by the Pirkanmaa Regional Fund of the Finnish Cultural Foundation, and grants from Finska Läkaresällskapet. TL and TN were financially supported by the Academy of Finland (grants 321351, 322098, 286284, 134309 [Eye], 126925, 121584, 124282, 129378 [Salve], 117787 [Gendi], and 41071 [Skidi]), Paavo Nurmi Foundation, Emil Aaltonen Foundation, and Finnish Medical Foundation. TL was supported by the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; The Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; Diabetes Research Foundation of Finnish Diabetes Association; EU Horizon 2020 (grant 755320 for TAXINOMISIS); European Research Council (grant 742927 for MULTIEPIGEN project); and Tampere University Hospital Supporting Foundation.

References

[1] E.B. Sgarbossa, S.L. Pinski, E.J. Topol, R.M. Califf, A. Barbagelata, S.G. Goodman, et al., Acute myocardial infarction and complete bundle branch block at hospital admission: clinical characteristics and outcome in the thrombolytic era. GUSTO-I Investigators. Global Utilization of Streptokinase and t-PA [tissue-type plasminogen activator] for Occluded Coronary Arteries, J. Am. Coll Cardiol. 31 (1998) 105–110, https://doi.org/10.1016/s0735-1097(97)00446-4.

[2] F. Baslaib, S. Alkaabi, A.T. Yan, R.T. Yan, P. Dorian, K. Nanthakumar, et al., QRS prolongation in patients with acute coronary syndromes, Am. Heart J. 159 (2010) 593–598, https://doi.org/10.1016/j.ahj.2010.01.007.

[3] H. Tolppanen, T. Javanainen, J. Sans-Rosello, J. Parenica, T. Nieminen, M. Pavlusova, et al., Prevalence, temporal evolution, and impact on survival of ventricular conduction blocks in patients with acute coronary syndrome and cardiogenic shock, Am. J. Cardiol. 122 (2018) 199–205, https://doi.org/10.1016/j.amjcard.2018.04.008.

[4] N.C. Wang, A.P. Maggioni, M.A. Konstam, F. Zannad, H.B. Krasa, J.C.J. Burnett, et al., Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction, JAMA 299 (2008) 2656–2666, https://doi.org/10.1001/jama.299.22.2656.

[5] A. Kashani, S.S. Barold, Significance of QRS complex duration in patients with heart failure, J. Am. Coll. Cardiol. 46 (2005) 2183–2192, https://doi.org/10.1016/j.jacc.2005.01.071.

[6] S. Baldasseroni, C. Opasich, M. Gorini, D. Lucci, N. Marchionni, M. Marini, et al., Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure, Am. Heart J. 143 (2002) 398–405.

[7] L.H. Lund, L. Benson, M. Stahlberg, F. Braunschweig, M. Edner, U. Dahlstrom, et al., Age, prognostic impact of QRS prolongation and left bundle branch block, and utilization of cardiac resynchronization therapy: findings from 14,713 patients in the Swedish Heart Failure Registry, Eur. J. Heart Fail. 16 (2014) 1073–1081, https://doi.org/10.1002/ejhf.162.

[8] R.J. Mentz, M.A. Greiner, A.D. DeVore, S.M. Dunlay, G. Choudhary, T. Ahmad, et al., Ventricular conduction and long-term heart failure outcomes and mortality in African Americans: insights from the Jackson Heart Study, Circ. Heart Fail 8 (2015) 243–251, https://doi.org/10.1161/CIRCHEARTFAILURE.114.001729.

[9] P. Eriksson, L. Wilhelmsen, A. Rosengren, Bundle-branch block in middle-aged men: risk of complications and death over 28 yearsThe Primary Prevention Study in Göteborg, Sweden, Eur. Heart J. 26 (2005) 2300–2306.

[10] Z.M. Zhang, P.M. Rautaharju, E.Z. Soliman, J.E. Manson, L.W. Martin, M. Perez, et al., Different patterns of bundle-branch blocks and the risk of incident heart failure in the women's health initiative (WHI) study, Circ. Hear Fail 6 (2013) 655–661, https://doi.org/10.1161/CIRCHEARTFAILURE.113.000217.

[11] M.C. Mandyam, E.Z. Soliman, S.R. Heckbert, E. Vittinghoff, G.M. Marcus, Long-term outcomes of left anterior fascicular block in the absence of overt cardiovascular disease, JAMA 309 (2013) 1587–1588, https://doi.org/10.1001/jama.2013.2729.

[12] G.W. Dec, V. Fuster, Idiopathic dilated cardiomyopathy, N. Engl. J. Med. 331 (1994) 1564–1575, https://doi.org/10.1056/NEJM199412083312307.

[13] E. Sze, A. Dunning, Z. Loring, B.D. Atwater, K. Chiswell, J.P. Daubert, et al., Comparison of incidence of left ventricular systolic dysfunction among patients with left bundle branch block versus those with normal QRS duration, Am. J. Cardiol. 120 (2017) 1990–1997, https://doi.org/10.1016/j.amjcard.2017.08.003.

[14] C. Vaillant, R.P. Martins, E. Donal, C. Leclercq, C. Thébault, N. Behar, et al., Resolution of left bundle branch block-induced cardiomyopathy by cardiac resynchronization therapy, J. Am. Coll. Cardiol. 61 (2013) 1089–1095, https://doi.org/10.1016/j.jacc.2012.10.053.

[15] B.E. Bussink, A.G. Holst, L. Jespersen, J.W. Deckers, G.B. Jensen, E. Prescott, Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City Heart Study, Eur. Heart J. 34 (2013) 138–146.

[16] P. Haataja, I. Anttila, K. Nikus, M. Eskola, H. Huhtala, T. Nieminen, et al., Prognostic implications of intraventricular conduction delays in a general population: the Health 2000 Survey, Ann. Med. 47 (2015) 74–80, https://doi.org/10.3109/07853890.2014.985704.

[17] A.L. Aro, O. Anttonen, J.T. Tikkanen, M.J. Junttila, T. Kerola, H.A. Rissanen, et al., Intraventricular conduction delay in a standard 12-lead electrocardiogram as a predictor of mortality in the general population, Circ. Arrhythm. Electrophysiol. 4 (2011) 704–710, https://doi.org/10.1161/CIRCEP.111.963561.

[18] D.P. Morin, L. Oikarinen, M. Viitasalo, L. Toivonen, M.S. Nieminen, S.E. Kjeldsen, et al., QRS duration predicts sudden cardiac death in hypertensive patients undergoing intensive medical therapy: the LIFE study, Eur. Heart J. 30 (2009) 2908–2914, https://doi.org/10.1093/eurheartj/ehp321.

[19] S. Heistaro, Methodology report, Health 2000 Survey, Publications of the National Health Institute B26/2008, 2008.

[20] R.J. Prineas, R.S. Crow, Z.-M. Zhang, The Minnesota code Manual of Electrocardiographic Findings, Springer Science & Business Media, 2009.

[21] D.G. Strauss, R.H. Selvester, G.S. Wagner, Defining left bundle branch block in the era of cardiac resynchronization therapy, Am. J. Cardiol. 107 (2011) 927–934, https://doi.org/10.1016/j.amjcard.2010.11.010.

[22] J. Pekkanen, A. Nissinen, P. Puska, S. Punsar, M.J. Karvonen, Risk factors and 25 year risk of coronary heart disease in a male population with a high incidence of the disease: the Finnish cohorts of the seven countries study, BMJ 299 (1989) 81–85.

[23] P. Pajunen, H. Koukkunen, M. Ketonen, T. Jerkkola, P. Immonen-Raiha, P. Karja-Koskenkari, et al., The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease, Eur. J. Cardiovasc. Prev. Rehabil. 12 (2005) 132–137.

[24] M.A. Vuori, J.A. Laukkanen, A. Pietilä, A.S. Havulinna, M. Kähönen, V. Salomaa, et al., The validity of heart failure diagnoses in the Finnish Hospital Discharge Register, Scand. J. Public Health 48 (2019) 20–28, https://doi.org/10.1177/1403494819847051.

[25] E. Peter, H. Per-Olof, E. Henry, D. Mikael, Bundle-branch block in a general male population, Circulation 98 (1998) 2494–2500, https://doi.org/10.1161/01.CIR.98.22.2494.

[26] R. Dhingra, M.J. Pencina, T.J. Wang, B.-H. Nam, E.J. Benjamin, D. Levy, et al., Electrocardiographic QRS duration and the risk of congestive heart failure: the Framingham Heart Study, Hypertens (Dallas, Tex, 1979) (47) (2006) 861–867, https://doi.org/10.1161/01.HYP.0000217141.20163.23.

[27] R. Imanishi, S. Seto, S. Ichimaru, E. Nakashima, K. Yano, M. Akahoshi, Prognostic significance of incident complete left bundle branch block

observed over a 40-year period, Am. J. Cardiol. 98 (2006) 644–648, https://doi.org/10.1016/j.amjcard.2006.03.044.
[28] C. Linde, M.R. Gold, W.T. Abraham, M. St John Sutton, S. Ghio, J. Cerkvenik, et al., Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study, Eur. Heart J. 34 (2013) 2592–2599, https://doi.org/10.1093/eurheartj/eht160.
[29] I. Goldenberg, V. Kutyifa, H.U. Klein, D.S. Cannom, M.W. Brown, A. Dan, et al., Survival with cardiac-resynchronization therapy in mild heart failure, N. Engl. J. Med. 370 (2014) 1694–1701, https://doi.org/10.1056/NEJMoa1401426.
[30] K. Vernooy, X.A.A.M. Verbeek, M. Peschar, H.J.G.M. Crijns, T. Arts, R.N.M. Cornelussen, et al., Left bundle branch block induces ventricular remodelling and functional septal hypoperfusion, Eur. Heart J. 26 (2004) 91–98, https://doi.org/10.1093/eurheartj/ehi008.
[31] O.A. Smiseth, J.M. Aalen, Mechanism of harm from left bundle branch block, Trends Cardiovasc. Med. 29 (2019) 335–342, https://doi.org/10.1016/j.tcm.2018.10.012.
[32] M. Rotman, J.H. Triebwasser, A clinical and follow-up study of right and left bundle branch block, Circulation 51 (1975) 477–484.
[33] S.W. Rabkin, F.A. Mathewson, R.B. Tate, Natural history of left bundle-branch block, Br. Heart J. 43 (1980) 164–169, https://doi.org/10.1136/hrt.43.2.164.
[34] P.V. Rasmussen, M.W. Skov, J. Ghouse, A. Pietersen, S.M. Hansen, C. Torp-Pedersen, et al., Clinical implications of electrocardiographic bundle branch block in primary care, Heart 105 (2019) 1160 LP–1167. https://doi.org/10.1136/heartjnl-2018-314295.
[35] A.O. Lehtonen, P. Puukka, J. Varis, K. Porthan, J.T. Tikkanen, M.S. Nieminen, et al., Prevalence and prognosis of ECG abnormalities in normotensive and hypertensive individuals, J. Hypertens. 34 (2016).
[36] W. Zareba, H. Klein, I. Cygankiewicz, W.J. Hall, S. McNitt, M. Brown, et al., Effectiveness of cardiac resynchronization therapy by QRS morphology in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT), Circulation 123 (2011) 1061–1072, https://doi.org/10.1161/CIRCULATIONAHA.110.960898.
[37] S. Ploux, J. Lumens, Z. Whinnett, M. Montaudon, M. Strom, C. Ramanathan, et al., Noninvasive electrocardiographic mapping to improve patient selection for cardiac resynchronization therapy: beyond QRS duration and left bundle branch block morphology, J. Am. Coll. Cardiol. 61 (2013) 2435–2443, https://doi.org/10.1016/j.jacc.2013.01.093.
[38] A.R. Pérez-Riera, R. Barbosa-Barros, R. Daminello-Raimundo, L.C. de Abreu, J.E. Tonussi Mendes, K. Nikus, Left posterior fascicular block, state-of-the-art review: A 2018 update, Indian Pacing Electrophysiol. J. 18 (2018) 217–230, https://doi.org/10.1016/j.ipej.2018.10.001.
[39] M.V. Elizari, R.S. Acunzo, M. Ferreiro, Hemiblocks revisited, Circulation 115 (2007) 1154–1163, https://doi.org/10.1161/CIRCULATIONAHA.106.637389.