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ORIGINAL PAPER

Left ventricular geometry and function in early repolarization: results from the population-based Gutenberg Health Study

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Abstract

Aims The electrocardiographic pattern of early repolarization (ER) is related to increased cardiac mortality in the general population. The pathophysiological basis of ER is largely unknown. We investigated the association of echocardiographic structural and functional parameters of the left ventricle with the presence of ER in the community.

Methods and results The presence of ER (ER+) was assessed in 13,878 participants (mean age 54.6 years, 51.1% women) of the Gutenberg Health Study and related to left ventricular structure and function derived from standard echocardiography. The prevalence of ER was 5.0% (694/13,878), with higher prevalence in men than women (6.6% vs. 3.5%, $p<0.001$). In men baseline characteristics differed including a lower BMI and a lower heart rate in ER+ individuals, whereas in women there were only minor differences. Multivariable-adjusted logistic regression analysis in men showed an association of ER with smaller diameters (left-ventricular end-diastolic diameter: OR 0.77 95% CI 0.69–0.86, $p<0.001$; left-ventricular end-systolic diameter: OR 0.86 95% CI 0.78–0.95, $p=0.0035$), and lower left-ventricular end-diastolic and end-systolic volume (OR 0.72 95% CI 0.65, 0.80, $p<0.001$ and OR 0.80 95% CI 0.72, 0.89, $p<0.001$). In women, the associations of ER with left ventricular diameters and volumes showed a similar direction, but were not as pronounced.

Conclusion In the community, the ER pattern predominantly occurs in men with a low heart rate and a slender habit. Furthermore, ER is not associated with higher left ventricular mass or size but rather with smaller left ventricular diameters and volumes with a regular systolic and diastolic function. Patterns were comparable in women, but less strong.

Keywords Early repolarization · Left ventricular geometry · Echocardiography · Epidemiology

Introduction

Early repolarization (ER) is an electrocardiographic pattern defined by an elevation of the J-point. An association of ER with sudden cardiac death and ventricular arrhythmias is known [1–3]. The prevalence of ER in the general population ranges between 2–13% [4–6]. Four high-risk subtypes of ER have been identified which are associated with a worse outcome including a high ER amplitude (> 2 mV), in particular in the inferior leads [4, 7], a notching morphology [8] and a horizontal/descending ST-segment [9]. However, the underlying pathology of ER causing ventricular arrhythmias remains unclear. One hypothesis is that ER is associated with structural changes of the left ventricle. While this premise has been evaluated in highly trained athletes [10–12], there are no data available on structural changes in ER-positive individuals in the community. Therefore, in the present study we investigated the relation of ER (and its subtypes) to left ventricular geometry and function in a large sample reflecting the general population.

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Methods

Study population

The Gutenberg Health Study is a population-based cohort located in the Rhein-Main region in Germany. It is designed as a prospective, observational single-center study for the evaluation and analysis of cardiovascular risk factors. Participants were chosen randomly from local governmental registries from the city of Mainz and Mainz-Bingen, women and men in a ratio 1:1. Details on the study design have been published elsewhere [13]. In brief, participants were between 35 and 74 years of age with a balanced gender ratio. All study participants provided written informed consent and the study has been approved by the Local Ethics Committee and is in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Definition of clinical characteristics in the study population

Family history of myocardial infarction was self-reported. Diabetes mellitus was defined as previous definite diagnosis by a physician or fasting blood glucose level of ≥ 126 mg/dl in the baseline examination or non-fasting blood glucose level ≥ 200 mg/dl. Hypertension was defined as use of antihypertensive drugs or mean systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Dyslipidemia was defined as LDL/HDL-ratio of > 3.5 or in case of a diagnosis of dyslipidemia by a physician. Current smokers comprised smokers and occasional smokers.

Echocardiographic assessment

All participants underwent an echocardiographic examination using an iE33 ultrasound system with an S5-1 sector array transducer (Philips Medical Systems, The Netherlands). Assessment of ventricular diameters, as well as systolic and diastolic function was performed in accordance with the current echocardiography imaging guidelines [14, 15].

In brief, measurements of left ventricular diameters and wall thickness were assessed in the left ventricular short axis on the level of the mitral valve leaflet tips. For linear measurements two-dimensional M-mode echocardiography was used or in cases where the M-mode cursor was not positioned perpendicular measurements were taken directly from two-dimensional images. Measurements of left ventricular volume and diastolic and systolic function were assessed in the apical four-chamber view and ejection fraction was calculated using the Simpson method. Diastolic function was measured using pulsed-waved Doppler across the mitral valve leaflets and tissue Doppler velocities of the mitral valve annulus. The following echocardiographic parameters were assessed: IVSD, interventricular septum thickness at end-diastole; LVEDD, left-ventricular end-diastolic dimension; LVPWD, left ventricular posterior wall thickness at end-diastole; LVESD, left ventricular end-systolic dimension; diastolic function (*E*/*A*, deceleration time, *E*′, *E*/*E*′), EDV; end-diastolic volume, ESV; end-systolic volume, SV; stroke volume. Left ventricular mass was calculated as $0.8 \times (1.04\ [(\mathrm{LVIDD} + \mathrm{IVST} + \mathrm{PWT})^3 - (\mathrm{LVIDD})^3]) + 0.6$ [16], relative wall thickness as (IVSD + LVPWD)/left ventricular end-diastolic inner diameter.

ECG analysis and definition of ER

A resting 12-lead ECG was recorded in every participant using GE Cardiosoft, (GE Healthcare, Germany) with an automated measurement of ECG time intervals. In case of a QRS duration of > 120 ms or a rhythm other than sinus rhythm, ECGs were excluded from the analysis. QT interval was calculated by Bazett formula. For ER classification, each ECG was assessed manually by two trained cardiologists (T.T., B.K. or W.R.). The presence of ER was defined as J-point elevation ≥ 0.1 mV (≥ 1 mm) in at least two adjacent leads as defined previously [1, 17]. Morphology of the J-point was categorized as notching, slurring or both. The region of ER was either inferior (II, III, aVF) or anterolateral (I, aVL, V4–V6) with exclusion of the leads V1–V3 to prevent an overlap with Brugada syndrome or right ventricular dysplasia. The ST-segment of each ER pattern was further classified as rapidly ascending (ST-segment elevation of > 0.1 mV within 100 ms after J-point peak or as persistently elevated ST-segment > 0.1 mV) or as horizontal/descending (≤ 0.1 mV elevation of the ST-segment within 100 ms after J-point peak). High-risk subtypes of ER were defined according to results of previous publications for region (inferior), amplitude (> 2 mV), morphology (notching) and ST-segment (horizontal/descending) [4, 7–9].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and compared using Student's t-test or as median (25th percentile, 75th percentile) and analyzed using Wilcoxon rank-sum test. Binary variables are displayed as frequencies, *n* (%) and between-group comparisons were performed using Chi-squared test. All analyses were stratified by sex to account for the biological differences between female and male left ventricular structure. For determination of an association of ER with echocardiographic parameters logistic regressions for each marker of left ventricular structure or function as the predictor of interest and ER as the dependent variable were computed. Analyses were adjusted for age and sex and, in multi-variable-adjusted models, additionally for BMI, hypertension, diabetes, dyslipidemia, current smoker, heart rate and corrected QT interval. All models also included interaction terms between sex and the respective echocardiographic parameter to estimate sex-specific odds ratios [18]. A p value of <0.05 was considered statistically significant. All computations were performed using R version 3.4.1 (2017-06-30).

Results

Baseline characteristics

Overall, 13,878 participants of the GHS cohort were included in the analysis. The clinical characteristics for male and female study participants are summarized in Table 1.

In male subjects the ER pattern was present in 6.6%. ER-positive (+) participants showed a significantly lower body mass index (26.7 vs. 27.9 $p<0.001$) compared to ER-negative (−) individuals. Furthermore, hypertension and diabetes were less common in ER+ individuals compared to ER− participants (46.5% vs. 54.1%; $p=0.0023$) and (6.1% vs. 8.9%, $p=0.047$), respectively. ER+ men had a significantly lower heart rate (65.6 vs. 68.1 bpm; $p<0.001$) and shorter corrected QT interval (406 vs. 414 ms; $p<0.001$).

In women, the prevalence of ER was 3.5% with ER+ participants being older than ER− individuals (56.0 vs. 54.4 years; $p=0.030$). There was no difference in body composition but significantly more women were smokers in the ER+ group compared to ER− women (23.7 vs. 17.9%; $p=0.024$). Heart rate did not differ in women, whereas the corrected QT interval was shorter in ER+ women (421 ms vs. 425 ms; $p=0.0098$).

Prevalence of ER subtypes

Representative examples of ER subtypes are displayed in Fig. 1 and the prevalence of ER subtypes is shown in Table 2. In men, the ER pattern was more prevalent in the antero-lateral region compared to women (34.0% vs. 22.5%; $p=0.002$), whereas in women localization of ER was more frequent in the inferior leads compared to ER+ men (67.5%, vs. 48.4%; $p<0.001$). Slurring morphology was higher in females (63.1% vs. 54.5%; $p=0.035$) and a combined ER type of slurring and notching was more present in males (28.2% vs. 20.9%; $p=0.044$). Overall, the ER amplitude was mainly ≤ 2 mV with no differences between men and women. There were more men than women with a rapidly ascending ST-segment (26.1% vs. 8%; $p<0.001$) and,

Table 1 Baseline characteristics of the study cohort

Men	All ($n=6784$)	ER+ ($n=445$)	ER− ($n=6339$)	p value
Age, years	54.7 ± 11.0	53.7 ± 10.8	54.7 ± 11.0	0.062
Body mass index, kg/m^2	27.8 ± 4.3	26.7 ± 3.8	27.9 ± 4.3	< 0.001
Hypertension, n (%)	3634 (53.6)	207 (46.5)	3427 (54.1)	0.0023
Diabetes, n (%)	593 (8.7)	27 (6.1)	566 (8.9)	0.047
Current smoker, n (%)	1432 (21.1)	110 (24.8)	1322 (20.9)	0.061
Dyslipidemia, n (%)	2476 (36.6)	146 (33.0)	2330 (36.8)	0.11
Family history of MI, n (%)	1032 (15.2)	63 (14.2)	969 (15.3)	0.57
Heart rate, bpm	68.0 ± 11.1	65.6 ± 10.7	68.1 ± 11.1	< 0.001
QTc, ms	413 ± 23	406 ± 22	414 ± 23	< 0.001
Women	**All ($n=7094$)**	**ER+ ($n=249$)**	**ER− ($n=6845$)**	**p value**
Age, years	54.5 ± 11.0	56.0 ± 10.3	54.4 ± 11.1	0.030
Body mass index, kg/m^2	26.8 ± 5.6	27.0 ± 6.2	26.8 ± 5.6	0.48
Hypertension, n (%)	3115 (43.9)	108 (43.5)	3007 (44.0)	0.95
Diabetes, n (%)	364 (5.1)	14 (5.6)	350 (5.1)	0.84
Current smoker, n (%)	1281 (18.1)	59 (23.7)	1222 (17.9)	0.024
Dyslipidemia, n (%)	1553 (22.0)	52 (20.9)	1501 (22.0)	0.73
Family history of MI, n (%)	1266 (17.8)	42 (16.9)	1224 (17.9)	0.74
Heart rate, bpm	70.0 ± 10.4	68.9 ± 10.3	70.0 ± 10.4	0.11
QTc, ms	425 ± 22	421 ± 22	425 ± 22	0.0098

All data are displayed as mean ± standard deviation, or as frequencies and percentages

ER early repolarization, *MI* myocardial infarction, *QTc* corrected QT interval

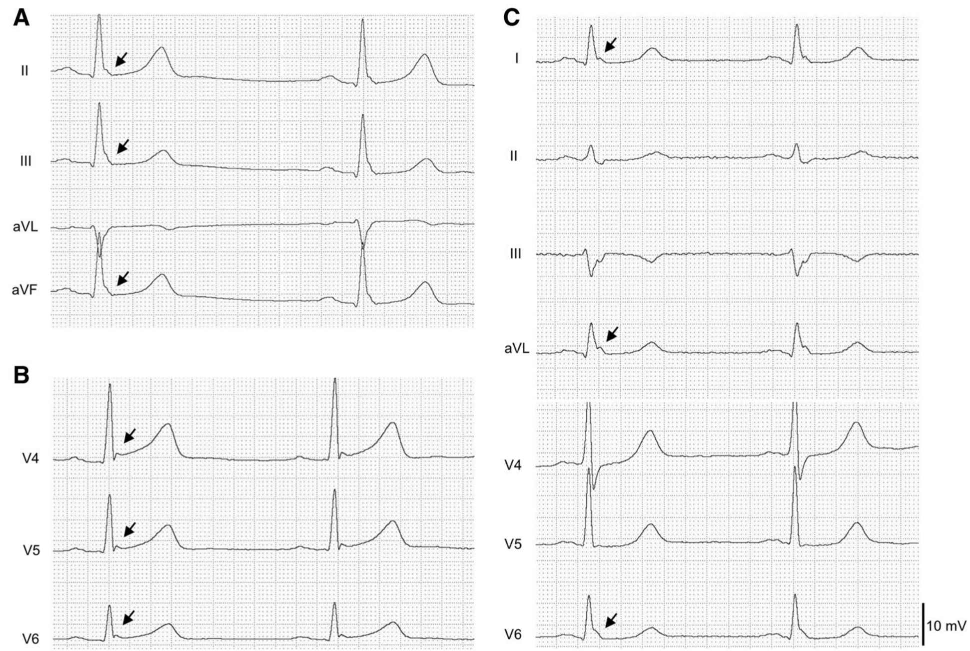

Fig. 1 Representative examples of the ER pattern in the Gutenberg Health Study. **a** Slurring type of the ER pattern in the inferior leads with a horizontal ST-segment. **b** Notching type of the ER pattern in the (antero)-lateral leads with an ascending ST-segment. **c** Combined ER pattern of notching (I, aVL) and slurring (V6) in the antero-lateral leads with a horizontal ST-segment

Table 2 Prevalence of early repolarization subtypes

ER subtype	All ER+ (n = **694**)	Men ER+ (n = 445)	Women ER+ (n = 249)	p value
Localization				
Antero-lateral, n (%)	207 (29.9)	151 (34.0)	56 (22.5)	0.002
Inferior, n (%)	383 (55.3)	215 (48.4)	168 (67.5)	< 0.001
Combined antero-lateral + inferior, n (%)	103 (14.9)	78 (17.6)	25 (10.0)	0.01
Morphology				
Notching, n (%)	117 (16.9)	77 (17.3)	40 (16.1)	0.74
Slurring, n (%)	399 (57.6)	242 (54.5)	157 (63.1)	0.035
Combined notching + slurring, n (%)	177 (25.5)	125 (28.2)	52 (20.9)	0.044
Amplitude				
≤ 2 mV, n (%)	505 (72.9)	314 (70.7)	191 (76.7)	0.11
> 2 mV, n (%)	188 (27.1)	130 (29.3)	58 (23.3)	0.11
ST-segment				
Rapidly ascending, n (%)	136 (19.6)	116 (26.1)	20 (8.0)	< 0.001
Horizontal/descending, n (%)	557 (80.4)	328 (73.9)	229 (92.0)	< 0.001

ER stands for early repolarization. All data are displayed as frequencies and percentages

respectively, more women showed a horizontal/descending ST-segment morphology.

Analysis of structural and functional echocardiographic characteristics

Left ventricular structure in ER+ men compared to ER− men (Table 3) showed a lower LVEDD (48.5 ± 5.3 mm vs. 49.7 ± 5.3 mm; $p < 0.001$) and LVESD (31.5 ± 4.7 mm vs. 32.2 ± 4.6 mm; $p = 0.0021$) in ER+ subjects. Furthermore, the absolute left ventricular mass as well as left ventricular mass indexed to BSA (body surface area) were lower in the ER+ group, [170 g (146, 198) vs. 178 g (153, 207); $p < 0.001$], [86 g/m^2 (73, 98) vs. 87 g/m^2 (76, 101); $p = 0.014$], respectively (Table 3).

Analysis of left ventricular diastolic function showed significantly higher values for E/A ratio [1.15 (0.94, 1.36) vs. 1.07 (0.87, 1.29); $p < 0.001$], E' [11.6 cm/s (9.3, 13.5) vs. 10.6 cm/s (8.5, 12.8); $p < 0.001$] and a lower E/E' ratio [6.4 (5.4, 8.0) vs. 7.0 (5.7, 8.7); $p < 0.001$]

Table 3 Echocardiographic characteristics by ER status in men

	All ($n=6784$)	ER+ ($n=445$)	ER− ($n=6339$)	p value
Markers of left ventricular structure				
IVSD, mm	10.6 ± 1.8	10.5 ± 1.8	10.6 ± 1.8	0.17
LVEDD, mm	49.6 ± 5.3	48.5 ± 5.3	49.7 ± 5.3	< 0.001
LVPWD, mm	9.5 ± 1.7	9.4 ± 1.7	9.5 ± 1.7	0.59
LVESD, mm	32.1 ± 4.6	31.5 ± 4.7	32.2 ± 4.6	0.0021
Relative wall thickness, %	41.1 ± 8.4	41.7 ± 8.9	41.0 ± 8.3	0.080
Left ventricular mass, g	177 (152, 207)	170 (146, 198)	178 (153, 207)	< 0.001
Left ventricular mass/BSA, g/m^2	87 (76, 101)	86 (73, 98)	87 (76, 101)	0.014
Markers of left ventricular diastolic and systolic function				
E/A	1.08 (0.87, 1.29)	1.15 (0.94, 1.36)	1.07 (0.87, 1.29)	< 0.001
Deceleration time, ms	215 (190, 250)	215 (190, 250)	215 (190, 250)	0.97
E', cm/s	10.7 (8.6, 12.9)	11.6 (9.3, 13.5)	10.6 (8.5, 12.8)	< 0.001
E/E' ratio	6.9 (5.7, 8.6)	6.4 (5.4, 8.0)	7.0 (5.7, 8.7)	< 0.001
EDV, mL	112 (93, 132)	105 (86, 123)	113 (93, 133)	< 0.001
ESV, mL	41 (33, 50)	39 (30, 47)	42 (33, 51)	< 0.001
Stroke volume, mL	70 (58, 83)	66 (54, 77)	70 (59, 83)	< 0.001
Ejection fraction (Simpson), %	63 ± 6	63 ± 6	63 ± 6	0.96

All data are displayed as mean ± standard deviation, or as median (interquartile range)

ER early repolarization, *IVSD* interventricular septum thickness in diastole, *LVEDD* left-ventricular end-diastolic dimension, *LVPWD* left ventricular end-diastolic posterior wall thickness (dimension), *LVESD* left ventricular end-systolic dimension, *BSA* body surface area, *EDV* end-diastolic volume, *ESV* end-systolic volume

in ER+ compared to ER− men. Parameters of systolic function revealed a lower left ventricular end-diastolic and end-systolic volume in ER+ male subjects [EDV: 105 ml (86, 123) vs. 113 ml (93, 133); $p < 0.001$ ESV: 39 ml (30, 47) vs. 42 ml (33, 51); $p < 0.001$] resulting in a lower stroke volume [66 ml (54, 77) vs. 70 ml (59, 83); $p < 0.001$]. However, analysis of left ventricular ejection fraction was similar between ER+ and ER− men (63 ± 6% vs. 63 ± 6%; $p = 0.96$).

In women (Table 4) IVSD (9.6 ± 1.7 mm vs. 9.3 ± 1.7 mm; $p = 0.0062$) and LVPWD (8.7 ± 1.6 mm vs. 8.5 ± 1.5 mm; $p = 0.02$) were higher in the ER+ group. Similar to ER+ men, ER+ women had smaller left ventricular diameters compared to ER− women (LVEDD: 44.7 ± 4.4 mm vs. 45.5 ± 4.8 mm; $p = 0.011$, LVESD: 28.5 ± 3.6 mm vs. 29.1 ± 4.0 mm; $p = 0.032$). There were no significant differences in left ventricular mass. Furthermore, analysis of left ventricular function showed no significant differences in diastolic function between the two groups. Parameters of systolic function showed a significantly lower end-diastolic volume in ER+ women compared to ER− women [82 ml (72, 96) vs. 86 ml (73, 102); $p = 0.017$], whereas the end-systolic volume showed only a trend towards a lower value in the ER+ group [30 ml (25, 36) vs. 31 ml (25, 37); $p = 0.095$]. However, the stroke volume was significantly lower in ER+ women [52 ml (46, 62) vs. 55 ml (46, 66); $p = 0.014$]. Ejection fraction did not differ between ER+ and ER− women.

Association of ER with left ventricular structure and function

In age-adjusted analyses (Fig. 2a) and after further adjustment for BMI, hypertension, diabetes dyslipidemia, current smoking, heart rate and corrected QT interval (Fig. 2b) presence of ER was associated with smaller left ventricular diameters in men and women. Whereas in men, ER was also associated with a lower left ventricular mass, this was not the case in women. However, in women presence of ER was associated with an increase in left ventricular wall thickness.

Results of the age-adjusted logistic regression analysis for left ventricular function are displayed in Fig. 3a which persisted after multivariable adjustment (Fig. 3b). In both models presence of ER in men was associated with an increase in *E*/*A* ratio and *E*′ values, whereas in women there was no association of ER with parameters of diastolic function. Furthermore, in men ER was associated with a lower end-diastolic and end-systolic-volume. This was not the case in women, neither in the age-adjusted analysis nor after multivariable adjustment. In men and women presence of ER was not associated with changes of ejection fraction.

Associations of ER high-risk subtypes with echocardiographic parameters

The results of the logistic regression analysis for ER high-risk subtypes are displayed in the Supplemental Tables 1 and

Table 4 Echocardiographic characteristics by ER status in women

	All (n = 7094)	ER+ (n = 249)	ER− (n = 6845)	p value
Markers of left ventricular structure				
IVSD, mm	9.3 ± 1.7	9.6 ± 1.7	9.3 ± 1.7	0.0062
LVEDD, mm	45.5 ± 4.8	44.7 ± 4.4	45.5 ± 4.8	0.011
LVPWD, mm	8.5 ± 1.5	8.7 ± 1.6	8.5 ± 1.5	0.020
LVESD, mm	29.1 ± 3.9	28.5 ± 3.6	29.1 ± 4.0	0.032
Relative wall thickness, %	39.6 ± 8.3	41.3 ± 8.1	39.5 ± 8.3	< 0.001
Left ventricular mass, g	131 (110, 155)	133 (111, 160)	131 (110, 154)	0.40
Left ventricular mass/BSA, g/m^2	74 (64, 85)	75 (65, 85)	74 (64, 85)	0.45
Markers of left ventricular diastolic and systolic function				
E/A	1.10 (0.86, 1.36)	1.11 (0.89, 1.31)	1.10 (0.86, 1.36)	0.74
Deceleration time, ms	210.0 (186.6, 240.0)	215.0 (187.0, 241.7)	210.0 (186.6, 240.0)	0.18
E′, cm/s	10.9 (8.6, 13.5)	10.8 (8.3, 13.2)	10.9 (8.6, 13.5)	0.27
E/E′ ratio	7.4 (6.1, 9.1)	7.7 (6.3, 9.3)	7.4 (6.1, 9.1)	0.077
EDV, mL	86 (72, 102)	82 (72, 96)	86 (73, 102)	0.017
ESV, mL	31 (25, 37)	30 (25, 36)	31 (25, 37)	0.095
Stroke volume, mL	55 (46, 65)	52 (46, 62)	55 (46, 66)	0.014
Ejection fraction (Simpson), %	64 ± 5	64 ± 5	64 ± 5	0.54

All data are displayed as mean ± standard deviation, or as median (interquartile range)

ER early repolarization, *IVSD* interventricular septum thickness in diastole, *LVEDD* left-ventricular end-diastolic dimension, *LVPWD* left ventricular end-diastolic posterior wall thickness (dimension), *LVESD* left ventricular end-systolic dimension, *BSA* body surface area, *EDV* end-diastolic volume, *ESV* end-systolic volume

2. In men and women analysis of inferior region and horizontal/descending ST-segment largely replicated the results of the entire ER+ group. Results of the notching subtype and the risk type with a high amplitude pointed in the same direction, but did not always reach statistical significance.

Discussion

Our study provides large-scale data on left ventricular structure and function in individuals with the ER pattern in the community. We could show that presence of ER is associated with a smaller size of the left ventricle, predominantly in men.

The prevalence of ER in the general population has been described between 2 and 13% [4–6, 19] and varies depending on several factors including age, sex and ethnicity of the population. Beside population-dependent factors the prevalence also differs according to the definition used for ER categorization. Applying established definitions [1, 17] the prevalence in our study was 5% with more men showing the ER pattern. A common finding is that ER mainly occurs in young, athletic men and reaches up to 44% prevalence in highly trained athletes [9]. Morphological analyses of ER+ individuals have also been performed predominantly in athletes showing a higher left ventricular mass [10] or an increased left ventricular diameter [20]. However, these studies did not examine sex differences, with markedly more male athletes showing the ER pattern in both studies. Therefore, differences in left ventricular mass or dimensions may be due to sex differences and must be investigated separately. In a sex-stratified analysis of highly trained elite athletes we could recently show that ER is not associated with distinct structural or functional echocardiographic changes [21]. Interestingly, the prototype of an ER+ athlete was male, lean, showed a lower heart rate and was rather involved in endurance sport disciplines [21]. These results are in line with our current study showing that the ER pattern predominantly occurs in men with a slender habitus. Although large-scale population-based studies have analyzed the impact of ER on mortality, investigations of left ventricular structure in ER+ individuals in the general population are lacking. One small study (n = 60) examined myocardial deformation parameters using speckle-tracking echocardiography in healthy individuals but failed to show differences between ER+ participants and ER− controls [22]. Furthermore, a recent meeting abstract from the Dallas Heart Study described ER to be associated with increased left ventricular mass. However, ER was more often present in blacks than non-blacks (14% vs 5.0%, $p < 0.00001$) [23] and a previous analysis from the Dallas Heart Study showed that left ventricular hypertrophy is more prevalent in blacks than non-blacks [24].

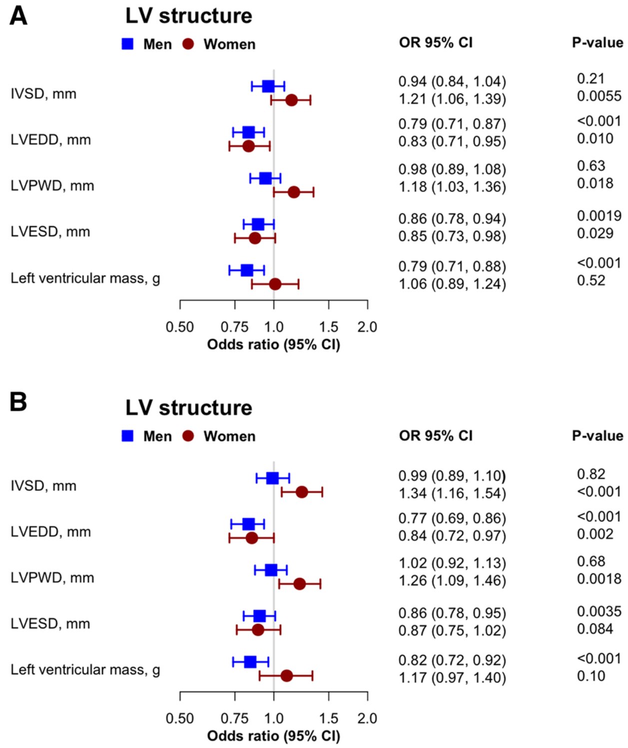

Fig. 2 Forest plots of the association of ER with left ventricular structure in the Gutenberg Health Study adjusted for age (**a**) and after multivariable adjustment including age, BMI, hypertension, diabetes, current smoker, heart rate and corrected QT interval (**b**). OR for presence of ER per unit standard deviation. *OR* odds ratio, *95% CI* 95% confidence interval

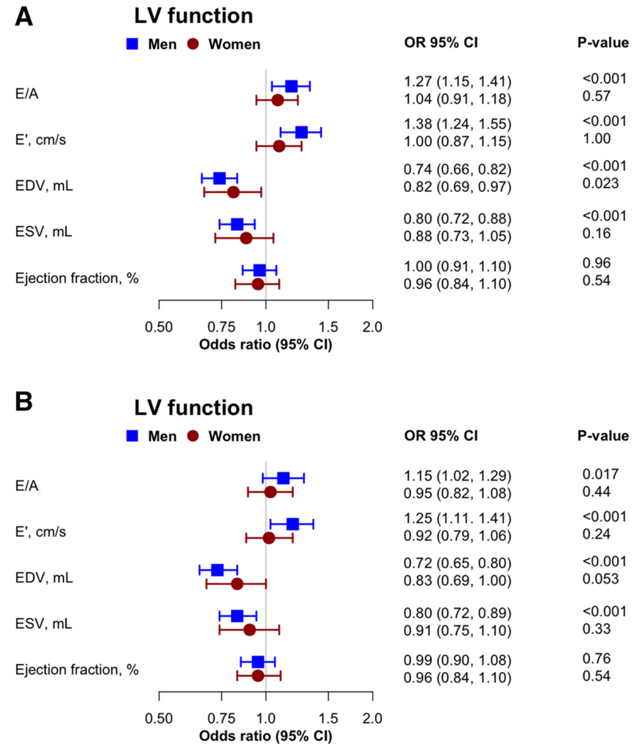

Fig. 3 Forest plots of the association of ER with left ventricular function in the Gutenberg Health Study adjusted for age (**a**) and after multivariable adjustment including age, BMI, hypertension, diabetes, current smoker, heart rate and corrected QT interval (**b**). OR for presence of ER per unit standard deviation. *OR* odds ratio, *95% CI* 95% confidence interval

In the present study we found robust results even after adjustment for confounders showing a smaller left ventricular cavity and lower left ventricular mass in men. In women, left ventricular diameters were also smaller, however statistical significance was not strong. One reason for this could be a lack of power in the female group due to a smaller sample size. Also, in women thickness of left interventricular septum and posterior wall were higher resulting in no difference in left ventricular mass.

Our findings in men were unexpected since the common opinion was that ER is present in male trained athletes with rather large left ventricles. In our sample the clinical picture of ER+ individuals predominantly includes male individuals with a slender habitus and a lower heart rate. Overall, this would reflect an asthenic body composition often accompanied by a high vagal activity, which is known to be present in ER+ individuals [22]. Interestingly, this does not reflect the traditional high cardiovascular risk phenotype, as higher heart rate and BMI are associated with increased cardiovascular mortality [25, 26]. However, the ER pattern is not a cardiovascular risk factor in the traditional sense leading to events such as myocardial infarction or stroke. ER is rather thought to represent an ECG variant which may confer an increased risk for malignant arrhythmias and sudden cardiac death in certain individuals. The exact mechanisms by which the ER pattern confers this risk are yet unclear. The current notion is that the ER pattern on the surface ECG reflects a form of transmural electrical heterogeneity eventually facilitating malignant ventricular arrhythmias [1, 27]. In terms of heart rate, ER associated ventricular arrhythmias have been shown to arise during periods of bradycardia, e.g., during sleep or rest [27, 28]. Whether the ER pattern is more likely to be present in individuals with a higher vagal activity or if a lower heart rate causes the ECG phenomenon of ER is currently unknown. However, it has been shown that intense physical training can induce ER [12] and the phenotype of ER can disappear when physical training is discontinued [20]. Similar findings have been described by Walsh and colleagues [29] showing that study participants presenting with ER were more likely to be male, lean, had a longer exercise duration and a lower heart rate. Interestingly, after 20 years of follow-up the majority of participants who presented with ER at age of 25 had lost the phenotype [29]. Predictors of ER maintenance included among others a low BMI and a lower left ventricular diastolic diameter, which is in line with our results.

Moreover, our data are supported by the fact that the results are consistent independent of the echocardiographic quantification method using either M-mode measurements for left ventricular diameters or planimetry for left ventricular volumes. This underlines a robust inverse association of ER with left ventricular size. Regarding left ventricular function, both diastolic and systolic function were regular in ER+ and ER− individuals. In men, presence of ER was associated with a slightly better diastolic function, whereas this was not the case in women. Although, higher BMI [30], and increased age [31] are risk factors for an impaired diastolic function the results remained consistent in the multivariable analysis. However, taking the differences in wall thickness between men and women into account the changes in diastolic function may only be a proxy of the left ventricular wall thickness.

Although by now four high-risk variants of ER have been identified, [4, 7–9], their role in individual risk prediction has not been sufficiently investigated. In the present study we could not detect a risk subtype which is associated with specific structural alterations. Overall, the high-risk subtypes showed similar results compared with the entire ER+ group. Therefore, the question remains how to deal with ER+ individuals in the daily routine. What helps us discriminate between the benign common ER pattern and its rare hazardous counterpart? It appears necessary not only to consider the ECG but rather the whole individual, including clinical characteristics and echocardiographic parameters. Our study is the first large-scale echocardiographic analysis of ER in the community. Importantly, presence of ER is not associated with pathologic structural or functional alterations in echocardiography. However, ER was more prevalent in young and slender men with smaller left ventricular dimensions. Our data add a further piece to the puzzle that the ER pattern may represent a primary electrophysiological disorder in otherwise healthy individuals, i.e., a channelopathy. However, learning from other arrhythmic diseases like Brugada syndrome [32] further studies including more subtle imaging like cardiac magnetic resonance imaging [33] are required. In addition, analyses combining cardiac imaging with ECG analysis like electrocardiographic imaging (ECGI) as well as studies characterizing genetic determinants [34] may help to further identify ER+ individuals at risk.

Limitations

There are some limitations which need to be considered when interpreting the findings of the present study. First, the cohort investigated is of European ancestry and therefore, the results of our study cannot necessarily be extrapolated to other populations. Second, our study investigated standard systolic left ventricular function variables. More novel parameters such as global longitudinal strain may provide further insights into possible associations of ER with cardiac systolic and diastolic function [35]. Another limitation of our analysis is that we did not correct for multiple testing.

Conclusion

In this large population-based cohort we observed small, yet distinct differences in structural and functional echocardiographic measurements between individuals with and without the ER pattern. In particular, in men ER is not associated with a higher left ventricular mass or size, but rather shows an association with smaller left ventricular diameters and volumes. Whether this observation helps to explain pathophysiological relations with increased risk of arrhythmias and sudden cardiac death needs to be shown.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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