Sex-specific aspects of phospholamban cardiomyopathy: The importance and prognostic value of low-voltage electrocardiograms

Remco de Brouwer, MD,*† Laura M.G. Meems, MD, PhD,* Tom E. Verstraelen, MD,‡ Belend Mahmoud, MD,* Virginnio Proost, MD,‡ Arthur A.M. Wilde, MD, PhD,‡ Laurens P. Bosman, MD,§ Esmée van Drie, MD,¶ Paul A. van der Zwaag, MD, PhD,‖ J. Peter van Tintelen, MD, PhD,¶ Arjan C. Houweling, MD, PhD,** Maarten P. van den Berg, MD, PhD,* Rudolf A. de Boer, MD, PhD*

*From the *Department of Cardiology, University Medical Centre Groningen, Groningen, The Netherlands, †Netherlands Heart Institute, Moreelsepark Utrecht, The Netherlands, ‡Heart Centre, Department of Cardiology, Amsterdam University Medical Centre, Amsterdam, The Netherlands, §Department of Cardiology, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands, ¶Department of Genetics, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands, ‖Department of Clinical Genetics, University Medical Centre Groningen, Groningen, The Netherlands, and **Department of Clinical Genetics, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, The Netherlands.*

BACKGROUND A pathogenic variant in the gene encoding phospholamban (PLN), a protein that regulates calcium homeostasis of cardiomyocytes, causes PLN cardiomyopathy. It is characterized by a high arrhythmic burden and can progress to severe cardiomyopathy. Risk assessment guides implantable cardioverter-defibrillator therapy and benefits from personalization. Whether sex-specific differences in PLN cardiomyopathy exist is unknown.

OBJECTIVE The purpose of this study was to improve the accuracy of PLN cardiomyopathy diagnosis and risk assessment by investigating sex-specific aspects.

METHODS We analyzed a multicenter cohort of 933 patients (412 male, 521 female) with the PLN p.(Arg14del) pathogenic variant following up on a recently developed PLN risk model. Sex-specific differences in the incidence of risk model components were investigated: low-voltage electrocardiogram (ECG), premature ventricular contractions, negative T waves, and left ventricular ejection fraction.

RESULTS Sustained ventricular arrhythmias (VAs) occurred in 77 males (18.7%) and 61 females (11.7%) ($P = .004$). Of the 933 cohort members, 287 (31%) had $\geq$1 low-voltage ECG during follow-up (180 females [63%], 107 males [37%]; $P = .006$). Female sex, age, age at clinical presentation, and proband status predicted low-voltage ECG during follow-up (area under the curve: 0.78). Sustained VA-free survival was lowest in males with low-voltage ECG ($P < .001$).

CONCLUSION Low-voltage ECGs predict sustained VA and are a component of the PLN risk model. Low-voltage ECGs are more common in females, yet prognostic value is greater in males. Future studies should determine the impact of this difference on the risk prediction of PLN cardiomyopathy and possibly other cardiomyopathies.

KEYWORDS Arrhythmogenic cardiomyopathy; Cardiogenetics; Low-voltage electrocardiogram; Personalized medicine phospholamban; Sex characteristics; Sex-related differences; Sex-specific differences

Funding Sources: This work was supported by a grant from the Leducq Foundation [Cure PhosphoLambaN induced Cardiomyopathy (Cure-PLaN)]; by grants from the Netherlands Heart Foundation (CVON PREDICT2 Grant 2018-30); by other grants (CVON-eDETECT Grant 2015-12, CVON SHE-PREDICTS-HF Grant 2017-21, CVON RED-CVD Grant 2017-11, CVON DOUBLE DOSE Grant 2020B005); and by a grant from the European Research Council (ERC CoG 818715, SECRETE-HF). Disclosures: The UMCG, which employs several of the authors, received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals Gmbh, Ionis Pharmaceuticals, Inc., Novo Nordisk, and Roche. Dr de Boer received speaker fees from Abbott, AstraZeneca, Bayer, Novartis, and Roche. Dr Wilde is a member of the steering committee of LQT Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. **Address reprint requests and correspondence:** Dr Rudolf A. de Boer, Department of Cardiology, University Medical Centre Groningen, Hanzeplein 1, Building 3215, Room 430, Internal code AB43, 9713 GZ, Groningen, The Netherlands. E-mail address: r.a.de.boer@umcg.nl.

https://doi.org/10.1016/j.hrthm.2021.11.009

Table 1 Total cohort

	Overall (N = 933)	Male (n = 412)	Female (n = 521)	*P* value
Age (y)	51.9 ± 18.0	51.9 ± 18.7	51.9 ± 17.4	.986
Age at first presentation (y)	42.4 ± 17.8	42.2 ± 18.3	42.6 ± 17.4	.734
Age at first symptom (y)	46.0 ± 14.4	45.0 ± 14.9	46.9 ± 14.0	.223
Hypertension	108 (13.6)	50 (14.2)	58 (13.1)	.724
Type 2 diabetes mellitus	31 (3.9)	18 (5.1)	13 (2.9)	.163
BMI (kg/m^2)	24.4 ± 4.3	24.5 ± 3.8	24.4 ± 4.6	.700
Echocardiographic LVEF (%)	47.4 ± 14.6	46.7 ± 15.0	47.9 ± 14.2	.323
PVCs per 24 h on Holter	179 [1145.3]	208.5 [1237.0]	173.5 [1085.8]	.471
Highest no. of PVCs per 24 h on Holter	2115.7 ± 4757.0	2188.6 ± 5123.7	2063.5 ± 4483.1	.748
Leads with inverted T waves	1.85 ± 2.4	1.78 ± 2.3	1.89 ± 2.5	.489
Sustained VA during follow-up	138 (14.8)	77 (18.7)	61 (11.7)	.004
Low-voltage ECG during follow-up	287 (30.8)	107 (26.0)	180 (34.5)	.006
Proband status	202 (21.7)	93 (22.6)	109 (20.9)	.597
Cardiovascular death	35 (3.8)	21 (5.1)	14 (2.7)	.080
Five-year risk of VA (%)	5.4 [12.1]	5.6 [11.3]	5.1 [13.0]	.911
Follow-up (y)	4.8 [6.8]	4.8 [7.4]	4.8 [6.5]	.737

Values are given as mean ± SD, n (%), or median [interquartile range] unless otherwise indicated.

BMI = body mass index; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; PVC = premature ventricular contraction; VA = ventricular arrhythmia.

Introduction

Phospholamban (PLN) cardiomyopathy is a specific subtype of hereditary cardiomyopathy caused by *PLN* p.(Arg14del), a pathogenic variant in the gene encoding PLN, which is a protein with a central role in calcium homeostasis in cardiac tissue. This protein ensures proper contraction and relaxation of the human heart.[1] Carriers of this pathogenic variant have a high risk of developing dilated cardiomyopathy (DCM), arrhythmic cardiomyopathy (ACM), or both.[2] They commonly have a high arrhythmic burden, with premature ventricular contractions (PVCs) and ventricular tachycardia, remarkable low-voltage electrocardiograms (ECGs), left ventricular dysfunction, and a positive family history for sudden cardiac death.[2–6]

PLN p.(Arg14del) cardiomyopathy has been found in several European countries, but also in the United States, Canada, and China.[7] On a global scale it is a rare disease, but it is particularly common in The Netherlands, with the pathogenic variant being present in 12% of all ACM patients and 15% of all DCM patients.[6] We have identified *PLN* p.(Arg14del) carriers throughout The Netherlands, enabling us to thoroughly investigate possible sex-related presentation or phenotypes.

Although it has been suggested that males with ACM more often suffer from arrhythmias than females, the size of the current cohort enables us to answer this question more definitively.[8,9] Sex-specific differences in risk factors may be helpful to refine personalized risk scores, which in turn might improve disease prognosis as well as clinical judgment throughout the management of the disease. The recently published risk prediction model[7] emphasizes 4 distinct components: left ventricular ejection fraction (LVEF), ventricular

Table 2 Low-voltage ECG cohort

	Overall (N = 287)	Male (n = 107)	Female (n = 180)	*P* value
Age (y)	58.5 ± 13.4	57.5 ± 13.6	59.1 ± 13.3	.339
Age at first presentation (y)	46.9 ± 13.8	44.6 ± 14.1	48.2 ± 13.4	.030
Age at first symptom (y)	46.7 ± 13.6	43.2 ± 13.7	49.3 ± 13.0	.003
Hypertension	30 (11.3)	11 (11.1)	19 (11.4)	1
Type 2 diabetes mellitus	12 (4.6)	8 (8.2)	4 (2.4)	.060
BMI (kg/m^2)	25.6 ± 4.2	25.7 ± 3.6	25.6 ± 4.6	.888
Echocardiographic LVEF (%)	38.5 ± 15.9	36.3 ± 15.9	39.9 ± 15.8	.081
PVCs per 24 h on Holter	958.0 [2452.0]	999.0 [2469.0]	928 [2343.5]	.724
Highest no. of PVCs per 24 h on Holter	3390.3 ± 4908.7	3377.3 ± 4928.6	3397.2 ± 4916.9	.978
Leads with inverted T waves	3.15 ± 2.9	3.46 ± 2.8	2.97 ± 2.9	.160
Sustained VA during follow-up	97 (33.8)	55 (51.4)	42 (23.3)	<.001
Proband status	133 (46.3)	58 (54.2)	75 (41.7)	.053
Cardiovascular death	25 (8.7)	14 (13.1)	11 (6.1)	.070
Five-year risk of VA (%)	16.0 [17.5]	14.2 [22.7]	16.8 [16.1]	.991
Follow-up time (y)	7.4 [9.4]	6.4 [8.2]	8.0 [9.4]	.084

Values are given as mean ± SD, n (%), or median [interquartile range] unless otherwise indicated.

Abbreviations as in Table 1.

arrhythmia (VA) burden (number of PVCs per day), low-voltage ECG, and the number of T waves with inversion on resting ECG. This risk model does not distinguish between males and females. Clearly, this harbors intrinsic limitations, as low-voltage ECG criteria are not similar for males and females, given sex-specific differences in body fat percentage, physical features, and lower ECG voltages in females in general.[10–12] To investigate whether sex-specific analysis is relevant, we evaluated the risk score components in male and female *PLN* p.(Arg14del) carriers and investigated their association with the incidence of VA.

Materials and methods

PLN Registry

We leveraged a subset of the Netherlands Arrhythmogenic Cardiomyopathy Registry (ACM Registry), a database containing the retrospective data gathered from a national observational cohort of patients with different ACMs, and their family members.[13] This database allowed for selection of *PLN* p.(Arg14del) carriers, and this subset will be referred to as the *PLN* Registry. This registry contains records from centers all across The Netherlands, minimizing center-based bias.[13] All members of the study cohort provided informed consent before genetic testing. The study was performed in accordance with the principles of the Helsinki Declaration as revised in 2013, and an institutional review board approved the study protocol.

Study population

The PLN Registry contained data from 1119 subjects with the PLN p.(Arg14del) variant. From this initial cohort, 186 were excluded for the following reasons: unknown sex (18), unknown pedigree (86), and unknown age at first clinical presentation (82), resulting in a cohort of 933 subjects (mean age 51.9 years; 55.8% female) with sufficient data available for analysis. Time-to-event data were available for 763 of 933 subjects. Patient information was obtained from first clinical presentation to the last follow-up appointment. Median [Q1–Q3] follow-up period was 4.8 [1.5–8.3] years.

All data in the PLN Registry were collected from (semi-) anonymized medical records. Demographics, medical and family histories, ECGs, exercise stress tests, Holter registration, signal-averaged ECGs, echocardiograms, magnetic resonance imaging, coronary angiographs, electrophysiological studies,

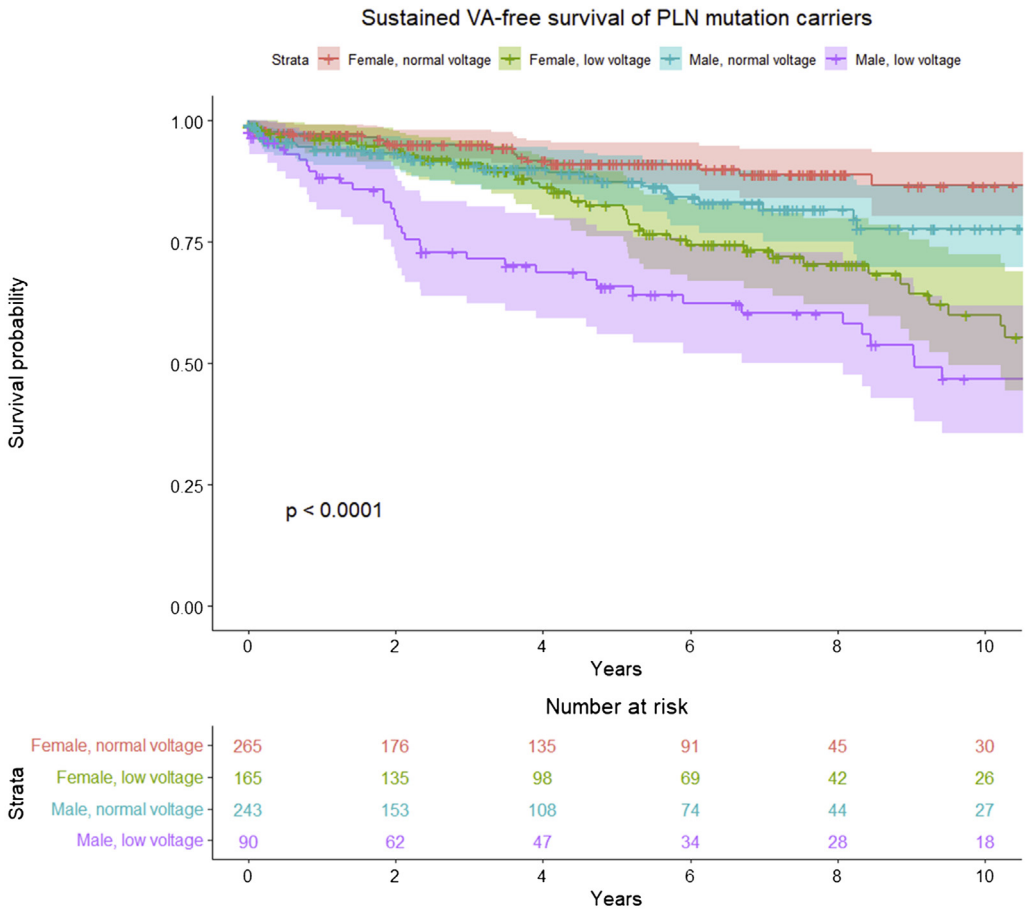

Figure 1 Time-to-event analysis showing probability of sustained ventricular arrhythmia (VA)-free survival. Males with ≥1 low-voltage electrocardiograms performed worse than all other subgroups. PLN = phospholamban.

biopsies, genetic tests, and pathology reports were collected for all patients, unless reported otherwise.

PLN pathogenic variant carriers were defined as subjects with an identified p.(Arg14del) variant. Probands were defined as the first (symptomatic) variant carrier per family to present clinically. Low-voltage ECGs were defined as ECGs with precordial lead (V_1–V_6) voltages $\leq$1.0 mV or inferior leads (I, II, and III) voltages $\leq$0.5 mV. Sustained VA was defined as ventricular tachycardia lasting $\geq$30 seconds, or <30 seconds when terminated electrically or pharmacologically, or ventricular fibrillation, or (aborted) sudden cardiac death. Death was defined as mortality independent of cause; cardiovascular death was defined as death of cardiovascular origin as determined by a cardiologist. Risk scores were calculated with the use of the PLN risk prediction model and baseline data. Baseline data were used in Tables 1 and 2, except for body mass index (BMI) and number of inverted T waves, where the highest value for each record was selected. All data pertaining to outcomes (arrhythmias, death, and others) were verified by a cardiologist.

Statistical analysis

Continuous data are given as mean ± SD in case of normally distributed data, or median [interquartile range] in case of non-normally distributed data. Categorical variables are given as absolute values (%). Due to rounding, percentages do not always add up to 100%. Baseline characteristics between males and females were compared using the χ^2 test for categorical variables, the Student *t* test for normally distributed continuous variables, and the Mann-Whitney *U* test for non-normally distributed continuous variables. The primary endpoint was defined as sustained VA during follow-up. Secondary endpoints were defined as all-cause mortality, cardiovascular death, and low-voltage ECG during follow-up.

Logistic regression analysis was performed to determine the predictive value of low-voltage ECG and primary endpoint. Sex-specific associations of low-voltage ECG with primary endpoint were evaluated using adjusted logistic regression analyses with interaction term *sex*low-voltage ECG*. To find factors predicting the occurrence of low-voltage ECGs during follow-up and to investigate the influence of sex on the prognostic value of low-voltage ECGs, logistic modeling was used. Potential predictive factors were hypothesized based on existing literature and the current risk prediction model. Their individual effect was then measured, and the 4 most impactful factors were selected. The relationship between a subject having $\geq$1 low-voltage ECGs during follow-up and experiencing a sustained VA during that same time period was investigated using the χ^2 test for independence. Subanalyses of the 2021 prediction model were performed,[7] using the same dataset used in that publication, by comparing the model with and without the use of an interaction term for low voltage with sex. Time-to-event analysis was performed using the date of acquisition of the first ECG as the baseline date. The earliest date between the date of the first sustained VA and the date of death was used as the event date. The association between survival time and selected predictor variables was analyzed using the Cox proportional hazards model. Survival curves were compared against one another to test for statistical significance using likelihood ratio testing.

Analyses were performed using R-Studio Version 1.3.1073 (R Studio, Boston, MA), a graphical interface for the R statistical package Version 4.0.2 (the R foundation for statistical computing platform, Vienna, Austria). Graphs were plotted using the *graphics*, *pROC*, *ggsurvplot*, and *ggplot2* packages. P <.05 were considered significant.

Table 3 Sustained VA in total cohort (N = 933)

	Normal voltage	Low voltage	*P* value
No sustained VA (%)	605 (65)	190 (20)	<.001
Sustained VA (%)	41 (4)	97 (10)	<.001

Values are given as n (%).
VA = ventricular arrhythmia.

Results

Baseline and follow-up characteristics for the overall cohort are listed in Table 1 and for the low-voltage ECG cohort in Table 2. Mean age and incidence of comorbidities did not differ significantly between males and females. Overall, cardiac function was comparable between males and females. Median [Q1–Q3] 5-year risk of VA was 5.6% [1.5%–12.7%] for males and 5.1% [1.3%–9.8%] for females (P = .911), calculated using baseline data. Sustained VA occurred in 77 males (18.7%) and in 61 females (11.7%) (P = .004). Analyzing the risk score components in males and females showed no significant differences in LVEF, PVCs per day, and number of inverted T waves on resting ECG. Of 521 females, 180 (35%) showed $\geq$1 low-voltage ECGs during median [Q1–Q3] follow-up of 4.8 [1.5–8.3] years. In 412 males, 107 (26.0%) showed $\geq$1 low-voltage ECGs during follow-up, the difference being significant (P = .006). Time-to-event analysis showed worse performance of male subjects with $\geq$1 low-voltage ECGs compared to all other subgroups (P <.001) (Figure 1).

Next, we assessed the importance of low-voltage ECGs in males and females. Both males and females with low-voltage ECGs more frequently reached the primary endpoint of sustained VA (Table 3). In addition, males with low-voltage ECGs reached the primary endpoint more often than females with low-voltage ECGs (Table 4). Sensitivity analysis

Table 4 Sustained VA in low-voltage cohort (N = 287)

	Female	Male	*P* value
No sustained VA	138 (48)	52 (18)	<.001
Sustained VA	42 (15)	55 (19)	<.001

Values are given as n (%).
VA = ventricular arrhythmia.

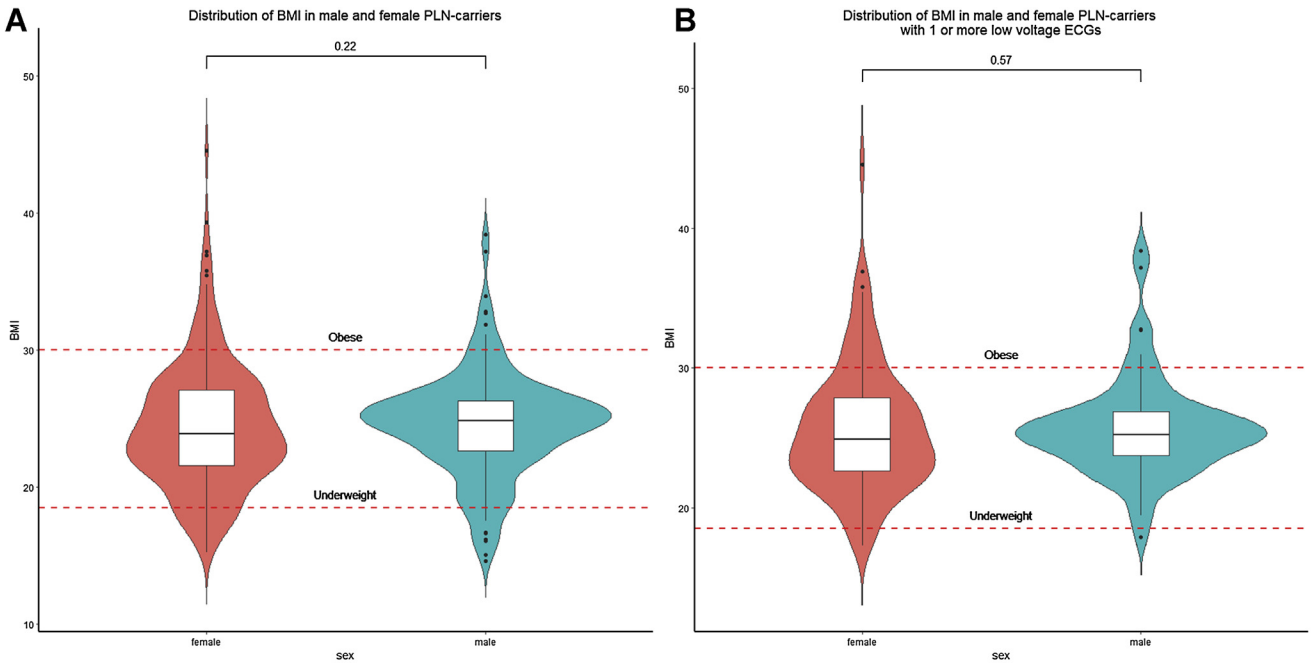

Figure 2 Graphical depiction of the distribution of body mass index (BMI) in male and female phospholamban (PLN) carriers, showing no significant difference between the groups. **A:** Total cohort. **B:** Low-voltage electrocardiogram (ECG) cohort.

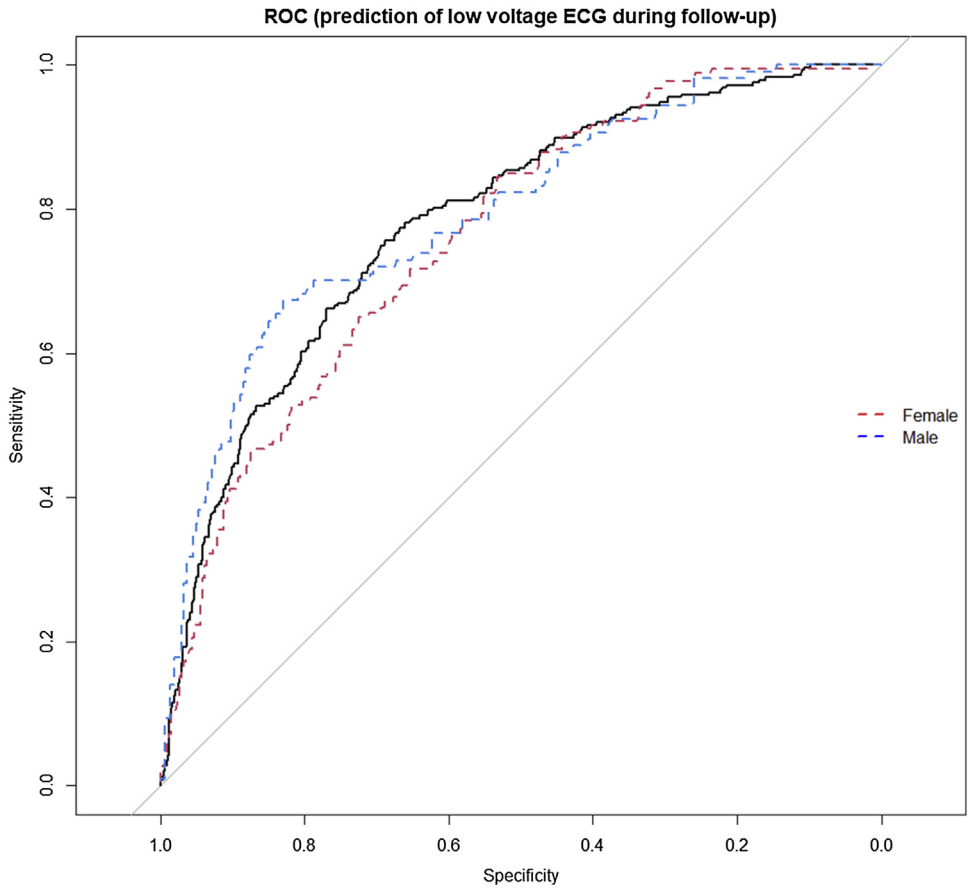

Figure 3 Receiver operating characteristic (ROC) curve of the low-voltage prediction model based on age, age at presentation, sex, and pedigree, showing an area under the curve of 0.78. ECG = electrocardiogram.

showed that the association between low-voltage ECG and VA was independent of BMI (Figure 2). Excluding subjects with BMI $\geq$30 kg/m^2 resulted in the same association (Supplemental Tables 1 and 2). The incidence of cardiovascular death did not significantly differ between males and females, either with or without low-voltage ECGs.

Logistic regression was used to identify predictors for low-voltage ECGs. Older age, younger age at presentation, female sex, and proband status were shown to be predictors of low-voltage ECGs with an area under the curve of 0.78 (Figure 3).

Cox proportional hazards analysis showed male sex and the acquisition of low-voltage ECG during follow-up to increase the risk of sustained VA, with multivariate analysis showing a hazard ratio of 1.7 for male sex (P = .002) and a hazard ratio of 2.8 for low-voltage ECG (P <.001) (Table 5).

Discussion

In this study, we examined the association between sex and several risk factors of a risk model of PLN p.(Arg14del) cardiomyopathy. Our most important finding is that the known association between low-voltage ECGs and sustained or life-threatening VA, one of the current pillars of risk prediction in *PLN* p.(Arg14del) cardiomyopathy, differs between male and female carriers. It has a reduced predictive power in females in our logistical regression analysis, and there is a significantly increased proportion of males with sustained VA in our low-voltage ECG cohort.

Strikingly, our results show that the prevalence of low-voltage ECGs was higher in females, whereas sustained VA during follow-up was more prevalent in males. We additionally identified predictors for low-voltage ECGs and sustained VA. Therefore, our main secondary findings are that (1) sustained VA during follow-up occurs significantly more often in male *PLN* p.(Arg14del) carriers; (2) male *PLN* p.(Arg14del) carriers have significantly shorter sustained VA-free survival; and (3) male *PLN* p.(Arg14del) carriers with $\geq$1 low-voltage ECGs reach the endpoint of sustained VA earlier than all other subgroups.

Sex-specific differences in heart failure

Our results show sex-specific differences in one specific type of hereditary cardiomyopathy and build on more than a decade of research on sex-specific differences in heart failure. Earlier research shows that males develop heart failure more frequently and at a younger age, whereas females have a higher risk of developing heart failure with preserved ejection fraction.[14,15] Heart failure may be caused by ischemia of, or injury to, the cardiac muscle, and the remodeling that occurs afterward is suggested to be sex-specific as well.[16] Furthermore, a 2020 review by Suthahar et al[17] lists several sex-related differences in biomarkers linked to heart failure. Given that sex-specific aspects may be of importance, we assumed that there may be sex-specific differences in PLN cardiomyopathy as well. Sex-specific differences in PLN p.(Arg14del) cardiomyopathy were investigated by van Rijsingen et al[8] in 2014, but at that time the aggregate number of patients was much smaller and no definitive conclusions could be drawn. The current larger cohort allowed us to investigate possible sex-specific differences more thoroughly.

Table 5 Cox proportional hazards analysis (N = 763)

	Coefficient	Hazard ratio	*P* value
Univariate analysis			
Male sex	0.4153	1.5149	.0139
Low-voltage ECG during follow-up	0.9522	2.5914	<.001
Multivariate analysis			
Male sex	0.5298	1.6986	.0018
Low-voltage ECG during follow-up	1.0139	2.7564	<.001

ECG = electrocardiogram.

Screening and prognosis of PLN cardiomyopathy

Close relatives of probands with a pathogenic variant mostly undergo screening in the setting of cascade genetic testing. If the specific pathogenic variant is identified, these genotype-positive relatives receive consecutive clinical screening, including physical examination, echocardiography, ambulatory (Holter) and regular ECG, and, in most cases, magnetic resonance imaging. In the initial risk score, LVEF <45% and/or a documented nonsustained ventricular tachycardia was deemed sufficient for implantable cardioverter-defibrillator (ICD) implantation.[7] This score was recently upgraded to an improved risk prediction model,[9] which includes LVEF, PVCs per 24 hours, number of ECG leads with negative T waves, and the presence of low-voltage ECGs as risk factors. This model is used to calculate the 5-year risk of VA in mutation carriers, and the current national standard recommends follow-up visits each 1–2 years. Supplemental Figure 1 illustrates how these 4 individual factors are used to calculate a total risk percentage. In The Netherlands, ICD implantation is recommended if risk is >5% (ie, >1% per year). Because the 2021 model is not sex-specific and includes the sex-specific low-voltage ECG criterion, we hypothesize that the accuracy of the risk prediction model may be increased by distinguishing between the sexes.

Clinical relevance

Currently, the 5-year risk of VA is an important figure in recommending an ICD as primary prevention in individuals carrying the PLN p.(Arg14del) variant. This study shows that the predictive power of low-voltage ECGs is lower in females than in males, which may result in overtreatment of females. ICD placement is not without risks, as up to 10% of patients experience at least 1 complication.[18,19] Therefore, our results should be taken into account by clinicians. A borderline ICD indication in a female mutation carrier may warrant closer examination,

for example, through more frequent clinic visits or Holter registration, before recommending ICD implantation. Taking our findings into account could increase the accuracy of a next iteration of the PLN risk prediction model, although our findings do not invalidate the effectiveness of the current model. As illustrated in Supplemental Figure 1, both males and females can reach the threshold for ICD implantation used in The Netherlands (5%) by the presence of low-voltage ECGs. Future studies should investigate the sex-specific validity of the tests currently used for PLN prognosis. It may be argued that using identical screening modalities for both sexes is suboptimal. In particular, low-voltage ECG threshold values should be further investigated, as these currently do not take sex into account.

This study also has implications for prognostic models used in other arrhythmogenic cardiomyopathies or types of heart failure. For instance, in arrhythmogenic right ventricular cardiomyopathy, QRS morphology is an element of the scoring system, and in heart failure with reduced ejection fraction the decision for biventricular pacing depends on QRS width. It remains to be evaluated whether the Task Force Criteria used in the diagnosis of arrhythmogenic right ventricular cardiomyopathy or heart failure guidelines could be further optimized by introducing sex-specific cutoff values.

Sex-specific ECG

In cardiac imaging, sex-specific normal values and threshold values are used. Additionally, measurements are often normalized using body surface area to compensate for inter-individual biological variation. Our findings show that what is already standard practice in cardiac imaging may be the next step in enhancing the diagnostic and predictive value of ECG, and that using a single set of normal or threshold values may create an upper bound in the clinical validity of ECG. This phenomenon was described earlier for hypertrophic cardiomyopathy,[20] yet adjusting ECG findings based on sex or body surface area is still not part of standard practice. Future research should be aimed at combining raw ECG data and matched clinical outcome data to calculate optimal *PLN*-specific low-voltage criteria.

Study limitations

The data from the PLN Registry is retrospective, and although its multicenter origin mitigates center-based bias, it is still open to selection bias due to the most affected subjects being more motivated to go through the registration process than asymptomatic family members without severely affected relatives. Working with retrospective data meant that we had to build our statistical analyses around the available data. As a consequence, the association of low-voltage ECG with outcomes could not be adjusted by BMI and may have been confounded by body habitus. Additionally, retrospective studies are vulnerable to recall bias, and we attempted to mitigate this by using, where possible, objective data such as dates of hospital admission and registered dates of clinical interventions instead of self-reported dates. Finally, misclassification bias is an inherent risk to retrospective studies, possibly causing subjects to be placed into the wrong analysis (sub)group. Stratifying VA events by their severity was not feasible with the available information, so we assumed equal importance of all documented sustained VAs and accept that some VA events may have been relatively benign.

Conclusion

Our results show sex-specific differences in low-voltage ECGs, which is 1 of the 4 components of the current PLN p.(Arg14del) risk prediction model. Low-voltage ECGs, currently used in the prognosis of PLN cardiomyopathy, occur more often in females but have greater predictive power in males. Males experience sustained VA sooner than females, and males with low-voltage ECGs even sooner. Further investigation is needed to determine whether these results merit another look at the definition of a low-voltage ECG, and whether identical threshold and normal values should be used for males and females.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.11.009.

References

1. Haghighi K, Kolokathis F, Gramolini AO, et al. A mutation in the human phospholamban gene, deleting arginine 14, results in lethal, hereditary cardiomyopathy. Proc Natl Acad Sci U S A 2006;103:1388–1393.
2. van der Zwaag PA, van Rijsingen IAW, Asimaki A, et al. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. Eur J Heart Fail 2012;14:1199–1207.
3. Liu G-S, Morales A, Vafiadaki E, et al. A novel human R25C-phospholamban mutation is associated with super-inhibition of calcium cycling and ventricular arrhythmia. Cardiovasc Res 2015;107:164–174.
4. Cuello F, Knaust AE, Saleem U, et al. Impairment of the ER/mitochondria compartment in human cardiomyocytes with PLN p.Arg14del mutation. EMBO Mol Med 2021;13:e13074.
5. Posch MG, Perrot A, Geier C, et al. Genetic deletion of arginine 14 in phospholamban causes dilated cardiomyopathy with attenuated electrocardiographic R amplitudes. Heart Rhythm 2009;6:480–486.
6. Hof IE, van der Heijden JF, Kranias EG, et al. Prevalence and cardiac phenotype of patients with a phospholamban mutation. Neth Heart J 2019;27:64–69.
7. Verstraelen TE, van Lint FHM, Bosman LP, et al. Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers–reaching the frontiers of individual risk prediction. Eur Heart J 2021;42:2842–2850.
8. van Rijsingen IAW, van der Zwaag PA, Groeneweg JA, et al. Outcome in phospholamban R14del carriers: results of a large multicentre cohort study. Circ Cardiovasc Genet 2014;7:455–465.
9. Choudhary N, Tompkins C, Polonsky B, et al. Clinical presentation and outcomes by sex in arrhythmogenic right ventricular cardiomyopathy: findings from the North American ARVC Registry. J Cardiovasc Electrophysiol 2016;27:555–562.
10. Macfarlane PW. The influence of age and sex on the electrocardiogram. Adv Exp Med Biol 2018;1065:93–106.
11. Fuchs A, Mejdahl MR, Kühl JT, et al. Normal values of left ventricular mass and cardiac chamber volumes assessed by 320-detector computed tomography angiography in the Copenhagen General Population Study. Eur Heart J Cardiovasc Imaging 2016;17:1009–1017.

12. Rijnbeek PR, van Herpen G, Bots ML, et al. Normal values of the electrocardiogram for ages 16–90 years. J Electrocardiol 2014;47:914–921.
13. Bosman LP, Verstraelen TE, van Lint FHM, et al. The Netherlands Arrhythmogenic Cardiomyopathy Registry: design and status update. Neth Heart J 2019; 27:480–486.
14. Meyer S, van der Meer P, van Deursen VM, et al. Neurohormonal and clinical sex differences in heart failure. Eur Heart J 2013;34:2538–2547.
15. Ho JE, Enserro D, Brouwers FP, et al. Predicting heart failure with preserved and reduced ejection fraction. Circ Heart Fail 2016;9(6):e003116.
16. Piro M, Della Bona R, Abbate A, Biasucci LM, Crea F. Sex-Related differences in myocardial remodeling. J Am Coll Cardiol 2010; 55:1057–1065.
17. Suthahar N, Meems LMG, Ho JE, Boer RA. Sex-related differences in contemporary biomarkers for heart failure: a review. Eur J Heart Fail 2020;22:775–788.
18. Ganesan AN, Moore K, Horton D, et al. Complications of cardiac implantable electronic device placement in public and private hospitals. Intern Med J 2020; 50:1207–1216.
19. van Barreveld M, Verstraelen TE, van Dessel PFHM, et al. Dutch outcome in implantable cardioverter-defibrillator therapy: implantable cardioverter-defibrillator–related complications in a contemporary primary prevention cohort. J Am Heart Assoc 2021;10:e018063.
20. Huurman R, Schinkel AFL, van der Velde N, et al. Effect of body surface area and gender on wall thickness thresholds in hypertrophic cardiomyopathy. Neth Heart J 2020;28:37–43.