The value of electrocardiography and echocardiography in distinguishing Fabry disease from sarcomeric hypertrophic cardiomyopathy

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The value of electrocardiography and echocardiography in distinguishing Fabry disease from sarcomeric hypertrophic cardiomyopathy

Abbreviated title: Diagnostic value of electrocardiography and echocardiography in Fabry disease

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Summary

Background. – Screening for Fabry disease is suboptimal in non-specialized centres.

Aim. – To assess the diagnostic value of electrocardiographic scores of left ventricular hypertrophy and a combined electrocardiographic and echocardiographic model in Fabry disease.

Methods. – We retrospectively reviewed the electrocardiograms and echocardiograms of 61 patients (mean age 55.6 ± 11.5 years; 57% men) with Fabry disease and left ventricular hypertrophy, and compared them with those from 59 patients (mean age 44.8 ± 18.3 years; 66% men) with sarcomeric hypertrophic cardiomyopathy. Six electrocardiography criteria for left ventricular hypertrophy were specifically analysed: Sokolow-Lyon voltage index; Cornell voltage index; Gubner index; Romhilt-Estes score; Sokolow-Lyon product (voltage index × QRS duration); and Cornell product (voltage index × QRS duration).

Results. – Right bundle branch block was more frequent in patients with Fabry disease (54% vs 22%; $P = 0.001$). QRS duration, Gubner score and Sokolow-Lyon product were significantly higher in patients with Fabry disease. Maximal wall thickness was higher in patients with sarcomeric hypertrophic cardiomyopathy (21.9 ± 5.1 vs 15.5 ± 2.9 mm; $P < 0.001$). Indexed sinus of Valsalva diameter was larger in patients with Fabry disease. After multivariable analysis, right bundle branch block, Sokolow-Lyon product, maximal wall thickness and aortic diameter were independently associated with Fabry disease. A model including these four variables yielded an area under the receiver operating characteristic curve of 0.918 (95% confidence interval 0.868–0.968) for Fabry disease.

Conclusion. – Our model combining easy-to-assess electrocardiographic and echocardiographic variables may be helpful in improving screening and reducing diagnosis delay in Fabry disease.

Résumé

Contexte. – Le dépistage de la maladie de Fabry reste sous optimal dans les centres non spécialisés.

Objectif. – L'objectif de notre étude est d'évaluer la valeur diagnostique des scores ECG d'hypertrophie ventriculaire gauche (HVG) et la valeur diagnostique pour le diagnostic de la maladie de Fabry d'un score combinant des critères électriques et échocardiographiques.

Méthodes. – Nous avons réalisé une étude rétrospective multicentrique comparant 61 patients (âge moyen 55,6 ± 11,5 ans ; 57 % d'hommes) atteints d'une maladie de Fabry avec HVG , à 59 patients

(âge moyen 44,8 ± 18,3 ans ; 66 % d'hommes) atteints d'une cardiomyopathie hypertrophique sarcomérique (CMH). Six critères ECG ont été analysés : index de Sokolow-Lyon ; index de Cornell ; index de Gubner ; score de Romhilt-Estes ; produit de Sokolow-Lyon ; et produit de Cornell.

Résultats. – Le bloc de branche de droit (BBD) était plus fréquent chez les patients Fabry (54 % vs 22 % ; *P* = 0,001). La durée des QRS, l'index de Gubner et le produit de Sokolow-Lyon étaient significativement plus élevés chez les patients atteints d'une maladie de Fabry. L'épaisseur maximale du VG était plus importante chez les patients atteints d'une CMH. Le diamètre aortique aux sinus de Valsalva était plus grand chez les patients atteints d'une maladie de Fabry. Après analyse multivariée, le BBD, le produit de Sokolow-Lyon, l'épaisseur maximale du VG et le diamètre aortique était associés de façon indépendante à la maladie de Fabry. Un modèle incluant ces 4 paramètres a permis d'obtenir une courbe ROC avec une AUC à 0.918 (intervalle de confiance à 95 % 0.868–0.968) pour la maladie de Fabry.

Conclusions. – Le produit de Sokolow-Lyon semble être le critère ECG le plus approprié pour distinguer maladie de Fabry et CMH. Notre modèle combinant des paramètres simples échographiques et électrocardiographiques pourrait améliorer le dépistage et le diagnostic de la maladie de Fabry.

KEYWORDS

Fabry disease;

Hypertrophic cardiomyopathy;

Electrocardiogram

MOTS CLÉS

Maladie de Fabry ;

Cardiomyopathie hypertrophique ;

Électrocardiogramme

Abbreviations: CI: confidence interval; HCM, hypertrophic cardiomyopathy; ICC, intraclass correlation coefficient; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular

ejection fraction; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; ROC, receiver operating characteristic.

Background

Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency of the enzyme α-A galactosidase. This enzyme deficiency generates a gradual accumulation of globotriaosylceramide and related glycosphingolipids in the lysosomes of many cell types, leading to a multisystemic disorder, including complex cardiomyopathy [1]. The prevalence of Fabry disease is historically estimated to be between 1/40,000 and 1/117,000 individuals; however, these data probably underestimate the true number of patients [2, 3].

Cardiac manifestations are mainly characterized by left ventricular hypertrophy (LVH), which might be the predominant feature of the disease [4]. Cardiac complications are associated with high morbidity and mortality because of arrhythmia and heart failure, and are currently the leading cause of death in Fabry disease [5, 6]. The recent guidelines from the European Society of Cardiology on hypertrophic cardiomyopathy (HCM) have strengthened their message regarding the importance of investigating rare causes of LVH, such as Fabry disease [7]. However, screening for Fabry disease remains suboptimal in non-specialized centres [8]. Improvements in diagnostic delay have not yet been achieved [9], and Fabry disease is often diagnosed late after the onset of the first clinical signs [10, 11]. As the efficiency of specific therapy for Fabry disease is heavily dependent on the stage of the disease [12], delays to diagnosis and starting treatment might result in a “loss of opportunity” for patients. This highlights the need to continue to develop screening tools for daily cardiology practice. Unlike amyloidosis, we still do not have a relevant echocardiographic tool that can differentiate Fabry disease from other more common causes of LVH [13]. Electrocardiography is an unavoidable first step when evaluating patients with HCM [7], and might suggest an underlying diagnosis [14]. Nevertheless, the electrocardiogram findings considered typical for Fabry disease (i.e. short PQ interval or atrioventricular block) might be present in other causes of HCM, and cannot be used alone as a specific marker of Fabry disease [14]. Similarly, the Sokolow-Lyon voltage index does not appear to be discriminatory for Fabry disease [15]. Other validated electrocardiographic criteria for LVH have been poorly investigated in Fabry disease.

In the present study, we aimed to evaluate: (1) the diagnostic value of the different electrocardiographic scores for LVH in Fabry disease; and (2) the diagnostic value for Fabry disease of a model combining electrocardiogram and echocardiographic criteria.

Methods

Population

We retrospectively included patients aged > 18 years with Fabry disease and LVH, who were admitted for routine follow-up to the outpatient department of five dedicated HCM centres in France between 2016 and 2019. The diagnosis of Fabry disease was confirmed by the low or missing level of activity of α-A galactosidase in leukocyte homogenates in men and mutational analysis of the α-A galactosidase genes in men and heterozygous women. Patients with Fabry disease were compared with patients with sarcomeric HCM selected randomly from two centres (Caen University Hospital and Pitié-Salpêtrière University Hospital) during the same period. The diagnosis of sarcomeric HCM was based on patient and family histories, typical echocardiographic findings, clinical exclusion of other differential diagnoses and genetic analysis. The medical records of all patients, including electrocardiographic and echocardiographic findings, were reviewed and entered into dedicated databases. Demographic details of age, sex, weight, height and heart rate were recorded. Body surface area was calculated according to the Dubois formula, and expressed in m^2. History of ischaemic stroke, proteinuria and cardiovascular risk factors were recorded. Cardiac symptoms and current medications, including Fabry disease-specific therapy, were noted. In the Fabry disease group, LVH was defined by a maximal wall thickness ≥ 13 mm using transthoracic echocardiography. In the sarcomeric HCM group, inclusion criteria were based on LVH ≥ 15 mm in sporadic cases, and ≥ 13 mm in the presence of a family history of HCM, also using transthoracic echocardiography.

Electrocardiogram analysis

Twelve-lead electrocardiograms at rest (speed recording of 25 mm/s, standardized calibration for 10 mm/mV) were separately reviewed by two readers (S. S. and N. J.), who were blinded to the cause of disease. The electrocardiogram reading was performed by consensus reading. Heart rate, presence of complete right bundle branch block (RBBB), left bundle branch block (LBBB), left anterior fascicular block, left posterior fascicular block, pathologic Q waves (defined by abnormal Q waves ≥ 40 ms in duration and/or ≥ 25% of the R wave in depth and/or ≥ 3 mm in depth in at least two contiguous leads except aVR [14]) and pre-excitation were noted. Corrected PQ interval (PQ interval/√RR, expressed in ms), QRS duration (ms) and corrected QT interval (calculated using the Bazett formula, and expressed in ms) were measured. Six electrocardiographic criteria for LVH were analysed according

to the specific American Heart Association guidelines [16]: Sokolow-Lyon voltage index (SV1 + RV5 or V6 ≥ 30 mm and ≥ 35 mm); Cornell voltage index (RaVL + SV3 ≥ 20 mm for women and ≥ 28 mm for men); Gubner index (RD1 + SV3 > 25 mm; Romhilt-Estes score; Sokolow-Lyon product (Sokolow-Lyon voltage index × QRS duration ≥ 3710 mm.ms); Cornell product (Cornell voltage index × QRS duration ≥ 2440 mm.ms). In cases of voltage differences within the same lead, only the largest complex was selected.

Two-dimensional transthoracic echocardiogram analysis

For each patient, a two-dimensional transthoracic echocardiogram was performed during the same consultation as the electrocardiogram, and was reviewed by a senior echocardiographer. The following variables were analysed: left ventricular ejection fraction (LVEF) using the modified biplane Simpson's rule; left ventricular (LV) maximal myocardial wall thickness measured from the parasternal short-axis view; presence of LV outflow tract obstruction secondary to a systolic anterior motion; and presence of right ventricular hypertrophy defined by a myocardial thickness > 5 mm in the long-axis view. Finally, the aortic root diameters were measured at the level of the sinuses of Valsalva and the tubular portion and indexed to body surface area. Left and right ventricular measurements, as well as aortic root diameters, were measured following the joint European Association of Echocardiography/American Society of Echocardiography guidelines [17]. Assessment of LV wall thickness and the presence of LV outflow tract obstruction were defined according to the European Society of Cardiology HCM guidelines [7].

Statistical methods

A comparative analysis of patients with Fabry disease and those with sarcomeric HCM was performed. Variables are expressed as means ± standard deviations (interquartile ranges) or as numbers and percentages. Continuous variables were compared by Student's *t* test. Qualitative variables were compared using Fisher's test or the χ^2 test. A multivariable analysis was performed, including all variables with $P \leq 0.10$ in the univariate analysis. A nomogram for the predictive value for Fabry disease was built to estimate the probability of Fabry disease based on the factors identified in the multivariable analysis. A receiver operating characteristic (ROC) curve was constructed to evaluate the predictive value of the previously defined model. The developed model was tested in the

specific subgroup of patients with the Asn215Ser mutation, the so-called “cardiac variant”. A reproducibility study of electrocardiogram tracings was performed by two observers (N. J., F. L.), who interpreted 10 tracings taken randomly from the sample. Intraobserver repeatability and interobserver reproducibility were assessed using the intraclass correlation coefficient (ICC); the 95% confidence interval (CI) was calculated using the delta method. Statistical analyses were carried out using R software, version 3.1.1.

Standard protocol approvals and patient consents

The study conformed to the principles outlined in the Declaration of Helsinki, and the ethics committee (CPP III Nord-Ouest) approved the research protocol.

Results

Overall, 61 patients with Fabry disease (men age 55.6 ± 11.5 years; 57% men) were included and compared with 59 patients with sarcomeric HCM (mean age 44.8 ± 18.3 years; 66% men). Patients with Fabry disease were older ($P < 0.001$). At the time of the clinical evaluation, 49 (80%) of the patients with Fabry disease were receiving a specific treatment for Fabry disease. Patients with Fabry disease and those with sarcomeric HCM were similar with respect to sex, tobacco, diabetes, cardiac symptoms and medication, except for beta-blockers and aldosterone antagonists, which were more frequently prescribed in the HCM group. Hypertension, ischaemic stroke and proteinuria were significantly more prevalent in patients with Fabry disease. The characteristics of our study population are given in Table 1.

Electrocardiography

QRS duration was significantly higher in the Fabry group (117 ± 27 vs 99 ± 25 ms; $P < 0.001$) and RBBB was more frequent in the Fabry group (54% vs 22%; $P = 0.001$). Heart rate, PQc and QTc intervals, LBBB, left anterior fascicular block, pre-excitation, pathologic Q waves and arrhythmia did not differ between the two groups. Regarding LVH indexes, the Gubner index (21.0 ± 14.0 vs 15.6 ± 13.0 mm; $P = 0.01$) and the Sokolow-Lyon product (3547 ± 1408 vs 2687 ± 1791 mm.ms; $P = 0.004$) were significantly higher in the Fabry group. The Sokolow-Lyon voltage index was higher in patients with Fabry disease, without reaching statistical significance (31.4 ± 12.4 vs 27.8 ± 16.7 ms; $P = 0.19$).

The Cornell voltage index, Romhilt-Estes score and Cornell product were similar in patients with Fabry disease and those with HCM. The results are shown in Table 2.

Echocardiography

Mean LVEF was lower in patients with Fabry disease, although LVEF was conserved in both groups, and only one patient with Fabry disease had an LVEF < 55%. The mean maximal thickness was higher in the HCM group (21.8 ± 4.8 vs 16.2 ± 3.5 mm; $P < 0.001$). The presence of right ventricular hypertrophy did not differ between the two groups. Aortic diameters for sinus of Valsalva and tubular aortic diameter were higher in patients with Fabry disease (Table 2).

Multivariable analysis

After multivariable analysis with electrocardiographic and echocardiographic variables, only RBBB, Sokolow-Lyon product, maximal wall thickness and indexed sinus of Valsalva diameter were independently associated with Fabry disease (Table 3). These four variables were included in a regression model, leading to the nomogram depicted in Fig. 1. ROC curves established to analyse predictive values of the Sokolow-Lyon product alone versus a full electrocardiographic and echocardiographic model are depicted in Fig. 2. A full model, including the Sokolow-Lyon product, RBBB, maximal wall thickness and indexed sinus of Valsalva aortic diameter yielded an area under the ROC curve of 0.918 (95% CI 0.868–0.968). The full model differed significantly compared with the Sokolow-Lyon product model.

We tested the proposed full model in the subgroup of patients with the Asn215Ser mutation, the so-called “cardiac variant”. Among our cohort of patients with Fabry disease, 13 (21%) had the Asn215Ser mutation (12 men; mean age 56 ± 10 years). The mean total score was 158 (range 149–185) in the Asn215Ser mutation group compared with 99 (range 68–133) in the sarcomeric HCM group.

Intraobserver repeatability and interobserver reproducibility

Intraobserver repeatability and interobserver reproducibility, assessed by the ICC, were excellent for all LVH electrocardiogram criteria, especially the Sokolow-Lyon product: intraobserver repeatability, ICC 0.99 (95% CI 0.96–0.99); interobserver reproducibility, ICC 0.98 (95% CI 0.95–0.99). The

Romhilt-Estes score showed the lowest reproducibility: intraobserver repeatability, ICC 0.84 (95% CI 0.38–0.96); interobserver reproducibility, ICC 0.86 (95% CI 0.45–0.96). The results are summarized in Table 4.

Discussion

In the present study, we aimed to assess the value of electrocardiographic and echocardiographic variables to discriminate Fabry disease and sarcomeric HCM. The most important finding of our analysis was the high diagnostic performance for the diagnosis of Fabry disease when combining the Sokolow-Lyon product and the presence of RBBB with maximal wall thickness and indexed aortic diameter. Using routine cardiological consultation criteria, we have provided a simple tool that might be helpful in increasing Fabry disease screening by cardiologists.

LVH is one of the most important warning signs for the identification of new patients with Fabry disease, providing cardiologists with an essential clue in the screening for this rare condition. Despite increased education, awareness messages and the emergence of new cardiac imaging tools, early diagnosis remains an unmet goal, especially in non-specialized cardiomyopathy centres. Magnetic resonance imaging myocardial T1 mapping is useful for diagnosing Fabry disease in cases of LVH [18], but is not yet widely available in all centres. The echocardiographic “red flags”, such as binary endocardium, papillary muscle hypertrophy, LVH pattern and LV circumferential strain analysis, are often disappointing or difficult to achieve in daily practice [19-21]. Electrocardiography is recommended in all patients with HCM, and might provide a clue in the diagnosis of rare aetiologies of HCM, especially when interpreted in conjunction with echocardiography [14]. Typical electrocardiogram findings in Fabry disease include PR interval shortening, increased QRS duration, voltage signs of LVH, repolarization abnormalities (including symmetric negative T waves) and various degrees of atrioventricular block [22]. Although “typical”, none of these signs is specific to Fabry disease [23]. Sarcomeric HCM may show the same electrocardiogram patterns, including LVH, negative T waves and ST-segment changes [24]. Unexplained LVH, in combination with pre-excitation or short PR interval, can be a characteristic of sarcomeric HCM or of *LAMP2* and *PRKAG2* mutations [25]. In our cohort, both PQ interval and pre-excitation were not relevant variables for differentiating Fabry disease and sarcomeric HCM. These results are in agreement with a large study of 207 patients with Fabry disease, where the PQ interval was not a common finding [26]. The increased QRS

duration is a common marker of the electrophysiological remodelling in Fabry disease [22, 27, 28], not only because of LVH [29], but also possibly because of the deleterious metabolic effects of the progressive infiltration of glycosphingolipids into the conduction tissue [30]. We observed an unexpectedly high prevalence of RBBB in our Fabry population; the more frequent right ventricular hypertrophy in patients with Fabry disease may be postulated to explain this finding. Besides, although speculative, initial elective injury to the right bundle branch by the gradual accumulation of globotriaosylceramide could also be evoked as another potential mechanism accounting for the greater frequency of RBBB in Fabry disease. Although RBBB was not helpful in differentiating Fabry disease and HCM in the work of Namdar et al. [15], previous studies and case reports have shown RBBB to be a frequent intraventricular conduction disorder in Fabry disease [27, 31]. In one of the first Fabry cohorts, Mehta et al. reported that RBBB was the most frequent evolution of intraventricular conduction defects [32], and Kramer et al. found RBBB in 15% of their patients with Fabry disease with severe myocardial fibrosis [27].

As suggested by our results and others [27, 31, 33], LBBB and QTc prolongation seem to be uncommon in Fabry disease, and should rather suggest other aetiologies of LVH [15, 31]. Among all the electrocardiogram criteria of LVH, the Sokolow-Lyon voltage index has been studied most in Fabry disease, despite its limitations; it is highly specific, but has low sensitivity compared with echocardiography or magnetic resonance imaging, especially in cases of eccentric LVH and RBBB [16]. This may explain why the Sokolow-Lyon voltage index did not discriminate patients with Fabry disease from HCM in the present and previous studies. The simple product of voltage criteria and QRS duration significantly improves the identification of LVH compared with voltage criteria alone [34, 35]. The value of the Sokolow-Lyon product in Fabry disease was previously suggested by Kampmann et al., who found a significant correlation between the Sokolow-Lyon voltage index $\times$ QRS duration product ($R2 = 0.52$) and LV mass [29]. Although the Sokolow-Lyon product might be the most appropriate electrocardiogram criteria for Fabry disease, and should be systematically calculated, its diagnostic performance was inferior to the full model combining electrocardiographic and echocardiographic variables. As there is no specific sign for Fabry disease considering both electrocardiography and transthoracic echocardiography, the addition of different electrocardiogram and echocardiographic variables could be of interest. Using mixed criteria, combining 12-lead QRS voltage < 30 mm and ratio of interventricular septal/posterior wall thicknesses < 1.6, Gustavsonn et al.

were able to differentiate hereditary transthyretin amyloidosis from sarcomeric HCM [36]. The unpredicted value of indexed aortic root diameter illustrates the potential value of mixed criteria. In a large cohort of patients with Fabry disease, Barbey et al. reported a dilation of the sinuses of Valsalva in one third of males and 5% of females, regardless of blood pressure level and other cardiovascular risk factors [37]. After multivariable analysis, sex, age and interventricular thickness were strongly associated with dilation at the sinus of Valsalva. Progressive accumulation of globotriaosylceramide in vascular smooth muscle cells in the media of the aorta [37-39] was proposed as a potential factor promoting structural aortic wall anomalies and dilation of the aorta, although exact underlying mechanisms remains to be elucidated. Although it is not considered as a marker of the disease alone, our full model assigned it an additional diagnostic value in the context of HCM with an electrical sign of LVH and RBBB. Of note, our model is compliant with the TRIPOD statement (see Appendix) [40]. A highly sensitive and specific model combining simple criteria available in the daily routine cardiology consultation might prevent dramatic delay in Fabry disease. As specific therapy efficiency appears lower when administered in an advanced stage of the disease [41], efforts must be aimed at developing diagnostic tools, improving diagnostic delay and starting specific treatment.

Study limitations

Our work had some limitations. We performed a retrospective study dealing with a relatively small number of patients with Fabry disease (although more than in most previous similar studies), which is an inherent problem with orphan diseases. We did not enrol newly diagnosed patients, which might have affected the results of the ROC curve analysis. The studied populations were not matched for age, which may have affected the results, especially electrocardiogram findings. However, voltages are liable to decline with increasing age, which would tend to underestimate the value of the Sokolow-Lyon voltage index. Moreover, the commonly used QRS voltage criteria applied in the present study can be applied to adults aged > 35 years [16]. In this study, we did not include recent, potentially helpful criteria, such as two-dimensional strain imaging. These modalities are still not used widely by cardiologists, and we wanted to examine the performance of simple and widely used criteria. We did not perform an external validation. Finally, we did not include other rare diseases, such as storage disorders (protein kinase adenosine monophosphate-activated non-catalytic subunit gamma 2 deficiency and Danon disease), mitochondrial disease and cardiomyopathies in neuromuscular

disease or Noonan's syndrome, which might be associated with LVH. In these rare disorders, extracardiac signs are usually the main clinical manifestations and strongly influence the diagnosis orientation, contrary to sarcomeric HCM and cardiac variant of Fabry disease.

Conclusions

The Sokolow-Lyon product might be the most appropriate electrocardiographic criterion for Fabry disease, and should be systematically calculated in case of HCM. We propose a combined model using electrocardiographic and echocardiographic variables available in routine cardiac consultation. This additional tool might be helpful in improving screening and reducing diagnostic and therapeutic delay in Fabry disease.

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Disclosure of interest

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The other authors declare that they have no conflicts of interest concerning this article.

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Figure legends

Figure 1. Nomogram for the predictive value for Fabry disease. The probability of Fabry disease is estimated on the “Total” axis by the sum of points for each co-variable value. The point for each co-variable is obtained by drawing a vertical line from the variable axis to the “Points” axis. As an example, a patient with a Sokolow-Lyon product of 3700 (20 points), right bundle branch block (30 points), a myocardial maximal thickness of 19.5 mm (60 points) and an indexed sinus of Valsalva aortic diameter of 22 mm/m² (50 points) has a total score of 160 points, leading to a probability of Fabry disease of > 90%.

Figure 2. Receiver operating characteristic curves for the predictive value for Fabry disease for the Sokolow-Lyon product (dotted line) and the full model, including electrocardiographic (Sokolow-Lyon product and right bundle branch block) and echocardiographic (myocardial maximal thickness and indexed sinus of Valsalva aortic diameter) variables. A significant difference was found between the two models ($P < 0.001$). AUC: area under the curve.

Table 1 Characteristics of the study population.

	Fabry disease (n = 61)	HCM (n = 59)	P
Age (years)	55.6 ± 11.5	44.8 ± 18.3	< 0.001
Male sex	35 (57)	39 (66)	0.42
Hypertension	26 (42.5)	11 (18.5)	0.008
Tobacco	11 (18)	10 (17)	1
Diabetes	8 (13)	5 (8.5)	0.6
NYHA			0.90
I	42 (69)	34 (57)	
II	12 (19.5)	15 (25)	
III/IV	7 (11.5)	11 (18)	
Angor	3 (5)	6 (10)	0.45
Supraventricular arrhythmia	17 (28)	12 (20)	0.45
Stroke	22 (36)	3 (5)	< 0.001
Proteinuria	21 (34)	1 (1.8)	< 0.001
ACE inhibitor/angiotensin II receptor blocker	26 (42.5)	14 (23)	0.08
Beta-blocker	16 (26)	50 (84)	< 0.001
Aldosterone antagonist	0	6 (10)	0.03
Diuretic	21 (34.5)	14 (23)	0.49
Anticoagulant	17 (28)	15 (25)	1

Data are expressed as mean ± standard deviation or number (%). ACE: angiotensin-converting enzyme; HCM: hypertrophic cardiomyopathy; NYHA: New York Heart Association.

Table 2 Electrocardiographic and echocardiographic characteristics of the study population.

	Fabry disease (n = 61)	HCM (n = 59)	P
Electrocardiogram			
Heart rate (beats/min)	64 ± 11	66 ± 15	0.66
Corrected PQ (ms)	164 ± 49	171 ± 38	0.37
QRS duration (ms)	117 ± 27	99 ± 25	< 0.001
Corrected QT (ms)	424 ± 29	427 ± 31	0.58
RBBB	33 (54)	13 (22)	0.001
LBBB	4 (6)	6 (10)	0.69
Left anterior hemiblock	15 (20)	8 (13)	0.70
Left posterior hemiblock	0	0	1
Pre-excitation	0	1 (1.7)	0.98
Pathologic Q wave	10 (16.5)	14 (23)	0.43
Atrial fibrillation	4 (6.6)	1 (1.7)	0.38
LVH indexes			
Cornell voltage index (mm)	19.7 ± 11.0	22.0 ± 13.0	0.24
Gubner index (mm)	21.0 ± 14.0	15.6 ± 13.0	0.01
Sokolow-Lyon voltage index (mm)	31.4 ± 12.4	27.8 ± 16.7	0.19
Romhilt-Estes score	7.0 ± 2.8	6.2 ± 3.0	0.07
Sokolow-Lyon product[a] (mm.ms)	3547 ± 1408	2687 ± 1791	0.004
Cornell product[a] (mm.ms)	2381 ± 1659	2290 ± 1861	0.77
Echocardiogram			
LVEF (%)	65 ± 6	69 ± 9.5	0.01
Myocardial maximal thickness (mm)	16.2 ± 3.5 (13–26)	21.8 ± 4.8 (13–32)	< 0.001
LV outflow tract obstruction	3 (5)	15 (25)	< 0.001
Right ventricular hypertrophy	14 (23)	2 (3.4)	0.004
Sinus of Valsalva diameter (mm/m²)	20.5 ± 3.9	18 ± 2.5	< 0.001
Tubular aortic diameter (mm/m²)	18.4 ± 3	16.8 ± 2.7	0.007

Systolic anterior motion	4 (6.6)	15 (25)	0.01

Data are expressed as mean ± standard deviation (interquartile range, if appropriate) or number (%). HCM: hypertrophic cardiomyopathy; LBBB: left bundle branch block; LV: left ventricular; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; RBBB: right bundle branch block.

[a] LVH index (mm) × QRS duration (ms).

Table 3 Multivariable analysis

Variables	Odds ratio (95% CI)	*P*
Sokolow-Lyon product (by 100 mm.mV)	1.048 (1.015–1.087)	< 0.01
Myocardial maximal thickness (mm)	0.707 (0.605–0.807)	< 0.001
Sinus of Valsalva diameter (mm/m²)	1.526 (1.209–20.42)	< 0.01
RBBB	12.276 (3.640–52.652)	< 0.001

CI: confidence interval; RBBB: right bundle branch block.

Table 4 Intraobserver repeatability and interobserver reproducibility of the electrocardiogram tracings.

LVH indexes	Intraobserver repeatability	Interobserver reproducibility
Sokolow-Lyon voltage index	0.99 (0.96–0.99)	0.98 (0.96–0.99)
Cornell voltage index	0.98 (0.92–0.99)	0.98 (0.84–0.99)
Gubner index	0.99 (0.98–0.99)	0.98 (0.93–0.99)
Romhilt-Estes score	0.84 (0.38–0.96)	0.86 (0.45–0.96)
Sokolow-Lyon product*	0.99 (0.96–0.99)	0.98 (0.95–0.99)
Cornell product*	0.98 (0.93–0.99)	0.98 (0.93–0.98)

Data are expressed as intraclass correlation coefficient (95% confidence interval). LVH: left ventricular hypertrophy.

[a] LVH index (mm) × QRS duration (ms).

Figure 1

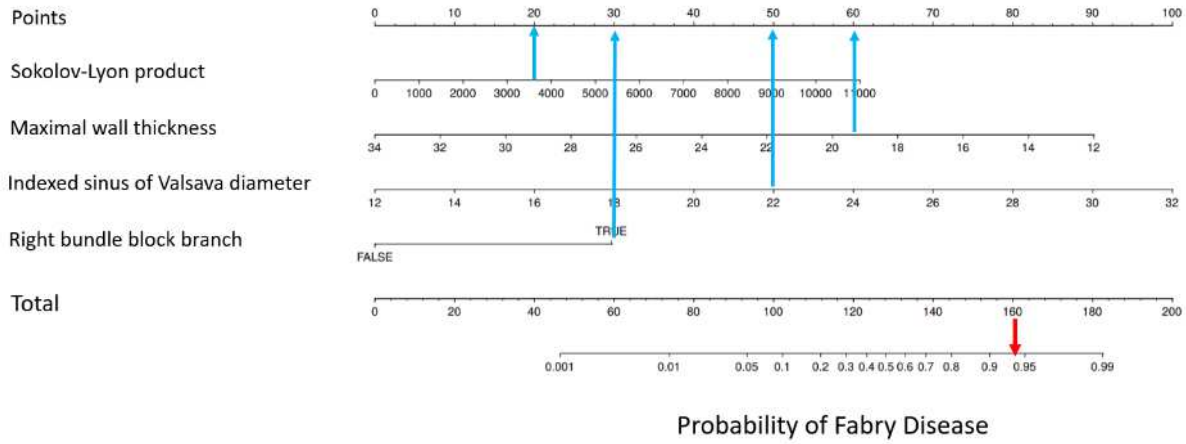
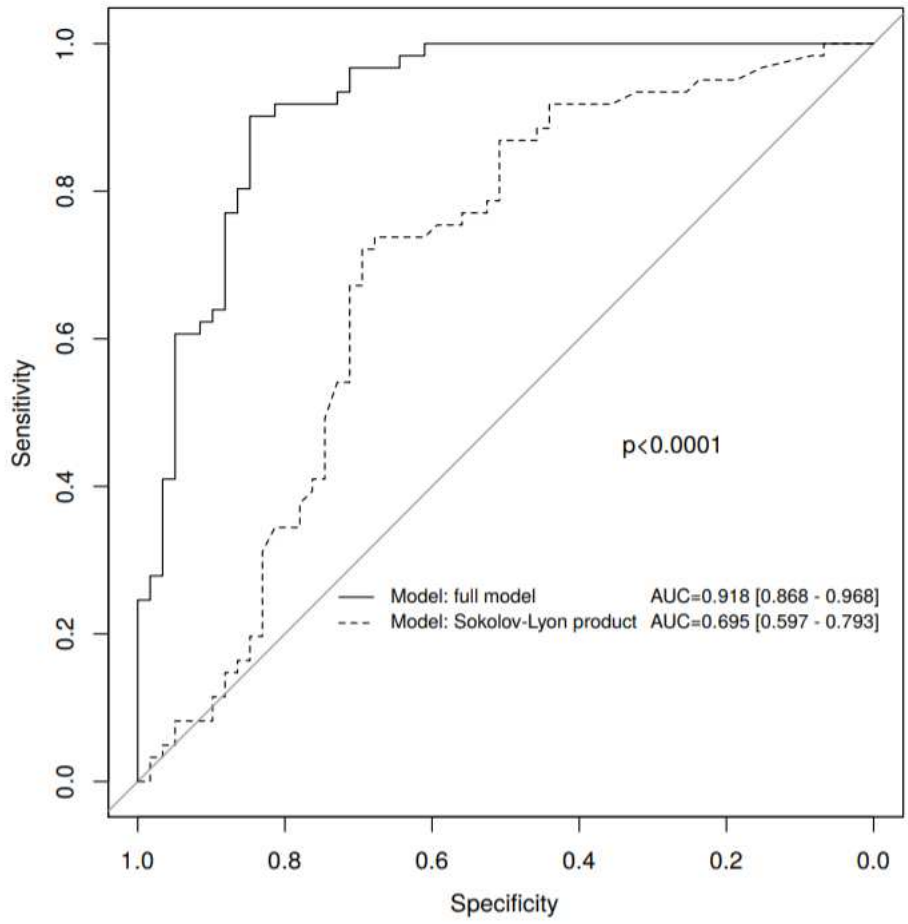

Points
Sokolov-Lyon product
Maximal wall thickness
Indexed sinus of Valsava diameter
Right bundle block branch
Total
0 10 20 30 40 50 60 70 80 90 100
0 1000 2000 3000 4000 5000 6000 7000 8000 9000 10000 11000
34 32 30 28 26 24 22 20 18 16 14 12
12 14 16 18 20 22 24 26 28 30 32
TRUE
FALSE
0 20 40 60 80 100 120 140 160 180 200
0.001 0.01 0.05 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 0.95 0.99
Probability of Fabry Disease

Figure 2


Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
1.0
0.8
0.6
0.4
0.2
0.0
Specificity
p<0.0001
Model: full model AUC=0.918 [0.868 - 0.968]
Model: Sokolov-Lyon product AUC=0.695 [0.597 - 0.793]