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The value of electrocardiogram and echocardiography to distinguish Fabry disease from sarcomeric hypertrophic cardiomyopathy

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Né (e) le 18/11/1992 à Châtenay-Malabry (92)

TITRE DE LA THÈSE :

**Valeur de l'électrocardiogramme couplé à
l'échocardiographie pour différencier une maladie de Fabry
d'une cardiomyopathie hypertrophique sarcomérique**

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Abbreviations

ACE: angiotensin-converting enzyme

BSA: body surface area

ESC: European Society of Cardiology

Gb3: globotriaosylceramide

HCM: hypertrophic cardiomyopathy

LVH: left ventricular hypertrophy

LAH: left anterior fascicular block

LBBB: left bundle block branch

LPH: left posterior fascicular block

LV: Left ventricle

LVEF: left ventricular ejection fraction

LVOTO: left ventricular outflow tract obstruction

NYHA: New-York Heart Association

RBBB: right bundle block branch

RVH: right ventricular hypertrophy

Tables

Table 1: Characteristics of the study population

Variables	Fabry (n=61)	HCM (n=59)	P
Age (years)	55.6 ± 11.5	44.8 ± 18.3	< 0.001
Gender, Man (%)	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
Supra ventricular 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 blockers	16 (26 %)	50 (84 %)	<0.001
Aldosterone antagonists	0	6 (10 %)	0.03
Diuretics	21 (34.5 %)	14 (23 %)	0.49
Anticoagulant	17 (28 %)	15 (25 %)	1

ACE: angiotensin-converting enzyme; HCM: Hypertrophic cardiomyopathy; NYHA: New-York Heart Association

Table 2: Electrocardiographic and echocardiographic characteristics of the study population

Variables	Fabry (n = 61)	HCM (n=59)	P
Electrocardiogram			
Heart rate (bpm)	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
<i>Left ventricular hypertrophy indexes</i>			
Cornell voltage criteria	19.7 ± 11	22 ± 13	0.24
Gubner index	21 ± 14	15.6 ± 13	0.01
Sokolov-Lyon	31.4 ± 12.4	27.8 ± 16.7	0.19
Rohmit Estes score	7 ± 2.8	6.2 ± 3	0.07
Sokolov-Lyon product*	3547 ± 1408	2687 ± 1791	0.004
Cornell product*	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
LVOTO	3 (5%)	15 (25 %)	<0.001
Right ventricular hypertrophy	14 (23 %)	2 (3.4 %)	0.004
Sinus de Valsava diameter (mm/m ²)	20.5 ± 3.9	18 ± 2.5	< 0.001
Tubular aortic diameter (mm/m ²)	18.4 ± 3	16.8 ± 2.7	0.007
Systolic anterior motion	4 (6.6 %)	15 (25 %)	0.01

RBBB : right bundle block branch ; LBBB : left bundle block branch ; LAH : left anterior hemiblock ; LPH : left posterior hemiblock ; HCM : hypertrophic cardiomyopathy ; bpm : beat per minute ; LVOTO: left ventricular outflow tract obstruction; * left ventricular hypertrophy index (mm) x QRS duration (ms); LVEF: left ventricular ejection fraction; HCM: hypertrophic cardiomyopathy

Table 3: Multi variate analysis

Variables	Odds Ratio [95%CI]	p
Sokolov-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 de Valsava diameter, mm/m ²	1.526 [1.209-20.42]	<0.01
Right bundle branch block	12.276 [3.640-52.652]	<0.001

Table 4: Interobserver and reproducibility and intraobserver repeatability of the ECG tracings

Left ventricular hypertrophy indexes	Intra observer reproducibility Intra Class correlation (95% Confident Interval)	Inter observer reproducibility Intra Class Correlation (95% Confident Interval)
Sokolov-Lyon	0.99 (0.96 - 0.99)	0.98 (0.96 - 0.99)
Cornell	0.98 (0.92- 0.99)	0.98 (0.84 - 0.99)
Gubner	0.99 (0.98 - 0.99)	0.98 (0.93 - 0.99)
Rohmit Estes score	0.84 (0.38 - 0.96)	0.86 (0.45 - 0.96)
Sokolov-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)

* left ventricular hypertrophy index (mm) x QRS duration (ms)

Figures

Figure 1

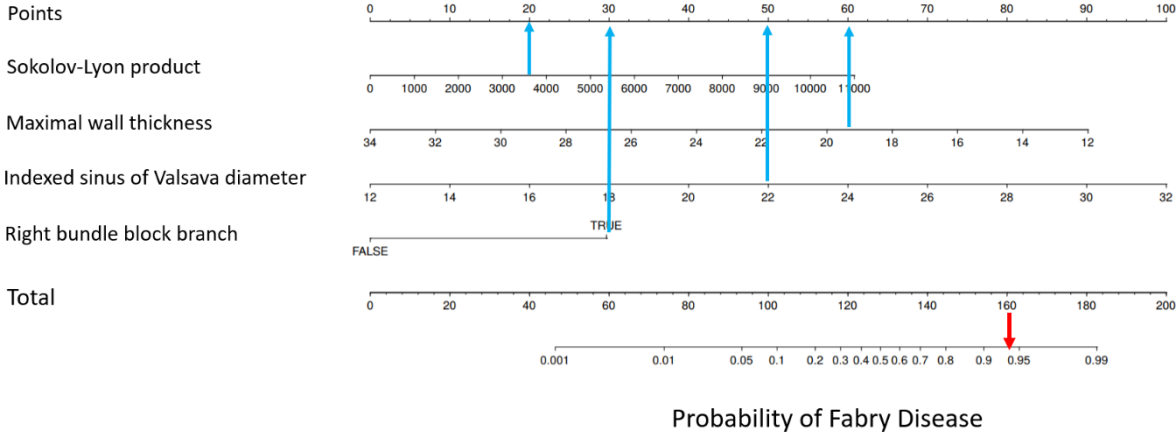


Figure 1: Nomogram for the predictive value for Fabry disease. The probability of Fabry disease is estimated on the “Total Points” axis by the sum of points for each co-variable value. The point for each co-variable is obtained by drawing a vertical line from the variable axis to the “Points” axis.

As an example, a patient with a Sokolov-Lyon product of 3700 (20points), a right bundle block branch (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 > 90 %.

Figure 2

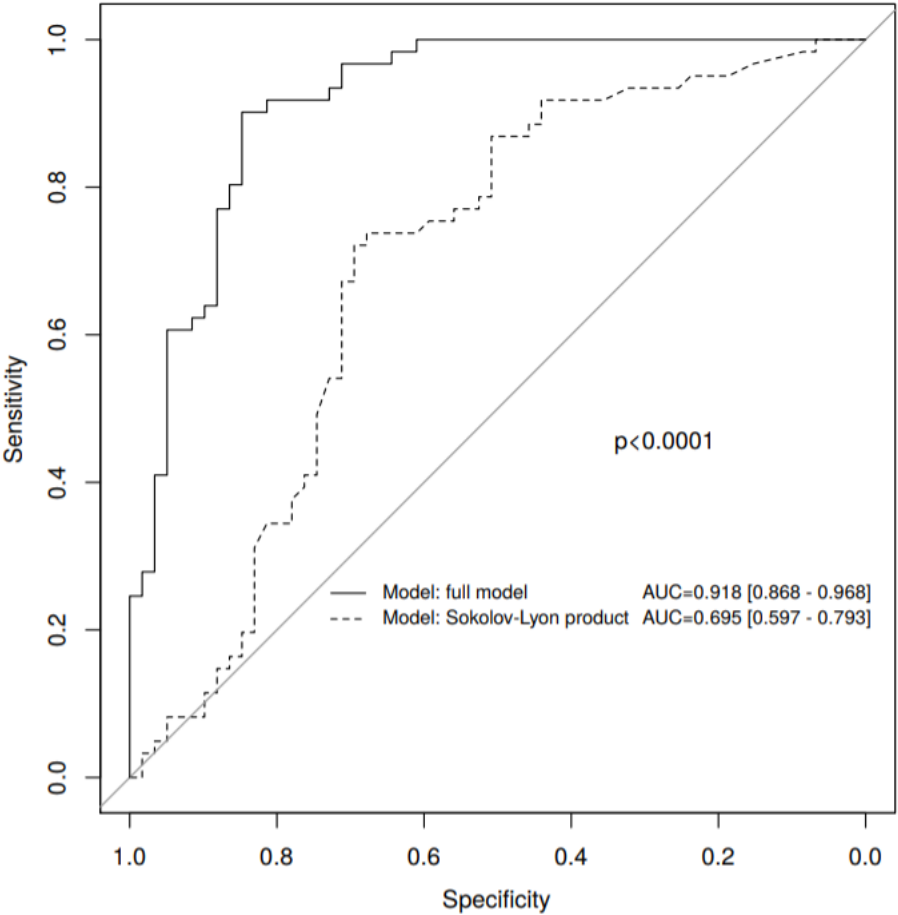


Figure 2 : Receiver operating characteristics curves for the predictive value for Fabry disease with Sokolov-Lyon product (dotted line) and full model including electric (Sokolov-Lyon product and right bundle block branch) and echocardiographic (myocardial maximal thickness and indexed aortic sinus of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

SUMMARY

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Introduction

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 (Gb3) 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 to 1/117 000 individual; however, these data likely 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 due to arrhythmia and heart failure and are currently the leading cause of death in Fabry disease [5, 6]. The recent guidelines of the European Society of Cardiology (ESC) 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 centers [8]. Improvements in diagnostic delay have not yet been achieved [9], and Fabry disease continues to be often diagnosed late after the onset of the first clinical signs [10, 11]. As the efficiency of specific Fabry therapy is heavily conditioned by the stage of the disease [12], both delayed diagnosis and start of treatment might result in a “loss of opportunity” for patients. This highlights the need to continue to develop screening tools for daily cardiology practice. Contrary to amyloidosis, we still do not have a relevant echocardiographic tool that could differentiate Fabry disease from other more common causes of LVH [13]. ECG remains an unavoidable first step when evaluating patients with HCM [7] and might suggest an underlying diagnosis [14]. Nevertheless, the ECG 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 Sokolov-Lyon index did not appear to be discriminatory for Fabry disease [15]. Other validated electrocardiographic criteria for LVH were poorly investigated in Fabry disease.

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

Methods

Population

We retrospectively included patients >18 years old with Fabry disease and LVH who were admitted for routine follow-up to the outpatient department of five French dedicated HCM centers between 2016 and 2019. The diagnosis of Fabry disease was confirmed by the low or missing activity of α -A galactosidase levels in leukocyte homogenates in men and mutational analysis of the α -A galactosidase genes in both men and heterozygous women. Patients with Fabry disease were compared with patients with sarcomeric HCM randomly selected from two centers (CHU de Caen, CHU La Pitié-Salpêtrière) 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 ECG and echocardiographic findings, were reviewed and entered into dedicated databases. Demographic details of age, gender, weight, height, and heart rate were recorded. Their body surface area (BSA) was calculated according to the Dubois formula and expressed in m². History of ischemic stroke, proteinuria, and cardiovascular risk factors were recorded. Cardiac symptoms and current medications, including Fabry-specific therapy, were noted. In the Fabry disease group, LVH was defined by a maximal wall thickness ≥ 13 mm using trans-thoracic 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, using trans-thoracic echocardiography too.

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 (SS and NJ) blinded to the cause of disease. The ECG reading was performed by consensus reading. Heart rate, presence of complete right bundle block branch (RBBB), left bundle block branch (LBBB), left anterior fascicular block (LAH), left posterior fascicular block (LPH), pathologic Q waves (defined by abnormal Q waves ≥ 40 ms in duration and/or $\geq 25\%$ 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/VRR, ms), QRS

duration (ms), and corrected QT interval (calculated using the Bazett formula, ms) were measured. Six electrocardiographic criteria for LVH were analyzed according to the specific American Heart Association guidelines [16]:

- 1) Sokolow-Lyon index (SV1 + RV5 or V6 \geq 30 mm and \geq 35 mm)
- 2) Cornell voltage index: RaVL + SV3 \geq 20 mm for women and \geq 28 mm for men
- 3) Gubner index: RD1+SV3 $>$ 25 mm
- 4) Romhilt-Estes score
- 5) Sokolow-Lyon voltage x QRS duration product: (SV1 + RV5 or V6) \times QRS duration \geq 3710 mm.ms.
- 6) Cornell voltage x QRS duration product: (RaVL + SV3) \times QRS duration \geq 2440 mm.ms.

In cases of voltage differences within the same lead, only the largest complex was selected.

2D transthoracic echocardiogram analysis

For each patient, the 2D transthoracic echocardiogram was performed during the same consultation as the ECG and was reviewed by a senior echocardiographer. The following parameters were analyzed: left ventricular ejection fraction (LVEF) using the modified biplane Simpson's rule, LV maximal myocardial wall thickness measured from parasternal short axis view, presence of left ventricular outflow tract obstruction (LVOTO) secondary to a systolic anterior motion, presence of right ventricular hypertrophy (RVH) defined by a myocardial thickness $>$ 5 mm in long axis view. Finally, the aortic root diameters, measured at the level of the Valsalva sinuses and tubular portion, were measured and indexed to BSA. Left and right ventricular measurements, as well as the aortic root diameters, were measured following the joined European Association of Echocardiography and American Society of Echocardiography guidelines [17]. Assessment of the LV wall thickness and the presence of LVOTO were defined according to the ESC-HCM guidelines [7].

Statistical methods

A comparative analysis of patients with Fabry disease and those with sarcomeric HCM was performed. Variables are expressed as the mean \pm standard deviation, interquartile ranges or as numbers and percentages. Continuous variables were compared by the Student t-test. Qualitative variables were compared using the Fisher test or Chi² test. A multivariate 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 multivariate analysis. A ROC (Receiving Operator Characteristic) 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 Asn 215 Ser mutation, so called 'cardiac variant'. Reproducibility study of ECG tracings was performed by two observers (NJ, FL) who interpreted 10 tracings randomly taken from the sample. Inter observer and intra observer reliabilities were assessed using the intraclass correlation coefficient (ICC). The 95% confidence interval (CI) was calculated using the delta method. The 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, the ethic committee (CPP III Nord-Ouest) approved the research protocol.

Results

Overall 61 patients with Fabry disease (Age: 55.6 ± 11.5 years, 57% men) were included and compared to 59 patients with sarcomeric HCM (Age: 44.8 ± 18.3 years, 66% men). Fabry patients were older ($p < 0.001$). At the time of the clinical evaluation 49 (80 %) of the Fabry patients received a specific treatment for Fabry disease. Fabry and sarcomeric HCM patients were comparable with respect to gender, tobacco, diabetes, cardiac symptoms, and medication excepted for beta blockers and aldosterone antagonists, more frequently prescribed in the HCM group. Hypertension, ischemic stroke, and proteinuria were significantly more prevalent in patients with Fabry disease. The characteristics of our study population are given in Table 1.

Electrocardiogram

QRS duration was significantly higher in the Fabry group (117 ± 27 ms 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, LAH, preexcitation, pathologic Q waves, and arrhythmia did not differ between two the groups. Regarding LVH indexes, Gubner index, and Sokolov-Lyon product were significantly higher

in the Fabry group (Gubner index: 21 ± 14 mm vs. 15 ± 13 mm, $p = 0.01$; Sokolov-Lyon product: 3547 ± 1408 vs 2687 ± 1791 mm.ms , $p = 0.004$). The Sokolov-Lyon voltage criterion was higher in patients with Fabry disease, without reaching statistical significance (Fabry: 31.4 ± 12.4 ms versus HCM: 27.8 ± 16.7 ms; $p = 0.19$). The Cornell voltage criteria, Rohmit Estes score, and Cornell product were comparable between Fabry patients and HCM group. The results are shown in Table 2.

Echocardiogram

The mean LVEF was lower in Fabry patients, though 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 (HCM: 21.8 ± 4.8 mm versus Fabry: 16.2 ± 3.5 mm, $p < 0.001$). 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 ECG and echocardiographic variables, only RBBB, Sokolov-Lyon product, maximal thickness wall, and indexed Valsalva sinus diameter were independently associated with Fabry disease (Table 3). These four variables were included in a regression model leading to the nomogram depicted in Figure 1. ROC curves established to analyze predictive values of both Sokolov-Lyon product alone versus a full ECG and echocardiographic model are depicted in Figure 2.

A full model, including the Sokolov-Lyon product, RBBB, maximal thickness wall, and indexed Valsalva aortic diameter yielded an area under the ROC curve of 0.918 [95% Confident Interval: 0.868–0.968]. The full model differed significantly compared to the Sokolov-Lyon product model.

We tested the proposed full model in the sub-group of patients with the Asn 215 Ser mutation, so called 'cardiac variant'. Among our cohort of Fabry patients, 13 patients (21 %) had the Asn 215 Ser mutation (12 males, mean age: 56 ± 10 years). The mean total score was 158 [149-185] in Asn 215 Ser mutation group vs 99 [68 - 133] in sarcomeric HCM group.

Interobserver reproducibility and intraobserver repeatability

The intra and interobserver reproducibility, assessed by ICC, were excellent for all LVH ECG criteria, especially for Sokolov-Lyon product (intra observer reproducibility, ICC: 0.99 (0.96-0.99); inter observer reproducibility, ICC: 0.98 (0.95-0.99)]. Rohmit Estes score showed the lowest reproducibility (intra observer reproducibility, ICC: 0.84 (0.38 - 0.96) ; inter observer reproducibility, ICC: 0.86 (0.45 - 0.96)].

Discussion

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

The LVH is one of the most important warning signs for the identification of new Fabry patients, providing cardiologists with an essential role in the screening of 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 cardiomyopathies centers. 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 centers. The echocardiographic 'red flags', such as binary endocardium, papillary muscle hypertrophy, LVH pattern or LV circumferential strain analysis, are often disappointing or difficult to achieve in daily practice [19, 20, 21]. ECG is recommended in all patients with HCM and might provide a clue for the diagnosis of rare etiologies of HCM, especially when interpreted in conjunction with echocardiography [14]. Typical ECG 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 the atrio-ventricular block [22]. Although 'typical', none of these signs are specific of Fabry disease [23]. Sarcomeric HCM may show the same ECG 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, LAMP2, and PRKAG2 mutations [25]. In our cohort, both PQ interval and pre-excitation were

not relevant parameters to differentiating Fabry disease and sarcomeric HCM. These results are in agreement with a large study of 207 Fabry patients, where the PQ interval was not a common finding [26]. The increased QRS duration is a common marker of the electrophysiological remodeling in Fabry disease [22, 27, 28], not only due to LVH [29] but also possibly because of the deleterious metabolic effects of the progressive infiltration of glycosphingolipids in the conduction tissue [30]. We observed an unexpectedly high prevalence of RBBB in our Fabry population. The more frequent right ventricular hypertrophy in Fabry patients may be postulated to explain this finding. Besides, although speculative, initial elective injury of the right bundle branch by the gradual accumulation of Gb3 could also be evoked as another potential mechanism accounting for the greater frequency of RBBB in Fabry disease. Even though RBBB was not helpful to differentiate Fabry disease and HCM in the work of Namdar et al. [15], previous studies and case reports have reported RBBB to be a frequent intraventricular conduction disorder in Fabry disease [31, 27]. In one of the first Fabry cohorts, Mehta et al. reported that RBBB was the most frequent evolution of the intraventricular conduction defects [32]. Kramer et al. found RBBB in 15% of their Fabry patients with severe myocardial fibrosis [27]. As suggested by our results and others [27, 31, 33], LBBB and QTc prolongation seems to be uncommon in Fabry disease and should rather suggest others etiologies of LVH [15, 31]. Among all the ECG criteria of LVH, the Sokolov-Lyon index has been the most studied in Fabry disease, despite its limitations. The Sokolov-Lyon index is highly specific but has low sensitivity compared to echocardiography or MRI, especially in cases of eccentric LVH and RBBB [16]. This may explain why the Sokolov-Lyon index did not discriminate Fabry patients from HCM in the present and previous studies. The simple product of voltage criteria and QRS duration significantly improves the identification of LVH compared to voltage criteria alone [34, 35]. The interest of Sokolov-Lyon voltage product in Fabry disease was previously suggested by Kampmann et al. who found a significant correlation between Sokolov-Lyon voltage x QRS duration product ($R^2 = 0.52$) and left ventricular mass [29]. Although the Sokolov-Lyon product might be the most appropriate ECG criteria for Fabry disease and should be systematically calculated, its diagnostic performance was inferior to the full model combining ECG and echocardiographic parameters. As there is no specific sign for Fabry disease considering both ECG and TTE, the addition of different ECG and echocardiographic parameters could be of interest. Using mixed criteria combining 12 lead QRS voltage < 30 mm and the ratio of interventricular septal/ posterior wall thicknesses < 1.6 , Gustavson et al. were able to

differentiate hereditary transthyretin amyloidosis from sarcomeric HCM [36]. The unpredicted value of indexed aortic root diameter illustrates the potential interest 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 the blood pressure level and other cardiovascular risk factors [37]. After multivariate analysis, gender, 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, 38, 39] was proposed as potential factor promoting structural aortic wall anomalies and dilation of the aorta, although exact underlying mechanisms remains to be elucidated. Even though 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 TRIPOD statement [40] (eTable, Supplement). A highly sensitive and specific model combining simple criteria available in the daily routine consultation of cardiology might prevent dramatic delay of 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.

Limitations

Our work had some limitations. We performed a retrospective study dealing with a relatively small number of patients with Fabry disease (although superior to most previous similar studies), which is an inherent problem with orphan diseases. We did not enroll newly diagnosed patients. This might have affected the results of the ROC curve analysis. The studied populations were not matched for age which could have impacted the results, especially ECG findings. However, voltages tending to decline with increasing age, which would tend to underestimate the value of Sokolov Lyon criteria. Moreover, the commonly used QRS voltage criteria applied in the present study can be applied to adults older than 35 years [16]. In this study, we have not included recent, potentially helpful criteria, such as two-dimensional strain imaging. These modalities are still not used widely among cardiologists, and we wanted to examine the performance of simple and widely used criteria. We did not perform an external validation. Finally, we have not included other rare diseases, such as storage disorders (protein kinase AMP-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 influenced the diagnosis orientation, contrary to sarcomeric HCM and cardiac variant of Fabry disease.

Conclusion

Sokolov-Lyon product might be the most appropriate ECG criteria for Fabry disease, and should be systematically calculated in case of HCM. We propose a combined model using ECG and echocardiographic parameters available in everyday cardiac routine consultation. This additional tool might be helpful to improve screening and reduce both diagnosis and therapeutic delay of Fabry disease.

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en date du 14 Décembre 1973

Pour le Président
de l'Université de CAEN et P.O

Le Doyen

ANNEE DE SOUTENANCE : 2020

NOM ET PRENOM DE L'AUTEUR : JUNQUA Nicolas

TITRE DE LA THESE : Valeur de l'électrocardiogramme couplée à l'échocardiographie pour différencier une maladie de Fabry d'une cardiomyopathie hypertrophique sarcomérique

RESUME DE LA THESE EN FRANÇAIS :

Contexte : Le dépistage de la maladie de Fabry reste sous optimal dans les centres non spécialisés. 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 atteints d'une maladie de Fabry avec HVG à 59 patients 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, produit de Cornell.

Résultats : 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 bloc de branche droit, le produit de Sokolow-Lyon, l'épaisseur maximale du VG et le diamètre aortique étaient 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 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.

MOTS CLES : Maladie de Fabry, cardiomyopathie hypertrophique, électrocardiogramme

TITRE DE LA THESE EN ANGLAIS : The value of electrocardiogram and echocardiography to distinguish Fabry disease from sarcomeric hypertrophic cardiomyopathy

RESUME DE LA THESE EN ANGLAIS :

Background : Screening for Fabry disease (FD) remains suboptimal in non-specialized centers.

Aims : We aimed to evaluate the diagnostic value of electrocardiographic (ECG) scores of left ventricular hypertrophy (LVH) and the diagnostic value of a combined ECG and echocardiographic model for FD.

Methods : We retrospectively reviewed the ECG and echocardiogram of 61 patients (age: 55.6 ± 11.5 years, 57% men) with FD and LVH, and compared them to 59 patients (age: 44.8 ± 18.3 years, 66% men) with sarcomeric hypertrophic cardiomyopathy (HCM). Six ECG criteria for LVH were specifically analyzed: 1) Sokolow-Lyon index 2) Cornell voltage index 3) Gubner index 4) Romhilt-Estes score 5) Sokolow-Lyon voltage x QRS duration product and 6) Cornell voltage x QRS duration product.

Results : Right Bundle Branch Block (RBBB) was more frequent in FD (54% vs. 22 %, $p = 0.001$). QRS duration, Gubner score, and Sokolov-Lyon product were significantly higher in FD.

Maximal thickness wall (MTW) was higher in sarcomeric HCM group (21.9 ± 5.1 mm vs 15.5 ± 2.9 mm in Fabry, $p < 0.001$). Indexed Valsalva sinus diameter was higher in patients with FD. After multivariable analysis RBBB, Sokolov-Lyon product, MTW and aortic diameter were independently associated with FD. A model including these 4 parameters yielded an area under the ROC curve of 0.918 [95% Confident Interval: 0.868–0.968] for FD.

Conclusion : Our model combining easy-to-assess ECG and echocardiographic parameters may be helpful to improve screening and reduce diagnosis delay of FD.

KEY WORDS : Fabry, hypertrophic cardiomyopathy, electrocardiogram