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Recognition of pre-hypertrophic cardiac involvement in Fabry Disease based on automated electrocardiographic measures☆

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ABSTRACT

Background: Various electrocardiographic (ECG) indices have been shown to be useful for early recognition and staging of cardiac involvement in Fabry Disease (FD). However, many of them lack acceptable sensitivity and specificity. We assessed the value of automated ECG measures to discriminate between pre-hypertrophic FD and healthy individuals.

Methods and results: Normal ECGs from 1496 healthy individuals (57.4% male, age 37.4 ± 13 years) were compared to those of 142 FD patients without LVH (37.3% male, age 41.5 ± 18 years). All ECGs were analyzed centrally and a total of 429 automated ECG measures per individual were included for step-wise analysis. The Cramer V statistic was first used to pick out those parameters which were helpful in discriminating between the two groups and a final selection was made by using two models, namely the FLD (Fisher Linear Discrimination) and the Logistic model, to optimise diagnostic performance for the detection of cardiac involvement in FD patients vs. specificity in healthy individuals.

The three-step statistical analysis identified 9 ECG parameters as most significant for the discrimination between the groups. The combined discriminant score yielded 64% sensitivity and 97% specificity for correct classification of FD patients in the test sample with a logistic area under curve of the ROC analysis of 0.97.

Conclusion: The combination of automated ECG measures identified via a stepwise statistical approach may be useful for detection of FD patients in the pre-hypertrophic stage. These data are promising for screening purposes in the very early stages of FD cardiomyopathy and warrant prospective confirmation.

1. Introduction

Fabry Disease (FD) is an inherited X-linked, recessive lysosomal storage disease caused by deficient activity of the lysosomal enzyme α-galactosidase A [1]. The resulting, progressive intracellular accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in cardiac, renal, neural, vascular, ocular and skin tissues is characteristic of the disease [1]. Cardiac involvement is reported to occur in up to 78% of these patients and nearly all affected patients will eventually develop left ventricular hypertrophy (LVH) [2]. While myocardial accumulation of Gb3 begins very early in the disease process, LVH manifests decades later, at an average age of 32 years in men and 40 years in women [3], suggesting that echocardiographic LVH might not be a suitable marker for early detection of the disease.

Accumulation of Gb3 not only affects cardiomyocytes, vascular tendothelial and smooth muscle cells but also the conduction system, eventually leading to significant cardiac damage even in the early - i.e. pre-hypertrophic - stages [4]. In adult patients, organ involvement at the time of diagnosis may already be characterized by extensive LVH and myocardial fibrosis, i.e. fully-fledged FD cardiomyopathy, which is irreversible and unresponsive to enzyme replacement therapy (ERT) [2,5]. Therefore, early diagnosis of Fabry cardiomyopathy is of paramount importance.

Various electrocardiographic (ECG) indices have been shown to be useful for early recognition and staging of cardiac involvement in FD. However, these consistently lack high sensitivity and specificity, limiting their clinical use for screening purposes [6–9]. Whether more sophisticated ECG parameters may be of diagnostic value in patients with FD remains questionable. The aim of this study was therefore to

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1
Baseline echocardiographic and genetic data of the Fabry cohort.

Parameter	n (%) or mean (SD) where applicable
Clinical / laboratory parameters manifestations	
Angiokeratoma	45 (32%)
Fabry Disease associated pain	84 (59%)
Diabetes mellitus	7 (5%)
Arterial Hypertension	5 (4%)
Dyslipidemia	27 (19%)
Transient ischemic attack	16 (11%)
Albuminuria	64 (45%)
NT-proBNP (ng/l)	245 ± 133
Echocardiographic parameters	
Septum wall thickness (mm)	8.7 ± 1.7
Posterior wall thickness (mm)	8.5 ± 1.4
Left ventricular mass index (g/m^2)	85.7 ± 11.1
Identified mutations	
c.-110-15T>G	10 (7%)
c.335 G>A // R112H	21 (15%)
Transition c.427 G>A // A143T	63 (44%)
c.937G>T // D313Y	48 (34%)

assess the value of automated measures of digital ECGs for the discrimination of patients with FD (without LVH) versus healthy individuals.

2. Methods

Twelve-lead ECGs from patients ($N = 142$) with a confirmed diagnosis of FD and echocardiographic exclusion of LVH - (i.e. maximal left ventricular wall thickness ≤ 12 mm) were collected in digital form from two different centers (Florence, Italy & Würzburg, Germany). Different electrocardiographs were used with a sampling rate of 500 samples/s. ECGs were sent as XML files to the ECG core-lab in the University of Glasgow, Scotland, where 1496 ECGs of apparently healthy individuals served as the comparison group. The composition of this cohort has previously been discussed [10]. Electrocardiographic measurements were obtained using the University of Glasgow automated ECG analysis program as described elsewhere [11].

Two main statistical methods - descriptive and discriminant analyses - were chosen in a three-step process for selection and analysis of ECG parameters. The aim of the first approach was to provide univariate statistics (mainly frequencies and percentages and related statistics) to describe each of the initial 429 ECG parameters. Further, multivariate analyses such as Multiple Correspondence Analysis (MCA) and Cramer's V statistic were applied in order to assess the discriminative power of each variable and/or the strength of the correlation between two variables. Thus, in a second selection step, ECG parameters with a Cramer's $V > 0.15$ were selected. Thereafter, collinearities were tested and a further selection performed (by dropping each ECG measure from any identified 2×2 correlation) for a Cramer's $V \geq 0.4$, thus yielding the most discriminative ECG parameters ($N = 41$).

For discriminant analyses, two discriminant methods were performed in order to assess similarities of results between both methods, validating each one against the other, namely Fisher's Linear Discriminant Function for 2 groups (FLD) on MCA factors and the logistic model. All methods processed an a-priori discretization into 5 categories of equal size for all continuous parameters. In addition, for each method, two validation processes were applied based on a learning and test sample, viz. 80% versus 20% of the global sample size, respectively. Further, a Bootstrap sampling of 70% of the overall data sample was performed in order to test the stability of both the decision rule and the third ECG selection step - based on a stepwise regression with the logistic and the FLD (on MCA factors) models. The latter served as a controller of the logistic model. However, instead of performing only one stepwise regression, the process was enhanced by performing 1000 regressions - one for each Bootstrap sample of 70% of the global sample size, resulting in 1000 samples and identifying ECG parameters that have been selected by the Bootstrap sampling more than 70% of the time ($N = 9$).

Finally, every patient had his/her total score calculated on the basis of the ECG findings (decision rule of Fisher, discriminant score normalized between 0 and 100 for each of the nine ECG parameters determined from a training set of 80% of both groups). The score was then applied for the assessment of diagnostic accuracy based on a bootstrap simulation and a 2×2 classification.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Table 2
Fabry versus normals: ECG parameters final selection from stepwise discrimination ($N = 9$).

Parameter	Category	Fabry %	Mean	Control %	Mean	Cramer's V	*t*-Test
Heart rate	40 to 62[a]	**47.2**[b]	65.3	18.1	73.3	0.21	<0.0001
	63 to 68	19.0		18.1			
	69 to 74	14.1		**21.7**			
	75 to 82	11.3		21.3			
	83 to 125	8.5		20.8			
P+ Amp I	0 to 71	**57.8**	68.0	16.1	98.5	0.31	<0.0001
	72 to 86	20.4		20.5			
	87 to 100	8.5		20.3			
	101 to 119	10.6		**21.6**			
	120 to 295	2.8		21.5			
P area V1	−616 to −71	**49.3**	-71.63	16.9	-12.3	0.24	<0.0001
	−70 to −30	17.6		21.0			
	−29 to −2	19.0		19.6			
	−1 to 36	7.0		21.1			
	37 to 352	7.0		**21.4**			
P Morph V3	−2, −1	7.0	0.88	0.33	1.1	0.2	0.0049
	1	**85.2**		**91.5**			
	2	7.6		8.2			
4/8 QRS	12 to 76	**50.0**	93.2	17.1	130.1	0.24	0.0001
	77 to 105	21.1		20.3			
	106 to 131	13.4		20.1			
	132 to 169	6.3		**21.5**			
	170 to 722	9.1		21.1			
LVH Score	0	19.0	156.2	**43.8**	48.9	0.2	<0.0001
	1 to 24	14.1		18.8			
	25 to 91	20.4		19.8			
	92 to 1186	**46.5**		17.7			
S Dur V1	0 to 49	**42.3**	44.4	18.6	55.3	0.17	<0.0001
	50 to 54	18.3		21.0			
	55 to 57	13.4		16.5			
	58 to 62	13.4		**24.5**			
	63 to 89	12.7		19.5			
ST60 Amp V2	−133 to 82	**61.3**	75.9	16.0	167.0	0.41	0.0005
	83 to 118	21.1		19.7			
	119 to 168	8.5		**21.7**			
	169 to 235	6.3		21.2			
	236 to 598	2.8		21.5			
QT dispersion	4 to 40	**42.7**	45.0	18.7	55.1	0.19	<0.0001
	42 to 50	18.3		17.6			
	52 to 58	8.5		**21.6**			
	60 to 68	9.7		**21.6**			
	70 to 130	19.8		20.6			

[a] Categories and where appropriate quartiles/quintiles of the quantitative parameters are given.
[b] Percentages in bold correspond to the highest prevalence of the respective parameter category/value within each group.

3. Results

There were 53 (37.3%) and 859 (57.4%) males in the Fabry ($N = 142$) and control group ($N = 1496$), respectively, with an overall

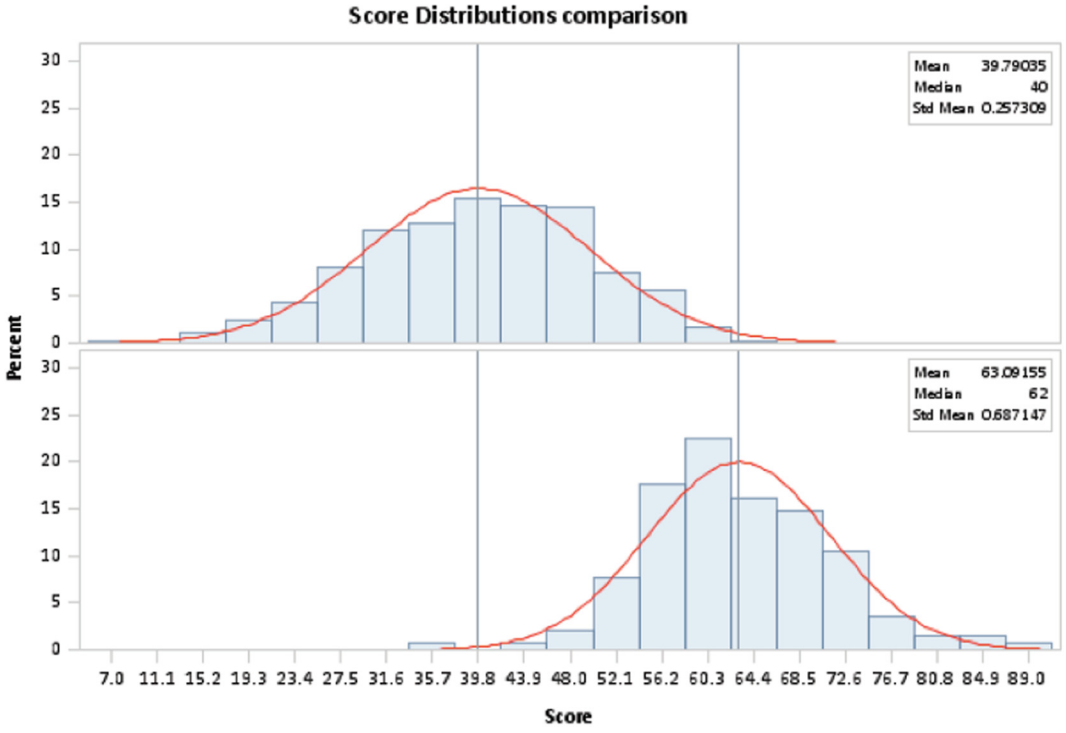

Fig. 1. Score distribution in the two study groups (based on the categorical or quantitative classification as shown in Table 3). The mean score value for the Fabry group was 63, with a standard deviation of 0.7 and for normal controls 40 with a standard deviation of 0.3. A negligible number of FD patients reached the mean score value of normal controls, and vice versa, allowing a good separation of the two groups with an acceptable overlap.

(males and females) mean age of 41.5 ± 18 years and 37.4 ± 13 years ($p < 0.05$ for gender and non-significant for age). Baseline parameters are given in Table 1. The stepwise statistical analysis identified 9 parameters as the most accurate in differentiating between the two groups and suitable for later scoring (Table 2; the 41 parameters identified based on the Cramer V statistic are shown in Supplemental Material, Table 1). These were:

1) *Heart rate (beats/min);*
2) *Amplitude of the positive component of the P wave in lead DI (P+ Amp I, μV);*
3) *P wave area in the precordial lead V1 (P Area V1, μV-milliseconds [μV.ms], defined as the algebraic sum of both the positive and negative areas or either alone if the P wave is not biphasic);*
4) *P wave morphology in the precordial lead V3 (categorical classification: 1 = single upright, −1 = single inverted, 2 = biphasic, leading positive, −2 = biphasic, leading negative);*
5) *4/8 QRS (time-normalized QRS spatial velocity at 4/8 of the total QRS duration, μV/ms);*
6) *LVH Score (derived from an age and sex based modified Romhilt-Estes score, dimensionless* [12]*);*
7) *duration of the S wave in the precordial lead V1 (S Dur V1; ms);*
8) *amplitude of the ST segment in the precordial lead V2 at 60 ms after the J point (ST60 Amp V2, μV).*
9) *QT Dispersion (ms) defined as the difference between the shortest and longest QT interval in the 12 lead ECG.*

Based on the design of the applied selection steps as well as the entry criterion for discriminant analyses, all 9 parameters showed statistically significant differences in the comparison between the FD and control groups, and were per definition independent of each other. As expected, mean heart rate was lower (65.3 bpm vs. 73.3 bpm, $p < 0.0001$) in the FD group. FD patients also showed a lower mean P+ Amp I (68 μV vs. 98.5 μV, $p < 0.0001$) along with a more negative mean P area in V1 (−71.63 μV.ms vs. -12.3 μV.ms, $p < 0.0001$, with 49.3% of them showing a purely negative value) and a lower percentage of a purely positive P wave morphology V3 (85.2% vs 91.5%, $p < 0.005$). Interestingly, the 4/8 QRS spatial velocity was also lower in the FD group (93.2 μV/ms vs. 130.1 μV/ms, $p = 0.0001$). Furthermore, the FD group had a more than threefold increase in LVH score (156.2 vs. 48.9, $p < 0.0001$), a shorter S Dur V1 (44.4 ms vs. 55.3 ms, $p < 0.0001$) and a greater proportion of a negative ST60 Amp V2 resulting in a lower mean value (75.9 μV vs. 167.0 μV, $p = 0.0005$) compared to controls. Finally, FD patients had a lower degree of QT dispersion (45 ms vs. 55.1 ms, $p < 0.0001$).

Fig. 1 shows the score distribution in the two groups (based on the categorical or quantitative classification as shown in Table 3). The mean score value for the Fabry group was 63, with a standard deviation of 0.7 and for the control group 40 with a standard deviation of 0.3. A negligible number of FD patients reached the mean score value of the control group, and vice versa, allowing a good separation of the two groups with an acceptable overlap. Accordingly, the calculated probability for assignment to one or the other group is shown in Fig. 2. A score below 51 excludes FD, while a score above 67 allows confirmation of the disease, in both cases in a categorical manner (i.e. 100% probability). Based on these analyses, we were able to assess diagnostic values for the discrimination of FD patients versus control group (Table 4). Fig. 3 shows the respective ROC curve with an excellent AUC value of 0.97 for the logistic and final analysis. Sensitivity, Specificity and diagnostic accuracy values for correctly detecting FD patients were 64%, 97% and 99%, respectively.

4. Discussion

To the best of our knowledge this work is the first to analyze advanced automated ECG measures in a relatively large cohort of patients with confirmed FD disease (but without echocardiographic evidence of LVH) and apparently healthy volunteers. We were able show a high discriminative power between the two groups using a robust hierarchical statistical approach as well as a weighted scoring system. Furthermore, our results allow a thorough and extended understanding of ECG

Table 3
Scoring based on decision rule of Fisher and the range/category of selected ECG parameters.

Parameter	Range/category	Score
Heart rate	40 to 62	9
	63 to 68	6
	69 to 74	3
	75 to 82	3
	83 to 125	0
LVH score	0	0
	1 to 24	3
	25 to 91	3
	92 to 1186	8
P area V1	−616 to −71	8
	−70 to −30	6
	−29 to −2	5
	−1 to 36	2
	37 to 352	0
P Morph V3	−2, −1	22
	1	5
	2	0
P Amp I	0 to 71	16
	72 to 86	13
	87 to 100	7
	101 to 119	9
	120 to 295	0
QT dispersion	4 to 40	6
	42 to 50	3
	52 to 58	0
	60 to 68	1
	70 to 130	2
S Dur V1	0 to 49	7
	50 to 54	5
	55 to 57	2
	58 to 62	0
	63 to 89	1
ST60 Amp V2	−133 to 82	15
	83 to 118	11
	119 to 168	7
	169 to 235	2
	236 to 598	0
4/8 QRS	12 to 76	8
	77 to 105	6
	106 to 131	4
	132 to 169	0
	170 to 722	4

Parameters in the left column (for abbreviations see main text), middle column with ranges or categories of measured parameters, right column with assigned scores per range.

Table 4
Fabry versus normals: percentages of classification and diagnostic values in the test sample.

	Normals	Fabry
Normals	297 (99.0%)	3 (1.0%)
Fabry	10 (35.7%)	18 (64.3%)
Diagnostic indices for Fabry		
Sensitivity	64%	
Specificity	97%	
Positive predictive value	86%	
Negative predictive value	99%	
Accuracy	96%	

changes, and thus electrophysiological phenomena as well as electroanatomical remodeling processes *before* macroscopic changes occur, i.e. in a pre-hypertrophic stage of the disease course, where imaging modalities may be unable to detect these subtle manifestations.

4.1. Electrocardiographic/electro-anatomical considerations

As the descriptive statistics of the second selection of ECG parameters has shown, more than 40 measures were significantly different between the two groups. This is a very interesting finding, since the two groups were expected to be comparable in the absence of any echocardiographic signs of FD underlying cardiomyopathy, supporting the idea that ECG parameters may unveil earlier pathophysiological processes compared to imaging, consistent with recent reports [13–15]. The nine ECG parameters identified in the final selection as the best discriminators between the two patient groups offer interesting insights in early atrial and ventricular electro-anatomical remodeling processes in pre-hypertrophic FD. Stratified according to a weighted scoring system and then combined, these nine ECG parameters showed a substantial diagnostic significance for the early, pre-echocardiographic recognition of the disease.

When looking at these nine discriminators individually, a lower P+ Amp I is an electrocardiographic signature of less pronounced vectorial forces from the right to the left atrium and may well be explained by lower heart rates in the FD group since the exit site from the sinus node shifts to a more inferior localization, generating an inter-atrial phase lag. Another explanation, however, may confirm an earlier observation, i.e. that a higher intra-atrial (musculo-muscular) conduction

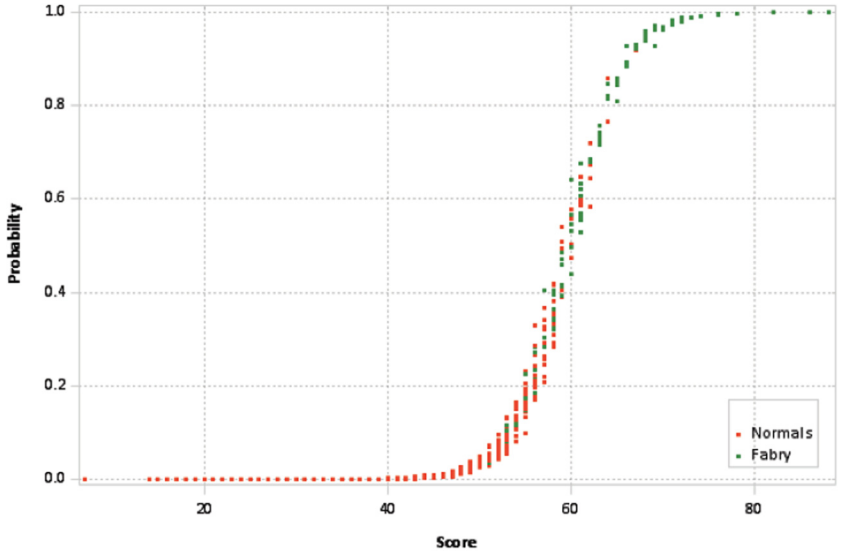

Fig. 2. Calculated probability for assignment to one or the other group. A score below 51 excludes FD, while a score above 67 allows confirmation of the disease.

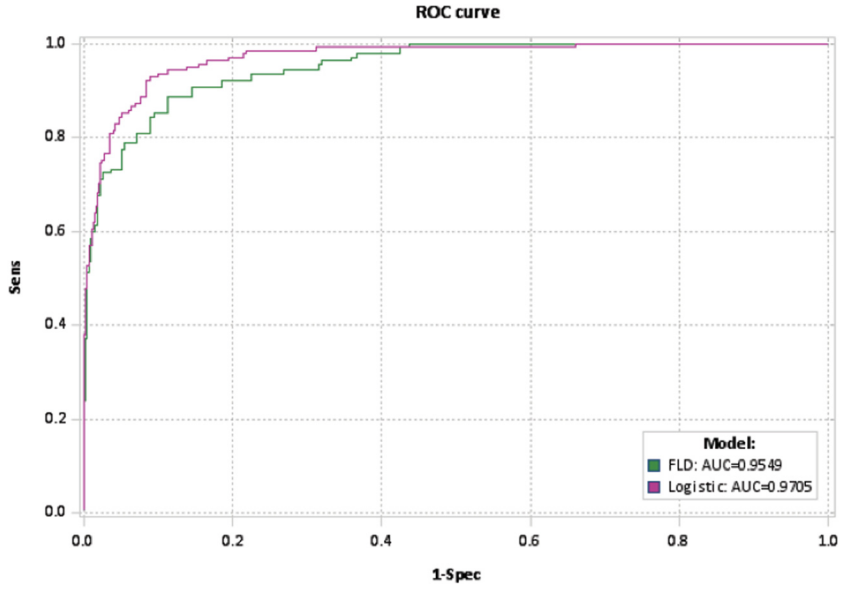

Fig. 3. ROC curve with an AUC value of 0.95 for the FLD (green) and 0.97 for the logistic and final analysis (purple).

velocity counterbalances the normally faster inter-atrial conduction via the Bachmann's bundle, and thus produces a coordinated and synchronous bi-atrial depolarization [8]. Interestingly, a recent analysis using a human stem cell model of FD showed indeed that affected cardiomyocytes displayed evidence of increased excitability, increased upstroke velocity of the action potential, which was also significantly shorter [16]. This phenomenon may also account for a more pronounced negative component of the normally biphasic (first positive component for right atrial and second negative component for left atrial depolarization) P wave in V1. Nevertheless, a larger proportion of the second – negative – component of the P wave in V1 may also reflect the electrical and potentially the structural remodeling of the left atrium [17]. This observation goes perfectly in line with the increased left ventricular mass and voltage indices (albeit still within normal ranges) seen in FD patients, as well as the prolonged R wave peak time, a very sensitive and early marker of left ventricular remodeling [18]. Accordingly, elevated ventricular tele-diastolic filling pressures are known to occur very early in the course of FD and may be translated into left atrial remodeling processes before overt "macroscopic" LVH and/or left atrial dilatation occur [19]. These observations may also be true for other forms of hypertrophic cardiomyopathies and their pre-hypertrophic phenotype.

Interestingly, the notion of FD-related LV remodeling is also reflected in the lower 4/8 QRS spatial velocity, i.e. a slower spread of excitation in the myocardium of FD patients. Whether the shorter S wave duration in lead V1 has a common denominator with the above-mentioned observations remains elusive. The greater proportion of a negative ST60 Amp in lead V2 in FD may on the other hand also indicate a "septal strain pattern", where the depression of the ST-segment is provoked by alteration of transmural *endo*-and epicardial action potential gradients (less negative than normal resting potential and less positive than normal depolarization potential in the endocardium). A similar effect is exerted by subendocardial ischemia related to microvascular dysfunction, known to occur very early in the pre-hypertrophic stage of FD [17,20]. These changes in *endo*-epicardial action potential gradients may further explain the differences in QT-dispersion. Of note, a normal upright T wave is asymmetric with a steeper downslope than its upslope and is a result of transmural endo-epicardial action potential gradients and their duration, with endocardial durations being physiologically slightly longer, and thus responsible for a physiological degree of QT-dispersion [21]. Consequently, any intramyocardial process in terms of disturbance of its microarchitecture and of the microcirculation not only entails changes in resting gradients and maximal potentials, but also affects action potential duration. Of note, early stages are characterized by endocardial shortening and a lesser degree of QT-dispersion, in contrast to later stages with manifest signs of a cardiomyopathy [7]. Further, in a recently published analysis of ECG parameters in pre-hypertrophic FD as compared to a normal cohort revealed measures similarly suggestive of these mechanisms [22]. However, since in contrast to the present study, manually analyzed advanced ECG parameters were included, it remains speculative whether an automated ECG analysis with the present statistical approach would have identified the same or other parameters to be significant. However, as shown in our supplemental data, some degree of overlap of identified measures in the first statistical step may be present (e.g. PR interval - P wave duration).

Based on these considerations, the selection of ECG parameters makes sound clinical sense from a pathophysiological point of view, besides being clinically accurate in early FD. An ECG scoring approach merits further investigation in an era of automated ECG measurement providing availability of massive data and machine learning algorithms, opening new paradigms and research opportunities for an improved diagnostic accuracy in large patient populations.

Of note, advances in tissue characterization by cardiac MRI now also allow early identification of organ damage in FD by T1 and T2 mapping, while LGE mostly reflects cardiac fibrosis occurring at later stages of disease. A reduction in T1 has been shown to be quite sensitive in highlighting myocardial storage and may therefore become a standard for early diagnosis of cardiomyopathy. A comparison between the extent and timing of these features with FD-related ECG abnormalities is, however, beyond the scope of the present work, and deserves future investigation.

4.2. Choice of statistical approach

For our statistical analysis, we deliberately chose to follow two different but complementary approaches, namely Descriptive and Discriminant analyses. The first provides univariate statistics (mainly frequencies and percentages and related statistics) to describe each of the selected ECG parameters and uses multivariate analyses such as MCA (Multiple Correspondence Analysis) resulting in factorial graphs (not shown), which explain the structure of the analyzed data. Further, the application of the Cramer's V statistic allows the

assessment of the discriminative power of each variable and/or the intensity of the correlation between two variables. Since all variables have been discretized, the interest of Cramer's V is that it integrates the size and the degree of freedom of the contingency table (*Variable X Response*) and, by doing so, it measures the strength of the association between one nominal variable with any other nominal or ordinal variable. This step is crucial, since many ECG measures are naturally correlated (e.g. heart rate and QT interval duration; presence of bundle branch block and QRS interval duration etc.) and may reach a statistically significant level for the differentiation between different groups. However, including correlated parameters for such a differentiation and/or evaluation of a prediction rule often represents an important source of statistical bias and should be avoided. On this basis, it is reasonable to state that no two of the nine parameters eventually selected are correlated and, thus, that each of them may stand for a single electrophysiologic and/or electroanatomical phenomenon. Finally, application of Bootstrap techniques to automated ECG measures has been reported in the past. However, with higher complexity of analyzed parameters and the consequent difficulty of anticipating the true confidence interval of such parameters, this approach has the great advantage of being much more accurate in the estimation of standard errors and confidence intervals. In short, this approach has allowed an estimate of the precision of the percentages of well classified individuals. Further, we could show an excellent stability of our results thanks to the acquired accuracy.

5. Limitations

A major limitation is the size of the test group, which consisted of 28 patients with FD although there were 307 healthy individuals. This is difficult to surmount without a collaborative effort to pool resources in order to produce a larger test population. The 80:20 split in training and test sets was necessary from a statistical point of view and so despite having 142 patients with FD in the study, the test results are of necessity based on a small number of patients. Specificity at 97% is excellent and should be robust while sensitivity at 64% is reasonable. However, confirmation in larger numbers of FD patients would be desirable. Furthermore, we encountered a high prevalence of females in the FD group and it is well known that some of them may not develop any cardiac involvement during their life due to possible skewed X chromosome inactivation. However, a follow-up of pre-hypertrophic patients was not the scope of the present analysis.

6. Conclusion

A selection of automated ECG measures yields an important pathophysiological insight for the understanding of pre-hypertrophic stages in FD. Furthermore, when combined and based on a scoring system, they show a substantial diagnostic value for early recognition of pre-hypertrophic Fabry Disease. Automated ECG analysis might represent a viable strategy for population screening of rare genetic heart diseases.

Declaration of Competing Interest

MN, PN, IO: Travel, Advisory board and Speakers fees and Research support from Sanofi-Genzyme and Takeda.

PR, NJ, DS and PMF: none declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.06.032.

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