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Vectorcardiographic diagnostic & prognostic information derived from the 12-lead electrocardiogram

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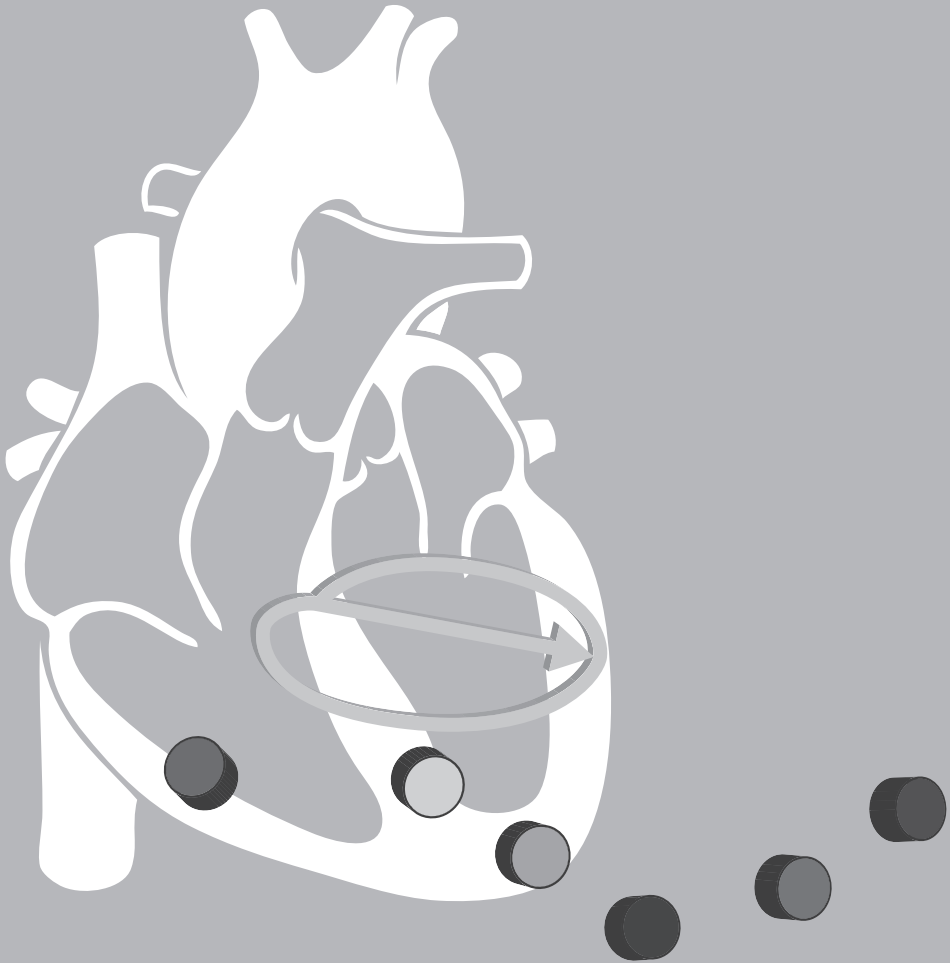


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Chapter 8

Role of the vectorcardiogram-derived spatial QRS-T angle and ventricular gradient in diagnosing left ventricular hypertrophy

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Abstract

Background

Current criteria for electrocardiographic (ECG) diagnosis of left ventricular hypertrophy (LVH) have a low diagnostic accuracy. Addition of demographic, anthropomorphic and additional ECG variables may improve accuracy. As hypertrophy affects action potential morphology and intraventricular conduction, QRS prolongation and T-wave morphology may occur and become manifest in the vectorcardiographic (VCG) variables spatial QRS-T angle (SA) and spatial ventricular gradient (VG). In this study, we attempted to improve the diagnostic accuracy for LVH by using a combination of demographic, anthropomorphic, ECG and VCG variables.

Methods

The study group (N=196) was divided in four subgroups with, on one hand, echocardiographically diagnosed LVH or a normal echocardiogram, and, on the other hand, with any of the conventional ECG signs for LVH or with normal ECGs. Each subgroup was randomly split into halves, yielding two equally-sized (N=98) data sets A and B. Age, sex, height, weight, body mass index, body surface area (BSA), frontal QRS axis, QRS duration, QT duration, maximal QRS vector magnitude, SA, VG magnitude and orientation were univariate studied by ROC analysis, and were used to build a stepwise linear discriminant model using $P < 0.05$ as entry and $P > 0.10$ as removal criterion. The discriminant model was built in set A (model A) and tested on set B. Stability checks were done by building a discriminant model on set B and testing on set A, and by cross-validation analysis in the complete study group.

Results

The discriminant model equation was $D = 5.130 \cdot BSA - 0.014 \cdot SA - 8.74$, wherein $D \geq 0$ predicts a normal echocardiogram and $D < 0$ predicts LVH. The diagnostic accuracy (79%) was better than the diagnostic accuracy of conventional ECG criteria for LVH (57%).

Conclusion

The combination of BSA and SA yield a diagnostic accuracy of LVH that is superior to that of the conventional ECG criteria.

Introduction

Electrocardiographic diagnosis of left ventricular hypertrophy (LVH) has challenged researchers for decades^{1,2}. Several criteria to diagnose LVH using the limb leads / frontal plane³⁻⁸ and the chest leads / transversal plane⁸⁻¹² are listed in the recommendation for standardization and interpretation of the electrocardiogram¹. All criteria have in common that they require R- and/or S-amplitudes to reach a given threshold, and, additionally, combinations with non-voltage criteria (*e.g.* left axis deviation) are also mentioned⁶. All proposed criteria were validated either by autopsy or by echocardiography. Evidently, none of the proposed criteria had sufficient diagnostic accuracy, as in the course of time several different diagnostic rules remained to be presented^{1,2}. In a recent review², the sensitivity and specificity of commonly-used ECG LVH criteria (*e.g.*, Sokolow-Lyon criterion) varied from 0-68% and 53-100%, respectively. Therefore, as recommended in the ECG LVH criteria guideline¹, further studies are needed to define a better LVH criterion, amongst others by inclusion of demographic, anthropomorphic (*e.g.* age, weight) and ECG variables (*e.g.* QRS duration)¹.

Hypertrophy is associated with alterations in the action potential morphology¹³⁻²⁰. In spatial electrocardiography (vectorcardiography, VCG), action potential morphology changes are reflected in the spatial ventricular gradient (SVG)²¹. Furthermore, hypertrophy causes alterations in conduction^{15,18-20} that is likely to be expressed in changes in the relationship between the ventricular depolarization and repolarization^{15,18-20}. It is conceivable that changes in the depolarization-repolarization relationship are reflected in the spatial QRS-T angle (SA^{21,22}). We hypothesized that SVG and SA could potentially contribute to a better diagnostic accuracy of the electrocardiographic diagnosis of LVH. Therefore, we studied the ECGs of patients with echocardiographically normal hearts or with echocardiographically demonstrated concentric LVH, who had either a normal ECG or whose ECG fulfilled at least one of the conventional LVH criteria, and compared the diagnostic performance of anthropomorphic, demographic, VCG, and other ECG criteria with that of the conventional ECG criteria.

Methods

Patient selection

The study group (N=196) was composed of a selection of patients who visited our outpatient clinic and in whom an echocardiogram was made. All studied subjects were older than 35 years at the time of the echocardiogram. Candidate LVH patients had the echocardiographic diagnosis of "Concentric LVH" (329 procedures), according to the septal wall thickness/ posterior wall thickness criteria $>1.2\text{cm}$ for women, and $>1.3\text{ cm}$ for men²³. This echocardiographic diagnosis had to be unique in that sense that no other, additional, echocardiographic abnormalities were reported. Then, we selected those cases in which a 10-s diagnostic 12-lead ECG was made within 3 months (preceding or following) from the recording date of the echocardiogram, and in whom medication had remained unchanged between the ECG and the echocardiogram (if the ECG was made first), or between the echocardiogram and the ECG (if the ECG was made last). When there was more than one ECG to choose from, the ECG that was closest in time to the echocardiogram was selected. When patients had more than one echocardiogram we selected the ECG-echocardiogram combination earliest in time.

In the remaining cases, we identified 2 subgroups of patients in whom the ECG either fulfilled one or more electrocardiographic LVH criteria (the ECHO+ ECG+ subgroup, consisting of 56 patients), or in whom the ECG was completely normal (the ECHO+ ECG- subgroup, consisting of 30 patients).

Subsequently, about 110 patients (about 2 times the size of the ECHO+ ECG+ group) older than 35 years were randomly selected from more than 10000 echocardiographic procedures with a diagnosis "normal heart". In this subpopulation, the reasons for the echocardiogram were 5x cardiac valve disease follow-up, 5x transient ischemic attack or stroke, 7x syncope, 8x atrial/ventricular arrhythmia follow-up, 12x chest pain, 13x post-myocardial infarction follow-up, 20x pre-/post- cardiac surgery and 40x cardiac screening. These patients were divided in 2 subgroups in whom the ECG either fulfilled one or more of the conventional electrocardiographic LVH criteria (the ECHO- ECG+ subgroup, consisting of 56 patients), or in whom the ECG was completely normal (the ECHO- ECG- subgroup, consisting of 54 patients). Patients with in their ECG any sign of Q waves, left/ right

electrical axis deviation, conduction disturbances (QRS \geq 110ms or QTc in men \geq 450 ms and QTc in women \geq 460 ms) or ST-T abnormalities were not included in the study.

Learning and test set

Each of the four subgroups ECHO+ ECG+, ECHO+ ECG-, ECHO- ECG- and ECHO- ECG+, were, by randomization, divided in two halves A and B in which the general patient characteristics did not differ. In case that, after randomization, there appeared to be a statistically significant difference between one or more of the general patient characteristics in the halves of a specific subgroup, one more randomization was done. By adding all thus constructed subgroup halves A and subgroup halves B, data sets A and B, each containing 98 patients, were formed.

ECG LVH criteria

The ECG criteria used for LVH diagnosis were at least one of:

- $R I > 15 \mu V^4$;
- $R I + S III > 25 \mu V^4$;
- $R aVL > 11 \mu V^8$;
- $S aVR > 19 \mu V^7$;
- $R aVF > 20 \mu V$; the Lewis index⁵;
- $S V1 > 23 \mu V^{12}$;
- $RV5 > 33 \mu V^{12}$;
- $RV6 > 25 \mu V^{12}$;
- $RV6:RV5 > 1.0^{24}$;
- $S V1/V2 + R V5/V6 > 35 \mu V^{10}$;
- $S V2 + R V5/V6 > 45 \mu V^{11}$;
- largest R + largest S in the precordial leads $> 35 \mu V^9$;
- Sokolow criterion⁸;
- 5 points in the Romhilt-Estes point score system⁶

Most ECG measurements were automatically done, using the ECG measurement matrix of the University of Glasgow ECG Analysis Program²⁵. When no measurement matrix was present, measurements / checks were done manually. Part of the point scoring system was measured by hand.

ECG processing

The 12-lead standard ECGs were recorded using an electrocardiograph with a sampling frequency of 500 samples per sec (25 mm/s, 10 mm/mV). The vectorcardiographic ECG analysis was done by using our custom-made program LEADS (26). VCGs were synthesized from the 8 independent ECG leads I, II, V1-V6 by using the Kors matrix²⁷. The following ECG/VCG characteristics were measured by LEADS: frontal QRS axis, QRS duration, QT duration, maximal QRS-vector amplitude (max-QRS), spatial QRS-T angle (SA, angle between the spatial mean QRS and spatial mean T vector), spatial ventricular gradient azimuth (VG_{azim}), spatial ventricular gradient elevation (VG_{elev}) and spatial ventricular gradient magnitude (VG_{mag}).

Statistical analysis

Patient characteristics of set A and B in each of the subgroups were compared, when appropriate, with the unpaired t-test or chi-square test. Receiver operating characteristic (ROC) analyses were made to visualize and quantize the diagnostic performance of the variables:

- Age,
- Sex,
- Weight,
- Height,
- Body mass index (BMI) = $\text{weight}(\text{kg}) / \text{height}(\text{m})^2$
- Body surface area (BSA) = $\sqrt{(\text{weight}(\text{kg}) * \text{height}(\text{cm})) / 3600}$ (28),
- QRS duration,
- QT duration,
- Frontal QRS axis,
- MaxQRS,
- SA,
- VG_{azim} ,
- VG_{elev} ,
- VG_{mag}

Then, stepwise linear discriminant analysis was performed; the discriminant model was built by using Wilks' lambda method, with an entry criterion of $P < 0.05$ and removal criterion of $P > 0.10$. Firstly, set A was used as learning set, this yielded

discriminant model A. Then, the diagnostic performance of model A was tested on set B. Secondly, to get an impression of the stability of model A in terms of performance, set B was used as learning set to construct discriminant model B, and set A was used as testing set for this model. Furthermore, a cross-validated (leave-one out classification) discriminant analysis of the whole study group (N=196) was done, again to test the stability of discriminant model A. All analyses were done in PASW Statistics (SPSS), version 18.0 (PASW Statistics; SPSS Inc).

Results

General patients' characteristics are given in Table 1. There were no statistically significant differences between any of the subsets A and B. The results of the vectorcardiographic analysis of subsets A and B are given in Table 2, and did not differ significantly between subsets A and B. The diagnostic accuracy of the conventional ECG criteria was 57% (by definition, this holds for the complete study group as well as for set A and for set B (Table 3).

TABLE 1. Group characteristics of the randomly assigned subsets A and B

Subgroup	ECHO–ECG–		ECHO–ECG+		ECHO+ECG–		ECHO+ECG+	
	A	B	A	B	A	B	A	B
Subset								
N	28	28	27	27	15	15	28	28
Sex (Male/Female)	15/13	14/14	17/10	17/10	2/13	6/9	16/12	14/14
Age (y)	51±13	54±12	55±13	57±14	65±12	63±14	63±16	65±16
Height (cm)	177±9	175±10	176±9	174±12	165±5	165±6	169±7	168±7
Weight (kg)	83±16	83±16	81±14	82±16	68±3	68±4	66±5	67±5
BMI (kg/m²)	26±4	27±5	26±4	27±4	25±2	25±2	23±3	24±3
BSA (m²)	2.0±0.2	2.0±0.2	2.0±0.2	2.0±0.3	1.8±0.0	1.8±0.1	1.8±0.1	1.8±0.1
Ischemic etiology	3 (11)	6 (21)	4 (13)	7 (26)	2 (13)	2 (13)	12 (43)	7 (25)
NYHA class 3	0 (0)	0 (0)	2 (7)	2 (7)	1 (7)	3 (20)	3 (11)	2 (7)
Echocardiographic parameters								
LVEF (%)	64±3	65±0	64±3	63±5	64±4	65±0	61±7	63±7
Aortic valve stenosis	0 (0)	1 (4)	0 (0)	0 (0)	2 (13)	4 (27)	5 (18)	9 (32)
Aortic valve insufficiency	1 (4)	2 (7)	1 (4)	1 (4)	2 (13)	1 (7)	6 (21)	6 (21)

Data between parentheses are percentages. Data separated by a ± sign are mean ± SD. BMI = body mass index; BSA = body surface area; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction. There was no significant difference between subsets A and B for any of the subgroups.

TABLE 2. Electrocardiographic/vectorcardiographic variables

Subgroup	ECHO–ECG–		ECHO–ECG+		ECHO+ECG–		ECHO+ECG+	
Subset	A	B	A	B	A	B	A	B
N	28	28	27	27	15	15	28	28
QRS duration (ms)	90±11	90±8	101±18	95±14	85±9	85±13	93±10	94±21
QT duration (ms)	387±47	380±29	397±26	386±32	386±21	371±31	393±35	390±50
Frontal QRS axis (°)	35±17	32±14	24±25	15±26	36±9	36±19	24±44	8±37
MaxQRS (µV)	1348±369	1281±361	1611±391	1515±448	1158±305	1144±361	1707±652	1711±676
SA (°)	53±24	51±25	64±34	75±37	64±33	69±27	98±39	112±45
VG azimuth (°)	-24±14	-23±18	-11±24	-16±28	-17±18	-18±33	-24±47	-17±50
VG elevation (°)	35±11	31±10	29±13	20±24	37±7	39±13	27±21	19±31
VG magnitude (mV·ms)	68±19	67±24	77±32	67±26	56±18	55±19	62±25	51±25

Data are given as mean ± SD. There were no significant differences between subsets A and B for any of the subgroups. MaxQRS= maximal QRS vector; SA= spatial QRS-T angle; VG = spatial ventricular gradient.

TABLE 3. Performance of conventional electrocardiographic LVH criteria

Study group (N=196)	ECHO+	ECHO–	
ECG+	56	54	PPV = 51%
ECG–	30	65	NPV = 65%
	Sensitivity = 65%	Specificity = 51%	Accuracy = 57%

At least one of the electrocardiographic left ventricular hypertrophy (LVH) criteria was fulfilled (ECG+); none of the electrocardiographic LVH criteria was fulfilled (ECG–); Echocardiographic diagnosed LVH (ECHO+); Echocardiographic normal heart (ECHO–); PPV = positive predictive value; NPV = negative predictive value. Because of the fact that each of the four subgroups was divided in two halves, thus constituting set A and set B (98 patients each), the diagnostic accuracies in set A and in set B equal the diagnostic accuracy in the complete study group.

ROCs were made for age, sex, weight, height, BMI, BSA (Figure 1, panel A), frontal QRS axis, QRS duration, QT duration, maxQRS, SA, VG_{azim} , VG_{elev} and VG_{mag} (Figure 1, panel B) to get an impression of their univariate diagnostic performance for LVH diagnosis. The ROC analyses (Table 4) showed that weight (area under the curve (AUC) 0.825, $P < 0.0001$), height (AUC 0.749, $P < 0.0001$), BMI (AUC 0.688, $P < 0.0001$), BSA (AUC 0.832, $P < 0.0001$), age (AUC 0.702, $P < 0.0001$), QRS duration (AUC 0.598, $P < 0.05$), SA (AUC 0.707, $P < 0.001$) and VG_{mag} (AUC 0.644, $P = 0.001$) had significant discriminative power for LVH (Figure 1).

Linear discriminant analysis modeling in set A selected the variables BSA and SA. The canonical discriminant coefficients of model A were: $D = 5.130 * BSA - 0.014 * SA - 8.74$; $D < 0$ predicts echocardiographic LVH diagnosis (LVH+) and $D \geq 0$ predicts a

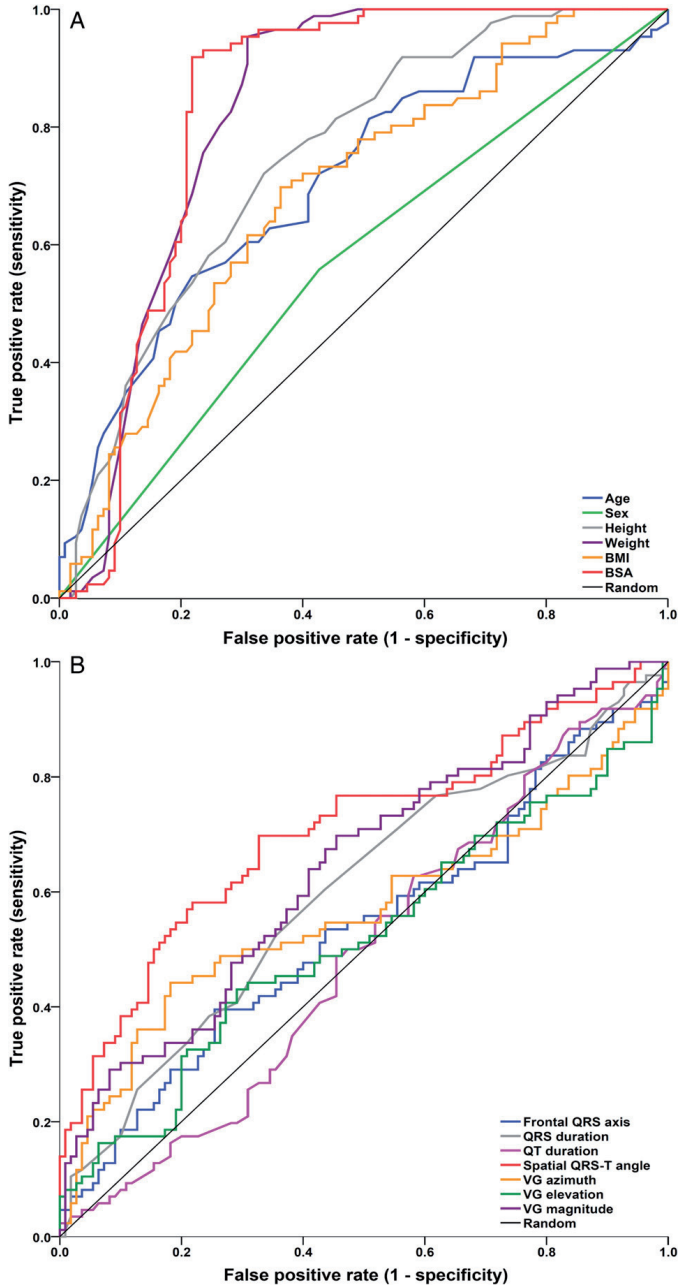


FIGURE 1. Panel A: receiver operating characteristics for demographic variables age, sex, and anthropomorphic variables weight, height, BMI and BSA. Panel B: receiver operating characteristics for electrocardiographic variables QRS duration, QT duration, frontal QRS axis, and vectorcardiographic variables maxQRS, SA, VG_{azim} , VG_{elev} and VG_{mag} . BMI = body mass index; BSA= body surface area; maxQRS = maximal QRS vector; SA= spatial QRS-T angle; VG_{azim} = ventricular gradient azimuth, VG_{elev} = ventricular gradient elevation and VG_{mag} = ventricular gradient magnitude.

normal echocardiogram (LVH-) (Table 4). In set A, the diagnostic accuracy was 79%; when tested on set B the performance was similar (79%; Table 4). To get an impression of the stability of discriminant model A, set B was used to build discriminant model B, and its performance was tested on set A. Discriminant model B included also BSA and SA: $D=4.490*BSA - 0.015*SA - 7.35$, wherein $D<0$ predicted LVH+ and $D\geq 0$ predicted LVH- (Table 5). The diagnostic accuracy in learning set B was 79%, and in test set A diagnostic accuracy was 78% (Table 5). A similar result was seen in the leave-one-out classification (cross-validated) discriminant analysis, using the whole study group of 196 patients: diagnostic accuracy was 78% (Table 6).

TABLE 4. Results of the receiver operating characteristics analyses

Variable	AUC	95% CI		P
		Lower bound	Upper bound	
Age	0.702	0.627	0.776	<0.0001
Height	0.749	0.682	0.816	<0.0001
Weight	0.825	0.765	0.885	<0.0001
BMI	0.688	0.614	0.762	<0.0001
BSA	0.832	0.771	0.894	<0.0001
QRS duration	0.598	0.517	0.679	0.02
SA	0.567	0.482	0.653	<0.0001
VG magnitude	0.702	0.627	0.776	<0.001

AUC= area under the curve; CI= confidence interval; BMI= body mass index; BSA= body surface area; SA= spatial QRS-T angle; VG= ventricular gradient. AUCs of sex, frontal QRS axis, QT duration, maximal QRS vector, ventricular gradient azimuth and elevation were not significant larger than 0.5 and therefore were not shown.

TABLE 5. Performance of discriminant model "A" for LVH diagnosis in learning set A and test set B

Learning set A N=98	ECHO+	ECHO-	
LVH+ (D<0)	35	13	PPV = 72%
LVH- (D≥0)	8	42	NPV = 84%
	Sensitivity = 81%	Specificity = 76%	Accuracy = 79%
Test set B N=98	ECHO+	ECHO-	
LVH+ (D<0)	38	15	PPV = 72%
LVH- (D≥0)	5	40	NPV = 89%
	Sensitivity = 88%	Specificity = 73%	Accuracy = 79%

Linear discriminant stepwise analysis using set A as learning set.

$D= 5.13 \times BSA - 0.014 \times SA - 8.74$. If $D<0$, left ventricular hypertrophy diagnosis is predicted (LVH+), while $D\geq 0$ predicts a normal echocardiogram (LVH-). PPV = positive predictive value; NPV = negative predictive value.

TABLE 6. Performance of discriminant model "B" for LVH diagnosis in learning set B and test set A

Learning set B N=98	ECHO+	ECHO-	
LVH+ (D<0)	32	10	PPV = 76%
LVH- (D≥0)	11	45	NPV = 80%
	Sensitivity = 74%	Specificity = 82%	Accuracy = 79%

Test set A N=98	ECHO+	ECHO-	
LVH+ (D<0)	33	12	PPV = 73%
LVH- (D≥0)	10	43	NPV = 81%
	Sensitivity = 77%	Specificity = 78%	Accuracy = 78%

Linear discriminant stepwise analysis using set B as learning set. Model equation: $D = 4.49 \times \text{BSA} - 0.015 \times \text{SA} - 7.35$. If $D < 0$, left ventricular hypertrophy diagnosis is predicted (LVH+), while $D \geq 0$ predicts a normal echocardiogram (LVH-). PPV = positive predictive value; NPV = negative predictive value.

TABLE 7. Performance of cross-validated (leave-one out classification) discriminant analysis for LVH diagnosis using the whole study group
Cross-validated (Leave-one out classification)

N=196	ECHO+	ECHO-	
LVH+	69	26	PPV = 73%
LVH-	17	84	NPV = 83%
	Sensitivity = 80%	Specificity = 76%	Accuracy = 78%

Left ventricular hypertrophy diagnosis is predicted (LVH+); normal echocardiogram (LVH-) is predicted; PPV = positive predictive value; NPV = negative predictive value.

Discussion

This is to our knowledge the first study that attempted to improve the diagnostic accuracy for electrocardiographic diagnosis of LVH by combining ECG variables (QRS duration, QT duration, frontal QRS axis), demographic/ anthropomorphic features (age, sex, weight, height, BMI, BSA) as recommended in the guidelines¹ and vectorcardiographic ECG characteristics (maximal QRS vector, spatial QRS-T angle, ventricular gradient magnitude and orientation) to the analysis. Consistently, in addition to BSA, the spatial QRS-T angle improved the discriminating of normal hearts from concentric-hypertrophic hearts. Our study also shows that other ECG/ VCG characteristics did not further contribute to the discrimination model (Table 4-5).

The conventional ECG LVH criteria did not discriminate very well in our study group: the diagnostic accuracy was only 57% (Table 3). Furthermore, in the

ROC analysis (Figure 1), maxQRS did not have discriminative power (AUC 0.501, $P=0.988$) for LVH diagnosis and, obviously, stepwise linear discriminant analysis did not select maxQRS to enter in the discriminant model. This is, in a way, a striking result, as one would expect that maxQRS, which is strongly related to QRS voltages in the scalar leads, would be a fair to good discriminator, as many of the conventional ECG criteria rely in one way or another on QRS voltages.

An explanation may be that electrical uncoupling in LVH actually causes a reduction in ECG voltage, as shown in a recent computer-model study of Bacharova *et al.*²⁹.

Similar to our study, Schlegel *et al.*³⁰ used vectorcardiographic variables as SA and VG magnitude and orientation in combination with conventional ECG criteria to develop a scoring model for detection and cardiac disease screening that included LVH, coronary artery disease and left ventricular systolic dysfunction³⁰. The contribution of SA and VG magnitude and VG orientation in the scoring model resulted in 79-92% sensitivity and 85-95% specificity in identifying cardiac disease. However, no comparison can be made with the diagnostic accuracy of our discriminant model because of the small numbers of patients with LVH in their study group. Okin *et al.* showed also that a vectorcardiographic variable, the time-voltage integral of the QRS complex, contributed to LVH diagnosis that resulted in a better sensitivity, but it was still relatively low 43-55%³¹.

The relation with hypertrophy and changes in SA may be found in the prolongation of the action potential duration and delayed conduction in the hypertrophic heart^{16;20;32;33}. Remarkable T-wave morphology changes, prolonged QT duration, QRS changes of amplitude and duration due to LVH have been shown by Bacharova *et al.*³⁴. SA is defined as the angle between the directions of ventricular depolarization and repolarization^{21;35}, hence, LVH-induced changes in the QRS complex / ventricular depolarization and T wave / ventricular repolarization should also affect SA. An increase of SA in relation to hypertension was already found by Dern³⁶, but in that study there was no imaging evidence included, hence a direct relation with hypertrophy was not demonstrated. Further studies are needed to clarify the relationship of SA and LVH.

In earlier studies³⁷⁻⁴¹, ECG LVH criteria adjusted by body habitus were shown to improve the sensitivity for LVH diagnosis. Obese persons who have often lower QRS voltages^{42,43} in the ECG may be underdiagnosed for LVH if the ECG criteria are not corrected for body habitus³⁷⁻⁴¹. This may be the reason that BSA was included in our discriminant model for LVH (Table 4-5).

Limitations

Several limitations apply to our study. We limited the echocardiographic diagnoses in our study group to normal hearts and concentric left ventricular hypertrophy. More echocardiographic diagnoses and other forms of hypertrophy complicate the situation further. Of the heterogeneous diagnoses (*e.g.* syncope, myocardial infarction, arrhythmia, healthy) in the ECHO– subgroups, myocardial infarction may have influenced intraventricular conduction, but we believe that this influence is minimal as we have selected only strictly normal ECGs.

Conclusion

It appears that, compared with the conventional ECG criteria for LVH (diagnostic accuracy 57%), the combination BSA and SA (diagnostic accuracy 79%) is superior in discriminating echocardiographically normal hearts from hearts with echocardiographically demonstrated concentric left ventricular hypertrophy. Studies in larger and more heterogeneous groups are needed to corroborate this finding.

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