Study protocol

Hypertrophy at ECG and its Regression during Treatment Survey (HEART Survey). Rationale, design and baseline characteristics of patients

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Key words:
Electrocardiography; Hypertension; Left ventricular hypertrophy; Prognosis.

Background. **Left ventricular hypertrophy (LVH) detected at electrocardiography (ECG) is a predictor of an increased cardiovascular risk in essential hypertension. However, uncertainty remains concerning the reproducibility of ECG LVH and the prognostic relevance of its regression over time in hypertension. The aim of this study was to determine the prognostic value of baseline ECG LVH and its serial changes in a large cohort of hypertensive patients.**

Methods. **The Hypertrophy at ECG and its Regression during Treatment Survey (HEART Survey) is a prospective observational study conducted in 66 Italian centers. Inclusion criteria are essential hypertension with ECG LVH defined by the Perugia score (Cornell voltage criteria and/or a typical left ventricular "strain" pattern and/or a Romhilt-Estes score ≥ 5 points) in subjects aged 45-84 years. The treatment of hypertension and other risk factors accords with current guidelines and is individually tailored. ECG is recorded twice at entry and periodically repeated over a 4-year follow-up period. Expert readers (unaware of the clinical findings) classify ECG. The incidence of major cardiovascular events in relation to baseline ECG and its changes over time are assessed, together with the reproducibility in the two baseline recordings. Overall, 708 patients aged 64 ± 9 years have been enrolled in centers from northern (27%), central (32%) and southern (41%) Italy. Their baseline characteristics are presented. Follow-up is ongoing.**

Conclusions. **The HEART Survey will examine the prognostic value of baseline ECG LVH and of its regression over time in a wide population of hypertensive patients.**

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Introduction

Left ventricular hypertrophy (LVH) carries an elevated risk for cardiovascular complications including myocardial infarction (MI), stroke, sudden death, congestive cardiac failure, cardiac arrhythmias and peripheral vascular disease[1-6]. It is therefore widely accepted that hypertensive patients with LVH should receive a more aggressive approach to optimize blood pressure control and reduce other modifiable cardiovascular risk factors[7-9].

Twelve-lead ECG is valuable for the diagnosis of LVH, although considerable variations exist in the sensitivity and specificity of the different criteria[10-14]. The Sokolow-Lyon criterion (sum of the S wave in lead V_1 and the tallest R wave in lead V_5 or $V_6 \geq 3.5$ mV) has a sensitivity of about 22% and a specificity of about 79%[10,11]. The Romhilt-Estes classification uses a point-score system; the Cornell system uses voltage (R in aVL plus S in lead $V_3 \geq 2.0$ mV in women and ≥ 2.8 mV in men)[10,11]. The product of the QRS voltage and the QRS duration seems to increase the sensitivity and specificity, but the technique requires machines with digital acquisition and post-processing of signals[12].

Some years ago, we proposed[15] a new criterion for the ECG identification of LVH (Perugia score) based on the combination of three highly specific standard ECG criteria: a modified Cornell voltage (SV_3 + RaVL > 2.4 mV in men, > 2.0 mV in women), typical left ventricular strain, and a Romhilt-Estes score of 5. LVH is defined as the presence of at least one of the above three criteria. The Cornell voltage has been modified for men on the basis of a receiver operating characteristic curve

analysis[15]. As compared with the other tested criteria, the Perugia score yielded a higher sensitivity (34%), while maintaining a good specificity (93%)[15]. The Perugia score identified the highest proportion of subjects with LVH (17.8%) and, while maintaining a high hazard ratio, it also carried the highest population-attributable risk for major cardiovascular events, accounting for 16% of all cases, whereas the Framingham and Romhilt-Estes scores and left ventricular strain accounted respectively for 3, 7 and 7% of all events[16].

The prognostic impact of serial changes of ECG LVH is supported by two studies in the Framingham population[17] and in a composite of high-risk subjects[18]. Other studies have addressed the issue of the prognostic impact of serial changes in left ventricular mass at echocardiography[19-22]. However, none of the above studies allowed a precise assessment of the prognostic impact of regression of ECG LVH in a large nationwide multicenter sample of subjects with essential hypertension.

The Hypertrophy at ECG and its Regression during Treatment Survey (HEART Survey) has been planned specifically to address the issue of the prognostic impact of ECG LVH and of its serial changes over time in a large sample of patients with essential hypertension and ECG evidence of LVH.

Design

The HEART Survey is a prospective observational study being performed in 66 centers in Italy (Fig. 1).

Inclusion criteria. The inclusion criteria are: treated or untreated systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, Caucasian race, age 45-84 years, ECG evidence of LVH documented by at least one of the following criteria (Perugia Score): a) the sum of the S wave in lead V_3 and the R wave in lead aVL ≥ 2.4 mV in men and ≥ 2.0 mV in women, b) a Romhilt-Estes score ≥ 5 in either sex, and c) typical left ventricular strain[15,16].

Exclusion criteria. The exclusion criteria are: a) previous cardiovascular events including an acute MI, angina with ST-T segment abnormalities at ECG, a transient ischemic attack, stroke, congestive heart failure, aortic dissection, peripheral vascular disease, previous vascular surgery, b) secondary hypertension, c) preexcitation syndrome, complete bundle branch block, second or third degree atrioventricular block, atrial fibrillation or flutter, d) renal (serum creatinine > 2.0 mg/dl) or liver failure, e) causes of LVH other than hypertension, f) important concomitant disease, g) alcohol abuse, and h) use of digoxin.

Methods. The study flow-chart is shown in table I; the duration is 4 years. Follow-up visits are scheduled after 3 and 6 months and then yearly until the end of the study. The clinic blood pressure is measured with the patient seated and using a standard mercury sphygmomanometer (SBP phase I, DBP phase V); baseline ECG is carried out twice at entry (interval of 1-7 days) to assess the reproducibility, and 4 more times at each year of follow-up. ECG tracings are coded and read by traditional visual analysis at a central laboratory by expert

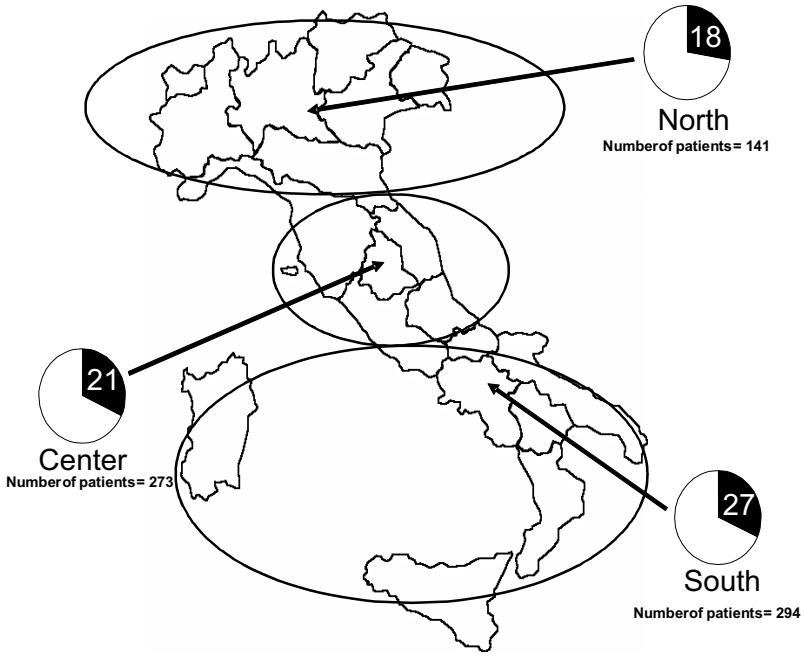

Figure 1. *HEART Survey. Number of centers and patients from northern, central and southern Italy.*

Table I. Flow-chart of the study.

Procedure	Visit 1 week 0	Visit 2 3rd month	Visit 3 6th month	Visit 4 1st year	Visit 5 2nd year	Visit 6 3rd year	Follow-up 4th year
BP and heart rate	*	*	*	*	*	*	
Weight	*		*	*	*	*	
ECG	**		*	*	*	*	
Treatment status	*	*	*	*	*	*	
Laboratory tests	*			*			
Informed consent	*						
Recognition of events		*	*	*	*	*	*

Laboratory tests include serum creatinine, common blood parameters, plasma glucose, uric acid, urea nitrogen, total cholesterol, HDL and LDL cholesterol, triglycerides, sodium, and potassium. BP = blood pressure.

readers blind to the clinical features of the patients. Routine blood and urine laboratory tests (serum creatinine, plasma glucose, uric acid, urea nitrogen, total cholesterol, HDL and LDL cholesterol, triglycerides, sodium, and potassium) are determined at entry and after 1 year.

Aims of the study. The aims of the study are to assess the relationship between a) serial changes in ECG LVH as determined using the Perugia score and subsequent cardiovascular events; b) the severity of ECG LVH at entry and subsequent cardiovascular events. The severity of ECG LVH will be graded on the basis of voltage criteria alone or combined with repolarization abnormalities.

Primary endpoints. The primary endpoint is a composite of fatal or non-fatal MI, stroke, transient ischemic attack, sudden cardiac death, congestive heart failure NYHA class III or IV, angina with documented ST-T changes, renal failure requiring dialysis, aortic dissection, peripheral vascular disease with evidence of > 75% stenosis, atrial fibrillation, sustained ventricular tachycardia or resuscitated ventricular fibrillation.

In patients with multiple events, only that which occurs first is considered for analysis.

MI is defined as follows:

1. Fatal MI: death within 7 days of the onset of a documented MI (see below).
2. Non-fatal Q-wave or ST-elevation MI: a Q-wave MI is defined by new significant Q waves (> 0.04 s duration or 3 mm in depth and loss in height of the ensuing R wave or new significant R waves in V_1-V_2) in at least 2 leads on the standard 12-lead ECG. ST-segment elevation is defined as a new ST-segment elevation of 0.1 mV in the limb leads or 0.2 mV in the precordial leads. New left bundle branch block in the clinical context of an MI is equivalent to a Q-wave MI. For a Q-wave MI or an ST-elevation MI there must be at least one of the following: a) typical chest pain, or b) an increase in the serum levels of creatine kinase (CK)-MB above the upper limit of normal within 36 hours of the onset of acute symptoms of MI (if CK-MB is not available, total CK levels at least twice the laboratory-specific upper limit of normal), or c) serum glutamic-oxoloacetic transaminase or lactate dehydrogenase levels at least twice the laboratory-specific upper limit, or d) elevated troponin T or I levels above the normal laboratory range.
3. Non Q-wave or non-ST-elevation MI: new-onset and persistent (> 24 hours) ST-segment or T-wave changes, accompanied by significant cardiac enzyme/marker elevation (see above) and/or typical symptoms of chest pain.
4. MI without significant ECG changes: typical symptoms with a significant elevation of cardiac enzymes (see above).
5. Periprocedural MI: new Q-wave MI or CK-MB or troponin levels at least 3 times the upper normal laboratory limits within 7 days of a percutaneous coronary intervention or within 30 days of coronary bypass surgery or of non-cardiovascular surgery.

Stroke is defined as follows:

1. Fatal stroke: death within 7 days of the onset of a documented stroke (see below).
2. Non-fatal stroke: acute focal neurological deficit thought to be of vascular origin and signs or symptoms lasting > 24 hours. On the basis of the symptoms and laboratory tests (computed tomography/magnetic resonance imaging) and/or necropsy results, stroke is classified as: a) definite or probable ischemic stroke, or b) definite or probable hemorrhagic stroke, or c) subarachnoid hemorrhage, or d) uncertain or unknown stroke.

A transient ischemic attack is defined as a focal neurological or monocular defect with associated symptoms lasting < 24 hours and thought to be due to occlusive (embolic or thrombotic) vascular disease.

As for atrial fibrillation, only those cases documented by ECG tracings are considered for adjudication. Paroxysmal atrial fibrillation is defined by a single or multiple episodes of atrial fibrillation that resolve during hospitalization, either spontaneously or following treatment.

Secondary endpoints. The secondary endpoints are a) fatal cardiovascular events, and b) all-cause mortality.

Adjudication procedures. Whenever a cardiovascular event is ascertained, all the relevant documentation (clinical record forms, ECG tracings, etc.) is shipped to the central laboratory for validation and adjudication, which is carried out by an independent *ad-hoc* Committee. The Committee may adjudicate the event, reject it for inconsistency or require further clinical documentation by the center.

Subprojects. The main subproject of the HEART Survey will be the assessment of the reproducibility of the baseline ECG LVH by comparing the two ECG tracings recorded at entry (at an interval of 1-7 days). Other subprojects will be a) the assessment of QT-interval dispersion and its association with subsequent cardiovascular events; b) the assessment of independent predictors of ECG LVH changes over time.

Sample size. The sample size has been determined on the following assumptions: a) the regression of ECG LVH in 50% of subjects; b) an event rate of 6% per year among subjects without LVH regression and of 3% per year among those with LVH regression; c) a type I error of 0.05 and a type II error of 0.10 (power of 90%). Overall, 616 patients completing the study would be needed to demonstrate the above assumptions (nQuery Advisor©, release 2.0, StatSol, Cork, Ireland). The expected drop-out rate was initially set at 25% and subsequently reduced to 12% on the basis of the positive feedback from the centers (May 2002 amendment), with a final estimate of 700 subjects for inclusion.

Data analysis will include standard descriptive statistics and survival analyses. Multivariate logistic regression models and semiparametric Cox models will be used. The planned predictors of outcome will include age, gender, cigarette smoking, diabetes, serum cholesterol, SBP and DBP, type of treatment and changes in ECG LVH over time (regression vs non-regression). A two-tailed α value ≤ 0.05 will be considered statistically significant to reject the null hypothesis.

Table II. Baseline characteristics of the study population.

No. patients	708
Male sex (%)	49.7
Age (years)	64 ± 9
Weight (kg)	81 ± 13
Height (cm)	163 ± 11
Body mass index (kg/m^2)	28 ± 9
Systolic blood pressure (mmHg)	161 ± 19
Diastolic blood pressure (mmHg)	93 ± 10
Heart rate (b/min)	70 ± 13
Current smokers (%)	10.9
Left ventricular hypertrophy at ECG	
Modified Cornell voltage (%)	73.0
Typical strain (%)	47.5
Romhilt-Estes of 5 points (%)	31.1
Typical strain + Romhilt-Estes of 5 points (%)	21.7
Modified Cornell voltage + typical strain (%)	25.7
Modified Cornell voltage + typical strain + Romhilt-Estes of 5 points (%)	14.3

Data are expressed as mean ± SD or as percentages for dichotomic variables.

Current status

Recruitment started on July 1, 2000 and closed on June 12, 2002. Overall, 708 Caucasian patients of either gender (49.7% male) aged 45-84 years (mean 64 ± 9 years) have been enrolled. Follow-up is ongoing. The main characteristics of the subjects are reported in table II.

Appendix

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