Association of Electrocardiographically Determined Left Ventricular Mass With Incident Diabetes, 1985–1986 to 2010–2011

Coronary Artery Risk Development in Young Adults (CARDIA) study

OBJECTIVE — Electrocardiographic indices reflecting left ventricular hypertrophy are associated with incident diabetes in clinical populations at risk for coronary heart disease. We tested whether electrocardiogram-determined left ventricular mass was positively associated with incident diabetes in a population sample.

RESEARCH DESIGN AND METHODS — Coronary Artery Risk Development in Young Adults (CARDIA) Study participants (n = 4,739) were followed from 1985–1986 to 2010–2011 for incident diabetes. Validated sex- and race-specific formulas were applied to standard electrocardiograms to determine left ventricular mass.

RESULTS — Over 25 years, 444 participants developed diabetes (9.4%). After adjustment for demographic, behavioral, and clinical covariates, participants in the highest quartile of left ventricular mass indexed to height (LVMI) were twice as likely to develop diabetes than participants in the lower three quartiles (hazard ratio 2.61 [95% CI 2.16–3.17]). Neither Cornell voltage nor Cornell voltage product was associated with incident diabetes in fully adjusted models.

CONCLUSIONS — Electrocardiogram-determined LVMI may be a useful noninvasive marker for identifying adults at risk for diabetes.

A post hoc analysis of the Losartan Intervention for Endpoint Reduction (LIFE) trial reported that improvements in electrocardiographically determined left ventricular hypertrophy over time were associated with lowered diabetes incidence (1.2). It was required that participants in the LIFE trial have hypertension, which could independently predispose to diabetes onset, and so it remains unknown whether electrocardiographically determined left ventricular mass is associated with diabetes incidence in healthy adults. We tested whether left ventricular mass, calculated from a single standard resting electrocardiogram in young adulthood (age 18–30 years), was positively associated with diabetes incidence over 25 years.

RESEARCH DESIGN AND METHODS — Participants (n = 4,739) from the Coronary Artery Risk Development in Young Adults (CARDIA) study who had valid electrocardiogram at baseline (1985–1986) and no evidence of intraventricular conduction defects or diabetes were included in the analysis sample (3). Institutional review boards at each study site approved the research. All participants provided written informed consent.

Measurements were collected using standard protocols across all study sites (n = 4). Age, race, sex, smoking, physical activity, medication use, height, weight, and waist circumference were determined at baseline. Hypertension was determined at each follow-up examination if any of the following criteria were met: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or participants reporting use of antihypertension medications.

Electrocardiographs were read centrally at the CARDIA ECG Reading Center (Wake Forest University, Winston-Salem, NC). Our primary exposure was left ventricular mass indexed to height (LVMI) (g left ventricular mass/m² height). Left ventricular mass (grams) was determined using the following race- and sex-specific formulas (4,5):

White women = (0.20 × Cornell voltage) + [1.12 × kg body wt] + 36.2

Black women = (0.23 × Cornell voltage) + [0.87 × kg body wt] + 37.6

White men = (0.26 × Cornell voltage) + [1.25 × kg body wt] + 34.4

Black men = (0.24 × Cornell voltage) + [1.18 × kg body wt] + 34.8

Secondary measures of left ventricular mass were Cornell voltage and the Cornell voltage product (6).
Blood was drawn from fasted (12 h) participants and processed at a central laboratory (3,7). Glucose was assayed using the hexokinase method. Diabetes was determined based on a combination of measures available at each examination: measured fasting glucose levels (≥126 mg/dL), self-report of oral hypoglycemic medications or insulin, or a 2-h postload glucose 200 mg/dL.

We used Cox proportional hazards modeling to calculate hazard ratios (HRs) (95% CI). To evaluate whether the left ventricular mass indices aided discrimination in the model, we calculated the C index (8). Finally, we excluded participants who had hypertension at baseline and updated hypertension status over follow-up to using a time-dependent Cox model. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). Statistical significance was determined as P < 0.05.

**RESULTS**—Mean ± SD age of participants was 24.9 ± 3.6 years at baseline; 50.3% were black, and 54.5% were female. Average BMI was 24.4 ± 5.0 kg/m²; 186 participants (3.9%) had hypertension, and of those, 56% were treated. BMI, waist circumference, glucose, and the prevalence of hypertension were each positively associated with LVMI quartile. Over 25 years, 444 participants developed incident diabetes (incidence rate 4.5/1,000 person-years). Because there was a threshold (nonlinear) effect, we modeled our associations comparing the uppermost quartile of each index to the bottom three quartiles combined. For each left ventricular mass measure, the rate of diabetes was highest in the uppermost quartile versus the lower three (Table 1). However, after statistical adjustment for potential confounders, only LVMI remained significantly associated with incident diabetes. The C index for a model that included all covariates except for LVMI was 0.698 (95% CI 0.672–0.723); the addition of LVMI improved the C index.

### Table 1—Diabetes incidence adjusted HRs (95% CI) by quartile of electrocardiographically determined left ventricular mass*

| Variables† | N events | Rate/1,000 person-years | Model 1 | Model 2 | Model 3 |
|------------|----------|------------------------|---------|---------|---------|
| LVMI       |          |                        |         |         |         |
| Quartile 4 | 214      | 8.94                   | 3.02 (2.50–3.65) | 2.72 (2.24–3.30) | 2.61 (2.16–3.17) |
| Quartiles 1–3 | 230   | 3.08                   | 1.07 (1.05–1.10) | 1.06 (1.03–1.09) | 1.05 (1.03–1.08) |
| Age (per 1 year) |          |                        |         |         |         |
| Sex (female vs. male) |          |                        |         |         |         |
| Race (white vs. black) |          |                        |         |         |         |
| Education (per 1 year) |          |                        |         |         |         |
| Antihypertension medication use (yes vs. no) |          |                        |         |         |         |
| Systolic blood pressure (per 1 mmHg) |          |                        |         |         |         |
| Smoking status (current or former vs. never) |          |                        |         |         |         |
| Physical activity (per 1 exercise unit) |          |                        |         |         |         |
| Fasting glucose (per 1 mg/dL) |          |                        |         |         |         |
| Cornell voltage |          |                        |         |         |         |
| Quartile 4 | 128      | 5.08                   | 1.24 (1.01–1.53) | 1.15 (0.93–1.42) | 1.16 (0.94–1.43) |
| Quartiles 1–3 | 316   | 4.30                   | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Age (per 1 year) |          |                        |         |         |         |
| Sex (female vs. male) |          |                        |         |         |         |
| Race (white vs. black) |          |                        |         |         |         |
| Education (per 1 year) |          |                        |         |         |         |
| Antihypertensive medication use (yes vs. no) |          |                        |         |         |         |
| Systolic blood pressure (per 1 mmHg) |          |                        |         |         |         |
| Smoking status (current or former vs. never) |          |                        |         |         |         |
| Physical activity (per 1 exercise unit) |          |                        |         |         |         |
| Fasting glucose (per 1 mg/dL) |          |                        |         |         |         |
| Cornell voltage product |          |                        |         |         |         |
| Quartile 4 | 131      | 5.27                   | 1.31 (1.06–1.61) | 1.19 (0.97–1.47) | 1.20 (0.97–1.48) |
| Quartiles 1–3 | 313   | 4.24                   | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Age (per 1 year) |          |                        |         |         |         |
| Sex (female vs. male) |          |                        |         |         |         |
| Race (white vs. black) |          |                        |         |         |         |
| Education (per 1 year) |          |                        |         |         |         |
| Antihypertensive medication use (yes vs. no) |          |                        |         |         |         |
| Systolic blood pressure (per 1 mmHg) |          |                        |         |         |         |
| Smoking status (current or former vs. never) |          |                        |         |         |         |
| Physical activity (per 1 exercise unit) |          |                        |         |         |         |
| Fasting glucose |          |                        |         |         |         |

*Adjusted additionally for field center. †Referent category listed second.
to 0.745 (0.720–0.770), indicating that LVMI significantly added to model prediction.

After exclusion of participants who had hypertension at baseline, LVMI remained significantly associated with incident diabetes in a fully adjusted model (HR 2.36 [95% CI 1.93–2.88], quartile 4 vs. quartiles 1–3). Results were similar when we updated hypertension incidence during the follow-up interval (2.27 [1.85–2.79], quartile 4 vs. quartiles 1–3).

**CONCLUSIONS**—Electrocardiographically determined LVMI in young adulthood was positively associated with diabetes in a population sample. The novel aspect of our study is that we identified an elevated incidence of diabetes in younger adults who had a relatively low burden of comorbid cardiovascular disease at the time of electrocardiogram measurement.

Our findings are consistent with those from the LIFE trial (1), but in a study by Verdecchia et al. (9) the significant relationship between left ventricular hypertrophy (as determined by the Peru-
gia score) and incident diabetes in models unadjusted for risk factors did not persist after taking into account other risk factors for diabetes. Obesity and insulin resis-
tance are proposed as unifying mecha-
nisms underlying the metabolic syndrome, which includes both hyper-
tension and diabetes. Because insulin may promote left ventricular growth independent of hypertension, it is plausible that greater left ventricular mass may be more than just a correlate of hypertension (10). Rather, higher left ventricular mass could be an intermediate manifestation of hyperinsulinemia that is present prior to development of frank diabetes.

By testing our hypothesis in a sample of young adults with a low prevalence of hypertension at baseline (4%), we reduced the possibility that residual confounding explained our observations. However, our findings must be inter-
preted in light of some limitations. A single measure of electrocardiographically deter-
mined left ventricular mass is subject to error based on biological day-to-day vari-
ability and variability in the site of electrode placement that could influence QRS voltage (6). Consequently, we chose to rely on Corn-
ell voltage to determine left ventricular mass rather than Sokolow voltage because Cornell relies on a mix of limb and chest leads, thus reducing error (6).

In summary, via application of validated formulas to determine left ventricular mass, a standard electrocardiogram can be used to identify adults who may have comorbid metabolic disorders that place them at risk for the development of diabetes. Electrocardiographically deter-
mined LVMI could be considered a useful tool to identify adults at risk for diabetes based on its ease of assessment, ready availability, and cost-effectiveness.

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