

# Electrocardiogram Abnormalities and Coronary Calcification in Postmenopausal Women

Siamak Sabour, MD, PhD<sup>1, 2\*</sup>, Diederick Grobbee, MD, PhD<sup>1</sup>, Annemarieke Rutten, MD<sup>3</sup>, Mathias Prokop, MD, PhD<sup>3</sup>, Marie-Louise Bartelink, MD, PhD<sup>1</sup>, Yvonne van der Schouw, PhD<sup>1</sup>, Michiel Bots, MD, PhD<sup>1</sup>

<sup>1</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands.

<sup>2</sup>Faculty of Health and Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran.

<sup>3</sup>Radiology Department, University Medical Center Utrecht, Utrecht, The Netherlands.

Received 07 July 2009; Accepted 18 November 2009

## Abstract

**Background:** An electrocardiogram (ECG) can provide information on subclinical myocardial damage. The presence, and more importantly, the quantity of coronary artery calcification (CAC), relates well with the overall severity of the atherosclerotic process. A strong relation has been demonstrated between coronary calcium burden and the incidence of myocardial infarction, a relation independent of age. The aim of this study was to assess the relation of left ventricular hypertrophy (LVH) and ECG abnormalities with CAC.

**Methods:** The study population comprised 566 postmenopausal women selected from a population-based cohort study. Information on LVH and repolarization abnormalities (T-axis and QRS-T angle) was obtained using electrocardiography. Modular ECG Analysis System (MEANS) was used to assess ECG abnormalities. The women underwent a multi detector-row computed tomography (MDCT) scan (Philips Mx 8000 IDT 16) to assess CAC. The Agatston score was used to quantify CAC; scores greater than zero were considered as the presence of coronary calcium. Logistic regression was used to assess the relation of ECG abnormality with coronary calcification.

**Results:** LVH was found in 2.7% ( $n = 15$ ) of the women. The prevalence of T-axis abnormality was 6% ( $n = 34$ ), whereas 8.5% ( $n = 48$ ) had a QRS-T angle abnormality. CAC was found in 62% of the women. Compared to women with a normal T-axis, women with borderline or abnormal T-axes were 3.8 fold more likely to have CAC (95% CI: 1.4-10.2). Similarly, compared to women with a normal QRS-T angle, in women with borderline or abnormal QRS-T angle, CAC was 2.0 fold more likely to be present (95% CI: 1.0-4.1).

**Conclusion:** Among women with ECG abnormalities reflecting subclinical ischemia, CAC is commonly found and may in part explain the increased coronary heart disease risk associated with these ECG abnormalities.

*J Teh Univ Heart Ctr 1 (2010) 19-24*

**Keywords:** Atherosclerosis • Hypertrophy, left ventricular • Myocardial ischemia • Women • Postmenopause

## Introduction

With an electrocardiogram (ECG), information can be

obtained on subclinical myocardial damage. The frontal T-axis has been postulated to be a general marker of ventricular repolarization abnormality and has been shown

\*Corresponding Author: Siamak Sabour, Assistant Professor of Clinical Epidemiology & Medicine, Department of Epidemiology & Biostatistics, Faculty of Health & Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran. 5166614711. Tel: +98 411 3357580-3. Fax: +98 411 3340634. Email: sabours@tbzmed.ac.ir.

to be a strong and independent risk indicator of fatal and non-fatal cardiac events in the elderly.<sup>1-3</sup> In addition, the spatial QRS-T angle, which is defined as the angle between the directions of ventricular depolarization and repolarization,<sup>4</sup> has been shown to be an important determinant of diagnosis and prognosis in patients presenting with acute chest pain.<sup>5</sup> The presence of spatial QRS-T angle relates to increased risk of cardiac death for coronary heart disease in postmenopausal women.<sup>6-9</sup> Findings from autopsy and clinical angiographic studies have suggested a link between left ventricular hypertrophy (LVH) and severity of coronary atherosclerosis.<sup>10, 11</sup> Clear associations between echocardiographically assessed LVH and coronary atherosclerosis risk factors have been reported<sup>12, 13</sup> and LVH has been shown to predict future cardiovascular disease.<sup>14, 15</sup>

Coronary atherosclerosis can be non-invasively assessed in a valid and reproducible manner by the measurement of coronary calcium using coronary computer tomography.<sup>16</sup> High coronary artery calcium (CAC) scores independently predict coronary heart disease (CHD).<sup>10, 14, 17</sup> It may also reflect the presence of subclinical ischemia.

We set out to investigate whether morphological cardiac abnormalities (LVH) and ECG parameters (T-axis and QRS-T angle) that reflect potential ischemic abnormalities related to CAC in postmenopausal women.

## Methods

We used data from a cross-sectional study among 566 postmenopausal healthy women as has been detailed earlier.<sup>18</sup> In short, these women were selected from participants of the PROSPECT study, one of the two Dutch cohorts participating in the European Prospective Investigation into Cancer and Nutrition (EPIC).<sup>19</sup> In PROSPECT 17, 357 healthy participants of a nationwide population-based breast-cancer screening program, aged 49-70 years, living in Utrecht and surroundings were enrolled between 1993 and 1997. Between October 2002 and April 2004, 1996 women were randomly selected from 5844 participants of the PROSPECT study who were postmenopausal and did not use contraceptives or hormone replacement therapy, and 1000 agreed to participate. Of these 1000 women, a random selection of 566 underwent a multislice CT examination at a second visit between January and December 2004.

At the first re-examination visit, smoking behavior and family history of coronary heart diseases (CHD) were assessed using a questionnaire. Age was calculated from birth date and date of investigation. Height and weight were measured and body mass index (BMI) was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). Waist-to-hip ratio (WHR) was assessed. Systolic and diastolic blood pressure (SBP & DBP) were measured at both arms with an automated and calibrated blood pressure device (DINAMAP™ XL,

Critikon, Johnson & Johnson, Tampa, Florida, USA) with the subject in supine position. A venous blood sample was drawn after an overnight fast of at least eight hours. Plasma total cholesterol, plasma triglycerides, and plasma glucose were measured using standard enzymatic procedures. High-density lipoprotein (HDL) cholesterol was measured via the direct method (inhibition, enzymatic). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. We defined hypertension as either using anti-hypertensive therapy or a systolic blood pressure  $> 140$  mmHg or a diastolic blood pressure  $> 90$  mmHg. Pulse pressure (PP) was defined as SBP -DBP.

The participants underwent a multi-detector computed tomography (MDCT) examination for the assessment of CAC. The amount of calcium in the coronary arteries was assessed with a MDCT scanner (Mx 8000 IDT 16, Philips Medical Systems, Best, The Netherlands). The subjects were positioned within the gantry of the MDCT scanner in supine position. During a single breath hold, images of the heart, from the level of the tracheal bifurcation to below the base of the heart, were acquired using prospective ECG triggering at 50-80% of the RR-interval, depending on the heart rate. Scan parameters were  $16 \times 1.5$  mm collimation, 205 mm field of view (FOV), 0.42 s rotation time, 0.28 s scan time per table position, 120 kVp and 40-70 mAs (patient weight  $< 70$  kg: 40 mAs; 70-90 kg: 55 mAs;  $> 90$  kg: 70 mAs). Scan duration was approximately 10 seconds, depending on heart rate and patient size.

Quantification of coronary calcium was performed on a separate workstation with software for calcium scoring (Heartbeat-CS, EBW, Philips Medical Systems, Best, The Netherlands). All regions with a density over 130 Hounsfield units were identified as potential calcifications. After completing a training-program, a trained scan reader, blinded for electrocardiographic results of the women, manually selected only the calcifications within the coronary arteries (left main, left anterior descending, left circumflex, right coronary artery, or posterior descending artery). To reduce the influence of noise, the minimum size of a calcified lesion was set at  $0.5 \text{ mm}^2$ . The peak density in Hounsfield units and the area in  $\text{mm}^2$  of each selected region were calculated. The Agatston<sup>20</sup> calcium score was obtained by multiplying the area by a weighting factor that is dependent on the peak signal anywhere in the lesion. The scores of individual lesions were added to obtain the Agatston calcium score for the entire coronary tree. Calcium presence was defined as score  $> 0$ . We performed reproducibility studies, in which 199 scans were read in duplicate, showing Intraclass correlation coefficients (ICCC) of  $> 0.95$  for the duplicate readings.<sup>21</sup> Another reproducibility study in which in 73 women a duplicate MDCT scan was made within three months of the first scan showed ICCC between repeat scans of  $> 0.90$ .<sup>22</sup>

A standard 12-lead electrocardiogram was recorded with the women lying in supine position using Cardio Perfect



equipment (Cardio Perfect Resting ECG, Welch Allyn Cardio Control, Delft, The Netherlands). ECGs were recorded at a sampling frequency of 300 Hz and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) as described and evaluated in detail earlier.<sup>23-25</sup> The program was extensively validated, and the outcomes of MEANS in population-based research were at least as good as ECG interpretation by a trained research physician except for myocardial infarction (cases of AMI and IMI are correctly diagnosed in only 43% and 54% of the cases, respectively).<sup>25</sup> MEANS as a well-known method introduced more than a decade ago computes a representative averaged beat for each of the 12 leads from which ECG measurements and a diagnostic interpretation are derived. Mean QRS and T axes were computed from vectorcardiographic X, Y and Z leads, which can, in good approximation, be constructed from the standard ECG leads.<sup>24</sup> The mean spatial axes are based on the areas of the wave components of the QRS complex and the T wave. The mean frontal T-axis is the angle between the X axis and the projection of the mean spatial T-axis on the frontal XY plane. The spatial QRS-T angle is the angle between the mean spatial QRS axis and the mean spatial T-axis. Electrocardiographic LVH was defined by using voltage and repolarization criteria, in which the age-adjusted Sokolow criterion pulse pressure (PP) was defined as SBP-DBP.

Women with T-axis 15-75 were considered "normal", -15 thru 14 as "borderline" and finally both -180 thru 16 and 106 thru 180 as "abnormal T-axis". We considered QRS-T angles 0 thru 105 as "normal", 106 thru 135 as "borderline"

and 136 thru 180 as "abnormal". Furthermore, we also combined borderline categories in abnormal and considered ECG abnormalities as dichotomized variables in part of our analysis.

The outcome variable for this analysis was total CAC, and the primary predictor variables were LVH and ECG abnormalities. The following covariates as potential confounders were used in the analysis: age, BMI, WHR, cigarette smoking status, SBP, DBP, PP, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, glucose, and family history of CHD. ECG abnormalities were divided into two categories 1: normal and 2: borderline or abnormal to assess the relation between ECG abnormalities and CAC. Logistic regression models were used to evaluate the associations under study. Odds ratio (OR) for CAC and 95% confidence intervals (CI) were determined. A significance level of 0.05 was used for all the analyses. Data analysis was performed using SPSS for Windows version 13.0.

## Results

Table 1 lists the characteristics of the study population in terms of the presence or absence of CAC. The prevalence of LVH was 2.7%, of T-axis abnormality 6%, and of QRS-T angle abnormality 8.5%. Sixty-two percent of the women had a coronary calcification score greater than zero.

Table 2 shows the associations between vascular risk factors and CAC as well as ECG parameters. Factors that were related to CAC were increased age, WHR, SBP, DBP,

Table 1. General characteristics of study population and relation of coronary artery calcification with clinical covariates\*

	CAC <sup>+</sup> (n = 348)	CAC <sup>-</sup> (n = 218)	Total (n = 566)
Age (y)	68.0±5.5	64.8±4.9	66.7±5.4
Body mass index (Kg/m <sup>2</sup> )	26.8±4.4	26.3±4.4	26.6±4.4
Waist-hip ratio	0.85±0.08	0.82±0.05	0.84±0.07
Systolic blood pressure (mmHg)	139.4±20.4	130.5±19.7	135.9±20.6
Diastolic blood pressure (mmHg)	73.3±8.8	70.1±9.8	72.1±9.3
Pulse pressure (mmHg)	66.0±16.3	60.4±14.2	63.8±15.7
Hypertension	57	38	50
Total cholesterol (mmol/l)	6.1±1.0	5.9±0.9	6.0±0.9
LDL cholesterol (mmol/l)	4.2±0.9	4.1±0.8	4.2±0.9
HDL cholesterol (mmol/l)	1.3±0.3	1.4±0.4	1.3±0.3
Triglyceride (mmol/l)	1.2±0.6	1.1±0.6	1.2±0.6
Glucose (mmol/l)	5.6±1.0	5.4±0.7	5.5±0.9
Current smoking	16	4	11
Former smoking	45	42	44
Family history of CHD in either parent	13	9	11
Coronary calcification	100	0	61.5
Left ventricular hypertrophy	3.4	1.4	2.7
T-axis abnormality	8.3	2.3	6.0
QRS-T angle abnormality	10.6	5.1	8.5

\*Data are presented as mean±SD or percentage

CAC<sup>+</sup>, Coronary artery calcification positive; CAC<sup>-</sup>, Coronary artery calcification negative; CHD, Coronary heart diseases; HDL, High-density lipoprotein; LDL, Low-density lipoprotein

Table 2. Age adjusted relation of coronary calcification, left ventricular hypertrophy and ECG abnormalities with clinical covariates

	OR (95% CI)			
	CAC	LVH	T-axis	QRS-T angle
Age (y)	1.12 (1.08-1.16)*	1.04 (0.95-1.14)	1.04 (0.98-1.11)	1.05 (1.00-1.11)*
Body mass index (Kg/m <sup>2</sup> )	1.02 (0.98-1.06)	1.01 (0.90-1.13)	1.04 (0.96-1.12)	1.08 (1.01-1.15)*
Waist-hip ratio	1.84 (1.40-2.43)*	1.31 (0.65-2.67)	1.79 (1.11-2.87)*	1.68 (1.11-2.54)*
Systolic blood pressure (mmHg)	1.01 (1.00-1.02)*	1.03 (1.01-1.05)*	1.01 (0.99-1.03)	1.02 (1.01-1.03)*
Diastolic blood pressure (mmHg)	1.04 (1.02-1.06)*	1.03 (0.98-1.09)	1.01 (0.98-1.05)	1.04 (1.01-1.07)*
Pulse pressure (mmHg)	1.01 (1.00-1.02)*	1.05 (1.02-1.08)*	1.01 (0.99-1.04)	1.02 (1.01-1.04)*
Hypertension (%)	1.78 (1.24-2.56)*	3.87 (1.06-14.12)*	2.34 (1.08-5.07)*	2.63 (1.34-5.16)*
Total cholesterol (mmol/l)	1.13 (0.94-1.36)	0.78 (0.45-1.35)	0.78 (0.54-1.12)	1.07 (0.80-1.45)
LDL cholesterol (mmol/l)	1.24 (1.01-1.52)*	0.87 (0.47-1.54)	0.79 (0.53-1.18)	1.07 (0.78-1.49)
HDL cholesterol (mmol/l)	0.56 (0.34-0.93)*	0.46 (0.08-2.45)	0.35 (0.11-1.10)	0.89 (0.37-2.10)
Triglyceride (mmol/l)	1.32 (0.97-1.79)	0.75 (0.27-2.05)	1.41 (0.85-2.32)	1.19 (0.75-1.89)
Glucose (mmol/l)	1.35 (1.05-1.72)*	1.16 (0.75-1.79)	1.39 (1.08-1.86)*	1.26 (0.98-1.61)
Current smoking (%)	6.16 (2.90-13.09)*	0.56 (0.07-4.40)	2.71 (1.16-6.32)*	1.45 (0.61-3.41)
Former smoking (%)	1.12 (0.78-1.60)	0.62 (0.21-1.85)	0.87 (0.43-1.77)	0.81 (0.44-1.48)
Family history of CHD in either parent	1.96 (1.09-3.53)*	1.30 (0.28-5.99)	1.11 (0.37-3.31)	0.34 (0.08-1.46)

\*p < 0.05

ECG, Electrocardiogram; CAC, Coronary artery calcification; LVH, Left ventricular hypertrophy; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; CHD, Coronary heart diseases

PP, presence of hypertension, increased LDL-C, decreased HDL-C, increased glucose, current smoking, and family history of CHD. SBP, pulse pressure, and hypertension were related to LVH. Factors related to T-axis abnormality were WHR, hypertension, glucose, and current smoking. Factors that were related to QRS-T abnormality were age, BMI, WHR, SBD, DBP, PP, and hypertension (Table 2).

Crude analyses showed no significant relation between LVH and the presence of CAC [OR = 2.5 (0.7-9.1)] and significant relations for both an abnormal T-axis [OR = 3.9 (1.5-10.1)] and an abnormal QRS-T angle [OR = 2.2 (1.1-4.5)]. In the age-adjusted models, abnormal T-axis was significantly related to CAC [OR = 3.8 (1.4-10.2)], and an odds ratio of 2.0 (1.0-4.1) was found for abnormal QRS-T angle. These relations attenuated when adjustments were made for additional vascular risk factors such as waist-hip ratio, systolic blood pressure, diastolic blood pressure, pulse pressure, and hypertension [OR = 1.6 (0.7-3.3)].

## Discussion

In the present study, we showed that in healthy postmenopausal women the presence of LVH and of subclinical myocardial damage as assessed by T-axis and QRS-T abnormalities related to the presence of coronary calcifications.

A few studies have examined the association of echocardiographically assessed LVH with CAC. In a Turkish population among 249 asymptomatic hypertensive patients, a positive association between concentric LVH and CAC was reported.<sup>26</sup> A study among 159 young to middle-

age African-American participants without hypertension or overt ischemic heart disease<sup>27</sup> showed that men with CAC had a significantly larger left ventricular mass and higher left ventricular mass index than did those without CAC, independent of other important atherosclerosis risk factors, with a parallel, but insignificant, trend in women. A study in 2,724 young African-American and white adults who participated in the CARDIA study reported that left ventricular mass was significantly associated with the extent of CAC among subjects who were positive for CAC, but not with the presence of CAC after multivariable adjustment.<sup>28</sup> Our findings expanding the evidence to women are in principle in agreement with these reports.<sup>29</sup> However, we did not find a statistically significant relation between LVH and CAC. The lack of reaching statistical significance can most likely be attributed to a relative small sample size in combination of a relatively modest sensitivity of the ECG to assess LVH. We feel that a lack of statistical significance does not rule out the existence of a relation in a larger study with more sensitive measurement to assess LVH.

Information on the relation between T-axis and QRS-T angle abnormalities and coronary calcification is absent. A Pub Med search (February 24, 2008) on terms as 'coronary calcium or coronary calcification' and 'T-axis or QRS-T angle' indicated no studies. Combining results from individual studies showing that CAC predicts future events results from studies indicating that ECG abnormalities predict events, and our current findings suggest that part of the increased risk through ECG abnormalities may be attributable to the presence of coronary atherosclerosis and vice versa.

One aspect of our study that may need consideration is the conclusion to be drawn from analyses adjusted for various





risk factors. One may argue that after our multivariate analyses, the statistical significance of the relations between ECG abnormalities and CAC was lost and our conclusions are, therefore, overstated. Alternatively, since these risk factors most likely causally relate to both the occurrence of ECG abnormalities and CAC and that ECG abnormalities and CAC both reflect stages of subclinical vascular damage, one may also argue that adjusted models indicate that the risk factors for these two conditions are similar. We support the latter reasoning.

## Conclusion

We found that among women with ECG (T-axis and QRS-T angle) abnormalities, reflecting subclinical ischemia, CAC is commonly found. Our finding may in part explain the increased coronary heart disease risk associated with these ECG abnormalities.

## Acknowledgment

This study was supported by grant 2100.0078 from The Netherlands Organization for Health Research and Development. The Medical Ethics Committee of the University Medical Center Utrecht approved the study and written informed consent was obtained from all the participants before enrolment. The first author was supported by the Health Ministry of Iran.

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