Calcification of the coronary arteries
Reproducibility, risk factors and risk

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Thesis, Utrecht University, Faculty of Medicine, with a summary in Persian.
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بنام خدا

تقدیم به مادر و خانواده عزیزم
و به یاد پدر و برادرانم پرویز و خسرو

To my dear mother and my family;
And in loving memory of my father and my brothers Parviz and Khosro

Calcification of the coronary arteries
Reproducibility, risk factors and risk

Verkalking van de kransslagaders :
reproduceerbaarheid van de meting,
determinanten en risico

(met een samenvatting in het Nederlands)

کلسیفیکاسیون عروق کرونر
قابلیت تکرار یکسان نتایج, عوامل خطر و خطرات ناشی از آن

(با خلاصه ای به زبان فارسی)

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Chapter
1

Introduction

Introduction

Cardiovascular disease is a major contributor of disability and death. [1] Development of atherosclerosis is the main underlying mechanism leading to the occurrence of vascular diseases. [2;3] Atherosclerosis tends to develop slowly and gradually over the years and remains subclinical, i.e., a-symptomatic for a long time. [4] Only when lesions or plaques rupture, acute symptoms occur, leading to disability or death. Indeed for a large proportion of the population sudden death is the only symptom from atherosclerosis development. [5] Traditionally, cardiovascular epidemiology focused on the relation between etiologic factors, i.e., vascular risk factors, and the occurrence of vascular events. In the past decades a shift has been made from events towards atherosclerosis, since the ability to obtain information on the atherosclerotic process using minimal or non-invasive approaches has dramatically increased. [6-9] This has lead to a large number of studies into the role of etiologic factors on subclinical atherosclerosis development, and studies on the presence and extent of subclinical atherosclerosis as a predictor of future events. In addition, studies have been launched to investigate the additional value of subclinical atherosclerosis measurements in the risk profiling of subjects. [10-12] Moreover, measurements of change in subclinical atherosclerosis are currently used in randomized controlled trials on the efficacy of drug treatment. [13;14]

At present there are several possibilities to assess atherosclerosis in a minimal or non-invasive approach as have been detailed in several reviews. [9;15-19] This includes for example ultrasound with measurement of (carotid) intima-media thickness (CIMT) [15], and plaques [16], magnetic resonance imaging [17] with measurement of plaques and plaque tissue characteristics and computed tomography [18;19] with measurement of arterial calcifications. Electron-beam computed tomography (EBCT) has been shown to be able to measure calcium deposits in the coronary arteries. These deposits have been validated with pathological anatomical specimens and shown to indeed reflect atherosclerosis in the coronary arteries. Although data on coronary calcium has mainly come from studies using EBCT, nowadays multi detector CT (MDCT) is much more widely available and also allows for measurement of coronary calcium.

The present thesis focuses on various aspects of the coronary calcium measurements on which information is not widely present. This includes studies into the reproducibility of the coronary calcium measurements by MDCT (chapter 2). Furthermore, several studies on the relation of presence and/or change in risk factors over time to coronary calcium and also the relation of risk factors to segment specific coronary calcium (chapter 3). In chapter 4 we examined the relation between coronary calcium and other marker of myocardial damage. Finally, the findings presented in this thesis are being put into perspective (chapter 5).

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Chapter

2

Reproducibility of Coronary calcium measuements

Abstract

Background:

Most studies on coronary calcium have been performed using electron beam computed tomography. EBCT scanners are not widely available. Recently, Multi Detector -Row Computed Tomography (MDCT) has been developed and is more readily available for assessment of coronary calcium. Studies on reproducibility however are limited. We set out to assess reproducibility of coronary calcium measurements with MDCT imaging and to evaluate whether different measurement protocols, slice thickness and cardiovascular risk factors affect inter and intra- observer reproducibility.

Design: Cross-sectional study

Materials and methods:

The study population comprised 199 healthy postmenopausal women. Coronary calcium was assessed using a 16-MDCT (Philips Mx 8000 IDT 16). Images were made using 1.5 and 3.0 mm slice thicknesses. To assess inter and intra-observer reproducibility, the images were read by two observers. One observer read the images of 52 subjects twice. The Agatston score, a volume measurement and a mass measurement were used to quantify coronary calcium. Reproducibility was determined by estimation of mean, absolute and relative differences between scores of the observers and by estimation of Intra-class correlation coefficients (ICCC).

Results:

One hundred and twenty participants (60.3%) had a positive calcium score. Median Agatston score for the first observer was 2.20 with a range of 0- 2019.The reproducibility of coronary calcium measurements between observers and within observers was excellent with Intra-class correlation coefficients of > 0.95, and small mean, absolute and relative differences. Reproducibility findings were similar for 1.5 mm slices as for 3.0 mm slices, andw equal for Agatston, volume and mass measurements. Of the established cardiovascular risk factors, none was significantly related to measurement error. However, the measurement error increased with increasing coronary calcium.

Conclusion:

Reproducibilility of measurement of coronary calcium using images from MDCT is excellent, irrespective of slice thickness and type of calcium parameter. The observation that coronary calcium levels were related to higher measurement errors are of consequence depending on the research question of a study, being either etiologic, diagnostic or prognostic.

Introduction

Cardiovascular disease is a main contributor to morbidity and mortality in industrialized countries. Atherosclerosis is one of the main underlying processes in the development of symptomatic vascular disease. Measurement of the extent of atherosclerosis is important for diagnostic and therapeutic purposes. Furthermore, invasive and non-invasive assessment of atherosclerosis may allows studies into the etiology (risk factors and treatment) and consequences of atherosclerosis in populations at large [1]. The quest for techniques to assess coronary atherosclerosis in a non-invasive manner has led to the use of computed tomography (CT). Coronary calcification assessed with CT has been shown to be related to unfavorable levels of risk factors, to atherosclerosis elsewhere in the arteries and to prevalent cardiovascular disease. Furthermore, increased coronary calcium is one of the strongest predictors of occurrence of coronary artery disease in the future [2].

Most of the evidence on determinants and consequences of coronary calcium have been based on images obtained by electron beam CT (EBCT) [3]. Recently, the Multi Detector -Row CT (MDCT) became available, which also allows for detection of coronary calcium and current data suggest that EBCT and MDCT give comparable results [4;5]. Since MDCT is more widely available than EBCT and therefore is likely to be used more widely, information on reproducibility of measurement of coronary calcium is relevant. Furthermore, due to technical improvement slice thickness of the images has become smaller which may affect the likelihood of detecting coronary calcium and its reproducibility.

We set out to study reproducibility of coronary calcium measurements from MDCT images and to evaluate whether its reproducibility varies with different measurement protocols, slice thicknesses and across selected cardiovascular risk factors.

Materials and methods

Study population

Participants were recruited from the PROSPECT study, one of the two Dutch cohorts participating in the European Prospective Investigation into Cancer and nutrition (EPIC) [6]. In PROSPECT, a total of 17,357 healthy breast-cancer screening participants, aged 49–70 years, living in Utrecht and surroundings, were enrolled between 1993 and 1997. The purpose of the PROSPECT-EPIC study is to assess the relation between nutrition and cancer and other chronic diseases. Of the 17,357 women 6,612 women were excluded because of death, participation in other studies, absence of written informed consent, or emigration. Other reasons for exclusion were premenopausal state (n = 1,309), missing data on menopausal status (n = 2,105) or use of oral contraceptives (OC) or postmenopausal hormone therapy (HT) in the year before or after the last menstruation (n = 1,487). Between October 2002 and December 2004, out of 5,844 eligible women, a random selection of 1,996 women were invited by a personal letter from the principal investigator of PROSPECT and 1,000 (50.1%) who were postmenopausal and did not use contraceptives or hormone replacement therapy answered positively. Of these 1000 women, a random selection of 573 underwent a MDCT examination during a single visit and 199 of them were scored by two independent readers.

The Medical Ethical Committee of the University Medical Center Utrecht approved the study and written informed consent was obtained from all participants. Current cardiovascular drug use (blood pressure lowering, lipid lowering and glucose lowering drugs) were assessed by asking women to bring all packages to the study centre. Smoking behavior and cardiovascular family history were assessed by a questionnaire. Age was calculated from birth date and date of investigation. Height and weight were

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measured and body mass index was calculated as weight divided by height squared (kg/m2). Waist-to-hip ratio (WHR) was assessed. Systolic and diastolic blood pressures 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 by the direct method (inhibition, enzymatic). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.

Coronary imaging and calcium measurements

The amount of calcium in the coronary arteries was assessed with a 16-MDCT scanner (Mx 8000 IDT 16, Philips Medical Systems, Best, The Netherlands). Participants were positioned within the gantry of the MDCT scanner in supine position. A 16-slice scanner with 0.42 seconds rotation time was used to obtain 1.5 mm thick sections. 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 duration was approximately 10 seconds, depending on heart rate and patient size. Radiation exposure for this coronary calcium scan depends on the patient size and gender. On average, values between 0.1 and 0.5 mSv are expected using a 16-slice scanner. The natural radiation exposure in Western Europe usually varies between 2 and 3 mSv per year. From the acquired raw data, 3 mm thick sections were reconstructed. 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, one scan reader manually selected only the calcifications within one of the coronary arteries (left main, left anterior descending, left circumflex, right coronary artery, and PDA). To reduce the influence of noise, the minimum size of a calcified lesion was set at 0.5 mm^2. The peak density in Hounsfield units and the area in mm^2 of each selected region were calculated. The Agatston calcium score was obtained by multiplying the area by a weighting factor that is dependent on the peak signal anywhere in the lesion [7]. The scores of individual lesions were added to obtain the Agatston calcium score for the entire coronary tree. The total calcium volume was calculated by multiplying the area of the calcified lesion (measured in square millimeters) by section thickness (1.5 mm & 3.0 mm). The calcium volume for each coronary vessel was computed by summing the volumes of the lesions in that vessel for all sections. Finally, the total volume from all the vessels became the calcium volume for a subject. The total coronary calcium mass uses volumetric, density information and a calibration phantom of hydroxyapatite to calculate the actual mass of the calcified plaques.

One reader (AR) scored all scans. For inter-observer reproducibility, the second reader (SS) scored coronary calcium of 199 participants separately with all scoring methods (Agatston, volume and mass score). To assess intra-observer reproducibility, one of the readers (SS) randomly selected and scored 52 scans for the second time.

Data analysis

The mean and standard deviations (SD) of coronary calcium were calculated for all scoring methods separately. Because of the skewed distribution of scores, medians were computed also. The Intra-class correlation coefficient was estimated for between observer data, for within observer data and for 1.5 mm and 3.0 mm slices separately.

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The mean difference in score between observers was calculated as well as the absolute and relative difference. In case the mean difference is close or equal to the absolute difference, a systematic error is present between readers, whereas when the mean difference is much smaller (around zero) than the absolute difference, the error in the measurement error occurs most likely in a random fashion. We defined the relative difference as absolute difference divided by the mean calcium level multiplied in 100 and expressed in percent.

To estimate a weighted kappa as measure of agreement of categorical variables, subjects were divided into four groups according to the mean Agatston score as proposed by Rumberger et al [8]. A: 0-9 (absent-minimal), B: 10-99 (mild), C: 100-399 (moderate) and D: ≥400 (sever degree of calcification).

The relation between risk factors and measurement error was assessed using Spearman correlation coefficients. Similarly, the relation between calcium level and measurement was examined.

Since logarithms of coronary calcification have often been used in statistical analyses to other papers, we also set out to study the reproducibility of logarthythmic transformed calcium score. Logarithmic analysis of coronary calcium scores was performed by calculating natural log of coronary calcium scores + 0.001 [ln (CCS + 0.001)] because logarithm of coronary calcium scores alone excludes all subjects with zero scores. Data analysis was performed (SPSS for windows, version 12.0). A statistically significant difference was assumed when the *p*- value was less than 0.05.

Results

Table 1 shows the general characteristics of the study population. In our study population, the prevalence of calcium score above zero was 60.3% (n= 120) using 1.5 mm slice thickness images and 48% (n=95) using 3.0 mm slice thickness images. Out of 199 subjects, 114 had a calcium level between 0-9, 47 between 10-99, 29 between 100-399 and only 9 subjects had a calcium level of 400 or above.

Table 2 presents information on calcium distributions by various scoring techniques and reproducibility results, by slice thickness. Overall, calcium scores were higher when based on the 1.5 mm slice thickness than based on the 3.0 mm slice thicknesses. The second reader had a higher calcium score compared to the first reader. The extent of the mean difference between readers was close to that of the absolute mean difference, suggesting a systematic process. Based on the kappa findings and the Intraclass correlation coefficients, the agreement between the two readings was high for Agatston, volume and mass measurements. This suggests that the individual ranking of subjects as well as the classification of subjects in categories is very close between the readers. The findings for the 1.5 mm slice thickness were similar to those found for the 3.0 mm slice thickness (Table 2).

Table 3 presents the associations of cardiovascular risk factors to inter-observer measurement error, i.e. the mean difference between readers and the absolute difference between reader as obtained for the 3.0 mm slices. None of the cardiovascular risk factors was related to measurement error, irrespective of its definition. The results for 1.5 mm slice thickness were identical.

When we took the mean difference in calcium scores between the readers (i.e., reader 1- reader 2), a borderline significant relation was shown (table 3). Since reader 2 had systematically higher calcium scores, the relation was inverse (table 3, figure 1). In contrast, there was a highly significant positive relation between calcium scores and

Table 1
General characteristics of the study population (n=199)

	Mean	Std. Deviation
Age (year)	66.4	5.5
Body mass index (Kg/ m^2)	26.3	4.3
Waist to hip ratio	0.84	0.07
Systolic blood pressure (mmHg)	134	21
Diastolic blood pressure (mmHg)	71	9
Heart rate (beat/sec)	71	11
Total cholesterol (mmol/l)	6.0	0.9
Low-density lipoprotein cholesterol (mmol/l)	4.2	0.9
High density lipoprotein cholesterol (mmol/l)	1.4	0.3
Triglycerides (mmol/l)	1.2	0.6
Glucose (mmol/l)	5.5	0.7
Hypertension (%)	27	
Current smoking (%)	10	
Previous coronary heart disease (%)	1.5	

Table 2
Characteristics and interobserver reproducibility results of different coronary calcium scoring methods, by slice thickness (n=199)

Slice thickness 1.5 mm						
Scoring protocols	**Mass**		**Volume**		**Agatston**	
Scores	**1st**	**2nd**	**1st**	**2nd**	**1st**	**2nd**
Mean	16.83	18.12	82.81	89.10	88.41	95.80
Median	0.60	0.90	5.25	7.50	2.20	2.80
Range	0 - 405	0 – 399	0 - 1654	0 - 1624	0 - 2019	0 - 1979
Agreement (k)	0.95		0.87		0.93	
Mean difference	1.2		6.2		7.3	
Absolute difference	2.5		12.7		14.3	
Relative difference (%)	14.6		14.8		15.5	
ICCC*	0.96		0.96		0.95	

Slice thickness 3.0 mm						
Scoring protocols	**Mass**		**Volume**		**Agatston**	
Scores	**1st**	**2nd**	**1st**	**2nd**	**1st**	**2nd**
Mean	13.42	14.95	69.88	78.01	72.09	80.67
Median	0.00	0.40	0.00	3.30	0.00	1.10
Range	0 - 354	0 - 354	0 - 1558	0 - 1554	0 - 1872	0 - 1886
Agreement (k)	0.93		0.90		0.93	
Mean difference	1.4		7.7		8.2	
Absolute difference	2.1		11.0		11.9	
Relative difference (%)	14.7		14.8		15.5	
ICCC*	0.95		0.95		0.95	

* Intra-class correlation coefficient

Table 3a

Relationship between cardiovascular risk factors and inter-observer measurement error of coronary calcium scoring methods by MDCT

	INTER OBSERVER DIFFERENCES								
SLICE THICKNESS	3.0 mm								
CCS METHODS	MASS			VOLUME			AGATSTON		
	r			r			r		
BIOLOGICAL VARIABLES	MEAN	ABSOLUTE	RELATIVE	MEAN	ABSOLUTE	RELATIVE	MEAN	ABSOLUTE	RELATIVE
Age (year)	-0.02	0.00	0.01	-0.02	0.00	0.01	-0.02	0.00	0.01
BMI* (Kg/m^2)	0.10	-0.02	-0.02	0.10	-0.03	-0.02	0.10	-0.02	-0.02
WHR	-0.06	0.04	0.06	-0.06	0.04	0.06	-0.00	0.04	0.06
SBP† (mmHg)	-0.03	0.00	0.00	-0.03	0.00	0.00	-0.03	0.00	0.00
DBP‡ (mmHg)	-0.11	0.00	0.00	-0.11	0.00	0.00	-0.11	0.00	0.00
Total cholesterol (mmol/l)	0.04	-0.12	-0.09	0.04	-0.12	-0.09	0.04	-0.12	-0.10
LDL¶ cholesterol (mmol/l)	0.01	-0.08	-0.06	0.01	-0.08	-0.06	0.01	-0.08	-0.06
HDL§ cholesterol (mmol/l)	0.02	-0.07	-0.06	0.02	-0.07	-0.06	0.02	-0.07	-0.06
Triglyceride (mmol/l)	0.08	-0.04	-0.02	0.08	-0.04	-0.02	0.08	-0.04	-0.02
Glucose (mmol/l)	0.11	0.03	0.04	0.16	0.03	0.04	0.11	0.03	0.04
Smoking	0.06	-0.09	-0.08	0.06	-0.09	-0.08	0.06	-0.09	-0.08
Hear rate (beat/sec)	0.12	-0.01	0.00	0.12	-0.01	0.00	0.12	-0.01	0.00

BMI= Body mass index, DBP= Diastolic blood pressure, HDL= High density lipoprotein, LDL= Low-density lipoprotein, SBP= Systolic blood pressure, WHR= Waist to hip ratio

Table 3b

Relationship between coronary calcium scores and inter-observer measurement error by MDCT

	INTER OBSERVER DIFFERENCES								
SLICE THICKNESS	3.0 mm								
CCS METHODS	MASS			VOLUME			AGATSTON		
	r			r			r		
Coronary calcium scores	MEAN	ABSOLUTE	RELATIVE	MEAN	ABSOLUTE	RELATIVE	MEAN	ABSOLUTE	RELATIVE
Mean Mass Score	-0.13	**0.46**	**0.45**						
Mean Volume				-0.12	**0.46**	**0.45**			
Mean Agatston							-0.13	**0.46**	**0.45**
Mean Log Mass	-0.10	**0.43**	**0.40**						
Mean Log Volume				-0.09	**0.41**	**0.39**			
Mean Log Agatston							-0.10	**0.43**	**0.40**
P.value for the **bold** numbers < 0.01									

Table 4

Characteristics of different coronary calcium scoring methods; effect of slice thickness on intra–observer reproducibility (n=52)

Slice thickness 1.5 mm						
Scoring protocols	Mass		Volume		Agatston	
Scores	1st	2nd	1st	2nd	1st	2nd
Mean	17.62	17.55	89.15	89.48	93.66	93.06
Median	3.60	3.50	20.40	21.52	19.60	16.60
Range	0 - 217	0 - 218	0 - 943	0 - 959	0 - 1108	0 - 1100
Agreement (k)	0.95		1		1	
Mean difference	-0.2		-1.6		-1	
Absolute difference	0.4		3.2		2.3	
Relative difference (%)	2.2		3.5		2.4	
ICCC*	0.99		0.99		0.99	

Slice thickness 3.0 mm						
Scoring protocols	Mass		Volume		Agatston	
Scores	1st	2nd	1st	2nd	1st	2nd
Mean	14.15	13.98	77.18	76.37	77.52	76.33
Median	3.00	2.05	18.30	15.00	12.20	8.70
Range	0 - 190	0 - 189	0 - 928	0 - 930	0 - 1126	0 - 1105
Agreement (k)	1		0.97		0.97	
Mean difference	0		-0.5		-0.2	
Absolute difference	0.3		2.5		1.9	
Relative difference (%)	2.1		3.2		2.4	
ICCC*	0.99		0.99		0.99	

* Intra-class correlation coefficient

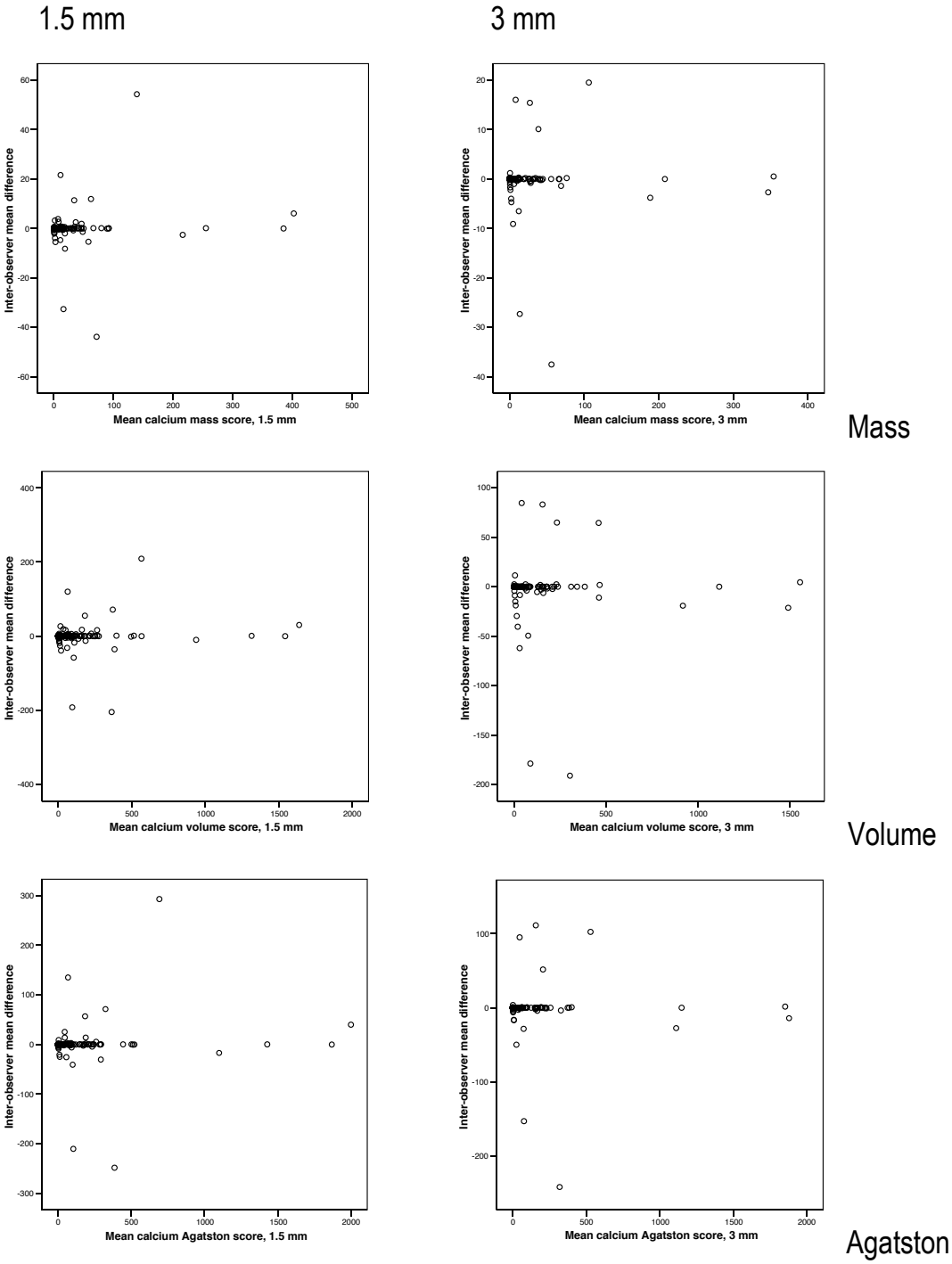
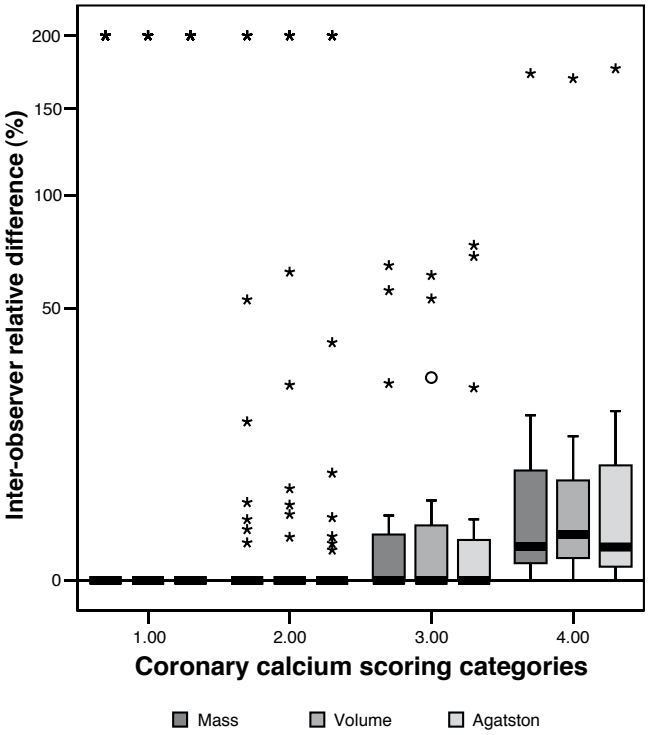


Figure 1

The association between mean coronary calcium score and inter-observer mean difference (Mass, volume and Agatston scoring algorithms in both 1.5 and 3 mm slice thickness)



Categories of coronary calcium scoring

1: 0-9 (absent-minimal)
2: 10-99 (mild)
3: 100-399 (moderate)
4: ≥400 (sever degree of calcification)

Figure 2

Inter-observer overall and median relative difference of coronary calcium score by MDCT in categories of mean Agatston score stratified by scoring methods (Slice thickness 3 mm). Results are given as box-whisker plots, with the lower border of the box indication the 25th percentile, the black line the 50th percentile, and the upper border of the box as the 75th percentile.

absolute differences in calcium scores between observers. The difference in strength of the relations between the mean scores and the absolute mean scores is due to the fact that in the calculation of the mean differences between reader 1 and reader 2, sometimes reader 2 has the highest score, and sometimes reader 1 has the highest score, which is somewhat more likely independent of the absolute calcium value. In contrast, in the calculation of the absolute difference in calcium scores between readers, all differences between values have a positive value, and thus indicate that indeed the measurement error increases when the level of calcium increases.

Our findings show that overall the relative difference between observers increases with increasing calcium score (Table 3), although in some participants up to 200% inter-observer difference in the overall relative difference was found in particular in subjects with absent-low coronary calcium (figure 2).

The results for intra-observer reproducibility were identical to those for inter-observer reproducibility, although no systematic differences between the first and second reading was found (Table 4). In order to remove any potential 'learning effect' of the reader we excluded the first 20 participants. The results did not materially change.

Discussion

We assessed inter- and intra-observer reproducibility of coronary calcium-scoring methods using MDCT imaging in a population of healthy postmenopausal women. Our findings indicate excellent inter and intra-observer reproducibility of coronary calcium measurements with respect to ranking of individuals. No differences between scoring methods (Agatston, volume and mass) or between slice thicknesses (1.5 and 3.0 millimeter) were found. Although no vascular risk factors were related to the measurement error, the measurement error increased with increasing level of coronary calcium.

The value of this reproducibility study is conditional on the assumption that MDCT is a valid method to assess coronary calcium. According to recent studies [5;9], MDCT is quiet equivalent to EBCT for the determination and quantification of coronary calcium. Apart from being more widely available because of use in clinical practice, one of the major advantages offered by MDCT for measuring coronary calcium is the lower equipment cost. Other advantages of MDCT over EBCT are less quantum noise, thinner section thickness, and simultaneous acquisition of four sections, which reduces registration artifacts. On the other hand, cardiac motion, which is known to artificially raise the calcium score, cannot always be avoided by using MDCT.

There have been several attempts to improve the reproducibility of coronary calcium scoring measurements. Callister et al [10] described a volumetric method for improving the reproducibility of scoring of coronary artery calcification(CAC) showing that the volumetric score had better reproducibility than the traditional Agatston score. Yoon and Mohlenkamp reported similar results [11,12]. Cheng Hong et al showed that the mass measurement may be more accurate, less variable, and more reproducible in coronary calcium quantification than measurement with other algorithms [13]. Besides different methods of calcium scoring, slice thickness of each method has been reported to affect the reproducibility of scoring protocols. Some authors [14] suggested that thinner-section protocols may improve the accuracy of calcium scoring as a result of decreased partial volume effects. Our findings expand on this issue for the MDCT scanner and indicate that the reproducibility of the coronary calcium measurements with respect to ranking and categorization of individuals was similar for 1.5 mm slices as for 3.0 mm slices, and equal for Agatston, volume and mass measurements. Our findings confirm the results by Rumberger and Kaufman [15].

Bielak and Devries [16;17] suggested that " the variability is partially a function of the absolute calcium score and inversely related to it", implicating that low coronary

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(14) Hong C, Becker CR, Schoepf UJ, Ohnesorge B, Bruening R, Reiser MF. Coronary artery calcium: absolute quantification in nonenhanced and contrast-enhanced multi-detector row CT studies. Radiology 2002; 223(2):474-480.

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calcium scores may not be reproducible. Although in our study we sometimes found large differences in coronary calcium measurements between observers among those with absolute low levels of coronary calcium, the overall relations indicated that measurement error increases with increasing mean coronary calcium score. The implication of the finding that measurement error increases with increasing calcium levels but not with cardiovascular determinants depends on the research question of the study. In etiologic studies, where the emphasis is on risk factor relations to coronary calcium, our observations indicate that there is non-differential misclassification of the outcome, i.e., the measurement error of coronary calcium is unrelated to the exposure of interest. Therefore attenuation of the relations may occur, whereas the direction is unlikely to change. However, in studies where coronary calcium serves as determinant of an outcome (say for example death), the relation is likely underestimated since measurement error is likely to be related to outcome. One option to overcome some measurement error is to perform duplicate reading of the scans.

Some limitations of our study need to be mentioned. We assessed reproducibility of MDCT in a relatively small sample size of 199 healthy women. The median Agatston score for the first reader in 1.5 mm slice thickness was 2.20 (range 0 – 2019). Our results need to be supported by more data preferably in a large number of patients with a higher prevalence of calcium deposit. Although we examined only women, we do not feel that our results should be restricted to women only, but can also be extrapolated to men as the measurement of coronary calcium in women is not likely different from that in men.

In conclusion, our findings demonstrate that coronary calcium scoring measurements by MDCT are highly reproducible and are not affected by scoring protocols and slice thicknesses. Measurement error of calcium scoring is not associated with selected cardiovascular risk factors, but increases with increasing calcium levels.

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(17) Devries S, Wolfkiel C, Shah V, Chomka E, Rich S. Reproducibility of the measurement of coronary calcium with ultrafast computed tomography. Am J Cardiol 1995; 75(14):973-975.

Abstract

Purpose:

To assess inter-scan reproducibility of coronary calcium measurements obtained from Multi Detector-Row CT (MDCT) images and to evaluate whether this reproducibility is affected by different measurement protocols, slice thickness, cardiovascular risk factors and/or technical variables.

Design: Cross-sectional study with repeated measurements.

Materials and Methods:

The study population comprised 76 healthy women. Coronary calcium was assessed in these women twice in one session using 16-MDCT (Philips Mx 8000 IDT 16). Images were reconstructed with 1.5 mm slice thickness and 3.0 mm slice thickness. The 76 repeated scans were scored. The Agatston score, a volume measurement and a mass measurement were assessed. Reproducibility was determined by estimation of mean, absolute, relative difference, the weighted *kappa* value for agreement and the Intra-class correlation coefficient (ICCC).

Results:

Fifty-five participants (72.4%) had a coronary calcification of more than zero in Agatston (1.5 millimeter slice thickness). The reproducibility of coronary calcium measurements between scans in terms of ranking was excellent with Intra-class correlation coefficients of > 0.98, and kappa values above 0.80. The absolute difference in calcium score between scans increased with increasing calcium levels, indicating that measurement error increases with increasing calcium levels. However, no relation was found between the mean difference in scores and calcium levels, indicating that the increase in measurement error is likely to result in random misclassification in calcium score. Reproducibility results were similar for 1.5 mm slices and for 3.0 mm slices, and equal for Agatston, volume and mass measurements.

Conclusion:

Inter-scan reproducibilility of measurement of coronary calcium using images from MDCT is excellent, irrespective of slice thickness and type of calcium parameter.

Introduction

A considerable proportion of the western society is at risk of suffering a cardiovascular event during life. Atherosclerosis is one of the main underlying processes. Non-invasive assessment of atherosclerosis is important since it allows studies into the etiology and consequences of early and advanced atherosclerosis in populations at large [1]. The last two decades, measurement of coronary artery calcification (CAC) using computer tomography (CT) has been used to assess coronary atherosclerosis non-invasively. The presence, and more importantly, the quantity of CAC, relates well with the overall severity of the atherosclerotic process [2]. Several studies have demonstrated a strong relation between coronary calcium burden and the incidence of myocardial infarction, a relation which was independent of age [3;4]

Most of the evidence on determinants and consequences of coronary calcium is based on data obtained with electron beam CT (EBCT) [5-7]. The availability of EBCT scanners is modest, whereas the Multi Detector-Row CT (MDCT) scanners are more widely available and also allow for detection of coronary calcium. Current data suggest that EBCT and MDCT give comparable results [8;9]. In contrast to EBCT, however, data on reproducibility of CAC measurements using MDCT images is not widely available [10;11], but information is relevant. Furthermore, due to technical improvement, slice thickness of the images has become smaller which may affect the likelihood of detecting coronary calcium, and hence its reproducibility.

We set out to study inter-scan reproducibility of coronary calcium measurements from MDCT images and to evaluate whether reproducibility is affected by different measurement protocols, slice thickness, selected cardiovascular risk factors and technical variables.

Materials and methods

Participants were recruited from the PROSPECT study [12], cohort of 17,357 healthy breast-cancer screening participants, aged 49–70 years, living in Utrecht and surroundings, enrolled between 1993 and 1997. Between October 2002 and December 2004, a random selection of 1,996 women were invited by mail and 1,000 (50.1%) who were postmenopausal and did not use contraceptives or hormone replacement therapy answered positively. Of these 1000 women, a random selection of 573 underwent a MDCT examination during a single visit and 76 of them were scanned twice. The Medical Ethical Committee of the University Medical Center Utrecht approved the study and written informed consent was obtained from all participants.

Current cardiovascular drug use (blood pressure lowering, lipid lowering and glucose lowering drugs) was assessed by asking women to bring all packages to the study centre. Smoking behavior, medical history and cardiovascular family history were assessed by a questionnaire. Height and weight were measured and body mass index was calculated as weight divided by height squared (kg/m2). Waist-to-hip ratio (WHR) was assessed. Systolic and diastolic blood pressures 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 by the direct method (inhibition, enzymatic). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.

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Coronary imaging and calcium measurements

The amount of calcium in the coronary arteries was assessed with a Multi Detector-Row CT (MDCT) scanner (Mx 8000 IDT 16, Philips Medical Systems, Best, The Netherlands). 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 16x1.5 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. We had the participant get up from the table and lay down again since in studies on change in CAC over one year it is not realistic to assume exactly the same position of the participant at both occasions. Therefore our patients sat up and consequently moved slightly between scans to mimic two separate scan runs.

From the acquired raw data, the whole volume was reconstructed with an intermediate reconstruction algorithm in non-overlapping data sets of 1.5 mm and 3 mm thick sections. 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, one scan reader (AR) who was unaware of the scores of the first scan, manually selected the calcifications within one of the coronary arteries (left main, left anterior descending, left circumflex, right coronary artery, and PDA) and scored the second scan of the participants. To reduce the influence of noise, the minimum size of a calcified lesion was set at 0.5 mm^2. The peak density in Hounsfield units and the area in mm^2 of each selected region were calculated. The Agatston [13] 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. The total calcium volume was calculated by multiplying the area of the calcified lesion (measured in square millimeters) by section thickness (1.5 mm & 3.0 mm). The calcium volume for each coronary vessel was computed by summing the volumes of the lesions in that vessel for all sections. Finally, the total volume from all the vessels became the calcium volume for a subject. The mass method uses volumetric, density information and a calibration phantom of hydroxyapatite to calculate the actual mass of the calcified plaques. [14]

In addition, information on breathing artifact (inconsistency of sternum bone in sagital section in mm), noise (standard deviation of enhancement in fixed cardiac area of 212 mm^2) and mean heart rate (beats/min) during scan acquisition was collected.

Data Analysis

The mean and standard deviations (SD) of coronary calcium were calculated for all scoring methods separately. Because of the skewed distribution of scores, medians were also computed. The Intra-class correlation coefficient was estimated for between scans data and for 1.5 and 3.0 mm slices thicknesses separately. The mean difference in score between scans was calculated as well as the absolute and relative differences.

To distinguish between random differences or systematic difference, information on mean and absolute differences is needed. One may assume a priori a non-differential misclassification in the calcium scores, but one has to show that with the results.

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When the chance of the 2nd result being higher or lower is equal, one would expect a mean difference of zero, with some standard deviation. The absolute difference will not be zero since all differences are 'absolutised', but it is expected that at least the mean difference is much less than the absolute difference. If however the chance of a higher or lower value in the 2nd scan is not equal, the mean difference will be plus or minus a certain value. In addition, the absolute difference will have a value close to that of the mean difference. Therefore we need both parameters.

To estimate a weighted kappa as measure of agreement of categorical variables, subjects were divided into four groups according to the mean Agatston score as proposed by Rumberger et al [15]: A: 0-9 (absent-minimal), B: 10-99 (mild), C: 100-399 (moderate) and D: ≥400 (severe degree of calcification). This categorization is specifically for the calcium scoring method according to Agatston. Therefore we additionally categorized all scoring methods in their quartiles to calculate kappa as measure of agreement for all scoring methods.

The relation between risk factors, technical variables and measurement error was assessed using Spearman correlation coefficients. In a similar manner the relation between calcium level and measurement error was examined. Since logarithms of coronary calcium scores have generally been used in statistical analyses in other papers, we also studied the reproducibility of logarithmic transformed calcium score. Logarithmic analysis of coronary calcium scores was performed by calculating natural log of coronary calcium scores + 0.001 (ln (CCS + 0.001)) because the logarithm of coronary calcium scores alone excludes all subjects with zero scores [16]. We defined relative difference as absolute difference divided by the mean calcium level multiplied in 100 and expressed in percent. Data analysis was performed with SPSS for windows, version 12.0. A statistically significant difference was assumed when the two-sided *p*- value was less than 0.05.

Results

Mean age was 67.3 ± 5.2 years. Fifty-five participants (72.4%) had a coronary calcification more than zero in Agatston (1.5 millimeter slice thickness). Table 1 shows the general characteristics of the 76 women who had two MDCT scans.

Table 2 presents information on calcium distributions by various scoring techniques and reproducibility results, by slice thickness. Overall, calcium scores were higher when based on the 1.5 mm slice thickness than based on the 3.0 mm slice thicknesses. The kappa agreement and Intra-class correlation coefficients between the two scans were high for all scoring methods, indicating that with respect to ranking of subjects all three methods are doing well. In addition, the mean differences in scores were relatively small compared to the absolute differences for all measurements, suggestion no systematic measurement errors. Finally, results for the scans with 1.5 mm slice thickness were similar to those for the 3.0 mm slice thickness (table 2).

Table 3 presents the relation of cardiovascular risk factors with inter-scan mean difference. No consistent relations were found between risk factor levels and measurement error.

Importantly, however was the observation that calcium level or the logarithm of the coronary calcium scores were not related to the mean difference between scans, whereas they were significantly related to the absolute and relative differences (table 4, figure 1 and figure 2). These observations suggest that measurement error increases with increasing CAC levels, yet that this occurs in a random way.

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Table 1

Characteristics of study population (N=76)

	Mean	Std. Deviation
Age (year)	67.3	5.2
Body mass index (Kg/ m^2)	26.3	3.9
Waist to hip ratio	0.84	0.06
Systolic blood pressure (mmHg)	133.9	18.9
Diastolic blood pressure (mmHg)	71.7	9.1
Total cholesterol (mmol/l)	6.09	0.86
Low density lipoprotein cholesterol (mmol/l)	4.31	0.97
High density lipoprotein cholesterol (mmol/l)	1.51	0.36
Triglycerides (mmol/l)	1.28	0.62
Glucose (mmol/l)	4.05	0.69
Heart rate (beat/minute)	72	11
Current smoking (%)*	11	
Former smoking (%)	43	
Previous cardiovascular diseases (%)	1	
Family history of CAD in either parents (%)	10	

Table 2

Characteristics of different coronary calcium scoring methods; effect of slice thickness on inter-scan reproducibility

Slice thickness 1.5 mm.

	Mass 1st Scan	Mass 2nd Scan	Volume 1st Scan	Volume 2nd Scan	Agatston 1st Scan	Agatston 2nd Scan
Mean	32.21	31.88	154.52	149.40	170.33	163.63
Median	6.15	6.05	39.97	36.52	31.85	32.00
Agreement (k) Rumberger categories	0.97		0.89		0.87	
Agreement (k) Quartiles	0.84		0.81		0.88	
Mean difference	0.3		5.1		6.7	
Absolute difference	4.0		22.3		24.3	
Relative difference (%)	12.4		14.6		14.5	
ICCC*	0.99		0.99		0.98	

Slice thickness 3.0 mm.

	Mass 1st Scan	Mass 2nd Scan	Volume 1st Scan	Volume 2nd Scan	Agatston 1st Scan	Agatston 2nd Scan
Mean	25.57	25.45	131.45	126.98	140.06	135.82
Median	4.00	3.65	30.30	21.90	20.30	18.00
Agreement (k) Rumberger categories	0.92		0.83		0.73	
Agreement (k) Quartiles	0.84		0.84		0.84	
Mean difference	0.1		4.4		4.2	
Absolute difference	3.5		18.7		21.3	
Relative difference (%)	13.7		14.7		15.4	
ICCC*	0.99		0.98		0.98	

* Intra-class correlation coefficient

Table 3

Relationship between cardiovascular risk factors and inter-scan mean difference of coronary calcium scoring methods by MDCT (Slice thickness 1.5 mm)

	INTER-SCAN MEAN DIFFERENCE					
CCS METHODS	**MASS**		**VOLUME**		**AGATSTON**	
BIOLOGICAL VARIABLES	**r**	**P.value**	**r**	**P.value**	**r**	**P.value**
BMI (Kg/m^2)	0.04	0.73	0.03	0.74	0.02	0.80
Age (year)	0.18	0.10	0.31	0.00	0.28	0.01
Smoking(Categorical)	-0.00	0.98	0.04	0.71	0.07	0.49
WHR	-0.03	0.73	0.08	0.48	0.13	0.24
SBP (mmHg)	0.10	0.37	0.16	0.14	0.24	0.03
DBP (mmHg)	0.16	0.14	0.05	0.61	0.11	0.34
Cholesterol (mmol/l)	-0.27	0.05	-0.12	0.40	-0.20	0.17
LDL (mmol/l)	-0.18	0.10	-0.19	0.09	-0.09	0.40
HDL (mmol/l)	-0.04	0.72	-0.16	0.14	-0.11	0.34
Triglyceride (mmol/l)	-0.02	0.85	0.13	0.24	0.11	0.34
Glucose (mmol/l)	0.16	0.24	-0.00	0.98	0.00	0.98
Mean heart rate	-0.03	0.77	-0.03	0.73	-0.02	0.81
TECHNICAL VARIABLES						
Mean breathing artifact	0.01	0.88	-0.03	0.78	-0.02	0.87
Mean SD of noise	0.13	0.26	0.08	0.49	0.07	0.52
CORONARY CALCIUM						
Mean mass score	0.00	0.98				
Mean volume score			0.03	0.75		
Mean Agatston score					0.02	0.86
Mean log mass score	0.00	0.99				
Mean log volume score			0.03	0.76		
Mean log Agatston score					0.02	0.85

BMI= Body Mass Index; DBP= Diastolic Blood Pressure; LDL=Low Density Lipoprotein; HDL= High Density Lipoprotein; r = spearman correlation coefficient; SBP=Systolic Blood Pressure; WHR= Waist to Hip Ratio

Table 4

Relationship between cardiovascular risk factors and inter-scan absolute and relative difference of coronary calcium scoring methods by MDCT (Slice thickness 1.5 mm)

	INTER-SCAN RELATIVE DIFFERENCE					
CCS METHODS	**MASS**		**VOLUME**		**AGATSTON**	
BIOLOGICAL VARIABLES	**r**	**P.value**	**r**	**P.value**	**r**	**P.value**
BMI (Kg/m^2)	0.07	0.53	0.08	0.46	0.09	0.43
Age (year)	0.21	0.06	0.24	0.03	0.l17	0.12
Smoking(Categorical)	-0.03	0.73	-0.07	0.51	-0.14	0.20
WHR	0.07	0.55	0.05	0.66	0.05	0.66
SBP (mmHg)	0.06	0.57	0.04	0.68	0.11	0.32
DBP (mmHg)	0.32	0.004	0.31	0.005	0.33	0.003
Cholesterol (mmol/l)	0.13	0.37	0.10	0.50	0.00	1.00
LDL (mmol/l)	-0.14	0.21	-0.17	0.12	-0.18	0.11
HDL (mmol/l)	0.07	0.52	0.04	0.67	0.06	0.57
Triglyceride (mmol/l)	0.03	0.78	0.07	0.49	0.00	0.99
Glucose (mmol/l)	0.23	0.09	0.26	0.05	0.24	0.08
Mean heart rate	-0.01	0.91	0.01	0.93	0.00	0.97
TECHNICAL VARIABLES						
Mean breathing artifact	0.10	0.44	0.09	0.49	0.15	0.23
Mean SD of noise	0.19	0.09	0.19	0.09	0.18	0.11
CORONARY CALCIUM						
Mean mass score	0.29	0.009				
Mean volume score			0.33	0.003		
Mean Agatston score					0.38	0.001
Mean log mass score	0.29	0.010				
Mean log volume score			0.33	0.003		
Mean log Agatston score					0.37	0.001

	INTER-SCAN ABSOLUTE DIFFERENCE					
CCS METHODS	**MASS**		**VOLUME**		**AGATSTON**	
TECHNICAL VARIABLES	**r**	**P.value**	**r**	**P.value**	**r**	**P.value**
Mean breathing artifact	0.12	0.32	0.12	0.33	0.15	0.22
Mean SD of noise	0.20	0.08	0.19	0.09	0.15	0.17
CORONARY CALCIUM						
Mean mass score	0.86	< 0.001				
Mean volume score			0.84	< 0.001		
Mean Agatston score					0.89	< 0.001
Mean log mass score	0.86	< 0.001				
Mean log volume score			0.83	< 0.001		
Mean log Agatston score					0.89	< 0.001

Abbreviation as table 3

Discussion

With respect to ranking of subjects, the inter-scan reproducibility of coronary calcium measurements by MDCT using Agatston, volume and mass scoring algorithms is excellent. The inter-scan reproducibility showed no major differences between scoring methods. The slice thickness did not affect reproducibility, nor did heart rate and technical parameters. Measurement error was related to increased coronary artery calcification, although our findings suggest that the error in the measurements is a random phenomenon.

Our findings, i.e., no major differences between scoring methods are in contrast with several reports on reproducibility based on EBCT scanning. Direct comparison of the findings of these studies with those of other is difficult since the parameters used to indicate reproducibility differ between studies. Furthermore, potentially the prevalence of CAC and its extent may affect reproducibility, as our findings suggest that measurement error increases with increasing CAC levels. Also the sizes of the

studies differ which have undeniable effects on reproducibility results. However, our results are similar to those of by Rumberger and Kaufman [17], who compared these three methods and did not find any one method preferable to another in terms of reproducibility of results from consecutive scans in a patient.

Although the correlation between inter-scan measurements is excellent [18;19], it still occurs that subjects with small deposits of calcium in scan one may have larger deposits of calcium in the 2nd scan, which leads to proportionally larger error in reproducibility. This has triggered other studies [20] on reproducibility to suggest that "the variability is partially a function of the absolute calcium score and inversely related to it", implicating that low coronary calcium scores may not be reproducible. However, our results could not confirm this.

Besides different algorithms for calcium scoring, slice thickness has been reported to affect the reproducibility of scoring protocols. In our study, the reproducibility of the coronary calcium measurements by MDCT was similar for 1.5 mm as for 3.0 mm slice thickness, and equal for Agatston, volume and mass measurements confirming the results by Rumberger and Kaufman. [21]

The implications of our main findings depend on the research question that is asked in studies using CAC measurements. When the interest is using CAC measurements for prognostic studies our results for kappa and ICCC show that ranking of subjects is adequate based on one CT scan. So the need for duplicate CAC scan is absent. The fact that measurement error increases with increasing CAC values, is in prognostic studies not of major importance since the categorization of individuals seems adequate. When the interest is in etiologic studies using CAC as outcome parameter, our findings show that risk factor relations will be validly estimated since none of the risk factors relates to measurement error. When the interest is in using CAC as risk factor for future events (assessment of relative risks), it is most likely that in analyses with CAC as continues variable the magnitude of association of high CAC levels with events reflects an underestimation of the true magnitude. The direction of the relation will not change since based on our results measurement error is random, leading to random misclassification of the exposure variable. When the interest is in diagnostic value of CAC measurements, which is usually done in categories of CAC, again the relations will be valid given our high kappa coefficients. Although our study was performed in healthy postmenopausal women, we expect that the finding will also be applicable for men.

Our findings are important in the light of the wider availability of MDCT in countries compared to EBCT. One reason for that is lower equipment cost. Other advantages of MDCT over EBCT have been suggested to be less quantum noise, thinner section

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thickness, and simultaneous acquisition of four sections (with 16-slice or with 64-slice), which is reported to reduce misregistration artifact.

In conclusion, our findings demonstrate that coronary calcium measurements by MDCT are highly reproducible and are not affected by scoring protocols, slice thicknesses and technical factors.

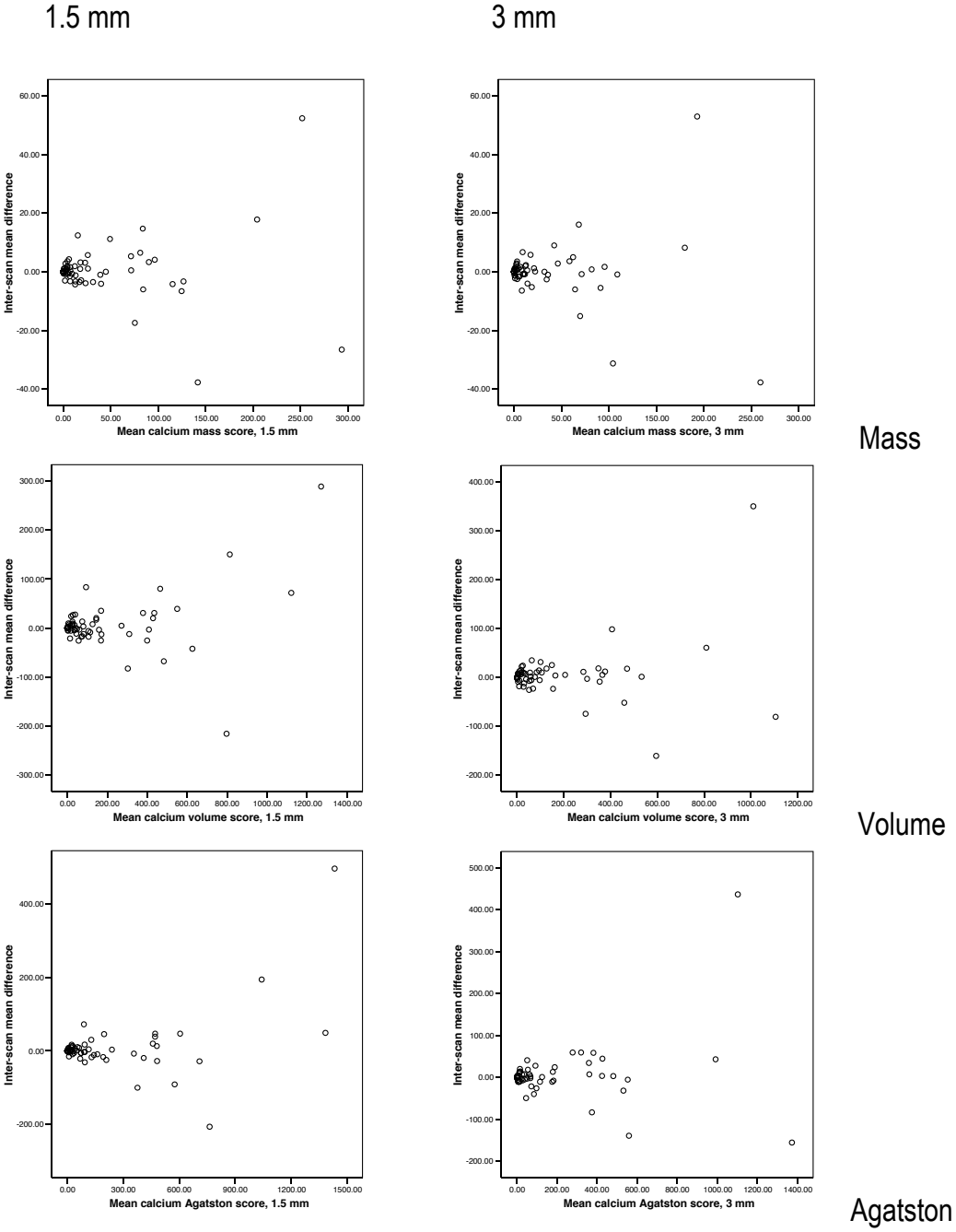

Figure 1
Relation between mean calcium score and inter-scan difference in mean calcium scores (Bland-Altman plots)

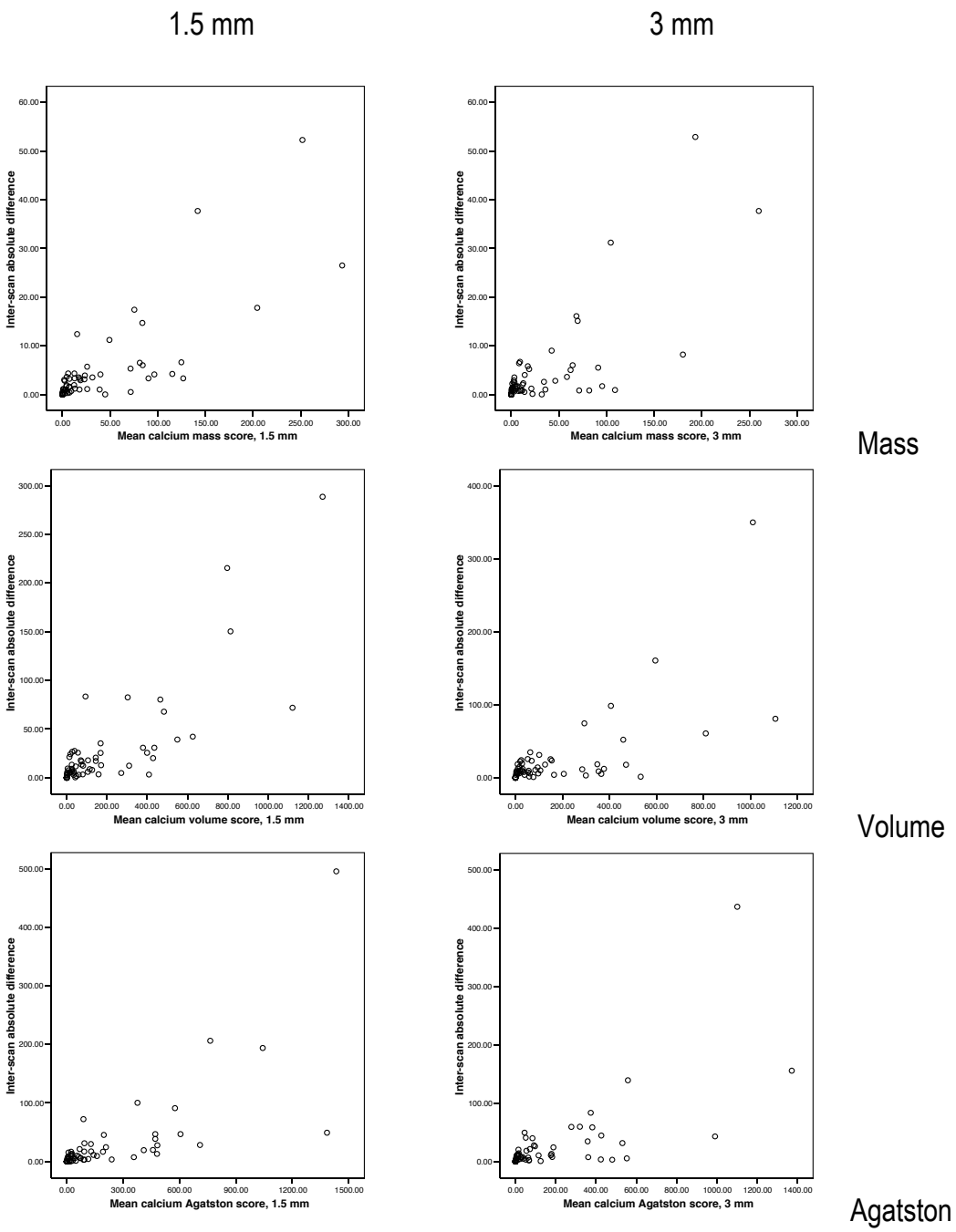

Figure 2
Relation between mean calcium score and inter-scan absolute difference

Abstract

Purpose:

A considerable proportion of pregnant women develop high blood pressure in pregnancy. Although it is assumed that this condition subsides after pregnancy, many of these women develop the metabolic syndrome later in life and are at increased risk to develop coronary heart disease. Atherosclerosis development is considered in between risk factors and occurrence of vascular symptoms. Therefore, we set out to study the relation of high blood pressure during pregnancy with risk of coronary calcification later in life.

Design: Cross-sectional study

Materials and Methods:

The study population comprised 491 healthy postmenopausal women selected from a population based cohort study. Information on high blood pressure during pregnancy was obtained using a questionnaire. Between 2004 and 2005, the women underwent a Multi Detector Computed Tomography (Philips Mx 8000 IDT 16) to assess coronary calcium. The Agatston score, volume and mass measurements were used to quantify coronary calcium.

Results:

30.7% of the women reported to have had high blood pressure in pregnancy. Body mass index (OR=1.05, 95% CI 1.01, 1.09) and diastolic blood pressure (OR=1.03, 95% CI 1.01, 1.05) were significantly related to a history high blood pressure in pregnancy. Age was significantly related to increased coronary calcification. Women with a history of high blood pressure during pregnancy had a 57% increased risk of having coronary calcification compared to those women without this condition (OR=1.57, 95% CI 1.04, 2.37). After adjusting for age, the relation did not change (OR=1.64, 95% CI 1.07, 2.53).

Conclusion:

High blood pressure during pregnancy is associated with an increased risk of coronary calcification later in life.

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Introduction

Hypertensive disorders are common complications of pregnancy, and rank among the leading causes of maternal and perinatal morbidity and mortality worldwide [1-3]. Depending on the definitions used and the populations studied, high blood pressure is reported to affect 2 to 35% of all pregnancies [4]. In the various classification schemes proposed, hypertension specific for and secondary to pregnancy is referred to as gestational hypertension, pregnancy-induced hypertension, or, when proteinuria is observed as well, pre-eclampsia. Pre-eclampsia in particular is associated with an increased risk of adverse pregnancy outcome for both the mother and the fetus.

During the last decade evidence has accumulated that hypertensive disorders of pregnancy, pre-eclampsia in particular, are associated with future hypertension and cardiovascular events. Pre-eclampsia and cardiovascular disease (CVD) share chronic hypertension, increased total cholesterol, decreased insulin sensitivity, and increased body mass index (BMI) as common risk factors [5]. Large epidemiological studies have demonstrated that women who have had pre-eclampsia are at high (2-fold) risk to develop CVD in later life [6-11]. Many of the women who have had pre-eclampsia in pregnancy, and who have no signs of clinical disease after pregnancy, exhibit the phenotype of the metabolic syndrome (overweight, latent hypertension, dyslipidemia, insulin resistance and hyperhomocysteinemia) and impaired endothelial function at 3 to 12 months postpartum [12-15]. Apparently, exposure of the women with this phenotype to the additional metabolic and cardiovascular challenges of pregnancy induces transient clinical disease (i.e. pre-eclampsia), that subsides after pregnancy but is likely to re-emerge later in life as CVD [16-18]. This knowledge has lead to the novel concept of pregnancy as a cardiovascular challenge test with development of high blood pressure or pre-eclampsia as a marker of increased risk to develop atherosclerosis and vascular events in the future. To further expand on this notion towards the development of atherosclerosis, we studied the relation of high blood pressure during pregnancy with coronary atherosclerosis. Increased coronary calcium is indeed one of the strongest predictors of occurrence of coronary artery disease in the future and appears to be a better predictor of risk of future events than conventional risk factors [19].

The use of coronary calcification as end point in clinical studies is gaining interest.

Arad et al. [20] demonstrated that individuals with higher calcium scores (CS > 160) were 35 times more likely to experience a cardiovascular event, and that CAC measurements were more predictive of such events than were more traditional risk factors determinates. Guerci et al. [21] found that the presence of coronary calcium was a “powerful predictor” of CAD regardless of other risk factors. In fact, recent evidence suggests that CAC quantification may be a better predictor of mortality than traditional Framingham risk factors, adding prognostic value when used in conjunction with traditional risk factor assessments [22]. There appears to be several valid indications for using CAC quantification as a screening test for CHD [23].

Materials and Methods

Population

We used data from a cross-sectional study among 573 post-menopausal healthy women. 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) [24]. In PROSPECT 17,357 healthy participants of a nationwide population-based breast-cancer screening programme, aged 49-70 years, living in Utrecht and surroundings were enrolled between 1993 and 1997. Between October

2002 and April 2004 a re- examination was planned in a sample in order to investigate the prognostic value of age at menopause on cardiovascular disease risk. For this purpose, 6,612 women of the total of 17,357 were excluded because of death, further participation in PROSPECT or in other studies, absence of written informed consent, or emigration. Other reasons for exclusion were premenopausal state (n=1309), missing data on menopausal status (n=2,105) or use of oral contraceptives or postmenopausal hormone therapy in the year before or after the last menstruation (n=1,487), because age at menopause cannot be estimated precisely then. Out of 5,844 eligible women, a random selection of 1,996 women were invited by a personal letter from the principal investigator of PROSPECT and 1,000 (50.1%) answered positively. Of these 1000 women, 573 women were randomly selected for CAC measurement. In 5 women, no calcium scores could be obtained. Furthermore, information on a history of high blood pressure in pregnancy was missing in 77 women, so the final study population comprised 491 women.

The Medical Ethical Committee of the University Medical Center Utrecht approved the study and written informed consent was obtained from all participants before enrolment.

At the baseline examination of the PROSPECT study women had been asked 'did you suffer from high blood pressure during pregnancy'. If confirmative, we regarded women to have had a hypertensive disorder of pregnancy. At the re-examination visit, smoking behavior and family history of CVD were assessed by a questionnaire. Age was calculated from birth date and date of investigation. Height and weight were measured and BMI was calculated as weight divided by height squared (kg/m^2). Waist-to-hip ratio (WHR) was assessed. Systolic and diastolic blood pressures (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 by 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.

Coronary calcium measurements

At a second visit between 2004 and 2005, the participants underwent a multi-detector row computed tomography (MDCT) examination (Mx 8000 IDT 16, Philips Medical Systems, Best, The Netherlands) for the assessment of coronary artery calcification (CAC). Subjects were positioned within the gantry of the MDCT scanner in supine position. A 16-slice scanner with 0.42 seconds rotation time was used to obtain 1.5 mm thick sections. 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 16x1.5 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. Between the two scans subjects sat upright and then lay down again. From the acquired raw data, 3 mm thick sections were reconstructed. 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 the obstetric history of the women,

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manually selected only the calcifications within one of 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 mm^2. The peak density in Hounsfield units and the area in mm^2 of each selected region were calculated. The Agatston [25] 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. The total calcium volume was calculated by multiplying the area of the calcified lesion (measured in square millimeters) by section thickness (1.5 mm). The calcium volume for each coronary vessel was computed by summing the volumes of the lesions in that vessel for all sections. Finally, the total volume from all the vessels became the calcium volume for a subject. The total coronary calcium mass uses volumetric, density information and a calibration phantom of hydroxyapatite to calculate the actual mass of the calcified plaques.

We performed a reproducibility studies in which 199 scans were read in duplicate, showing Intraclass correlation coefficients (ICCC) of > 0.95 for the duplicate readings. A reproducibility study in which in 73 women a duplicate MDCT scan was made showed ICCC between repeat scans of > 0.90 for all estimates of coronary calcification (volume, mass, Agatston score) (Unpublished observations).

Data Analysis

First, the relation between potential confounding factors and a history of high blood pressure in pregnancy was examined using logistic regression models. In a similar manner, the relation of risk factors with coronary calcification in 1.5 mm slice thicknesses was examined. Factors that showed significant relations with both a history of high blood pressure in pregnancy and coronary calcification were considered as confounders. Distinction was between factors not in the causal pathway and those potentially in the causal pathway. The relation between a history of high blood pressure in pregnancy with the outcome variable (coronary calcium absent / present) was investigated using logistic regression models. The relations were quantified by odds ratios with corresponding 95% confidence limits. Data analysis was performed using SPSS for windows version 12.0

Since the information on a history of high blood pressure in pregnancy was collected at the baseline examination of the PROSPECT study (long after the last pregnancy), those with chronic hypertension might recall high blood pressure in pregnancy better than those women who at baseline did not suffer from hypertension (i.e. recall bias). To examine this, we repeated the analyses after subjects with hypertension at baseline were excluded (n=104).

Results

Information on a history of high blood pressure in pregnancy was present in 491 women. Women who had never been pregnant and those who reported an onset of hypertension before the age of 45 years were excluded. The general characteristics of the study population are given in table 1. In our study population, the prevalence of a history of high blood pressure in pregnancy was 30.7% (n=151). The high prevalence is most likely a consequence of the fact that our measurement of 'hypertension in pregnancy' includes women not only brief and modest elevation of blood pressure during pregnancy but also women with (pre)eclampsia. Coronary calcification, i.e. an

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Agatston score of 1 or above, was found in 62.9% of our study population (n=305). The median Agatston score was 9.90. (Interquartile range is 0 and 93.1)

Table 2 shows the relations of general characteristics with a history of high blood pressure in pregnancy. Increased BMI, SBP, DBP and presence of hypertension were significantly related to a history of high blood pressure in pregnancy. Increased age, WHR, SBP, DBP and presence of smoking were significantly related to presence of CAC. Based on this information a parameter of overweight, and of blood pressure may be considered as potential confounders, although one may also argue these factors are intermediate parameters in the causal pathway.

In an unadjusted model, a history of high blood pressure during pregnancy was significantly related to presence of CAC (Agatston score). We obtained the same results for volume and mass score. The risk increased with 57% compared to women without a history of high blood pressure during pregnancy (OR=1.57, 95% CI 1.04, 2.37). Adjustments for age did not substantially alter the association (OR=1.64, 95% CI 1.07, 2.53). When factors that may be regarded as intermediate factors in the causal pathway from a history of high blood pressure during pregnancy to atherosclerosis development, i.e., BMI, SBP, DBP, WHR, the magnitude of the association attenuated and the relation did not reach statistical significance.

We repeated the analysis of a relation between a history of high blood pressure in pregnancy and CAC in participants without self reported hypertension at baseline (n=387) to control for potential recall bias. The magnitude of the finding did not materially differ [Age adjusted OR (95% CI) =1.53 (0.88- 2.64)], although statistical significance was not reached.

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Table 1

General characteristics of study population (N=491)

General Characteristics	Mean	Std. Deviation
Age (year)	66.8	5.4
Body mass index (Kg/ m^2)	26.8	4.5
Waist to hip ratio	0.84	0.06
Systolic blood pressure (mmHg)	136.9	20.1
Diastolic blood pressure (mmHg)	72.3	9.2
Use of blood pressure lowering drugs (%)	24.6	
Hypertension (%)	32.3	
Total cholesterol (mmol/l)	5.97	0.89
Low density lipoprotein cholesterol (mmol/l)	4.21	0.91
High density lipoprotein cholesterol (mmol/l)	1.37	0.36
Triglycerides (mmol/l)	1.24	0.62
Glucose (mmol/l)	4.28	0.90
Current smoking (%)	12.0	
Former smoking (%)	43.7	
Previous Cardio vascular diseases (%)	4.0	
Pregnancy induced hypertension (%)	30.7	
Family history of Coronary heart diseases (%)	11.2	

Cardio Vascular Diseases (cardiac arrest, AMI, coronary stenosis, carotid stenosis, stroke)

Table 2

Relation of characteristics with a history of high blood pressure during pregnancy and coronary calcification.

Risk factors	High blood pressure during pregnancy	Coronary calcification
	OR (95% CI)	OR (95% CI)*
Age (year)	0.99 (0.96 - 1.03)	
BMI (Kg/ m^2)	1.05 (1.01 - 1.09)	1.00 (0.95 - 1.06)
WHR	1.26 (0.96 - 1.66)	1.81 (1.25 - 2.61)
SBP (mmHg)	1.01 (1.00 - 1.02)	1.01 (1.00 - 1.02)
DBP (mmHg)	1.03 (1.01 - 1.05)	1.03 (1.01 - 1.06)
Cholesterol (mmol/l)	1.14 (0.67 - 1.92)	1.49 (0.70 - 3.16)
LDL (mmol/l)	0.96 (0.78 - 1.19)	1.16 (0.88 - 1.53)
HDL (mmol/l)	0.97 (0.57 - 1.65)	0.69 (0.37 - 1.28)
Triglycerides (mmol/l)	0.90 (0.66 - 1.23)	1.03 (0.71 - 1.48)
Glucose (mmol/l)	0.89 (0.53 - 1.50)	2.05 (0.83 - 5.05)
Current smoking (%)	1.11 (0.59 - 2.06)	11.72 (4.10 -33.51)
Former smoking (%)	1.05 (0.70 - 1.59)	1.76 (1.06 - 2.92)
Hypertension (%)	2.49 (1.66 - 3.73)	1.12 (0.64 - 1.96)
Previous CHD (%)	1.22 (0.47 - 3.12)	4.53 (0.90 -22.70)
FH of CHD in either parents (%)	1.34 (0.74 - 2.41)	1.85 (0.85 - 4.03)

* Age adjusted relation between characteristics and coronary calcification in participants without a history of high blood pressure during pregnancy. (n=340)

Body Mass Index, Coronary Heart Diseases, Diastolic Blood Pressure, Family History, Low Density Lipoprotein, High Density Lipoprotein, Systolic Blood Pressure, Waist to Hip Ratio

TABLE 3

Relationship between a history of high blood pressure during pregnancy and coronary calcification in study population (n=491)

High blood pressure in pregnancy	Coronary calcification
	OR (95% CI)
High blood pressure in pregnancy	1.57 (1.04 - 2.37)
High blood pressure in pregnancy adjusted for age	1.64 (1.07- 2.53)
High blood pressure in pregnancy adjusted for age, WHR, DBP & SBP	1.43 (0.91- 2.24)
High blood pressure in pregnancy adjusted for age, BMI, WHR, DBP & SBP	1.52 (0.96 - 2.39)

Body Mass Index, Diastolic Blood Pressure, Systolic Blood Pressure, Waist to Hip Ratio

Discussion

To the best of our knowledge, the present study is the first to show that a history of high blood pressure during pregnancy is related to coronary calcification later in life.

Many of the women who have had pre-eclampsia exhibit the phenotype of the metabolic syndrome and impaired endothelial function at 3 to 12 months postpartum.[12-15] In addition, observational studies demonstrated that pre-eclampsia is associated with an increased risk of cardiovascular events and death in later in life [6-11]. Our finding is in line with these observations and expands the evidence to an increased risk of atherosclerosis. It has been well established that increased coronary calcification is a significant predictor of subsequent cardiovascular disease and total mortality [26-28].

Based on our way of assessment of exposure, the increased risk appears not to be restricted only to those women with pre-eclampsia, but also applies to those with nonproteinuric hypertension or mild elevation of blood pressure in pregnancy. Unfortunately, blood pressure levels during pregnancy of these women were not available.

High blood pressure in pregnancy usually subsides when the pregnancy is over. The accumulating evidence in the literature, and our present findings, support the concept of pregnancy as a cardiovascular challenge test, with hypertensive disorders in pregnancy as 'positive test results', marking those at increased risk of future cardiovascular disease. These women might benefit from cardiovascular risk factor management, starting soon after pregnancy, at an age that they are more likely to benefit from secondary prevention. At present, however, it is not clear if and how risk factor management can be achieved in these women, and what benefit may be expected from such a strategy. Studies addressing these issues are on their way.

Some limitations of our study need to be addressed. The information on history of high blood pressure during pregnancy was obtained by questionnaire when the participants were at or above middle age. This may have lead to misclassification. The question was not directed towards the more severe hypertensive disorder of pregnancy, i.e., pre-eclampsia. So, milder variants of hypertension in pregnancy have been included too. Therefore, one might question its effect on the validity and magnitude of our findings. If only severe elevated blood pressure during pregnancy is related to increased risk of atherosclerosis, then the magnitude of our finding is clearly an underestimation the truth. The direction of the relation is however valid. Despite the impossibility to precisely classify hypertension in pregnancy on basis of this information, a positive history of high blood pressure was related to coronary calcification later in life. We therefore assume that the true relationship may be actually stronger than the one we observed, rather than attenuated.

Another aspect is that recall bias may have affected the relationship between high blood pressure in pregnancy and coronary calcification. Recall bias means that those with hypertension at baseline may recall having had a high blood pressure in pregnancy 'better' than normotensive. Since hypertension is a determinant of CAC, [29;30] the magnitude of the reported association may have been biased upwards.

Our stratified analysis shows however, that the magnitude of the relation among normotensive women is similar to those of the entire group, and therefore, the reported relation does not seem to be biased. The fact that the results of that stratified analyses are not statistically significant can most likely be attributed to the smaller sample size.

Furthermore, It can be asked that 781 exclusion (because of death) may have biased our results in any way. However we do not believe such a selection through death may be an issue. Finally, the relatively small sample size in our study puts some restriction to the precision of the estimates. Future studies with a larger sample size are needed to support or refuse our findings. Strengths of the study are its population-based nature and the CAC measurements were performed according to the

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highest standards. MDCT for detection of CAC, which we have used in our study, has an excellent accuracy and reproducibility with an Intra Class Correlation Coefficient (ICCC) of 0.99 and kappa value of around 0.90.

In conclusion, we have shown that high blood pressure in pregnancy is associated with increased coronary calcification later in life.

Perspectives:

Our finding may have important implications for the management of women who have had high blood pressure in pregnancy. Up to now it has been assumed that high blood pressure subsides after pregnancy, and there was no structured follow-up of the women who experienced it. This (lack of) policy needs reconsideration. Novel strategies of follow-up and cardiovascular risk factor reduction in women who have had hypertension in pregnancy must be developed and evaluated for their potential to reduce CVD in the future.

Abstract

Purpose:

The objective of this study was to examine the relation between 9 year change in abdominal adiposity, as assessed by waist-to-hip ratio (WHR) and risk of coronary artery calcification.

Design: Cohort study

Subjects and methods:

The study population comprised 573 healthy postmenopausal women selected from a population based cohort study. Data on coronary risk factors were collected at baseline (1993-1997) and follow-up (2002-2004). At follow-up, the women underwent a multi-detector computed tomography (MDCT) (Philips Mx 8000 IDT 16) to assess coronary calcium. The Agatston score was used to quantify coronary calcium. Logistic regression models were used to evaluate the relations under study. Change in waist to hip ratio (WHR) was categorized into four groups: low at baseline-low at follow-up (low was defined as below the median); high-low; low-high; and high-high.

Results:

Compared to subjects whose WHR remained below the median of the distribution at both occasions, those with a WHR above the median at both occasions had a 2.7 [95% CI 1.8-4.0] fold increased risk of CAC. Women whose WHR rose over the 9 year period from below the median to above the median had a 2.5 [95%CI 1.4-4.5] fold increased risk of CAC, whereas the women whose WHR became lower had a non-significant 1.6 fold increased risk of CAC [95% 0.8-3,2]. In contrast, change in body mass index was not related to risk of CAC.

Conclusion:

This observational study among healthy postmenopausal women supports the existing evidence that persistent abdominal adiposity as well as an increase in abdominal fat over time relates to an increased risk of coronary atherosclerosis.

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Introduction

Obesity is a major health problem in industrialized countries. A causal relationship between myocardial infarction (MI) and obesity in the absence of the well-known risk factors for MI has been reported.[1] The prevalence of overweight and obesity has increased dramatically in last decades in the USA,[2] Finland,[3] Denmark,[4] Great Britain,[5] the Netherlands [6] and Belgium.[7] In particular, visceral or abdominal adiposity is an important indicator of cardiovascular risk. [8-11] Abdominal obesity has been shown to be a stronger predictor of cardiovascular risk than increased body mass index.[12] This was found for men and women, in the young and the old and across populations of different ethnic origin.[13] Visceral obesity appears to be the driving force for a number of metabolic abnormalities including raised blood pressure, dyslipidemia and insulin resistance, that promote cardiovascular disease.[13,15] Atherosclerosis is a key factor in the pathogenesis of cardiovascular disease[16] and is considered to be a slowly progressive phenomenon, starting at young age and having its clinical manifestation in later decades. Atherosclerosis in the coronary arteries can be accurately and reproducibly assessed with Multi-Detector Computed Tomography (MDCT) in a non-invasive way [17]. From the CT images a coronary artery calcium (CAC) summary score can be constructed. CAC is increasingly used as a marker of disease risk or of subclinical atherosclerosis. It is well established that the presence of coronary calcification is a significant predictor of subsequent cardiovascular disease and total mortality.[18-20]
Although randomized controlled trials have indicated that weight loss may benefit levels of risk factors, trials were usually of modest duration. [21,22] The aim of this study was to determine the impact of change in abdominal adiposity, as assessed by change in waist-to-hip ratio during over a 9 year period, on risk of coronary calcification in a population based sample of 573 healthy postmenopausal women.

Materials and Methods

Population

Participants were recruited from the PROSPECT study, [23] a cohort of 17,357 healthy breast-cancer screening participants, aged 49–70 years, living in Utrecht and surroundings, 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 573 underwent a multislice CT examination at a second visit between January and December 2004 as has been detailed elsewhere.[24] The Medical Ethical Committee of the University Medical Center Utrecht approved the both the baseline and follow-up studies and written informed consent was obtained from all participants before enrolment.

At the baseline and first follow-up visit, smoking behavior and family history of cardiovascular diseases (CVD) were assessed by 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 (kg/m2). 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 (DINAMAPTM XL, Critikon, Johnson & Johnson, Tampa, Florida, USA) with the subject in supine position. We defined pulse pressure (PP) as difference between systolic and diastolic blood pressure. In the baseline samples (1993-1997), serum total cholesterol and glucose levels were determined in non-fasting venous blood samples using an automated enzymatic procedure on a Vitros 250 (Johnson & Johnson, Rochester, New

York, USA). Serum LDL was measured directly and HDL- cholesterol levels was determined with a colorimetric assay on a Hitachi 904 (Johnson & Johnson, Rochester, New York, USA). At baseline lipid measurements were only performed in a 10% random sample of the full cohort (n=1736). In 2002-2004, lipids were determined in a venous blood sample drawn after an overnight fast of at least eight hours in all subjects of the follow-up study. Plasma total cholesterol and plasma glucose were measured using standard enzymatic procedures. HDL cholesterol was measured by the direct method (inhibition, enzymatic). LDL cholesterol was calculated using the Friedewald formula. We defined hypertension as present when women reported that a physician had diagnosed hypertension that needed treatment at baseline or had a systolic blood pressure >140 mmHg or a diastolic blood pressure > 90 mmHg. At baseline, diabetes mellitus was defined present when women reported that a physician had diagnosed this disorder. At follow-up, diabetes mellitus was defined present when women had fasting blood glucose > 6.9 mmol/l and/or reported the use of anti-diabetic medication.

Coronary calcium measurements

The amount of calcium in the coronary arteries was assessed with a multi-detector computed tomography (16-MDCT) scanner (Mx 8000 IDT 16, Philips Medical Systems, Best, The Netherlands). Subjects were positioned within the gantry of the MDCT scanner in supine position. A 16-slice scanner with 0.42 seconds rotation time was used to obtain 1.5 mm thick sections. 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 16x1.5 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. All regions with a density over 130 Hounsfield units were identified as potential calcifications. A trained reader scored coronary calcification of all participants. To reduce the influence of noise, the minimum size of a calcified lesion was set at 0.5 mm^2. The Agatston calcium score was obtained. We performed reproducibility studies, showing Intraclass correlation coefficients of > 0.95 for the duplicate readings. A reproducibility study in which in 73 women a duplicate MDCT scan was made showed Intraclass correlation coefficients between repeat scans of > 0.90 for all estimates of coronary calcification (Agatston, volume and mass score). [25]

Data Analysis

The main objective of the present study was to characterize the relation between change in waist to hip ratio (WHR) from 1993 to 2004 and coronary artery calcification in 2004. The dependent (i.e., outcome) variable for the analysis was the presence or the absence of coronary artery calcification as measured by multi-detector computed tomography. The independent (i.e., exposure) variables were the change in WHR. Change in WHR was categorized into four groups: low at baseline - low at follow-up = (low-low), increased = (low-high), decreased = (high-low) and high constant = (high-high). The cut-off point was based on the median. The strength of the association between these categories and coronary calcification was estimated using logistic regression with the low-low or (no-no) group as reference category. In a similar manner, the relation between change in body mass index (BMI) and coronary calcification was studies. Since information on blood pressure and smoking was also collected, change in these risk factors was studied as well.

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In order to see whether part of the WHR findings works through blood pressure, multivariate analyses with CAC as outcome and change in WHR, SBP and smoking as dependent variables were done. Also we run a model for DBP in stead of SBP with and without BMI adjustments for both models. The relations were quantified by odds ratios with corresponding 95% confidence limits. A significance level of 0.05 was used for all analysis. Data analysis was performed using SPSS for windows version 13.0

Results

Table 1 describes the risk factors levels, measured at baseline and follow-up.

The levels of body mass index, waist-to-hip ratio, systolic blood pressure, pulse pressure and glucose increased during the follow-up period, and decreased for HDL cholesterol and diastolic blood pressure. The frequency of smoking fell, whereas the prevalence of diabetes mellitus increased. In our study population (n=573), the prevalence of coronary artery calcification in 1.5 mm slice thickness was 61.5% (n=348). Of those, 13.3% (n=75) had coronary calcification ranging from 1 to 9; 24.4% (n=138) ranging from 10 to 99; 15.5% (n=88) ranging from 100 to 399 and 8.3% (n=47) CAC values of 400 or above.

The relations between risk factors and coronary calcification for both baseline and follow-up measurements are given in Table 2. Of the risk factors measured at baseline, increased age, waist-to-hip ratio, systolic and diastolic blood pressure, pulse pressure, current smoking and hypertension were related to presence of CAC 10 years later. In contrast to WHR, an increased BMI was not related to CAC.

The main findings for 9 years change in risk factors and risk of CAC are presented in table 3. Compared to subjects whose WHR remained below the median of the distribution at both occasions, those with a WHR above the median at both occasions had a 2.7 [95% CI 1.8-4.0] fold increased risk of CAC. Women whose WHR rose over the 9 year period from below the median to above the median had a 2.5 [95%CI 1.4-4.5] fold increased risk of CAC. In contrast to waist circumference, 9 year change in body mass index was not related to risk of CAC (table 3). Findings for systolic, diastolic and pulse pressure, hypertension, and smoking resembled those for WHR.

Importantly, the risk of CAC among those who went from high WHR to a lower WHR was non- significantly increased as compared to those WHR remained below the median at both occasions. Again, no appreciable relation was found for body mass index. The findings for diastolic blood pressure and smoking seem to resemble that of WHR (table 3).

When adjustments were made for age, systolic pressure and smoking, the risk of CAC as compared with the low-low WHR group, was 1.59 [0-79-3.16] in the high-low WHR group, 2.33 [1.26-4.29] in the low-high WHR group and 2.11 [1/36-3.26] in the high-high WHR group. The findings did not material change when diastolic pressure was used in the multivariate models in stead of systolic pressure.

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Table 1

General characteristics of study population (n=573)

Risk factors	Mean (SD)		P value *
	Baseline (1993-1997)	Follow-up (2002-2004)	
Age (year)	57.2 ± 5.2	66.8 ± 5.5	<0.001
BMI (Kg/ m^2)	25.6 ± 4.0	26.7 ± 4.4	<0.001
WHR	0.78 ± 0.05	0.84 ± 0.07	<0.001
SBP (mmHg)	131 ± 19	136 ± 21	<0.001
DBP (mmHg)	78 ± 10	72 ± 9	<0.001
Pulse pressure (mmHg)	52 ± 14	64 ± 16	<0.001
Cholesterol (mmol/l) (n=89)	5.9 ± 0.9	6.2 ± 1.0	0.078
LDL cholesterol (mmol/l) (n=89)	4.0 ± 0.9	4.2 ± 0.9	0.118
HDL cholesterol (mmol/l) (n=89)	1.6 ± 0.4	1.4 ± 0.4	<0.001
Glucose (mmol/l) (n=89)	4.3 ± 0.9	5.6 ± 1.0	<0.001
Current smoking (%)	18	11	<0.001
Former smoking (%)	37	44	<0.001
Hypertension § 140/90 (%)	28	27	0.178
Diabetes (%)	1	6	<0.001

Body Mass Index, Diastolic Blood Pressure, Low Density Lipoprotein, High Density Lipoprotein, Systolic Blood Pressure, Waist to Hip Ratio, **§** Based on systolic, diastolic and history of having hypertension in baseline questionnaire, * Paired sample T.test

Table 2

Relation between cardiovascular risk factors measured 1993-1997 (baseline) and measured at 2004-2005 (follow-up) and coronary calcification measured in 2004-2005.

RISK FACTORS	CORONARY CALCIFICATION	
	Baseline OR (95% CI)	Follow-up OR (95% CI)
Age (years)	1.12 (1.08 – 1.16)	1.12 (1.08 – 1.16)
BMI (kg/ m^2)	1.03 (0.99 – 1.08)	1.02 (0.98 – 1.06)
Waist to hip ratio (WHR)	2.34 (1.66 – 3.30)	1.93 (1.47 – 2.52)
SBP (mmHg)	1.02 (1.01 – 1.03)	1.02 (1.01 – 1.03)
DBP (mmHg)	1.02 (1.01 – 1.04)	1.04 (1.02 – 1.06)
Pulse pressure (mmHg)	1.03 (1.01 – 1.04)	1.02 (1.01 – 1.03)
Cholesterol (mmol/l)	1.50 (0.91 – 2.47)	1.06 (0.89 – 1.25)
LDL cholesterol (mmol/l)	1.55 (0.94 – 2.57)	1.21 (1.00 – 1.46)
HDL cholesterol (mmol/l)	0.68 (0.22 – 2.07)	0.58 (0.36 – 0.94)
Glucose (mmol/l)	1.24 (0.73 – 2.11)	1.05 (0.89 – 1.24)
Current smoking	2.45 (1.50 – 4.00)	4.54 (2.20 – 9.39)
Former smoking	1.00 (0.71 – 1.43)	1.10 (0.78 – 1.55)
Hypertension § 140/90 (%)	1.95 (1.30 – 2.92)	2.13 (1.34 – 3.38)
Diabetes (%)	0.40 (0.04 – 3.59)	1.21 (0.59 – 2.49)

Body Mass Index, Diastolic Blood Pressure, Low Density Lipoprotein, High Density Lipoprotein, Systolic Blood Pressure, Waist to Hip Ratio, § Based on systolic, diastolic and history of having hypertension in baseline questionnaire.

Table 3

Risk of coronary calcification in categories of change in cardiovascular risk factors

Baseline	Follow-up	Participants	Age-adjusted OR (95% CI)
Body Mass Index			
Low	Low	250	1
High	Low	22	0.97 (0.39-2.46)
Low	High	45	1.36 (0.68-2.71)
High	High	255	1.12 (0.77-1.63)
Waist to Hip Ratio			
Low	Low	227	1
High	Low	49	1.62 (0.83-3.16)
Low	High	71	2.48 (1.38-4.46)
High	High	224	2.65 (1.76-3.99)
Systolic Blood Pressure			
Low	Low	215	1
High	Low	78	2.12 (1.21-3.70)
Low	High	92	2.40 (1.41-4.12)
High	High	188	2.20 (1.41-3.43)
Diastolic Blood Pressure			
Low	Low	205	1
High	Low	91	1.57 (0.92-2.69)
Low	High	97	1.87 (1.11-3.17)
High	High	180	2.73 (1.74-4.28)
Pulse Pressure			
Low	Low	192	1
High	Low	93	1.57 (0.92-2.68)
Low	High	98	1.90 (1.11- 3.22)
High	High	190	1.54 (0.97-2.42)
Total cholesterol			
Low	Low	26	1
High	Low	17	2.60 (0.65-10.29)
Low	High	29	2.57 (0.79-8.35)
High	High	23	3.60 (0.97-13.35)
Low Density Lipoprotein			
Low	Low	34	1
High	Low	15	1.12 (0.27-4.56)
Low	High	16	0.24 (0.07-0.90)
High	High	30	1.00 (0.32-3.18)
High Density Lipoprotein			
Low	Low	30	1
High	Low	6	0.64 (0.10-4.11)
Low	High	14	2.60 (0.56-11.96)
High	High	45	1.72 (0.62-4.72)
Glucose ¶			
Low	Low	43	1
High	Low	24	2.09 (0.66-6.64)
Low	High	12	2.24 (0.41-12.35)
High	High	11	1.20 (0.30-4.92)
Smoking			
No	No	462	1
No	Yes	6	-
Yes	No	45	1.46 (0.74-2.88)
Yes	Yes	60	5.63 (2.64-12.02)
Hypertension 140/90			
Low	Low	266	1
High	Low	40	1.53 (0.75-3.12)
Low	High	53	1.74 (0.92-3.27)
High	High	61	2.00 (1.03-3.90)
Diabetes mellitus			
No	No	525	1
No	Yes	35	1.22 (0.58 – 2.59)

¶ After exclusion of diabetic cases

Discussion

We related change in adiposity measure, notably WHR and BMI, in a nine year time period to presence of coronary calcification in postmenopausal women. Those with a WHR below the median at both occasions had the lowest risk of CAC. Those with a WHR above the median at both occasions and those showing an increase in WHR over time had higher CAC levels.

Change in WHR towards a lower level was related to a lower risk of CAC. In contrast to WHR, no relations were found for change in body mass index. These findings were independent of change in smoking and blood pressure.

Some potential explanations for the discordance between abdominal fat, as assessed using waist-to-hip ratio, and body mass index may be given. It has been well established that in contrast to peripheral fat, the visceral fat is a metabolically active tissue and is related to dyslipidemia, elevated blood pressure and insulin resistance.[14,15] These established risk factors have been shown to related to CAC in many studies [26,27] and as well as in the current study. A second additional explanation might be a role for a change in fat around the coronary arteries. We and others have recently showed that the visceral fat is strongly related to the fat surrounding the coronary arteries. [28,29] Fat around the coronary arteries, i.e., epicardial adipose tissue (EAT) appears to originate from the same brown adipose tissue of infancy as visceral fat does and is a rich source of bioactive molecules directly surrounding the coronary arteries.[30]

Coronary atherosclerosis is considered an excessive inflammatory and proliferative process inside the vascular wall.[31, 32] There is growing evidence that the presence of inflammatory mediators in the tissues surrounding the epicardial coronary arteries plays an important role in this process.[33-36] It is therefore conceivable that EAT contributes to the local development of atherosclerosis. Thus changes in abdominal fat may closely be related to changes in EAT, and thus reduce the risk of coronary atherosclerosis. Further studies into this aspect are however needed. Irrespective of the underlying mechanism, our results support the notion that a continuous low waist-to-hip ratio is preferred for development of coronary calcification.

Blood pressure changes closely followed the findings of visceral adiposity and not that of body mass index. The multivariate results indicated that the relations of change in WHR and BP with CAC are independent of each other and independent of smoking changes. The latter was related with coronary calcification. Risk of coronary calcification in subjects who smoked at both baseline and follow-up was much higher compared to never smokers. Interestingly, the risk among those who had stopped in the past 9 years was much lower confirming the effectiveness of smoking cessation. [37, 38]

To appreciate these findings, some aspects of this study need to be addressed. Unfortunately, for the analyses regarding baseline and change in glucose and lipids, our analysis was restricted in precision since information on only 89 subjects was available. Firm conclusions therefore can not be made. In addition, the reasons for change in risk factor levels, being drug use, life style changes, have not been ascertained. Finally- due to the lack of data- we did not assess the effect of change in WHR on EAT. Strengths of the study are its population based nature which enhances generalizability. Also, the cross-sectional analyses of risk factor levels and CAC are in agreement earlier studies, which indicated the validity of our measurement.

In conclusion, this observational study among healthy postmenopausal women supports the existing evidence that persisting abdominal adiposity or an increase in abdominal adiposity relates to an increased risk of coronary atherosclerosis.

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Abstract

Purpose:

This study was designed to examine the association between cardiovascular risk factors and segment specific coronary artery calcification.

Design: Cross-sectional study

Materials and Methods:

The study population comprised 573 healthy postmenopausal women selected from a population based cohort study. Established vascular risk factors were measured. The women underwent a Multi Detector-Row computed tomography (16-MDCT) (Philips Mx 8000 IDT 16) to assess coronary calcium. The Agatston score was used to quantify coronary calcium. Logistic regression models were used to assess the relations.

Results:

The prevalence of coronary artery calcification (Agatston score > 0) was 62.5% (n=348). CAC was most common in the left anterior descending (LAD) artery with a prevalence of 44%, prevalence in the right coronary artery (RCA), the circumflex (CRX), the left main artery (LM), and the posterior descending artery (PDA) were 23%, 19%, 16% and 0.3%, respectively. In multivariate regression models age was predominantly related to the calcification in the LAD and CRX, low density lipoprotein to calcification in the LAD and cholesterol to the calcification of RCA. Hypertension, systolic and diastolic blood pressure were related to the calcification of CRX, whereas smoking was predominantly related to the calcification of both LAD and RCA. Finally, age, body mass index (BMI) and systolic blood pressure (SBP) were significantly related to calcification in LM.

Conclusion:

Our findings showed that the consequences of elevated risk factor levels on development of atherosclerosis appear to be different across the segments of the coronary arteries.

Introduction

Acute myocardial infarction occurs in varying anatomical locations, ranging from anteroseptal zone (septal, apical, and/or anteroseptal, extensive anterior, and limited anterolateral) to the inferolateral zone (lateral, inferior, and inferolateral).[1] In general, the circumflex artery (CRX) serves the lateral and posterior walls of the myocardium, and the right coronary artery (RCA) serves the inferior wall. In an anterior MI, the left anterior descending artery (LAD) which serves the left ventricle, parts of the septum and papillary muscles is obstructed. [2] Different locations of a myocardial infarction are expected to be due to atherosclerosis development at different coronary segments, for example among patients with an anterior myocardial infarction the coronary artery showing the most severe atherosclerosis is generally the LAD. Furthermore, myocardial infarctions at different locations have been related to different sets of risk factors. Age over 65 and hypercholesterolemia are independent risk factors for anterior MI, whereas smoking and diabetes are independent risk factors for inferior MI.[3] In a retrospective study over a 7-year period, common finding on angiography was single-vessel disease causing infarction of the inferior wall (62%), and the major risk factor was tobacco use (81%), followed by family history (40%), hypertension (26%), and hyperlipidemia. [4]

These findings indicate that risk factors differently affect different parts of the myocardium. Since atherosclerosis is one of the main underlying abnormalities leading to coronary heart disease, we hypothesize that risk factors differ in their relation with segment specific development of coronary atherosclerosis. Coronary atherosclerosis can be validly and non-invasively assessed using computer tomography. For example, Multi-Detector-Row Computed Tomography (MDCT) has been shown to be an accurate, non-invasive and reproducible method to quantify CAC. [5]

We set out to study the relation of vascular established risk factors to segment specific coronary calcification in a population-based sample of healthy postmenopausal women.

Materials and Methods

Population

We used data from a cross-sectional study among 573 post-menopausal healthy women as has been described previously. [6] 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). In PROSPECT 17,357 healthy participants of a nationwide population-based breast-cancer screening programme, aged 49-70 years, 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 573 underwent a multislice CT examination at a second visit between January and December 2004. The Institutional Review Board of the University Medical Center Utrecht approved the study and written informed consent was obtained from all participants before enrolment.

Cardiovascular risk factors

At the re-examination visit, smoking behavior and family history of cardiovascular diseases (CVD) were assessed by a questionnaire. Smoking was categorized as current versus past and never. Age was calculated from birth date and date of investigation. Height and weight were measured and body mass index (BMI) was calculated as

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(2) Ayling J. Ready to go. Emerg Med Serv 2003; 32(4):97.

(3) Fabijanic D, Giunio L, Culic V, Bozic I, Martinovic D, Miric D. Predictors of type and site of first acute myocardial infarction in men and women. Ann Saudi Med 2005; 25(2):134-139.

(4) Kanitz MG, Giovannucci SJ, Jones JS, Mott M. Myocardial infarction in young adults: risk factors and clinical features. J Emerg Med 1996; 14(2):139-145.

(5) Thompson BH, Stanford W. Update on using coronary calcium screening by computed tomography to measure risk for coronary heart disease. Int J Cardiovasc Imaging 2005; 21(1):39-53.

(6) Sabour S, Franx A, Rutten A, Grobbee DE, Prokop M, Bartelink ML et al. High blood pressure in pregnancy and coronary calcification. Hypertension 2007; 49(4):813-817.

weight divided by height squared (kg/m^2). Waist-to-hip ratio (WHR) was assessed. Systolic and diastolic blood pressures (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. HDL cholesterol was measured by the direct method (inhibition, enzymatic). LDL cholesterol was calculated using the Friedewald formula. We defined hypertension as being under hypertensive therapy or a systolic blood pressure equal or higher than 140 mmHg or a diastolic blood pressure equal or higher than 90 mmHg. Pulse pressure (PP) was defined as SBP – DBP.

Coronary calcium measurements

The amount of calcium in the coronary arteries was assessed with a multi-detector computed tomography (MDCT) scanner (Mx 8000 IDT 16, Philips Medical Systems, Best, The Netherlands). Subjects were positioned within the gantry of the MDCT scanner in supine position. A 16-slice scanner with 0.42 seconds rotation time was used to obtain 1.5 mm thick sections. 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 16x1.5 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. From the acquired raw data, 3 mm thick sections were reconstructed. 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 the results of cardiovascular risk factors, manually selected only the calcifications within one of the coronary arteries (left main (LM), left anterior descending (LAD), left circumflex (CRX), right coronary artery (RCA) , or posterior descending artery (PDA). To reduce the influence of noise, the minimum size of a calcified lesion was set at 0.5 mm^2. The peak density in Hounsfield units and the area in mm^2 of each selected region were calculated. An overall Agatston [7] 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 individual segments and for the entire coronary tree.

(7) Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990; 15(4):827-832.

Data Analysis

The main objective of the present study was to characterize the relation between coronary risk factors and segment specific coronary calcification. The dependent variable for the analysis was the presence or the absence of coronary artery calcification in a particular segment as measured by MDCT. The independent variables were coronary risk factors.

First, the general characteristics of study population are described. Then, the relation between cardiovascular risk factors and total coronary calcification was examined using logistic regression models. After that, we assessed age adjusted relations between risk factors and segment specific coronary calcification. Finally, the relation between risk factors and segment specific coronary calcification was investigated adjusted for age and coronary calcification in the other segments.

The relations were quantified by odds ratio with corresponding 95% confidence limits. A significance level of 0.05 was used for all analysis. Data analysis was performed using SPSS for windows version 13.0

Results

Table 1 describes the general characteristics of our population. In our study population (n=573), information on coronary calcification was present in 566 women. The prevalence of coronary artery calcification was 61.5% (n=348). Of those, 15.8% (n=90) had coronary calcification in LM, 43.9% (n=249) in LAD, 23.1% (n=131) in RCA, 19.4% (n=110) in CRX and 0.3% (n=2) had calcification in PDA. In our study population, 13.3% (n=75) had an Agatston score of less than 10 and 8.3% (n=47) of greater than 400.

The age adjusted relations between risk factors and coronary calcification are given in Table 2. Increased age itself, increased levels of WHR, SBP, DBP, PP, LDL, current smoking, and previous cardiovascular diseases were significantly related to increased levels of CAC. Decreased level of HDL was also significantly related to increase CAC.

Age adjusted relation of risk factors with segment specific CAC are given in table 3. After extra adjustment for calcification of the other coronary segments (table 4), increased SBP and DBP were significantly related to the calcification of circumflex segment [OR=1.01 (1.00 - 1.02)] and [OR=1.04 (1.01 - 1.07)] per mmHg, respectively.

The age relation remained significant for LAD and circumflex [OR =1.09 (1.05 – 1.13) and 1.08 (1.03 – 1.13)]. BMI, SBP and family history of CVD were statistically significant related to calcification of LM [OR =1.05 (1.00 – 1.10) per kg/m^2, 1.01 (1.00 – 1.02) mmHg and 2.25 (1.10 – 4.57)] respectively. Previous CVD with right coronary artery (RCA) [OR=3.79 (1.23 – 11.63)] and LDL cholesterol with LAD [OR=1.36 (1.09 – 1.71)]; however, total cholesterol was related to RCA [OR= 1.25 (1.00 – 1.57)]. A strong significant relation was found between current smoking and coronary calcification but only in LAD [OR=3.21 (1.60 – 6.45)] and RCA [OR= 2.99 (1.48 – 6.02)]. The relation of the other risk factors with calcification in a specific segment of coronary artery did not reach statistical significance.

Table 1

General characteristics of study population (n=573)

	Mean ± SD
Age (years)	66.8 ± 5.5
Body mass index (Kg/ m^2)	26.7 ± 4.4
Waist to hip ratio	0.84 ± 0.07
Systolic blood pressure (mmHg)	136 ± 21
Diastolic blood pressure (mmHg)	72 ± 9
Pulse pressure (mmHg)	64 ± 16
Total cholesterol (mmol/l)	6.1 ± 1.0
Low density lipoprotein cholesterol (mmol/l)	4.2 ± 0.9
High density lipoprotein cholesterol (mmol/l)	1.4 ± 0.4
Triglycerides (mmol/l)	1.2 ± 0.6
Glucose (mmol/l)	5.6 ± 1.0
Current smoking (%)	11
Former smoking (%)	44
Hypertension § 140/90 (%)	35
Diabetes (%)	6
Previous cardiovascular diseases (%)	4
Family history of cardiovascular diseases (%)	11

§ Based on systolic, diastolic and use of anti-hypertensive therapy

Table 2

Age adjusted relations between cardiovascular risk factors and coronary calcification

	Coronary Calcification
RISK FACTORS	OR (95% CI)
Age (years)	1.13 (1.10 – 1.17)
Body mass index (Kg/ m^2)	1.01 (0.97 – 1.05)
Waist to hip ratio	1.78 (1.26 – 2.50)
Systolic blood pressure (mmHg)	1.01 (1.00 – 1.02)
Diastolic blood pressure (mmHg)	1.03 (1.01 – 1.05)
Pulse pressure (mmHg)	1.01 (1.00 – 1.02)
Total cholesterol (mmol/l)	1.17 (0.98 – 1.40)
Low density lipoprotein cholesterol (mmol/l)	1.24 (1.02 – 1.51)
High density lipoprotein cholesterol (mmol/l)	0.48 (0.30 – 0.80)
Triglycerides (mmol/l)	1.38 (1.03 – 1.85)
Glucose (mmol/l)	1.05 (0.90 – 1.24)
Current smoking	8.50 (4.15 – 17.43)
Former smoking	1.40 (0.95 – 2.03)
Hypertension § 140/90	1.30 (0.85 – 1.98)
Diabetes	1.16 (0.56 – 2.40)
Previous cardiovascular diseases	6.29 (1.74 – 22.76)
Family history of cardiovascular diseases	1.68 (0.96 – 2.93)

§ Based on systolic, diastolic and use of anti-hypertensive therapy

Table 3

Age adjusted relation between cardiovascular risk factors and segment specific coronary calcification

Risk factors	Segment specific coronary calcification OR (95% CI)			
	LM n= 90	LAD n= 249	CRX n= 110	RCA n= 131
BMI (Kg/ m^2)	**1.05 (1.00 – 1.10)**	0.99 (0.95 – 1.03)	1.01 (0.97 – 1.06)	1.04 (0.99 – 1.08)
WHR	1.42 (0.93 – 2.16)	**1.59 (1.13 – 2.23)**	**1.81 (1.20 – 2.73)**	**1.81 (1.24 – 2.65)**
SBP (mmHg)	**1.01 (1.00 – 1.02)**	**1.00 (1.00 – 1.01)**	**1.01 (1.00 – 1.02)**	1.00 (0.99 – 1.01)
DBP(mmHg)	1.01 (0.98 – 1.03)	**1.02 (1.00 – 1.04)**	**1.03 (1.01 – 1.06)**	**1.02 (1.00 – 1.04)**
Cholesterol (mmol/l)	1.12 (0.98 – 1.38)	1.10 (0.93 – 1.31)	1.04 (0.84 – 1.28)	**1.25 (1.02 – 1.52)**
LDL (mmol/l)	1.00 (0.78 – 1.29)	**1.27 (1.04 – 1.55)**	0.97 (0.76 – 1.24)	1.00 (0.80 – 1.25)
HDL (mmol/l)	0.58 (0.29 -1.16)	0.44 (0.26 – 0.74)	0.48 (0.24 – 0.93)	0.67 (0.37 – 1.21)
Triglycerides (mmol/l)	**1.42 (1.01 – 2.01)**	**1.35 (1.02 – 1.81)**	1.18 (0.83 – 1.67)	1.30 (0.95 – 1.79)
Glucose (mmol/l)	0.97 (0.76 – 1.24)	1.09 (0.93 – 1.29)	1.05 (0.85 – 1.31)	0.82 (0.63 – 1.08)
Current smoking	**3.39 (1.68 – 6.84)**	**5.41 (2.88 – 10.17)**	**2.80 (1.44 – 5.45)**	**5.12 (2.74 – 9.57)**
Past smoking	**1.82 (1.08 – 3.07)**	1.35 (0.92 – 1.98)	1.04 (0.64 – 1.67)	1.57 (0.99 – 2.47)
Hypertension §	**2.15 (1.25 – 3.70)**	1.34 (0.87 – 2.05)	**2.58 (1.49 – 4.46)**	**1.75 (1.08 – 2.83)**
Diabetes	1.12 (0.44 – 2.84)	1.20 (0.57 – 2.51)	0.88 (0.34 – 2.29)	0.42 (0.14 – 1.23)
Previous CVD	**3.22 (1.25 – 8.30)**	**6.14 (1.93 – 19.56)**	**6.35 (2.38 – 16.89)**	**7.42 (2.81 – 19.59)**
FH of CVD	**2.13 (1.11 – 4.10)**	1.14 (0.65 – 1.98)	1.07 (0.52 – 2.21)	1.63 (0.89 – 2.99)

BMI=Body Mass Index, WHR=Waist to Hip Ratio, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, LDL=Low density lipoprotein, HDL=High density lipoprotein, FH=Family history, CVD=Cardiovascular Diseases
LM=Left main, LAD=Left anterior descending, CRX=Circumflex, RCA=Right coronary artery

Table 4a

Relation between cardiovascular risk factors and segment specific coronary calcification adjusted for age and calcification of the other segments of coronary arteries

Risk factors	Segment specific coronary calcification OR (95% CI)			
	LM n= 90	LAD n= 249	CRX n= 110	RCA n= 131
Age (years)	1.03 (0.98 – 1.08)	**1.09 (1.05- 1.13)**	**1.08 (1.03 – 1.13)**	1.02 (0.98 – 1.07)
BMI (Kg/ m^2)	**1.05 (1.00 – 1.10)**	0.97 (0.93 – 1.02)	1.00 (0.95 – 1.06)	1.04 (0.99 – 1.09)
WHR	1.04 (0.66 – 1.64)	1.26 (0.87 – 1.85)	1.43 (0.90 – 2.28)	1.48 (0.96 – 2.27)
SBP (mmHg)	**1.01 (1.00 – 1.02)**	1.00 (0.99 – 1.01)	**1.01 (1.00 – 1.02)**	1.00 (0.99 – 1.01)
DBP(mmHg)	1.00 (0.97 – 1.03)	1.00 (0.98 – 1.02)	**1.04 (1.01 – 1.07)**	1.01 (0.99 – 1.04)
Cholesterol (mmol/l)	1.06 (0.83 – 1.35)	1.02 (0.84 – 1.24)	0.93 (0.73 – 1.18)	**1.25 (1.00 – 1.57)**
LDL (mmol/l)	1.00 (0.77 – 1.30)	**1.36 (1.09 – 1.71)**	0.90 (0.69 – 1.17)	0.94 (0.74 – 1.20)
HDL (mmol/l)	0.83 (0.40 – 1.71)	0.51 (0.30 – 0.91)	0.72 (0.35 – 1.50)	1.08 (0.56 – 2.11)
Triglycerides (mmol/l)	1.29 (0.90 – 1.87)	1.26 (0.91 – 1.75)	0.93 (0.63 – 1.39)	1.13 (0.78 – 1.63)
Glucose (mmol/l)	0.92 (0.69 – 1.23)	1.14 (0.96 – 1.36)	1.09 (0.88 – 1.35)	0.77 (0.57 – 1.05)
Current smoking	1.66 (0.77 – 3.61)	**3.21 (1.60 – 6.45)**	1.03 (0.48 – 2.20)	**2.99 (1.48 -6.02)**
Past smoking	1.70 (0.97 – 2.97)	1.22 (0.80 – 1.87)	0.70 (0.40 – 1.22)	1.43 (0.85 – 2.39)
Hypertension §	1.48 (0.81 – 2.74)	0.91 (0.55 – 1.51)	**2.00 (1.06 – 3.76)**	1.24 (0.70 – 2.20)
Diabetes	1.18 (0.41 – 3.36)	1.47 (0.66 – 3.25)	1.00 (0.35 – 2.87)	0.37 (0.12 – 1.15)
Previous CVD	1.26 (0.45 – 3.51)	2.26 (0.67 – 10.32)	2.49 (0.80 – 7.85)	**3.79 (1.23 – 11.63)**
Family history of CVD	**2.25 (1.10 – 4.57)**	0.91 (0.49 – 1.71)	0.91 (0.40 – 2.08)	1.58 (0.78 – 3.16)

Abbreviation as table 3

Table 4b

Relation between cardiovascular risk factors and segment specific coronary calcification adjusted for age and calcification of the other segments of coronary arteries

	segment specific coronary calcification OR (95% CI)			
Risk factors	LM	CRX	LAD	RCA
Body Mass Index (Kg/ m^2)	**1.05 (1.00 – 1.10)**			
Family history of CVD	**2.25 (1.10 – 4.57)**			
Systolic blood pressure (mmHg)	**1.01 (1.00 – 1.02)**	**1.01 (1.00 - 1.02)**		
Diastolic blood pressure (mmHg)		**1.03 (1.00 - 1.06)**		
Hypertension§		**1.99 (1.06 – 3.75)**		
Age (years)		**1.08 (1.03 – 1.13)**	**1.09 (1.05 – 1.13)**	
Low density lipoprotein (mmol/l)			**1.36 (1.08 – 1.71)**	
Current smoking			**3.21 (1.60 – 6.45)**	**2.98 (1.47 – 6.01)**
Previous CVD				**3.78 (1.23 – 11.63)**
Cholesterol (mmol/l)				**1.25 (1.00 – 1.57)**

Abbreviation as table 3

Discussion

We found that different cardiovascular risk factors had different relations with calcification of a particular segment in coronary arteries.

To appreciate our findings, some limitations of our study need to be addressed. First, a causal interpretation of our findings is inherently restricted by the cross-sectional nature of the study design. Also, our study population comprised healthy women and thus our results should be confirmed by other studies with a large number of patients in both men and women.

Although heritability plays a significant role in coronary calcification at the LM and the proximal part of coronary arteries, [8] it has been shown that also non-genetic factors such as age over 65 and hypercholesterolemia are independent risk factors for anterior MI, whereas smoking and diabetes are independent risk factors for inferior MI. In a retrospective study over a 7-year period to define the risk factors and clinical presentation of patients with an acute MI, a common finding on angiography was single-vessel disease (62%) causing infarction of the inferior wall (CRX and RCA), and the major risk factor was tobacco use (81%), followed by family history (40%), hypertension (26%), and hyperlipidemia (20%). [4] Our results extended present knowledge on the relation between risk factors and location of MI with segment-specific coronary atherosclerosis and different risk factors.

Age is an independent predictor of CHD event fatality [9] having a strong association with total coronary calcification; however, in our study, after adjusting for calcification of the other coronary segments, this relation remained significant just for LAD and CRX. In other words, age is significantly related to the location of MI (Anterior) and the calcification of particular coronary segments (LAD and CRX). It seems the higher our age, the higher the likelihood of developing coronary calcification in LAD and CRX as well as anterior MI.

Since the location of current and prior MI predicts short and long term risk of death [10], there have been efforts to predict the location of a future myocardial infarction based on the location of ischemia. [11] Although in the setting of severely depressed ejection fraction (≤30%), inferior MI has been shown to be associated with a significantly higher risk of mortality than anterior MI (hazard ratio 1.58, p = 0.048),[12] it has been shown that the rate of reinfarction or death is almost two times higher in patients with anterior than inferior infarction.[13] Also in patients with a LAD lesion, proximal lesion location correlate with adverse outcomes even after adjustment for coronary blood flow and other covariates.[14] However, there is evidence that adverse prognosis associated with anterior myocardial infarction is related to differences in etiology rather than to infarction size.[15] Therefore, regarding the adverse prognosis of MI, not only the location and size of the MI but also different risk factors are related to the outcome.

Patients with anterior infarctions are significantly more likely never to have smoked than patients with inferior infarctions. They have a higher prevalence of hypertension and a higher mean cholesterol level. [15] We found a significant association between hypertension and coronary calcification. Our results indicated that after adjusting for calcification of other segments, both systolic and diastolic blood pressures as well as hypertension – according to our definition – had significant relation with calcification of CRX which serves the lateral and posterior walls of the myocardium; and the relation between LDL cholesterol and coronary calcification is significant just for LAD which is obstructed in an anterior MI.

It has been reported that after adjustment for other risk factors, smokers are more likely to have more advanced atherosclerosis in the LAD than non smokers. This is true for the RCA as well [16]. We confirmed previous results by showing that indeed among coronary segments, only calcifications of LAD and RCA are related to smoking. Finally,

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(11) Miller GL, Herman SD, Heller GV, Kalla S, Levin WA, Stillwell KM et al. Relation between perfusion defects on stress technetium-99m sestamibi SPECT scintigraphy and the location of a subsequent acute myocardial infarction. Am J Cardiol 1996; 78(1):26-30.

(12) Gomez JF, Zareba W, Moss AJ, McNitt S, Hall WJ. Prognostic value of location and type of myocardial infarction in the setting of advanced left ventricular dysfunction. Am J Cardiol 2007; 99(5):642-646.

(13) Welty FK, Mittleman MA, Lewis SM, Healy RW, Shubrooks SJ, Jr., Muller JE. Significance of location (anterior versus inferior) and type (Q-wave versus non-Q-wave) of acute myocardial infarction in patients undergoing percutaneous transluminal coronary angioplasty for postinfarction ischemia. Am J Cardiol 1995; 76(7):431-435.

our results showed that family history of CVD was related to LM calcification, whereas previous CVD had a significant relation with calcification of the RCA.

In conclusion, our study shows that the consequences of elevated risk factor levels on development of atherosclerosis appear to be different across the segments of the coronary arteries.

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(16) Zieske AW, McMahan CA, McGill HC, Jr., Homma S, Takei H, Malcom GT et al. Smoking is associated with advanced coronary atherosclerosis in youth. Atherosclerosis 2005; 180(1):87-92.

Chapter
4

Markers of myocardial damage and coronary calcium

Abstract

Purpose:

To assess the relation of left ventricular hypertrophy (LVH) and electrocardiogram (ECG) abnormalities reflecting subclinical myocardial damage with coronary artery calcification (CAC).

Design: Cross-sectional study

Materials and 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 presence of coronary calcium. Logistic regression was used to assess the relation of ECG abnormality with coronary calcification.

Results:

Left ventricular hypertrophy 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. Coronary artery calcification (CAC) was found in 62% of the women. Women with LVH on the ECG had a non-significantly 2.3 fold increased risk of CAC (95% CI 0.6-8.7). 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). These relations were attenuated after adjustment for vascular risk factors.

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.

Introduction

With an electrocardiogram, information can be obtained on subclinical myocardial damage. The frontal T- axis has been postulated to be a general marker of ventricular repolarization abnormality, indicative of subclinical myocardial damage, and has been shown to be a strong and independent risk indicator of fatal and non-fatal cardiac events in the elderly. [1-3] Furthermore, in addition to the frontal T-axis, the spatial QRS-T angle [4] has been shown to be an important determinant of diagnosis and prognosis in patients presenting with acute chest pain.[5] Spatial QRS-T angle, which is defined as the angle between the directions of ventricular depolarization and repolarization, has been shown to be an important risk factor for cardiac death [6-8] and also coronary heart disease (CHD) events as well as mortality in postmenopausal women. [9] In addition, findings from autopsy and clinical angiographic studies have suggested a link between LVH and severity of coronary atherosclerosis.[10;11] Already in young adults a significant association between echocardiographic LVH and coronary atherosclerosis, as assessed by coronary calcifications, has been reported. [12;13] As LVH is an important risk factor for cardiovascular disease; [14;15] part of that relation may be due to presence of coronary atherosclerosis.
Coronary atherosclerosis can be non-invasively assessed in a valid and reproducible manner by measurement of coronary calcium using coronary computer tomography.[16] High coronary artery calcium (CAC) scores independently predict coronary heart disease (CHD).[10;17;18] Part of this association has been attributed to the fact that CAC reflects atherosclerosis in the coronary arteries, but it may also reflect presence of subclinical ischemia.

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

Materials and Methods

Population

We used data from a cross-sectional study among 566 post-menopausal healthy women as has been detailed earlier.[19] 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).[20] In PROSPECT 17,357 healthy participants of a nationwide population-based breast-cancer screening programme, 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 573 underwent a multislice CT examination at a second visit between January and December 2004. The Medical Ethical Committee of the University Medical Center Utrecht approved the study and written informed consent was obtained from all participants before enrolment.

Classical cardiovascular risk factors

At the first re-examination visit, smoking behavior and family history of coronary heart diseases (CHD) were assessed by 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 (kg/m^2). Waist-to-hip ratio (WHR) was assessed. Systolic and diastolic blood pressures (SBP & DBP) were measured at both arms with an automated and calibrated blood pressure device

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(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 by 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.

Coronary calcium measurements

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). 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 16x1.5 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. 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 mm^2. The peak density in Hounsfield units and the area in mm^2 of each selected region were calculated. The Agatston [21] 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. (Unpublished) 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. [22]

ECG abnormalities and left ventricular hypertrophy

A standard 12-lead electrocardiogram (ECG) 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). [23] MEANS 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. [24] 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

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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 a MEANS interpretation of possible, probable, or definite LVH were considered to have evidence of LVH. [25] 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 thru135 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.

Data 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 as 1: normal, 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 analysis. Data analysis was performed using SPSS for windows version 13.0.

Results

Table 1 lists characteristics of the study population by presence or absence of CAC. The prevalence of left ventricular hypertrophy 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, 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).

Table 3 shows the relation of LVH and ECG abnormalities with presence of CAC adjusted for age and additionally for other potential confounders.

Due to the low prevalence we found no significant relation between LVH and presence of CAC [OR=2.54 (0.71 – 9.13)]. However, both an abnormal T-axis [OR=3.86 (1.46 – 10.11)] and an abnormal QRS-T angle [OR=2.23 (1.11 – 4.47)] were significantly related to presence of CAC. In the age adjusted models increased CAC was related to increased risk of abnormal T-axis being present [OR=3.79 (1.40 -10.23)]. This relation was further attenuated when adjustments were made for additional vascular risk factors (table 3). In the age adjusted model increased CAC was not significantly related to presence of abnormal QRS-T angle [OR=1.97 (0.96 – 4.05)]. The relation further attenuated when risk factors were accounted for.

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Table 1

General characteristics of study population and relation of coronary artery calcification with clinical covariates (N=566)

Risk Factors	CAC + (n=348) mean (SD)	CAC – (n=218) mean (SD)	Total (n=566) mean (SD)
Age (year)	68.0 (5.5)	64.8 (4.9)	66.7 (5.4)
Body Mass Index (Kg/ m^2)	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)
Triglycerides (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

Table 2

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

Risk Factors	OR (95% CI)			
	CAC	LVH	T-axis	QRS-T angle
Age (year)	**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^2)	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)
Triglycerides (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 coronary heart diseases (%)	**1.96 (1.09 – 3.53)**	1.30 (0.28 – 5.99)	1.11 (0.37 – 3.31)	0.34 (0.08 – 1.46)

Table 3

The relation of markers of coronary risk with coronary artery calcification

ECG markers of coronary risk	coronary artery calcification OR (95% CI)	
	Model 1	Model 2
LVH*	2.33 (0.62 – 8.69)	1.92 (0.51 – 7.19) *
T- axis	3.79 (1.40 – 10.23)	2.70 (0.93 – 7.78) ¶
QRS-T angle	1.97 (0.96 – 4.05)	1.55 (0.74 – 3.27) §

Model 1= Age adjusted relation; Model 2= Adjusted for age and other vascular risk factors as follow: * SBP, PP and hypertension, ¶ WHR, hypertension, glucose and current smoking § WHR, SBP, DBP, PP and Hypertension

Discussion

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

Before we can interpret our findings, some issues need to be addressed. The current analysis concentrates on electrocardiographic indications of hypertensive damage. From literature it is known that the sensitivity and specificity of the diagnostic interpretation by the MEANS computer program, taking cardiologists as a reference, are high. With respect to LVH, a sensitivity of 88.9% and a specificity of 99.1% were yielded. [25]

A few studies have examined the association of echocardiographically assessed LVH with CAC. A study conducted in a Turkish population among 249 asymptomatic hypertensive patients reported a positive association between concentric LVH and CAC. [26] A study among 159 young to middle-age African-American participants without hypertension or overt ischemic heart disease [27], 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 extent of CAC among subjects who were positive for CAC, but not with the presence of CAC after multivariable adjustment. [28] Our findings are in agreement with these reports, and expand the evidence into healthy menopausal women.

Furthermore, we showed that T-axis and QRS-T angle abnormalities that indicate subclinical ischemic damage were related to CAC. These repolarization abnormalities have been associated with considerable increased risks of cardiac death in populations based studies [6] and have been shown to be more common (by almost 2-fold) in diabetic compared to non-diabetic subjects. [29] Our findings indicate that part of the increased risk may be attributable to presence of coronary atherosclerosis and not only ischemic changes per se.

In 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.

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Chapter

5

Discussion & summary

Discussion & Summary

The aims of the studies described in this thesis were:

1. To assess reproducibility of coronary calcium measurements with multi detector computed tomography (MDCT) imaging and to evaluate whether different measurement protocols, slice thickness and cardiovascular risk factors affect reproducibility of MDCT.
2. To determine whether a history of high blood pressure during pregnancy marks an increased cardiovascular risk as shown by coronary calcification later in life.
3. To examine the relation between changes in abdominal adiposity, as assessed by waist-to-hip ratio (WHR) and risk of coronary artery calcification.
4. To examine the association between cardiovascular risk factors and segment specific coronary artery calcification.
5. To assess the relation of left ventricular hypertrophy (LVH) and electrocardiogram (ECG) abnormalities reflecting subclinical myocardial damage with coronary artery calcification

The present chapter provides a general discussion in the light of current knowledge in the field of coronary artery calcification. It includes the background of the thesis and main findings.

Introduction

Coronary artery disease (CAD) is the number one killer of adults in westernized societies. Development of coronary atherosclerosis is the main underlying mechanism [1;2] Atherosclerosis tends to develop slowly and gradually over the years and remains subclinical, i.e., a-symptomatic for a long time.[3] Means to detect atherosclerosis in a non-invasive manner have been subject of research over the past decades. Early detection of vascular damage may be done using computed tomography (CT) of the coronary arteries. Coronary CT has been shown to be an accurate, non-invasive method to quantify coronary calcification burden in patients. Evidence shows that calcium measurements by CT correlate well with histological plaque analyses and that CAC measurement accurately reflect disease severity. Furthermore, increased coronary calcium is a strong predictor of future coronary events and as such it may be useful to assess individual risk for coronary heart disease. Although data on coronary calcium has mainly come from studies using EBCT, multi detector CT (MDCT) is much more widely available and also allows for measurement of coronary calcium.

Non-invasive measurement of coronary calcification has opened new areas of research. Where the epidemiology in etiologic and prognostic research traditionally used clinical events as primary outcome, now presence or absence of atherosclerosis can be used as primary outcome as an alternative for cardiovascular events. This change made it possible to address etiologic research questions using a much smaller group of participants and also in participants of younger age.

Coronary artery calcification

The most important cause of morbidity and mortality in individuals with cardiovascular risk factors is coronary atherosclerosis. The ability to predict the majority of coronary events is limited. [4] Assessment of established risk factors to identify high-risk subgroups is neither highly sensitive nor highly specific. Thus, there is a clear need for new strategies in primary prevention to prevent clinical manifestations of CAD. In recent years, an alternative approach to risk stratification has been proposed: non-invasive evaluation of coronary calcification. This strategy is based on the close histopathological correlation between coronary calcium deposits and the total amount of coronary atherosclerosis. [5]

It has been suggested that early calcification in coronary arteries results from calcification of smooth muscle cell organelles [6], and that it is an active process. [7] The presence, and more importantly, the quantity of coronary arterial calcification, correlates well with the overall severity of the atherosclerotic process [8;9]. The absence of detectable CAC reflects a low likelihood of a major cardiac event within the next 2–5 years (5–10% overall risk) [10;11]. In fact, recent evidence suggests that CAC quantification may be a better predictor of mortality than traditional Framingham risk factors, adding prognostic value when used in conjunction with traditional risk factor assessments. [12]

Detection of coronary calcification by MDCT

Calcifications of the coronary artery wall are regarded as a recognized marker of coronary atherosclerosis [13]. Most of the information on coronary calcifications has been based on images obtained from electron beam computed tomography (EBCT). Since EBCT is very sparsely available, for example there is only one EBCT scanner in the Netherlands, the use of a multi detector CT (MDCT) for the measurement of coronary calcium is more than welcome. Continued advances in MDCT scanner technology have resulted in significant improvements in the ability of these scanners to perform coronary calcium measurements. Indeed MDCT has been used for detection and quantification of coronary artery calcium [14-16] and has been shown to be particularly

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sensitive for detecting coronary calcifications [17]. New technical developments, such as 16 and 64 row MDCT [18-20], may further increase the potential of MDCT. Few studies have however, compared the accuracy or reproducibility of EBCT with MDCT. The limited available evidence does suggest no significant differences between the two modalities, although more evidence is needed. [16;21]

Coronary Calcium Scoring

While traditional Agatston-derived calcium scores have been widely adopted as the means for quantifying CAC, recent evidence suggests that calcium volume and particularly mass measurements are more accurate measurements of disease. The need for an easily reproducible parameter in the assessment of coronary artery calcium seems to inspire the development of several alternative scoring methods such as volume scoring or quantitative assessment of the absolute calcium mass. Volume scoring appears to show less variability in volume and mass quantification than calcium scoring according to the method of Agatston [22].

Criticism of the Agatston-derived calcium score stems mainly from the arbitrary nature of the qualitative weighting factor incorporated into the score based upon the peak density of the calcium deposit. Conversely, the volume measurement technique expounded by Callister et al. [23] which relies on isotropic interpolation of data to calculate the volume of a lesion above a prescribed threshold, has been reported to result in improved score reproducibility, as it is independent of slice thickness.[16] Likewise, CT derived calcium mass measurements provide a quantitative assessment of the mineral content of a lesion independent of slice thickness and spatial resolution of the acquisition. Furthermore, the quantitative measurement of the mineral mass of calcified coronary lesions has been shown to significantly reduce measurement variability [24]. Mineral mass measurements derived from prospectively ECG-triggered MDCT provided the most accurate and reproducible equivalent of the actual mineral content of coronary calcifications in vivo [25]. Calcium mass probably has the greatest potential to increase accuracy, consistency and reproducibility of coronary calcium assessment [26] and thus may replace traditional scoring methods in the future [27]. However, the fact that the reproducibility of mass measurements for spiral CT scans was lower than for Agatston or volume , highlights a problem that has been described previously [28].

Recent studies describe better results for inter-scan and inter- and intra-observer variability with use of quantitative measures (volume and mass) as compared to the traditional Agatston scoring method [29-32]. Rumberger and Kaufman[33] however, comparing these three methods found no appreciable difference in the results, reporting an similar 38% averaged variability on consecutive scans when mass, volume, or Agatston calcium score measurements were used . Rumberger and Kaufman also attempted to establish risk stratification of 11,490 individuals, and found similar risk assessments for patients regardless if the Agatston score, calcium mass and volume measurements were used. However, studies using the MDCT scan that evaluate systematically the differences in reproducibility between Agatston, mass or volume measurements have not been done.

Reproducibility of CAC measurements

We set out to assess reproducibility of coronary calcium measurements with MDCT imaging and to evaluate whether different measurement protocols slice thickness and cardiovascular risk factors affect inter and intra- observer reproducibility (**Chapter 2.1**). The study population comprised 199 healthy postmenopausal women. Coronary calcium was assessed using a 16-MDCT (Philips Mx 8000 IDT 16). Images were made using 1.5 and 3.0 mm slice thicknesses. To assess inter and intra-observer reproducibility, the images were read by two observers. One observer read the images of 52 subjects twice. The Agatston score, a volume measurement and a mass measurement

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were used to quantify coronary calcium and reproducibility was determined by estimation of mean, absolute and relative differences between scores of the observers and by estimation of Intra-class correlation coefficients (ICCC). One hundred and twenty participants (60.3%) had a positive calcium score. Median Agatston score for the first observer was 2.20 with a range of 0- 2019.The reproducibility of coronary calcium measurements between observers and within observers was excellent with Intra-class correlation coefficients of > 0.95, and small mean, absolute and relative differences. Reproducibility findings were similar for 1.5 mm slices as for 3.0 mm slices, and equal for Agatston, volume and mass measurements. Of the established cardiovascular risk factors, none was significantly related to measurement error. However, the measurement error increased with increasing coronary calcium. Therefore, we concluded that reproducibilility of measurement of coronary calcium using images from MDCT is excellent, irrespective of slice thickness and type of calcium parameter.

In **chapter 2.2**, we assessed inter-scan reproducibility of coronary calcium measurements in 76 healthy women obtained from Multi Detector-Row CT (MDCT) images and evaluated whether this reproducibility is affected by different measurement protocols, slice thickness, cardiovascular risk factors and/or technical variables. Coronary calcium was assessed in these women twice in one session using 16-MDCT (Philips Mx 8000 IDT 16). Fifty-five participants (72.4%) had a coronary calcification of more than zero in Agatston (1.5 millimetre slice thickness). The reproducibility of coronary calcium measurements between scans in terms of ranking was excellent with Intra-class correlation coefficients of > 0.98, and kappa values above 0.80. The absolute difference in calcium score between scans increased with increasing calcium levels, indicating that measurement error increases with increasing calcium levels. However, no relation was found between the mean difference in scores and calcium levels, indicating that the increase in measurement error is likely to result in random misclassification in calcium score. Again reproducibility results were similar for 1.5 mm slices and for 3.0 mm slices, and equal for Agatston, volume and mass measurements.

We concluded that the inter-scan reproducibility of coronary calcium measurements by MDCT using Agatston, volume and mass scoring algorithms is excellent showing no major differences between scoring methods. The slice thickness did not affect reproducibility, nor did heart rate and technical parameters. Our findings, i.e., no major differences between scoring methods were in contrast with several reports on reproducibility based on EBCT scanning. Direct comparison of the findings of these studies with those of other is difficult since the parameters used to indicate reproducibility differ between studies. Furthermore, potentially the prevalence of CAC and its extent may affect reproducibility, as our findings suggest that measurement error increases with increasing CAC levels. Also the sizes of the studies differ which have undeniable effects on reproducibility results. However, our results are similar to those of by Rumberger and Kaufman [33], who compared these three methods and did not find any one method preferable to another in terms of reproducibility of results from consecutive scans in a patient.

Our findings are important in the light of the wider availability of MDCT in most countries compared to EBCT. One reason for that is lower equipment cost. Other advantages of MDCT over EBCT are lesser quantum noise, thinner section thickness, and simultaneous acquisition of four sections (with 16-slice or with 64-slice), which is reported to reduce misregistration artefact. In conclusion, our findings demonstrate that coronary calcium measurements by MDCT are highly reproducible and are not affected by scoring protocols, slice thicknesses and technical factors.

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Coronary calcification as primary outcome, as an alternative for vascular events

The attraction of CAC measurements as a primary outcome variable in observational studies has been recognized widely. A large number of studies have been done on the determinants of CAC. [34;35] The CAC in these studies was used as a marker of vascular risk, based on the findings in several studies that increase in CAC shows a strong and graded relationship with the incidence of cardiovascular disease. [36-38] In addition, CAC has been used as a measure of atherosclerosis in studies that try to make the link between elevated risk factors or change in risk factors, development of atherosclerosis and the occurrence of future events. By way of example, in the current thesis we applied this principle to fill an existing gap between high blood pressure in pregnancy and future vascular risk, by showing that part of this relationship works through atherosclerosis development. In addition, we showed that change in risk factors relates to change in risk of development of atherosclerosis and we make an effort to show that risk factors have different relations with atherosclerosis and coronary heart disease symptoms.

In **chapter 3.1**, we studied the relation of high blood pressure during pregnancy with risk of coronary calcification as a measure of cardiovascular disease risk. Our study population comprised 491 healthy postmenopausal women selected from a population based cohort study. Information on high blood pressure during pregnancy was obtained using a questionnaire. 30.7% of the women reported to have had high blood pressure in pregnancy. Women with a history of high blood pressure during pregnancy had a 57% increased risk of having coronary calcification compared to those women without this condition (OR=1.57, 95% CI 1.04, 2.37). After adjusting for age, the relation did not change (OR=1.64, 95% CI 1.07, 2.53). We concluded that high blood pressure during pregnancy is associated with an increased risk of coronary calcification later in life. Our finding may have important implications for the management of women who have had high blood pressure in pregnancy. Up to now it has been assumed that high blood pressure subsides after pregnancy, and there was no structured follow-up of the women who experienced it. This (lack of) policy needs reconsideration. Novel strategies of follow-up and cardiovascular risk factor reduction in women who have had hypertension in pregnancy must be developed and evaluated for their potential to reduce CVD in the future.

The objective of **chapter 3.2** was to examine the relation between 9 year change in abdominal adiposity, as assessed by waist-to-hip ratio (WHR) and risk of coronary artery calcification. The study population comprised 573 healthy postmenopausal women. Data on coronary risk factors were collected at baseline (1993-1997) and follow-up (2002-2004). At follow-up, the women underwent a multi-detector computed tomography (MDCT) (Philips Mx 8000 IDT 16) to assess coronary calcium. The Agatston score was used to quantify coronary calcium. Change in waist to hip ratio (WHR) was categorized into four groups: low at baseline-low at follow-up (low was defined as below the median); high-low; low-high; and high-high. Our results indicated that compared to subjects whose WHR remained below the median of the distribution at both occasions, those with a WHR above the median at both occasions had a 2.7 [95% CI 1.8-4.0] fold increased risk of CAC. Women whose WHR rose over the 9 year period from below the median to above the median had a 2.5 [95%CI 1.4-4.5] fold increased risk of CAC, whereas the women whose WHR became lower had a non-significant 1.6 fold increased risk of CAC [95% 0.8-3,2]. Our study supports the existing evidence that persistent abdominal adiposity as well as an increase in abdominal fat over time confers an increased risk of coronary atherosclerosis.

Chapter 3.3 examines the association between cardiovascular risk factors and segment specific coronary artery calcification in 573 healthy postmenopausal women. The prevalence of coronary artery calcification (score > 0) was 62.5% (n=348). CAC

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was most common at the left anterior descending (LAD) with a prevalence 44%, next the right coronary artery (RCA) with 23%, the circumflex (CRX) with 19, the left main (LM) with 16% and the posterior descending artery (PDA) with 0.3%. In multivariable regression models age was predominantly related to the calcification in the LAD and CRX, and low density lipoprotein to the LAD. Hypertension, systolic and diastolic blood pressure were related to the calcification of CRX, whereas smoking was predominantly related to the calcification of both LAD and RCA. Our findings showed that the consequences of elevated risk factor levels on development of atherosclerosis appear to be different across the segments of the coronary arteries. To the best of our knowledge, our study is the first to assess such a relation; however, some limitations of our study need to be addressed. The present study is cross-sectional and thus we are not able to directly establish causal relations between risk factors and segment specific coronary calcification. Also, our study population comprised healthy women and thus our results should be confirmed by other studies with a large number of patients in both men and women.

The results of chapter 3 may be of interest to health care providers and clinicians. Prevention strategies which clearly remain a top priority to reduce the high mortality rate of heart disease can benefit of our results. Knowing that certain risk factors or change in risk factors affect coronary atherosclerosis, and perhaps differently may further lead to intensification of prevention efforts.

Coronary calcification and other measure of cardiac ischemic damage

With CAC we obtain information on a person's risk of future vascular events, a finding that is well established. It may be that other markers of cardiac risk strongly relate to CAC, which may have important implication for health care. In **Chapter 4**, we assessed the relation of ECG markers of coronary risk and coronary calcification in 566 postmenopausal women. 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. Left ventricular hypertrophy 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. Coronary artery calcification (CAC) was found in 62% of the women. Among women with CAC, LVH and ECG abnormalities were significantly more common. Compared to women with normal T-axis, in women with borderline or abnormal T-axis, CAC was 3.8 fold more likely to be present [OR=3.8, 95%CI (1.4 – 10.1)]. Similarly, compared to women with normal QRS-T angle, in women with borderline or abnormal QRS-T angle, CAC was 2.2 fold more likely to be present [OR=2.2, 95%CI (1.1 – 4.4)]. However, these relations were attenuated after adjustment for potential confounders. We concluded that among women with high CAC scores, LVH and ECG abnormalities reflecting subclinical ischemia are commonly found. In our study, as one of the first to assess the relation of both LVH and ECG abnormalities with coronary calcification in postmenopausal women, we showed that an increased CAC in healthy postmenopausal women relates to increased presence of LVH and of subclinical myocardial damage as assessed by T-axis and QRS-T abnormalities. The clinical implication of our findings might be ECG abnormalities in postmenopausal women reflect coronary atherosclerosis (CAC scores higher than 0) apart from ischemic changes. Furthermore, healthy postmenopausal women with higher CAC scores appear to have a higher risk of either LVH or ischemic repolarization being present. This may to some extent explain why increased CAC relates to increased CHD risk in the future.

Conclusion

The studies described in this thesis have expanded the evidence on the role of coronary artery calcification in cardiovascular research and prevention.

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Algemene discussie en samenvatting

De doelen van de onderzoekingen weergegeven in dit proefschrift waren:

1. het vaststellen van de reproduceerbaarheid van het meten van calcium in de kransslagaders met behulp van Multi Detector computer tomografie (MDCT), en nagaan in hoeverre de mate van reproduceerbaarheid afhangt van beeldvorming-protocollen en van niveau's van cardiovasculaire risicofactoren.
2. het vaststellen in hoeverre het hebben doorgemaakt van een verhoogde bloeddruk tijdens de zwangerschap gepaard gaat met een toegenomen kans op verkalkingen in de kransslagaders later in het leven
3. het bestuderen in hoeverre verandering in overgewicht, vastgesteld door het meten van de taille-heup omvang, gepaard gaat met een toegenomen kans op verkalkingen in de kransslagaders.
4. het bestuderen van de samenhang tussen risicofactoren voor hart- en vaatziekten en de plaats van de verkalkingen in de kransslagaders.
5. het vaststellen van de verbanden tussen linkerventrikel hypertrofie en repolarisatie stoornissen op het ECG en aanwezigheid van verkalkingen in de kransslagaders.

In dit hoofdstuk worden de bevindingen van het proefschrift samengevat en geplaatst in het huidige stand van zaken op dit gebied.

Inleiding

Coronaire hartziekte is doodsoorzaak nummer één in geïndustrialiseerde landen. Ontwikkeling van verkalkingen in de kransslagaders ligt vaak ten grondslag aan het optreden van coronaire hartziekte. Slagaderverkalking ontwikkelt zich gedurende het leven op een langzame en progressieve manier, en geeft gedurende lange tijd geen aanleiding tot het ontstaan van klachten. Mogelijkheden om slagaderverkalking vast te stellen op een niet-invasieve wijze is de afgelopen jaren onderwerp van cardiovasculair epidemiologisch onderzoek geweest. Vaststelling van verkalkingen in de kransslagader op een valide en reproduceerbare manier is goed mogelijk gebleken met behulp van een electron beam CT (EBCT) scan. De door CT vastgestelde verkalkingen komen goed overeen met tekenen van slagaderverkalking in histologisch onderzoek. Toegenomen verkalkingen in de kransslagaders gaan gepaard met een hogere kans op het krijgen van hart- en vaatziekten. Op basis van deze gegevens zou het meten van kransslagaderverkalkingen in een individu kunnen bijdragen aan de individuele kansschatting op hart- en vaatziekten bij dat individu. Tot op heden komen de meeste gegevens uit onderzoek met een EBCT scanner. In Nederland zijn echter maar twee EBCT scanners, terwijl MDCT scanners door veel meer klinieken gebruikt wordt. Met de MDCT scanner kan eveneens verkalking van de kransslagaders worden vastgesteld, hoewel onderzoek gebruikmakend van deze scanners minder gedaan is.

Niet invasieve methoden om slagaderverkalking vast te stellen heeft wegen geopend naar nieuwe onderzoeksgebieden. Waar traditioneel vasculair etiologisch en prognostisch epidemiologisch onderzoek zich richtte op klinische uitkomsten, kan aan- of afwezigheid van slagaderverkalking thans gebruikt worden als een alternatieve uitkomst voor klinische eindpunten. Deze verandering maakt het mogelijk etiologische onderzoeksvragen te beantwoorden in kleinere groepen van deelnemers en jongere deelnemers, nog voordat symptomen passend bij hart- en vaatziekten zijn opgetreden.

Verkalkingen in de kransslagaders

Het meest belangrijke proces dat ten grondslag ligt aan het optreden van coronaire hartziekte is verkalking van de kransslagaders. De mogelijkheid om het optreden van een coronaire hartziekte voor een individu te voorspellen is op dit moment beperkt en er is duidelijk behoefte deze voorspelling te verbeteren. Eén van de mogelijkheden die

kunnen leiden tot verbetering, is naast het vastleggen van informatie over cardiovasculaire risicofactoren, het meten van kransslagaderverkalking op een niet invasieve manier middels coronair CT. De hoeveelheid kalk op de CT beelden hangt sterk samen met de hoeveelheid kransslagaderverkalking. Inmiddels is aangetoond dat afwezigheid van kalk op de coronaire CT scan gepaard gaat met een lage kans op het optreden van een hartziekte in de nabije toekomst. Daarentegen verhoogt aanwezigheid van veel kalk op de CT beelden de kans op een nieuwe uiting van coronaire hartziekte aanzienlijk. Het lijkt zo te zijn dat het meten van verkalking van de kransslagader middels coronair CT een duidelijk toegevoegde waarde heeft boven op de traditionele risicofactoren in het voorspellen van de kans op een hartziekte in een individu.

Vastleggen van verkalkingen in kransslagaders met MDCT

In het overgrote deel van de onderzoekingen waarin verkalking van de kransslagaders is vastgelegd, werd een EBCT scan gebruikt. Echter, een EBCT scan is slechts zeer beperkt beschikbaar, in Nederland zijn slechts 2 scanners aanwezig. Met een MDCT scanner is het ook mogelijk verkalkingen van de kransslagaders vast te leggen en te kwantificeren. Door recente vernieuwingen in de MDCT scanner, bijvoorbeeld de 16 slice en 64 slice scanner, is men met de MDCT scanner steeds beter in staat verkalkingen in beeld te brengen. In een aantal studies is onderzocht in hoeverre de kalkmetingen met de EBCT scan overeenkomen met die van de MDCT scan. Uit deze studies komt naar voren dat er geen significante verschillen in detectie van kransslagaderverkalking bestaat tussen beide scans.

Meten van kransslagaderverkalking van de beelden

Traditioneel wordt de Agatston score gebruikt voor het kwantificeren van verkalkingen in de slagaders. Er worden metingen verricht aan specifieke segmenten van de kransslagaders waarna de scores van alle segmenten worden opgeteld om te komen tot een ‘totaal’ score. Uit de literatuur is ook naar voren gekomen dat mogelijk een volumemeting dan wel een massameting als maat voor verkalking van de kransslagaders beter zou zijn. Er zijn echter ook studies die hebben laten zien dat er nauwelijks verschil tussen beide methoden zit in termen van reproduceerbaarheid en risicostratificatie. Deze studies zijn gedaan op basis van beeldvorming door een EBCT scan, terwijl dergelijke gegevens voor scan met een MDCT scan nauwelijks voorhanden zijn.

Reproduceerbaarheid van het meten van verkalkingen in de kransslagaders

In hoofdstuk 2.1. hebben wij nagegaan hoe de reproduceerbaarheid is van het meten van verkalkingen van de kransslagaders aan de hand van MDCT beelden. Tevens is onderzocht of de reproduceerbaarheid afhangt van het afbeeldingsprotocol, de ‘slice’ dikte, en risicofactoren van hart- en vaatziekten. Het onderzoek werd gedaan met CT beelden van 199 gezonde postmenopauzale vrouwen. Beeldvorming werd verricht met een 16-MDCT scanner. Beelden hadden een ‘dikte’ van 1.5 mm en 3.0 mm. De beelden werden gelezen door twee ‘lezers’. Eén van de lezers heeft de CT beelden van 52 vrouwen tweemaal gelezen. Als maten voor kransslagaderverkalking werden de Agatston score, de volumescore en de massascore gebruikt. Reproduceerbaarheid werd vastgesteld door het berekenen van de Intraclass correlatie coëfficiënt (ICC) tussen de twee ‘lezingen’, van het gemiddelde verschil tussen twee lezingen, en het absolute gemiddelde verschil tussen twee lezingen. De resultaten gaven aan dat de reproduceerbaarheid goed was met een hoge ICC (>0.95), kleine gemiddelde verschillen tussen twee lezingen, en kleine absolute verschillen tussen twee metingen. Deze resultaten waren hetzelfde voor de verschillende scores en de ‘slice’dikte. De meetfout in de vaststelling van de kransslagaderverkalking hield geen verband met één van de cardiovasculaire risicofactoren. De meetfout nam echter toe met de hoeveelheid kalk.

Dit zou gevolgen kunnen hebben voor de statistische analyse van de resultaten in een onderzoek, afhankelijk van de onderzoeksvraag.

In hoofdstuk 2.2. hebben we de reproduceerbaarheid van het meten van kransslagaderverkalking vastgesteld wat betreft het tweemaal scannen van een deelnemer. Dit onderzoek werd gedaan bij 76 vrouwen bij wie tweemaal een MDCT scan werd gedaan met een kort tijd ertussen. De scans werden gelezen door één 'lezer'. In dit onderzoek was de ICC > 0.98 en de kappa > 0.80, beide duidend op goede reproduceerbaarheid. Geen verschil in reproduceerbaarheid werd gevonden tussen de verschillende scores, noch tussen verschillende beeldvormende protocollen. Het aanvangsniveau van verkalking hield geen verband met het gemiddelde verschil in verkalkingen tussen beide scans. Dit duidt erop duidt dat de meetfout een willekeurig fenomeen was: af en toe een te hoge waarde, af en toe een te lage waarde.

Onze bevindingen zijn van belang omdat de MDCT scanner meer voorkomt in ziekenhuizen dan de EBCT scanner en derhalve dus verkalkingen van de kransslagaders vaker zullen worden vastgelegd met een MDCT scanner. Tevens is van belang zich te realiseren dat de ontwikkeling van de scanner in toenemende mate leidt tot minder ruis in de beelden, dunnere slices, en simultane acquisitie van 4 delen, hetgeen theoretisch zal moeten leiden tot afname van de beeldartifacten.

Verkalking in de kransslagader als alternatief eindpunt voor klinische hartvaatziekte

In verschillende onderzoeken is het heel aantrekkelijk om verkalking in de kransslagader te gebruiken als belangrijkste uitkomst in een studie dan bijvoorbeeld een klinisch eindpunt, zoals een hartinfarct of een beroerte. Om dit te doen is het noodzakelijk dat verkalking in de kransslagaders gepaard gaat met een toename van de kans op hart- en vaatziekten. Dat laatste is consistent in verschillende onderzoekingen aangetoond: er is een geleidelijke toename van het risico met een geleidelijke toename van de aanwezigheid van verkalkingen. Op basis van deze gegevens kan inderdaad verkalking in de kransslagader als eindpunt voor cardiovasculair risico gebruikt worden. Dit principe hebben we toegepast in een aantal hoofdstukken in het proefschrift.

In hoofdstuk 3.1 hebben we bestudeerd of het gehad hebben van een verhoogde bloeddruk tijdens de zwangerschap gepaard gaat met meer verkalkingen in de kransslagaders later in het leven. Het bleek inderdaad dat vrouwen met een verhoogde bloeddruk in de zwangerschap een 57% hogere kans hadden op kransslagaderverkalking dan vrouwen die geen verhoogde bloeddruk hadden tijdens de zwangerschap. Deze bevinding sluit goed aan bij de literatuur waaruit reeds naar voren was gekomen dat vrouwen met een verhoogde bloeddruk tijdens de zwangerschap later vaker hoge bloeddruk hadden en een hogere kans hadden op het krijgen van hart- en vaatziekten. De consequentie van deze consistente bevindingen is dat wellicht onderzocht moet worden of, en zo ja hoe, vrouwen met een verhoogde bloeddruk in de zwangerschap, na de zwangerschap behandeld moeten worden om hun verhoogde risico op hart- en vaatziekten te beteugelen.

In hoofdstuk 3.2 maken we wederom gebruik van kransslagaderverkalking als primaire uitkomst, in plaats van hart- en vaatziekten. In dit hoofdstuk laten we zien dat toename in vetverdeling, gemeten door de taille-heup ratio en opgetreden in de afgelopen 9 jaar, samenhangt met een toename van kransslagaderverkalking, en dus het risico op coronaire hartziekte. Deze vrouwen hadden een 2.5 keer hogere kans op kransslagaderverkalking dan vrouwen wiens taille-heup ratio in deze periode nagenoeg constant gebleven was. Bij vrouwen die gedurende de gehele periode een hoge taille-heup ratio hadden werd een 2.7 verhoogd risico gevonden. Deze bevindingen bevestigen dat een hoge taille-heup ratio gepaard gaat met een toegenomen kans op coronaire ziekte.

In hoofdstuk 3.3 hebben we onderzocht in hoeverre risicofactoren verband houden met verkalkingen in specifieke kransslagaders. Het is bekend dat sommige personen een hartinfarct krijgen gelegen aan de voorwand van het hart, terwijl anderen een onderwandinfarct krijgen. Het is tevens bekend dat bepaalde risicofactoren meer samenhangen met voorwandinfarcten en andere risicofactoren meer met onderwandinfarcten. De verklaring zou kunnen liggen in verschillen in de mate van verkalkingen in de kransslagaders. We vonden in ons onderzoek dat inderdaad bepaalde risicofactoren meer verband hielden met verkalkingen in bepaalde kransslagaders, terwijl andere risicofactoren vooral verbanden lieten zien met verkalkingen in andere kransslagaders. Het onderzoek is echter klein wat betreft aantal deelnemers en deze bevindingen zullen moeten worden bevestigd in toekomstig onderzoek.

Kransslagaderverkalking en andere maten voor cardiale afwijkingen

Hoewel verkalking van de kransslagader van groot belang is voor het optreden van hartziekte, kan aanwezigheid van verkalking ook een gedeeltelijke weerspiegeling zijn van andere afwijkingen aan het hart die ook gepaard gaan met een hogere kans op hartziekte. In hoofdstuk 4 hebben we nagegaan in hoeverre een verdikte hartspier en tekenen van zuurstoftekort in de hartspier, beide vastgesteld door middel van een ECG, samengaan met verkalkingen in de kransslagaders. Inderdaad, bij vrouwen met deze afwijkingen kwam kransslagaderverkalking vaker voor. Met name bij vrouwen met tekenen van zuurstof tekort (repolarisatiestoor-nissen) kwam kransslagaderverkalking 3.8 maal meer voor. Onze bevinding laat zien dat afwijkingen aan het hart die gepaard gaan een toegenomen kans op hartziekte vaak samen voorkomen.

Conclusie

De studies in dit proefschrift dragen bij aan de kennisvermeerdering over de bijdrage van kransslagaderverkalking in epidemiologisch onderzoek naar oorzaken en gevolgen van hart- en vaatziekten.

بحث و خلاصه

هدف از تحقیقات توصیف شده دراین پایان نامه عبارتند از

1- ارزیابی قابلیت تکرار یکسان نتایج اندازه گیری کلسیم عروق کرونر با تصویر برداری Multi-Detector Computed Tomography (MDCT) و بررسی اینکه آیا پروتکل های مختلف اندازه گیری کلسیم عروق کرونر، ضخامت قطع برش وعوامل خطر بیماریهای قلب و عروق بر این قابلیت MDCT اثر می گذارند یا خیر.

2- معین کردن اینکه سابقه فشار خون بالا در طی دوران بارداری ، باعث افزایش خطر کلسیفیکاسیون عروق کرونر که نشان دهنده بیماری قلب و عروقی است در مراحل بعدی زندگی می شود یا خیر .

3- بررسی ارتباط بین تغییرات درآدیپوزیتی شکم که با (WHR) waist-to-hip ratio ارزیابی می شودو خطر کلسیفیکاسیون عروق کرونر.

4- بررسی ارتباط بین عوامل خطر بیماریهای قلب و عروق و کلسیفیکاسیون بخشی مشخص از عروق کرونر.

5- بررسی رابطه هیپرتروفی بطن چپ(left ventricular (LVH hypertrophy واختلالات نوار قلبی (الکتروکاردیوگرافی ECG) که بیانگر آسیب به عضله قلب (میو کارد) می باشند با کلسیفیکاسیون عروق کرونر.

در این فصل یک بحث کلی در مورد علم موجود در زمینه کلسیفیکاسیون شریانهای قلب (عروق کرونر) ارائه می شود که شامل اطلاعات مقدماتی در مورد این پایان نامه و همچنین یافته های اصلی آن می شود.

مقدمه

بیماریهای عروق کرونر(CAD) اولین عامل کشنده در سنین بزرگسالی در جوامع غربی میباشند. پیشرفت تصلب شرایین قلبی (آترواسکلروزیس), مکانیزم اصلی در بر گیرنده است .

آترواسکلروزیس به تدیج پیشرفت می کند و طی سالها به آرامی به وجود می آید و به صورت subclinical باقی می ماند (یعنی بدون تظاهرات بالینی در مدت طولانی). بررسی آترواسکلروزیس به شیوه غیرتهاجمی (non- invasive) موضوع تحقیق چند دهه گذشته بوده است. تشخیص اولیه آسیب عروقی می تواند با استفاده از توموگرافی کامپیوتری (CT) عروق کرونری حاصل شود. توموگرافی کامپیوتری عروق کرونر روشی بسیار دقیق و غیر تهاجمی برای ارزیابی کلسیفیکاسیون عروق کرونر در بیماران میباشد.

مدارک موجود نشان می دهدکه اندازه گیری کلسیم عروق کرونر با CT به خوبی با آنالیز بافت شناسی پلاک مرتبط بوده و اندازه گیری کلسیم عروق کرونر به درستی شدت بیماری را منعکس می کند . علاوه بر این افزایش کلسیم کرونری عامل پیش بینی کننده دقیقی برای حوادث آینده است که می تواند برای عروق کرونری رخ دهد و بنا براین اندازه گیری آن ممکن است برای شناختن خطر بیماری های عروق کرونری مفید می باشد. اگر چه اطلاعات در مورد کلسیم عروق کرونر اساسا از تحقیقاتی بدست می آید که در آنها Electron-beam CT (EBCT) استفاده شده, اماMDCT بیشتر در دسترس قرار داشته و همچنین قابلیت اندزه گیری دقیق کلسیم عروق کرونر را دارد.

ارزیابیهای غیر – تهاجمی کلسیفیکاسیون عروق کرونر, عرصه جدید تحقیقات پزشکی است . قبلا تحقیقات اتیولوژیکی و پروگنوستیک رخداد های بالینی را به عنوان پیامداولیه در نظر میگرفتنداماامروزه وجود یا عدم وجود آترواسکلروزیس می تواند به عنوان پیامداصلی استفاده شود. این تغییر, بررسیهای اتیولوژیک را بااستفاده از تعداد کمتری از شرکت کنندگان و همینطور شرکت کنندگان جوان میسر کرده است.

کلسیفیکاسیون عروق کرونر

مهمترین علت ناخوشی و مرگ و میر در افراد با عوامل خطر آفرین قلبی و عروق, آترو اسکلروزیس کرونری است. توانایی پیش بینی اکثر حوادث عروق کرونری محدوداست. ارزیابی عوامل مشخص خطر آفرین برای شناسایی گروههای پر خطر, نه حساسیت زیادی داشته و نه

بسیار خاص میباشد. بنا براین مشخص است که به استراتژی های جدیدی در پیشگیری اولیه نیاز است تا از تظاهرات بالینی بیماری های عروق کرونر جلو گیری شود. در سالهای اخیر, شیوه دیگری برای شناسایی خطر پیشنهاد شده است:

بررسی غیر تهاجمی کلسیفیکاسیون کرونری

این استراتژی بر محور یک ارتباط نزدیک هیستو پاتولوژی(بافت – آسیب شناسی) بین رسوبات کلسیم کرونری و کل مقدار آترواسکلروزیس کرونری استواراست. نشان داده شده است که کلسیفیکاسیون اولیه در عروق کرونری ناشی از کلسیفیکاسیون در ارگانلهای سلول ماهیچه ای صاف است که فرآیندی فعال می باشد. وجود و مهمتر از آن, مقدار کلسیفیکاسیون عروق کرونر با شدت کلی فرآیند atherosclerotic ارتباط نزدیکی دارد. عدم وجود کلسیفیکاسیون قابل تشخیص عروق کرونر, بیانگر یک احتمال ضعیف در بروز یک حادثه قلبی مهم طی 2 الی 5 سال آینده میباشد (5 الی 10 درصد). در حقیقت, شواهد جدید نشان می دهد مقدار کلسیفیکاسیون عروق کرونر شاید بتواند عامل پیش بینی کننده بهتری برای تخمین میزان مرگ و میر نسبت به فاکتور های خطر سنتی فرامینگهام باشد چرا که وقتی به ارزیابیهای سنتی عوامل خطر اضافه میگردد, ارزش پیشگویی بیشتری خواهیم داشت.

تشخیص کلسیفیکاسیون عروق کرونر بوسیله MDCT

کلسیفیکاسیون دیواره عروق کرونر به عنوان عامل شناخته شده آترواسکلروزیس کرونری تلقی می شود. اکثر اطلاعات موجود در این زمینه بر اساس تصاویر بدست آمده از EBCT حاصل شده است . از آنجائیکه EBCT به ندرت در دسترس است , مثلا فقط یک اسکنر EBCT در هلند وجود دارد, استفاده از MDCT در ارزیابی کلسیم کرونری شایع تر میباشد. پیشرفت های مداوم در تکنولوژی اسکنر MDCT باعث تقویتهای بسیار مهمی در توانایی این اسکنر هادر اندازه گیری کلسیم کرونری شده است. در واقع MDCT برای آشکار سازی و تشخیص مقدار کلسیم عروق کرونر استفاده شده و نشان داده شده است که برای تشخیص کلسیفیکاسیون عروق کرونر حساسیت قابل توجهی دارد.

پیشرفتهای جدید در زمینه ی فناوری های 16و64 برش MDCT, پتانسیل MDCT را افزایش داده است. اما تحقیقات بسیار معدودی به مقایسه صحت و قابلیت تکرار نتایج EBCT با MDCT پرداخته اند. هرچند به مدارک و تحقیقات بیشتری نیاز میباشد ولی شواهد موجود تفاوت های بارزی را بین این دو نوع اسکنر نشان نمی دهند.

درجه بندی کلسیفیکاسیون عروق کرونر

با اینکه برای اندازه گیری مقدار کلسیم عروق کرونر درجه بندی سنتی Agatston (آگاتستون) استفاده گسترده ای داشته است , اما تحقیقات جدید نشان می دهند حجم کلسیم و بخصوص اندازه گیری جرم آن, اندازه گیریهای دقیق و صحیح تری برای تشخیص بیماری میباشند. نیاز به داشتن یک پارامتر ساده با قابلیت تکرار یکسان در اندازه گیری کلسیم عروق کرونر ظاهرا الهام بخش توسعه روشهای دیگر مثل سنجش حجم یا اندازه گیری کمیت جرم مطلق کلسیم بوده است. ظاهرا درجه بندی بر اساس حجم کلسیم, تغیرات کمتری در اندازه گیری حجم و جرم نسبت به سنجش کلسیم در روش آگاتستون دارد.

انتقاد های مربوط به سنجش کلسیم در روش آگاتستون اساسا" مشتق از ماهیت قرار دادی فاکتور وزن سنجی کیفی است که بر اساس رسوب کلسیم بدست می آید. بر عکس, روش اندازه گیری حجم کلسیم ارائه شده توسط کالیستر و همکاران, متکی به استفاده از داده های ایزو تروپی برای استفاده از حجم توده کلسیم که بالاتر از آستانه پیشنهادی است میباشد و نتایج بهتری هم ارائه داده است چرا که مستقل از ضخامت برش می باشد. همینطور اندازه گیری جرم کلسیم با CT که اندازه گیری کمی مقدار این ماده معدنی رسوب کرده در عروق کرونر میباشد تغییرات را بسیار کاهش داده است. اندازه گیری جرم این ماده معدنی با MDCT که با نوار قلبی بیمار هماهنگ و تنظیم شده, بسیار دقیق تر بوده و معادل با مقدار واقعی کلسیفیکاسیون این ماده در بدن است. احتمالا جرم کلسیم پتانسیل بسیاربالایی برای افزایش صحت و قابلیت تکرار اندازه گیری کلسیم کرونر دارد و بنا براین می تواند جانشین روشهای سنتی در آینده شود. با این همه حقیقت این است که قابلیت تکرار نتایج به روش اندازه گیری جرم

توسط CT اسکن های spiral نسبت به روشهای آگاتستون و اندازه گیری حجم کمتر میباشد.

تحقیقات جدید نتایج بهتری را برای تغییرات بین دواسکن و بین دو ناظر و همچنین تغییرات نتایج یک ناظر در زمانهای متفاوت با استفاده از ارزیابیهای کمی(حجم و جرم) در مقایسه با شیوه سنتی آگاتستون نشان می دهند هرچند, رامبرگر و کافمن(Rumberger and Kaufman) این روشهای اندازه گیری کلسیم را مقایسه کرده و تفاوت قابل توجهی در نتایج این روشها نیافتند و درجه بندی مقدار کلسیم به روشهای حجم, جرم یا به شیوه آگاتستون را دارای تغیرات یکسان و معادل 38% گزارش کردند. همچنین رامبرگر و کافمن سعی کردند تا میزان خطر را بین 11940 نفر بررسی کنند و دریافتند اگر شیوه آگاتستون یا اندازه گیری حجم و یا جرم کلسیم استفاده شود, در هر حال میزان خطری مشابه, بیماران را تهدید میکند. با این وجود تحقیقاتی بااستفاده از MDCT اسکن انجام نشده تا به صورت سیستماتیک تفاوت در قابلیت تکرار یکسان نتایج را مابین شیوه آگاتستون, حجم و جرم نشان دهد.

قابلیت تکرار یکسان نتایج اندازه گیریهای کلسیم عروق کرونر

فصل 1-2 به اندازه گیری کلسیم عروق کرونر بااسکنر MDCT پرداخته و همچنین تاثیر پروتکل های متفاوت اندازه گیری کلسیم, ضخامت قطع برش و اثر عوامل خطر آفرین بیماریهای قلب و عروق راروی تغییرات نتایج بین دواسکن و بین دو ناظر و همچنین تغییرات نتایج یک ناظر در زمانهای متفاوت بررسی نموده است.

افراد مورد مطالعه شامل 199 زن سالم بودند که دوران یائسگی را می گذراندند. با استفاده از اسکنر 16-MDCT (16 IDT Mx 8000 فیلیپس) کلسیم کرونر در ضخامتهای قطع برش 3 and 1.5 میلی متراندازه گیری شد. به منظور بررسی قابلیت تکرار یکسان نتایج, تصاویر توسط دو کارشناس بطور مستقل خوانده شدند. از این تعداد 52 اسکن برای بار دوم توسط یکی از کارشناسان خوانده شد و میزان کلسیم عروق کرونر درجه بندی گردید. روشهای آگاتستون, اندازه گیری حجم و جرم برای تعیین مقدار کلسیم کرونری مورد استفاده گرفته و قابلیت تکرار

یکسان نتایج با محاسبه میانگین اختلاف , تفاوت های مطلق و نسبی بین مقادیر بدست آمده از ناظران و تخمین Intra-class correlation coefficient (ICCC) مورد ارزیابی قرار گرفت.

120 شرکت کننده در مطالعه (60/3%) دارای مقادیر مثبت کلسیم در عروق کرونرخود بودند. میانه درجه آگاتستون برای اولین کارشناس معادل با 2.20 بود (range =0 -2019). قابلیت تکرار یکسان نتایج اندازه گیری کلسیم کرونر عالی با ICCC بیشتر از0.95 بود و تفاوت های نسبی, مطلق و میانه تفاوت اندک بود. این یافته ها برای برش 1.5 mm مشابه با 3.0 mm و همچنین برای پروتکل های اندازه گیری حجم , جرم و آگاتستون یکسان بودند.

از عوامل خطر شناخته شده بیماریهای قلب و عروق, هیچکدام ارتباط معنی داری با خطای اندازه گیری نداشتند. با این همه, خطای اندازه گیری با افزایش کلسیم عروق کرونر افزایش یافت. در نتیجه چنین استنتاج کردیم که قابلیت تکرار یکسان نتایج اندازه گیری کلسیم کرونر با استفاده از اسکنر MDCT عالی است و به ضخامت قطع برش و پروتکل های اندازه گیری کلسیم ارتباطی ندارد.

در فصل 2-2, قابلیت تکرار یکسان نتایج MDCT بین دو اسکن را میان 76 زن سالم بررسی نموده و ارزیابی کردیم که آیا این قابلیت تحت تاثیر روشهای متفاوت اندازه گیری کلسیم, ضخامت قطع برش, عوامل خطر بیماریهای قلب و عروق و متغیرهای فنی هست یا نه. بدین منظور در یک جلسه دو بار اندازه گیری کلسیم عروق کرونر با استفاده از MDCT 16 اجرا شد. 55 شرکت کننده (72/4%) دارای مقادیر کلسیفیکاسیون کرونر بیش از صفر به روش آگاتستون (با ضخامت برش 1.5 میلی متر)بودند. قابلیت تکرار یکسان نتایج اندازه گیری کلسیم کرونری بین اسکن ها عالی باICCC بیش از0.98 و مقادیر kappa بالای 0.80 بود. تفاوت مطلق در مقدار کلسیم بین دواسکن با افزایش سطوح کلسیم, افزایش یافت و نشان داد خطای اندازه گیری با افزایش سطح کلسیم زیاد می شود. با این وجود ارتباطی بین میانگین تفاوت دو اسکن و سطح کلسیم دیده نشد تا نشان دهد افزایش در خطای اندازه گیری احتمالا ناشی از طبقه بندی نادرست تصادفی (random misclassification) در درجه بندی کلسیم میباشد. نتایج

برای مقاطع 1.5 میلی متر همانند3 میلی متر و یکسان برای روشهای اندازه گیری حجم, جرم و آگاتستون بود.
چنین نتیجه گرفتیم که قابلیت تکرار یکسان نتایج اندازه گیری کلسیم کرونری با MDCT میان دواسکن با همه الگوریتم های اندازه گیری حجم, جرم و آگاتستون عالی است و تفاوتهای مهمی ما بین روشهای مختلف سنجش وجود ندارد. این قابلیت تحت تاثیر ضخامت قطع برش اسکن, پارامتر های فنی اسکن و تعداد ضربان قلب بیمار نبود.
یافته ها ی ما, یعنی عدم وجود تفاوت مهمی بین شیوه های سنجش مغایر با یافته های گزارش شده ای بود که با EBCT انجام شده است. مقایسه مستقیم این یافته ها با یافته های تحقیقات دیگر مشکل است زیرا پارامتر های مورد استفاده برای نشان دادن قابلیت تکرار یکسان نتایج بین تحقیقات فرق می کند. علاوه بر این احتمالا شیوع و شدت کلسیفیکاسیون عروق کرونر می تواند بر قابلیت تکرار یکسان نتایج اثر بگذارد و یافته های ماهم نشان داد که خطای اندازه گیری باافزایش سطوح کلسیفیکاسیون عروق زیاد می شود.
همچنین تعداد افراد شرکت کننده در تحقیقات متفاوتند که بنوبه خود تاثیرات غیر قابل انکاری را بر نتایج مطالعات خواهد داشت. یافته های ما هم نشان داد که خطای اندازه گیری باافزایش سطوح کلسیفیکاسیون عروق کرونر زیاد می شود.
با این وجود نتایج ما مشابه با نتایجی است که رامبرگر و کافمن با مقایسه پروتکل های مختلف اندازه گیری کلسیم بدست آورده و شیوه ای که بر دیگری ترجیح داشته باشد را پیدا نکردند.
یافته های ما به علت در دسترس بودن گسترده تر MDCT دراکثر کشور ها در مقایسه با EBCT, ازاهمیت زیادی برخوردار است. کمتر بودن هزینه های اسکن یکی از عوامل مهم این امر میباشد. مزایای دیگر MDCT بر EBCT این است که نویز کوآنتومی کمتری دارد و ضخامت قطع برش اسکن باریک تر است .
بطور خلاصه، یافته های ما نشان می دهد قابلیت تکرار یکسان نتایج اندازه گیری کلسیم کرونر با اسکنر MDCT بسیار خوب بوده و تحت تاثیر پروتکل های اندازه گیری کلسیم, ضخامت برش و متغیرهای فنی اسکن نیست.

کلسیفیکاسیون کرونر به عنوان پیامد اولیه و جایگزینی مناسب برای حوادث عروق کرونر

کلسیفیکاسیون کرونر به عنوان یک پیامداولیه در تحقیقات صورت گرفته پزشکی، بسیار مورد توجه واقع شده است. مطالعات فراوانی در رابطه با شناسایی عوامل ایجاد کننده کلسیفیکاسیون عروق کرونر صورت گرفته است. در این تحقیقات کلسیفیکاسیون کرونر بعنوان مارکری برای خطرات عروقی استفاده شده است. بر اساس یافته های چندین تحقیق دیگر افزایش کلسیفیکاسیون عروق کرونر یک رابطه قوی با بروز بیماریهای قلب و عروق نشان می دهد.

علاوه بر این، کلسیفیکاسیون عروق کرونر بعنوان تخمینی از آترواسکلروزیس در نظر گرفته شده است تا ارتباط بین افزایش و یا تغییر در عوامل خطر, پیشرفت آترواسکروزیس و وقوع حوادث قلبی عروقی آینده شناسایی شود. در این پایان نامه، این اصل را برای پر کردن خلا موجود بین فشار خون بالا در هنگام بار داری و خطرات عروقی آینده اعمال کردیم و نشان دادیم که بخشی از این رابطه ازطریق پیشرفت اترواسکلروزیس قابل بیان میباشد. علاوه بر این، نشان دادیم که تغییر در عوامل خطر با تغییر در خطر پیشرفت اترواسکروسیس ارتباط دارد و سعی کردیم تا مشخص شود عوامل خطرآفرین روابط متفاوتی با نشانه های بیماری های عروق قلبی و آترواسکروزیس دارند.

در فصل 3.1 رابطه فشار خون بالا در زمان بارداری را با خطر کلسیفیکاسیون عروق کرونر بعنوان تخمینی از خطربیماری قلبی عروقی بررسی کردیم. جمعیت مورد مطالعه ما از 491 زن یائسه سالم تشکیل شده بود. اطلاعات در مورد فشار خون بالا طی بارداری با ارائه یک پرسشنامه بدست آمد. 30.7 % از زنان در دوران بارداری خود تجربه فشار خون بالا را گزارش نمودند. زنانی که سابقه فشار خون بالا طی بارداری داشتند، 57 درصد نسبت به زنانی که این شرایط را نداشتند, در معرض افزایش خطر کلسیفیکاسیون عروق کرونر بودند. (OR=1.57, 95% CI 1.04 – 2.37) پس از اصلاح نقش سن, در این رابطه تغییری حاصل نشد.

(OR=1.64 95% CI1.07 – 2.53) بنا بر این چنین نتیجه گرفتیم که فشار خون بالا طی دوران بار داری در آینده افزایش خطر کلسیفیکاسیون کرونری را به همراه دارد.

یافته های ما احتمالا کاربردهای مهمی برای ارزیابی زنانی که فشار خون بالا در بارداری داشته اند، خواهد داشت. تا به امروز تصور می شده است که فشار خون بالا پس از دوران بار داری فروکش می کند و یک برنامه پیگیری مدون برای زنانی که این فشار خون را تجربه می کنند ،وجود نداشته است. این خط مشی و باور باید تجدید نظر شود. می بایست استراتژی های جدید بمنظور پیگیری و همچنین کاهش عوامل خطر قلبی-عروقی در زنانی که طی دوران بار داری، فشار خون بالا را تجربه کرده اند، توسعه یابد و تاثیر کاربری این استراتژیها در کاهش بیماریهای قلبی-عروقی در آینده، مورد ارزیابی قرار بگیرد.

هدف از فصل 3.2 بررسی ارتباط موجود بین تغییر 9 ساله در آدیپوز شکمی (چربی شکمی یا مرکزی) و خطر کلسیفیکاسیون عروق کرونر میباشد. در این مطالعه 573 زن سالم که دوران یائسگی را می گذراندند شرکت کردند. اطلاعات مربوط به عوامل خطر آفرین کرونری در ابتدای مطالعه (1997-1993) و زمان پیگیری مجدد (2004-2002) گرد آوری شد. در زمان پیگیری زنان تحت MDCT قرار گرفتند تا کلسیم عروق کرونر آنان اندازه گیری شود. روش آگاتستون برای اندازه گیری کلسیم عروق کرونر استفاده شد. بر اساس مقادیر (WHR) waist to hip ratio در زمانهای بدو مطالعه و پیگیری،افراد مورد مطالعه به چهار گروه تقسیم شدند. مقادیر WHR پایین تر از مقدار میانه توزیع بعنوان کم در نظر گرفته شد.

	ابتدای مطالعه	*زمان پیگیری*
1-	کم	کم
2-	زیاد	کم
3-	کم	زیاد
4-	زیاد	زیاد

نتایج ما نشان داد در مقایسه با افرادی که WHR آنها زیر مقدار میانه توزیع در دو مدت زمانی بدو مطالعه و پیگیری

بود، افرادی که WHR بالای مقدار میانه توزیع در دو موقعیت زمانی داشتند *(4.0 – 1.8 95% CI)* 2.7 برابر بیشتر درمعرض خطر کلسیفیکاسیون عروق کرونر قرار داشتند وافرادی که WHR آنها طی این 9 سال از مقادیر زیر میانه افزایش یافته و به مقادیر بالاتر از میانه رسید، *(4.5 – 1.4 95% CI)* 2.5 برابر بیشتر در معرض خطر کلسیفیکاسیون عروق کرونر بودند.

شواهدی وجود دارد که نشان می دهد آدیپوزیتی شکمی مداوم (persistent abdominal adiposity)و همینطور افزایش در چربی شکمی در طول زمان باعث افزایش خطر آترواسکلروزیس کرونری می شود. نتایجی که ما بدست آوردیم هم صحت این شواهد را تائید می کند.

فصل 3.3 ارتباط بین فاکتور های خطرآفرین بیماریهای قلبی عروقی و کلسیفیکاسیون بخش خاصی از عروق کرونر را در 573 زن یائسه بررسی می کند. شیوع کلسیفیکاسیون عروق کرونر (score > 0) 62.5 درصد بود (n=348). رگ کرونری قدامی نزولی چپ (LAD) left anterior descending بیشترین مقدار کلسیفیکاسیون را با شیوع 44 درصد داشت. پس از آن رگ کرونری راست (RCA) right coronary artery با شیوع 23 درصد، سیرکمفلکس (CRX) circumflex با 19 درصد، شاخه اصلی چپ (LM) left main با 16 درصد و رگ کرونری خلفی نزولی (PDA) posterior descending artery با شیوع 0.3 درصدکلسیفیکاسیون عروق کرونر قرار داشتند.

در مدل های رگرسیون چند متغیره، سن بطور غالب با کلسیفیکاسیون LAD و CRX، و لیپوپروتنین با دانسیته پایین (LDL) با کلسیفیکاسیون LAD ارتباط داشت. فشار خون بالای دیاستولی و سیستولی بطور معنی دار با کلسیفیکاسیون CRX مربوط می شد, در حالیکه سیگار کشیدن بیشتر با کلسیفیکاسیون LADوRCA ارتباط پیدا می کرد. یافته های ما نشان داد که پیامد های افزایش سطوح فاکتور های خطر آفرین روی پیشرفت آترواسکلروزیس ظاهرا در بخشهای مختلف عروق کرونری، فرق دارد.

مطالعه ما، اولین تحقیقی است که این رابطه را مورد بررسی قرار می دهد. اگر چه برخی از محدویتهای این مطالعه هم بایستی در نظر گرفته شود. این تحقیق یک مطالعه مقطعی میباشد و بنابراین ما نتوانستیم بطور مستقیم رابطه علیتی را بین عوامل خطر آفرین

وکلسیفیکاسیون در بخشهای خاص عروق کرونری مشخص کنیم. همچنین، جمعیت مورد مطالعه ما از زنان سالم تشکیل شده بود وبنابراین نتایج مطالعه ما باید با تحقیقات دیگر که تعداد بیماران بیشتری داشته و هر دو جنس را(زن و مرد) مورد بررسی قرار میدهند، تایید شود. تنایج فصل 3 شاید مورد توجه پزشکان و متخصصان علوم پیشگیری و بهداشت قرار بگیرد. استراتژی های پیشگیری که به وضوح در اولویت اول جهت کاهش نرخ بالای مرگ و میر ناشی از بیماریهای قلب و عروق قرار دارند، می توانند از نتایج ما بهره مند گردند. با شناختن عوامل خطر خاص بیماریهای قلب و عروق و نقش تغییر این عوامل خطر بر آترواسلکروزیس کرونر،و شاید به گونه ای متفاوت باعث تقویت تلاشهایی شود که در جهت جلو گیری از این بیماریها پیش می روند.

کلسیفیکاسیون عروق کرونر و دیگر فاکتورهای نشاندهنده ضایعات ایسکمیک قلبی

کلسیفیکاسیون عروق کرونر اطلاعاتی در مورد خطر ابتلا به بیماریهای قلبی عروقی در آینده بدست میدهد. دیگر فاکتورهای نشاندهنده خطر بیماریهای قلبی ممکن است ارتباطی قوی با کلسیفیکاسیون عروق کرونر داشته باشند که بنوبه خود میتواند کاربردهای مهمی در مراقبتهای پیشگیری و بهداشت داشته باشد.

در فصل 4 به بررسی رابطه تغییرات نوار قلبی نشاندهنده خطر ضایعات ایسکمیک قلبی و کلسیفیکاسیون عروق کرونر روی 566 زن یائسه پرداختیم. اطلاعات در مورد هیپرتروفی بطن چپ (LVH) و اختلالات رپلاریزاسیون(محور T و زاویه QRS-T) با استفاده از نوار قلبی (الکترو کاردیوگرافی) بدست آمد.

Modular ECG analysis system (MEANS) برای ارزیابی اختلالات نوار قلبی استفاده شد. هیپرتروفی بطن چپ در2.7 درصداز زنان(پانزده نفر) یافت شد. شیوع اختلالات T-axis 6 درصد (n=34) بود. در حالیکه 8.5 درصد (n=48) افراد مطالعه اختلالات زاویه QRS-T را داشتند و کلسیفیکاسیون عروق کرونری در 62 درصد زنان یافت شد.

در میان زنان با کلسیفیکاسیون عروق کرونر، اختلالاتنوار قلبی و هیپرتروفی بطن چپ بطور معنی داری شایعتر بود. در مقایسه با

زنانی که محور T نرمال داشتند،در زنان با اختلالات T-axis،
کلسیفیکاسیون عروق کرونر 3.8 برابر بیشتر بود.
[OR=3.8, 95% CI (1.4 – 10.1)] همینطور،در مقایسه با زنانی که زاویه
QRS-T نرمال داشتند،در زنان با اختلالات زاویه QRS-T،
کلسیفیکاسیون عروق کرونر 2.2 برابر بیشتر بود.
[OR=2.2, 95% CI (1.1 – 4.4)] با این وجود این روابط پس از اصلاح مخدوش کننده های بالقوه، ضعیفتر شدند. ما نتیجه گرفتیم زنانی که مقدار کلسیفیکاسیون عروق کرونر بیشتری داشتند، هیپرتروفی بطن چپ و اختلالات نوار قلبی که نشاندهنده ایسکمی تحت بالینی است بیشتر یافت می شوند. در این مطالعه که یکی از اولین تحقیقهای انجام شده روی رابطه هیپرتروفی بطن چپ و اختلالات نوار قلبی با کلسیفیکاسیون کرونری در زنان یائسه میباشد، نشان دادیم افزایش کلسیفیکاسیون عروق کرونر در زنان یائسه با شیوع بیشتر هیپرتروفی بطن چپ و آسیب تحت بالینی میو کارد که با اختلالات نوار قلبی بررسی میگردند، همراه میباشد.

مفهوم بالینی یافته های ما،اختلالات نوار قلبی را جدای از تغییرات ایسکمی، منعکس کننده کرونری آترواسکلروزیس (مقدار کلسیم بیشتر از صفر) میداند. علاوه بر این زنان یائسه با مقادیر بیشتر کلسیفیکاسیون عروق کرونر، در معرض خطر بیشتری برای ابتلا به هیپرتروفی بطن چپ و اختلالات نوار قلبی قرار داشتند . این مهم می تواند تا حدی توضیح دهد که چراافزایش کلسیفیکاسیون عروق کرونر باافزایش خطر بیماریهای قلبی عروقی در آینده ارتباط دارد.

نتیجه گیری

تحقیقات توصیف شده در این پایان نامه شواهد مربوط به نقش کلسیفیکاسیون عروق کرونر در تحقیقات بیماریهای قلبی – عروقی و پیشگیری از این بیماریها را توسعه داده است.

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Publications

1. **S.Sabour**, F.Atsma, A.Rutten, D.E.Grobbee, W.P.Mali, M.Prokop, M.L.Bots; Reproducibility of coronary calcium measurements using Multi Detector-Row Computed Tomography (MDCT) Accepted (Journal of Clinical Epidemiology,2006)
2. **S.Sabour**, A.Rutten, Y.T.van der Schouw, F.Atsma, D.E.Grobbee, W.P.Mali, M.E.L.Bartelink, M.L.Bots, M.Prokop; Inter-scan reproducibility of coronary calcium measurements using Multi Detector-Row Computed Tomography (MDCT). In press (European journal of epidemiology , 2007)
3. **S.Sabour,** A. Franx, A. Rutten, M. E. L. Bartelink, D.E. Grobbee**,** M. Prokop, Y.T.van der Schouw, M. L. Bots; High blood pressure in pregnancy and risk of coronary calcification later in life. Hypertension, 2007;49:813-817
4. **S.Sabour,** A. Rutten, M. E. L. Bartelink, D.E. Grobbee**,** M. Prokop, Y.T.van der Schouw, M. L. Bots; Change in abdominal adiposity and coronary calcification. Submitted
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Presentations

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28 Feb - 03 Mar 2007	47th Annual Conference of Cardiovascular Disease Epidemiology, American Heart Association, Orlando, Florida, USA
28 Jun – 02 July 2006	European Congress of Epidemiology, Utrecht, The Netherlands
27 Feb – 03 Mar 2006	European Congress of Radiology, Vienna, Austria
14 – 17 Dec 2004	14th Iranian Congress of Ophthalmology, Tehran, I.R. Iran