Coronary and Aortic Calcifications Inter-relationship in Stable Angina Pectoris: A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) – Israeli Spiral Computed Tomography Substudy

Alon Eisen MD[1], Alexander Tenenbaum MD[1], Nira Koren-Morag PhD[1], David Tanne MD[2], Joseph Shemesh MD[1], Avivit Golan MD[3], Enrique Z. Fisman MD[1], Michael Motro MD[1], Ehud Schwammenthal MD[1] and Yehuda Adler MD[1,3]

[1]Cardiac Rehabilitation Institute and [2]Stroke Center, Department of Neurology, Sheba Medical Center, Tel Hashomer, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[3]Leumit Health Services, Israel

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Abstract

Background: Coronary heart disease and ischemic stroke are among the leading causes of morbidity and mortality in adults, and cerebrovascular disease is associated with the presence of symptomatic and asymptomatic CHD. Several studies noted an association between coronary calcification and thoracic aorta calcification by several imaging techniques, but this association has not yet been examined in stable angina pectoris patients with the use of spiral computed tomography.

Objectives: To examine by spiral CT the association between the presence and severity of CC and thoracic aorta calcification in patients with stable angina pectoris.

Methods: The patients were enrolled in ACTION (**A C**oronary Disease **T**rial **I**nvestigating **O**utcome with **N**ifedipine GITS) in Israel. The 432 patients (371 men and 61 women aged 40–89 years) underwent chest CT and were evaluated for CC and aortic calcification.

Results: CC was documented in 90% of the patients (n=392) and aortic calcification in 70% (n=303). A significant association ($P < 0.05$) was found between severity of CC and severity of aortic calcification (as measured by area, volume and slices of calcification). We also found an association between the number of coronary vessels calcified and the presence of aortic calcification: 90% of patients with triple-vessel disease (n=157) were also positive for aortic calcification ($P < 0.05$). Age also had an effect: 87% of patients ≥ 65 years (n=219) were positive for both coronary and aortic calcification ($P = 0.005$) while only 57% ≤ 65 (n=209) were positive for both ($P = 0.081$).

Conclusions: Our study demonstrates a strong association between the presence and severity of CC and the presence and severity of calcification of thoracic aorta in patients with stable angina pectoris as detected by spiral CT.

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Coronary heart disease and ischemic stroke are among the leading causes of morbidity and mortality in adults. Both diseases share common risk factors and pathogenesis, i.e., atherosclerosis. The presence of cerebrovascular disease is associated with the presence of symptomatic and asymptomatic CHD [1]. Furthermore, a higher severity of angina pectoris is associated with an increased risk of ischemic stroke [2].

Coronary calcium is associated with atherosclerosis and can be diagnosed either by invasive techniques such as angiography or by non-invasive techniques, e.g., spiral computed tomography [3]. Calcium is often found in the aorta as well but in contrast to the atherosclerotic nature of coronary calcification, aortic calcification can be divided into two pathophysiological processes: intimal, which is mostly atherosclerotic, and medial, which is not atherosclerotic [4].

A few studies in recent years have noted an association between CC demonstrated on angiography and CT thoracic aorta calcification [5,6]. This association was also shown in hypertensive patients with the use of spiral CT [7]. However, a possible association between the presence and severity of CC and thoracic aorta calcification in patients with stable angina pectoris has not been investigated. The purpose of the present study, therefore, was to examine by spiral CT the inter-relationship between the presence and severity of CC and thoracic aorta calcification in patients with stable angina pectoris enrolled in ACTION (**A C**oronary Disease **T**rial **I**nvestigating **O**utcome with **N**ifedipine GITS) in Israel.

Patients and Methods

Study population

This research studied the spiral CT scans of 569 patients with stable angina pectoris participating in the ACTION study in Israel. ACTION was a multi-center randomized placebo-controlled double-blind trial that compared the effect on clinical outcomes of long-acting nifedipine or placebo in patients with angina pectoris attributable to coronary disease. A detailed description of the trial has been published elsewhere [8]. In brief, three categories of ambulatory patients aged 35 years or older, had angina pectoris that had been stable for at least 1 month and needed

CHD = coronary heart disease
CC = coronary calcification

oral or transdermal treatment either to treat or prevent anginal attacks, were eligible for the study: a) those with a history of myocardial infarction, b) those with angiographic coronary artery disease but no history of myocardial infarction, and c) those with a positive exercise test or perfusion defect who had never had coronary angiography and had no history of myocardial infarction. Locally measured left ventricular ejection fraction had to be at least 40%. Reasons for exclusion were: overt heart failure, any major cardiovascular event or intervention within the preceding 3 months, planned coronary angiography or intervention, known intolerance to dihydropyridines, clinically significant valvular or pulmonary disease, unstable insulin-dependent diabetes mellitus, any gastrointestinal disorder that could compromise absorption of nifedipine GITS or passage of the tablet, any condition other than coronary artery disease that limited life expectancy, symptomatic orthostatic hypotension or supine systolic blood pressure of 90 mmHg or less, systolic blood pressure of ≤ 200 mmHg, diastolic blood pressure ≤105 mmHg or both, creatinine more than twice the local upper limit of normal, and alanine or aspartate transaminase greater than three times the local upper limit of normal.

Over the course of 6 years, 569 patients underwent chest CT to measure CC and thoracic aorta calcification. The primary CT scans in the ACTION trial constitute the basis of this study. The study protocol was approved by the Institutional Review Board (Helsinki Committee). After excluding patients for technical reasons (sub-optimal images, pacemakers, and coronary artery bypass grafting staples interference on CT), a total of 432 patients (371 men and 61 women aged 40–89 years) were included in the study.

Spiral CT: image acquisition

CT scan was performed according to a previously described protocol [3] using a commercially available double-helical scanner (Twin, Philips Ltd.) and spiral scanning mode (without injection of contrast material). Scanning time was 1 second for two continuous 2.5 mm sections and 15–22 seconds for the entire zone of interest. Examination was performed during a single unforced withheld inspiration. During helical scanning, with the tube rotating at 1 revolution per second and the table moving at 5 mm/sec with a 1:1 scanning pitch, images were obtained with an effective section thickness of 3.2 mm (a nominal section width of 2.5 mm) and a reconstruction increment of 1.5 mm (overlapping section method). Scanning was performed with 120 kVp and 210 mAs, standard resolution, and a 43 cm field of view. For scoring of calcification, the 40 most cephalic contiguous sections were selected, starting at the level of the first visible coronary artery – left main coronary artery or left anterior descending. This provided 6 cm coverage of the proximal portion of the coronary tree including the ascending aorta and proximal 10 cm of the descending aorta without the aortic arch.

Determination of coronary calcification

A calcific lesion was defined as an area within a coronary artery with CT attenuation above a threshold of 90 HU, and covering an area of at least 0.5 mm^2. Regions of interest around all lesions were placed by an experienced reader and were automatically analyzed by the Philips software. A modification of Agatston's scoring method [9] was applied with a threshold of 90 HU instead of 130 HU, and attenuation factor for each lesion was determined: 1 = 90–199 HU, 2 = 200–299 HU, 3 = 300–399 HU, and 4 ≥ 400 HU. Coronary calcium score for each region of interest was calculated automatically by multiplying the attenuation factor by the area. The total calcium score was the combined sum of the lesion scores for all sections. Severity of calcification was also assessed by the area of calcification and its volume.

Determination of aortic calcification

A positive test for the presence of calcification of the aorta was defined as the presence of at least one detectable lesion of calcified deposit within the area of the aorta wall. The severity of the calcification was assessed by the number of consecutive slices in which calcium was present and by the area and volume of calcification (measured using the modified Agatston's scoring method [9] with a threshold of 90 HU instead of 130 HU).

Risk factors

All patients suffered from stable angina pectoris, and the following cardiovascular risk factors were evaluated: hypertension, diabetes mellitus, hypercholesterolemia, smoking, and positive family history of CHD. Hypertension was defined as blood pressure ≥ 140/90 mmHg; diabetes mellitus was defined as hyperglycemia requiring previous or ongoing pharmacological therapy; hypercholesterolemia was defined as a total cholesterol level of > 200 mg/dl; smoking was defined as > 10 pack-years of cigarette use.

Statistical methods

The data were analyzed using SPSS statistical software version 12.0. The association between categorical variables was assessed using Pearson's chi-square test and *P* for trend. Continuous variables were analyzed for differences between groups using analysis of variance (ANOVA) and by independent *t*-test. The following variables were included for assessing difference between groups: age, gender, hypertension, diabetes mellitus, hypercholesterolemia, smoking, and family history of CHD. Correlations between severity of CC and severity of aortic calcification (as measured by area, volume and slices of calcification) were assessed by Spearman correlation.

Results

Altogether, 432 patients with stable angina pectoris were included in the study (371 men and 61 women, age range 40–89 years). CC was present in 91% (n=392) and aortic calcification in 70% (n=303) [Table 1]. There were no inter-group differences between patients with and without CC regarding risk factors for atherosclerosis, but patients with CC were older (65 ± 9 vs. 62 ± 10 years, $P < 0.03$). Also patients with aortic calcification were older (68 ± 8 vs. 59 ± 9, $P < 0.001$) and smoked less frequently

Table 1. Presence of calcifications in the study patients

Calcification variable	No. of patients (%)
LAD calcification	375 (86.8%)
LCX calcification	260 (60.2%)
RCA calcification	267 (61.8%)
Total coronary calcification	392 (90.7%)
Ascending aortic calcification	209 (48.3%)
Descending aortic calcification	254 (58.8%)
Total aortic calcification	303 (70.1%)

LAD = left anterior descending, LCX = left circumflex, RCA = right coronary artery

(15% vs. 25%, $P = 0.021$) than their counterparts without aortic calcification. All other inter-group differences in risk factors for atherosclerosis were not statistically significant. Table 2 shows the clinical characteristics of patients in accordance with their coronary and aortic calcification. A significant association was found between the presence of CC and aortic calcification [Table 3].

We divided the patients into five subgroups according to CC severity and examined the association between CC severity groups and the concordant aortic calcification variable. We found significant associations between the CC area and the aortic calcification area ($P = 0.004$) and also between CC and aortic calcification volumes ($P = 0.02$). These associations were demonstrated in the ascending aorta as well as in the descending aorta. Descending aorta calcification values were higher then ascending values. Furthermore, there was a significant association between coronary calcium score and aortic calcification mean score. ($P < 0.001$). Moreover, we found a strong association between the number of calcified coronary arteries and the presence of the aortic calcification: for example, 82.6% of patients with three calcified coronary arteries (n=157) also presented aortic calcification [Figure 1] (P for trend < 0.05).

The association between CC and aortic calcification was age-related: 80% of the patients ≥ 65 years old (n=176) had both coronary and aortic calcification ($P = 0.005$), while only 57% of the patients ≤ 65 (n=106) demonstrated both calcifications ($P = 0.081$). There were no significant difference between men and women regarding the association between coronary and aortic calcification ($P = 0.179$).

Table 2. Clinical characteristics of patients in accordance with their coronary and aortic calcification

	Coronary calcification +	Coronary calcification	*P*	Aortic calcification +	Aortic calcification	*P*
Gender(M/F)	337/55	34/6	NS	258/45	113/16	NS
Age (mean ± SD) (yrs)	65 ± 9	62 ± 10	< 0.03	68 ± 8	59 ± 9	< 0.001
Hypertension	187 (61.1%)	21 (61.8%)	NS	144 (63.7%)	64 (56.1%)	NS
Diabetes mellitus	94 (30.7%)	7 (20.6%)	NS	69 (30.5%)	32 (28.1%)	NS
Smoking	55 (18%)	8 (24%)	NS	34 (15%)	29 (25%)	0.021
Family history of CHD	146 (48.9%)	13 (39.4%)	NS	106 (48.2%)	53 (47.3%)	NS
Hypercholesterolemia	237 (77.7%)	23 (67.6%)	NS	172 (76.4%)	88 (77.2%)	NS

Table 3. Presence of coronary calcifications in patients with and without aortic calcifications

	Aortic calcification +	Aortic calcification –	*P*
LAD calcification	274 (73.1%)	101 (26.9%)	0.001
LCX calcification	204 (78.5%)	56 (21.5%)	≤ 0.001
RCA calcification	213 (79.8%)	54 (20.2%)	≤ 0.001
Total coronary calcification	285 (72.7%)	107 (27.3%)	≤ 0.001

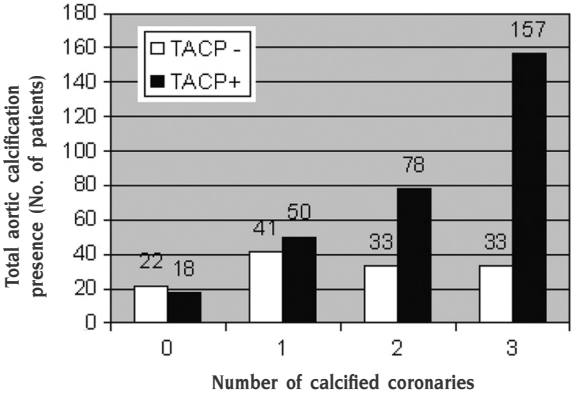

Figure 1. Association between number of calcified coronaries and total aortic calcification presence (TACP), P for trend < 0.05

Discussion

This is the first report on the inter-relationship between the prevalence and severity of CC and thoracic aorta calcification in patients with stable angina pectoris enrolled in the ACTION trial in Israel. We found a strong association between the presence and severity of CC and the presence and severity of aortic calcification, as detected by spiral CT, in stable angina pectoris patients. Our data are in line with previous studies using different techniques such as X-ray, angiography and electron beam CT [5,6].

The association found in this study may have important clinical relevance. The presence of cerebrovascular disease is associated with the presence of CHD [1]. In the Framingham study, a history of CHD increased the risk of stroke almost threefold [10]. Severity of angina pectoris class also correlates with ischemic stroke risk [2]. Cerebrovascular disease is a significant factor in all cardiovascular mortality and is the leading cause of long-term severe disability, therefore it is imperative to define and isolate its risk factors and antecedents. Thoracic aorta atherosclerosis has been shown to be an important cause of cerebrovascular mortality [11-13] and is associated with hypertension and an increased prevalence of myocardial infarction [14].

The relation between atherosclerosis and calcification of the thoracic aorta is complex. In contrast to the atherosclerotic nature of CC, aortic calcification can be divided into two pathophysi-

ological processes: intimal, which is mostly atherosclerotic, and medial, which is not atherosclerotic [4]. Intimal calcification occurs in the internal elastic lamina as part of the atherosclerotic plaque. It is associated with inflammatory cells, lipid and vascular smooth muscle cells and it has a spotted appearance. In contrast, medial calcification occurs as an independent process and is usually associated with several conditions such as aging, end-stage renal disease, diabetes, neuropathy, and several rare genetic syndromes. It is associated with the presence of elastin and vascular smooth muscle and is usually seen as linear deposits in the elastic lamellae. The effects of medial calcification on cardiac and vascular function are not fully understood. Yet, calcification of the aorta, detected on chest X-ray, has been independently associated with an increased risk of CHD severity and extent [5].

Clinical implications

Spiral CT is a rapidly evolving and effective non-invasive technique for cardiac imaging that has gained popularity in recent years. This modality has improved greatly since the development of multi-row detector CT scanners, which have faster acquisition speed. The detection of aortic calcification on spiral CT indicates the higher probability of coronary artery atherosclerosis and should be further evaluated. Furthermore, the presence of coronary artery disease might suggest the presence of an atherosclerosis process in the aorta, which would support further evaluation of the thoracic aorta. Spiral CT, especially when contrast-enhanced, is a useful modality for non-invasive detection of protruding aortic atheromas [11,12], an important risk factor for ischemic stroke. Newer and faster multi-slice spiral CT modalities have high sensitivity for detecting calcium deposits, and are therefore especially useful for assessing the presence and extent of such calcium deposits in the aorta.

Conclusions

Our study demonstrates a strong association between the presence and severity of calcification of the coronary arteries and the presence and severity of calcification of thoracic aorta in patients with stable angina pectoris as detected by spiral CT. This finding can partially explain the inter-relationship between ischemic coronary artery disease, atherosclerosis and cerebrovascular disease.

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Correspondence: Dr. Y. Adler, Cardiac Rehabilitation Institute, Sheba Medical Center, Tel Hashomer 52621, Israel.
Phone: (972-3) 530-2361
Fax: (972-3) 530-3084
email: yadler@leumit.co.il

Feeling gratitude and not expressing it is like wrapping a present and not giving it

William Ward (1921-1994), U.S. writer

Capsule

A new regulator in RA

Rheumatoid arthritis (RA) is an autoimmune condition that leads to joint inflammation. Lee et al. have identified a new regulator of the cellular organization of the synovium that might also provide a potential therapeutic target for inflammatory arthritis. Mice lacking the cell adhesion molecule cadherin 11 showed significantly reduced growth of the synovium and were resistant to the development of an experimentally induced RA-like condition. Joint inflammation in mice could be inhibited with a monoclonal antibody to cadherin-11.

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Eitan Israeli