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Coronary calcium score — a non-invasive method for the detection and quantification of coronary atherosclerosis

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Abstract

Cardiovascular diseases pose a significant medical problem in the developed world. Coronary heart disease (CHD) is the most common of these and is the cause of more than half the cases of heart failure in the general population below 75 years of age. Atherosclerosis lies at the basis of the majority of CHD cases. As the early detection of asymptomatic CHD may lower patient morbidity and mortality, there is an ongoing search for non-invasive diagnostic techniques. Computed tomography, which enables coronary artery calcification to be assessed, is one of these. Examples of the implementation of a calcium score, both in asymptomatic patients and in patients with diagnosed CHD, are presented in this paper. (Folia Cardiol. 2006; 13: 459–464)

Key words: coronary heart disease, computed tomography, coronary artery calcium score

Introduction

In view of their prevalence and related costs, cardiovascular diseases pose a significant medical problem in the developed world. Coronary heart disease (CHD) is the most common of them and is the cause of more than half the cases of heart failure in the general population below the age of 75 [1, 2]. Cardiovascular diseases do not predominate as a cause of death until the age of 45 in males and 65 among females. In 2001, 173 809 people died of cardiovascular diseases in Poland and the main cause of these deaths was coronary heart disease, including myocardial infarction, totalling 53 800 and 28 100 deaths respectively, which amounted to 31% and 16% of deaths from all circulatory causes [3].

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In more than 85% of cases atherosclerosis lies at the basis of CHD, an inflammatory-degenerative process which takes place in the internal membrane of the large and medium-caliber arteries and is responsible for the formation of atherosclerotic plaques in the vessel lumen. Coronary artery calcification can already be detected in 10–20-year olds. The deposition of hydroxyapatite is responsible for the calcification process. So far it has been believed that calcium accumulations are the result of the degenerative process, but the latest research indicates that an active process, perhaps a reaction to injury, may be responsible for their creation [4].

In 1995 the American Heart Association proposed a macroscopic assessment of atherosclerotic plaques, on the basis of which they were divided into early plaques (type I–III), observed in early childhood, distinguished from reversible and complex plaques (type IV–V), characterised by progressive capsule fibrosis and calcification. A complication of these plaques may be the erosion of the membrane covering the plaque and its rupture (type VI), which is responsible for the occurrence of acute coronary syndrome [5].

Because early CHD detection in asymptomatic patients may lower the morbidity and mortality arising from the condition, new non-invasive diagnostic methods are sought. One of these methods is computed tomography (CT) on the basis of the properties of calcium, which, with its high atomic number, absorbs X-ray radiation. As a result of this, calcified lesions show up as white on CT scans and are easily distinguished from the surrounding soft tissues so that contrast administration is not required in the examination.

At present two different CT methods are used: electron-beam computed tomography (EBCT) and classical CT. The first research on coronary artery calcification was possible because of the development of EBCT in the late 1980s. Because the speed of these devices was much higher than that of existing devices, there was the option of "stopping" the heart motion in order to assess coronary artery calcification [6, 7].

In this machine, all mechanical motion was eliminated and the beam created in the so-called electron section diverted by the magnetic field and directed to one of four tungsten anodes in the form of a ring. The whole circuit runs in a high vacuum. X-ray radiation is emitted from the anode and, after passing through the patient, is recorded in one of two detector circuits.

As a result of EBCT it is even possible to detect plaques calcified in 10–20%, which is not possible using standard diagnostic tests [6].

Three-dimensional images can be obtained from step-volume scanning, which uses two-dimensional images and continuous volume. Two-dimensional scanning, ECG signal-gated, is the most commonly used method. The collection of data usually takes place during diastole in order to reduce artefacts created as a result of heart motion. Images are obtained from 3 mm slices for the detection of calcium in the coronary arteries. The whole heart is depicted during one or two breaths of the patient.

Computed tomography in heart imaging became more widely used after the introduction of multi-slice computer tomography (MSCT). In these machines an X-ray is emitted by a tube rotating around the patient. Heart imaging can be performed both through sequential scanning (as in step-volume scanning in EBCT) or spiral scanning (as in continuous-volume scanning in EBCT). Both types of data collection can be ECG signal-gated, although the lower rotation velocity of the lamp around the patient, in contrast to EBCT, requires at least 250 ms in modern machines. For the detection of coronary artery calcifications the slice thickness oscillates between 1.25 and 3 mm. The whole heart can be depicted during one breath of the patient [7].

Assessment of coronary artery calcification

In coronary artery assessment, both in the EBCT method and in MSCT, various algorithms are employed. The most popular is the Agatston score, introduced in the late 1990s to assess coronary artery calcifications in EBCT [8].

The Agatston score is based on a maximal X-ray absorption factor measured in Hounsfield units (HU) and the measurement of calcium accumulation size. On the basis of histological research the structure is recognised as calcified if it absorbs 130 HU or more [9]. Each coronary artery is evaluated and the results obtained are summarised to receive a coronary calcium score.

The limitation of this method is the inability of EBCT to image a single calcification while showing total a calcium score (CS). This means that two or three single 30% stenotic lesions are shown as one 70–80% stenosis.

Alternative methods of calcification evaluation are as follows:

— volume scoring (VS) — as in the Agatston score, 130 HU is the detection threshold; the volume score equals the voxel number (three-dimensional pixel equivalent) and single-voxel volume product. The total VS is the sum of the individual results obtained in the examination.
— mass scoring (MS) — coronary artery calcification assessment based on the calculation of total calcification mass, the sum of individual calcification masses in the arteries. This test requires what is known as calibration factor calculation, taking into consideration the density of the hydroxyapatite which builds the calcification. Because the CT number of all materials, except for water, is dependent on the X-ray spectrum, calibration factors are taken into consideration in every CT machine and in every research protocol. MS is given in milligrams. Initial research has demonstrated that the results obtained in this way are more reproducible than those obtained from the Agatston score, but the method requires further research [10].

As a result of CT (EBCT and MSCT) it is possible to evaluate not only the prevalence but also the density of atherosclerotic plaques. This is crucial, since calcified plaques are considered to be stable. On the basis of previous research it is assumed that soft atherosclerotic plaque has an X-ray

absorption factor below 50 HU, that fibrous plaque has a factor of 50–130 HU, that fibrous-calcified plaque has a factor of 130–300 HU and that massive calcifications have a factor of over 300 HU [11, 12].

Research comparing the calcification scores obtained from EBCT and MSCT has demonstrated a close correlation, particularly with values over 11 [13].

Calcium score application

Guidelines suggest that CHD prevention in the elderly should be based on the evaluation and modification of possible risk factors. For this purpose well-documented risk factor evaluation is used on the basis of the Framingham trial, in which a correspondence was demonstrated between CHD morbidity and mortality and environmental and intracorporal, modifiable and non-modifiable factors which influence the progress and course of CHD [14]. Autopsies on patients who had died from acute myocardial infarction or sudden cardiac death proved that the intensity of atherosclerosis is a more important factor than the degree of stenosis [15]. After the introduction of EBCT and the opportunity of CS assessment, therefore, numerous trials were performed to evaluate the prognostic value of the coronary artery CS and its possible application as an accessory factor which would improve CHD risk evaluation according to the Framingham scale [16–18].

The basic assumption that the higher CS, the greater the probability of the existence of coronary artery lesions was confirmed in the very first trial [8]. In the trial performed by Rumberger et al. [16] a CS above 371 had a specificity of 90% in detecting artery lumen stenosis above 70%. Specificity decreases with patient age and increases with the number of affected vessels and total CS. Patient prognosis worsened with an increase in CS. It was demonstrated that the degree of coronary artery calcification was a good prognostic factor of the progress of symptomatic coronary heart disease.

Guerci et al. [17] performed angiography in asymptomatic patients with elevated CS values. Not only elevated CS values (average 573 ± 504) but also coronary arteries stenotic lesions (with an average stenosis of 45% ± 16%) were shown in these patients. Average artery stenosis was dependent on CS elevation in all patients.

Behrenbeck et al. [18] showed that in persons with a low or moderate CHD risk CS evaluation is more economically reasonable than performing a stress test, perfusion scintigraphy or stress echo.

In the trial by Detrano et al. [19], the Framingham scale and EBCT were of similar efficacy in detecting CHD risk in asymptomatic patients. It was also demonstrated that a tomographic CS increases in proportion to the number of traditional risk factors. Hoff et al. [20] showed in a group of 30 908 healthy people (men and women) a statistical correspondence between elevated CS values and cigarette smoking, hypercholesterolaemia, diabetes and arterial hypertension. Unfortunately, although typical risk factor assessment enables most coronary events to be predicted, they also occur in people without typical risk factors and with low calcium scores [20].

Although the Framingham study [14] and the Multiple Risk Intervention Trial [21] demonstrated the relationship between cholesterol level and mortality from CHD, a quarter of deaths still occur in patients with a cholesterol level of around 182––244 mg% [21]. In these cases it is suggested that the cause of death could be plaques which do not occlude the vessel lumen.

In an autopsy trial Taylor et al. [22] compared the Framingham risk factors, the extent of calcification and histological features of atherosclerotic plaques in individuals who had died from sudden cardiac death. In the majority of cases (50 out of 79) the extent of plaque calcification was related to the Framingham risk score. In other cases, amounting to about 25%, atherosclerotic plaque erosion resulting in thrombus formation was the cause of death. These patients had both a significantly lower CS and lower Framingham index values.

Following on from this, despite numerous reports on the rationale of CS assessment, a document published in June 2000 by the American College of Cardiology (ACC) and the American Heart Association (AHA) in the Journal of the American College of Cardiology summarising AHA opinion regarding CS evaluation found no grounds for a wider use of EBCT in screening tests for CHD in asymptomatic patients [6].

In recent years, further research has been undertaken to determine the probability of CHD occurrence in different groups of patients (those with undiagnosed chest pain, those who have undergone PCI and those with modifiable CHD risk factors) or in an attempt to employ EBCT for the evaluation of atherosclerotic plaque progression and regression.

Moser et al. [23], on the basis of examination of 794 asymptomatic patients, found that the greatest benefit from CS evaluation concerns patients with three or more CHD risk factors, because CS values observed in them correlates with medium

and extensive coronary artery calcifications (Agatston score = 101–400), while only 41% of these patients showed an abnormal SPECT test result. This finding can be explained by the fact that perfusion scintigraphy detects stress-induced ischaemia but not atherosclerotic plaques. The authors suggested that myocardial SPECT evaluation should not be made before CS level reaches 400.

2003 saw the conclusion of a CHD prevention trial, the St. Francis Heart Study [24], which included 5585 patients (with an average age of 59, 30% of them female) without a history of CHD or signs of coronary vessel atherosclerosis. In all the patients evaluated EBCT was performed to assess the extent of calcification. The Agatston scale was used. During a 4.5-year follow-up at least one atherosclerotic event (non-fatal myocardial infarction, coronary related death, CABG, PTCA, ischaemic stroke, peripheral vessel surgery) occurred in 122 patients. It was shown that CS obtained from EBCT enabled an independent and more precise prediction to be made of coronary events than did standard coronary artery disease risk factors, particularly in moderate and high-risk groups according to the Framingham criteria. Furthermore, it was demonstrated that according to CS individuals at moderate risk of CHD were present in low-risk groups as well as in high-risk groups according to the Framingham study. The authors have suggested that there is an argument for adding an EBCT examination for the evaluation of CS to risk-factor assessment in men and women between the ages of 50 and 70 at moderate risk of CHD.

It was shown in this trial that the prevalence of coronary events gradually increased along with an increase in calcium score. Participants in whom a coronary event occurred during the trial had a calcium score which was four times higher at the beginning of the trial. The event frequency after 4.3 years of follow-up in participants with a calcium score of zero was 0.5%, whereas it was 14.1% for those with a score above 600 ($p < 0.0001$).

On the basis of CS results researchers have also put forward diagnostic and therapeutic recommendations. Where the CS fell within the 100 to 200 range and the frequency of coronary events was at least 2% during one year the researchers suggested primary prevention of atherosclerotic plaques, for example by daily aspirin administration. Where CS ranged from 200 to 400, it was proposed to add hypolipidaemic treatment. Patients who are asymptomatic but with high calcium scores (between 200 and 400) in whom numerous disseminated but not lumen-occluding atherosclerotic lesions are found should undergo diagnostic stress tests, which may reveal possible silent ischaemia. However, the authors did not suggest routine haemodynamic examination after EBCT in asymptomatic patients.

Calcium score evaluation can be used to predict the natural history of atherosclerosis. Schermund et al. [25] assessed the tomographic CS in 330 patients who had undergone EBCT for CHD symptoms in the previous three months and who had been personally referred for EBCT because of the risk of CHD being present. It was shown that in patients with coronary artery disease and a lower CS the most frequently affected vessel was the left anterior descending artery (54% of the patients) followed by the right coronary artery (25% of the patients).

Left main involvement was found in 10 out of 139 patients (7%) with single and double-vessel disease and in 17 out of 77 patients (23%) with triple-vessel disease. Most frequently calcification was found in the proximal segment of the left anterior descending artery and then in the proximal segment of the circumflex artery and the right coronary artery. Moreover, whereas in the right coronary artery calcifications were located symmetrically, in the left coronary artery there was a tendency for the development of calcifications in the proximal segment, especially in the left anterior descending artery.

Calcium score evaluation may serve for the assessment of lesion dynamics in patients with stable coronary heart disease. Examination of 388 patients performed with multi-slice CT showed that where there was stable coronary heart disease there was a significant progression of lesions in the coronary arteries in follow-up four years and more after the first evaluation.

Cigarette smoking and entry tomographic CS were independent prognostic factors in this trial and the presence of new lesions in the coronary artery wall was found in 56% of subjects [26].

Furthermore, it was found in the PREDICT Study that in CS evaluation of type 2 diabetics the extent of coronary artery calcifications was closely dependent on waist-hips ratio, systolic blood pressure and male gender, a finding which may be related to the prevalence of the metabolic syndrome in these subjects [27].

Calcium score evaluation can also be useful in monitoring the results of therapy. Budoff et al. [28] evaluated the efficacy of hypolipidaemic treatment with statins in 299 subjects who were treated for basic conditions such as arterial hypertension, hyperlipidaemia and diabetes. EBCT was performed before the initiation of treatment and after at least 12 months of therapy. In the group treated with

Table 1. Recommendation summarising the application of calcium score (CS) for coronary heart disease (CHD) risk evaluation in asymptomatic patients (25) (According to: [30]).

CS acc. EBCT	Atherosclerotic plaques	Significant CHD probability	Risk factors implications	Recommendations
0	No plaques	Very low, usually < 5%	Very low	Explain main principles of primary CHD prevention
1–10	Minimal plaques present	Low probability < 10%	Low	Explain main CHD prevention methods
11–100*	At least two plaques present	Minimal or non-significant artery stenosis	Moderate	Attempt to modify risk factors, strict implementation of primary prevention guidelines NCEP ATP II. Daily ASA dosage**
101–400*	At least moderate plaques present	Non-occluding artery stenosis very probable but total occlusion possible	Moderately high	Risk-factor modification, following secondary prevention guidelines NCEP ATP II. Stress tests to evaluate future risk
> 400*	Severe atherosclerotic	At lest one "significant" plaques stenosis very probable (> 90%)	High	Very aggressive risk-factor modification. Stress test or stress echocardiography to detect stress inducible ischaemia

*If the score is > 75 percentile for age/gender, one should switch to the recommendation for the next CS level; **orally 80–325 mg; ASA — acetylsalicylic acid; NCEP ATP II — National Cholesterol Education Program (Adult Treatment Panel II); EBCT — electron-beam computed tomography

statins a 61% slow-down in CS progression was observed, and of 60 patients treated with statin monotherapy 37% showed a decrease in CS was compared to the entry result.

Calcium score assessment may gain significance in cardiological diagnostics because it allows data to be obtained that is different from that acquired by the non-invasive methods that have been used so far in patients at risk of CHD. It has been said that the main advantage of EBCT is its potential as a screening test to uncover CHD in young asymptomatic subjects with one or more CHD risk factors. EBCT is of limited value in elderly subjects, in whom calcifications frequently occur (for example in patients with chronic renal failure). In view of this, the detection of calcifications may not be synonymous with CHD prevalence [29].

The main limitation of this method is still access to technologically advanced CT machines, which so far makes it impossible to apply it in Polish conditions.

Recommendations are given in Table 1 which summarise the use of CS for CHD risk evaluation in asymptomatic patients [30].

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