Age and Gender Distribution of Coronary Artery Calcium Measured by Four-Slice Computed Tomography in 2,030 Persons With no Symptoms of Coronary Artery Disease

Axel Schmermund, MD, Raimund Erbel, MD, and Sigmund Silber, MD, for the MUNICH Registry Study Group*

Currently, the Agatston criteria[1] are widely applied for defining the quantity of coronary calcium ("Agatston score").[2] To interpret the clinical significance of a given Agatston score, it is essential to consider the age and gender of the individual patient.[3,4] Agatston score percentile values have been established on the basis of measurements from electron beam computed tomography (EBCT).[5,6] Because of the distinct scanning modalities, these values may not be relevant for 4-S-computed tomographic (CT)-derived measurements. There are no 4-S-CT-derived data regarding the distribution of the calcium score. Therefore, it was the aim of the present study to establish such values in patients with no symptoms of coronary artery disease in close analogy to the Multi-Ethnic Study of Atherosclerosis (MESA) protocol for 4-S-CT. MESA is a population-based study currently being conducted in the United States to evaluate different modalities for detecting subclinical atherosclerotic disease. In addition, the influence of cardiovascular risk factors on the 4-S-CT calcium score was analyzed.

• • •

The MUltislice Normal Incidence of Coronary Health (MUNICH) Registry includes patients referred by their primary physicians for a coronary calcium scan at the Heart Diagnostic Center (Munich, Germany) for the purpose of risk stratification (see Appendix). All such patients were included in the present study in a consecutive fashion. On the basis of a physician-directed interview, clinical symptoms and established risk factors were assessed at the scanning center. A physical examination was performed to rule out clinically apparent coronary or peripheral artery disease. Only patients with no history or symptoms suggesting coronary artery disease were included. Between July 1999, when the CT scanner was installed, and May 2001, a total of 2,030 patients fulfilled the inclusion criteria.

Apart from age, gender, and body mass index, the risk factors systemic hypertension, diabetes, smoking, hypercholesterolemia, and family history of coronary artery disease were assessed. Systemic hypertension was established if patients reported standard sphygmomanometric measurements with systolic and/or diastolic blood pressure values ≥140 mm Hg and ≥90 mm Hg, respectively, on ≥3 occasions, if patients were receiving antihypertensive treatment, or both. Diabetes was defined as fasting blood glucose ≥126 mg/dl, use of antidiabetic drug treatment, or both. Smoking was classified as never, former, or current. Hypercholesterolemia was defined at a total cholesterol level >240 mg/dl as reported by the patient, the use of lipid-lowering medication, or both. A positive family history was noted if a first-degree relative of the patient had known clinical coronary artery disease. For some analyses, the continuous variables age and body mass index were also categorized. Men aged >55 years were classified as "risk factor present" as were women aged >65 years. For body mass index, a cutoff value of >25 kg/m^2 was used to indicate "present."

Native CT scans were performed with an Mx-8000 4-S-CT scanner (Philips, formerly Marconi, Cleveland, Ohio). Patients were positioned supine, feet-first in the scanner. The heart was localized by low-dose and low-resolution spiral CT imaging of the chest. High-resolution scanning of the heart was begun at the level of the bifurcation of the main pulmonary artery and proceeded caudad through the cardiac apex. Patients were instructed to hold their breath in inspiration during the (single breath-hold) procedure. Because of the fast rotation time and simultaneous acquisition of 4 slices, breath-hold time was restricted to <20 seconds.

TABLE 1 Patient Demographics, Risk Factors, and Calcium Scores

	All Patients (n = 2,030)	Men (n = 1,515)	Women (n = 515)
Age (yrs)	56 ± 10	55 ± 10	59 ± 10*
Body mass index (kg/m^2)	26.2 ± 3.8	26.7 ± 3.4	24.7 ± 4.4*
Systemic hypertension	820 (42%)	599 (41%)	221 (45%)
Hypercholesterolemia†	1,046 (57%)	778 (57%)	268 (57%)
Diabetes mellitus	119 (6%)	96 (7%)	23 (5%)
Active smoking	433 (22%)	348 (24%)	85 (17%)*
Positive family history	861 (45%)	605 (43%)	256 (54%)*
4-S-CT calcium score (mean)	176 ± 463	217 ± 532	105 ± 338*
4-S-CT calcium score >0	1,238 (61%)	990 (65%)	248 (48%)*

*p <0.001 versus "men."
†Total cholesterol >240 mg/dl, use of lipid-lowering medication, or both.

From the Department of Cardiology, University Clinic, Essen; and Heart Diagnostic Center, Munich, Germany. Dr. Silber's address is: Heart Diagnostic Center, Herzdiagnostikzentrum, Tal 34, D-80331 Munich, Germany. E-mail: info@herzdiagnostik.com. Manuscript received December 5, 2001; revised manuscript received and accepted March 18, 2002.

*See Appendix for the list of members in the MUNICH Registry.

0002-9149/02/$–see front matter
PII S0002-9149(02)02445-1

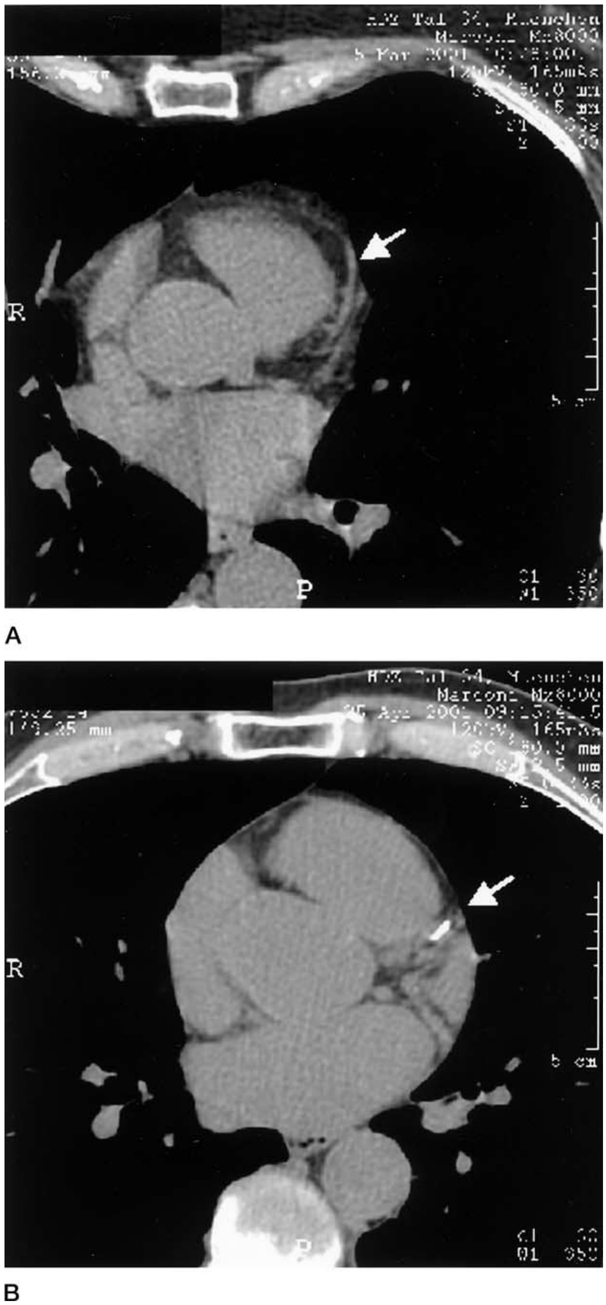

FIGURE 1. Tomographic sections of the base of the heart acquired with 4-slice multidetector CT using prospective electrocardiographic triggering in sequential mode. *A,* normal findings (no calcium, 4-S-CT calcium score = 0) in a 45-year-old male previous smoker with moderately elevated cholesterol. The *arrow* points to the left anterior descending coronary artery. *B,* isolated calcified plaque in the left anterior descending artery *(arrow)* of a 59-year-old man without known risk factors. The 4-S-CT calcium score was 502 and thus above the 75th percentile.

Scanning analogous to the MESA protocol was done with prospective electrocardiographic triggering in a consecutive slice mode at 120 kV and 165 mAs. The collimated and effective slice thickness was 2.5 mm. The table increment was 10 mm after every series of 4 slices, resulting in contiguous noninterlaced slices. The trigger point was set at 60% of the expected next RR interval (AccuSync, Milford, Connecticut). Because of the system-inherent loading time, triggering of data acquisition was induced by every consecutive R wave for heart rates <58 beats/min and by every other R wave for higher heart rates.

TABLE 2 Age, Gender, and Risk Factors as Independent Predictors of the 4-S-CT Calcium Score in the Total Patient Population*

Variable	Coefficient	SE	T Value	p Value
Age (yrs)	0.12	0.006	20.45	<0.001
Men	1.36	0.124	10.97	<0.001
Systemic hypertension	0.45	0.086	4.10	<0.001
Active smoking	0.42	0.132	3.15	0.002
Hypercholesterolemia	0.25	0.108	2.36	0.02
Diabetes mellitus	0.44	0.226	1.95	0.05

*The r^2 value was 0.24.

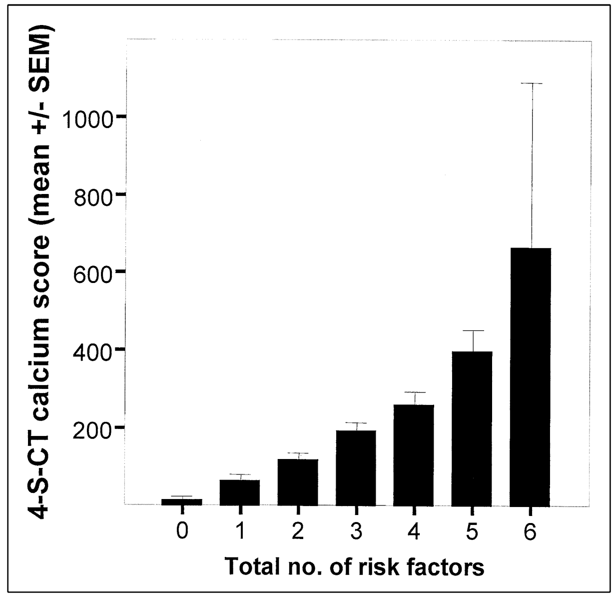

FIGURE 2. Significant increase in mean 4-S-CT calcium scores (± SEM) in patients classified according to the total number of risk factors (p <0.001, Kruskal-Wallis test).

The images were analyzed using a field of view of 18 × 18 cm and software inherent to the scanner (HeartBeat CS, version 2.7, Philips, Cleveland, Ohio). In accordance with the Agatston criteria,[1] calcium was defined as a hyperattenuating lesion with a CT density ≥130 Hounsfield U in an area of at least 0.5 mm^2. Calcified lesions were encircled manually and included in the analysis only if strictly in the trajectory of the coronary arteries. Calcium of the valves, aorta, and ostial plaques was excluded.

The calcium score was calculated as the product of the area of the lesion and a factor rated 1 through 4 dictated by the maximum CT density within that lesion.[1] The sum of all lesion scores was used to generate the total calcium score. Separately, scores were computed for each of the major coronary arteries (left main, left anterior descending, left circumflex, and right coronary arteries).

It is not clear if retrospective electrocardiographic triggering of 4-S-CT images obtained in the continu-

TABLE 3 Age-dependent 4-S-CT Calcium Score Percentile Distribution in Men

Age (yrs)	30–39 (n = 94)	40–44 (n = 125)	45–49 (n = 200)	50–54 (n = 256)	55–59 (n = 362)	60–64 (n = 250)	65–69 (n = 126)	≥70 (n = 102)
				Percentiles				
10	0	0	0	0	0	0	0	2.5
25	0	0	0	0	0	1	21	51
50	0	0	0	7	35	59	136	211
75	0	4	40	99	201	247	553	891
90	24	44	181	299	730	793	1,452	1,693
Mean	12	20	79	122	247	279	465	583
SD	44	68	245	301	553	579	747	947

TABLE 4 Age-dependent 4-S-CT Calcium Score Percentile Distribution in Women

Age (yrs)	30–39 (n = 15)	40–44 (n = 22)	45–49 (n = 48)	50–54 (n = 68)	55–59 (n = 127)	60–64 (n = 87)	65–69 (n = 60)	≥70 (n = 88)
				Percentiles				
10	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	16
50	0	0	0	0	0	4	20	100
75	0	1	0	3	25	49	103	314
90	27	7	17	135	138	122	635	591
Mean	4	2	22	42	63	82	217	248
SD	17	4	130	128	251	343	566	431

ous scanning spiral mode will provide superior image quality and more sensitive detection of coronary calcium than the prospective triggering performed in the current investigation. In 30 consecutive subjects with a calcium score of zero as measured in the prospectively triggered consecutive slice mode, retrospectively gated, spiral acquisition was performed additionally with a collimated slice thickness of 1 mm, resulting in an effective slice thickness of 1.3 mm. Forty percent of these patients were men (mean age 55 ± 9 years [range 35 to 66]. In all cases, the second "retrospective" calcium score was also zero.

Statistical analyses were performed using the SPSS software package (release 10.0.5, SPSS Inc., Chicago, Illinois). Mean values ± SDs are presented if not noted otherwise. Risk factor information is given as percentage of patients. Differences in the presence of coronary calcium between the 2 groups were assessed using a comparison of proportions, and differences in the calcium score using the nonparametric Mann-Whitney test. Multivariate linear regression analysis was performed to analyze the influence of various parameters on the calcium score. For this analysis, a $\log_e\{x + 1\}$ transformation of the calcium score was made to account for its non-normal distribution. A 2-tailed p value <0.05 was considered significant.

Patient demographics, risk factors, and calcium scores in the overall population and separately in men and women are listed in Table 1. Although women were significantly older and appeared to have more risk factors (with the exception of active smoking), coronary calcium was detected more frequently and to a greater extent in men. Figures 1A and 1B show representative tomographic images at the base of the heart. Age, gender, and all of the established causal risk factors were independently associated with calcium scores (Table 2); furthermore, the calcium score increased significantly with an increasing number of risk factors (Figure 2).

Tables 3 and 4 and Figures 3 and 4 show the 4-S-CT calcium score percentile distribution in men and women.

The calcium scores of the major coronary arteries were all significantly different from each other. The greatest calcium score was observed in the left anterior descending coronary artery (95.5 ± 217.3), followed by the right (59.4 ± 245.1), the left circumflex (24.5 ± 90.0), and the left main coronary (8.4 ± 35.0) arteries. In the 1,238 patients with a positive total calcium score, 1 of the major coronary arteries was calcified in 462 patients (37%, 2 in 288 (23%), 3 in 306 (25%), and all 4 in 182 (15%). If only 1 of the major coronary arteries was calcified, it was usually the left anterior descending (in 73%) or the right coronary artery (in 15%).

• • •

The present report from the MUNICH registry presents the first database regarding 4-S-CT in such a population. The percentile values observed with the acquisition protocol of the MUNICH registry correlated well with previous reports on EBCT-derived percentile values (Figures 3 and 4). The good agreement between our scores measured with 4-S-CT and the scores published for EBCT may be somewhat unexpected, because the Agatston score is directly related to the slice thickness and the EBCT slice thickness of 3.0 mm cannot be accomplished by the

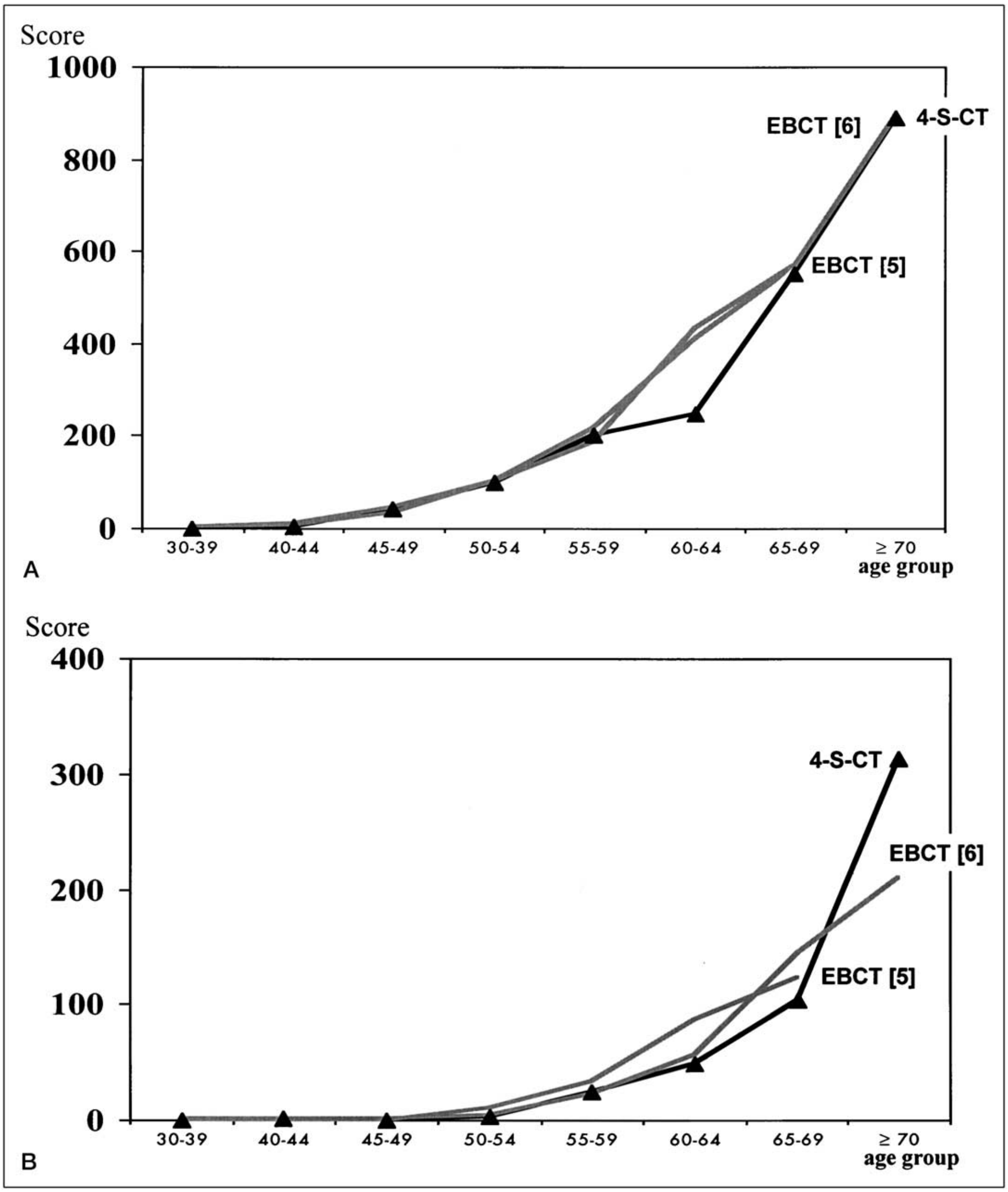

FIGURE 3. Comparison of the 75th percentile value of the Agatston calcium score obtained from measurements derived from EBCT in previous studies compared with the present study in men *(A)* and women *(B)*.

4-S-CT: in the sequential mode, collimated (and effective) slice thickness is 2.5 mm. For a given scan length, more slices are acquired with 4-S-CT than with EBCT, and one would therefore expect 23% higher Agatston scores for 4-S-CT. On the other hand, a lower slice thickness might have reduced the density of the calcified lesion in some slices.

Of the major coronary arteries, the left anterior descending coronary artery was most frequently and most extensively calcified, followed by the right coronary artery. This is consistent with reports on the natural history of coronary calcium detected by EBCT[7,8] and with data from histopathologic and angiographic series.[9–11]

Our results can only be applied for the acquisition method used (prospective triggering, sequential mode). In contrast to EBCT (always prospectively triggered, always sequential mode), 4-S-CT gives more possibilities of data acquisition: prospective or retrospective triggering and sequential or helical imaging. Unfortunately, unlike the standards for EBCT,[1,12,13] no standards have been adopted to allow for comparable measurements of coronary calcium using 4-S-CT. The "ideal" acquisition protocol is a matter of substantial controversy[13–15]; untriggered imaging, however, should be avoided.[16] In the MUNICH registry, we have decided to come as close as possible to the EBCT standard and the 4-S-CT method used in the United States MESA study, with its sequential image acquisition and prospective triggering at 50%

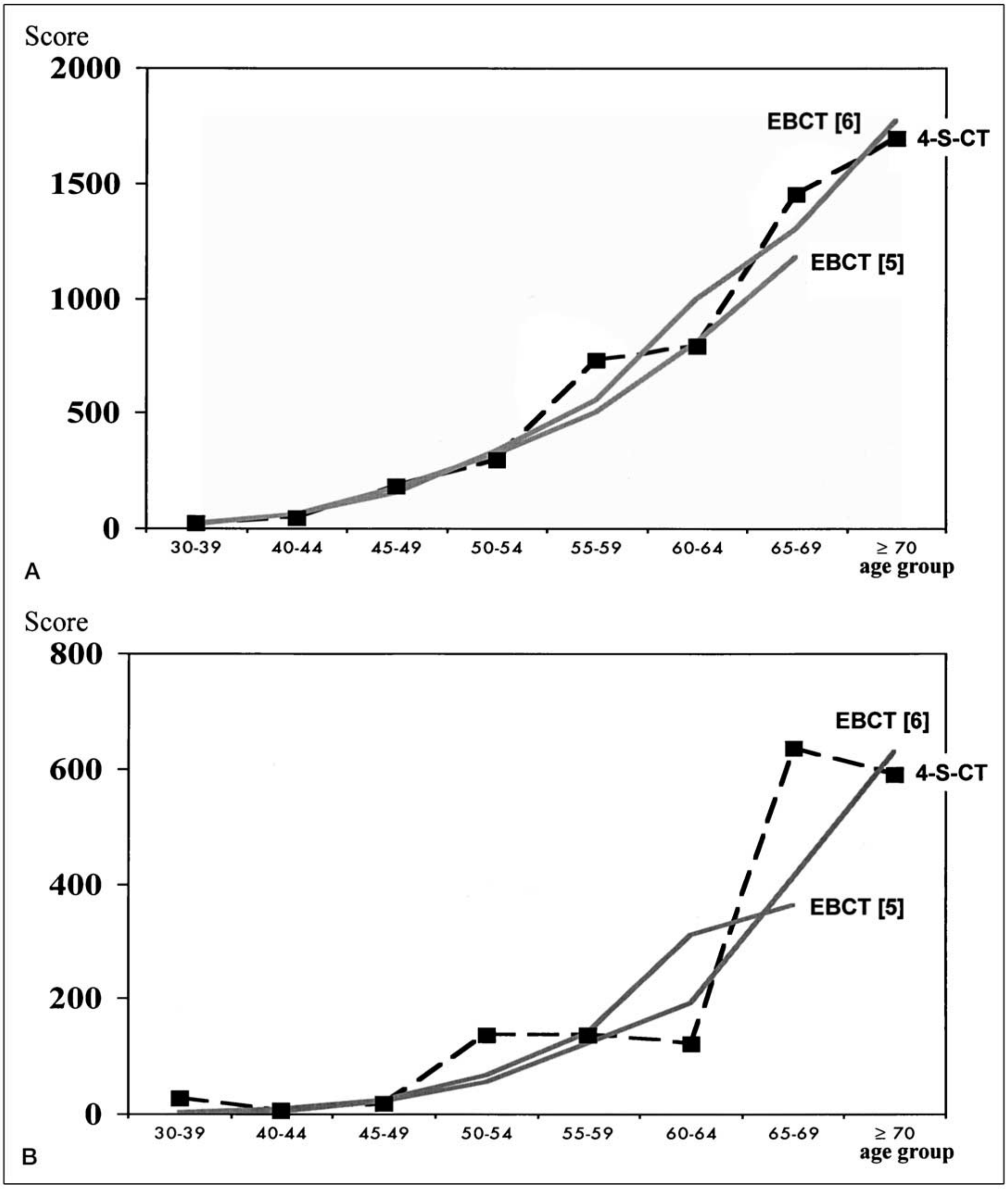

FIGURE 4. Comparison of the 90th percentile value of the Agatston calcium score obtained from measurements derived from EBCT in previous studies compared with the present study in men *(A)* and women *(B)*.

after the R wave. These methods (50% or 60% of the RR interval) make acquisition of the images likely to be in the diastolic phase, still before the "atrial kick" with its associated motion artifacts. This is especially true for the right coronary artery. We believe that ongoing developments in multislice spiral CT technology with still faster acquisition of more and thinner slices will render different scanning protocols than the current one. The only way to achieve a standardized interpretation of scans acquired with different scanning technologies will ultimately be calcium mass measurements validated by constant phantom calibration. However, such measurements are not widely available. In the meantime, the present protocol offers a reasonable option for the 4-S-CT technology, with lower radiation exposure than that with retrospective gating.

We established percentile values of the coronary calcium score by using 4-slice multidetector CT (4-S-CT) in 2,030 subjects (56 ± 10 years, 75% men) asymptomatic for coronary artery disease. Scanning was done with prospective electrocardiographic triggering at 60% of the RR interval using a slice width of 2.5 mm, offering a database for calcium scores determined by using 4-S-CT and prospective electrocardiographic triggering in apparently healthy subjects. We observed a close association of the calcium scores with risk factors,

and a considerable similarity to percentile values previously reported in studies with EBCT.

APPENDIX

The MUNICH registry: participating physicians: Stefan Ascher, MD, Munich; Michael Bader , MD, Uffing; Gerhard Bäuerlein, MD, Munich; Hannes Baur, MD, Kaufbeuren; Hans-Joachim Becker, MD, Heidenheim; Wolfgang Bogner, MD, Starnberg; Gerhard Breyer, MD, and Karl Kruis, MD, and Joaehim Lehnert, MD, Munich; Peter Denkl, MD, Wiessee Bad; Rudolf Dietl, MD, Ingolstadt; Rolf Dörr, MD, Dresden; Gert Eisele, MD, Munich; Hans-Jürgen Eulitz, MD, Wolfratshausen; Egbert Feder, MD, Garmisch-Partenkirchen; Carl A. Geser, MD, Garmisch-Partenkirchen; Veit Göller, MD, Memmingen; Franz Goss, MD, Munich; Birgit Gruschka-Hellemann, MD, Munich; Winfried Haerer, MD, Ulm; Klaus Hanke, MD, Pullach; Franz Haslinger, MD, Deggendorf; Anton Huber, MD, Unterschleißheim; Maike Janson, MD, Munich; Gerd Jennerwein, MD, Geisenfeld; Hans Kaufmann, MD, Eichstätt; Rainer Klima, MD, Munich; Markus Kreil, MD, Grünwald; Peter Krieger, MD, Weilheim; Irmtraut Kruck, MD, Ludwigsburg; Karl Kruis, MD, Munich; Wolfgang Kühner, MD, Ebersberg; Michael Kuntze, MD, Gauting; Thomas Lange, MD, Passau; Joachim Lehnert, MD, Munich; Eckard Licht, MD, Dachau; Peter Lidzba, MD, Penzberg; Martin Linke, MD, Munich; Peter Mathes, MD, Munich; Bernd Metzger, MD, Stuttgart; Dieter Miller, MD, Starnberg; Matthias Neff, MD, Mindelheim; Hans Pösl, MD, Munich; Wolfgang Poetsch, MD, Munich; Lymperis Potolidis, MD, Augsburg; Martin Prohaska, MD, Mühldorf; Karl-Heinz Regele, MD, Olching; Bernd Reiff, MD, Munich; Josef Reisinger, MD, Freising; Peter Rixner, MD, Munich; Franz Roth, MD, Munich; Eckehard Sauer, MD, Landshut; Walter Schießler, MD, Weilheim; Karl-Michael Schmid, MD, Munich; Konrad Schmid, MD, Schongau; Hans Schneider, MD, Ebersberg; Wolfgang Schneider, MD, Ebersberg; Norbert Schön, MD, Mühldorf; Stephan Seifert, MD, Traunstein; Wolfgang Sonne, MD, Munich; Christoph Steidle, MD, Höhenkirchen; Günter Steinebach, MD, Garmisch-Partenkirchen; Rainer Steinhard, MD, Dachau; Thomas Straßer, MD, Munich; Michael Struppler, MD, Munich; Sofia Tourlakidou, MD, Munich; Hans-Christoph Vogel, MD, Passau; Jürgen Wagner, MD, and Alexander Zitzmann, MD, Munich; Berthold Wauer, MD, Munich; Reinhard Winter, MD, Penzberg; Lorenz Würfl, MD, Schondorf; Kurt Wybitul, MD, Freiburg; Adolf Zuber, MD, Hohenpeiβenberg.

1. 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;15:827–832.

2. O'Rourke RA, Brundage BH, Froelicher VF, Greenland P, Grundy SM, Hachamovitch R, Pohost GM, Shaw LJ, Weintraub WS, Winters WL Jr, et al. American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol* 2000;36:326–340.

3. Janowitz WR, Agatston AS, Kaplan G, Viamonte M Jr. Differences in prevalence and extent of coronary artery calcium detected by ultrafast computed tomography in asymptomatic men and women. *Am J Cardiol* 1993;72:247–254.

4. Rumberger JA, Brundage BH, Rader DJ, Kondos G. Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons [erratum in *Mayo Clin Proc* 1999;74:538]. *Mayo Clin Proc* 1999;74:243–252.

5. Raggi P, Callister TQ, Cooil B, He ZX, Lippolis NJ, Russo DJ, Zelinger A, Mahmarian JJ. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000; 101:850–855.

6. Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. *Am J Cardiol* 2001;87:1335–1339.

7. Schmermund A, Möhlenkamp S, Baumgart D, Kriener P, Pump H, Grönemeyer D, Seibel R, Erbel R. Usefulness of topography of coronary calcium by electron-beam computed tomography in predicting the natural history of coronary atherosclerosis. *Am J Cardiol* 2000;86:127–132.

8. Schmermund A, Baumgart D, Möhlenkamp S, Kriener P, Pump H, Grönemeyer D, Seibel R, Erbel R. Natural history and topographic pattern of progression of coronary calcification in symptomatic patients: an electron-beam CT study. *Arterioscler Thromb Vasc Biol* 2001;21:421–426.

9. Montenegro MR, Eggen DA. Topography of atherosclerosis in the coronary arteries. *Lab Invest* 1968;18:586–593.

10. Halon DA, Sapoznikov D, Lewis BS, Gotsman MS. Localization of lesions in the coronary circulation. *Am J Cardiol* 1983;52:921–926.

11. Proudfit WL, Shirey FK, Sones FM Jr. Distribution of arterial lesions demonstrated by selective cinecoronary arteriography. *Circulation* 1967;36:54–62.

12. Erbel R, Moshage W. Tätigkeitsbericht Arbeitsgruppe Elektronenstrahltomographie. *Z Kardiol* 1999;88:459–465.

13. Achenbach S, Daniel WG, Moshage W. Recommendations for standardization of EBT and MSCT scanning. *Herz* 2001;26:273–277.

14. Budoff MJ, Mao S, Zalace CP, Bakhsheshi H, Oudiz RJ. Comparison of spiral and electron beam tomography in the evaluation of coronary calcification in asymptomatic persons. *Int J Cardiol* 2001;77:181–188.

15. Silber S. Comparison of spiral and electron beam tomography in the evaluation of coronary calcification in asymptomatic persons, letter to the editor, *Int J Cardiol* 2002;82:297.

16. Silber S. Importance of ECG-Triggering for Ruling Out Coronary Calcification with the Multi-Slice-CT in Individuals Asymptomatic for Ischemic CAD. *Herz* 2001;26:260–272.

0002-9149/02/$–see front matter
PII S0002-9149(02)02446-3