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Predominance of Aortic Calcification as an Atherosclerotic Manifestation in Women: The Reykjavík Study

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ABSTRACT. Since 1967 the Reykjavík study has monitored coronary artery disease and its risk factors in randomly selected cohorts. From 1979 to 1984, 3246 men and 3545 women aged 45–74 years were studied. Routine biplane chest X rays were assessed by a radiologist who noted the presence or absence of aortic calcification (AC), but had no detailed knowledge of the subjects. Overall, AC was diagnosed in 283 (8%) women, but in only 54 of the men (1.7%). In the women, the prevalence of AC increased from 2.0% at age 45–49 years to 17.1% at the age of 70–74 years, while in men it was 0 and 8.3%, respectively. In women, multivariate analysis of risk factors showed AC to be positively related to systolic and negatively related to diastolic blood pressure, indicating a potential relation to pulse pressure. Furthermore, AC was independently associated with age, drug treatment for hypertension, nonfasting blood sugar, use of antidiabetic drugs, total serum cholesterol levels, and the amount of smoking. Too few men had AC for multivariate assessment of risk factors. In addition, in women AC was also related to a previous myocardial infarction ($p < 0.05$), mortality from coronary artery disease ($p < 0.01$), and the presence of intermittent claudication ($p < 0.01$). In men, however, AC was related only to total mortality ($p < 0.05$). Thus, these data show AC to be more prevalent in women, independently associated with recognized atherosclerotic risk factors, and a potential marker for coronary and peripheral artery disease. J CLIN EPIDEMIOL 49;3:383–387, 1996

KEY WORDS. Aortic calcification, prevalence, atherosclerotic risk factors, coronary heart disease, peripheral artery disease

INTRODUCTION

Although atherosclerosis is presumed to be the consequence of a basic pathophysiological mechanism affecting the entire arterial tree, its distribution within the arterial system may vary considerably [1–3]. Various manifestations of atherosclerosis have usually been considered to be more prevalent in men [4,5], while other studies indicate different risk profiles and gender distribution depending on the localization of the atherosclerotic process and the methods of assessment [3,6,7].

In addition to the potential association between aortic calcification (AC) and coronary artery disease and other peripheral artery diseases, there is increasing interest in the importance of aortic atherosclerosis as an embolic source and causative factor in stroke [8,9]. Furthermore the presence of AC imposes increasing technical problems in heart surgery as the population that undergoes such operations gets older [10].

This study evaluates the prevalence of AC in a randomly selected population of both sexes, evaluated from biplane chest X rays. The AC findings are related to an extensive profile of clinical, electrocardiographic, and chemical data prospectively gathered as a part of an epidemiological survey of coronary artery disease and its risk factors in the Reykjavík study. Finally, the predictive value of AC for manifestations of coronary artery disease, intermittent claudication, stroke, and all causes of mortality was evaluated.

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MATERIALS AND METHODS

Study Population

Since 1967 the Icelandic Heart Association Research Center has conducted a prospective epidemiological survey on coronary artery disease and its risk factors. The population in Iceland is of Nordic origin and is ethnically relatively homogeneous. The population numbers somewhat over a quarter of a million people, of which about half lives in the Reykjavík area. The standard of living is relatively high by western comparison and similar to that in the other Scandinavian countries.

Recruitment

Epidemiological data have been obtained at baseline during different stages (I–V) of the Reykjavík study from a random sample of the general population in the capital area (Fig. 1). Overall, the participation rate in the study has been 72% for men and 80% for women. Each survey sample comprises a unique group of participants and for the present article baseline data completed during 1979–1984 (stage IV) have been used. The age of the study group ranged from 45 to 74 years.

All participants underwent a clinical examination and filled out a detailed health questionnaire. Blood pressure was measured by a mercury sphygmomanometer (Erka, Germany) after 5 minutes of rest. Total serum cholesterol, triglycerides, and blood sugar were measured by standard methods as previously described in detail [4]. After an overnight fast, postprandial blood sugar was measured 90 minutes after the intake of 50 g of glucose in 250 ml of water. A 12-lead electrocardiogram was obtained in all participants and evaluated according to the

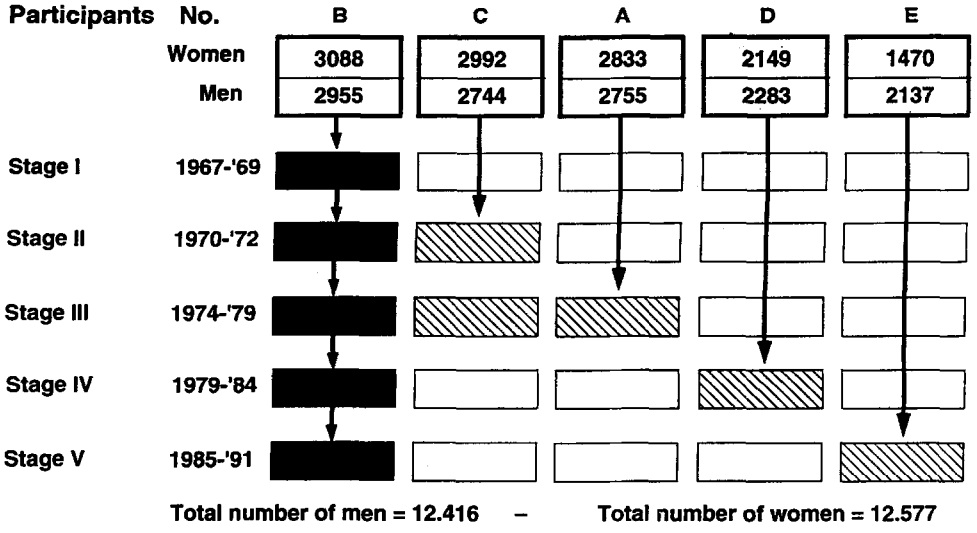

FIGURE 1. The study plan for different stages and groups in the Reykjavík study. The number of men and women originally selected is shown.

Minnesota code. If a participant answered yes to the question: "Have you ever been hospitalized because of heart disease?" his hospital records were reviewed. Subsequently, a previous myocardial infarction, both symptomatic or silent, was defined in accordance with the World Health Organization (WHO) criteria in the MONICA study from the electrocardiographic findings (Minnesota codes 1:1:1–1:2:8), clinical history, and enzyme changes [11]. The clinical diagnosis of intermittent claudication was made by the examining doctor. A biplane chest X ray was taken and routinely assessed by the same radiologist without detailed knowledge of the subjects, who noted the presence or absence of AC.

Follow-up

A mortality follow-up was completed until the end of 1987. The mean follow-up time for men and women was 7.3 ± 2.1 and 5.2 ± 1.3 years, respectively. Causes of death were determined by review of all death certificates from a file in the Statistical Bureau of Iceland, using the *International Classification of Diseases* (ninth revision). In addition, all autopsy reports were reviewed for further ascertainment of the cause of death and for information on the atherosclerotic involvement of the aorta. The necropsy rate was about 30–40%.

Statistics

Univariate relations for variables associated with the presence or absence of AC were assessed separately in women and men by a two-tailed, unpaired Student's *t*-test and a chi-square test (with Yate's correction), as appropriate. Multivariate analysis was performed by stepwise logistic regression to find the independent association between variables and the presence or absence of AC in women.

RESULTS

Overall, 3246 men and 3544 women aged 45–74 years were studied. The mean age for men and women was 57.2 ± 7.5 and 58.4 ± 7.3 years, respectively. Aortic calcification was diagnosed in 283 (8%) of the women, but in only 54 (1.7%) of the men. In women the prevalence of AC increased from 2.0% at the age of 45–49 years to 17.8% at the age of 70–74 years, while in men it was 0 and 8.3%, respectively (Fig. 2).

Aortic Calcification in Relation to Risk Factors

UNIVARIATE ANALYSIS. The univariate relations between various factors and the presence or absence of AC, in women and men separately, is shown in Tables 1 and 2. The women with AC were older and somewhat smaller than those without AC. Their systolic blood pressure was higher and a greater number were taking antihypertensive drugs. Both fasting and postprandial blood sugar values were higher in women with AC and more of them had recognized diabetes and were on antidiabetic drugs. Total serum cholesterol and triglycerides were also increased in women with AC and a higher percentage of them were smokers.

In men, however, the presence of AC was related only to increased age, somewhat increased height and lower weight, and an increased systolic blood pressure. No association was found with other risk factors. The number of men with AC was surprisingly small and they were excluded from further multivariate analysis.

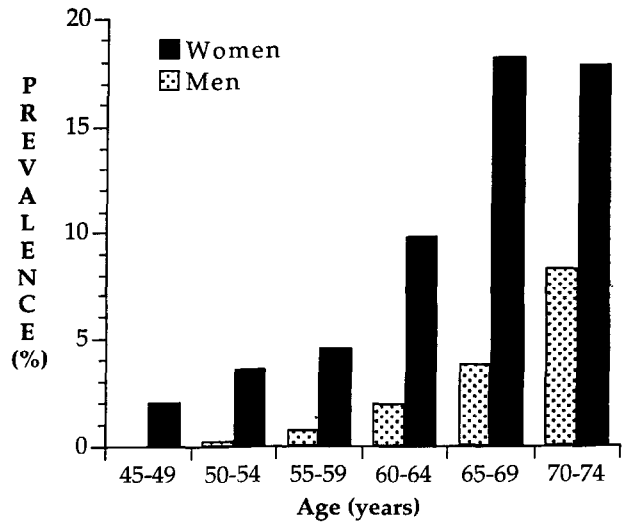

FIGURE 2. The prevalence of aortic calcification according to age in women and men.

TABLE 1. Univariate relations for variables in relation to the presence or absence of aortic calcification in women (n = 3545)

Variable	Aortic calcification: Present (n = 283)	Aortic calcification: Absent (n = 3262)
Age (years)	63.4 ± 6.9	57.7 ± 7.2***
Height (cm)	161.2 ± 5.6	162.9 ± 5.7***
Weight (kg)	66.6 ± 12.8	67.0 ± 11.7
BMI (kg/m^2)	25.6 ± 4.7	25.3 ± 4.3
Systolic BP (mmHg)	141.1 ± 20.3	132.7 ± 19.5***
Diastolic BP (mmHg)	82.6 ± 9.9	82.8 ± 9.5
Antihypertensive drugs [n (%)]	81 (28.6)	546 (16.7)***
Fasting BS (mg/dl)	83.4 ± 25.6	78.3 ± 14.5***
90-min postprandial BS (mg/dl)	120.7 ± 51.8	104.3 ± 35.1***
Known diabetes [n (%)]	16 (5.7)	53 (1.6)***
Antidiabetic drugs[a] [n (%)]	12 (4.2)	23 (0.7)***
Se-total cholesterol (mg/dl)	260.3 ± 40.5	248.3 ± 40.9***
Se-triglycerides (mg/dl)	116.4 ± 62.0	103.7 ± 53.1***
Never smoked [n (%)]	109 (28.6)	1492 (45.8)*
Former smoker [n (%)]	54 (19.1)	599 (18.4)
Smokes pipe/cigars [n (%)]	8 (2.8)	65 (2.0)
Smokes cigarettes [n (%)]	112 (39.6)	1105 (33.9)*
Family history of CAD [n (%)]	55 (19.4)	768 (23.6)

Abbreviations: BP = blood pressure; BMI = body mass index; BS = blood sugar; CAD = coronary artery disease; Se = serum.
[a]Insulin or tablets.
*$p < 0.05$.
**$p < 0.001$.
***$p < 0.001$.

TABLE 2. Univariate relations for variables in relation to the presence or absence of aortic calcification in men (n = 3246)

Variable	Aortic calcification: Present (n = 54)	Aortic calcification: Absent (n = 3192)
Age (years)	66.7 ± 5.5	57.2 ± 7.4***
Height (cm)	171.9 ± 5.5	171.5 ± 6.3***
Weight (kg)	74.7 ± 12.3	80.4 ± 12.4***
BMI (kg/m^2)	25.2 ± 3.9	25.8 ± 3.5
Systolic BP (mmHg)	143.5 ± 22.2	137.7 ± 20.7*
Diastolic BP (mmHg)	87.4 ± 10.6	87.5 ± 10.1
Antihypertensive drugs [n (%)]	10 (18.5)	422 (13.2)
Fasting BS (mg/dl)	82.6 ± 14.4	81.8 ± 15.5
90-min postprandial BS (mg/dl)	112.7 ± 42.6	105.4 ± 37.8
Known diabetes [n (%)]	3 (5.6)	111 (3.5)
Antidiabetic drugs[a] [n (%)]	2 (3.7)	42 (1.3)
Se-total cholesterol (mg/dl)	229.5 ± 36.9	238.2 ± 37.6
Se-triglycerides (mg/dl)	109.6 ± 49.8	119.8 ± 67.9
Never smoked [n (%)]	12 (22.2)	767 (24.0)
Former smoker [n (%)]	19 (35.2)	1043 (32.7)
Smokes pipe/cigars [n (%)]	13 (24.1)	661 (20.7)
Smokes cigarettes [n (%)]	10 (18.5)	721 (22.6)
Family history of CAD [n (%)]	8 (14.8)	544 (17.0)

Abbreviations: BP = blood pressure; BMI = body mass index; BS = blood sugar; CAD = coronary artery disease; Se = serum.
[a]Insulin or tablets.
*$p < 0.05$.
**$p < 0.001$.
***$p < 0.001$.

MULTIVARIATE ANALYSIS. In women, by stepwise logistic regression analysis, AC was positively associated with systolic blood pressure and negatively with diastolic blood pressure, indicating a potential relation to pulse pressure. Furthermore, AC was independently associated with age, drug treatment for hypertension, nonfasting blood sugar values, use of antidiabetic drugs, total serum cholesterol, and the amount of smoking (Table 3).

Aortic Calcification in Relation to Cardiovascular Diseases

At the time of the initial examination, in women, AC was related to a previous myocardial infarction ($p < 0.05$) and the presence of intermittent claudication ($p < 0.01$) (Table 4). At follow-up, AC in women was associated with an increased coronary mortality ($p < 0.01$), but not with total or stroke mortality. In men, however, AC was related to total mortality ($p < 0.05$), but only weakly with coronary ($p = 0.08$) or stroke mortality ($p = 0.09$).

DISCUSSION

Various manifestations of atherosclerosis have usually been considered to be more prevalent in men [1–4]. The present study, however, carried out in a nonselected random population in the Reykjavík area found AC to be more predominant in women, irrespective of age, and associated with well-confirmed atherosclerotic risk factors in Icelandic females [12]. Of further importance, AC was shown to be a potential marker for both coronary and peripheral artery disease, mainly in women. Our findings contrast with results from the Framingham study that showed AC to be more frequent in men, although the women caught up with the men at the age of 60 years [7]. A Dutch study found AC to be more prevalent in men up to the age of 65 years, while after this age the sex ratio reversed, with AC reaching a prevalence of 75% in women and only 45% in men [13]. An autopsy study also found the prevalence of AC in women to approach that of men only after 55 years of age [6]. Depending on geographic location, some pathology studies have found AC to be more frequent in men, others in women [5], while still others claim no sex difference in atherosclerotic aortic disease [2]. The contradictions in gender predominance and other findings between these studies may in part be due to a difference in study subject selection, age distribution, and the methods used to detect AC. The Reykjavík study used biplane chest X rays,

TABLE 3. Stepwise logistic regression analysis of variables associated with presence or absence of aortic calcification (Women, n = 3545)

Dependent Variables	Women: OR	Women: p Value
Age (years)	1.105	<0.001
Systolic BP (mmHg)	1.016	<0.001
Diastolic BP (mmHg)	0.959	<0.001
Antihypertensive drugs [n (%)]	1.49	0.013
90-min postprandial BS (mg/dl)	1.004	0.011
Antidiabetic drugs[a] [n (%)]	3.22	0.023
Se-total cholesterol (mg/dl)	1.004	0.011
Smokes pipe/cigars [n (%)]	2.00	0.10
Smokes 1–14 cigarettes [n (%)]	1.53	0.02
Smokes 15–24 cigarettes [n (%)]	1.99	<0.001
Smokes >25 cigarettes [n (%)]	2.37	0.02

Abbreviations: BP = blood pressure; BS = blood sugar; OR = odds ratio.
[a]Insulin or tablets.

TABLE 4. Aortic calcification in relation to other cardiovascular manifestations

	AC present		AC absent	
	Men (n = 54)	Women (n = 283)	Men (n = 3192)	Women (n = 3262)
		At recruitment		
Myocardial infarction	2(3.7%)	5 (1.8%)*	71 (2.2%)	19 (0.6%)
Intermittent claudication	2 (3.7%)	8 (2.8%)**	59 (1.8%)	24 (0.7%)
		At follow-up		
Coronary mortality	4 (7.4%)	4 (1.4%)**	83 (2.6%)	6 (0.2%)
Stroke mortality	2 (3.7%)	0 (0%)	23 (0.7%)	2 (0.1%)
Total mortality	10 (18.5%)*	5 (1.8%)	305 (9.6%)	38 (1.2%)

*$p < 0.05$.
**$p < 0.01$

while in the Framingham study only an anterior projection was used. The Dutch investigation used bilateral X rays of the lumbar spine to detect AC. However, routine chest and lumbar X rays have been found to be relatively accurate in detecting AC in comparison to autopsy data [14].

The presence of AC in women was found to be associated with well-recognized risk factors for atherosclerosis, mainly those for coronary artery disease [12,15]. This, in fact, is in agreement with the Framingham study, which also found cardiovascular risk factors to be more strongly associated with AC in younger subjects and in women [7]. The Framingham study also found an increased risk for coronary artery disease, stroke, and intermittent claudication among middle-aged women with AC, while these factors had less impact in men [7]. The Dutch study found AC to be associated with cardiovascular risk factors in both sexes, but AC was an independent predictor of cardiovascular death only in men [13]. Atherosclerotic aortic plaques detected by transesophageal echocardiography have also been demonstrated to be markers for coronary artery disease [8].

The Reykjavík study found increased systolic blood pressure to be strongly associated with the presence of AC, while by contrast a negative association was found with diastolic blood pressure. This is in contrast with the Framingham study, which found both systolic and diastolic blood pressure to be positively related to the prevalence of AC in women, while in men only an association with diastolic blood pressure was revealed [7]. The Dutch study found a relation between systolic blood pressure and AC in both sexes [13]. Our findings, however, indicate that pulse pressure may be a more important factor. A study using transesophageal echocardiography to assess atherosclerosis of the thoracic aorta found hypertension to be the only independent risk factor [8]. Isolated systolic hypertension is more common in women than in men, increases with age, and is seen conjointly with increased pulse pressure and decreased compliance of the aorta with age [16]. This, and a potential influence of menopause, might be an important factor relating to increased prevalence of AC in women with age [17].

The presence of AC was also found to be related to increased total serum cholesterol levels and, in agreement with several other atherosclerotic studies, to smoking [2–4]. Furthermore, a positive relation between AC and nonfasting blood sugar values, and in particular with the use of antidiabetic drugs, was also found. By contrast, the Framingham study found a positive relation between the prevalence of AC and increased serum cholesterol levels in women, but no significant association with smoking or blood sugar levels [7]. The Dutch study found AC to be associated with total serum cholesterol in both men and women, but with smoking in men only [13]. In type 2 diabetic subjects, abnormalities in very low-density lipoprotein (VLDL) metabolism and increased systolic blood pressure have been associated with the development of AC and a higher prevalence of aortic and lower limb intimal calcification than in controls [18]. Of interest, in diabetics aortic atherosclerosis has been demonstrated to be associated with changes in the intimal deposition of glycosaminoglycans [19]. A study using computerized tomography (CT) to assess AC found it to be related to age, smoking habits, hypertension, diabetes, relative body weight, hyperlipidemia, and alcohol consumption. Furthermore, AC was demonstrated to be strongly associated with cardiovascular disease [20].

The detection of AC is of increasing importance, but few epidemiological studies on the prevalence of AC exist. It is a potential marker for coronary artery disease [7,8], is increasingly recognized as an embolic source in patients with stroke evaluated by transesophageal echocardiography [9], and during manipulation of the aorta during heart surgery [10]. Although detection of AC on a chest X ray is a crude method, it does show a strong association with recognized atherosclerotic risk factors and makes interesting comparison with other methods to evaluate atherosclerosis [20–22]. Most promising is the possibility of studying the atherosclerotic process in the aorta and other arteries by various ultrasound techniques. This opens up the possibility of studying the evolution of the atherosclerotic process and the composition of individual plaques. The role of multiple risk factors and their varied effects on different segments of the arterial tree might then be determined [21,22].

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References

1. Ross R. The pathogenesis of atherosclerosis. In: **Heart Disease: A Textbook of Cardiovascular Medicine.** (Braunwald E, ed.). W. B. Saunders, Philadelphia, 1992, pp. 1106–1124.
2. Epstein FH. Risk factors for peripheral and cerebral atherosclerosis: Similarities and differences with coronary atherosclerosis. In: **Extracoronary Atherosclerosis** (Ventana A, Crepaldi G, Senin U, eds.). Monogr. Atherosclerosis, Vol. 14. S. Karger, Basel, 1986, pp. 1–5.
3. Vigna GB, Bolzan M, Romagnoni F, *et al.* Lipids and other risk factors selected by discriminant analysis in symptomatic patients with supra-aortic and peripheral atherosclerosis. **Circulation** 1982; 85(6): 2205–2211.
4. Sigfússon N, Sigvaldason H, Steingrímsd ttir L, Gudmundsdóttir H, Stefánsd ttir I, Thorsteinsson Th, Sigurdsson G. Decline in ischemic heart disease in Iceland and change in risk factor levels. **Br Med J** 1991; 302: 1371–1375.
5. Tejadac C, Strong JP, Montenegro MR, Restrepo C, Solberg LA. Distribution of coronary and aortic atherosclerosis by geographic location, race and sex. **Lab Invest** 1968; 18: 509–526.
6. Mitchell JRA, Adams JH. Aortic size and aortic calcification. A necropsy study. **Atherosclerosis** 1977; 27: 437–446.
7. Witteman JCM, Kannel WB, Wolf PA, Grobbe DE, Hofman A, D'Agortius RB, Cobb JC. Aortic calcified plaques and cardiovascular disease (the Framingham Study). **Am J Cardiol** 1990; 66: 1060–1064.
8. Fazio GP, Redberg RT, Winslow T, Schiller NB. Transesophageal echocardiographically detected atherosclerotic aortic plaque is a marker for coronary artery disease. **J Am Coll Cardiol** 1993; 21: 144–150.
9. Karalis DG, Chandrasekaran K, Victor MF, Ross JJ, Mintz GS. Recognition and embolia potential of intraaortic atherosclerotic debris. **J Am Coll Cardiol** 1991; 17: 73–78.
10. Blanth CI, Cosgrove DM, Webb BW, Ratliff NB, Boylan M, Piedmonte MR, Lyttle BW, Loop FD. Atheroembolism from the ascending aorta. An emerging problem in cardiac surgery. **J Thorac Cardiovasc Surg** 1992; 103: 1104–1111.
11. World Health Organization Principal Investigators (prepared by Tunstall-Pedoe H). The World Health Organization MONICA project (MONItoring trends and determinants in CArdiovascular disease): A major international collaboration. **J Clin Epidemiol** 1988; 41: 105–114.
12. Thorgeirsson G, Davidsson D, Sigvaldason H, Sigfússon N. Major risk factors for coronary heart disease mortality in Icelandic women. **Eur Heart J** 1990; 11(Suppl.): 326.
13. Witteman JCM, Kok FJ, Van Saase JLCM, Valkenburg HA. Aortic calcification as a predictor of cardiovascular mortality. **Lancet** 1986; 2: 1120–1122.
14. Hyman JB, Epstein FH. A study of the correlation between roentgenographic and post-mortem calcification of the aorta. **Am Heart J** 1954; 47: 540–543.
15. Castelli WP. Cardiovascular disease and multifactorial risk: Challenge of the 1980's. **Am Heart J** 1983; 106: 1191–1200.
16. Amery A, Fagard R, Guo C, Staessen J, Thijs L. Isolated systolic hypertension in the elderly: An epidemiological review. **Am J Med** 1991; 90(3A): 64S–70S.
17. Witteman JCM, Grobbe DE, Kok FJ, Hofman A, Valkenburg HA. Increased risk of atherosclerosis in women after the menopause. **Br Med J** 1989; 298: 642–644.
18. Niskanen LK, Suhonen M, Siitonen O, Lehtinen J, Nusitupa MI. Aortic and lower limb artery calcification in type 2 (non-insulin dependent) diabetic patients and non-diabetic control subjects. A five year follow-up study. **Atherosclerosis** 1990; 84: 61–71.
19. Wasty F, Alavi MZ, Moore S. Distribution of glycosaminoglycans in the intima of human aortas: Changes in atherosclerosis and diabetes mellitus. **Diabetologia** 1993; 36: 316–322.
20. Govich J, Zuna I, Merle M, Beyer-Enke IA, Merple N, Weigelbaum K, Van Kaick G. Aortic calcification in CT. Correlation with risk factors and cardiovascular disease. **Radiologe** 1989; 29: 614–619.
21. Pandrian MG, Hsu TL. Intravascular ultrasound and intracardiac echocardiography: Concepts for the future. **Am J Cardiol** 1992; 69: 6H–17H.
22. Seward JB, Khandhenia BK, Edwards WD, Oh JK, Freeman WK, Tajik AJ. Biplane transesophageal echocardiography: Anatomic correlations, image orientation, and clinical applications. **Mayo Clin Proc** 1990; 64: 1193–1213.