Coronary artery ectasia*

Jiří Knot, Josef Bis*, Richard Rokyta Jr.**, Josef Šťásek*, Petr Widimský

*Cardiocenter, Department of Cardiology, 3rd Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Prague, *Department of Medicine I, Hradec Králové University Hospital and Charles University School of Medicine, Hradec Králové, **Department of Medicine I, Plzeň University Hospital and Charles University School of Medicine, Plzeň, Czech Republic*

Knot J, Bis J*, Rokyta R Jr.**, Šťásek J*, Widimský P (Cardiocenter, Department of Cardiology, 3rd Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Prague, *Department of Medicine I, Hradec Králové University Hospital and Charles University School of Medicine, Hradec Králové, **Department of Medicine I, Plzeň University Hospital and Charles University School of Medicine, Plzeň, Czech Republic). **Coronary artery ectasia.** *Cor Vasa 2008;50(12):455–459.*

Background: Localized or diffuse dilatation of the coronary arteries (coronary ectasia) is a well-known, albeit rare, angiographic finding. Its incidence ranges from 0.2% to 5.3% in the literature. We aimed to determine its incidence, baseline characteristics, and prognosis in patients in the Czech Republic.
Methods and Results: All 6,997 consecutive coronary angiograms performed through 12 months in three cardiac centers in the Czech Republic were analyzed. The follow-up period was one year. Of the 6,997 patients, only 52 (0.7%) were assigned to the coronary artery ectasia group. The right coronary artery was the most common vessel affected by coronary artery ectasia. The majority (82.7%) were males. The median age was 65 years. A total of 23% of patients were diagnosed to have diabetes mellitus, 78.8% hypertension, 61.5% dyslipidemia, more than half were smokers (55.5%). Patients with coronary artery ectasia without coexisting coronary artery disease had no history of myocardial infarction. No death occurred in this group throughout the follow-up period of one year. A comparison of traditional risk factors for coronary artery disease and mortality between patients with isolated coronary artery ectasia and those with ectasia coexisting with stenosed coronary artery disease revealed no statistically significant differences in its incidence.
Conclusion: The incidence of coronary artery ectasia in our study was 0.7%. The majority of patients were males; they had hypertension and dyslipidemia, and a history of cigarette smoking. The most affected vessel was the right coronary artery. Isolated coronary ectasia occurred in 15.4%, no death in this group was noted
Key words: Coronary artery ectasia – Aneurysm – Dilatation – Atherosclerosis

Knot J, Bis J*, Rokyta R jr.**, Šťásek J*, Widimský P (Kardiocentrum, III. interní klinika, Fakultní nemocnice Královské Vinohrady a 3. lékařská fakulty Univerzity Karlovy, Praha, *I. interní klinika, Fakultní nemocnice Hradec Králové a Lékařská fakulta Univerzity Karlovy, Hradec Králové, **I. interní klinika, Fakultní nemocnice Plzeň a Lékařská fakulta Univerzity Karlovy, Plzeň, Česká republika). **Koronární ektazie.** *Cor Vasa 2008;50(12):455–459.*

Úvod: Lokalizované nebo difuzní rozšíření koronárních tepen (koronární ektazie) je dobře známým, ale vzácným angiografickým nálezem. Incidence výskytu ektazií je v literatuře uváděna od 0,2% do 5,3%. Naším cílem bylo stanovit výskyt, charakteristiku a prognózu těchto pacientů v České republice.
Metody a výsledky: V průběhu jednoho roku podstoupilo koronarografii ve třech kardiocentrech v České republice 6997 pacientů. Z tohoto souboru byli vybráni a dále sledováni po dobu 12 měsíců pacienti s nálezem koronárních ektazií, což bylo 52 osob, tj. 0,7%. Nejčastěji byla postižena pravá koronární tepna. Velkou část (82,7 %) souboru tvořili muži. Průměrný věk byl 65 let; 23% pacientů mělo diabetes mellitus, 78,8% byli hypertonici, 61,5% trpělo dyslipidemií a více než polovina pacientů byli kuřáci (55,8 %). Pacienti s ektaziemi bez koexistující obliterující aterosklerózy neměli v anamnéze infarkt myokardu a v průběhu jednoletého sledování nebylo zaznamenáno v této skupině žádné úmrtí. Při srovnání tradičních rizikových faktorů pro ischemickou chorobu srdeční a mortality mezi pacienty s izolovanými ektaziemi a pacienty s ektaziemi v kombinaci se stenotickým postižením koronárních tepen nebyly nalezeny statisticky významné rozdíly.
Závěr: Incidence koronárních ektazií v naší studii byla 0,7%. Velkou část pacientů tvořili starší muži, kteří trpěli hypertenzí, dyslipidemií a kouřili. Nejčastěji postiženou tepnou byla pravá koronární arterie. Izolované koronární ektazie se vyskytovaly u 15,4% pacientů a v této skupině nedošlo k žádnému úmrtí.
Klíčová slova: Koronární ektazie – Aneurysma – Dilatace – Ateroskleróza

Address: Dr. Jiří Knot, Cardiocenter, Department of Cardiology, 3rd Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Šrobárova 50, 10034 Prague, Czech Republic, e-mail: knot@fnkv.cz

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INTRODUCTION

Coronary artery ectasia (CAE) is a rare finding encountered during diagnostic cardiac catheterization. It was first described by Morgani[1] in 1761. Before the advent of angiography, all cases were diagnosed by postmortem examination. The first ante mortem diagnosis was made in 1958.[2] CAE, defined as aneurysmal dilatations >1.5 times the normal coronary artery segment, can be divided into discrete aneurysm (localized dilatation, either saccular or fusiform) or ectasia (diffuse dilatation involving ≥ 50% of the artery)[3] *(Figure 2)*. Ectasia was classified into four distinct types by Markis et al. according to the extent of involvement of the coronary vessels. Type I was described as diffuse ectasia of two or three major vessels, type II as diffuse disease in one vessel and localized disease in another vessel, type III as diffuse ectasia of one vessel only and, finally, type IV as localized or segmental involvement only.[4] The incidence of CAE ranges from 0.2% to 5.3%.[4-6] The largest ante mortem incidence of CAE was found in the Coronary Artery Surgery Study (CASS) data registry (4.9% of 20,087 patients referred for coronary angiography).[6] CAE can be seen with the coexistence with obstructive coronary artery disease. Isolated CAE, in which coronary artery stenosis and anomalies, valvular and other cardiac defects are not present, is sometimes called dilated coronaropathy.[7] Despite extensive literature, many questions still remain about its exact etiology and pathogenesis, prognosis and causal therapy.

ETIOLOGY

More than 50% of CAE are attributed to atherosclerosis. On the other hand, CAE has been observed in association with connective tissue disorders such scleroderma,[8] Ehler-Danlos and Marphan's syndrome,[9] polyarteriitis nodosa and Kawasaki disease.[10] An increased incidence of CAE has also been reported in several other disorders. Examples include heterozygous familial hypercholesterolemia, use of substances including herbicide sprays, acetylcholine esterase inhibitors and nitrates, previous arterial balloon angioplasty.[11] Cocaine use may predispose to the formation of an coronary artery aneurysm.[3] In 20–30% of cases, CAE have been supposed to be a congenital coronary anomaly.[12]

PATHOGENESIS

The pathogenic mechanisms underlying this phenomenon are still poorly understood. Because of histopatological findings, CAE is thought to be of atherosclerotic origin. Hyalinization, lipid deposition, focal calcification, fibrosis, and destruction of the media have been implicated. A foreign body giant cell reaction has also been reported to be present. Despite the intact intima, extensive media degeneration and hyalinization, possibly as a result of chronic vascular inflammation, are the common denominator in all cases with CAE.[13] Yetkin et al. aimed to compare the plasma levels of cystatin C and transforming growth factor-beta1 in patients with CAE. The plasma levels of cystatin C and transforming growth factor-beta1 were significantly higher in patients with combined CAE and coronary artery disease (CAD) than in those with CAD alone. This suggest that the pathogenesis of CAE might have some pathways different from those of atherosclerosis with respect to the regulation of extracellular matrix remodeling.[14] Yildirim et al. aimed to evaluate the expression of CD11b and CD45 adhesion molecules in peripheral blood granulocytes, monocytes, and lymphocytes of patients with CAE as possible markers of inflammation. The mean fluorescence intensity of CD45 and CD11b on the monocyte and lymphocyte surfaces of CAE patients was higher than that of controls. This may be a marker of endothelial activation and inflammation and is likely to be in the causal pathway leading to CAE.[15] Vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs) and tissue inhibitors of MMP (TIMPs) contribute to vascular remodeling.[16] Savino et al. showed that patients with CAE have decreased plasma levels of TIMP-2 and raised plasma levels of VEGF. This suggests an accelerated and persistent extracellular matrix remodeling process favoring arterial remodeling and aneurysm formation.[17] The inflammatory vascular hypothesis supports the finding of elevated plasma levels of V-CAM, I-CAM and E-selectin.[18] Stajduhar et al. described a higher coincidence of CAD with aortic aneurysm.[19] Similarly, Yetkin et al. have shown that CAE patients have an increased prevalence of varicocele compared with those with CAD.[20] This finding may reflect the genetic aspect of CAE.

IMAGING

The main coronary angiography characteristics of CAE are impaired coronary blood flow, delayed antegrade coronary dye filling, segmental back flow phenomenon (milking phenomenon), and stasis with local deposition of dye in the dilated coronary segment.[7] Senen et al.[21] and Papadakis et al.[22] have documented slow coronary flow using TIMI (thrombolysis in myocardial infarction) frame count method in patients with isolated CAE. Slow flow has also been recently evaluated using Doppler wire by Akyurek et al.[23] The coronary flow reserve (CFR) was significantly reduced in patients with diffuse CAE compared to a matched control group. Although volumetric coronary blood flow is significantly higher in CAE, microcirculatory dysfunction, that is reflected as depressed CFR and significantly lower myocardial blush grade,[24] may be the underlying cause of exercise-induced myocardial ischemia.

CLINICAL MANIFESTATION

The clinical course of CAE depends mainly on the coexistence with CAD. Although patients with CAE present mainly with symptoms of exertional angina, myocardial infarction may occur. An explanation is thrombus formation in the ectatic segment of the vessel and distal microembolism. Nevertheless, the presence of CAE did not affect the 5-year medical survival of patients with CAD.[6]

METHODS

All the 6,997 consecutive coronary angiograms performed throughout 12 months in three cardiac centers in the Czech Republic were analyzed. We included consecutively all patients undergoing their first cardiac catheterization throughout the above period for different indications: stable angina, unstable angina, STEMI and NSTEMI acute coronary syndromes, and other reasons. Coronary angiograms were described by experienced interventional cardiologists. Each coronary vessel (left main, left anterior descending, circumflex, and right coronary artery) was assessed. The number of diseased vessels and the visual estimation of the percent luminal reduction for each lesion were reported. Multiple projections were acquired to discern the maximal coronary artery luminal narrowing. Angiographic abnormalities were considered significant if >60% luminal diameter stenosis was found in any vessel. Furthermore, a *qualitative* description was added to this (semi)quantitative description. It was based on a retrospective review of 2,778 coronary angiograms performed one year ago in one of the centers. We defined 10 distinct qualitative types of angiographically visible coronary involvement:

1. coronary artery ectasia,
2. diffuse coronary calcifications,
3. thrombosis or embolism in otherwise normal arteries,
4. diffuse "diabetes-like" coronary disease without calcifications,
5. isolated plaques (focal atherosclerosis),
6. coronary fistula or other congenital anomaly,
7. coronary spasm,
8. muscle bridges,
9. spontaneous coronary dissection and
10. normal coronary angiography.

This classification is NOT based on the presence or absence of coronary luminal narrowing, but ONLY on a meticulous visual assessment of the qualitative type of involvement. Patients fulfilling criteria to ≥ 2 groups (types) were allocated to the type with the lowest type number. We defined CAE as segmental aneurysmal dilatation of at least of one epicardial coronary artery or diffuse aneurysmal dilatation of at least of two major arteries. In either case, the luminal diameter should be ≥ 5 mm, irrespective of the presence or absence of coronary stenosis or occlusion. Acute coronary occlusion (STEMI) with ectasias was considered CAE. We opted for the ≥ 5 mm threshold, because in many ectatic coronary arteries, the involvement is diffuse and normal reference segment may not be apparent. All patients were followed for a period of one year after the coronary angiography. We investigated the incidence, risk factors, vessels involvement, and the one-year mortality in CAE patients undergoing diagnostic coronary angiography in three cardiac centers across the Czech Republic. Statistical analysis was performed using GraphPad Prism version 2.0 software. For dichotomous variables, Fischer's exact test was used, for continuous variables Student's t test was used.

RESULTS

Of the 6,997 patients, only 52 (0.7%) were assigned to the CAE group. Of these 52 patients with CAE, 43 (82.7%) were males and only 9 (17.3%) were women. The mean age of patients was 65 years (64 in males, and 74 in females). We also investigated the traditional risk factors for CAD. Diabetes mellitus was present in 12 patients (23%), hypertension in 41 patients (78.8%), dyslipidemia in 32 patients (61.5%), while 29 patients were current smokers (55.8%). The mean platelet volume was 191 fentoliters *(Table I)*. Coronary angiograms revealed only 8 patients had only CAE without stenosis, while the remaining patients had 1-vessel, 2-vessel, 3-vessel, or left main disease. Twenty-six patients (50%) had a history of myocardial infarction. Of the patients with CAE without coexisting CAD, no patient had a history of previous myocardial infarction, and there was no death in this group. Over the follow-up period of 12 months, only two deaths occurred. One of these patients had CAE coexisting with 3-vessels disease, the second patient had left main plus 3-vessel disease. A comparison of traditional risk factors and mortality between patients with CAE only, and those with CAE and CAD is shown in *Table II*. There were no significant differences.

DISCUSSION

In previous studies, the incidence of CAE has been reported to be in the range between 0.2 and 5.3%. The largest registry of patients with CAE is the Coronary Artery Surgery Study. In this data registry, in which the data of 20,087 patients had been entered, 978 (4.9%) were found to have CAE.[6] The incidence of CAE of 0.7% in our project confirms the previous findings. A high prevalence of 16.4% was reported by Hall et al. in an Egyptian population, where the only risk factor was obesity.

The right coronary artery, regardless of concomitant CAD, was the most common vessel affected by the ectatic process – 43 patients (82.7%). This is consistent with previously published data.[25,26] The left anterior descending artery (31.5%), circumflex artery

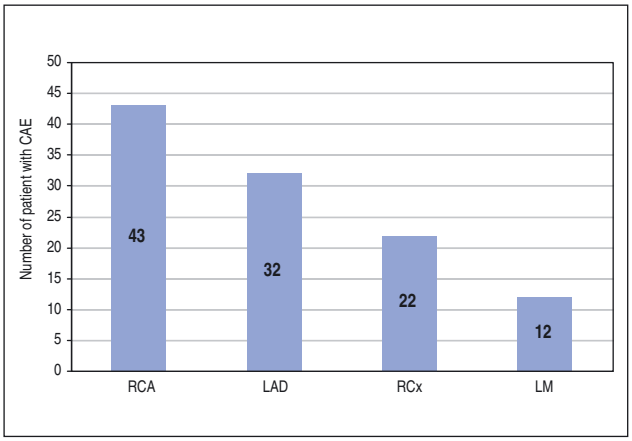

Figure 1 Distribution of CAE in different coronary vessels

CAE – coronary artery ectasia, RCA – right coronary artery, LAD – left anterior descending coronary artery, RCx – ramus circumflex, LM – left main

Table I
Baseline patients characteristic

	Patients with CAE
N	52
Male, n (%)	43 (82.7%)
Mean age, years	65
Diabetes mellitus, n (%)	12 (23%)
Hypertension, n (%)	41 (78.8%)
Dyslipidemia, n (%)	32 (61.5%)
History of smoking, n (%)	29 (55.8)
Mean platelet volume, fentoliters ± SD	8.0 ± 1.335

CAE – coronary artery ectasia

(42.3%), and the left main artery (23.1%) were the less affected vessels in a descending order *(Figure 1).*

Giannoglu et al.[27] studied 287 patients with CAE. Coronary artery ectasia was markedly more prevalent in men than in women ($p < 0.0001$). This male predominance was also supported by studies performed by Swaye[6] and Swanton.[25] In our population of patients with CAE, the male gender was represented in 82.7%.

The mean age in our patients was 65 years. On the other hand, some authors have reported a higher prevalence of CAE in younger patients.[3,27] These contradictory results may be caused by the prolonging life expectancy of the population.

We have also studied traditional risk factors for obstructive coronary artery disease, such as diabetes mellitus, hypertension, dyslipidemia, and a history of smoking. Androulakis et al.[28] examined the relation between diabetes mellitus and ectasia of coronary vessels. Diabetes mellitus was found to be independently but inversely associated with CAE (relative risk 0.603, 95% confidence interval 0.375 to 0.960, $p = 0.037$). Also in our population, diabetes mellitus occurred in only less than one in four patients (23%). Hypertension and dyslipidemia is more common in patients with CAE.[29] In our registry, 25% of subjects had hypertension and 61.5% dyslipidemia. Fifty percent of our patients had a history of myocardial infarction. This is in contradiction with the higher incidence of documented

Table II
Comparison of traditional risk factors and mortality between patients with CAE only and CAE + CAD

	CAE (n = 8)	CAE + CAD (n = 44)	p value
Mean age, years (n)	63.5	65.0	NS
Male (n)	6	37	NS
Diabetes mellitus (n)	1	11	NS
Hypertension (n)	5	36	NS
Dyslipidemia (n)	4	28	NS
Smoking (n)	2	27	NS
Deaths (n)	2	0	NS

CAE – coronary artery ectasia, CAD – coronary artery disease

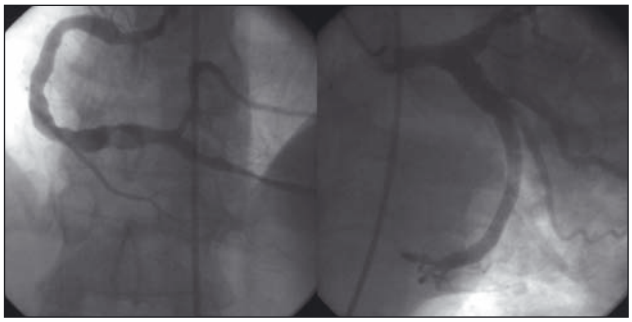

Figure 2 Ectasia of the right coronary artery with a large thrombus (left), ectasia of the left coronary artery (right)

myocardial infarction published previously (52.9% vs. 47.0%; $p < 0.001$).[6] Bitigen et al. sought to evaluate platelet function by measuring mean platelet volume (MPV), which is a marker of platelet reactivity. The MPV values of CAE patients were significantly higher than those of controls ($p < 0.0001$). Increased MPV may indicate altered platelet reactivity and aggregation and may thus be associated with ischemic events, observed in patients with isolated CAE. The mean value of MPV was 8.0 ± 1,335 fentoliters, with a laboratory range from 7 to 12 fentolitres. Comparing patients with CAE alone and CAE + obstructive CAD, no differences in the incidence of hypertension, diabetes mellitus, history of smoking and one-year mortality were found. The same conclusion was made by Swaye and coauthors.[6]

TREATMENT

Anticoagulation has been suggested by some authors,[25] but it has not been tested and could not be recommended unless supported by subsequent studies. The administration of platelet inhibitors as prophylaxis against ischemic syndromes is indispensable in all forms of CAE.[30] The administration of nitroglycerin has no therapeutic benefit in "dilated coronaropathy" and should be avoided.[7] Development of ischemia in patients with isolated CAE has been shown to be dependent on heart rate. Therefore, a reasonable therapeutic approach might be the administration of beta-blockers due to their negative chronotropic effect and reduction of myocardial oxygen consumption in the absence of vasodilatation.[31]

CONCLUSION

The incidence of CAE in our study was 0.7%. The majority of patients were males with a mean age of 65 years, who had hypertension, dyslipidemia, and had a history of cigarette smoking. The right coronary artery was the vessel most commonly affected by CAE. Only 8 patients had CAE only without coexisting coronary stenosis, these eight patients had no myocardial infarction in their history. We did not find any significant differences in the traditional risk factors for atherosclerosis and in one-year mortality rate between patients with coronary artery ectasia compared with those with coronary artery ectasia and coexisting coronary artery disease.

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