International Heart and Vascular Disease Journal
Volume 5, Number 13, March 2016

Journal of the Cardioprogress Foundation

Endocrine system pathology as the risk factor of acute coronary syndrome without ST segment elevation in intact coronary arteries

Sapozhnikov A.N., Leonova E.E., Danilova K.S., Jahina G.Kh.

Ulyanovsk State University, Ulyanovsk, Russia

Authors:

Alexandr N. Sapozhnikov*, M.D., Ph.D., associate professor of the Department of hospital therapy, Ulyanovsk State University, Ulyanovsk, Russia

Ekaterina E. Leonova, clinical assistant of the Department of hospital therapy, Ulyanovsk State University, Ulyanovsk, Russia

Kristina S. Danilova, student of the medical faculty, Ulyanovsk State University, Ulyanovsk, Russia

Gulnara K. Jahina, M.D., PhD student, Department of hospital therapy, "Ulyanovsk state University", Ulyanovsk, Russia

Summary

Objective

Investigate endocrinological pathologies associated with acute coronary syndrome (ACS) in case of intact coronary arteries.

Materials and methods

We examined 168 patients with the diagnosis of acute coronary syndrome and analyzed the results of routine laboratory tests including carbohydrate metabolism and thyroid function parameters.

Results

In case of suspected ACS females have intact coronary arteries more often than males. More than 90% of this group of patients have arterial hypertension, often they have dyslipidemia, arrhythmias, history of old myocardial infarction. Myocardial infarction's possibility appears more often when there is concomitant diabetes mellitus.

Conclusion

Females under 75 years old with thyroid gland pathology, impaired carbohydrate metabolism and elevated blood pressure have higher possibility to develop ACS without ST segment elevation in intact coronary arteries. It is reasonable to include thyroid hormone blood levels estimation into standard ACS diagnostic algorithm and intact coronary arteries detection.

* Corresponding author. Tel 8-927-272-55-30. E-mail: 1nilych1972@mail.ru.

Key words
Acute coronary syndrome, intact coronary arteries, arterial hypertension, hypothyroidism, diabetes mellitus, females under 75 years old.

Introduction

According with the World Health Organization (WHO), 17.5 million people died from cardiovascular diseases in 2012, of these deaths, an estimated 7.4 million (42.3%) were due to coronary heart disease (CHD). According with the Federal State Statistics Service (Rosstat), mortality due to cardiovascular system diseases was 49.6% of total number of death cases. CHD is the cause of death in more than half of all cases, and it corresponds to 26.7% of all number of deaths [1]. Therefore, cardiovascular diseases and CHD in particular remain one of the main causes of mortality in the Russian Federation.

The term "acute coronary syndrome" (ACS) as a working diagnosis was introduced by the specialists of Russian Society of Cardiology (RSC) to indicate exacerbation of CHD. Coronary artery (CA) thrombosis occurring at the place of atherosclerotic plaque rupture with consequent development of ischemia is considered to be a typical pathogenetic mechanism of ACS. Formation of occluding (sub-occluding) thrombus at the place of atherosclerotic plaque erosion is possible in some cases [2]. But the phenomenon of unstable angina occurring within mildly changed and unchanged CA had been described in the sixties of XX century [3]. According with the results of national and international studies, the frequency of mildly changed and unchanged CA varies between 10 and 30% [4, 5].

The GUSTO IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes) trial (n=12142) detected non-significant CA changes in 30.5% and 14.9% of female and male patients, respectively. The results of this study have been further proved by the TIMI IIIb trial (Thrombolysis in Myorardial Infarction, Phase IIIb) (n=1473) that identified mildly changed CA in 14-19% of patients with ACS.

According with the results of one Russian study of 2015 (n=711), the frequency of unchanged or mildly changed CA during examination of patients with suspected ACS was 37.9% [6].

Therefore, ACS pathogenesis is a complex phenomenon that cannot always be explained by "typical" pathological mechanism. Because of this, several etiological and pathogenetic theories of ACS development in mildly changed CA have been proposed: vasospastic, metabolic [7], related to CA tortuosity [8], coronary microcirculation impairment [9], endothelial dysfunction, decreased local NO production, pathologic susceptibility to heartache, and others [10, 11].

Consequently, detection of unchanged and mildly changed CA in ACS becomes a complex diagnostic and therapeutic problem [12-14].

Materials and methods

1292 patients aged up to 75 years with diagnosis "ACS without ST segment elevation" and discharge diagnosis "Unstable angina" had been admitted to Ulyanovsk Regional hospital for in-patient treatment or for diagnostic coronary angiography (CAG) during the period of 2011-2015. 168 individuals with intact/mildly changed CA were selected from all admitted patients (1019 males and 273 females). Average age of patients was 56.34±8.79 years (varying from 27 to 75 years).

All patients underwent CAG (Siemens Axiom Artis, Germany angiography equipment with a pixel size of 184 μm); not less than 5 views of left CA and not less than 2 views of left CA have been analyzed.

Standard laboratory tests were performed using Olympus AU-400 (Japan) equipment and software and included obligatory analysis of carbohydrate metabolism characteristics. Thyroid gland (TG) function was assessed by estimation of thyrotropic hormone (TTH), thyroxin (T4), triiodothyronine (T3), thyroid peroxidase (TPO) antibodies levels measured in 84 patients.

Exclusion criteria for this study were the following: patients' renunciation of CAG intervention, age above 75 years, extracardiac causes of chest pain – acute attacks of peptic ulcer disease, reflux esophagitis, exacerbation of cervical and thoracic osteochondrosis, congenital and acquired valvular heart disease.

We estimated the significance of differences between studied characteristics using x2 criteria and Spearman's correlation analysis. Statistical analysis of results was performed using Statistica 10 software. The differences were considered statistically significant, if the p-value was less than 0.05.

Results and discussion

Statistical analysis revealed that up to 30% of females admitted to hospital with the diagnosis of ACS with-

out ST elevation have mildly changed or intact CA significantly more frequently than males (Table 1)

Table 1. **Gender differences of mildly changed CA occurrence in ACS without ST elevation**

Mildly changed/intact CA	Females	Males
yes	82	86
not (stenosing atherosclerosis)	191	933

Comorbidity estimation revealed that 157 (93%) patients have arterial hypertension (AH), 137 (82%) have dyslipidemia, 61(36%) have different arrhythmias (mostly extrasystoles). 25 (15%) individuals have history of myocardial infarction (MI). TG pathology was observed in 35 (42%) patients, 28 (17%) patients have obesity and impaired carbohydrate metabolism, including 18(10.7%) individuals with diabetes mellitus (DM), 17 (10%) patients have osteochondrosis of the spine, 8 (9%) males have prostate adenoma, 12 (7%) patients have lower extremity varicous veins, 5 (6%) female patients have uterine myoma, 5 (3%) patients have chronic pyelonephritis and bronchial asthma, 3(2%) have chronic bronchitis, urolithiasis and cholelithiasis (Figure 1).

Initially 11% of patients had the history of TG disorders. Hypothyroidism in elderly people has non-specific clinical manifestations and is often asymptomatic that complicates diagnosis verification. According with the results of Colorado study, finished in 2000 and involved 25862 patients, 25% of patients had apparent hypothyroidism without any symptoms, and 35% of patients had subclinical hypothyroidism [15]. Laboratory tests for TG function revealed pathological changes in 41.6% of patients, and hypothyroidism was the dominant pathology presented in 71.4% of cases. It is known that the number of hypothyroidism cases increases with age, especially in females. Average hypothyroidism occurrence in elderly women is 10 times higher than in elderly men [16]. The results of the Whickham study (n=2779) revealed that total prevalence of hypothyroidism was 14 cases per 1000 females (or 19 cases per 1000 females, taking into account possibly omitted cases) and 1 case per 1000 males [17].

It was demonstrated that hypothyroidism leads to coronary circulation impairment [18]. According with the results of meta-analysis of 11 prospective studies (n=55287), the presence of hypothyroidism (TTH levels elevation > 10 μU/L) increases the risk of CHD development and death from it [19].

Glucose metabolism impairment was detected in 29 patients (17.2%), and 18 patients (10.7%) had DM. 33.3% of them (n=6) have the history of MI. Prevalence of MI history in individuals without DM is significantly lower (12.6%). Some studies demonstrate the existence of interrelation between hypothyroidism and DM. One of possible mechanisms underlying it may be explained by gluconeogenesis suppression that leads to decreased glucose synthesis with further compensation of this insufficiency by decreased glucose utilization by muscles and other peripheral tissues [20]. There are evidences about increased glucose-induced insulin secretion in hypothyroidism that is decreased during therapy with L-thyroxine. [21]. Combination of hypothyroidism and DM increases

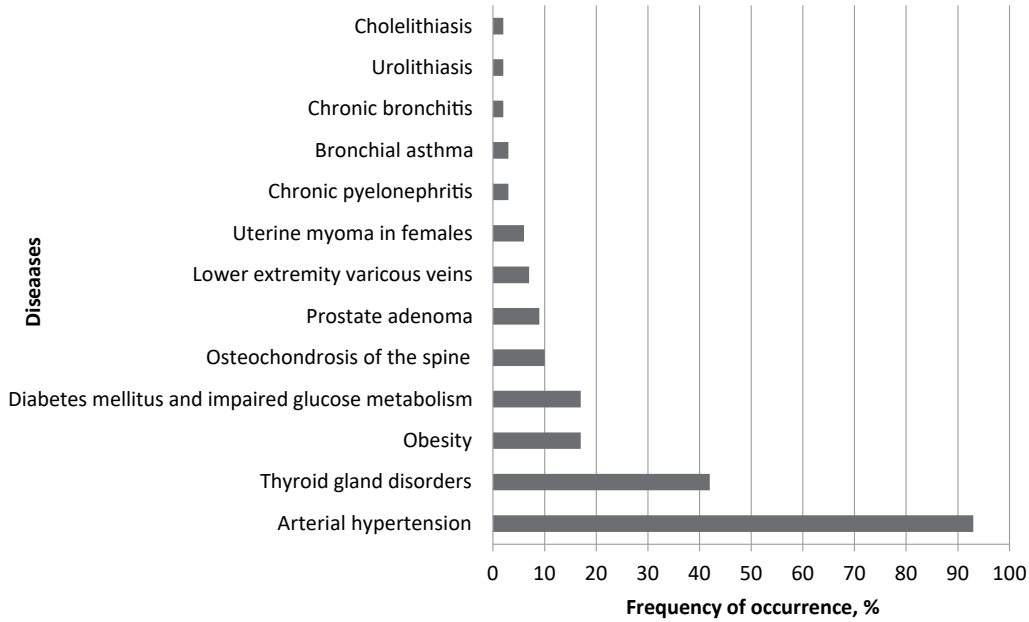

Figure 1. The frequency of different diseases occurrence in ACS without ST segment elevation with mildly changed CA.

the risk of cardiovascular diseases, and TG pathology is more significant. Patient with DM and subclinical hypothyroidism have higher cardiovascular risk comparing with patients with DM and compensated TG pathology [22].

Investigation of correlation between TTH levels and lipid spectrum characteristics revealed unidirectional changes. There was a moderate direct correlation between TTH and low density lipoprotein (LDL) levels ($p<0.05$, $r=0.53$)and high density lipoprotein (HDL) levels ($p<0.05$, $r=0.4$), and cholesterol (Ch) levels ($p<0.05$, $r=0.4$).

Hypothyroidism can be the cause of unidirectional changes of blood lipid spectrum [23]. Hepatic lipase and cholesterylester transfer protein regulate lipoprotein levels [24]. These enzymes remodel lipoproteins, exchange Ch and triglycerides' esters between lipoproteins. Enzymes' activity changes considerably in case of hypothyroidism, and it results in increased blood lipoprotein levels [25].

TG hormones deficiency decreases the amount of LDL receptors in liver and consequently diminishes LDL excretion and increases their levels. TG hormones' effects are mediated by nuclear receptors of thyroid hormones having the ligand-binding site and the site interaction with deoxyribonucleic acid (DNA). Thyroid hormones interact with ligand-binding domain of the receptor, after it DNA-binding domain interacts with DNA-hormone-sensitive fragment, responsible for LDL receptor gene transcription [26].

More than that, unlike other organic compounds consumed with food or synthesized in organism, structural base of cholesterol cannot be decomposed into CO2 and H2O. That's why the major part of Ch is excreted with bile acids. Thyroid hormones regulate the activity of cholesterol-7-α-hydroxyilase, enzyme participating in bile acids synthesis from Ch [27]. The activity of this enzyme reduces in case of hypothyroidism, and it, in its turn, increases Ch levels [28].

Therefore, all discussed above mechanisms in some extent lead to unidirectional changes of blood lipid spectrum in hypothyroidism.

Conclusion

We identified that around 30% of females under the age of 75 years, admitted to the hospital with provisional diagnosis of "ACS without ST elevation", have intact CA, this phenomenon is observed significantly more often in female patients comparing with males.

AH is the most frequent pathology in patients with ACS and mildly changed CA, being present in around 93% of all cases. The risk of MI development in this group of patients increases significantly in case of concomitant DM-2 type.

Changes of lipid metabolism characteristics in case of unchanged CA majorly evidence TG pathology. Endocrine system diseases (impaired carbohydrate metabolism and TG pathology) aggravate CAD treatment and can be considered as predictors of coronary artery insufficiency even in mildly changed and intact CA.

Conflict of interests: None declared

References

1. Sherbakova EM. Demographic results for the first half of 2015 (Part I). Demoskop Weekly. 2015; 653-4. Russian
2. Gratsiansky N.A. Management of acute coronary syndromes without persistent ST segment elevation. Recommendations of the Russian Society of Cardiology. http://www.scardio.ru/rekomendacii/rekomendacii_rko/nacionalnye_rekomendacii_po_lecheniyu_ostrogo_koronarnogo_sindroma_bez_stoykogo_podema_st_na_ekg. Russian
3. Proudfit WL, Shirley EK, Sones FM. Selective cine coronary arteriography: Correlation with clinical findings in 1000 patients. Circulation. 1966; 33 (6): 901-10.
4. Lykov AV, Parhomenko JuV, Ivanov PA. The myocardial infarction in patients with unchanged coronary arteries. Vserossijskij zhurnal nauchnyh publikacij. 2013; 4 (19): 6-8. Russian
5. Kemp HG, Kronmal RA, Vlietstra RE. Seven year survival of patients with normal or near normal coronary arteriograms: A CASS registry study. J Am Coll Cardiol. 1986; 7 (3): 479-83.
6. Korok EV, Sumin AN, Sin'kov MA. Unchanged coronary arteries according to the coronary angiography: frequency and reasons. Contradictions of modern cardiology: arguable and unsolved problems: Proceedings of IV international conference. 16-17 oktyabrya 2015. Samara; 2015: 68. Russian
7. Crea F, Lanza A. Angina pectoris and normal coronary arteries: cardiac syndrome X. Heart. 2004; 90 (4): 457-63.
8. Sebov DM, Markina EV. Angiographic features of coronary arteries morphology in patients with coronary syndrome X. Vestnik Rossiyskoy Voenno-meditsinskoy akademii. 2013; 4 (44): 95-7. Russian
9. Cannon RO, Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. Am J Cardiol. 1988; 61 (13): 1338-43.
10. Pasceri V, Lanza GA, Buffon A. Role of abnormal pain sensitivity and behavioral factors in determining chest pain in syndrome X. J Am Coll Cardiol. 1998; 31 (1): 62-6.
11. Rosen SD, Paulesu E, Wisw RJS. Central neural contribution to the perception of chest pain in cardiac syndrome X. Heart. 2002; 87 (51): 513-9.

12. Bugiardini R, BaireyMerz CN. Angina with "normal" coronary arteries: a changing philosophy. JAMA. 2005; 293 (4): 477-84.
13. Bugiardini R, Manfrini O, De Ferrari GM. Unanswered Questions for Management of Acute Coronary Syndrome: Risk Stratification of Patients With Minimal Disease or Normal Findings on Coronary Angiography. Arch Intern Med. 2006; 166 (13): 1391-5.
14. Cannon RO. III Chest pain with normal coronary angiograms. N Engl J Med. 1993; 328 (23): 1706-8.
15. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160: 526-34.
16. Vanderpump MPJ. Th e epidemiology of thyroid diseases. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's Th e Th yroid: A Fundamental and Clinical Text. 2005, 9th edn, pp 398-406. JB Lippincott-Raven, Philadelphia.
17. Tunbridge WMG, Evered DC, Hall R, et al. Th e spectrum of thyroid disease in the community: the Whickham survey. Clin Endocrinol 1977; 7:481-93.
18. Biondi B. Mechanisms in endocrinology: Heart failure and thyroid dysfunction. European Journal of Endocrinology 2012; 167(5):609-18.
19. Rodondi N, den Elzen WP, Bauer DC, et al. Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA: The Journal of the American Medical Association 2010; 304: 1365-74.
20. McCulloch AJ, Johnston DG, Baylis PH, et al. Evidence that thyroid hormones regulate gluconeogenesis from glycerol in man. Clin Endocrinol (Oxf). 1983; 19(1): 67-76.
21. Handisurya A, Pacini G, Tura A, et al. Effects of thyroxine replacement therapy on glucose metabolism in subjects with subclinical and overt hypothyroidism. Clin Endocrinol (Oxf). 2008; 69(6): 963-9.
22. Amati F, Dube JJ, Stefanovic-Racic M, et al. Improvements in insulin sensitivity are blunted by subclinical hypothyroidism. Med Sci Sports Exerc. 2009; 41(2): 265-9.
23. Shin DJ, Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through Sterol Regulatory Element-Binding Protein. Biol Chem. 2003; Vol. 278: 34114-8.
24. Franco M, Castro G, Romero L. Decreased activity of lecithin: acyltransferase and hepatic lipase in chronic hypothyroid rats: implications for reverse cholesterol transport. Mol Cell Biochem. 2003; 246 (1-2): 51-6.
25. Zambon A, Bertocco S, Vitturi N. Relevance of hepatic lipase to the metabolism of triacylglycerol rich lipoproteins. BiochemSoc Trans. 2003; Vol. 31: 1070-4.
26. Bakker O, Versinga VM. Resistance to thyroid hormones. Tironet. 2001; 4. Russian
27. Drover VAB, Agellon LB. Reguation of the human holesterol 7à-hydroxylase gene (CYP7A1) by thyroid hormone in transgenic mise. Endocrinologist. 2004; Vol.145: 547-81.
28. Rush J. Role of thyroid disease in the development of statin-induced myopathy. Endocrinologist. 2006; Vol.16: 279-85.