HISTOLOGICAL AND HISTOCHEMICAL CHARACTERISTICS OF RAT MYOCARDIUM IN CADMIUM TOXICOSIS

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Carcinogenic effects of cadmium on lungs, testicles and prostate are well known, so as cumulative and toxic effects on kidney, liver and bones; however, there have not been many published articles about the effects of cadmium on myocardium. The aim of this study was to estimate the morphological changes in rat myocardium chronically treated by cadmium.

The study was carried out on male albino Wistar rats (n=30, age=35-37 days, body mass 120g +/- 10g). The animals were raised in controlled laboratory conditions and provided with standard laboratory rat food and tap water ad libitum. The rats were divided into two groups: ten animals composed the control group and did not undergo any treatment. The 20 experimental rats were exposed to 10mg of CdCl2 /L drinking water for 90 days. After 90 days, all animals were victimized and after the macroscopic inspection of the heart, myocardial tissue was routinely processed and embedded in paraffin. Sections 5 micrometers thick were stained by HE method and histochemical PAS-AB (pH 2, 5), Masson trichrome method for demonstrating collagen fibers and Toluidine blue for mast cells identification.

Cross-striated banding pattern of cardiac cells was ruined. Noticeable atrophy and hydropic degeneration of subendocardial localized cardiac cells were found, with the focal presence of myocytolysis. Endothelial cell hyperplasia and edema of the intima were present on arteriolar type blood vessels causing the focal subocclusion. Fibrocytes, histiocytes and mast cells were numerous, perivascularly localized. Mast cells were polymorphic, larger than normal, oval and mostly degranulated. Instead of scanty endomysium, there is a noticeable interstitial fibrillar fibrosis with few fields of collagen in all myocardium layers between cardiac cells, which is particularly prominent around the larger blood vessels.

Cadmium has pronounced vasculotropic properties causing morphological changes of cardiomyocytes, myocardial interstitial fibrillar collagen network and on the heart small blood vessels. *Acta Medica Medianae 2013;52(2):15-22.*

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Introduction

Cadmium (Cd) was discovered by German chemist F. Strohmeier in 1817, and it belongs to the group of heavy metals and is very spread in nature in the form of cyanide salt, nitrite, chloride and halides. Large part of cadmium comes from occupational exposure that occurs during the processing of ores and metal smelting. Cadmium compounds are used for protection against corrosion, battery and accumulators production. Also, pure cadmium or alloys are used as a pigment in the manufacturing of paints, glass, ceramics and enamels. Cadmium is also used in the production of plastics, pesticides, in the electronics industry (for the production of fluorescent screens) and in the nuclear industry (as a neutron absorber in reactors) (1-3).

Cadmium accumulates in the atmosphere during progressive process of erosion and abrasion of rock and soil, caused by events such as forest fires and volcanic eruptions (4). Significant concentrations of cadmium in soil and water has contributed to its presence in the animal meat, fish, vegetables and fruit, so that contaminated food is the major source of population exposure to cadmium (5,6). As cigarettes contain from 0.3 to 0.5 mg Cd, tobacco smoke is also an important factor for contamination of the general population (7,8). Through tobacco smoke, 50% of cadmium is absorbed from the lungs into the systemic circulation (3,7).

In persons occupationally exposed to cadmium, the main route of entry into the body is cadmium inhalation, but also the intake of cadmium via digestive tract and skin contributes to the total exposure. Once cadmium enters the circulation, it is transported to certain depots, and the most important are kidneys, liver and muscles. Cadmium is eliminated from the body through the digestive tract and urine, but due to the low level of excretion from the body and its

excessive accumulation in the blood and depots, it has a biological half-life of up to 30 years (19).

Chronic exposure to cadmium is associated with increased incidence of various neoplastic and non-neoplastic diseases of kidney, liver, lungs, bone, brain, thyroid gland and other organs (10-13). It was also found that cadmium has a neurotoxic effect because it affects the integrity of the blood-brain barrier (14), but the report on structural changes in the myocardium under the influence of cadmium are rarely found in literature (15).

Aim

Histological and histochemical examination of myocardium of rats chronically treated with cadmium.

Material and methods

White male Wistar rats, weighing 120g (+/- 10g) and 35-37 days old, were used in the present study. There were 30 rats divided into control (n=10) and experimental (n=20) groups. All rats were raised in controlled laboratory conditions (in an animal room, with a 12h light/ 12h dark cycle, at 22+/-2°C). The animals were provided with standard laboratory rat food and with "ad libitum" access to tap water. Ten rats from the control group were not subjected to any treatment. Twenty rats in the experimental group were treated with 15mg/kg dissolved cadmium (as CdCl2) in the drinking water.

Animals were sacrificed after 90 days, and after macroscopic examination of the rat hearts, heart tissue were fixed in Bouin's solution for 24 hours. Myocardial tissue was routinely processed and embedded in paraffin. Sections 5 micrometer thick were used for classic HE staining, histochemical AB-PAS method (pH2, 5), histochemical Masson-trichrome and cytochemical Toluidine blue staining for mast cells identifying.

The experimental procedure of this work was previously approved by the local ethics committee.

Results

The pathological changes were not found during histopathological examination of control group myocardium. Cardiomyocytes of this group were normal in size, elongated, branched with visible cross-striation and intercalated discs. Around cardiac cells, delicate sheaths of endomysium containing a rich capillary network were seen.

In all experimental animals, the changes that indicate toxic cardiomyopathy in myocardial tissue were verified. A cross-striated banding pattern of cardiac cells was ruined. Prominent atrophy and hydropic degeneration of subendo-cardial localized cardiac cells with focal myo-cytolysis was found in the experimental group myocardium (Figure 1). Endothelial cell hyper-plasia and intimal edema was present in the arteriolar blood vessels (Figure 2), and these changes caused focal arteriolar subocclusion.
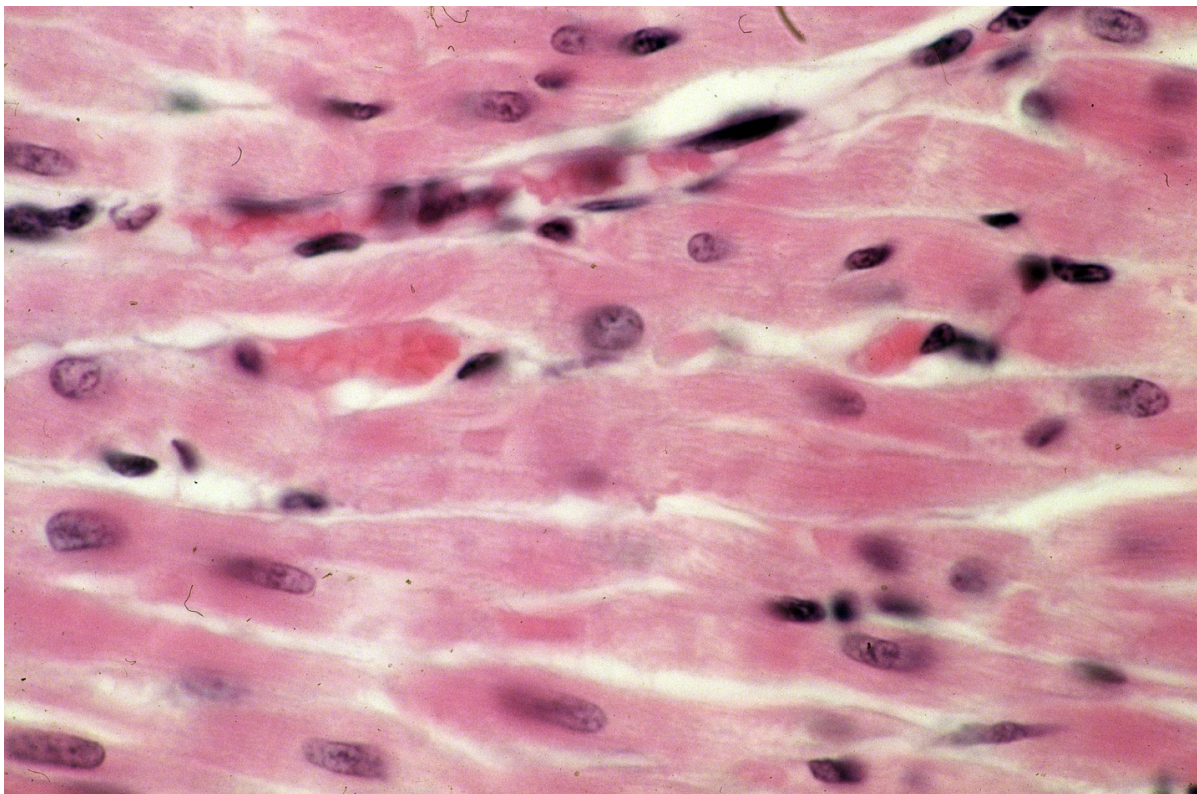

Figure 1. Hydropic degeneration of muscle fibers with focal myocytolysis (H&Ex400)
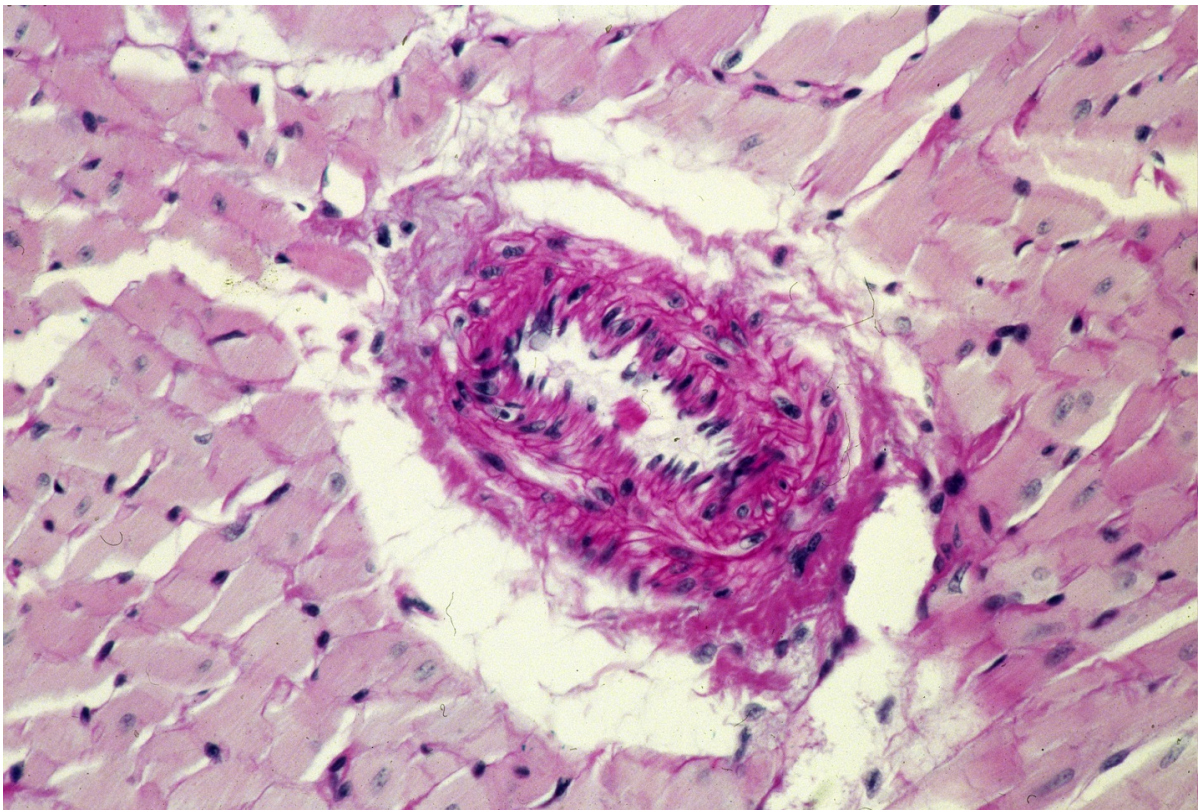
Figure 2. Cross-section of myocardial artery: narrowed lumen due to endothelial hyperplasia and PAS-positive protein insudation in the wall. Significant perivascular edema. Striking focal glycogen depletion, of pale-pink color, present in the surrounding cardiomyocytes (AB-PAS x 250)
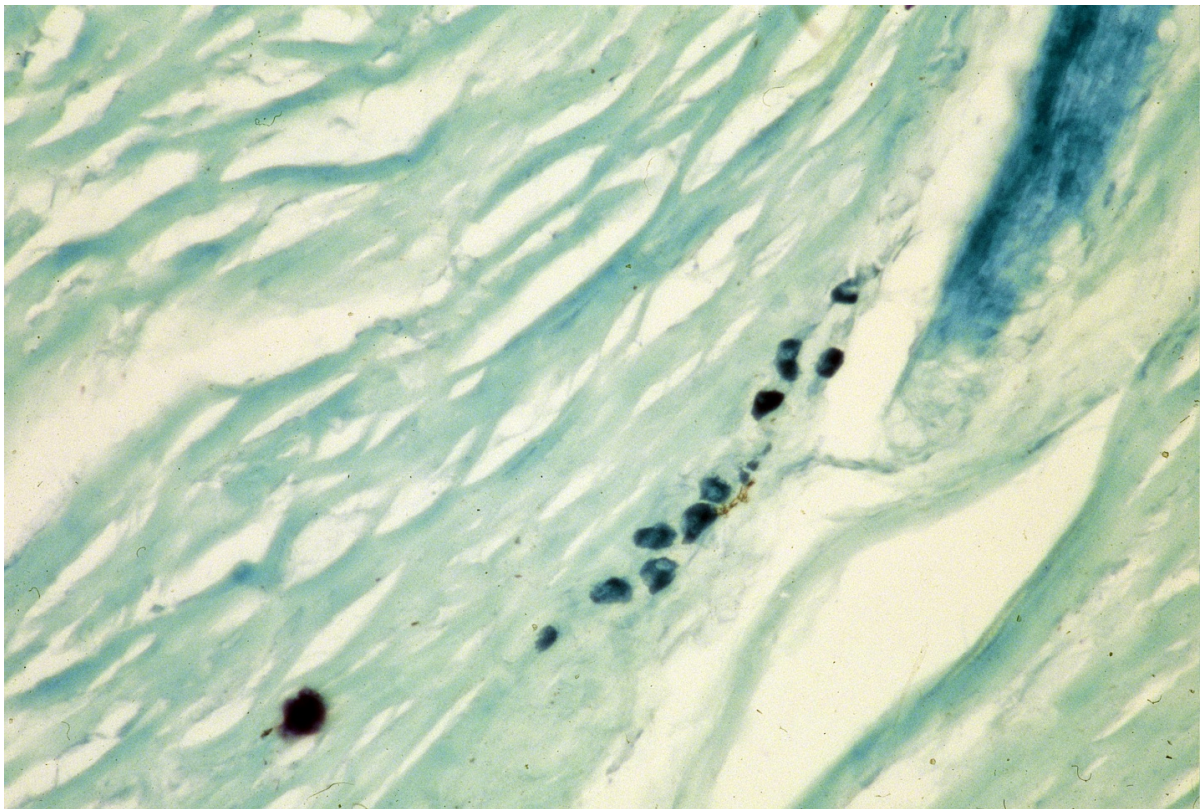

Figure 3. Numerous mast cells hyperstained and partly degranulated in extensive collagen field (Toluidine blue X 400)
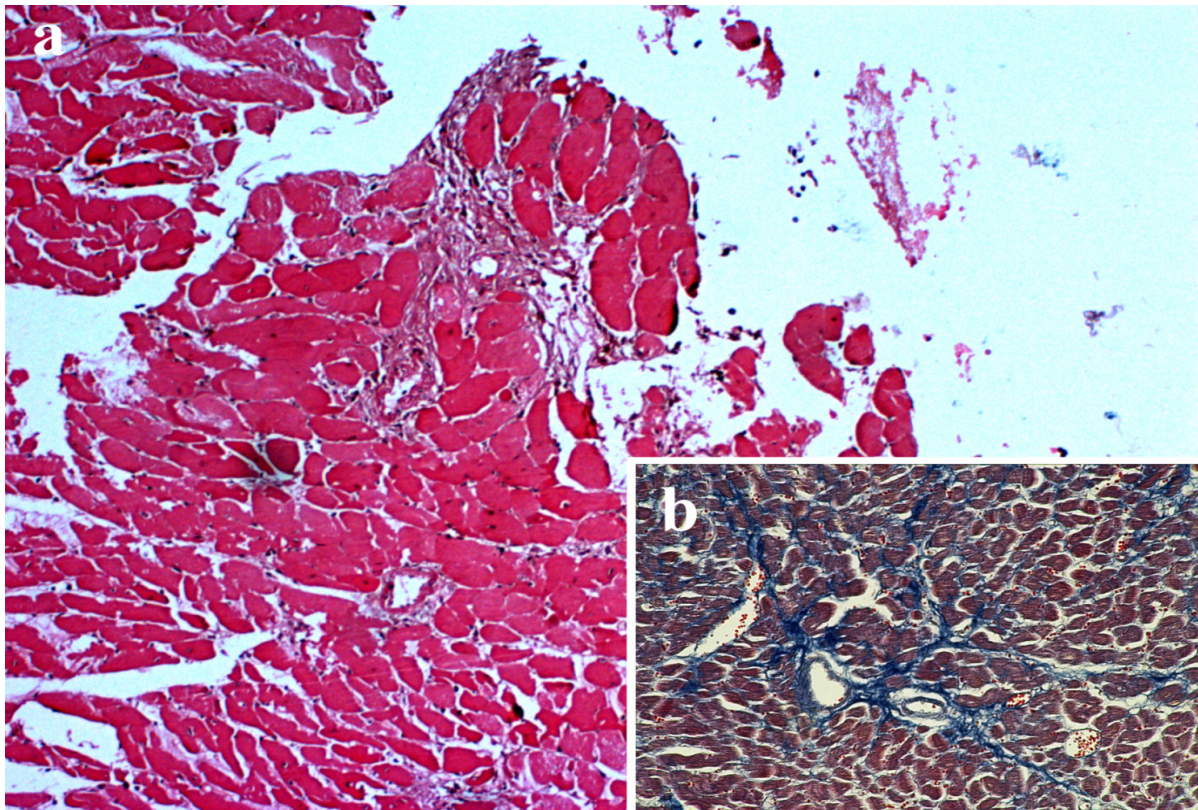
*Figure 4.(a) Myocardial interstitial fibrosis with cardiac cells fragmentation (H&E X 200)
(b) Prominent perivascular fibrosis (Masson trichrome X 250)*

Multifocal capillary hemorrhage was also present in the myocardium. A large number of fibrocytes, histiocytes, lymphocytes and mast cells were present in the perivascular regions (Figure 3). Numerous mast cells were polymorphic, larger than normal, oval and mostly degranulated (Figure 3). Instead of scanty endomysium, there is a noticeable interstitial fibrillar fibrosis with few fields of collagen in all myocardium layers between cardiac cells, which is particularly prominent around the larger blood vessels (Figure 4).

Discussion

Because of its extreme toxicity and wide distribution in the nature, the U.S. Agency for Environmental Protection classified cadmium among 126 priority pollutants. It is considered that exposure to tobacco smoke, contaminated water and food, and occupational exposure are the most common sources of Cd exposure (1,3,6,7). Cadmium is present in almost all food, but depending on the food type and the level of external contamination, Cd concentration varies. The high concentration of Cd is present in the offal, also in crabs and molluscs such as oysters. Plant origin food contains higher concentrations of Cd than meat, eggs, milk and dairy products and fish meat (16).

It has been shown that exposure to cadmium is associated with benign and malignant tumors of lung, prostate, pancreata, kidneys, breast, thyroid gland and bladder in humans (1,12,13,17,18). Therefore, the International Agency for Research on Cancer and The National Toxicology Program of the U.S. classified cadmium in human carcinogens I group category (17,19).

Except in chronic cadmium toxicosis in our experiment, mast cell hyperplasia, perivascular aggregation of histiocytes and fibroblasts with marked interstitial myocardial fibrosis with fields of collagen are described in hypertensive rats (20) and in rats with postmyocarditis dilated cardiomyopathy (21).

Interstitial fibrillar fibrosis with degenerative changes and focal necrosis of cardiomyocytes in human pathology was already described in heart patients after several months of doxorubicin treatment (22,23), in patients with primary hypothyroidism (24) and in patients with transplanted heart (25). Recent studies have suggested that interstitial myocardial fibrosis is an important marker of early diabetic cardiomyopathy (26).

It is considered that the toxicity of cadmium, among other things, comes from cadmium reaction with sulfhydryl groups, thus changing the activity of many enzymes. Although cadmium is not a redox-active metal, it indirectly leads to oxidative stress and tissue damage (2,10). This metal has a long biological half-life of 15-30 years, primarily because of its low excretion and excessive accumulation in the blood, kidney, liver and other organs (9).

Even in the seventies, it was observed that cells exposed to cadmium showed significant changes in the cell organelles such as ribosomes disintegration, EPR destruction and mitochondrial swelling (27). Later findings established that Cd in mammalian cells directly inhibits or stimulates the activity of different enzymes (28), disrupts the proper formation of membrane proteins and secreting proteins (29) and inhibits the activity of antioxidant enzymes directing cytoplasmic redox potential toward oxidation, with increased reactive oxygen species (ROS) and reactive nitrate compounds (12, 30).

There is accordance in the literature that mitochondria are key intracellular targets for Cd due to their ability to accumulate Cd and sensitivity of mitochondrial enzymes because of the damage caused by Cd. Because of the mitochon-dria central role in the critical cellular processes such as bioenergetics, redox signaling and cell death, mitochondrial damage induced by Cd has long-term consequences for cell function, energy homeostasis and survival of the organism (31,32).

Cadmium changes the activity of many mitochondrial proteins, leading to inhibition of mitochondrial enzymes, membrane potential collapse and swelling of mitochondria, with subsequent respiration inhibition, loss of inner mitochondrial membrane potential and loss of accumulated calcium. At the same time, produced mitochondrial swelling associated with abnormal acidification due to lactate production indicates a disruption of oxidative metabolism. Cd binds to the inner membrane and thus accelerates lipid peroxidation and disturbs the integrity of the mitochondrial membrane (31). Mitochondria have many potentially harmful proteins. The increased permeability of mitochondrial membranes is a critical event that results in the release of various molecules, such as molecules that switch on pro-caspases, Cyt-C (caspase activator) (33). Cd-induced cell death occurs trough caspase-dependent way associated with the release of cytochrome C or caspase-independent pathway over the cell death associated with ROS (34). Production of reactive oxygen species has proved to be one of the first steps in Cd-induced cyto-toxicity which precedes mitochondrial damage. ROS leads to an attack on membrane phospho-lipids and loss of mitochondrial membrane potential (35,36).

Cadmium-induced oxidative stress causes not only DNA damage (mutations) and protein oxidation but also lipid peroxidation in many organisms (35,37). Lipid peroxidation is the oxidative damage which affects cell membranes, lipoproteins, and other lipid-containing molecules under conditions of oxidative stress. Membrane lipids are the most common substrates of oxidative attack. Free radicals are the initiators of lipid peroxidation process. Once initiated, auto-catalytic reaction continues, has progressive course and outcome as structural and functional changes of substrate (2,35).

Among other things, exposure to cadmium causes necrotic cell death (37,38), which we also demonstrated in the myocardium of our experi-mental animals. Reference literature points out that apoptosis and necrosis may be induced by increased accumulation of ROS (40,41) and increased lipid peroxidation (35,42).

Interstitial fibrosis, which was found in all of our experimental animals, can be explained by proliferation of mast cell and its degranulation causing release of regulatory cytokine tryptase. Cytokine tryptase stimulates fibroblast prolife-ration and the creation of fibrous tissue as collagen fields and interstitial fiber depoes (43). The possible pathogenetic explanation could be that exposure of cells to a variety of stresses, including chemical stress, elicits an up-regulation of a number of cytoprotective systems (44), amongst which the heat shock response is one of the most studied (45). In this response, the synthesis of a number of proteins (heat shock proteins, HSPs) is up-regulated. These proteins play a role in maintaining protein structure/ function by acting as chaperones to sites of degradation and as facilitators of folding (46). Many members of heat shock family proteins such Hsp70, Hsp27 and Hsp47 were induced by a few metals, including Cd. The cardiac function of inducible Hsp70 knockout mice is markedly impaired by ischemia/reperfusion injury (47). The synthesis of HSP47 is not observed in non-collagen secreting cells, and it is therefore apparent that HSP47 expression is always in parallel to collagen biosynthesis and secretion. Also, constitutive expression of HSP47 in non-stressed cells is accompanied by collagen secretion (48). HSP47 is a potential biomarker and therapeutic target for fibrosis, and it requires proper modulation of its expression, because overexpression or impaired expression could be exacerbating factors in fibrosis (48).

It should be emphasized that the mechanism of Cd-induced cytotoxicity is not well-defined and is still in the research phase.

Conclusion

Cadmium has a pronounced vasculotropic properties causing morphological changes of cardio-myocytes, myocardial interstitial fibrillar collagen network and on the heart small blood vessels. Understanding the precise mechanisms of collagen biochemistry and its association with stress responses is deemed necessary for further investigations.

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HISTOLOŠKE I HISTOHEMIJSKE KARAKTERISTIKE MIOKARDA PACOVA U KADMIJUMSKOJ TOKSIKOZI

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Karcinogeni efekti kadmijuma na pluća, testise i prostatu dobro su poznati, kao i kumulativni i toksični efekti na bubreg, jetru i koštano tkivo, ali uticaji kadmijuma na miokard nedovoljno su proučeni, pa je naš cilj bio ispitivanje miokarda pacova hronično tretiranih kadmijumom.

Za eksperiment je korišćeno 30 belih Wistar pacova, muškog pola, težine oko 120g (+/-10g), starosti 35-37 dana. Sve životinje su čuvane u istim uslovima laboratorijske štale. Hranjene su uobičajenom hranom za pacove i pile vodovodnu vodu „at libitum". Nikakvom tretmanu nije bilo podvrgnuto deset pacova iz kontrolne grupe. Iz eksperimentalne grupe tretirano je dvadeset pacova 15mg CdCl2 rastvorenog u pijaćoj vodi.

Posle 90 dana, sve životinje su žrtvovane i nakon makroskopskog pregleda srca, uzimano je tkivo miokarda, koje je rutinski obrađivano i kalupljeno u parafin. Na presecima debljine 5 mikrometara primenjene su klasična HE, histohemijske AB-PAS (pH2,5), Masson trihromne metode i citohemijska Toluidine blue tehnika za prikazivanje mastocita.

Utvrđena je upadljiva atrofija i hidropična degeneracija subendokardijalno lokali-zovanih mišićnih vlakana, sa fokalno prisutnom miocitolizom. Na krvnim sudovima tipa arteriola prisutna je hiperplazija endotelnih ćelija i edem intime. Perivaskularno su umnoženi fibrociti, histiociti i mastociti. Mastociti su polimorfni i hipogranulisani. Multi-fokalno su u miokardu prisutna kapilarna krvarenja. U svim slojevima miokarda, peri-vaskularno, izražena je vlaknasta fibroza.

Kadmijum ispoljava izražena vaskulotropna svojstva izazivajući morfološke promene na miokardu i sitnim krvnim sudovima srca. *Acta Medica Medianae 2013; 52(2):15-22.*

Ključne reči: cadmium, pacovi, kardiomiopatija