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Intramyocardial Small Vessel Disease

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The structural abnormalities in intramyocardial arteries were studied in three groups of autopsies: 1) 466 consecutive autopsies of persons above 25 years of age; 2) 102 cases of sudden unexpected death (mean age 56.70±1.54 years); 3) 70 randomly selected autopsies (mean age 57.41±2.18 years). Intramyocardial small vessel disease (IMSVD) was established in 19,31% for the first, in 34.31% for the second and in 67.14% for the third group. High incidence of IMSVD was established in essential hypertension (17.96%), essential hypertension matched with diabetes (28.86%), chronic alcoholism (44.44%) and rheumatic heart disease (41.67%). Idiopathic IMSVD was rarely seen (7 cases). There was a wide spectrum of lesions in intramyocardial arteries often with narrowing of the lumen. IMSVD is a heterogeneous group concerning its etiology and morphology. IMSVD may cause myocardial ischemia, electric instability of the heart and sudden death.

Key words: intramyocardial small vessel disease, histopathology, essential hypertension, diabetes, chronic alcoholism.

Introduction

The significance of IMSVD in human pathology is not well understood and remains controversial [8, 10, 17]. Most of the morphological studies are performed on biopsy material or on small series and single cases of sudden death [2, 3, 14, 16, 17]. There is no generally accepted terminology and classification of the changes in intramyocardial arteries. Various terms like "Intramyocardial microarteriopathy", "Intramyocardial small vessel disease", "Coronary small vessel disease"' "Small vessel disease" etc. are used [3, 12, 14, 15, 17, 19]. There are suggestions that IMSVD may contribute to the pathogenesis of the so called "X-syndrome" and in some cases may result in sudden death [2, 3, 4, 5, 7, 8, 9, 20].

The ***aim*** of this study is to describe structural abnormalities in intramyocardial arteries in order to determine the incidence, etiology and morphologic appearance of IMSVD.

Material and Methods

Three groups of patients were studied:

First group: 466 consecutive autopsies of patients over the age of 25 - 310 of them being male and 156 female. Autopsies were performed at the Department of General and Clinical Pathology of Medical University of Varna.

Second group: 102 patients (82 male and 20 female, of average age 56.7± 1.54 yrs) with unexplained sudden death. Autopsies were performed at the Department of Forensic Medicine and Deontology of Medical University of Varna.

Third group: 70 autopsies of randomly selected autopsies of patients who died between the age of 1 month to 85 years during the period 1994-1996 (average age 57.41±2.18 yrs). Autopsies were performed at the Department of General and Clinical Pathology of Medical University of Varna.

In the first and the second group serial paraffin sections of routinely obtained myocardial material were studied. In each case of the third group were analyzed 8 pieces of the myocardium, including left and right ventricle, left and right atrium and materials obtained from left and right coronary artery. The sections were stained with HE, Cruchay trichrome stain, van Gieson–elastica, orcein, iron colloid stain+PAS and PTAH. Morphological alterations in intramyocardial the arteries with diameter under 1 mm were evaluated. The size of the vessels was determined by linear morphometry with ocular morphometer. The statistical evaluation of the differences between groups was carried with alternative analysis at a confidence threshold established at $P<0,05$.

Results

Incidence

IMSVD was found in 90 (19.31±3.56%) out of totally 466 patients analyzed in the first group. Changes in the intramyocardial arteries were found more frequently in suddenly died patients (second group) compared to the first group - 35 out of totally 102 cases (34.31±9.21%) ($p<0.001$). In the third group where large areas of myocardium were analyzed IMSVD was observed in 47 (67.14±11.00%) cases. In outher 20 (28.57±10.38%) cases in that group were found single arteries with intimal fibrosis or intimal cushions.

Significance of underline diseases

Analysis of the relation between IMSVD and underline diseases found at necropsy (Fig. 1) showed that a combination of essential hypertension and diabetes mellitus results in statistically significant increase of IMSVD compared to the group with hypertension alone. In both the first and second group 83% of the cases were with severe atherosclerosis of subepicardial coronary arteries and signs of ischemic heart disease. IMSVD was found significantly less frequently in patients who had suffered IHD alone (10.34%) ($p<0.01$). IMSVD was more often observed in cases with chronic alcoholism (44.44%) and rheumatic disease (41.67%) ($p<0.01$). In 5 cases with marked IMSVD there was no significant coronary atherosclerosis or other heart diseases that could explain the changes in the intramyocardial arteries.

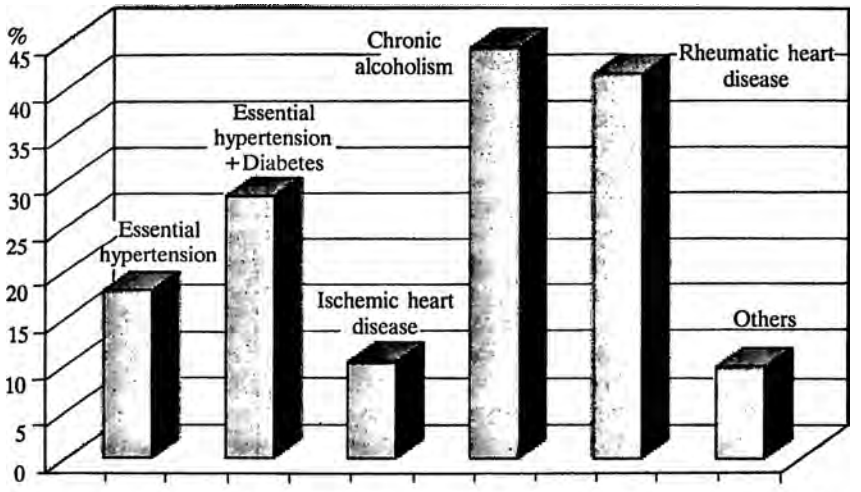

Fig. 1. Significance of underline diseases for the incidence of IMSVD (First group n=466)

Histopathology of IMSVD

Morphological changes in intramyocardial arteries show wide variety in topography, spreading and character. They were focal and affect short segments of the arteries. Most severe changes were located in the lateral wall of left ventricle and papillary muscles. Most frequent was concentric and eccentric intimal fibrosis with narrowing of arterial lumen (Fig. 2). It was usually accompanied by hyperplasia and myoelastofibrosis of media with formation of intimal cushions, the latter being found usually in muscular arteries with diameter up to 300 μm. They were on a large basis and significantly narrow the arterial lumen (Fig. 3).

In larger muscular arteries with diameter between 300 to 800 μm there was myointimal dysplasia with irregular thickening of intimal and medial layers and expansion of oblique and longitudinal muscle fascicles. Morphological changes in these arteries resemble "blockade arteries" (Sperrarterien) or fibro-muscular dysplasia of the arterial wall (Fig. 4). In the intima of single larger arteries (diameter 400-1000 μm) of patients with a combination of hypertension and diabetes were found atherosclerotic-like lesions with eccentric intimal thickening, focal deposition of glucosaminglycans and damage of the internal elastic membrane (Fig. 5).

Clinicopathological correlation

The clinical importance of IMSVD is determined by the wide spreading of changes and the degree of narrowing of intramyocardial arteries. Of major importance is also the status of subepicardial coronary arteries. Wide spread IMSVD with significant narrowing of the arterial lumen in the majority of cases was accompanied by severe atherosclerosis of coronary arteries in all three analyzed groups. Therefore it is not likely that IMSVD alone has an independent pathogenic role in thanatogenesis. In only about one third of the cases of IMSVD in first and third group (I group – 30 cases /33.33%/; III group. – 20 cases/ 28.57%/) there was severe intramyocardial arteriopathy with no or mild atherosclerosis of coronary arteries. Probably in part of these cases IMSVD has contributed to the cause of death.

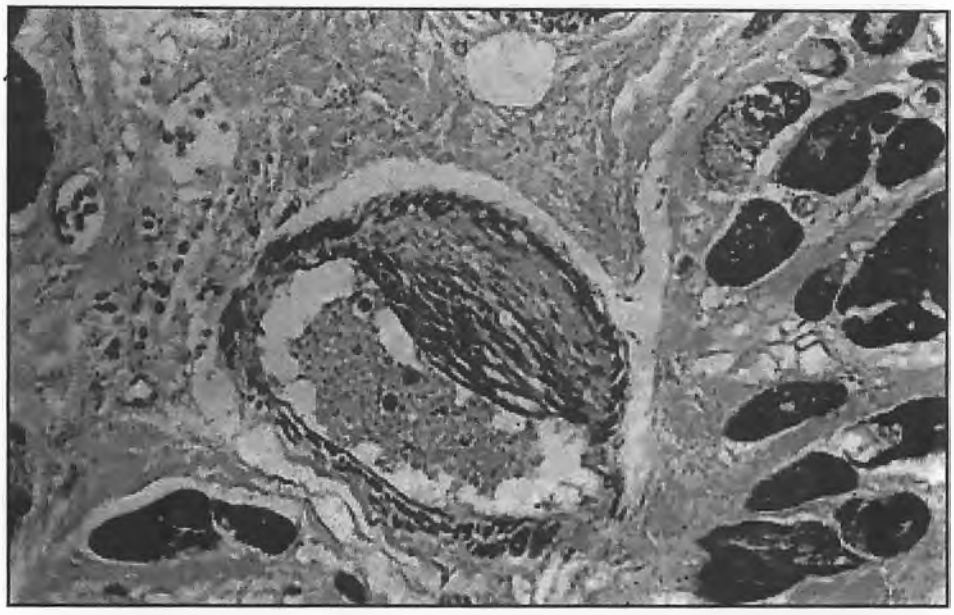

Fig. 2. Eccentric intimal fibrosis in muscle artery with diameter 200 μm, van Gieson-elastica (Microphoto × 160)

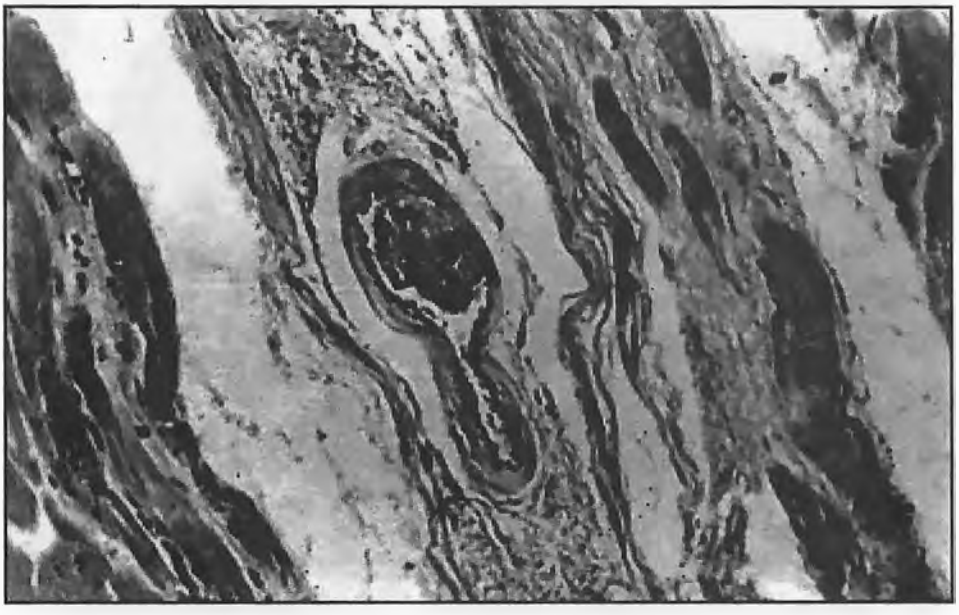

Fig. 3. Intimal pillow with de novo formation of elastic fibers in artery with diameter 200 μm, van Gieson-elastica (Microphoto × 160)

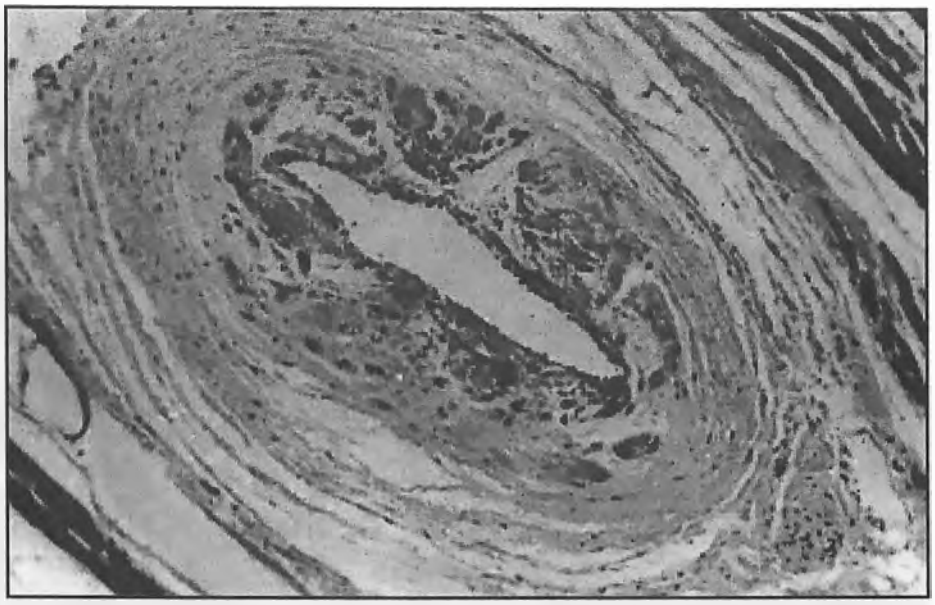

Fig. 4. Myointimal dysplasia in muscle artery with diameter 800μm, HE (Microphoto × 63)

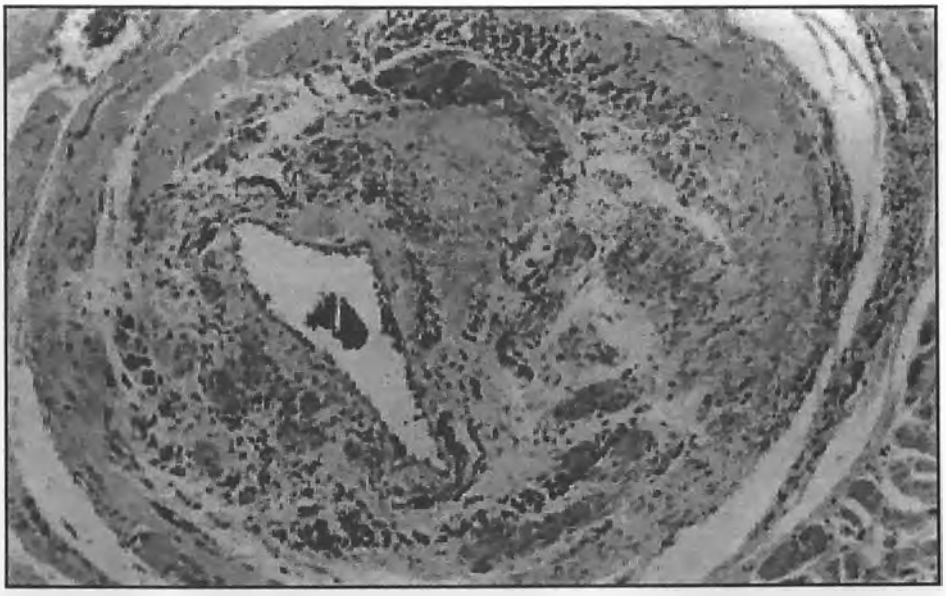

Fig. 5. Atherosclerotic-like lesion in artery with diameter 1 mm, van Gieson-elastica (Microphoto ×63)

In the group of suddenly died patients in 29 out of 35 cases with IMSVD the cause of death was IHD (severe coronary atherosclerosis with acute myocardial infarction or cicatrices after MI). In only two cases in that group no other cause of death was found morphologically. In these cases IMSVD probably was the direct cause of sudden death but the exact mechanisms of tanathogenesis (myocardial ischemia, disorders of heart rhythm) remained unclear.

Discussion

This study demonstrates that IMSVD was found commonly in archival necropsy material (19.31%). In cases of sudden death the incidence of IMSVD is significantly higher ($p<0.001$). In the third group where all heart areas were thoroughly studied IMSVD was found in 67.14% – incidence similar to that determined by endomyocardial biopsies-61% (17.19).

Idiopathic form of IMSVD was rarely seen in our material (5 cases in group I and 2 cases in group II) compared to the results reported by Matoba, R. et al. [11] in 1999 who found (9%) 18 cases of intramyocardial arteriopathy without other diseases in a group of 200 patients with unexplained sudden death.

IMSVD alone is not a separate clinical-pathological entity. It is a heterogeneous group concerning both its etiology and morphologic features. Most commonly IMSVD was related to diseases like essential hypertension, diabetes mellitus and IHD which are well known for their ability to affect the small vessels. It is worth mentioning that IHD alone, not accompanied by essential hypertension and diabetes, did not increase the risk of damaging the intramyocardial arteries. Probably hemodynamic stress of vessel walls caused by arterial hypertension contributed to the pathogenesis of IMSVD. Analysis of different topographic areas of myocardium revealed that most severe damage was found in the hemodynamically burdened areas. Experimental morphological studies of intramyocardial arteries of spontaneously hypertensive rats also support this view [1, 6, 7, 18]. Hyperplasia of arterial media in essential hypertension was partly due to effects of different growth factors like platelet growth factor, angiotensin II and epidermal growth factor [13]. Probably metabolic disturbances in diabetes mellitus in combination with hemodynamic stress in arterial hypertension together increased these effects and resulted in significantly more frequent and more severe damage of intramyocardial arteries [12, 16, 19, 21].

It is interesting to mention also the severe damage found in intramyocardial arteries in patients with chronic alcoholism. The pathogenesis of IMSVD related to chronic alcoholism remains unclear. Suggestions were made about endothelial damage from ethyl alcohol alone, acetaldehyde, biogenic amines and as well as magnesium deficiency [3, 4).

What is the exact morphogenesis of IMSVD still remains unclear. The prevalence of intimal changes in intramyocardial vessels suggests endothelial damage as a possible mechanism. The common finding of focal destruction of internal elastic membrane with formation de novo of rough elastic fibers with disturbed spatial orientation suggests that degenerative changes and disturbances in elastogenenesis contribute to the pathogenesis of IMSVD.

The functional importance of IMSVD is determined by narrowing of vessel lumen and by disturbed vasomotion caused by severe damage of internal elastic membrane and media [10]. Severe and wide spread damages of intramyocardial arteries can lead to decrease coronary reserve and disturbed collateral circulation. The involovement of conducting systems' arteries, as shown in other studies [2, 8, 17], results in electrical instability of the heart, disorders of rhythm, and sudden death.

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