Ukrainian journal of cardiovascular surgery
March 2019;1 (issue 34):71–77
https://doi.org/10.30702/ujcvs/19.35/17(071-077)

Morphological Changes on the Interventricular Septal Myocardium within the First Hours after Alcohol Septal Ablation in Patients with Hypertrophic Cardiomyopathy

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Abstract. The surgical method is the gold standard for the treatment of obstructive HCM. However, it cannot be used in patients whose condition causes a high cardiosurgical risk. In addition, successful surgical treatment of HCM is possible only in medical centers where there is a highly qualified multidisciplinary team of specialists.

ASA is an alternative treatment for HCM. The literature does not reflect myocardial changes in the first hours after ASA.

Objective: to describe the data on the study of morphological changes in the myocardium of two patients with obstructive HCM one and ten hours after ASA.

Patients. Patient G., 55 years old, NYHA class III, pressure gradient on the LV outflow tract – 116 mm Hg, IVS thickness of 2.2 cm, mitral regurgitation – 35%. During ASA, there developed bradycardia which turned into asystole. Hemodynamics was restored. However, an hour later recurrent asystole occurred which led to death. Patient K., 66 years old with clinical signs corresponding to NYHA class III, LV systolic pressure gradient – 49 mm Hg., IVS thickness – 2.4 cm, 28% mitral regurgitation. One hour after ASA, there appeared the signs of hemodynamic deterioration which resulted in death in 10 hours. The autopsy showed that the cause of death was bleeding from the subclavian artery at the puncture site of the central venous catheter.

Methods. Macroscopy, microscopy of histological samples stained with hematoxylin and eosin, Van Gieson's picrofuchsin, Weigert's fuchselin by MSB method modified by Zerbino-Lukasevich.

Results: In microvessels, there were changes in the walls associated with alcohol coagulation of their structures. The lumens of arteries and arterioles were occluded with "shadows" of red blood cells or with small blood clots which caused ischemic

damage to CMC. Alcohol leakage beyond the capillaries was accompanied with coagulation necrosis of the surrounding CMC. 10 hours after ASA, WBC infiltrates were present in the affected areas.
Keywords: *hypertrophic cardiomyopathy, interventricular septum, alcohol septal ablation, morphology.*

Hypertrophic cardiomyopathy (HCM) is genetically determined primary myocardial disease with an autosomal dominant pattern of inheritance characterized by asymmetric myocardial hypertrophy, an increase in the area of the mitral valve (MV) cusps with subsequent conduction disorders. This pathology is reported in the general population in 0.2-0.5% of cases. The natural course of the disease is associated with a high risk of sudden death (3-6% of patients with HCM per year). There is obstructive and non-obstructive HCM forms, depending on the presence of narrowing in the left ventricle outflow tract (LVOT). Obstructive HCM is characterized by more severe clinical manifestations. Recently, several approaches to its treatment have been proposed: drug therapy, electrophysiological treatment (DDD pacemaker implantation), endovascular – alcohol septal ablation (ASA), and surgical treatment. Drug therapy in patients with obstructive HCM as a monotherapy is currently not commonly used due to poor immediate and long-term results. The dual-chamber pacing method also did not live up to expectations, since long-term results did not differ from the placebo effect in this cohort of patients [2]. The surgical method is considered to be the “gold standard” for the treatment of obstructive HCM, but it cannot be used in patients whose condition causes a high cardiosurgical risk. In addition, successful surgical treatment of HCM is possible only in medical centres where there is a high-qualified multidisciplinary team of specialists. Alcohol septal ablation is an alternative method for patients who cannot receive surgical treatment. Long-term and immediate results in most patients after ASA are good [2, 3]. Thus, a team of authors from the M.M. Amosov National Institute of Cardiovascular Surgery [2], in their scientific work devoted to the study of ASA outcomes in 123 patients, observed a decrease in systolic pressure gradient from 91.7 ± 8.3 mmHg up to ≤ 30 mmHg in 81% of patients in the follow-up period. A. Batzner et al. [3] in their study which included 952 patients determined a decrease in systolic pressure gradient on LVOT from 63.9 ± 38.2 mmHg to 33.6 ± 29.8 mmHg at rest and from 104.6 ± 44.0 mmHg to 56.5 ± 41.0 mmHg with the Valsalva manoeuvre in the early period of observation. In 98.6% of cases these patients reached a 5-year control point without significant cardiovascular events.

Scientific studies on the morphological changes of the interventricular septal (IVS) myocardium occurring at different times after ASA are not numerous based on single observations, and therefore do not reflect all pathogenesis stages. Thus, A. L. Baggish et al. describe changes in the myocardium after ASA in 4 patients within 2 days to 14 months [4]. The earliest changes in myocardium after ASA have not been

described in the literature. In our centre there were two fatal cases – 1 and 10 hours after ASA.

The **purpose** of the work is to describe the data on the study of morphological changes in the myocardium of two patients with obstructive HCM one and ten hours after ASA.

Materials and methods

Patient G., 55 years old (died 1 hour after ASA), was admitted with clinical signs consistent with NYHA FC III: complaints of shortness of breath and chest pain on exertion, palpitations, and general weakness. No specific changes were observed on the ECG. Echocardiography data: systolic pressure gradient (SPG) in LVOT – 116 mmHg, the IVS thickness – 2.2 cm, MV regurgitation – 35%. According to the results of coronary ventriculography (CVG), no hemodynamically significant constriction was detected in the coronary arteries. During ASA, sinus bradycardia occurred in the patient after the introduction of 2 ml of ethanol into the septal branch (SB) of the anterior descending coronary artery, which turned into asystole. Resuscitation was effective, it was possible to restore haemodynamics for 1 hour, then asystole appeared again, which led to death.

Patient K., 66 years old (died 10 hours after ASA), referred to the clinic with complaints of severe shortness of breath on exertion and sometimes at rest, weakness, lower extremity oedema, attacks of cardiac asthma. On the ECG – scar cardiosclerosis on the anterior wall of the left ventricle. Echocardiography: SPG on LVOT – 42 mm Hg, the IVS thickness – 2.4 cm, MV regurgitation – 28%, in the pericardium on the posterior wall – 0.9 cm of fluid, signs of severe diastolic myocardial dysfunction. According to the CVG, the coronary arteries are intact. ASA of the 3rd SB of the anterior descending coronary artery was performed. One hour after ASA, signs of hemodynamic deterioration appeared with increasing signs of shock. The patient died after 10 hours of treatment in the ICU. Pathomorphological examination showed that the cause of death was bleeding from the subclavian artery at the puncture site of the central venous catheter.

Macroscopic examination of the heart and other organs was performed during the autopsy, followed by examination of histological preparations obtained from different sites of the IVS and free walls of the left ventricle (LV) of the heart. Paraffin sections were prepared according to the conventional procedure and stained with hematoxylin and eosin (for observational microscopy), Van Gieson's picrofuchsin (for differentiation of muscle and collagen fibres), Weigert's fuchselin on elastin, by MSB method modified by Zerbino-Lukasevich. The latter technique allows the detection of fibrin of varying degrees of maturity, as well as to evaluate the functional status of cardiomyocytes (CMC) [1].

Results

The morphological examination of the heart of the patient G. showed a thickened basal segment of the IVS. The endocardium reaches a thickness of 1.5

mm in this area due to the growth of collagen and elastic fibres, with thin layers consisting of dystrophically altered muscle cells between them (Fig. 1A, 1B).

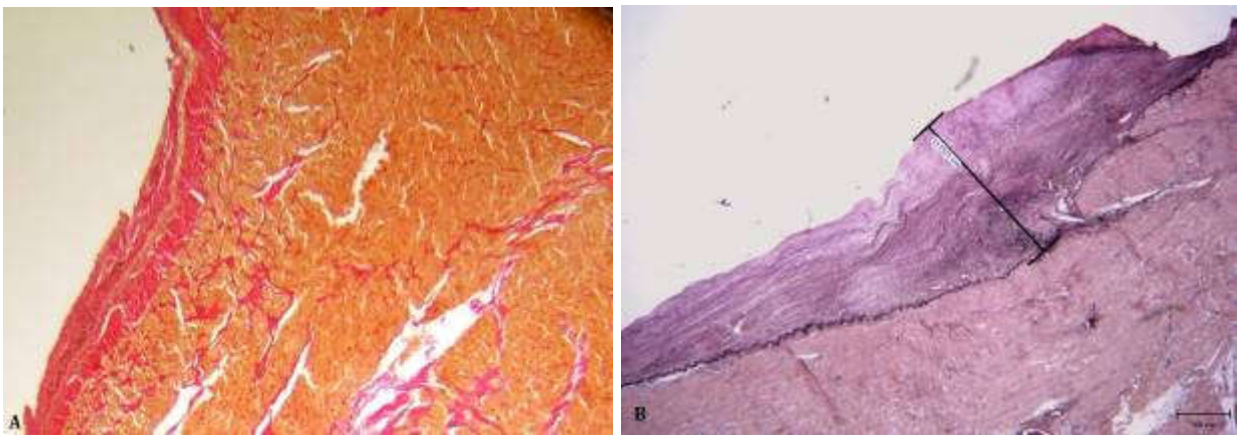

Fig. 1. Patient G. Endocardial fibrosis of the sub-aortic IVS segment, extending along the interstitium into the myocardial thickness: A – Van Gieson's picrofuchsin staining, x40 magnification; B – Weigert's fuchselin staining, x20 magnification

The fibrous tissue strands from the endocardium extend into the thickness of the myocardium (Fig. 1A). In the deep layers of the myocardium, there are other changes that point to HCM: CMC hypertrophy which goes into the stage of decompensation with signs of dystrophy, apoptosis and development of replacement fibrosis in many areas (Fig. 2).

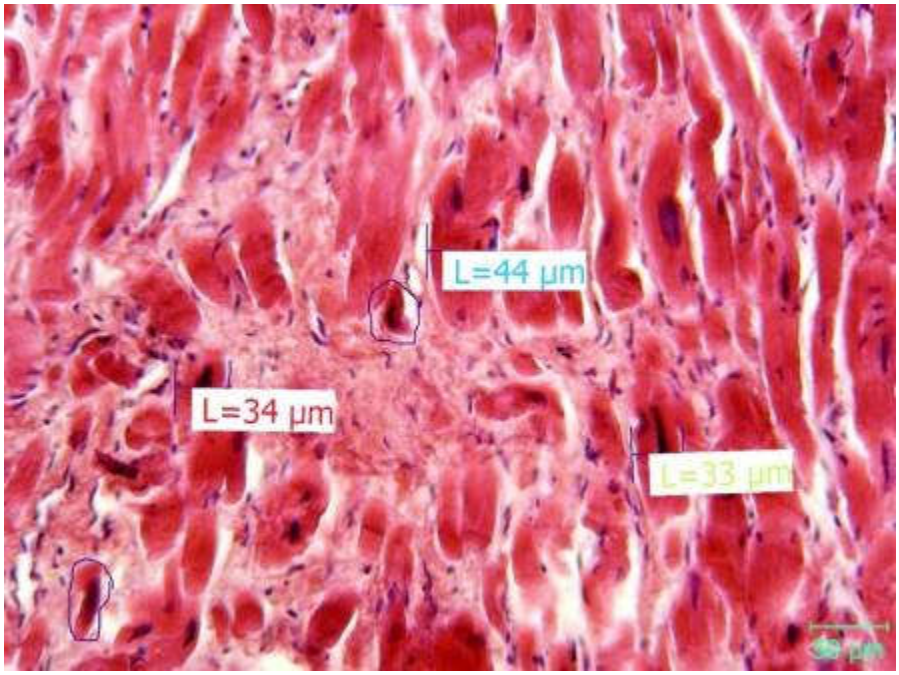

Fig. 2. Patient G. Basal part of the IVS. CMC hypertrophy with replacement fibrosis. Haematoxylin and eosin staining, x200 magnification

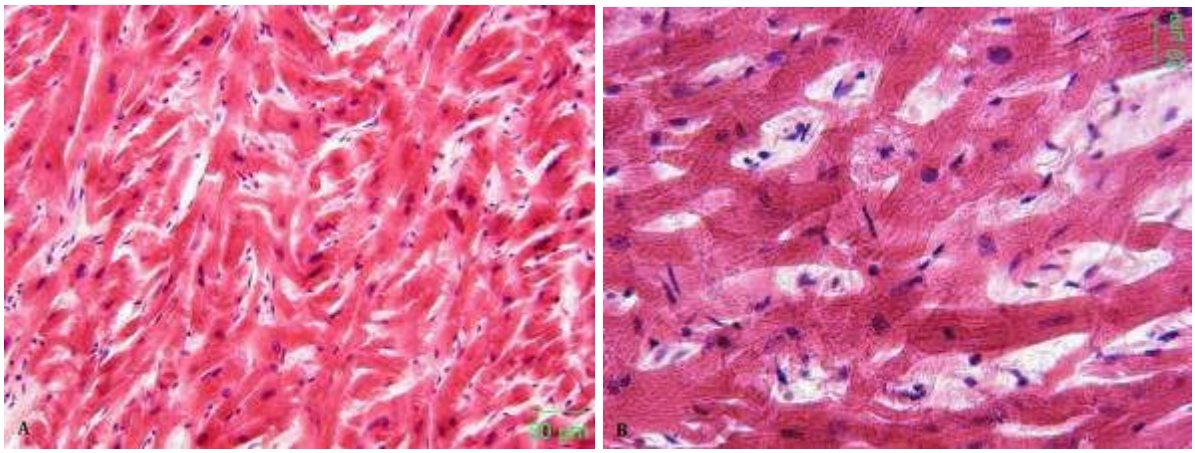

Fig. 3. Patient G. Disarray in the basal part of the IVS. Haematoxylin and eosin staining. A x200, B x400 magnification

In addition, as in most cases of HCM, the disarray CMC zones are visualized in the deep layers of the IVS, especially in the basal area in patient G. (Figs. 3A, 3B). At the same time, in many myocytes upon large magnification it was possible to see the effect of intracellular multidirectional location of myofibrils (Fig. 3B).

However, in the IVS of the patient G., in addition to the peculiarities of the structure inherent to HCM, there were other changes that can be associated with the procedure of alcohol ablation. In the proximal section of the SB of the anterior descending coronary artery into which alcohol was injected, the lumen was filled with coagulated plasma elements and membranes of lysed erythrocytes glued, fixed with alcohol. In this situation, an increased number of leukocytes differentiated, which probably fell into the area of damage from the central coronary blood flow (Fig. 4A). The smaller arteries in the ablation zone were completely obstructed by blood clots with lysed erythrocytes. Some authors identify such intravascular deposits as platelets [4]. However, in the areas of destruction of the vascular walls, true blood clots were formed (Fig. 4B).

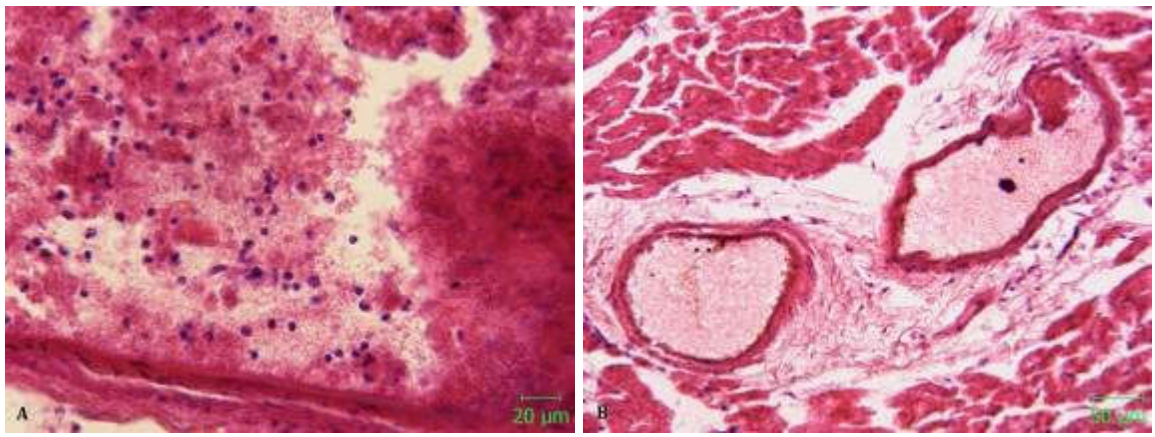

Fig. 4. Patient G. IVS arteries in the area of alcohol ablation, haematoxylin and eosin staining: A – fragment of an artery with coagulated elements of plasma and red blood cells in the lumen; x400 magnification; B – small arteries, top right – destruction of the vascular wall with the formation of a blood clot; x200 magnification

The smallest arteries and arterioles were completely obstructed by fresh blood clots due to the blockage of blood flow in the proximal part of this vascular pool.

As a result of blood stasis, CMC hypoxia occurs, the earliest signs of which are muscle cell contracture (Fig. 5B). Contractures of some sarcomeres may cause myocyte fibre rupture in the adjacent area with blockade of excitation pulse and decreased contractility of the damaged muscle bundle.

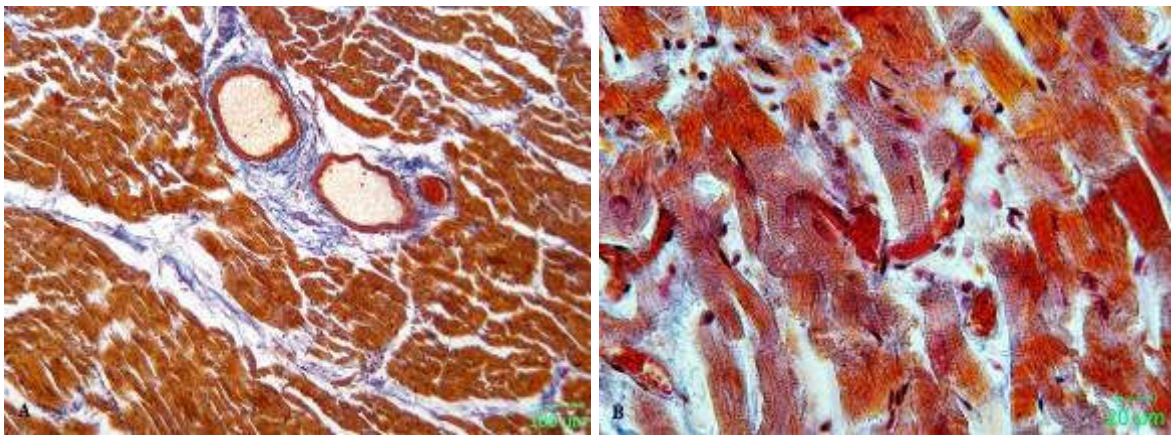

Fig. 5. Patient G. Small arteries and arterioles of the IVS in the area of alcohol ablation. MSB staining: A – two intramural arteries filled with elements of coagulated blood; x100 magnification; B – thrombosed arterioles, CMC with contracture zones

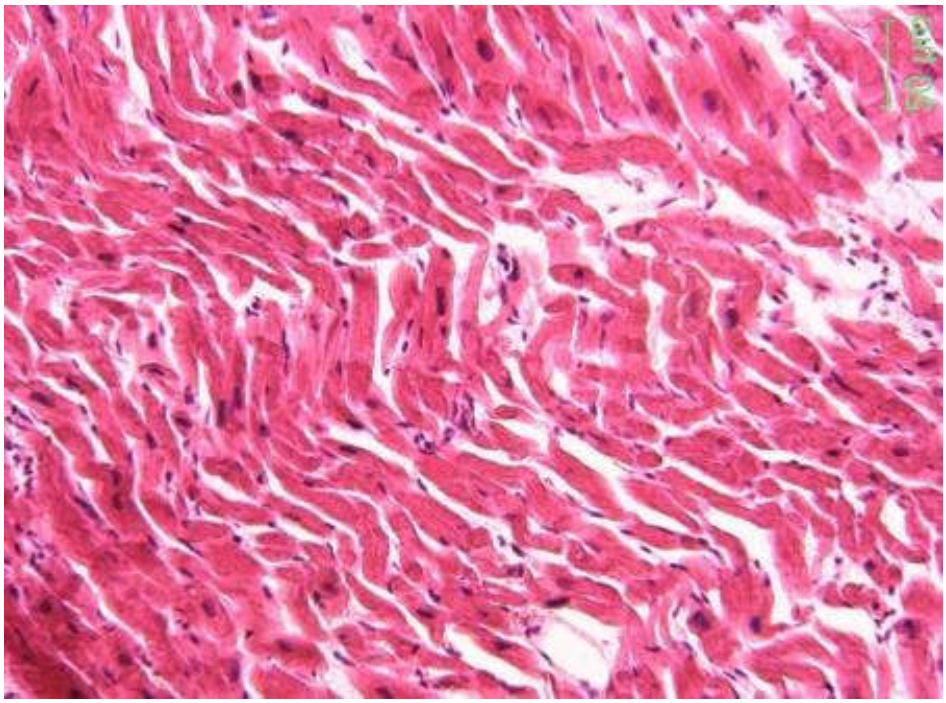

Fig. 6. Patient G. Wavy degeneration of IVS CMC. Haematoxylin and eosin staining, x100 magnification

Another most early sign of myocardial hypoxia is the so-called wavy CMC degeneration (Fig. 6). In the patient G. this sign was present in the preparations from the middle and even the apical segment to a greater extent than in the basal

segments. Most likely, it is associated with the fact that ASA was performed not through the 1st SB of the anterior descending coronary artery due to its very narrow ostium, but through the 2nd one. In addition, in this observation, the peculiarity of the structure of SB of the anterior descending coronary artery was that distal to the ostium of the 2nd SB, it bent almost at a right angle and, deforming, entered the myocardium.

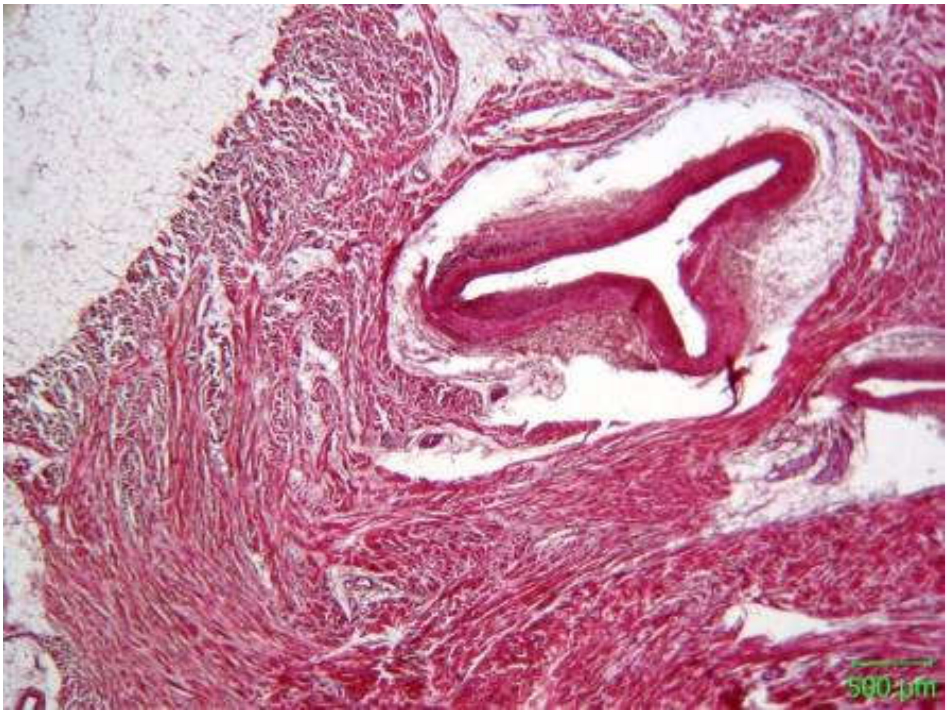

Fig. 7. Patient G. Anterior descending coronary artery immersed in the myocardium and surrounded by circulating CMC clusters. Haematoxylin and eosin staining, x20 magnification

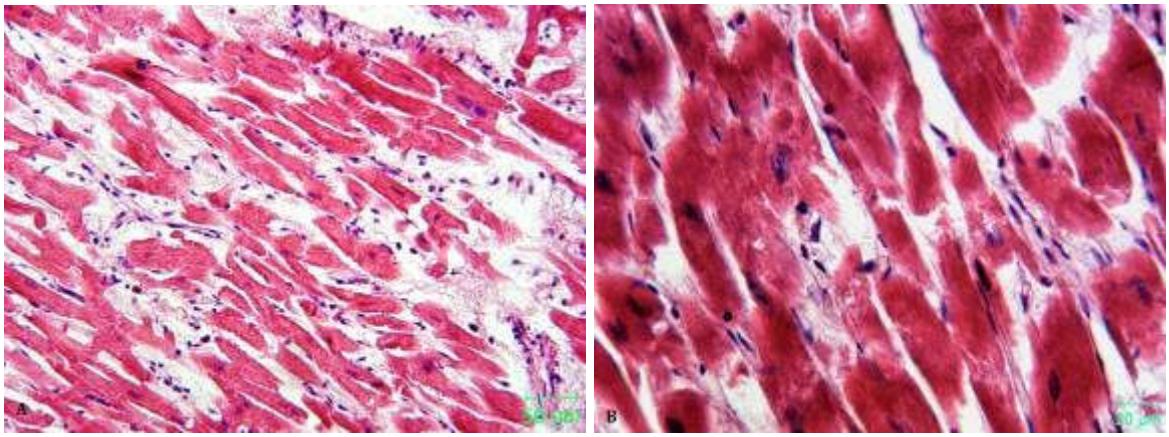

Fig. 8. Patient G. IVS myocardium. Haematoxylin and eosin staining: A – capillaries expanded with transparent fluid, impaired integrity of myocytes fibres, x200 magnification; B – coagulation necrosis of CMC in the area of destruction of the capillary, which was filled with transparent fluid, contractures of sarcomeres, x400 magnification

Histologically, it can be seen that at this point CMCs in the form of a sphincter cover the described vessel which during systole (especially upon endovascular manipulations) could limit the passage of blood to the myocardium of the middle and apical IVS segments.

However, in addition to the early signs of CMC hypoxia, there were also changes in the middle and basal segments of the IVS of patient G. There were changes that could be related more to the direct impact of alcohol on CMC. This was observed in areas of the myocardium where the capillaries were free of blood, but they not only did not stick together during the treatment of preparations, but vice versa: their lumen looked distended (Fig. 8A). The destruction of the wall of such capillaries was accompanied with coagulation necrosis of the adjacent CMC (Fig. 8B). It is likely that the blood in these capillaries was displaced by the alcohol that fixed them, but when it entered the interstitial space, it had a direct toxic effect on CMC and, to a lesser extent, on connective tissue endomysium.

Microscopic examination of the IVS myocardium of the patient K. showed that the fields of small-fragmented CMCs formed on the background of the endomysium connective tissue expanded with oedema 10 hours after the alcoholic ablation in the areas of hypoxic myocardial contractures (Figs. 9, 10).

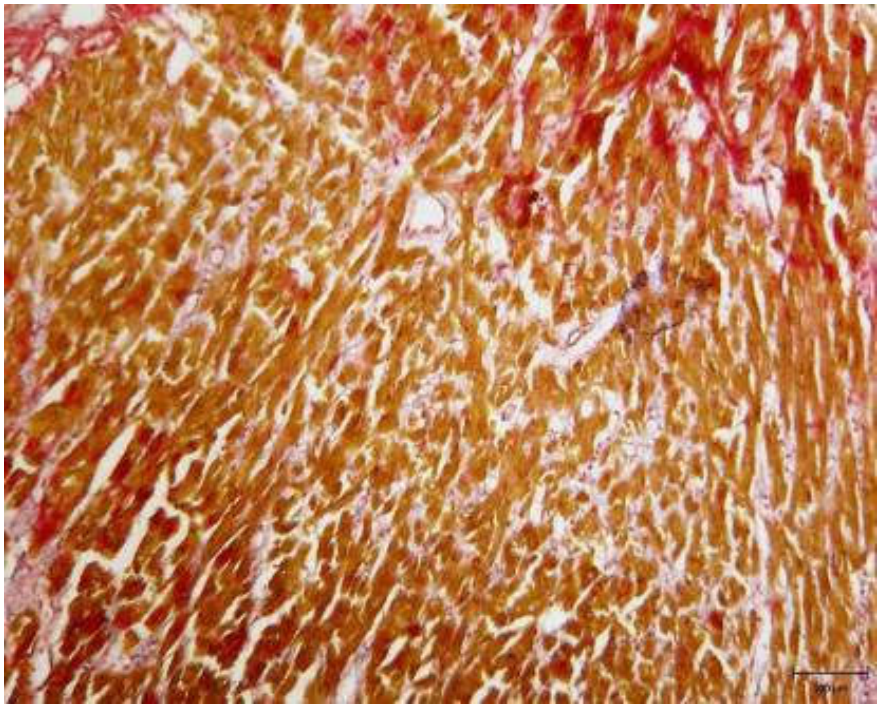

Fig. 9. Patient K. CMC fragmentation and stroma oedema in the area of myocardial contracture. MSB painting, x100 magnification

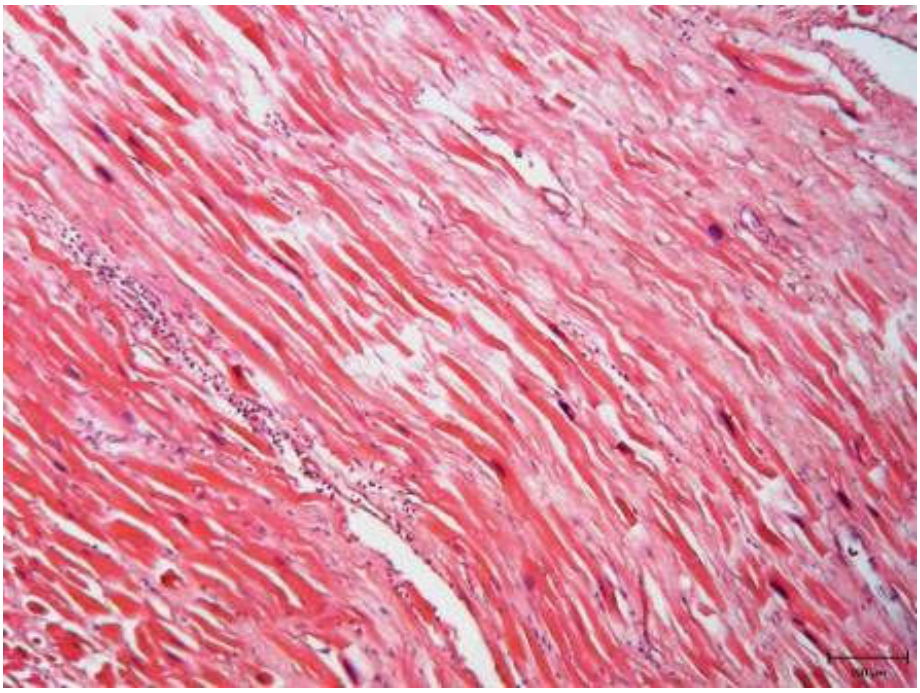

Fig. 10. Patient K. CMC overstretching and lysis with leukocyte infiltration. Haematoxylin and eosin staining, x100 magnification

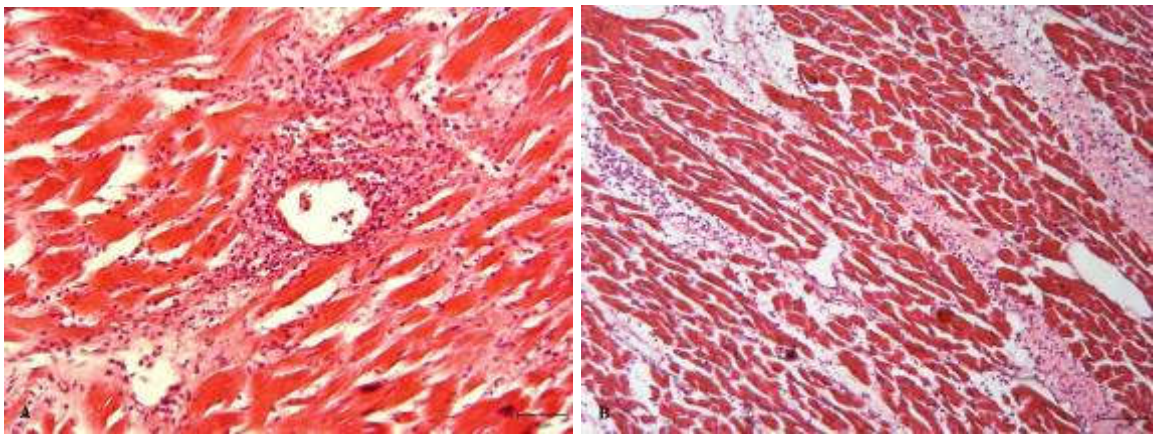

Fig. 11. Patient K. Myocardium on the border with lesions. Leukocyte infiltration: A – perivascular, x200 magnification; B – in the interstitial connective tissue layers. Haematoxylin and eosin staining, x100 magnification

Signs of myocytolysis dominated in other sites. At the same time the preserved CMCs were overstretched, their nuclei were rod-shaped (Fig. 10).

In addition to the intensification of muscle tissue alteration, the preparations obtained 10 hours after ablation showed the manifestation of the body's response to damage in the form of leukocyte infiltration. This process was most pronounced in the perifocal areas around the collateral vessels (Fig. 11A) and in the layers of the swollen connective tissue (Fig. 11B).

Small vessels with a large number of leukocytes were also observed in the area of damage. But in the lumen of such vessels clots of coagulated blood were also differentiated, and the vascular wall was more or less destroyed. This

contributed to the migration of leukocytes into the perivascular tissue (Fig. 12A) and to the loci of CMC damage (Fig. 12B).

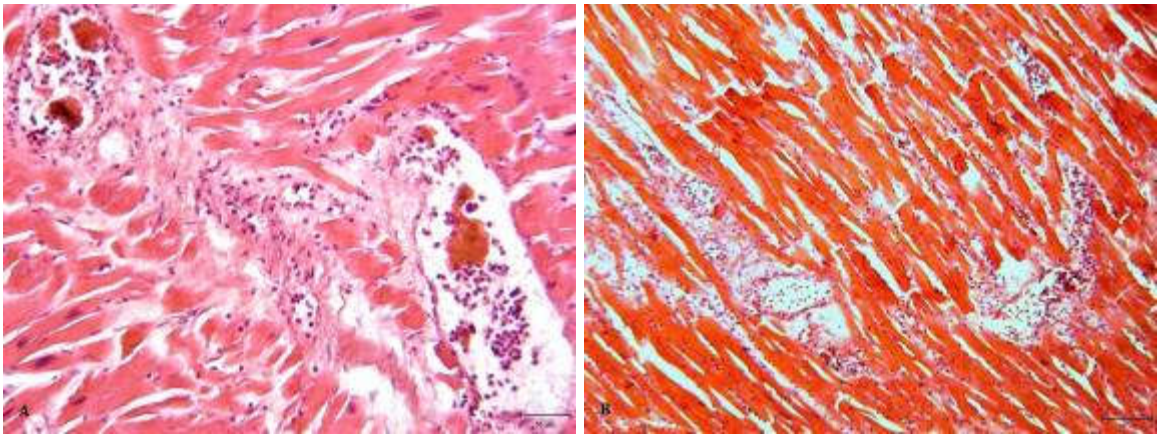

Fig. 12. Patient K. Myocardium in the lesion. Staining with haematoxylin and eosin: A – small vessels with destroyed walls, with leukocytes and clots of coagulated blood in the lumen, x200 magnification; B – leukocyte infiltration: perivascular and around the damaged CMC, x100 magnification

The larger branches of the artery into which the alcohol was introduced were completely obliterated with a conglomerate of glued erythrocytes, which could only be determined by the pale staining of their membranes (Fig. 13).

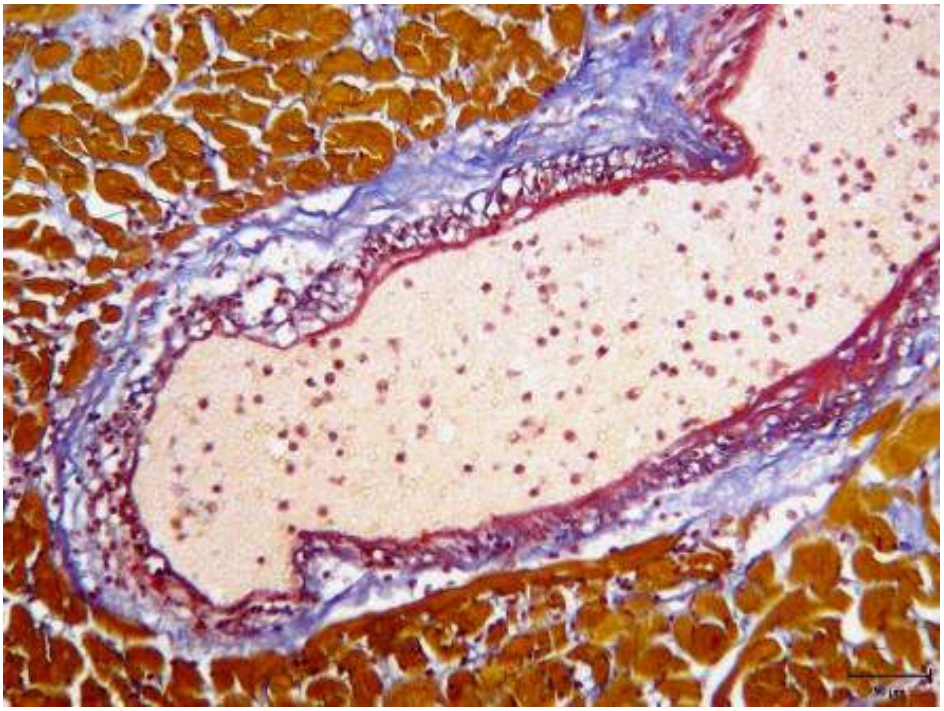

Fig. 13. Patient K. Intramural artery with obstructed lumen, with wall structures dystrophically altered and swollen. MSB staining, x200 magnification

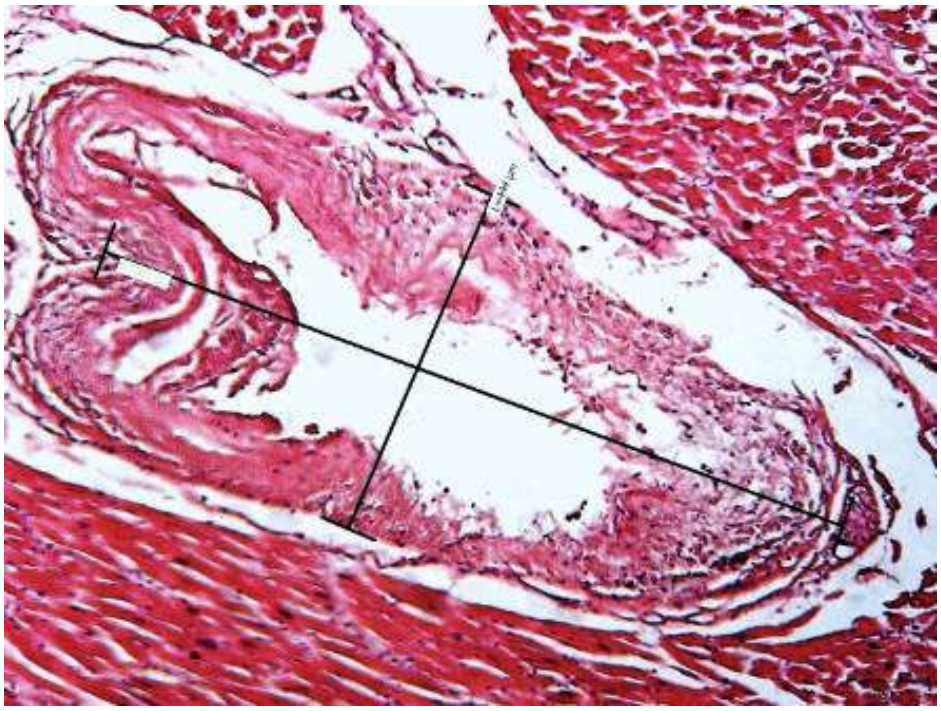

Fig. 14. Patient K. Ostium of the 1st SB of the anterior descending coronary artery. Destroyed vessel walls as a result of mechanical injury. Haematoxylin and eosin staining, x200 magnification

In the presence of the altered erythrocytes, few leukocytes were also scattered, which were also in a state of dystrophy. Blood stasis in the arterial lumen was accompanied with swelling and focal destruction of the internal elastic membranes of its walls and pronounced intra- and pericellular oedema of the media. From the side of adventitia, the artery wall was infiltrated with leukocytes, which increased the process of alteration.

In the 1st SB of the anterior descending coronary artery, near the area of alcohol introduction, the intima of the vessel and the inner layer of the media were impaired to a considerable extent with extending tissue defects to different depths of the artery wall. Moderate leukocyte infiltration was observed in the adventitia of the damaged segment. The arterial lumen was free of blood and deformed as a result of the invagination of one section of the wall into it. These changes can be attributed to the mechanical injury of the vessel during alcohol ablation. However, the described lesions should not be considered as complication of the medical tactics, since the purpose of this procedure is to block the blood flow along the SB of the anterior descending coronary artery for ischemization of the hypertrophied myocardium of the basal part of the IVS.

Conclusions

1. In the IVS myocardium of both patients there were morphological changes characteristic of HCM (CMC hypertrophy, endocardial and interstitial fibrosis, disarray figures)

2. ASA procedure causes damage to the arterial walls and intravascular coagulation of the blood with subsequent myocardial hypoxia.

3. Alcohol leakage beyond the capillaries has a direct toxic effect on CMC.

4. 10 hours after ASA, a leukocyte response to damage of histological structures is observed in the myocardium.

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