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Morphological changes in structural components of human heart valves associated with chronic haemodynamic trauma

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Abstract. The heart valve design is optimally adapted to their physiological function, i.e., the uniform distribution of blood flow in the heart chambers, so even small changes in the structural components of the valves, which are initially functionally compensated, play a significant role in the development of heart disease in the later stages of a patient's life. The study aimed to determine the effect of chronic haemodynamic trauma on the structural reorganisation of human heart valves. A total of 1377 human heart valves were evaluated, which were obtained during valve prosthetics at the Amosov National Institute of Cardiovascular Surgery from 2010 to 2022. The study identified a full range of macro- and microscopic changes in morphological structures that are characteristic of rheumatic heart disease, infective endocarditis, dysplastic and destructive changes in heart valves. The set of all morphological features was combined into the algorithm "Morphological manifestations of acquired heart disease of different genesis". It has been established that changes in the mitral valve architecture can cause the transformation of its structural components, which causes a violation of the valve's functional capabilities. The study demonstrated that persistent changes associated with chronic haemodynamic injury reduce the mechanical strength of the valve, despite the compensatory mechanism of subendothelial smooth muscle fibre hyperplasia in the heart valve leaflets. Subsequently, these damages can, on the one hand, be complicated by fibrosis, fatty degeneration and calcification, and on the other hand, compensatory mechanisms are involved in the process, namely hyperplasia of subendothelial muscle cells, which often form continuous layers that should strengthen and strengthen the mechanical strength and thus the functional competence of the valves. Mitral valve dysplasia can develop secondary infective endocarditis, rheumatism, and degenerative valve disease. The algorithm for determining the patterns of morphological changes in the valvular apparatus of the heart in various

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variants of acquired defects of inflammatory and non-inflammatory genesis can be used to improve the etiopathogenetic drug treatment of patients with acquired heart disease, as well as a theoretical basis for the development of new types of valve-preserving operations

Keywords: morphological changes; cardiac valve system; haemodynamic trauma; light microscopy

INTRODUCTION

The heart valves are in constant motion, performing the function of a gate valve, which is associated with changes in internal cardiac blood pressure. Therefore, they must be sufficiently elastic and at the same time have a significant margin of safety [1, 2]. The architectonics of heart valves is optimally adapted to their physiological function – the distribution of intracardiac blood flow. This is ensured by the peculiarities of the structural organisation of the valves, namely, the outer dense layers of the valve leaflets separated by a thin loose spongiosis layer are complementary to the directions of intracardiac blood flow, as confirmed by S.D. Chen *et al.* [3]. Violation of this complementarity can cause damage to the structural components of the valves, and then secondary changes in the systolic and diastolic function of the heart [4], causing the development of both congenital and acquired heart disease (AHD). B. Zebhi *et al.* [5], S. Kraler *et al.* [6], and M. Chernykh *et al.* [7] have shown that in case of changes in the structure of valve structures, their complementarity concerning the hydrodynamic effect of blood on them may be disturbed with a change in the mechanical load on the entire valve or its parts and, possibly, with damage to some structures of the heart valves. Therefore, even small congenital changes in the structure of the valves, which are initially functionally compensated, can significantly contribute to the development of heart disease at later stages of a patient's life [8]. Modern literature reviews indicate that in the case of severe congenital pathology, the initial dysfunction leads to early clinical manifestation of heart disease and, in favourable cases, to its surgical resolution [9, 10].

According to Ukrainian researchers, the proportion of rheumatic endomyocarditis as a cause of AHD requiring surgical treatment decreased from 56% to 31.4% between 2009 and 2021 [11], which is attributed to improved prevention of rheumatic diseases, and on the other hand, a decrease in the immunological status of the Ukrainian population. At the same time, a decline in immunity contributes to an increase in the number of cases of acute infective endocarditis (IE), which causes valve destruction and the formation of valve failure. According to I. Karavanska [12], the incidence of IE in different regions of Ukraine ranges from 20 to 70 per 1,000,000 population per year. However, even in the treatment of patients with NSTEMI of known aetiology, questions sometimes arise that cardiologists cannot provide a convincing answer to. For example, it remains unclear why a valvular heart disease acquired as a result of an active rheumatic process, after a certain period of remission, begins to show signs of increasing haemodynamic disorders without signs of rheumatic activation. Local changes in the valves that contribute to the development of the so-called primary infective endocarditis are unclear.

These problems cannot be solved only by clinical methods, so they need to be studied using morphological techniques that will allow to assessment of the nature and degree of pathological transformation of various valve structures, in particular the endothelium and connective tissue structures of valve leaflets and chords in AHD of various etiologies, which is important due to the fibrous framework of the valve ensuring its mechanical strength and elasticity, and, accordingly, the performance of the main functions of the valve. In the vast majority of scientific studies, there is no comprehensive approach to the study of the peculiarities of the organisation of structural components of heart valves in acquired pathology, and this aspect of the development of cardiac pathology is still poorly understood and insufficiently described. Therefore, the purpose of the study was to investigate the features of morphological changes in heart valves that occurred as a result of hemodynamic trauma.

MATERIALS AND METHODS

The study examined 1,377 human heart valves received during valve replacement surgery at the Amosov National Institute of Cardiovascular Surgery from 2010 to 2022. Among them were 556 mitral valves (MV), 478 aortic valves (AV), and 343 tricuspid valves (TV) Among the patients were 925 men and 452 women, aged 8 to 76 years (mean age – 43.2±11.6 years). The material for the study was collected in compliance with ethical and legal standards and requirements for scientific morphological studies [13].

The surgical material was examined macroscopically and microscopically. From the most and least damaged areas of the heart valves, pieces of leaflets or flaps were cut from the right or left fibrous ring to the edge, and the affected tendon strings were removed. Frozen sections were made from part of the material, which was stained with haematoxylin-eosin and Giemsa III-IV to identify fat-containing structures.

The rest of the material from similar valve areas was dehydrated in an alcohol bank of ascending concentration and paraffin-embedded at 640°C. Serial histological sections of 5-8 μm thickness were made on a sled microtome, after which the deparaffinised preparations were stained with haematoxylin-eosin. The conditions of collagen fibres were assessed by staining the sections with Van Gieson's picrofuchsin. Elastic fibres were selectively detected with fuchsin by Weigert. Fibrin of various degrees of maturity and blood cells were detected using the MSB (Marcius-Scarlet-Blue) technique in the Zerbino-Lukasevich modification [14, 15].

Light microscopy of histological sections, digital image processing and photographic documentation of the material was performed using a video image analysis unit CX-41 (OLYMPUS, Japan). The macroscopic examination of the heart valves assessed the thickness, density, and types of deformation of the leaflets (L), crescentic valves (CV), the overall degree of fibrosis, as well as fibrosis of adhesions and lines of closure of the leaflets, attention was paid to

the presence or absence of calcifications, warts, erosions, ulcers, abscesses, perforations, aneurysms, vegetations, haematomas, lipid stains, as well as signs of oedema and hyperaemia in various valve structures. Furthermore, the condition of the papillary-trabecular apparatus was studied in the MV: the length of tendon strings, the presence of tears, the degree of fibrosis, and the presence or absence of signs of dysplasia.

Microscopy of histological preparations of heart valves was performed consistently to assess morphological changes in structural components. In describing the surface of the heart valve leaflets/CV, the presence or absence of the endothelial layer, the condition of endothelial cells, and signs of their dystrophy, desquamation, and proliferation were noted. In the dense layers of the L/CV valves, the presence or absence of fibrosis, calcification or necrosis was assessed, including the presence of scars, collagen and elastic fibre bundles, and their fragmentation. The condition of the infiltrate cells was assessed: the presence or absence of morphological signs of dystrophy and the degree of their severity. The presence or absence of cholesterol crystals and proliferating smooth muscle cells was of particular importance. When describing the spongiosal layer of the L/CV of heart valves, its thickness, presence or absence of hematomas, cholesterol crystals, morphological signs of oedema, as well as the state of connective tissue fibres (their fragmentation, collagen cords from dense layers, fibroblast proliferation, fatty transformation, fibrosis and calcification of varying degrees) were determined. Similarly to the dense layers, signs of cellular infiltration were recorded by the presence of neutrophils, histiocytes, lymphocytes, macrophages and lipophages. The condition of blood vessels was determined by their wall thickness, lumen size, presence or absence of fibrinoid necrosis, leukocyte infiltration, destruction, fibrosis and hyperaemia in their membranes.

At the initial stage of the study, a complete set of variants of macro- and microscopic changes in morphological structures characteristic of rheumatic heart disease, infective endocarditis (IE), dysplastic and destructive changes in heart valves was determined. The set of all morphological features was combined into the algorithm "Morphological manifestations of AHD of different genesis".

The statistical processing of digital data was carried out in the environment of a licensed copy of the Excel computer program (version XP, Microsoft® Corp.) by programming the appropriate calculation algorithms with their subsequent processing. For the analysis of the results, one of the MS Office applications, the spreadsheet processor MS Excel 2003, was chosen for statistical analysis necessary for further discussion of the results, finding the minimum and maximum values, the mean and standard error of measurements, and determining the level of reliability.

RESULTS

The creation of the algorithm "Morphological manifestations of AHD of different genesis" determined a complete list of structural changes in heart valves of different aetiologies. In particular, when assessing the physical parameters of morphological changes in the L MV and CV AV of the heart, it was found that in 94.8% of cases of dysplasia, their area increased, which was not observed in any observation in IE-I and AHD (Table 1).

Table 1. Frequency of L and MV physical changes in various forms of AHD

No.	Morphological changes	AHD forms, %						Total
		AR n = 209	HA-PM n = 375	IE-I n = 190	IE-II n = 105	VD n = 207	RC n = 291	n = 1,377
1.	Expanded surface	11.5	23.7	0	19.2	94.8	0	28.5
2.	Reduced surface	0	0	79.6	72.3	7.4	0	17.4
3.	Thickened L or CV	100	100	42.8	61.7	90.2	68.5	85.1
4.	Thinned L or CV	0	0	58.1	38.3	9.8	8.3	14.7

Notes: CV – crescentic valves; AR – active rheumatism; NAR – non-active rheumatism; IE-I – initial infective endocarditis; IE-II – secondary infective endocarditis; VD – structural valve dysplasia; RC – regression changes
Source: compiled by the authors

In rheumovalvulitis, the L/CV surface was increased by 23.7% maximum of observations and was never reduced. Reduction of their leaflet area was a characteristic morphological sign of IE. For AHD of noninflammatory genesis, reduction of the area of the L/CV was also not typical, although it was found in 7.4% of cases of heart valve dysplasia. The thickness of the leaflets increased due to fibrosis and calcification in 100% of observations in patients with rheumovalvulitis, and in the active stage of the disease – also due to oedema. In IE-I, they were both thickened due to the presence of oedema and vegetation of the L or CV (41.9%) and thinned due to the dominance of lytic processes (58.1%).

In AHD that developed due to subclinical forms of valve dysplasia, in 90.2% of observations, the L/MV was thickened due to either calcification or oedema of the spongiosal layer. In 68.5% of AHD cases, the leaflets or MV were also thickened as a result of coarse calcifications; 8.3% of leaflets or CV had atony and thinning due to widespread fatty regression of their connective tissue structures; in the remaining 23% of valves in this group, the thickness of the leaflets or CV was slightly changed, although foci of slight yellow-orange thickening were observed under the endothelial layer. In IE-II, L or CV in the area of adhesions and marginal sections were thickened only in those patients with a history of rheumatic heart disease (17.0%).

In valves with dysplasia due to calcifications surrounded by fibrous capsules (44.4%), L or CV were usually thickened and dense, in other cases – soft, sometimes

swollen. Calcification also determined the high density of 56.1% of valves in RC AHD. Of this group, 7.7% of the L or CV valves appeared soft, atonic, thinned, sometimes with a finely ribbed surface relief. In general, among 1377 observations, valves with dense (59.7%) and thickened L or CV were the most common. Moreover, if the density was determined mainly by fibrosis and calcification, the increase in thickness could also be caused by significant oedema and overlapping vegetation. Features of morphological macroscopic signs in the removed valves were also determined by the presence of erosions, ulcers, oedema, foci of hyperaemia and perforations (Table 2). Erosions of various sizes and shapes appeared as loose areas without the typical lustre of surfaces, and sometimes their edges were exfoliated. Erosions were detected in the majority of observations of inflammatory AHDs, as well as in 28.3% of cases of valve dysplasia and 28.9% of valves removed for RC heart disease. In total, erosion was detected in 71.4% of cases.

Table 2. Frequency of macroscopic erosions, ulcers, oedema, hyperaemia, vegetations, lipid stains, haematomas, abscesses, warts and aneurysms of valve structures in different AHD forms

No.	Morphological feature	AHD forms, %						Total n = 1,377
		AR n = 2,097	NAR n = 375	IE-I n = 190	IE-II n = 105	VD n = 07	RC n = 291	
1.	Erosions	88.8	91.1	100	100	28.3	28.9	71.4
2.	Ulcers	77.8	86.5	100	100	23.5	13.1	70.2
3.	Oedema	84.0	0	100	100	89.6	34.5	54.3
4.	Hyperaemia	31.8	0	82.6	90.3	0	0	22.2
5.	Vegetations	0	0	100	100	0	0	21.7
6.	Lipid spots	60.8	92.6	0	72.8	73.1	88.9	73.1
7.	Warts	100	95.7	17.4	83.6	88.4	15.5	72.6
8.	Haematomas	6.4	2.3	0	22.5	0	0	4.3
9.	Abscesses	0	0	26.8	33.8	0	0	5.0

Notes: AR – active rheumatism; NAR – non-active rheumatism; IE-I – initial infective endocarditis; IE-II – secondary infective endocarditis; VD – valve dysplasia; RC – regression changes
Source: compiled by the authors

In 70.2%, ulcers were detected, which most often formed over large calcifications, forming tissue defects up to 2 cm in diameter. Such ulcers usually had a calcified bottom, which was imbibed with blood and covered with fibrin clots. Ulcers were observed in the area of fibrous adhesions and the absence of calcifications. In these cases, the tissue defect had a linear shape in the direction from the fibrous ring of the valve to its lumen. In IE, deep damage to the L structures was caused by tissue lysis, which was present in 100% of observations.

A sign of L/CV oedema was recorded in 54.3% of cases. In AR, oedema of the surface layers of the structural components of the valves was manifested by their swelling and translucent appearance. The fibrous tissue of the deeper layers also swelled and became less dense and compact. No signs of oedema were present in NAR. In IE, as in other inflammation, oedema occurred in 100% of cases. The valve leaflets with signs of dysplasia often (85.6%) had a myxomatous appearance: diffuse throughout or in some areas. Their middle layer increased in volume and became almost transparent and slippery to the touch. Hyperaemia of the L/CV occurred only in the active inflammatory process: in 31.8% of cases of active rheumovalvulitis, as well as in EI-I and EI-II (82.6% and 90.3%, respectively). As it turned out, vegetations are a pathognomonic sign of EI. They were detected in all cases of both EI-I and EI-II and were not recorded in other pathological processes.

A yellow-orange lipid stain located under the endothelium in the areas subjected to the greatest haemodynamic load was a frequent finding (72.2% of all observations) in the macroscopic examination of heart valves. They were present in 60.8% of valves with AR, 92.6% of inactive valves, 73.1% of IE-II observations, 73.1% of valves with dysplasia, and 88.9% of cases of RC AHD. This was absent only in IE-I.

The growth of loose fibrous connective tissue in the form of warts along the edges of the L and CV, as well as in areas of relief altered by fibrosis and calcification, was found in all groups: most often in rheumovalvulitis (100% of observations of active rheumatic process and 95.7% of inactive rheumatic process), EI-II (83.6%) and heart valve dysplasia (88.4%). In the case of dysplasia and RC of their structures, warts were detected much less frequently (17.4% and 15.5%, respectively).

In only 4.1% of cases, haematomas were observed in the damaged L and CV. They were most often recorded in EI-II (22.5%), less often in active rheumovalvulitis (6.4%), and even less often (2.3%) in inactive rheumocarditis. In the other groups, haematomas were not observed. Similarly to vegetation, macroabscesses were a pathognomonic feature of IE. They were not formed in every case of IE. In particular, macroabscesses were detected in 26.8% of IE-I, and 33.8% of IE-II. Macroabscesses were not observed in other forms of IE. Therefore, the detection of vegetation and abscesses in the heart valves can reliably testify in favour of IE. In the study of MV, special attention was paid to the condition of the tendon strings of the papillary-trabecular apparatus of the heart (Table 3).

Table 3. Frequency of detection of macroscopic changes in tendon strings of the MV in various forms of AHD

No.	Morphological feature	AHD forms, %						Total n = 1,377
		AR n = 209	NAR n = 375	IE-I n = 190	IE-II n = 105	VD n = 207	RC n = 291	
1.	Normal length TS	27.1	22.1	100	71.6	8.1	92.8	43.6
2.	Long TS	15.6	16.0	0	7.8	78.6	5.7	23.1
3.	Short TS	64.2	65.3	0	23.1	25.6	0	34.9
4.	Fibrosis 0	0	0	100	65.0	11.1	100	35.8
5.	Fibrosis 1+	48.9	22.7	0	20.3	75.7	0	29.0
6.	Fibrosis 2+	52.2	74.6	0	14.6	11.1	0	34.3
7.	Dysplasia	0	2.7	0	26.9	100	0	21.1
8.	Tears	0	0	43.2	37.8	13.5	0	10.9

Notes: TS – tendon strings; AR – active rheumatism; NAR – non-active rheumatism; IE-I – initial infective endocarditis; IE-II – secondary infective endocarditis; VD – valve dysplasia; RC – regression changes
Source: compiled by the authors

It was found that only in IE-I, in 100% of observations, tendon string lengths were unchanged. In IE-II, this figure was 71.6% and in RC AHD – 92.8%. In AR and NAR, as well as in valve dysplasia, tendon strings of normal length were found much less frequently: 27.1%, 22.1% and 8.1%, respectively. Moreover, in dysplasia, both elongated (78.6%) and shortened tendon strings (25.6%) could be found in the same valve.

In rheumatism, short tendon strings of the MV were most common: in AR they were recorded in 64.2%, and inactive rheumatism – in 65.3%. Long tendon strings were differentiated in only 15.6 % of AR and 16.0% of NAR. In IE-II and RC AHD, L with long tendon strings were relatively rare: 7.8 % and 5.7 %, respectively. Shortening of tendon strings in IE-II (23.1%) was due to initial post-stroke fibrosis or fibrosis associated with papillary trabecular apparatus dysplasia since in these groups of patients fibrosis of tendon strings, as well as of the cusps, was the most common: in dysplasia – 88.9%, NAR and AR – 100%. It should only be noted that in rheumovalvulitis, valves with gross fibrosis dominated, whereas in papillary-trabecular dysplasia, not all tendon strings were affected by fibrosis and the degree of fibrosis was moderate in most cases (75.7%). Fibrosis of tendon strings was not typical for valves with RC AHD.

Signs of congenital abnormality of the papillary-trabecular apparatus of the MV were detected in 100 % of valves in the dysplasia group, as well as in 26.9% of valves with IE-II and 2.7% of observations of inactive rheumovalvulitis. Signs of tendon string rupture were not recorded in any case of rheumovalvulitis and RC AHD, but signs were found in IE-I (43.2%), IE-II (37.8%) and papillary-trabecular dysplasia (13.5%). A detailed microscopic examination of the structural components of the heart valves revealed that their surface was in no case intact throughout, the endothelium was damaged (Table 4).

Table 4. The frequency of detection of valve endothelial changes in various forms of AHD

No.	Morphological feature	AHD forms, %						Total n = 1,377
		AR n = 209	NAR n = 375	IE-I n = 190	IE-II n = 105	VD n = 207	RC n = 291	
1.	Normal surface	0	0	0	0	0	0	0
2.	Erosions	88.5	93.3	100	100	96.5	80.9	93
3.	No endothelium changes	0	0	0	0	0	0	0
4.	Endothelium exfoliated	88.8	97.4	100	100	96.4	100	97.1
5.	Endothelial dystrophy	77.4	27.5	100	100	71.3	61.8	63.2
6.	Endothelial proliferation	0	0	0	0	23.2	33.2	8.9

Notes: AR – active rheumatism; NAR – non-active rheumatism; IE-I – initial infective endocarditis; IE-II – secondary infective endocarditis; VD – valve dysplasia; RC – regression changes
Source: compiled by the authors

In IE-I and IE-II, as well as in RC AHD, endothelial desquamation was found in 100% of observations. Somewhat less frequently, in 88.8 – 97.4% of cases, this morphological sign was present in active and inactive rheumovalvulitis and AHD associated with heart valve dysplasia.

Various signs of endothelial dystrophy were found in an average of 63.2% of observations, with IE causing endothelial dystrophy in 100%. In NAR, areas with dystrophically altered endothelial layer were detected in 27.5% of patients, in the other groups this sign

was noted in 77.4% of AR, in 71.3% of valve dysplasia and 61.8% in RC AHD. In noninflammatory AHD, signs of increased endothelial cell proliferation were sometimes observed on the surface of the valve leaflets: in valve dysplasia in 23.2%, and RC in 33.2%. Endothelial damage was often accompanied by significant changes in the dense surface layers of the L and CV of the heart valves, as shown in Table 5.

Table 5. Frequency of detection of necrotic and fibrotic changes in connective tissue structures of dense layers in various forms of AHD

No.	Morphological feature	AHD forms, %						Total
		AR n = 209	NAR n = 375	IE-I n = 190	IE-II n = 105	VD n = 207	RC n = 291	n = 1,377
1.	Fibrinoid necrosis	100	16.2	4.8	16.1	0	0	20.3
2.	Enzymatic lysis	0	0	100	100	0	0	56.7
3.	Cholesterol necrosis	59.8	90.5	0	50.7	59.5	100	68.7
4.	Scars	100	100	0	56.4	0	0	51.1
5.	Fibrosis	37.8	36.8	0	53.2	45.6	68.7	42.1
1.	Smooth muscle cell proliferation	1.7	3.2	0	20.4	84.6	0	19.1
2.	Loosening of layers	0	0	0	9.4	83.0	0	16.5
3.	Collagen fibre fragmentation	0	0	0	8.6	66.3	0	12.8
4.	Intercellular substance accumulation	100	0	14.3	11.2	68.9	29.2	30.5
5.	Calcification	100	100	33.2	54.3	63.8	68.9	77.5

Notes: AR – active rheumatism; NAR – non-active rheumatism; IE-I – initial infective endocarditis; IE-II – secondary infective endocarditis; VD – valve dysplasia; RC – regression changes
Source: compiled by the authors

Thus, in AR, signs of fibrinoid necrosis of connective tissue structures of dense surface layers of the L and CV of heart valves were detected in 100% of observations. In NAR, fibrinoid necrosis was detected in histological specimens in only 16.2% of patients, but in these cases, fibrinoid necrosis showed signs of calcification in the central parts of the lesions and fibrosis in the periphery. Changes in collagen structures characteristic of fibrinous necrosis were sometimes also found in IE, and in IE-II - much more often than in IE-I: 16.1% vs. 4.8%. It was noteworthy that foci of fibrinous necrosis were often located around the blood vessels away from the main focus of valve damage in subacute and recurrent forms of IE. In NAV of noninflammatory origin, classical manifestations of fibrinous necrosis were not observed in any case. However, these valves showed zones of collagen homogenisation, which, unlike eosinophilic fibrinoid necrosis, usually had a slightly basophilic colour. Necrosis of the dense layers of the L and CV of the heart valves, which was caused by the lytic action of neutrophil lysosomal enzymes and microbial waste products, was pathognomonic for both groups of IE. This morphological sign was found in 100% of observations in IE, whereas in other forms of AHD, necrosis of the dense layers of the L and CV of the valves was absent.

The most frequent morphological sign (68.7%) in all material was cholesterol necrosis, which gave a positive sudan III-IV stain and was often accompanied by the presence of lipophages and cholesterol crystals. Such changes were recorded in 100% of observations in RC AHD, in 90.5% in NAR, in 50-60% in AR, IE-II and valve dysplasia. IE-I was included in this group only in the absence of other morphological changes, including cholesterol necrosis. Gross scarring deformation of the dense surface layers of the L and CV along the line of their closure, in the area of adhesions, as well as tendon strings of the MV, was detected in all cases of AR and NAR. At the same time, the central parts of the L and CV were fibrosed much less. In 56.4 % of cases of IE-II, these changes developed against the background of scarred valve structures. In IE-I and AHD of non-inflammatory genesis, scarring changes in the heart valves were usually not detected. However, quite often in the latter two groups, there was a diffuse increase in the fibrous component of the dense layers of the L and CV: in the initial valve dysplasia – in 45.6%, in the RC AHD group – in 68.7%. Fibrosis of the valve structures without disturbance of collagen fibre orientation was also detected in 37.8% of A-RM cases, 36.8% of NAR cases and 53.2% of observations in IE-II. It should be noted that fibrosis without scarring changes was usually localised on the periphery of the main foci of fibrosis and calcification.

Other morphological changes were often detected in the surface layers of the L and CV, in particular, in 19.1% of observations, a peculiar subendothelial layer of smooth muscle cells, which is not characteristic of normal heart valves, was differentiated in histological preparations of heart valves. Most often (84.6%) it was detected in the L and CV with signs of dysplasia. In IE-II, this morphological sign was present in 20.4% of cases, in AR – only in 1.7%, and in NAR – in 3.2% of cases. The subendothelial layer of smooth muscle cells was not detected at all in IE-I and in RC of the heart.

There are two morphological signs (thinning of the dense surface connective tissue layers of the L and CV and fragmentation of collagen fibres), which were largely observed only in congenital heart valve disease (83.0% and 66.3%, respectively), as well as in IE-II, which developed against the background of valve structure dysplasia (9.4%, 8.6%). Swelling of the connective tissue due to the accumulation of intercellular substance in it was recorded in the dense surface layers of the L and CV in all cases of AR, in 14.3% of cases of IE-I, in 11.2% of observations of IE-II, in 68.9% of cases – in the L and CV of heart valves with initial dysplasia and 29.2% of valves with RC of their structures.

Calcification of the heart valve structures was one of the most frequent morphological features (77.5% of cases). Moreover, in both groups of rheumatic fever, calcification was found to a greater or lesser extent in all valves. Calcification was detected in 63.8% of patients with non-inflammatory AHD, in patients with valve dysplasia and 68.9% of patients with RC AHD. In patients with IE, calcification in the thickness of fibrotic altered valve structures was detected only in IE-II. In addition, a feature of infectious valvulitis was the presence of calcium in the vegetation. It was this localisation of calcification that led to 33.2% of observations of this sign in patients with IE-I. In patients with IE-II, calcification was observed in 54.3%.

In addition, the presence of nuclear detritus was noted, which was present in 100% of IE-I and IE-II observations and was completely absent in other forms of AHD. When assessing the spongiosis layer of the L and CV of the heart valves, its thickness was prioritised (Table 6). In rheumatic malformations, this layer was rarely dilated and often not differentiated at all due to severe fibrosis. In IE-I, in the L and CV, namely in areas that were not destroyed by lysis and massive cellular infiltration, the spongiosis layer was found to be expanded in 85.4% of cases, and in IE-II only in 45.9%. Different types of valve dysplasia were accompanied by diffuse or focal expansion of the spongiosis layer in 100%. In RC AHD, this sign was present in 38.5 %.

Table 6. The frequency of detection of morphological changes in the spongiosal layer in various forms of AHD

No.	Morphological feature	AHD forms, %						Total
		AR n = 209	NAR n = 375	IE-I n = 190	IE-II n = 105	VD n = 207	RC n = 291	n = 1,377
1.	Expansion	0	0	86.4	45.9	100	38.5	38.4
2.	Oedema	28.2	0	85.4	0	100	38.5	36.3
3.	Fragmentation of connective tissue fibres	0	0	0	0	97.2	0	18.1
4.	Collagen cords from dense superficial layers	0	0	0	17.3	74.2	0	16.4
5.	Fat transformation	0	0	0	0	47.8	13.0	10.8
6.	Fibrosis	100	100	0	68.4	31.4	43.9	65.1
7.	Calcification	81.3	100	45.1	53.2	17.5	46.9	62.9

Notes: AR – active rheumatism; NAR – non-active rheumatism; IE-I – initial infective endocarditis; IE-II – secondary infective endocarditis; VD – valve dysplasia; RC – regression changes
Source: compiled by the authors

Spongiosal oedema was detected in 28.2% of valves in AR, in 86.4% of IE-I observations, and 100% of specimens obtained from valves with signs of dysplasia. Primary RC of the L and CV were accompanied by oedema of the spongiosal layer in 38.5% of cases. Heart valves with subclinical forms of congenital pathology were characterised by fragmentation of connective tissue fibres of the spongiosal layer (97.2%), spread of collagen fibre strands from the dense surface layers of the L and CV (74.2%), and transformation of loose fibrous connective tissue of the spongiosal layer into adipose tissue, which was recorded in 47.8% of cases.

In other AHD forms, these morphological signs were almost always absent, only 17.3% of IE-II showed collagen fibre disruption of dense layers and 13.0% of RC AHD had fatty transformation of the spongiosal layer. Fibrosis of the spongiosis layer of the L and CV of the heart valves was noted in 100% of rheumovalvulitis, both active and inactive, in 68.4% of observations in IE-II, in 31.4% of cases in patients with cardiac valvular dysplasia and 43.9% in patients with RC AHD. Calcification of the L and CV of the heart valves extended to the spongiosis layer with greater or lesser frequency in all groups of observations: in active rheumovalvulitis – in 81.3% of observations, in NAR – in 100% of cases, in IE-I – in 45.1%, in IE-II – in 53.2% of observations, in dysplasia – in 17.5%, in AHD heart disease – in 46.9% of cases.

The analysis of the frequency of macro- and microscopic changes in heart valves allowed us to identify several morphological features that are detected with varying degrees of probability in AHD of various genesis. This made it possible to carry out morphological diagnostics of the morphogenesis of acquired heart valve defects, as well as to verify the nosological affiliation of the AHD for which patients were operated with maximum objectivity.

AV Bicuspid was an AV defect. The macroscopic characteristics of this pathology are well known and consist of an increase in the thickness of one of the valves, in the centre of which crestal transverse thickenings were usually detected. According to the results of light microscopy, AV calcification developed as a consequence of fatty degeneration of the connective tissue, which was detected even in patients under the age of 20 (Fig. 1).

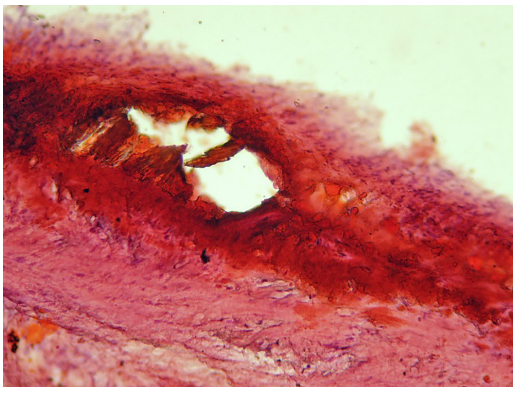

Figure 1. Bicuspid AV;
fatty degeneration, calcification. Sudan III-IV. x40
Source: compiled by the authors

In addition, the aortic surface of such a valve was finely ribbed, with small areas of irregular fibrosis and sometimes with thinning, up to leaflet tears, which were usually oriented parallel to the thickened layer due to fibrosis and translucent overlays in the form of warts. Macroscopic characteristics of congenital MV pathology consisted mainly of dysplasia of the papillary-chordal apparatus, which was manifested by irregular arrangement of tendon strings, decrease or increase in their number, and changes in their thickness, length and direction. This resulted in the pulling of one or more heads of papillary muscles to the valves and lengthening of others with their subsequent fibrosis. There was uneven swelling of the valves, their deformation due to the formation of aneurysm-like protrusions towards the atrium. Such changes were noted in areas that were not supported by tendon strings. The edges of the heart valve leaflets had a fistulous appearance, and translucent growths in the form of warts were localised on them.

Microscopic examination of the heart valves obtained at autopsies showed that the L TV and pulmonary trunk valves had a normal structure with a clear parallel orientation of collagen fibres and preserved endothelium. The surface dense layers of the aortic valve were unchanged in the CV, with a parallel orientation of intact collagen fibre bundles, and moderate oedema of the CV spongiosal layer without specific signs of inflammation. Light microscopy in the L MV of the heart MVs showed a significant expansion of the middle spongiosal layer due to its oedema, as well as stratification of collagen fibre bundles of the dense outer layers of the L, and moderate fibroblast proliferation in the spongiosal layer.

In the base of the Valsalva sinuses in the CV aortic valve leaflet, smooth muscle proliferation occurred in dysplasia of its structures, as well as in MV dysplasia. Since a particularly pronounced disorganisation of the connective tissue fibres of the valve with a sharp swelling and expansion of the spongiosis layer, as well as loss of compactness of the surface dense layers was observed, smooth myocyte layers often looked like single compact areas in this part of the V or CV. At the same time, valves were often observed with further proliferation of young connective tissue and transformation of loose fibrous connective tissue into adipose tissue, which reduced the mechanical strength of the valve (Fig. 2).

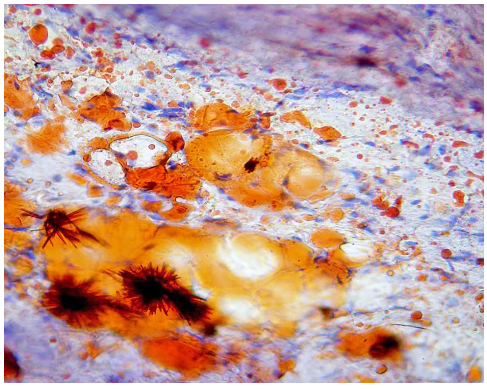

Figure 2. Fatty transformation of the spongiosis layer. Sudan III-IV. X 200
Source: compiled by the authors

In the areas of the leaflets without mechanical support of tendon strings, whole layers of hyperplastic subendothelial smooth muscle fibres were naturally detected, which can be considered as a compensatory reaction of the body aimed at enhancing the reduced mechanical properties of the heart valve leaflets (Fig. 3).

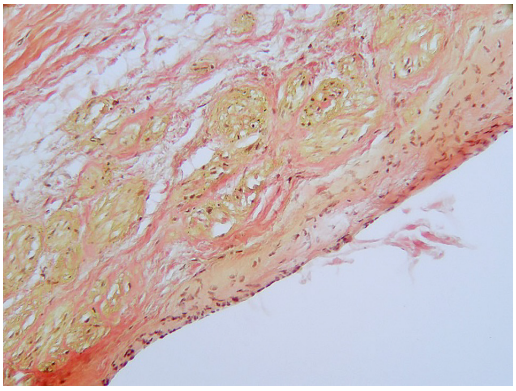

Figure 3. MV dysplasia, compensatory hyperplasia of subendothelial smooth muscle fibres. Hematoxylin-eosin. X 100
Source: compiled by the authors

In patients aged 28 ± 5.3 years, homogenisation of the CV surface layers was observed in some areas of the aortic valve leaflet. At the same time, the layer in the corresponding area expanded, swelled and acquired a slightly basophilic tint with a loss of fibrous connective tissue structure. Subsequently, calcium was deposited in these areas, which led to pronounced deformation of the valve flap. Focal homogenisation of one of the dense surface layers was accompanied by the narrowing of the dilated spongiosis layer and disorganisation of connective tissue structures of the dense surface layer of the opposite side. In patients aged 37 ± 7.4 years, calcification became the dominant morphological sign of the disease.

All the changes described above can be attributed to chronic haemodynamic trauma to the valve structures. Until a certain point, these changes had no clinical manifestations. However, they can be considered factors that create prerequisites for the development of more severe pathological processes that give rise to certain clinical symptoms. In particular, areas of the valves without a protective endothelial layer are often the entrance gate for infection, which leads to the development of heart valve IE [16].

In addition, MVs with subclinical forms of congenital pathology are early exposed to RC [17]. In this case, endothelial exfoliation occurred, areas of the damaged surface with signs of active fibrogenesis were detected, and connective tissue fibres within the leaflets were homogenised, infiltrated by fat cells and calcified, which led to rapid decompensation of the valve defect. In addition, the deendothelialised surface areas were covered with a thin layer of fibrin, in which lymphocyte cells were localised, and signs of endothelial cell proliferation were still detected on the surface of some areas. This was true for both areas with damaged surfaces (Fig. 4) and internal connective tissue structures that were subjected to particularly high mechanical stress.

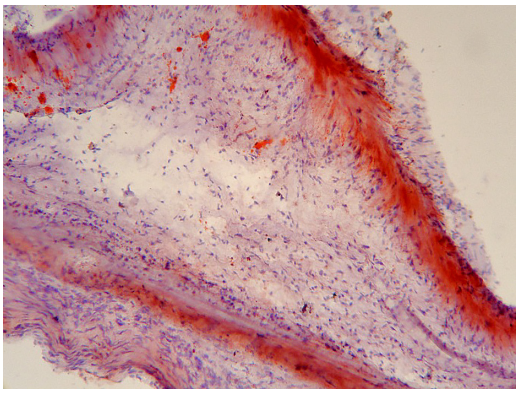

Figure 4. MV dysplasia. Sudanophilic degeneration of connective tissue structures of L Sudan III-IV. X 40
Source: compiled by the authors

Among the 556 MVs studied, it was noted that in 126 patients (22.7%), congenital valve disease began to be detected in adulthood, even without concomitant pathology. This was the group of the youngest patients with severe primary dysplasia. In 45 patients, valve dysplasia was complicated by IE. In 39 cases, signs of congenital MV pathology were detected in poststroke valvular fibrosis and calcification. The largest group consisted of patients with valve dysplasia combined with severe degenerative changes in connective tissue structures. In 285 cases (51.2%), lipoidosis with calcification was the only factor that complicated the initial dysplasia. However, in 61 patients, more than two etiopathogenetic factors were noted (lipoidosis and EI or lipoidosis and rheumatism).

The group with significant RC signs consisted of patients of more mature age (48.2 ± 9.3 and 46.6 ± 11.7). However, the age of patients whose valves were affected by a degenerative process without underlying dysplasia was also investigated and found to be 60.8 ± 14.5 years, which is significantly higher than the age of patients with degenerative valve disease that developed on the background of MV dysplasia. Thus, changes in the structural organisation of heart valves associated with chronic haemodynamic trauma affect the functional capacity of the valve.

DISCUSSION

Modern methods of clinical and instrumental diagnostics allow to establishment of the mechanical characteristics of the defect (stenosis or insufficiency), determine the severity of the valvular lesion, the presence and severity of haemodynamic disorders [18]. The mechanical functions of damaged valves are currently restored by surgical correction of the defect, including valve prosthetics. However, to determine adequate pre- and postoperative drug treatment regimens for patients, it is also important to establish the aetiology of the defect (rheumatism, infective endocarditis, dystrophic changes, coronary heart disease, etc.), and in the presence of a systemic inflammatory process, its activity.

AHD is caused by a variety of pathological processes, most of which have certain morphological characteristics that allow distinguishing the processes from each other [19, 20]. At the same time, many years of experience in the morphological study of heart valves removed for AHDs have shown that histological specimens often reveal features that have not received much attention from researchers [21, 22].

According to the authors of this study, which is also confirmed by the studies of other researchers [23, 24], in most cases, the AHD was localised in the valves of the left heart (MV and AV), which is associated with the greatest mechanical load on these valves, as high blood pressure is created here. Only recently have there been defects in the AHD in which the tricuspid valve is involved in the pathological process. This is associated with infective endocarditis in drug addicts, as well as in people who have undergone various intravenous manipulations.

Haemodynamic disorders that occur in AHD are caused by changes in the macro- and microarchitecture of heart valves [25, 26], structural reorganisation of the connective tissue components of the valvular apparatus [27] and endothelium. At the same time, the most vulnerable are the edges of the leaflets, the lines of leaflet closure, the pericommissural areas of the AV, MV, and TV, as well as the bases of the MC chords, i.e. the areas that are exposed to the greatest hemodynamic impact. According to O. Papuha [28], dynamic mechanical impact on the subject causes the accumulation of hyaluronic acid in the medium, which causes the homogenisation of collagen fibres. Static mechanical impact does not have this property.

The data obtained in the present study coincide with those of the authors who studied not only the structural organisation of heart valves but also the morphological causes of cardiac conduction disorders. According to M. Sugiura *et al.* [29], calcifications acting on the anatomical bifurcation of the bundle cause various conduction disorders, but the most observed blockade of the left or right pedicle or simultaneous blockade of the right pedicle and the anterior branch of the left pedicle, i.e. bifascicular block. In some cases, calcifications spreading beyond the fibrous ring of the aorta, towards the apex of the interventricular septum, gradually mechanically press on the relevant parts of the conduction system. In other cases, calcification spreads beyond the fibrous ring of the aorta by sprouting the muscular ridge of the interventricular septum, destroying the tendon strings, which occurs, for example, in rheumatic damage to the AV.

The significant role of haemodynamic trauma in the development of AHD is supported by the data of T.S. Momberger *et al.* [30], which show that it is the dynamic mechanical effect that stimulates the accumulation of hyaluronic acid in the interstitial tissue, which causes swelling of the interstitium and collagen fibres. Even minimal morphological changes of a congenital nature in heart valves lead to an increasing remodelling of heart valve structures, which is consistent with the data of E. Aikawa & J.D. Hutcheson [31]. The process of transformation of the valve leaflets occurs through morphological changes, namely fragmentation and stratification of collagen fibre bundles with swelling of the spongiosis layer. The surface of such valves, especially along the line of leaflet closure, at the base of the tendon strings of the MV and in the commissures, is damaged. All these changes are a consequence of the chronic mechanical effect of blood flow on the valve structures. Subsequently, these

damages can, on the one hand, be aggravated by fibrosis, fatty degeneration, and calcification, and on the other hand, compensatory mechanisms are involved in the process that improves mechanical strength and thus the functional capacity of the valves, namely, the authors of this paper consider hyperplasia of subendothelial smooth muscle cells to be a compensatory mechanism.

This study also examined a group of isolated abnormalities of valve structures (minimal forms of dysplasia) that did not impair valve function in the first decades of life and, accordingly, did not produce any clinical manifestations. When non-inflammatory NAV affects people of young and mature age, clinicians define the defect as idiopathic. This includes, for example, Barlow's disease, which occurs in 1.5-17% of the population [32]. However, after 20-30 years, according to the above studies, this pathology led to the early development of degenerative changes in connective tissue structures. Over time, the changes caused by dysplasia were complicated by calcification, and then clinicians diagnosed either calcifying heart disease or stenosing calcification. This pathology was manifested by significant haemodynamic disorders and required surgical correction.

However, many doctors consider age-related changes in heart valves (primarily in the AV) to be almost normal and do not pay attention to the appearance of a systolic murmur in the aorta when monitoring a patient. In addition, as a result of environmental changes and an increase in the prevalence of anthropogenic factors that accelerate the development of calcific heart disease, this disease began to occur at the age of 45-50 years [33]. At the same time, with age, small forms of valvular pathology acquire the character of a clinically significant process and are often mistakenly interpreted as infective endocarditis, rheumatism, etc. Thus, AHD occurs as a result of various factors that determine the development of morphological changes in the valvular apparatus of the heart, which are characteristic of each of the nosological forms.

However, the morphogenesis of the AHD contains elements that are common to all or most types of acquired defects. Specific features include fibrinoid necrosis, Ashof-Talalayev granulomas, productive-destructive vasculitis - in rheumatic heart disease; leukocyte infiltration with numerous neutrophils, lysis of heart valve structures, vegetations, abscesses – in IE; changes in the number of CVc valve leaflets, disorders of the architecture of the papillary-trabecular apparatus and MV leaflets, as well as compensatory hyperplasia of subendothelial smooth muscle cells – in AHD developing against the background of subclinical forms of valve dysplasia; age-related degenerative changes in connective tissue with lipoidosis and subsequent calcification - in AHD of degenerative genesis.

All heart valves are united by the fact that they are in the heart cavities and are subject to constant systolic and diastolic effects of intracardiac blood flow. Therefore, AHD is characterised by morphological changes associated with chronic haemodynamic trauma. In addition, the heart valves are constantly in direct contact with a large amount of blood, and therefore any damage to the endothelial layer provides access to the valve structures for lipids and peroxidation products that are present in the blood in varying amounts. Consequently, changes in the architectonics of the MV lead to the transformation of its structural components, which causes a violation of the valve's functionality. Hemodynamic trauma with damage to the endothelial layer and lipoidosis of valve structures plays an important role in the formation of heart disease.

CONCLUSIONS

Persistent changes in the architecture of heart valves lead to chronic haemodynamic injury, causing the transformation of structures with impaired valve functionality. Hyperplasia of subendothelial smooth muscle fibres in L valves with mild dysplasia can be regarded as a compensatory mechanism associated with the need to increase mechanical strength and thus the functional capacity of valves. MV dysplasia can lead to the development of IE-II, rheumatism, and RC heart valve disease. It should be noted that secondary valve deformation associated with rheumatic sclerosis or RC exacerbates hemodynamic injury and contributes to the morphogenesis of mitral heart disease.

A wide range of changes is recorded in the structures of the heart valves, which are present in varying degrees of severity in the case of AHD of different genesis. Signs of significant calcification were detected in 65.7% of non-inflammatory AHD, including 14.1 % of the defect associated with age-related degenerative changes in the connective tissue structures of the valve and 13.3 % with subclinical dysplasia. Dystrophic changes in the structures are manifested by homogenisation of collagen fibres with their subsequent fatty infiltration (in 100% of cases of degenerative AHD, 64% of cases of AHD with subclinical forms of dysplasia, 59.8% of cases of rheumatism and 51.1% of cases of secondary infective endocarditis), as well as fatty transformation of the loose connective tissue of the spongiosal layer. These changes are accompanied by lipophage accumulation and calcification. Morphological studies have established that, unlike acute rheumatic heart disease, in chronic active and inactive rheumatism, factors caused by chronic haemodynamic trauma to the deformed valves (fibrogenesis on the damaged leaflet surface in 100% of cases of active rheumatic heart disease and 97.8% of cases of inactive rheumatism), as well as degenerative changes in scar tissue, are involved in the formation of AHD. The intracardiac localisation of heart valves causes a constant haemodynamic influence of systolic and diastolic blood flows on their structures. At the same time, any changes in valve architecture cause absolute hemodynamic damage to the endothelium, which contributes to the development of AHD of various genesis and is manifested by morphological changes in endothelial cells with various types of damage. Thus, mechanical overload of valves in hemodynamic injury precedes the development of valve failure. Further morphological diagnostics of AHD will allow for accurate verification of the defect and the development of adequate postoperative treatment regimens.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Морфологічні зміни структурних компонентів клапанів серця людини, які пов'язані з хронічною гемодинамічною травмою

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Анотація. Архітектоніка клапанів серця оптимально адаптована до їх фізіологічної функції – рівномірному розподілу потоків крові в камерах серця, тому навіть невеликі зміни структурних компонентів клапанів, які спочатку є функціонально компенсованими, відіграють значну роль у розвитку вади серця на більш пізніх етапах життя хворого. Метою дослідження було з'ясувати вплив хронічної гемодинамічної травми на структурну реогранізацію клапанів серця людини. Досліджено 1377 клапанів серця людини, які отримані під час операції протезування клапанів у Національному інституті серцево-судинної хірургії ім. М. М. Амосова з 2010 по 2022 рік. Під час дослідження визначався повний набір варіантів макро- та мікроскопічних змін морфологічних структур, які характерні для ревматичної хвороби серця, інфекційного ендокардиту, диспластичних і деструктивних змін клапанів серця. Сукупність всіх морфологічних ознак були об'єднані в алгоритм «Морфологічні прояви набутих вад серця різного ґенезу». Встановлено, що зміна архітектоніки мітрального клапана приз¬водять до

тран¬сформації його структурних компонентів, що викликає порушення функціональних можливостей клапана. Було досліджено, що стійкі зміни, які пов'язані з хронічною гемодинамічною травмою, зменшують механічну міцність клапана, незважаючи на компенсаторний механізм гіперплазії субендотеліальних гладких м'язових волокон у стулках клапанів серця. У подальшому дані пошкодження можуть, з однієї сторони, поглиблюватися за рахунок фіброзу, жирової дегенерації та кальцинозу, а з іншої – у процес включаються компенсаторні механізми, а саме гіперплазія субендотеліальних м'язових клітин, яка часто формує суцільні пласти, що повинні посилити та укріпити механічну міцність, і тим самим – функціональну компетентність клапанів. Дисплазія мітрального клапана може призвести до розвитку вторинного інфекційного ендокардиту, ревматизму та вади клапана дегенеративного ґенезу. Алгоритм визначення закономірностей морфологічних змін клапанного апарату серця при різнома¬нітних варіантах набутих вад запального та незапального ґенезів може бути використаний при удосконаленні схем етіопатогенетичного медикаментозного лікування хворих з набутими вадами серця, а також – в якості теоретичної основи для розробки нових видів клапанозберігаючих операцій

Ключові слова: морфологічна перебудова; клапанна система серця; гемодинамічна травма; світлова мікроскопія