

MORPHOLOGICAL CHANGES OF HEART VALVES AND MYOCARDIUM IN POSTNATAL ONTOGENESIS IN OFFSPRING BORN TO MOTHERS WITH METABOLIC SYNDROME

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RELEVANCE

Metabolic syndrome is one of the pressing problems of modern medicine, and its components - obesity, insulin resistance, hyperglycemia, dyslipidemia, and arterial hypertension - can affect not only the maternal body but also the formation of fetal and subsequent generation health. The fact that metabolic disorders in the mother's body affect the cardiovascular system from the time of fetal development and subsequently form a predisposition to cardiac pathology is of particular importance from the perspective of the concept of fetal programming.

Cardiac valves are complex connective tissue structures that ensure hemodynamic stability, and their postnatal maturation is closely linked to the formation and reorganization of extracellular matrix components, specifically collagen and elastic fibers. Therefore, studying the morphological maturation of the offspring's heart and the structural reorganization of the valvular apparatus under conditions of metabolic disorders in the mother's body is important for identifying early signs of pathological remodeling.

The relevance of this study is determined by the need for a comprehensive morphological and morphometric assessment of the impact of changes in the maternal body on the heart wall and valvular apparatus of the offspring at various stages of postnatal ontogenesis under conditions of metabolic syndrome. The study primarily examined the dimensions of cardiomyocytes in the myocardium, the interstitial and perivascular zones, as well as the valve thickness, stroma area, and cell density of the mitral, tricuspid, aortic, and pulmonary valves.

Purpose of the study

Assessment of morphological and morphometric changes in the heart wall and valvular apparatus of offspring born to mothers with experimental metabolic syndrome at various stages of postnatal ontogenesis.

Materials and methods

The study was conducted between 2021 and 2024 at the Department of Human Anatomy of the Termez branch of Tashkent State Medical University, the vivarium of the Tashkent

Medical Academy, and the university's Central Research Laboratory. Sexually mature white laboratory rats with a body weight of 180–200 g and their offspring were used as the research material.

The female rats were divided into control and experimental groups. In the experimental group, a metabolic syndrome model was formed using a high-fat and high-carbohydrate diet: 60% of the diet consisted of standard laboratory feed, 20% of sheep fat, and 20% of fructose; instead of drinking water, a 20% fructose solution was administered. The formation of the model was assessed based on weight gain, blood glucose, lipid metabolism indicators, and arterial blood pressure; the main criteria were a 20% or more increase in body weight compared to the control and a glucose level exceeding 6.7 mmol/L.

The heart wall and valvular apparatus of the offspring were studied using general histological, morphological, morphometric, immunohistochemical, and statistical methods. Morphometric analyses were performed using the NanoZoomer digital scanner and QuPath software. The results were processed using variational and correlational statistical methods, and $p < 0.05$ was taken as the criterion for statistical reliability.

Results

In the control group, a consistent course of physiological morphogenesis of the heart wall and valvular apparatus was established during postnatal ontogenesis at 7–60 days. At the 7-day stage, the cardiomyocytes were relatively small, with a diameter of $9.5 \pm 0.7 \mu\text{m}$ and a length of $95 \pm 8 \mu\text{m}$; the interstitial area was $14.2 \pm 1.1\%$. By the 14th day, the diameter of the cardiomyocytes increased to $11.2 \pm 0.8 \mu\text{m}$, and the length to $105 \pm 9 \mu\text{m}$. On the 21st day, these indicators were $12.7 \pm 0.9 \mu\text{m}$ and $122 \pm 11 \mu\text{m}$, respectively, with an orderly arrangement of myocardial fibers and a pronounced formation of transverse striations. By the 30th day, the myocardial architecture is almost fully formed, and the interstitial area decreases to $13.5 \pm 1.4\%$. On the 60th day, the cardiomyocyte diameter was $11.2 \pm 0.8 \mu\text{m}$, the length was $110 \pm 9 \mu\text{m}$, and the interstitial area was $13.2 \pm 1.5\%$.

In the control group, age-related physiological maturation of the valve apparatus was also noted. In the 14-day period, the thickness of the mitral valve was $38.6 \pm 3.2 \mu\text{m}$, the tricuspid valve was $34.2 \pm 2.8 \mu\text{m}$, the aortic valve was $41.8 \pm 3.6 \mu\text{m}$, and the pulmonary valve was $36.1 \pm 3.0 \mu\text{m}$. By day 21, the valve thickness in all valves significantly increased ($p < 0.05$), the stroma area expanded, and cellular density physiologically decreased. On the 60th day, the valve apparatus reached a morphologically mature state, and the valve thickness in the mitral, tricuspid, aortic, and pulmonary valves was 72.3 ± 5.1 ; 66.8 ± 5.0 ; 79.1 ± 5.6 and $70.5 \pm 5.3 \mu\text{m}$, respectively.

In offspring born to mothers with metabolic syndrome, postnatal morphological maturation of the heart wall slowed down compared to the control group. As early as the 7th day, a relatively irregular arrangement of myocardial fibers, weak eosinophilicity of the cardiomyocyte cytoplasm, an expansion of the intermyocardial space, and a relative increase

in interstitial connective tissue were observed. During this period, the cardiomyocyte diameter was $8.9 \pm 0.6 \mu\text{m}$, the length was $91 \pm 7 \mu\text{m}$, and the interstitial area was $15.6 \pm 1.2\%$.

By the 14th day of life, pathological changes became more pronounced; the cardiomyocyte diameter was $10.5 \pm 0.7 \mu\text{m}$, the length was $100 \pm 8 \mu\text{m}$, and the interstitial area was $15.2 \pm 1.3\%$. The perivascular area was $8.4 \pm 0.8\%$, the area of collagen fibers was $6.2 \pm 0.7\%$, and the area of elastic fibers was $3.1 \pm 0.5\%$. During this period, initial signs of pathological reorganization of the extracellular matrix were observed.

By the 21st day, disruptions in the ordered arrangement of myocardial fibers persisted, and vacuolar-dystrophic changes were noted in some cardiomyocytes. Cardiomyocyte diameter was $11.8 \pm 0.8 \mu\text{m}$, length was $115 \pm 9 \mu\text{m}$, interstitial area was $15.0 \pm 1.4\%$, and perivascular area was $8.8 \pm 0.9\%$. While the area of collagen fibers increased to $6.9 \pm 0.8\%$, the valve thickness in all valves was significantly higher than in the control group, increasing by 18–22% in the mitral valve, 15–20% in the tricuspid valve, 22–27% in the aortic valve, and 12–15% in the pulmonary valve ($p < 0.05$). The greatest change was observed in the aortic valve.

In offspring born under the influence of metabolic syndrome at 30 days of age, myocardial remodeling intensified further. Cardiomyocyte diameter was $11.6 \pm 0.8 \mu\text{m}$, length was $112 \pm 8 \mu\text{m}$, interstitial area was $15.8 \pm 1.5\%$, and perivascular area was $9.1 \pm 0.9\%$. An increase in the area of collagen fibers to $7.4 \pm 0.8\%$ and an increase in the area of elastic fibers to $3.1 \pm 0.5\%$ indicates the pathological reorganization of the extracellular matrix and the intensification of fibrous processes. During this period, the valve thickness was 20–24% higher in the mitral valve, 18–22% in the tricuspid valve, 24–28% in the aortic valve, and 14–17% in the pulmonary valve compared to the control group ($p < 0.05$).

Morphological changes were most pronounced at 60 days of age. Cardiomyocyte diameter was $10.8 \pm 0.7 \mu\text{m}$, length was $106 \pm 8 \mu\text{m}$, interstitial area was $16.3 \pm 1.6\%$, and perivascular area was $9.5 \pm 1.0\%$. The area of collagen fibers increased to $8.2 \pm 0.9\%$, and the area of elastic fibers decreased to $2.9 \pm 0.4\%$. Histologically, disorganization of myocardial fibers, atrophic-dystrophic changes in individual cardiomyocytes, expansion of interstitial and perivascular connective tissue, and a dense accumulation of collagen fibers were noted.

In the valvular apparatus, signs of pathological remodeling also intensified with age. In the 60-day period, the thickness of the mitral valve valve was 20–25% higher than in the control group, the tricuspid valve was 18–22%, the aortic valve was 25–30%, and the pulmonary valve was 15–18% higher ($p < 0.05$). Stroma area was noted to be 18–22%, 16–20%, 20–25%, and 14–18% higher, respectively. The most pronounced changes were observed in the aortic valve, which is explained by its sensitivity to remodeling processes under conditions of high hemodynamic load.

CONCLUSION

In offspring born to mothers with experimental metabolic syndrome, postnatal morphological maturation of the heart wall and valvular apparatus slows down compared to

the control group. This process manifests as a reduction in the size of cardiomyocytes, expansion of the interstitial and perivascular zones, disruption of the architecture of myocardial fibers and myofibrils, as well as pathological reorganization of the extracellular matrix.

Under the influence of metabolic syndrome, an increase in valve thickness, stroma area, and cell density indicators is observed in the mitral, tricuspid, aortic, and pulmonary heart valves compared to the control group. These changes persist throughout postnatal ontogenesis and intensify with age. In particular, the high degree of morphometric changes in the aortic valve indicates its sensitivity to structural remodeling under conditions of high hemodynamic load.

Thus, metabolic syndrome in the mother's body creates a morphological basis for the pathological remodeling of the myocardium and valvular apparatus in the heart of the offspring from the early postnatal period. The excessive accumulation of collagen fibers, the disruption of elastic fiber architecture, and increased stroma sclerosis indicate the progressive nature of the reorganization of the extracellular matrix and fibrous processes of the heart. The results obtained serve as a scientific basis for the early morphological assessment of cardiovascular system changes and the improvement of preventive monitoring in offspring born to mothers with metabolic risk factors.

Key Conclusion: The impact of maternal metabolic syndrome manifests not only in functional risk in the heart of the offspring, but also in specific structural reorganizations observed during postnatal ontogenesis.