https://doi.org/10.46389/rjd-2024-1573
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2024; volume 31, issue 3, pages 298–304

Original Article

# Quantitative morphological assessment of the structural changes in the arterial bed of the cardiac ventricles in diabetes mellitus and post-resection pulmonary hypertension

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Received: 15 March 2024 / Accepted: 9 August 2024

## Abstract

Cardiovascular disease and diabetes mellitus have been recognized as global challenges of the 21st century. The study aimed to evaluate the structural changes in the arterial bed of the heart chambers in diabetes mellitus and pulmonary hypertension. The myocardium of 54 rats divided into 4 groups was studied morphologically. The outer diameter of small-caliber arteries of the right ventricle in diabetes mellitus statistically significantly ($p<0.05$) increased by 3.0%; in post-resection pulmonary hypertension – by 4.1% ($p<0.05$); in combined lesions, this morphometric index increased by 18.7% ($p<0.001$). In the presence of diabetes mellitus in the right ventricle, the internal diameter of small arteries decreased statistically significantly ($p<0.01$) by 8.6%, in the case of post-resection pulmonary hypertension – by 23.2% ($p<0.001$), and in the combination of pathology – by 57.4% ($p<0.001$). In small-caliber arteries of the right ventricle, the thickness of the media increased by 11.0% in diabetes mellitus, adventitia by 37.1%, in post-resection pulmonary hypertension by 28.8% and 65.5%, respectively, and in the combination of these two pathologies by 89.0% and 251.7%, respectively. In diabetes mellitus and post-resection pulmonary hypertension, hemodynamic and structural changes occur in the arterial bed of the heart, which significantly disrupts the blood supply to the myocardium, worsens its trophic supply, and plays an important role in the photomorphogenesis of its diseases.

**Keywords:** myocardium, microcirculation, rats, histology.

## Introduction

An actual problem of modern morphology is the study of the structure of intact organs, tissues and cells and the patterns of changes in their structure under the influence of various endogenous and exogenous factors. This fully applies to the heart – the central organ of haemocirculation, which is one of the first to respond to the effects of external and internal environments [1, 2]. Recent decades have seen significant progress in the prevention, diagnosis and treatment of heart and vascular disease, which has substantially reduced mortality and disability from cardiovascular disease in most economic regions. At the same time, it should be noted that these achievements do not remove the priority of studying this important issue [1].

Morphologists studying biological objects are increasingly using quantitative morphological methods (morphometry), which allow them to obtain an objective quantitative morphological characterization of

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the structural changes in organs and body systems during various physiological and pathological processes and interpret them logically [3–5].

In recent years, our knowledge of the structure and function of cardiomyocytes has expanded significantly. At the same time, the issues of joint functioning of the cardiomyocyte within the whole organ are not fully understood, especially in functional and pathological changes of these cells and in the conditions of physiological regulation of functions, as well as when pathological factors act on the body [1, 6].

Most researchers argue that prolonged hypertension in the pulmonary artery system of various origins leads to hyperfunction and hypertrophy of the heart's right ventricle, i.e., the pulmonary heart. Chronic pulmonary heart disease is believed to be a syndrome characterized by hypertrophy and dilatation of the right heart due to the development of pulmonary hypertension in patients with various pulmonary diseases that lead to respiratory failure [1, 2].

Nowadays, lung resection is often performed in surgical clinics, which, when 50.0% of the lung parenchyma volume or more is removed, leads to post-resection arterial hypertension in the pulmonary circulation and is complicated by the development of chronic pulmonary heart disease and its decompensation. Post-resection pulmonary arterial hypertension leads to structural changes in organs of the systemic circulation, abdominal cavity and pelvis, and remodeling of their structures. It is essential to note that the peculiarities of the structural changes in the arterial bed of the heart chambers in post-resection pulmonary arterial hypertension have not been sufficiently studied [1, 5].

Clinicians and morphologists have increasingly started to pay attention to the peculiarities of remodeling the structures and vascular beds of the heart in diabetes mellitus (DM) [6]. There is a pathogenetic link between cardiovascular disease and diabetes mellitus, which is on the rise both in Ukraine and in other countries. Scientists have shown that in the presence of diabetes alone, mortality from coronary disease increases 4 times and stroke – 3–4 times compared to the population of patients without diabetes mellitus [7]. It turned out that the pathogenetic mechanisms of DM influence the development of cardiac pathology are more significant than traditional classical factors such as hypercholesterolemia, smoking, obesity, arterial hypertension etc.

The probability of chronic heart failure is significantly correlated with the presence of diabetes mellitus [6–9]. More than half of patients with DM have pathology of the cardiovascular system. Frequent and severe complications of diabetes mellitus include acute vascular disorders that can cause myocardial infarction, heart failure, ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) and cardiac arrest.

Hyperglycaemia underlies the pathophysiological changes in diabetic cardiomyopathy. In diabetes mellitus, myocardial glucose transport and utilization are significantly reduced. The basis of diabetic cardiomyopathy is the dysfunction of small vessels of the heart (microangiopathy). In this case, microcirculation is disturbed, and myocardial morphological and functional changes develop. Particular importance is attached to disorders of myocardial bioelectrical activity, a decrease in its contractility and the development of myocardial decompensation [5–8]. Thus, in patients with cardiomyopathy in the setting of diabetes, there are preconditions for cardiac rhythm and conduction disorders.

This study aimed to conduct a morphometric analysis of the structural changes in the arterial bed of the heart chambers in patients with diabetes mellitus and pulmonary hypertension after pulmonectomy.

## Material and methods

A set of morphological methods was used to analyze the myocardium of the right and left ventricles of 54 white male rats, which were divided into four groups: a control group, which included 12 intact animals; the main group with modeled DM – 14 rats; the main group with pulmonary hypertension (PH) after pneumonectomy – 14 animals and the main group with combined pathology of PH and DM – 14 rats. It should be noted that in the main group with DM – 1 animal died (mortality rate 7.14%), in the main group after pneumonectomy without DM – 3 animals died (mortality rate 21.42%), and in the combination of these two pathologies 3 animals died (mortality rate 21.42%). These animals were not taken into account in the statistical processing of the results of myocardial morphological parameters.

The model of experimental diabetes mellitus was reproduced by injecting rats with streptozotocin intraperitoneally at a dose of 50 mg/kg after dissolving it in 0.1M citrate buffer solution (pH 4.5). The development of hyperglycemia was monitored by blood glucose level – 24.24±0.79 mmol/l. In the control group – 8.03±0.4 mmol/l [10]. The blood glucose concentration (mmol/L) in laboratory animals was determined by

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the enzymatic colorimetric method (GOD/POD/PAP) using a semi-automatic analyzer BS-3000M manufactured by Sinnowa (China), using biochemical kits from Diagnosticum Inc (Hungary). Post-resection pulmonary hypertension in experimental animals was modeled by performing right-sided pneumonectomy under ketamine anesthesia at a dose of 50 mg/kg body weight. Animals were euthanized by bleeding under thiopental anesthesia 28 days after the start of the experiment. Pieces of sufficient size were cut from the anterior and lateral walls of the left and right ventricles, which were fixed in a 10% neutral formalin solution, 96° ethyl alcohol, and after appropriate passage through ethyl alcohols of increasing concentration, they were embedded in paraffin. Heidenhain stained microtome sections (5–7 μm thick) with Van Gieson's stain and iron hematoxylin [3, 4]. In the left ventricle (LV) and right ventricle (RV) of the heart, the following were measured: outer and inner diameters of the arterial vessel; medial thickness and thickness of the arterial vessel adventitia; Vogenworth index – the ratio of the vessel wall area to its lumen; Kernogan index – the ratio of the vessel lumen area to the vessel wall area; endothelial cell height; nuclear diameter; nuclear-cytoplasmic ratio in endothelial cells; relative volume of damaged cells [1, 11]. Quantitative indicators were processed statistically. The results were processed at the I's Department of Systematic Statistical Research. Horbachevsky Ternopil National Medical University using the STATISTIKA software package. The difference between comparative values was determined by the Student's criterion [12]. Experiments and euthanasia of experimental animals were carried out in compliance with the "General Ethical Principles for Animal Experiments" approved by the First National Congress on Bioethics (Kyiv, 2001), by the "European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes", as well as the Law of Ukraine "On Protection of Animals from Cruelty" (from 21.02.2006).

## Results

A comprehensive analysis of the data in this table revealed a pronounced structural restructuring of the arterial bed of the heart's ventricles, which was confirmed by significant changes in the morphometric parameters studied. The study's results are presented in Table 1.

Table 1: Morphometric characteristics of small-caliber arteries of the ventricles of experimental animals (M±m).

| Indicator | Monitoring groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Control group | | Main group with diabetes mellitus | | Main group with pulmonary hypertension | | Main group with diabetes mellitus and pulmonary hypertension | |
| | Left ventricle | Right ventricle | Left ventricle | Right ventricle | Left ventricle | Right ventricle | Left ventricle | Right ventricle |
| **The outer diameter of the arterial vessel (μm)** | 36.20 ± 0.48 | 36.40 ± 0.48 | 37.70 ± 0.45* | 37.50 ± 0.45* | 37.92 ± 0.45* | 37.90 ± 0.42* | 41.30 ± 0.57*** | 43.20 ± 0.9*** |
| **Internal diameter of the arterial vessel (μm)** | 23.20 ± 0.21 | 23.30 ± 0.21 | 20.90 ± 0.21*** | 21.45 ± 0.21*** | 19.30 ± 0.18*** | 18.90 ± 0.18*** | 15.70 ± 0.21*** | 14.80 ± 0.33*** |
| **Media thickness (μm)** | 7.30 ± 0.12 | 7.30 ± 0.12 | 8.30 ± 0.12*** | 8.10 ± 0.12*** | 8.80 ± 0.12*** | 9.40 ± 0.09*** | 9.80 ± 0.15*** | 13.80 ± 0.30*** |
| **Adventitious thickness** | 5.70 ± 0.04 | 5.80 ± 0.04 | 8.50 ± 0.12*** | 7.95 ± 0.12*** | 9.60 ± 0.12*** | 9.6 ± 0.12*** | 15.9 ± 0.18*** | 14.6 ± 2.1*** |
| **Vogenworth index (%)** | 243.5 ± 4.8 | 242.1 ± 5.1 | 325.9 ± 2.1*** | 305.6 ± 2.1*** | 386.60 ± 2.7*** | 402.2 ± 2.7*** | 693.5 ± 9.2*** | 852.05 ± 12.40*** |
| **Kernogan index (%)** | 41.1 ± 0.3 | 41.0 ± 0.3 | 30.7 ± 0.03*** | 32.7 ± 0.3*** | 25.90 ± 0.24*** | 24.88 ± 0.12*** | 14.45 ± 0.12*** | 11.74 ± 0.18*** |


https://doi.org/10.46389/rjd-2024-1573
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Table 1: Continued.

| Indicator | Monitoring groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Control group | | Main group with diabetes mellitus | | Main group with pulmonary hypertension | | Main group with diabetes mellitus and pulmonary hypertension | |
| | Left ventricle | Right ventricle | Left ventricle | Right ventricle | Left ventricle | Right ventricle | Left ventricle | Right ventricle |
| **Endothelial cell height (μm)** | 6.20 ± 0.12 | 6.30 ± 0.12 | 6.54 ± 0.12* | 6.56 ± 0.0.09* | 6.62 ± 0.09** | 6.62 ± 0.09* | 6.40 ± 0.09** | 6.75 ± 0.09* |
| **Diameter of endothelial cell nuclei (μm)** | 3.10 ± 0.06 | 3.15 ± 0.05 | 3.52 ± 0.04** | 3.47 ± 0.04** | 3.70 ± 0.03*** | 3.58 ± 0.03*** | 3.45 ± 0.05* | 3.76 ± 0.05*** |
| **Nuclear-cytoplasmic ratio** | 0.250 ± 0.003 | 0.250 ± 0.003 | 0.290 ± 0.003* | 0.280 ± 0.003** | 0.310 ± 0.003*** | 0.294 ± 0.003*** | 0.294 ± 0.003*** | 0.310 ± 0.04*** |
| **Relative volume of damaged cells (%)** | 2.10 ± 0.03 | 2.05 ± 0.02 | 16.20 ± 0.30*** | 15.30 ± 0.27*** | 31.5 ± 0.4*** | 34.30 ± 0.36*** | 39.20 ± 0.45*** | 49.50 ± 1.20*** |

Note: * – p<0.05; ** – p<0.01; *** – p<0.001 compared to group 1.

Thus, the outer diameter of small-caliber arteries of the left ventricle in DM statistically significantly (p<0.05) increased by 4.1%, and in PH and a combination of pathologies, this morphometric index increased by 4.8% (p<0.05) and 14.1% (p<0.001), respectively. The internal diameter of small-caliber arteries of the left ventricle decreased in the modeled experimental conditions. Thus, in DM, the internal diameter of the studied vessels statistically significantly (p<0.001) decreased by 10.0%, in PH – by 16.8% and in the main group with DM and PH – by 32.3%. It should be noted that the narrowing of the arterial lumen was evidenced by a marked increase in the Vogenworth index in DM, PH and a combination of these pathologies by 1.34, 1.59 and 2.85 times and a decrease in the Kernogan index in animals of the above experimental groups by 25.3%, 37.0% and 284% of the normal control group, indicating a decrease in the capacity of small-caliber arteries of the left ventricle and a deterioration in its blood supply.

It was also found that with a statistically significant difference (p<0.001) in small-caliber arteries of the left ventricle, the thickness of the medial wall increased by 13.7% in DM, adventitia – by 49.1%, in PH – by 20.5%, 68.4%, and in the combination of PH and DM – by 34.2% and 278.9%. The height of endothelial cells of small arterial vessels and the diameter of their nuclei in the left ventricle in PH also changed. In the main group with DM, the height of endothelial cells increased by 5.5% (p<0.05), and the diameter of their nuclei increased by 13.5% (p<0.01), which led to pronounced changes in nuclear-cytoplasmic relations in these cells. Under these experimental conditions, the above morphometric parameter increased by 16.0% (p<0.01), indicating a significant disturbance of structural cellular homeostasis. The relative volume of damaged endothelial cells in the studied vessels in diabetes increased by 7.7 times (p<0.001).

In the main group, the height of endothelial cells in the studied vessels of the left ventricle changed more in the presence of PH. This quantitative morphological index increased by 6.8% (p<0.01). The diameters of the nuclei of the studied cells in this pathology increased by 19.3% (p<0.001). The nuclear-cytoplasmic ratio in endothelial cells of the left ventricular arterial vessels exceeded the same control value by 24.0% (p<0.001), indicating a violation of structural cellular homeostasis. The relative volume of damaged endothelial cells in the studied vessels of the left ventricle in postresection pulmonary hypertension increased by 15.0 times (p<0.001). In the main group, under DM and PH conditions, endothelial cells' height in the studied left ventricular vessels increased by 3.2% (p<0.01). Nuclear diameters of the studied cells increased by 11.3% (p<0.01). The nuclear-cytoplasmic ratio in the endothelial cells of the left ventricular arterial vessels exceeded the same control value by 17.6% (p<0.001), which indicated a violation of structural cellular homeostasis. The relative volume of damaged endothelial cells increased by 18.7 times (p<0.001).

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The morphometric parameters of small arterial vessels of the right ventricle changed similarly, but to a greater extent compared with the left ventricle. Thus, the outer diameter of the small caliber arteries of the right ventricle in DM statistically significantly ($p<0.05$) increased by 3.0%, in PH – by 4.1% ($p<0.05$), in DM and PH, this morphometric index increased by 18.7% ($p<0.001$), respectively. In the main group with DM, the internal diameter of small arteries in the right ventricle decreased statistically significantly ($p<0.01$) by 8.6%, in the group with PH – by 23.2% ($p<0.001$), and in the main group with DM and PH – by 57.4% ($p<0.001$). The Vogenworth index in the main groups with DM, PH and DM with PH increased by 1.26, 1.66 and 3.53 times compared with the control group. There was a decrease in the Kernogan index in animals of the above main groups by 25.4%, 64.8% and 349%, respectively, indicating a decrease in the capacity of small-caliber arteries of the right ventricle and a deterioration in its blood supply. The thickness of the media and adventitia of these vessels also changed. It was found that with a statistically significant difference ($p<0.001$) in small-caliber arteries of the right ventricle, the thickness of the medial wall increased by 11.0% in DM, and the thickness of the adventitia by 37.1%, in PH – by 28.8%, 65.5%, respectively, and in the combination of DM and PH- by 89.0% and 251.7%, respectively.

The height of small arterial vessel endothelial cells and the diameter of their nuclei in the right ventricle in DM increased by 4.1% ($p<0.05$) and 10.2% ($p<0.01$), respectively, which led to marked changes in nuclear-cytoplasmic relations in these cells. Under these experimental conditions, this morphometric parameter increased by 12.0% ($p<0.01$), indicating a significant disruption of structural cellular homeostasis. The relative volume of damaged endothelial cells in the studied vessels increased by 7.46 times ($p<0.001$).

In the main group, the height of endothelial cells in the studied vessels changed more under the condition of PH. This quantitative morphological index increased by 5.1% ($p<0.01$). The diameters of the nuclei of the studied cells in this pathology increased by 13.7% ($p<0.001$). The nuclear-cytoplasmic ratio in endothelial cells of the right ventricular arterial vessels exceeded the same control value by 17.6% ($p<0.001$), which indicated a violation of structural cellular homeostasis. The relative volume of damaged endothelial cells in the studied vessels increased by 16.7 times ($p<0.001$).

In the main group with DM and PH, changes in the height of endothelial cells in the studied right ventricular vessels were dominant. The height of endothelial cells increased by 7.1% ($p<0.01$). Nuclear diameters of the studied cells increased by 19.4% ($p<0.01$). The nuclear-cytoplasmic ratio in endothelial cells of the arterial vessels of the right ventricle exceeded the same control value by 24.0% ($p<0.001$), which indicated a violation of structural cellular homeostasis. The relative volume of damaged endothelial cells in the studied vessels of the right ventricle in the combination of DM with PH increased 24.1 times ($p<0.001$).

The presented and analyzed morphometric parameters indicate that the remodeling of small arterial vessels of the heart in the combination of DM and PH was more pronounced compared with other modeled pathologies and dominated in the right ventricle, which can be associated with a greater degree of its functional load and impaired metabolic processes in the heart structures.

## Discussion

It is known that vascular endothelial cells produce various biologically active substances necessary to regulate vital body processes. They perform barrier, production, hemostatic, metabolic, transport, and reparative functions and synthesize nitric oxide (NO), endothelin, angiotensin-II, thromboxane, and prostaglandin NO [5]. The pronounced structural changes in the small-caliber arteries of the heart ventricles one month after right-sided pneumonectomy indicated their special functional activity in redistributing blood flow in the setting of postresection pulmonary hypertension. The thickening of the wall of these vessels and narrowing of their lumen was due to an increase in the thickness of the media and adventitial membrane, as well as increased tone, hyperplasia and hypertrophy of smooth muscle cells. The pronounced tortuosity of the internal elastic membrane of the studied arteries indicated their increased tone. Damage to a significant number of endothelial cells led to their dysfunction, blockade of NO synthase, reduction of NO synthesis, activation of its degradation, and increased synthesis of vasoconstrictors: endothelin, angiotensin-II, thromboxane, and prostaglandin, which increased spasm and vasoconstriction, and significantly impaired blood supply to the organ and was complicated by hypoxia. The described structural changes in the small-caliber arteries of the left and right ventricles of the heart significantly affected the regulation of blood flow in postresection pulmonary hypertension and provided optimal blood supply to the organ under these pathological conditions [13].


https://doi.org/10.46389/rjd-2024-1573
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It is also known that small-caliber arteries in intact organs bear the main burden in regulating blood circulation and are the first to be damaged in pathology.

It is well known that cardiovascular complications are the main cause of death in patients with DM. The vessel wall is the main target for damage in DM. The main damaging factor is hyperglycemia, which, through the activation of the sorbitol pathway, protein kinase C and protein glycation, leads to the development of oxidative stress, a decrease in the formation of nitric oxide, and activation of the proinflammatory NF-kB pathway. On the one hand, an increase in the synthesis of extracellular matrix proteins by vascular wall cells contributes to the accelerated development of atherosclerosis and the progression of macroangiopathies and, on the other hand, causes damage to the hemomicrocirculatory system. In addition, the processes of vascular repair and neovascularisation are carried out with the participation of circulating endothelial progenitors recruited from the bone marrow in response to ischemia and vascular damage. Considering the complex multi-level interaction system between cells and regulatory cytokines, the study of angiogenesis remains relevant, especially in hyperglycemia [5, 9]. The main step in angiogenesis is the growth of new vessels from existing ones. When local ischemia occurs, endothelial cells (ECs) are activated because under hypoxia, tissue cells increase the expression and secretion of angiogenic factors, primarily vascular endothelial growth factor (VEGF), the receptors for which are selectively expressed on ECs. The interaction of VEGF with receptors activates the expression of proteases in ECs; they destroy intercellular contacts and the basement membrane and begin to actively divide and migrate into the ischaemic tissue along the chemoattractant gradient with the formation of a new vascular process [13].

The studies and the results obtained indicate that in diabetes mellitus and post-resection pulmonary hypertension, the arterial (arterioles, precapillary arterioles) and metabolic (hemocapillaries) parts of the hemomicrocirculatory system are narrowed, and the venous part (postcapillary and venules) is expanded. The degree of the detected changes in the arterial bed was dominant in the right ventricle. It is also worth noting that the detected structural changes in the vessels of the arterial bed were pronouncedly prevalent in post-resection pulmonary hypertension and combination with diabetes mellitus.

The predominance of morphological and morphometric changes in the right ventricle's vessels can be explained by the high degree of its functional load associated with increased pressure in the pulmonary circulation and metabolic and cardiac disorders in diabetes mellitus.

## Conclusion

The data obtained indicate that in conditions of diabetes mellitus and pulmonary hypertension, there are pronounced hemodynamic and structural changes in the arterial bed of the heart, which significantly impairs blood flow to this organ, worsens its trophic supply and plays an important role in the pathomorphogenesis of its lesions. The most pronounced degree of arterial vessel remodeling was found in the combination of diabetes mellitus and pulmonary hypertension, which leads to a pronounced structural remodeling of the vascular bed and parts of the myocardium, characterized by stromal and perivascular edema, foci of cardiomyocyte and endothelial dystrophy and necrosis, foci of infiltration and cardiosclerosis. The detected pathomorphological changes were dominant in the right ventricle and pulmonary hypertension in combination with diabetes mellitus.

## Conflict of interest

The authors declare no conflict of interest.

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