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The role of connexin 43 in remodeling cardiomyocyte intercellular contacts in hypertrophic cardiomyopathy

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ABSTRACT

BACKGROUND: Intercellular gap junctions play a special role in the biology of cellular interactions. Their structural and dispositional changes can affect some biological functions, including disruption of electrical pulse propagation, which is primarily important for myocardial function.

AIM: The aim was to evaluate the morphological characteristics and localization of connexin 43-containing ($Cx43^+$) gap — junctions and to determine their association with changes in myocardial morphology of the interventricular septum and clinical parameters in patients with hypertrophic cardiomyopathy.

MATERIALS AND METHODS: Morphometry and immunohistochemistry of interventricular septal myocardium were performed in patients with hypertrophic cardiomyopathy (n = 62, aged 18 to 61 years) compared with subjects without cardiovascular disease (n = 8, aged 25 to 54 years). Resection of the interventricular septum of the right ventricle was performed in patients with hypertrophic cardiomyopathy. $Cx43^+$ gap junctions were identified in cardiomyocytes and their location and ultrastructural arrangement were determined. The data obtained were compared with clinical parameters of patients with hypertrophic cardiomyopathy.

RESULTS: In the interventricular septal myocardium of patients with hypertrophic cardiomyopathy, a redistribution of Cx43+ gap junctions from intercalated discs to the lateral surfaces of cardiomyocytes was observed. Gap junction changes are more frequent and more extensive in patients with hypertrophic cardiomyopathy than in the control group. They are typical of patients with the most severe morphological and functional cardiac condition, as evidenced by echocardiographic data such as significant thickening of the interventricular septum and a decrease in the volume of the left ventricular cavity. Morphologically complex remodeling of the myocardium is manifested by hypertrophy of the cardiomyocytes and partial loss of their myofibrils. Ultrastructurally, 28.1% of patients with hypertrophic cardiomyopathy had gap junction defects in the myocardium such as sites of localized divergence of intercalated disc membranes and abnormal ring structures formed by invaginations of gap junction-containing sarcolemma.

CONCLUSION: The location of $Cx43^+$ gap junctions on the lateral surfaces of cardiomyocytes and changes in their ultrastructure suggest cardiomyocyte immaturity of the interventricular septum, which is typical of patients with hypertrophic cardiomyopathy and may cause a disruption of the electromechanical coupling of the myocardium.

Keywords: hypertrophic cardiomyopathy; cardiomyocytes; intercellular interactions; gap junctions; connexin 43.

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Роль коннексина 43 в ремоделировании межклеточных контактов кардиомиоцитов при гипертрофической кардиомиопатии

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АННОТАЦИЯ

Обоснование. В биологии клеточных взаимодействий особую роль играют межклеточные щелевые контакты. Изменение их структуры и расположения может привести к изменению ряда биологических функций, в том числе к нарушению распространения электрического импульса, что в первую очередь важно для работы миокарда.

Цель — оценка морфологических особенностей и локализации коннексин 43-содержащих ($Cx43^+$) щелевых контактов и определение их взаимосвязи с изменениями морфологии миокарда межжелудочковой перегородки и клиническими параметрами пациентов с гипертрофической кардиомиопатией.

Материалы и методы. Проведено морфометрическое и иммуногистохимическое исследование миокарда межжелудочковой перегородки пациентов с гипертрофической кардиомиопатией (*n*=62, возраст от 18 до 61 года) в сравнении с группой лиц без сердечно-сосудистой патологии (*n*=8, возраст от 25 до 54 лет). Пациентам с гипертрофической кардиомиопатией выполнена резекция миокарда межжелудочковой перегородки со стороны правого желудочка. В кардиомиоцитах выявлены $Cx43^+$-щелевые контакты, определена их локализация и ультраструктурная организация. Полученные данные сопоставлены с клиническими параметрами пациентов с гипертрофической кардиомиопатией.

Результаты. В миокарде межжелудочковой перегородки пациентов с гипертрофической кардиомиопатией обнаружено перераспределение $Cx43^+$-щелевых контактов из вставочных дисков на боковые поверхности кардиомиоцитов. Изменение локализации щелевых контактов встречается чаще и в большем объёме у пациентов с гипертрофической кардиомиопатией по сравнению с контрольной группой и характерно для пациентов с наиболее тяжёлым морфо-функциональным состоянием сердца, по результатам эхокардиографического обследования — со значительным утолщением межжелудочковой перегородки и уменьшением объёма полости левого желудочка. Морфологически комплексное ремоделирование миокарда проявляется в гипертрофии кардиомиоцитов и явлениях частичной утраты в них миофибрилл. На ультраструктурном уровне в миокарде 28,1% пациентов с гипертрофической кардиомиопатией обнаружены дефекты щелевых контактов: зоны локальных расхождений мембран вставочного диска кардиомиоцитов и аномальные кольцевые структуры, образованные инвагинациями сарколеммы, содержащей щелевые контакты.

Заключение. Расположение $Cx43^+$-щелевых контактов на боковых поверхностях кардиомиоцитов и изменение их ультраструктуры является признаком незрелости кардиомиоцитов межжелудочковой перегородки, характерным для пациентов с гипертрофической кардиомиопатией и может быть причиной нарушения электромеханического сопряжения миокарда.

Ключевые слова: гипертрофическая кардиомиопатия; кардиомиоциты; межклеточные взаимодействия; щелевые контакты; коннексин 43.

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连接蛋白43在肥厚型心肌病心肌细胞间接触重塑中的作用

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摘要

论证。在细胞相互作用的生物学中，细胞间间隙连接发挥着特殊的作用。它们的结构和功能的变化可以导致一系列生物功能的变化，包括电脉冲传播的破坏，这对于心肌功能是首当其冲的。

目的 — 评估肥厚型心肌病患者含连接蛋白43 (Cx43) 的缝隙连接的形态学特征和定位，并确定其与室间隔心肌形态学变化和临床参数的关系。

材料和方法。对肥厚型心肌病患者（*n*=62，年龄在18至61岁之间）与无心血管病患者（*n*=8，年龄在25至54岁之间）的室间隔心肌进行了形态计量学和免疫组化学研究。肥厚型心肌病患者接受了右心室室间隔心肌切除术。在心肌细胞中检测到了$Cx43^{+}$缝隙连接，并确定了它们的定位和超微结构组织。获得的数据与肥厚型心肌病患者的临床参数进行了比较。

结果。在肥厚型心肌病患者的室间隔心肌中发现，$Cx43^{+}$缝隙连接从闰盘重新分布到心肌细胞的外侧表面。根据超声心动图检查的结果，肥厚型心肌病患者的室间隔明显增厚，左心室腔容积缩小。肥厚型心肌病患者的缝隙连接位置变化比对照组更频繁，体积也更大，是心脏形态功能状态最严重的患者的特征。形态学上复杂的心肌重塑表现为心肌细胞肥大和肌原纤维部分丧失的现象。在28.1%的肥厚型心肌病患者的心肌超微结构中发现缝隙连接缺陷：心肌细胞闰盘膜的局部分叉区和含有缝隙连接的肌纤维膜内陷形成的异常环状结构。

结论。心肌细胞外侧表面的$Cx43^{+}$缝隙连接位置及其超微结构的变化是室间隔心肌细胞不成熟的标志，是肥厚型心肌病患者的特征，可能是心肌机电耦合失调的原因。

关键词：肥厚型心肌病；心肌细胞；细胞间相互作用；缝隙连接；连接蛋白43。

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BACKGROUND

Intercellular gap junctions play a crucial role in cell-to-cell communication. Alterations in their structure and function can lead to changes in various biological processes, including adhesion, invasion, and electrical conductivity, ultimately affecting contractile function. Specific intercellular gap junctions between cardiomyocytes (CMs) are essential for electrical impulse conduction in the heart and synchronization of myocardial contractions. Gap junctions are located along the longitudinal segments of intercalated discs and ensure the propagation of electrical impulses in intact myocardium along the long axis of the CMs. The permeability of gap junctions is regulated by changes in intracellular pH, calcium ion concentration, and direct phosphorylation or ubiquitination of connexins [1]. Being the primary component of ventricular CM gap junctions, connexin 43 (Cx43) phosphorylation is regulated by more than ten kinases and phosphatases, influencing protein synthesis, assembly, and the electrical conductivity of gap junctions [2]. In ventricular CMs, Cx43-containing gap junctions are predominantly located within intercalated discs, whereas in atrial CMs, they can also be distributed along the lateral surfaces of myocytes [3]. Beyond the plasma membrane, Cx43 is localized to the inner mitochondrial membrane, where it influences respiration and reactive oxygen species production within the cell [1].

In neonatal CMs, the components of the intercalated disc, which are gap junctions and desmosome-like contacts, are dispersed throughout the cell surface and remain unlinked. As CMs differentiate, these components aggregate and relocate to the transverse ends of the cells, forming a fully developed intercalated disc. The coordinated activity of all intercalated disc components—connexins, desmosomes, and desmosome-like adherens junctions (*fasciae adherentes*)—is essential for maintaining mechanical coupling and electrical impulse transmission between CMs. Disruptions in these structures may contribute to both arrhythmias and heart failure [4].

In the myocardium of patients with cardiovascular pathology, Cx43-containing gap junctions have been observed to relocate to the lateral surfaces of CM sarcolemma. Such changes have been identified in patients with hypertrophic cardiomyopathy (HCM) [5, 6], in the peri-infarct zone of the left ventricle (LV) in ischemic heart disease (IHD) [7], in arrhythmogenic cardiomyopathy [8], as well as in experimental studies [4, 9, 10]. Lateralization of gap junctions occurs as part of a broader cellular remodeling process and is accompanied by the displacement of other intercalated disc components [6].

AIM

To assess the ultrastructure and localization of Cx43-containing gap junctions and determine their relationship with morphological changes in the interventricular septum (IVS) CMs and clinical myocardial parameters in patients with HCM compared to the control group.

MATERIALS AND METHODS

Study design

A single-center, retrospective, observational, non-randomized, controlled study was conducted.

Eligibility criteria

The inclusion criterion for adult patients with obstructive HCM was an IVS thickness greater than 10 mm. In the comparison group, which included individuals who died from non-cardiovascular causes or fatal trauma, the IVS thickness did not exceed 10 mm.

The exclusion criterion was the presence of severe comorbidities of internal organs or the brain.

Study conditions

The myocardial specimens were obtained during surgical procedures performed by Academician L.A. Bokeria, MD, PhD, at the A.N. Bakulev National Medical Research Center for Cardiovascular Surgery, Moscow, Russia.

Study duration

The material was collected as patients were enrolled and was examined simultaneously according to the study protocol.

Description of medical intervention

Patients with HCM underwent myocardial resection of the IVS (myectomy) from the right ventricle, following the surgical technique developed by L.A. Bokeria [11].

Primary study outcome

Immunohistochemical identification of Cx43-containing gap junctions and electron microscopic examination of gap junctions in IVS CMs.

Secondary study outcome

Morphometric characterization of the IVS myocardium, including the assessment of CM diameter.

Group analysis

The study included patients with obstructive HCM and individuals who had died from non-cardiovascular causes or fatal trauma.

Registration of outcomes

For morphometric examination of the myocardium an d immunohistochemical detection of Cx43-containing gap junctions, myocardial tissue samples from the IVS were fixed in 10% buffered formalin (pH 7.4, Bio-Optica, Italy), embedded in paraffin, and sectioned at 4–5 μm thickness. The sections were then processed with: 3% hydrogen

peroxide solution(H_2O_2), trypsin solution (Sigma, USA); incubation with rabbit monoclonal antibodies against human Cx43 (Sigma, USA), then incubation with HRP Rabbit/Mouse solution (ChemMate™ DAKO EnVision™/HRP, Rabbit/Mouse, DAKO, USA). The samples were developed with 3,3'-tetrachloride diaminobenzidine (ChemMate™ DAB+ Chromogen, ChemMate™ Substrate Buffer, DAKO, USA) until a brown color appeared, followed by counterstaining with Mayer's hematoxylin. As a negative control, an immunohistochemical reaction was performed without incubation with primary antibodies; as a positive control, staining of intercalated discs in CMs on ventricular myocardium sections was used in accordance with the manufacturer's specifications. To assess the localization of $Cx43^+$ gap junctions on longitudinal sections passing through the nucleus and intercalated discs, at least 50 CMs were analyzed using the ImagePro morphometric program to measure the length of $Cx43^+$ segments on the lateral surfaces of CMs, as well as the diameter and length of CMs (×630). The ratio of the total length of $Cx43^+$ gap junctions on the lateral surfaces of CMs to twice the length of the myocyte was calculated and expressed as a percentage (relative length). Quantitative values were expressed as median (Me [Q1; Q3]).

Additionally, on longitudinal CMs sections, passing through the nucleus, myofibril content was graded using a 4-point scale (×400 magnification): MF-0 — myofibrils occupy <50% of sarcoplasm; MF-1 — 50–75% of sarcoplasm is filled with myofibrils; MF-2 — 75–90% of sarcoplasm is occupied by myofibrils; MF-3 — >90% of sarcoplasm is filled with myofibrils. For each patient, myofibril content was represented as an integral indicator (median value) and expressed as a percentage.

For electron microscopic examination, myocardial fragments from 48 HCM patients were: fixed in 2.5% glutaraldehyde and 1% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4); post-fixed in 1.5% osmium tetroxide (OsO_4), dehydrated and embedded in Araldite. Ultrathin sections (30–70 nm) were prepared using an UltraCut ultramicrotome (Leica, Germany). Sections were contrasted with uranyl acetate and lead citrate and examined using an electron microscope Philips CM 100 (Netherlands). Gap junction presence and distribution in intercalated discs and lateral CM surfaces were evaluated via electron microscopy.

Ethical approval

The study was approved by the Ethics Committee of the A.N. Bakulev National Medical Research Center for Cardiovascular Surgery (protocol No. 3, dated June 22, 2023). The study adhered to the Declaration of Helsinki guidelines of the World Medical Association. All participants voluntarily signed informed consent forms before enrollment, approved as part of the study protocol by the Ethics Committee.

Statistical analysis

Sample size calculation principles. Morphological findings from the HCM patient group and the control group were compared with each other and with the clinical examination data of the patients. The maximum available sample size was used.

Statistical methods. Data analysis was performed using Statistica v. 10 (StatSoft, Inc., USA). Comparisons between HCM patients and the control group were conducted using the Mann–Whitney U test(significance level $p < 0.05$). Correlation analysis was performed using Spearman's nonparametric correlation coefficient ($p < 0.05$).

RESULTS

Study objects

The study included 62 patients with obstructive HCM, whose IVS thickness was 24.5 (20.0; 27.0) mm. End-systolic volume (ESV) and end-diastolic volume (EDV) of the LV: 19 (14.4; 29.0) mL and 71.5 (62.0; 93.0) mL, respectively. Mitral valve pressure gradient: 3.4 (3.0; 4.2) mmHg. Left ventricular ejection fraction (LVEF): 75 (71; 80)%. The comparison group consisted of 8 individuals who died from non-cardiovascular causes or fatal trauma, with IVS myocardial samples obtained from the same anatomical location.

Primary study results

The control group. Immunohistochemical analysis revealed that in control group CMs, $Cx43^+$ gap junctions were primarily localized within intercalated discs. Only small areas of gap junctions were present along lateral CM surfaces (Figure 1*a*). Total lateral $Cx43^+$ gap junction length: 5.2 (4.7; 7.3) μm, relative lateral length: 4.1 (3.4; 6.5)% (Figure 2*a*, 2*b*). Relative gap junction length in the control group did not correlate with: age, CM diameter and length, myofibril content; indicating completed CM differentiation in these individuals.

Patients with HCM. $Cx43^+$ gap junctions were detected in both intercalated discs and lateral CM surfaces in most HCM patients, where they were arranged either as punctate clusters or as extended zones (Figure 1*b*, 1*c*). Patients with moderate or severe myofibril loss (MF-1, MF-0) showed diffuse $Cx43^+$ localization across the entire CM sarcolemma, resembling poorly differentiated CMs. In areas with non-parallel myofibril arrangement, $Cx43^+$ gap junctions were found within intercalated discs, additional intercalated disc-like structures and lateral CM surfaces. Thus, in patients with HCM, $Cx43^+$ gap junctions formed "side-to-side" connections between neighboring CMs. Total lateral $Cx43^+$ gap junction length in HCM patients: 16.5 (10.5; 26.1) μm; relative lateral length: 9.7 (7.7; 14.7)% (Figure 2*a*, 2*b*). These indicators of gap junction redistribution from intercalated discs to the lateral surfaces of CMs were significantly higher than those in the control group (p <0.05). Relative $Cx43^+$ gap junction length in HCM patients positively correlated with

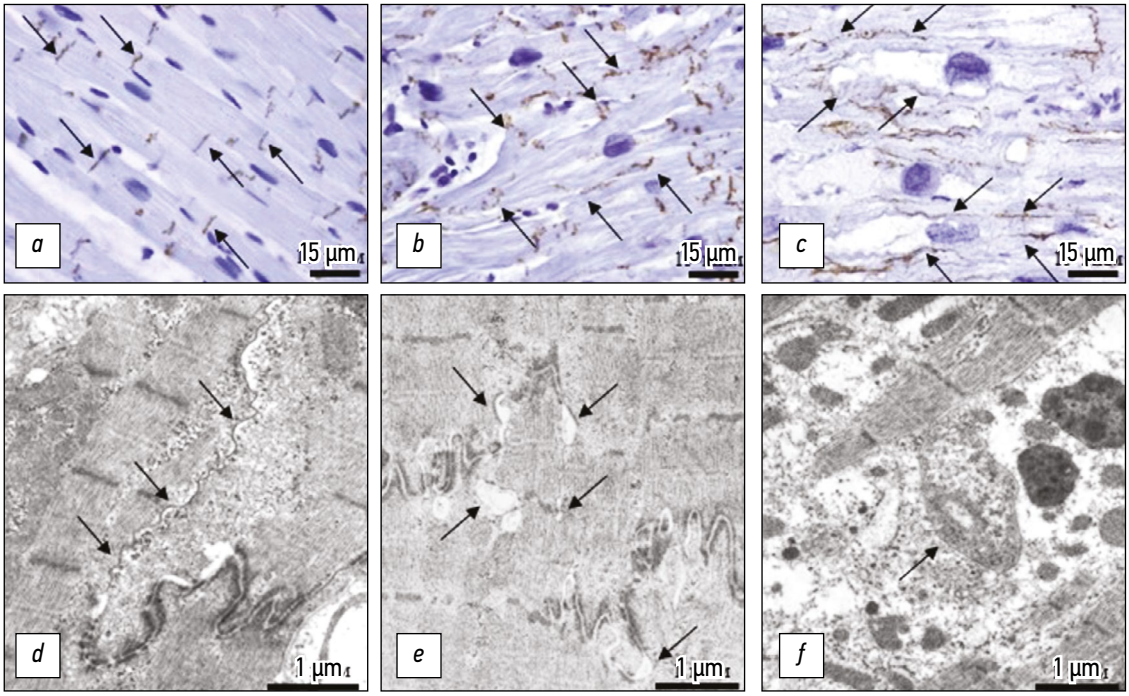

Fig. 1. Gap junctions in cardiomyocytes of the interventricular septum of patients with hypertrophic cardiomyopathy: *a* — Cx43+-gap junctions in the intercalated discs of the cardiomyocytes. Control group. A 54-year-old patient; *b* — polygonal cardiomyocytes. Multiple additional intercalated discs containing Cx43+-gap junctions on the lateral surfaces of the cardiomyocytes. A 27-year-old patient with hypertrophic cardiomyopathy; *c* — cardiomyocytes with pronounced loss of myofibrils. Cx43+-gap junctions (arrows) are diffusely located over the entire surface of the cardiomyocytes. A 44-year-old patient with hypertrophic cardiomyopathy; *d* — gap junction (arrows) on the longitudinal section of the intercalated disc of the cardiomyocytes. A 58-year-old patient with hypertrophic cardiomyopathy; *e* — areas of local divergence of longitudinal parts of the intercalated disc of the cardiomyocytes (arrows). A 59-year-old patient with hypertrophic cardiomyopathy; *f* — annular areas of membrane invaginations on the lateral surfaces of the myocyte containing gap junctions (arrow), lipofuscin granules. A 39-year-old patient with hypertrophic cardiomyopathy. *a–c* — immunoperoxidase reaction, antibodies to Cx43; *d–f* — electron micrographs.

increased CM diameter (r = 0.60; p_S = 0.000002), increased CM length (r = 0.50; p_S = 0.00004), lower myofibril content (r = -0.40; p_S = 0.001) and showed an inverse correlation with patient age (r = –0.26; p_S = 0.037) (Fig. 2*c*). According to echocardiographic examination, the lateral localization of gap junctions was characteristic of patients with the most severe functional state of the heart, as indicated by a thickened IVS (r = 0.38; p_S = 0.004), a reduced LV EDV (r = –0.28; p_S = 0.036) (Fig. 2*d*), and a high pressure gradient across the mitral valve (r = 0.78; p_S = 0.004).

At the ultrastructural level, it was demonstrated that in patients with HCM, gap junctions within mature intercalated discs of CMs were localized on the longitudinal portions of the intercalated disc (Fig. 1*d*). In 28.1% of adult patients with HCM, areas of local membrane separation within the longitudinal segments of the intercalated disc were identified (Fig. 1*e*), presumably associated with a defect in gap junctions or their relocation to the lateral surfaces of CMs. Additionally, ring-like structures formed by invaginations of lateral sarcolemma segments containing gap junctions were observed within the sarcoplasm of CMs (Fig. 1*f*). These alterations in gap junction localization and structure within intercalated discs are likely to contribute to the disruption of both mechanical and electrical coupling between adjacent CMs.

Secondary study results

The control group. The diameter of CMs in the control group was 13.4 (12.6; 16.3) μm, while their length was 63.3 (57.6; 68.5) μm. The myofibril content in CMs did not correlate with age. The proportion of CMs with MF-2 and MF-3 (75% and 16%, respectively) increased, while the proportion of CMs with MF-1 (8%) decreased with increasing cell diameter.

Patients with HCM. The diameter of CMs in HCM patients was 21.4 (18.7; 25.9) μm, and their length was 79.9 (69.1; 91.9) μm. Among patients with HCM, CMs with moderate and severe myofibrillar loss (MF-1 and MF-0) accounted for 20.3% and 2.2% of cells, respectively.

DISCUSSION

Summary of primary study results

Immunohistochemical detection of Cx43-containing gap junctions, electron microscopic examination of gap junctions in IVS CMs, and morphometric analysis of IVS myocardium were performed. In control group patients, gap junctions were primarily localized within the intercalated discs of CMs. In patients with HCM, remodeling of $Cx43^+$ gap junctions was observed, with their redistribution from intercalated discs to the lateral surfaces of CMs, occurring significantly more

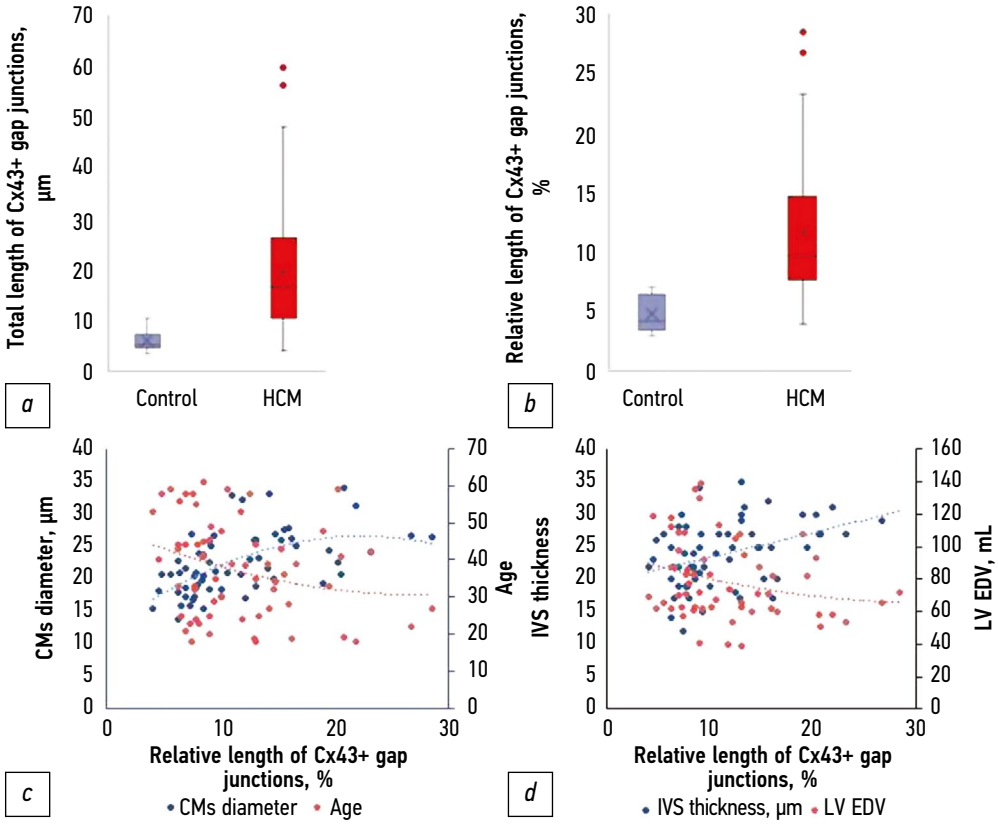

Fig. 2. Total (*a*) and relative (*b*) length of Cx43+ gap junctions in the cardiomyocytes of patients with hypertrophic cardiomyopathy. Correlations of the relative length of Cx43+ gap junctions in the cardiomyocytes of patients with hypertrophic cardiomyopathy with the cardiomyocytes diameter and the age of patients (*c*, $r = 0.60$; $p < 0.0001$ and $r = –0.26$; $p = 0.038$) and the interventricular septum thickness and left ventricular end-diastolic volume (*d*, $r = 0.38$; $p = 0.004$ and $r = –0.28$; $p = 0.036$).

frequently and occupying a larger surface area than in the control group.

Discussion of primary study results

During ontogenetic development, the density and localization of gap junctions in CMs undergo significant changes: in neonatal CMs, $Cx43^+$ gap junctions are distributed across the entire cell surface, whereas during the formation of intercalated discs between myocytes, gap junctions migrate to the transverse ends of the cell within the intercalated discs [3]. Localization of $Cx43^+$ gap junctions within intercalated discs is considered a marker of CMs differentiation. The absence of correlations between the density of $Cx43^+$ gap junctions on the lateral surfaces of CMs, cell size, and myofibril content in the control group confirms the completion of CM differentiation. Conversely, a high relative abundance of $Cx43^+$ gap junctions on the lateral surfaces of CMs suggests incomplete differentiation or partial dedifferentiation under cardiovascular pathology.

In HCM, remodeling of $Cx43^+$ gap junctions was observed in the IVS myocardium of patients with the most severe disease, as indicated by echocardiographic data—marked IVS thickening, low LV EDV, and high mitral valve pressure gradient. Notably, $Cx43^+$ contacts on the lateral surfaces of CMs were more frequently found in hypertrophic myocytes with low myofibril content and poorly differentiated intercalated discs. It can be hypothesized that IVS CM hypertrophy, combined with the immaturity of the contractile apparatus and altered distribution of $Cx43^+$ gap junctions, contributes to frequent arrhythmia episodes. It is known that 66% of HCM patients exhibit electrocardiographic abnormalities, including ventricular extrasystoles, atrioventricular block, and atrial fibrillation [12], often necessitating pacemaker implantation. Such arrhythmogenic remodeling of the myocardium in HCM patients is frequently accompanied by significant interstitial fibrosis. The highest volume of fibrotic myocardium has been observed in HCM patients with atrial fibrillation, as demonstrated using cardiac magnetic resonance imaging with ECG synchronization before and after gadolinium contrast administration [12].

In hypertrophic myocardium, changes in gap junction topology, which are responsible for electromechanical coupling between adjacent CMs, are believed to compensate for increased mechanical load by increasing the total number and area of cell-cell contacts per CM [5]. In HCM patients, the relative abundance of laterally located $Cx43^+$ gap junctions was higher than in the control group, likely reflecting reduced CM differentiation and representing a nonspecific compensatory adaptation to myocardial overload. Similar

changes have been described in the LV myocardium of patients with ischemic heart disease (IHD) and HCM [7], aortic valve stenosis, and mitral valve regurgitation [13]. Furthermore, a reduction in Cx43$^+$ gap junctions has been reported in patients with cardiovascular pathology and arrhythmias [8].

Experimental studies on Cx43 expression and localization in the myocardium have demonstrated the relocation of Cx43$^+$ gap junctions to the lateral surfaces of CMs and a >40% reduction in Cx43 expression compared to control across various cardiovascular pathologies [9,10]. A similar pattern of lateral Cx43$^+$ gap junction localization has been observed in rats with experimentally induced pulmonary hypertension and right and LV hypertrophy [4], as well as in the LV myocardium of dogs with arrhythmogenic heart failure [14]. Additionally, C.M. Ripplinger et al. reported changes in the density of Cx43$^+$ gap junctions in the myocardium of genetically modified rabbits carrying mutations associated with HCM (cardiac troponin I cTnI^{146Gly} and β-myosin heavy chain β-MyHC-Q403) [15]. These literature data confirm the consistent pattern of Cx43$^+$ gap junction remodeling in the myocardium of both patients and experimental animals with various cardiovascular diseases. Such changes appear to be a stereotypical manifestation of CM morphological remodeling and are evidently associated with varying degrees of CM differentiation.

Study limitations

A limitation of this study is the inability to examine the ultrastructure of gap junctions in CMs from the intact myocardium of the control group, as rapid fixation of the material, required for electron microscopy, was not feasible for autopsy samples.

CONCLUSION

This study demonstrated that Cx43$^+$ gap junction remodeling in the CMs of HCM patients is more pronounced compared to control myocardium. The IVS myocardium of HCM patients is characterized by the lateral localization of Cx43$^+$ gap junctions in CMs, which is more frequently observed in hypertrophic CMs with partial myofibrillar loss and correlates with IVS thickening, decreased LV cavity volume, and a high mitral valve pressure gradient.

ADDITIONAL INFORMATION

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