



ANNOTATION

to the dissertation of Maksat Abdimanapovich Zhakayev entitled
“Surgical Treatment of Obstructive Hypertrophic Cardiomyopathy”, submitted
for the degree of Doctor of Philosophy (PhD) in specialty 8D10103 – “Medicine”

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Relevance of the Research Topic

Obstructive hypertrophic cardiomyopathy (oHCM) is among the most common inherited cardiomyopathies and is an important cause of heart failure, sudden cardiac death, and reduced quality of life in working-age patients. The disease is characterized by asymmetric hypertrophy of the left ventricular myocardium, dynamic obstruction of the left ventricular outflow tract, and impaired diastolic function. In some patients, severe symptoms persist despite medical therapy, necessitating septal reduction therapy.

Septal myectomy remains the principal surgical treatment for symptomatic oHCM; however, the outcomes of the procedure depend on accurate determination of the site and extent of resection, the anatomical features of the mitral valve apparatus, and the experience of the surgical team. In a substantial proportion of patients, obstruction is accompanied by systolic anterior motion (SAM) and mitral regurgitation, highlighting the need to improve valve-sparing techniques for mitral valve correction and intraoperative visualization.

A promising direction is the integration of preoperative MRI mapping of the interventricular septum, morphogenetic assessment, and advanced surgical technologies. In the Republic of Kazakhstan, data on the morphogenetic characteristics of oHCM and the outcomes of surgical treatment remain limited. This substantiates the need for a comprehensive study aimed at individualizing surgical strategy, improving the precision of septal myectomy, and enhancing treatment outcomes in patients with oHCM.

Aim of the Dissertation Research

To improve the surgical treatment of obstructive hypertrophic cardiomyopathy in patients refractory to medical therapy through a comprehensive assessment of genetic and morphological characteristics and the implementation of new technologies—MRI mapping of the interventricular septum, a septal retractor, and transaortic mitral valve plication.

Research Objectives

1. To investigate the genetic, histomorphological, and phenotypic characteristics of patients with oHCM.
2. To develop a method of transaortic mitral valve plication for correction of SAM and evaluate its effectiveness.
3. To develop a combined surgical method for oHCM using interventricular septal mapping and a septal retractor for transaortic septal myectomy and to evaluate its effectiveness.
4. To develop a clinical algorithm for applying the comprehensive method in real-world clinical practice.

Materials and Methods

The study population comprised patients with obstructive hypertrophic cardiomyopathy who underwent surgical treatment; the subject of the study included genetic, histomorphological, clinical and instrumental characteristics, surgical treatment technologies, and their outcomes. The work included a systematic review and meta-analysis, descriptive clinical studies, and a retrospective cohort study.

The systematic review was conducted in accordance with PRISMA using publications indexed in PubMed, Web of Science, the Cochrane Library, and

ScienceDirect from January 2014 to May 2025. Twenty-four studies involving 3,732 patients were included: 2,824 after surgical myectomy and 908 after transapical beating-heart septal myectomy (TABSM). The protocol was registered in PROSPERO (CRD420251075522). Risk of bias was assessed using ROBINS-I; meta-analysis was performed in RStudio using a random-effects model, with assessment of Cochran's Q, I², τ^2 , publication bias, and meta-regression.

For the first objective, a comparative descriptive analysis was performed in four patients who underwent surgery for oHCM at the Research Institute of Cardiology and Internal Medicine in 2020–2021. Resected tissue was examined morphologically; molecular genetic testing included a panel of 17 genes associated with HCM. Owing to the small sample size, a descriptive comparative analysis was used.

For the second objective, a method of plication of the A2 segment of the anterior mitral leaflet for correction of SAM was developed and tested in a clinical case. Changes in LVOT obstruction, mitral regurgitation, and functional competence of the valve were assessed.

For the third objective, a retrospective cohort study was conducted at the Research Institute of Cardiology and Internal Medicine in Almaty for the period 2015–2023. The study included 76 patients with confirmed oHCM, a peak LVOT gradient ≥ 50 mmHg at rest and/or with physiological provocation, interventricular septal thickness ≥ 15 mm on echocardiography or MRI, and no previous intervention on the interventricular septum. Medical records, echocardiographic data, preoperative MRI mapping, operative characteristics, complications, mortality, and long-term survival were analyzed.

Statistical analysis was performed using SPSS 26.0. Continuous data were presented as mean $\pm$ standard deviation, and categorical data as absolute and relative frequencies. Student's t-test or the Mann–Whitney U test and the χ^2 test or Fisher's exact test were applied as appropriate. Survival was assessed using the Kaplan–Meier method, log-rank test, and Cox regression with hazard ratios (HRs) and 95% confidence intervals (CIs); the proportional hazards assumption was tested using Schoenfeld residuals, and model performance was assessed using Harrell's C-index. Statistical significance was set at $p < 0.05$. The study was approved by the Bioethics Committee of Asfendiyarov Kazakh National Medical University, Protocol No. 1071 dated March 31, 2021; written informed consent was obtained.

Description of the Main Research Results

For the first objective, all four patients demonstrated cardiomyocyte hypertrophy and parenchymal degeneration, a positive PAS reaction, and cardiosclerosis. Genetically positive patients (MYH7; MYH7+GLA+PRKAG2) showed more pronounced cardiomyocyte disarray and nuclear polymorphism; combined mutations were associated with coarse-fibrous cardiosclerosis and a “perforated nuclei” phenomenon. In the genetically negative and control patients, myocardial architecture was more orderly.

For the second objective, the developed focal plication of the A2 segment reduced systolic anterior motion of the leaflet and mitral regurgitation while preserving mitral valve mobility and coaptation. In the presented clinical case, the maximum LVOT gradient decreased from 98 to 15 mmHg, and mitral regurgitation decreased from grade III to 0.

The retrospective cohort included 76 patients: 43.4% men (n=33) and 56.6% women (n=43), with a mean age of 54±14 years. Diabetes mellitus was present in 19.7% (n=15), elevated body mass index in 31.6% (n=24), and coronary artery disease in 35.5% (n=27). Before surgery, all patients had severe symptoms: 67.1% were in NYHA functional class III and 32.9% in class IV. Dyspnea was reported in 98.7%, chest pain in 73.7%, dizziness in 48.7%, and syncope in 15.8%. The cohort was characterized by severe left ventricular outflow tract obstruction, with the peak gradient exceeding 100 mmHg in a substantial proportion of patients.

After the comprehensive surgical intervention, the peak LVOT gradient decreased from 40±8 to 12±4 mmHg, the thickness of the basal interventricular septum decreased from 25±4 to 13±2 mm, and left ventricular end-diastolic volume increased from 92±20 to 115±18 mL. Left ventricular ejection fraction changed from 66±9% to 57±9%, which was interpreted as normalization of the initially hyperdynamic systolic function after relief of obstruction. Left atrial volume decreased from 71±23 to 61±18 mL. These changes reflect relief of obstruction, improved diastolic filling, and reduced chronic pressure overload.

After surgery, mitral regurgitation was absent in 36% of patients and was grade I in 56%, whereas before surgery grade III was recorded in 38.2% and grade II in 40.8%. The Alfieri edge-to-edge technique was used in 14 patients (18.4%), and anterior mitral leaflet plication using the developed technique was performed in 11 (14.5%). The most frequent conduction disturbance was complete left bundle branch block (69.7%); atrioventricular block occurred in 10.5%, postoperative atrial fibrillation in 3.9%, and stroke in 2.6%. In-hospital mortality was 1.3% (1/76). The estimated mean survival was 57.3 months (95% CI 54.8–59.9); the median was not reached, and the final cumulative risk of adverse events was approximately 0.05.

For the fourth objective, the results were integrated into a clinical algorithm comprising four interrelated stages: clinical and instrumental patient selection and preoperative planning using MRI navigation; optimization of septal myectomy using the developed septal retractor and, when indicated, focal plication of the anterior mitral leaflet; postoperative monitoring of clinical and instrumental outcomes; and morphogenetic analysis with risk-group stratification. MRI mapping enables detailed assessment of interventricular septal morphology and the spatial relationships of outflow tract structures, while the septal retractor improves visualization of the resection area. The morphogenetic stage includes identification of pathogenic variants and provides a basis for subsequent follow-up of patients and their first-degree relatives.

Scientific Novelty

1. For the first time in the Republic of Kazakhstan, the genetic and morphofunctional heterogeneity of oHCM has been established, providing a basis for individualized selection of surgical strategy.

2. For the first time, a method of transaortic mitral valve plication for correction of SAM has been developed, and its hemodynamic and clinical effectiveness has been evaluated.

3. For the first time, a comprehensive surgical approach incorporating preoperative MRI mapping of the interventricular septum has been proposed, and a septal retractor for transaortic septal myectomy has been developed to improve the

precision and safety of the intervention.

4. For the first time, an algorithm for applying the comprehensive method, taking into account clinical, instrumental, and morphogenetic criteria in real-world clinical practice, has been proposed and scientifically substantiated.

Main Provisions Submitted for Defense

1. The genetic and histomorphological characteristics of patients with obstructive hypertrophic cardiomyopathy are associated with the anatomical and functional parameters of the interventricular septum and determine the mechanisms of obstruction.

2. The developed method of transaortic mitral valve plication is an effective and safe method for correcting SAM in patients with oHCM, providing a reduction in systolic anterior motion of the mitral valve leaflets, a decrease in the degree of mitral regurgitation, and improvement in hemodynamic parameters while preserving the functional and anatomical integrity of the mitral valve.

3. The combined surgical approach, including preoperative mapping of the interventricular septum, use of the developed septal retractor to optimize visualization and surgical access, and transaortic mitral valve plication, significantly improves clinical outcomes of the intervention and increases patient survival.

4. The developed and scientifically substantiated algorithm for selecting patients with oHCM, based on a combination of clinical, instrumental, and morphogenetic criteria, enables stratification of patients according to the expected effectiveness of surgical intervention and facilitates a personalized treatment approach in real-world clinical practice.

Practical Significance of the Results

A method of transaortic mitral valve plication for correction of SAM has been developed and implemented in clinical practice, expanding the possibilities of valve-sparing mitral surgery. A method of preoperative mapping of the interventricular septum has been developed to determine the site, direction, and safe extent of myectomy. A septal retractor for transaortic septal myectomy has been created to improve visualization of the operative field and reproducibility of the surgical technique. A clinical algorithm for applying the comprehensive method in real-world clinical practice has been developed. The results have been implemented at the Research Institute of Cardiology and Internal Medicine (Almaty), the E.N. Meshalkin National Medical Research Center, and the I.V. Davydovsky City Clinical Hospital. The work resulted in Invention Patent No. 36799, two certificates of state registration of rights to copyrighted works in the Republic of Kazakhstan, and five certificates of implementation of research results.

Personal Contribution of the Doctoral Candidate

The doctoral candidate's personal contribution consisted of developing the theoretical and methodological framework of the study, organizing and conducting the research, participating in all stages of the study, performing statistical data processing, writing all sections of the dissertation, analyzing and discussing the results obtained, formulating the main provisions submitted for defense, and preparing the conclusions and practical recommendations.

Conclusions

1. Histological examination of two of the four genetically positive patients (MYH7, GLA, PRKAG2) revealed disorganized cardiomyocyte arrangement, marked nuclear pleomorphism, and predominantly fine-fiber perivascular and pericellular cardiosclerosis. In patients with combined mutations, coarse-fiber cardiosclerosis and the “punched-out” nuclear phenomenon in cardiomyocytes were observed. The genetically negative patient and the control patient showed a more orderly arrangement of cardiomyocytes, focal coarse-fiber fibrosis, and no nuclear pleomorphism. Regardless of genetic status, all patients had signs of cardiomyocyte hypertrophy and dystrophy, as well as a positive PAS reaction.

2. Experience with anterior mitral leaflet plication to correct systolic anterior motion (SAM) in obstructive hypertrophic cardiomyopathy suggests that this method may effectively relieve symptoms by reducing the severity of SAM and mitral regurgitation, while maintaining a favorable functional outcome. The procedure reduced the postoperative maximum left ventricular outflow tract (LVOT) gradient from 98 mmHg to 15 mmHg and mitral regurgitation from grade III to none.

3. The combined surgical approach demonstrated substantial clinical effectiveness: the left ventricular outflow tract gradient decreased from 40 ± 8 to 12 ± 4 mmHg, and interventricular septal thickness decreased from 25 ± 4 to 13 ± 2 mm. Functional status improved considerably, with 93.3% of patients moving to NYHA class II after surgery. Postoperative mortality was 1.3%; overall, four deaths occurred in the early postoperative period. The cumulative risk of fatal events was 0.05. Mean survival was 57.3 months (95% CI 54.8–59.9), and the median was not reached, indicating favorable long-term outcomes.

4. An algorithm for selecting patients with obstructive hypertrophic cardiomyopathy was developed and scientifically substantiated. Based on a combination of clinical, instrumental, and morphogenetic criteria, it enables effective stratification of patients according to the expected benefit of surgery and supports a personalized approach in clinical practice.

Approbation of the Dissertation Results

The dissertation findings were presented and discussed at the 29th Scientific Meeting of the International Society of Hypertension (Kyoto, Japan, October 12–16, 2022).

Publications

Four scientific papers have been published on the dissertation topic, including one article in an international journal indexed in Scopus and Web of Science and three articles in journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Republic of Kazakhstan. Publication indexed in international databases: Zhakayev M., Tuleutayev R., Nurbay Z., Izmailovich M. Comparison of morrow procedure and transapical beating-heart septal myectomy in patients with hypertrophic obstructive cardiomyopathy: a systematic review and meta-analysis. *Frontiers in Surgery*. 2025;12:1666236. Scopus CiteScore – 3.3, 69th percentile; Web of Science – Q2. Publications in journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Republic of Kazakhstan: 1) Zhakayev M.A., Nurbay Zh.N., Tuleutayev R.M., Kodasbayev A.T. Hypertrophic cardiomyopathy: the current state of a multifaceted problem (review).

Bulletin of Asfendiyarov Kazakh National Medical University. 2022;3(3(62)):113–126; 2) Zhakayev M.A., Tuleutayev R.M., Sultanov G.B., Sergeyeva Ye.N. New technique of anterior mitral leaflet plication for correction of SAM syndrome in obstructive hypertrophic cardiomyopathy. Clinical case. Science & Healthcare. 2025;27(6):237–243; 3) Zhakayev M.A., Toktarova A.B., Tuleutayev R.M., Sergeyeva Ye.N. Morpho-genetic variability in myocardial tissue after septal myectomy in patients with obstructive hypertrophic cardiomyopathy: a four-case series study. Science & Healthcare. 2025;27(6):30–37.

Dissertation Length and Structure

The dissertation comprises 108 pages including appendices and consists of an introduction, a literature review, a chapter on materials and methods, a chapter presenting the results of the original research, conclusions, and practical recommendations. The reference list includes 95 sources. The dissertation contains 8 tables and 29 figures and includes 10 appendices.