

UNIVERSITY OF MEDICINE, PHARMACY, SCIENCES AND TECHNOLOGY
"GEORGE EMIL PALADE" OF TÂRGU MUREȘ

**The role of clinical-histological correlations in the evaluation and follow-up of the
operated patient, in cardiovascular surgery**

DOCTORAL THESIS SUMMARY

PhD **Dr. Carmen Elena Chincișan (Opriș)**

PhD coordinator **Prof. Dr. Simona Gurzu**

TÂRGU MUREȘ 2025



UNIVERSITATEA DE MEDICINĂ,
FARMACIE, ȘTIINȚE ȘI TEHNOLOGIE
„GEORGE EMIL PALADE”
DIN TÂRGU MUREȘ

Both morphologically and functionally, the mitral valve is a complex apparatus represented by the mitral valve, the annulus, and the subvalvular apparatus, which consists of tendinous cords and papillary muscles. Mitral regurgitation has different etiologies, and its mechanisms (primary or secondary) dictate the therapeutic approach. Primary mitral regurgitation is due to intrinsic valvular pathology. Secondary regurgitation occurs in distortion of a normal mitral valve due to damage to the left ventricle and the subvalvular mitral apparatus.

The studies of the present research have as main objectives:

1. Establishing the significance of inflammation-related markers and histopathological features in mitral valve insufficiency
2. Establishing the link between inflammatory markers, the histopathological appearance of the mitral valve, and the occurrence of flail in patients with mitral valve prolapse
3. Establishing some correlations between the genetic analysis and the histopathological appearance of the mitral valve in patients with mitral insufficiency
4. Follow-up of complications in LVAD patients
5. Monitoring the importance of transesophageal echocardiography in the operating room in mitral valve plasty

In the first two studies, we analyzed the correlation between inflammatory markers and the echocardiographic appearance of the mitral valve in patients with mitral valve prolapse. The results are presented in the article Significance of inflammation-related markers and histopathological features in mitral valve regurgitation published in no. 65 -vol 4 from 2024 of the Romanian Journal of Morphology and Embryology. We specifically looked for the presence of a mitral valve flail, which is defined as a chordae rupture. SIR parameters can be used to assess the state of inflammation in mitral valve disease and to establish the risk of cord rupture in cases of mitral valve prolapse. There is a relationship between the degree of fibrosis and the chances of mitral valve flail: the higher the degree of fibrosis, the lower the chance of mitral valve flail. The mean LMR and CLR values are higher in the low-fibrosis group, and the lower the severity of fibrosis in mitral valve prolapse, the higher the risk of mitral valve chordal rupture and flail. LMR and PLR are inflammatory markers significantly associated with hyalinization in the mitral valve. An increased value of PNR and FAR indicates a lower chance of severe myxoid degeneration, and an increased value of PLR indicates a higher chance of severe myxoid degeneration. Increased monocyte count increases the chance of hyalinization found on histopathological examination of the mitral valve and reduces the chance of flailing.

Second, we analyzed the correlation between the presence of mitral valve flail assessed by transesophageal echocardiography and the histopathological appearance of valve significance: fibrosis, hyalinization, and myxoid degeneration. A statistically significant association exists between flail and fibrosis, meaning that a greater degree of fibrosis is present in patients without flail. In our analysis, hyalinization and myxoid showed no significant relationships with flail at the conventional 0.05 significance level.

Third, we analyzed the correlation between multiple inflammatory markers and the histopathological appearance of the mitral valve and demonstrated that hyalinization shows a significant positive association with LMR and PLR ($p=0.041$ and $p=0.03$, respectively) and with NLR at the p level <0.1 . ($p=0.093$).

In the third study, we explored the possible influence of genetic background on mitral valve structure and function. Four genes, FBN1, FNLA, MMP2, and SOX9, were examined from tissue and blood samples. Unlike comparing the results on the tissue sample, FBN1 and SOX9 are associated in the blood sample, so they are in a causal relationship. We demonstrate that parallel determination from blood and tissue could add additional data that may be useful for understanding the involvement of genes in mitral valve regurgitation, both at the tissue and circulatory levels. This comparison allowed us to determine whether the presence of mitral regurgitation is associated with changes in mRNA levels in patients with mitral regurgitation.

The results reflect two gene-based trends in valve degeneration: one dictated by valve aging and the FNLA gene; the second being probably influenced by the inflammatory environment, especially by the number of circulating lymphocytes and monocytes, the microenvironment being probably modulated by the FBN1 and MMP2 genes. The data are presented in the article Significance of Fibrillin-1, Filamin A, MMP2 and SOX9 in Mitral Valve Pathology published in No. 25 of 2024 of the International Journal of Molecular Sciences. Further studies are needed to confirm the hypotheses highlighted in the present paper and partially supported by the literature data.

The degree of hyalinization of the mitral valves increases with age. The reduced expression of FNLA and SOX-9 influences the aging process of the valve, which is reflected by the degree of

hyalinization. Our data show that FLNA gene expression decreases in correlation with patient age, especially in men independent of ejection fraction or inflammatory environment, increasing hyalinization. We can talk about a physiological reduction of FLNA in old age, which external factors cannot influence. On the other hand, high SOX9 gene expression was an indicator of low hyalinization observed on histopathological examination. Since neither SOX9 was associated with other parameters, it can be assumed that the two examined genes do not influence inflammatory processes but are negatively correlated with aging. Also, LV end-diastolic diameter, as a marker of ventricular remodeling that occurs in severe mitral valve regurgitation, increases by 4.56 units in low FLNA tissue expression compared to regular expression (coeff 4.56, $p=0.88$ observed at a significance level $p<0.1$). Many studies have investigated its role in cardiac remodeling after myocardial infarction, so FLNA may be a target for gene therapy to prevent ventricular remodeling.

On the other hand, high mRNA expression for SOX9 was indicative of low hyalinization observed under the microscope. Since SOX9 did not show an association with other parameters, it can be assumed that the two examined genes do not influence inflammatory processes but are negatively correlated with the aging process. However, if the level of SOX9 could be therapeutically upregulated, it could protect valvular aging.

In this study, a high expression of the FBN1 gene reflected a low MRL and a high number of circulating monocytes but also a high fibrosis score. This conclusion was also demonstrated in the first part of our study, where a low LMR was statistically significantly associated with an increase in the degree of fibrosis of the mitral valvular structures. On the other hand, a high expression of the MMP2 gene was associated with a high number of circulating lymphocytes but a lower fibrosis score, especially in women. It can be hypothesized that high serum levels of MMP2-related lymphocytes could be a protective factor against mitral valve fibrotic degeneration, but the FBN1 gene influences monocyte proliferation, and their upregulation contributes to the risk of fibrosis. It seems that there is a negative correlation between MMP2 and FBN1. Thus, mitral valve fibrosis could be influenced by their interaction, which also modulates the systemic inflammatory response of the human body. Increasing the degree of fibrosis decreases the risk of mitral valve rupture in patients with mitral valve prolapse.

The role of morphophonological examinations in patients with LVAD

Regarding the role of morphophonological examinations in LVAD patients, the two cases presented highlight the vascular, renal, and cerebral lesions induced by the continuous circulatory flow created by the LVAD. These lesions are not only related to increased fragility but also to a progressively established glomerulosclerosis. Our patients had a Heartware-type LVAD implanted, which, during the study, was withdrawn from the market due to related hemorrhagic complications. LVADs currently in use utilize full MagLev Flow Technology in the pump that maintains gentle blood handling to minimize complications and adverse events related to hemocompatibility.

The role of transesophageal echocardiography in the operating room: Echocardiography has an important role in identifying the mechanism of mitral insufficiency and measuring cardiac parameters to help the surgeon perform plastic surgery. Whenever mitral valve repair is planned in a patient, a multiparametric algorithm should be followed to achieve a perfect result and avoid complications, including the occurrence of SAM.

Conclusions: Incorporating genetic insights alongside clinical assessments and advanced imaging techniques can significantly improve our understanding of the mechanisms driving the progression of mitral valve disease. This integrated approach not only helps to map complex interactions at the genetic level but also to identify potential therapeutic targets for more effective treatment strategies.