SEX-SPECIFIC CARDIAC REMODELING AND FUNCTIONAL RECOVERY: INSIGHTS INTO PROTEOMIC MECHANISMS

Doctoral dissertation

Bálint András Barta MD

Albert-Ludwigs University, Freiburg, Germany
Semmelweis University, Budapest, Hungary

universität freiburg
Semmelweis University

Freiburg
2026

Introduction

Cardiovascular disease remains the leading global cause of death, imposing immense economic strain. Men and women diverge early in cardiac development through chromosomal and epigenetic mechanisms, further shaped by lifelong hormonal environments. These differences translate into distinct clinical phenotypes: women experience myocardial infarction and obstructive coronary disease later, but suffer higher early mortality. Sex-specific remodeling patterns are also evident. After infarction, males typically develop dilatation and eccentric hypertrophy, whereas females favour concentric geometry and stable scarring. In pressure-overload states, men progress toward classic systolic failure, while women more often develop HFpEF-like phenotypes with preserved ejection fraction but increased stiffness. Fibrosis, metabolic reprogramming, and immune signalling also differ by sex at transcriptomic and proteomic levels. Cardiac remodeling itself encompasses inflammatory activation, matrix degradation, fibrosis, hypertrophy, and eventual deterioration or—if afterload is relieved—reverse remodeling. Yet reverse remodeling

responses vary widely, implying underlying molecular determinants such as sex steroids, whose influences on mitochondrial function, calcium handling, fibrosis, and apoptosis remain incompletely mapped. Proteomics offers a high-resolution view of these processes, surpassing genomics and transcriptomics by capturing functional protein networks. Advances in high-resolution MS, TMT multiplexing, and bioinformatic pipelines now allow quantification of thousands of cardiac proteins, but few studies integrate these datasets with load-independent haemodynamics. This thesis addresses these gaps using complementary rodent models—diffuse ischaemic injury via isoproterenol and pressure overload via aortic banding and debanding—combined with pressure–volume analysis, steroid-omics, and deep proteomics.

Objectives

This study aims to (1) characterize early sex-specific functional and proteomic changes in a rat model of isoproterenol induced myocardial ischemia; (2) analyse steroid-hormone profiles in ischemic female rats and determine their impact on cardiac function; (3) assess how sex influences reverse remodeling using a standardized aortic banding–debanding model; and (4) identify molecular and functional markers that quantify reverse remodeling and predict outcomes. Overall, the goal is to define the mechanisms by which biological sex shapes ventricular adaptation, supporting the development of sex-aware cardioprotective strategies.

Methods

This study complied with EU Directive 2010/63/EU and NIH animal-care guidelines. All procedures were approved by the relevant ethical committees in Hungary and Germany and followed ARRIVE guidelines. Myocardial ischemia study: Young adult Wistar rats were assigned to sex-matched control and ischemic groups. Ischemia was induced by two daily subcutaneous injections of isoproterenol (85 mg/kg), while controls received saline. Cardiac function was assessed 48 h later using pressure–volume (PV) analysis. Aortic banding–debanding study: Prepubertal Sprague–Dawley rats underwent abdominal aortic banding (AB) or sham surgery. A 22-gauge needle standardized the constriction across sexes. Only rats with confirmed pressure overload (systolic BP ≥180 mmHg) were included. After 6 weeks, subsets underwent debanding surgery and were followed to week 12. Ten experimental groups covered sham, AB, and DB conditions in both sexes. Echocardiography: Serial imaging with a Vevo 2100 system measuring diameters, wall thicknesses, and left ventricular (LV) mass. Hemodynamics: A microtip conductance catheter

measured LV-PV loops. Load-independent indices were obtained during transient IVC occlusion. τ (Tau) was derived using the Glantz method. After measurements, hearts were excised, perfused, and weighed; HW/TL was calculated. Histology: LV sections were stained with H&E and picrosirius red. Necrosis and fibrosis were quantified using QuPath and ImageJ. qRT-PCR: LV RNA was isolated, reverse-transcribed, and normalized to GAPDH. Steroid hormone profiling: Serum steroids were quantified by HPLC–MS. Western blot: Proteins were extracted, separated by SDS-PAGE, transferred, probed with antibodies, and normalized to GAPDH. Proteomics: ISO samples underwent TMT-labeling. LC–MS/MS data were processed with MaxQuant or FragPipe, with MSstatsTMT for quantification, batch correction, and imputation. Statistics: Normality testing preceded ANOVA, t-tests, or nonparametric tests as appropriate. Proteomic differential expression used limma with FDR correction. MixOmics enabled PLS-DA and sPLS-DA. LASSO identified LV parameters most strongly linked to protein abundance. GO enrichment used clusterProfiler; network and subnetwork analyses were performed with STRING and MCODE.

Results

ISO induced comparable myocardial necrosis in both sexes, with increased HW/TL but unchanged collagen content. Mortality was higher in males. Functionally, males showed a marked fall in MAP, SW, EF and PRSW, indicating impaired systolic performance, whereas females primarily developed diastolic dysfunction with higher τ, LVEDP and EDPVR. Proteomics (2,224 proteins) revealed: females upregulated more proteins—particularly cytoskeletal, contractile, ECM-repair and inflammatory mediators—while males showed stronger downregulation of mitochondrial and metabolic enzymes. Western blots confirmed sex-specific induction of VASP and OPN in females. In F-Isch animals, 2-hydroxyestrone strongly correlated with PRSW, τ, dP/dtmin and HW/TL. GO analysis linked 2-OHE1 and estradiol to fatty acid oxidation and oxidative phosphorilation. In the AB–DB study, males consistently exhibited larger LV mass, chambers, CD, and higher myh7/myh6 ratios, while females displayed higher LVESP, Ea, ESPVR and shorter τ. Under pressure overload, males showed greater decline in contractility and worse diastolic function by week 12.

Debanding induced robust reverse remodeling in both sexes—reducing LVmass, HW/TL, CD, nppa and myh7/myh6—but fibrosis regressed more in females. Proteomics (2,348 proteins) showed similar pressure overload-induced changes in both sexes, dominated by downregulated lipid-catabolic pathways. After unloading, females nearly normalized their proteome, particularly restoring fatty acid oxidation, whereas males retained substantial residual alterations. sPLS-DA, DE analysis and GO mapping confirmed sex-specific inflammatory (female) vs. cytoskeletal/translation (male) signatures. Reanalysis identified τ as the functional parameter most strongly linked to proteomic remodeling (842 proteins). τ-associated proteins spanned energy metabolism, sarcomeric renewal, RNA processing and stress signalling. ROC analysis identified τ-linked proteins (e.g., GSTK1, COQ9, TMOD4, SORBS2, NRAP) with AUC>0.85 for detecting active remodeling. Network analysis revealed tightly interconnected τ-driven modules, and transcription-factor mapping highlighted MAX, MYC, ATF3, MAFF and IRF1 as key regulators.

Conclusions

This work compared male and female rat hearts across diffuse ischemia, pressure-overload hypertrophy, and reverse remodeling, integrating load-independent PV metrics with deep TMT-proteomics. Early isoproterenol-induced injury was largely sex-neutral, but females preserved contractility by up-regulating contractile, cytoskeletal, and chaperone proteins, whereas males showed greater metabolic suppression and lower mechano-energetic efficiency. Females exhibited transient diastolic stiffening linked to enriched ECM-repair signatures. Steroidomics identified 2-hydroxyestrone as a key predictor of better female functional recovery through enhanced mitochondrial and fatty-acid-oxidation pathways. In pressure-overload unloading, both sexes regressed hypertrophy similarly, though females showed greater collagen resorption, while males displayed stronger rebound due to worse baseline function. Across models, the relaxation constant τ most closely tracked proteomic remodeling, yielding a protein panel that sensitively detects active cardiac remodeling.

Bibliography

Scientific publications in the current dissertation

Barta BA, Ruppert M, Fröhlich KE, Cosenza-Contreras M, et al. Sex-Related Differences of Early Cardiac Functional and Proteomic Alterations in a Rat Model of Myocardial Ischemia. J Transl Med. 2021, 19:1–15.

Ruppert M*, Barta BA*, Korkmaz-Icöz S, Loganathan S, et al. Sex Similarities and Differences in the Reverse and Anti-Remodeling Effect of Pressure Unloading Therapy in a Rat Model of Aortic Banding and Debanding. Am J Physiol Heart Circ Physiol. 2022;323(1):H204–H222.

Barta BA, Spiesshofer S, Ruppert M, Pinter N, Brombacher E, Kreutz C, Korkmaz-Icoz S, Olah A, Sayour AA, Szabo G, Merkely B, Radovits T, Schilling O. Myocardial Active Relaxation Mirrors the Myocardial Proteome in Remodelling and Reverse Remodelling. Manuscript accepted at ESC Heart Fail.

Scientific publications not involved in the current dissertation

Bálint T, Ruppert M, Ágg B, Nagy D, Pálóczi K, Szenthe K, Bánáti F, Sayour AA, Oláh A, Barta BA, Barallobre-Barreiro J, Ferdinandy P, Merkely B, Radovits T. Atrial fibrillation is not associated with altered left atrial microRNA expression profile in patients with advanced heart failure. Heart Rhythm. 2026;23(2):462–472. doi:10.1016/j.hrthm.2025.05.041.

Nagy D, Onódi Z, Kocsis M, Tóth A, Bálint T, Oláh A, Sayour AA, Barta BA, Merkely B, Ferdinandy P, Radovits T, Varga ZV, Ruppert M. Multiorgan characterization of inflammasome component expression in a rat model of advanced heart failure. ESC Heart Fail. 2025;12(5):3601–3613.

Oláh A, Bódi B, Barta BA, Bottlik O, Sayour AA, Ruppert M, Kolodziejska KK, Kovács A, Varga ZV, Ferdinandy P, Schilling O, Papp Z, Merkely B, Radovits T. Long-term exercise training is associated with unique cardiac troponin I phosphorylation pattern and benign myocardial hypertrophy in the right ventricle in an experimental

model of exercise-induced myocardial remodelling. J Mol Cell Cardiol. 2025;207:81–91.

Nagy D, Radovits T, Bálint T, Horváth Z, Kocsis-Balogh P, Tóth ÁG, Oláh A, Sayour AA, Barta BA, Merkely B, Ruppert M. The anti-fibrotic effects of novel heart failure pharmacotherapies in advanced heart failure patients. Br J Pharmacol. 2026;183(7):1502–1516.

Sayour AA, Oláh A, Ruppert M, Barta BA, Merkely B, Radovits T. Effect of pharmacological selectivity of SGLT2 inhibitors on cardiovascular outcomes in patients with type 2 diabetes: a meta-analysis. Sci Rep. 2024;14(1):2188.

Székely A, Pállinger É, Töreki E, Ifju M, Barta BA, Szécsi B, Losoncz E, Dohy Z, Barabás IJ, Kosztin A, Buzás EI, Radovits T, Merkely B. Recipient pericardial apolipoprotein levels might be an indicator of worse outcomes after orthotopic heart transplantation. Int J Mol Sci. 2024;25(3):1752.

Barta BA*, Radovits T*, Dobos AB, Kozma GT, Mészáros T, Berényi P, Facskó R, Fülöp T, Merkely B, Szebeni J. Comirnaty-induced cardiopulmonary distress and other symptoms of complement-mediated pseudo-

anaphylaxis in a hyperimmune pig model: Causal role of anti-PEG antibodies. Vaccine X. 2024;19:100497.

Oláh A, Barta BA, Ruppert M, Sayour AA, Nagy D, Bálint T, Nagy GV, Puskás I, Szente L, Szőcs L, Sohajda T, Zima E, Merkely B, Radovits T. A Comparative Investigation of the Pulmonary Vasodilating Effects of Inhaled NO Gas Therapy and Inhalation of a New Drug Formulation Containing a NO Donor Metabolite (SIN1A). Int J Mol Sci. 2024;25:7981.

Vogele D, Woehrle S, Saller BS, Froehlich K, Barta BA, Cosenza-Contreras M, Gross O, Schilling O. Size exclusion chromatography based proteomic and degradomic profiling of inflammasome-activated, murine bone marrow-derived dendritic cells highlights complex retention and release of cleavage products. Mol Omics. 2024;20(9):595–610.

Kökény G, Bakos T, Barta BA, Nagy GV, Mészáros T, Kozma GT, Szabó A, Szebeni J, Merkely B, Radovits T. Zymosan Particle-Induced Hemodynamic, Cytokine and Blood Cell Changes in Pigs: An Innate Immune Stimulation Model with Relevance to Cytokine Storm

Syndrome and Severe COVID-19. Int J Mol Sci. 2023;24:1138.

Kocsmár É, Schmid M, Cosenza-Contreras M, Kocsmár I, Föll M, Krey L, Barta BA, Rácz G, Kiss A, Werner M, Schilling O, Lotz G, Bronsert P. Proteome alterations in human autopsy tissues in relation to time after death. Cell Mol Life Sci. 2023;80:117.

Oláh A, Sayour AA, Ruppert M, Barta BA, Merkely B, Kovács A, Radovits T. Dynamics of exercise training and detraining induced cardiac adaptations. Curr Opin Physiol. 2023;33:100657.

Siegel PM*, Barta BA*, Orlean L, Steenbuck ID, Cosenza-Contreras M, Wengenmayer T, Trummer G, Wolf D, Westermann D, Schilling O, Diehl P. The serum proteome of VA-ECMO patients changes over time and allows differentiation of survivors and non-survivors: an observational study. J Transl Med. 2023;21(1):319.

Ruppert M, Korkmaz-Icöz S, Benczik B, Ágg B, Nagy D, Bálint T, Sayour AA, Oláh A, Barta BA, Benke K, Ferdinandy P, Karck M, Merkely B, Radovits T, Szabó G. Pressure overload-induced systolic heart failure is associated with characteristic myocardial microRNA

expression signature and post-transcriptional gene regulation in male rats. Sci Rep. 2023;13(1):16122.

Tokodi M, Oláh A, Fábián A, Lakatos BK, Hizoh I, Ruppert M, Sayour AA, Barta BA, Kiss O, Sydó N, Csulak E, Ladányi Z, Merkely B, Kovács A, Radovits T. Novel insights into the athlete's heart: is myocardial work the new champion of systolic function? Eur Heart J Cardiovasc Imaging. 2022;23(2):188–197.

Dézsi L, Mészáros T, Kozma GT, H-Velkei M, Oláh CZs, Szabó M, Patkó Z, Fülöp T, Hennies M, Szebeni M, Barta BA, Merkely B, Radovits T, Szebeni J. A naturally hypersensitive porcine model may help understand the mechanism of COVID-19 mRNA vaccine-induced rare (pseudo) allergic reactions: complement activation as a possible contributing factor. Geroscience. 2022;44(2):597–618.

Lakatos BK, Ruppert M, Tokodi M, Oláh A, Braun Sz, Karime C, Ladányi Z, Sayour AA, Barta BA, Merkely B, Radovits T, Kovács A. Myocardial work index: a marker of left ventricular contractility in pressure- or volume overload-induced heart failure. ESC Heart Fail. 2021;8(3):2220–2231.

Oláh A, Barta BA, Sayour AA, Ruppert M, Virág-Tulassay E, Novák J, Varga ZV, Ferdinandy P, Merkely B, Radovits T. Balanced Intense Exercise Training Induces Atrial Oxidative Stress Counterbalanced by the Antioxidant System and Atrial Hypertrophy That Is Not Associated with Pathological Remodeling or Arrhythmogenicity. Antioxidants. 2021;10(3):452.

Sayour AA, Ruppert M, Oláh A, Benke K, Barta BA, Zsáry E, Ke H, Horváth EM, Merkely B, Radovits T. Left Ventricular SGLT1 Protein Expression Correlates with the Extent of Myocardial Nitro-Oxidative Stress in Rats with Pressure and Volume Overload-Induced Heart Failure. Antioxidants. 2021;10(8):1190.

Sayour AA, Ruppert M, Oláh A, Benke K, Barta BA, Zsáry E, Merkely B, Radovits T. Effects of SGLT2 inhibitors beyond glycemic control—focus on myocardial SGLT1. Int J Mol Sci. 2021;22(18):9852.

Bódi B, Kovács Á, Gulyás H, Mártha L, Tóth A, Mátyás C, Barta BA, Oláh A, Merkely B, Radovits T, Papp Z. Long-term PDE-5A inhibition improves myofilament function in left and right ventricular cardiomyocytes

through partially different mechanisms in diabetic rat hearts. Antioxidants. 2021;10(11):1776.

Török M, Monori-Kiss A, Pál É, Horváth E, Jósvai A, Merkely P, Barta BA, Mátyás C, Oláh A, Radovits T, Merkely B, Ács N, Nádasy GYL, Várbíró Sz. Long-term exercise results in morphological and biomechanical changes in coronary resistance arterioles in male and female rats. Biol Sex Differ. 2020;11(1):7.

Ruppert M, Lakatos BK, Braun Sz, Tokodi M, Karime C, Oláh A, Sayour AA, Hizoh I, Barta BA, Merkely B, Kovács A, Radovits T. Longitudinal Strain Reflects Ventriculoarterial Coupling Rather Than Mere Contractility in Rat Models of Hemodynamic Overload-Induced Heart Failure. J Am Soc Echocardiogr. 2020;33(10):1264–1275.e4.

Sayour AA, Oláh A, Ruppert M, Barta BA, Horváth EM, Benke K, Pólos M, Hartyánszky I, Merkely B, Radovits T. Characterization of left ventricular myocardial sodium-glucose cotransporter 1 expression in patients with end-stage heart failure. Cardiovasc Diabetol. 2020;19(1):159.

Gazdag P, Oravecz K, Acsai K, Demeter-Haludka V, Ördög B, Szlovák J, Kohajda Z, Polyák A, Barta BA, Oláh A, Radovits T, Merkely B, Papp JGy, Baczkó I, Varró A, Nagy N, Prorok J. Increased Ca^{2+} content of the sarcoplasmic reticulum provides arrhythmogenic trigger source in swimming-induced rat athlete's heart model. Sci Rep. 2020;10(1):19596.

Oláh A, Kovács A, Lux Á, Tokodi M, Braun Sz, Lakatos BK, Mátyás C, Kellermayer D, Ruppert M, Sayour AA, Barta BA, Merkely B, Radovits T. Characterization of the dynamic changes in left ventricular morphology and function induced by exercise training and detraining. Int J Cardiol. 2019;277:178–185.

Ruppert M, Korkmaz-Icöz S, Loganathan S, Jiang W, Oláh A, Sayour AA, Barta BA, Karime C, Merkely B, Karck M, Radovits T, Szabó G. Incomplete structural reverse remodeling from late-stage left ventricular hypertrophy impedes the recovery of diastolic but not systolic dysfunction in rats. J Hypertens. 2019;37(6):1200–1212.

Ruppert M, Bódi B, Korkmaz-Icöz S, Loganathan S, Jiang W, Lehmann L, Oláh A, Barta BA, Sayour AA, Merkely B, Karck M, Papp Z, Szabó G, Radovits T. Myofilament Ca^{2+} sensitivity correlates with left ventricular contractility during the progression of pressure overload-induced left ventricular myocardial hypertrophy in rats. J Mol Cell Cardiol. 2019;129:208–218.

Oláh A, Mátyás C, Kellermayer D, Ruppert M, Barta BA, Sayour AA, Török M, Koncsos G, Giricz Z, Ferdinandy P, Merkely B, Radovits T. Sex Differences in Morphological and Functional Aspects of Exercise-Induced Cardiac Hypertrophy in a Rat Model. Front Physiol. 2019;10:889.

Mátyás C, Kovács A, Németh BT, Oláh A, Braun S, Tokodi M, Barta BA, Benke K, Ruppert M, Lakatos BK, Merkely B, Radovits T. Comparison of speckle-tracking echocardiography with invasive hemodynamics for the detection of characteristic cardiac dysfunction in type-1 and type-2 diabetic rat models. Cardiovasc Diabetol. 2018;17(1):13.

Ruppert M*, Barta BA*, Korkmaz-Icöz S, Li S, Oláh A, Mátyás C, Németh BT, Benke K, Sayour AA, Karck M, Merkely B, Radovits T, Szabó G. A hipertrófiás

myocardium reverz elektromos remodellációjának vizsgálata patkánymodellben. Cardiol Hung. 2018;48(2):118–128.

Ruppert M, Korkmaz-Icoz S, Loganathan S, Jiang W, Lehmann LH, Oláh A, Sayour AA, Barta BA, Merkely B, Karck M, Radovits T, Szabó G. Pressure-volume analysis reveals characteristic sex-related differences in cardiac function in a rat model of aortic banding-induced myocardial hypertrophy. Am J Physiol Heart Circ Physiol. 2018;315(3):H502–H511.

Mátyás C, Németh BT, Oláh A, Török M, Ruppert M, Kellermayer D, Barta BA, Szabó G, Kökény G, Horváth EM, Bódi B, Papp Z, Merkely B, Radovits T. Prevention of the development of heart failure with preserved ejection fraction by the phosphodiesterase-5A inhibitor vardenafil in rats with type 2 diabetes. Eur J Heart Fail. 2017;19(3):326–336.