„VICTOR BABEȘ“ UNIVERSITY
OF MEDICINE AND PHARMACY
FROM TIMISOARA

16th NEW FRONTIERS IN CARDIOVASCULAR RESEARCH

France & Central Europe

SCIENTIFIC MANIFESTATIONS

may
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2026

PROGRAMME & ABSTRACT BOOK

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„VICTOR BABEȘ" UNIVERSITY OF MEDICINE AND PHARMACY FROM TIMISOARA

16th Meeting NEW FRONTIERS IN CARDIOVASCULAR RESEARCH: France & Central Europe

May 27th – 29th, 2026

Timișoara, Romania

PROGRAMME & ABSTRACT BOOK

Editors: Danina M. Muntean, Adrian Sturza

Dear Colleagues,

It is our great pleasure to welcome you to the **16th Meeting** "**New Frontiers in Cardiovascular Research: France & Central Europe**" held in Timișoara, Romania, on May 27-29, 2026.

The meeting is hosted by "Victor Babeș" University of Medicine and Pharmacy from Timișoara and organized by the *Centre for Translational Research and Systems Medicine* in partnership with the *Research Centre of Timișoara Institute of Cardiovascular Diseases.*

This conference series, initiated in Prague back to 1994 under the leadership of Professor Bohuslav Ošťádal (Czech Republic) and Professor Rodolphe Fischmeister (France), has become a tradition of collaboration between basic scientists and clinicians, a forum where laboratory discoveries meet clinical experience, and where new ideas are transformed into meaningful advances in cardiovascular medicine.

Building on fifteen successful editions, this thought-provoking conference features basic and clinical sessions, lectures of invited keynote speakers and oral communications selected from the submitted abstracts. The strength of this meeting lies precisely in this dialogue between disciplines — from pathophysiological mechanisms and translational models to clinical research and emerging therapeutic strategies.

A particularly important aspect is the active participation of young investigators, PhD students and early-career trainees. We are especially pleased to offer opportunities for young investigators to discuss their latest results and to compete in both oral and poster sessions and we strongly encouraged the free attendance from undergraduate students. Scientific progress depends on nurturing the next generation of researchers, and we are proud that this meeting continues to serve as a platform for learning, mentorship, and inspiration.

Thank you all for being part of this important tradition.

On behalf of the Organizing Committee,

Danina M. Muntean
Adrian Sturza
Dan Gaiță
Claudia Borza
Daniel F. Lighezan

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Conference Programme

DAY 1 (May 27, 2026) *Aula Magna Hall*	
8:30 -	**Registration –** Central Lobby of the University
9:00-9:20	**OPENING ADDRESS** **Daniel Lighezan (Honorary President of the Meeting)** **Rodolphe Fischmeister (Paris, France, Founding Chair)** **Bohuslav Ošťádal (Prague, Czech Republic, Founding Chair)** **Danina Muntean (Chair of the Meeting)** **Dan Gaiță (Vice-Chair of the Meeting)** **Claudia Borza (Vice-Chair of the Meeting)**
9:20-10:30	**SESSION 1**
Chairs:	**Rodolphe Fischmeister (France), Bohuslav Ošťádal (Czech Republic)**
09:20-9:40	**Bohuslav Ošťádal (Prague, Czech Republic)** *Perinatal Hypoxia and the Developing Heart*
09:40-10:00	**Rodolphe Fischmeister (Paris-Orsay, France)** *Cardiac Gene Therapy with Phosphodiesterases Limits Maladaptive Remodeling in Heart Failure*
10:00-10:20	**Stefan Chlopicki (Krakow, Poland)** *Heterogenous Mechanisms of Endothelial Dysfunction: An Insight From In Vivo Studies*
10:20-10:30	Q&A
10:30-11:00	**Coffee Break**
11:00-12:45	**SESSION 2**
Chairs:	**Ivan Zahradnik (Slovakia), Alain Lacampagne (France)**
11:00-11:20	**Alain Lacampagne (Montpellier, France)** *Role of the Ryanodine Receptors in the Heart-Brain Dialogue*
11:20-11:40	**Ramaroson Andriantsitohaina (Montpellier, France)** ***Extracellular Vesicles-Guided Delivery and NLRP3 Blockade: A Hypothalamic Therapeutic Roadmap for Atherosclerosis and Atrial Fibrillation***
11:40-12:00	**Ivan Zahradnik (Bratislava, Slovakia)** *Three Stories on the Structure-Function Relationship in Cardiac Myocytes*
12:00-12:20	**Martin Štěrba (Hradec Králové, Czech Republic)** *Understanding the Role of DNA Damage and DDR Signalling in the Cardiotoxicity and Anticancer Efficacy of Anthracycline Chemotherapeutics*
12:20-12:40	**Simina Crișan (Timișoara, Romania)** *From Heart Failure to Coronary Artery Disease: An Integrated Inflammatory Approach*
12:40-12:50	Q&A
12:50	**GROUP PHOTO in front of the University**
13:00-14:00	**Lunch Break** *(lunch boxes provided)*

14:00-15:45	**SESSION 3**
Chairs:	**Tatiana Ravingerova (Slovakia), Antigone Lazou (Greece)**
14:00-14:20	**Antigone Lazou (Thessaloniki, Greece)** *Restoring Myocardial Metabolic Flexibility in the Diabetic Heart*
14:20-14:40	**Tatiana Ravingerova (Bratislava, Slovakia)** *Physical Exercise as a Non-Invasive Strategy to Trigger Cellular Mechanisms of Cardioprotection in Healthy and Diseased Heart*
14:40-15:00	**Petra Alánová (Prague, Czech Republic)** *The Role of HIF-1α and Mitochondria in Cardioprotection Induced by Chronic Hypoxia*
15:00:15:20	**Jitka Žurmanova (Prague, Czech Republic)** *The Mechanism of Cold-Induced Cardioprotection* Differs *Depending on the Regimen*
15:20-15:35	**Andrea Mičurová (Bratislava, Slovakia)** *The Role of Dimethyl Fumarate in the Heart of Female Hypertriglyceridemic Rats Exposed to Chronic Psychosocial Stress*
15:35-15:50	**Maria Dănilă (Timișoara, Romania)** *The Role of P2Y11 Receptor Signaling in Cardiovascular Protection*
15:50-16:15	**Coffee Break**
16:15-17:45	**SESSION 4**
Chairs:	**Jerzy Beltowski (Poland), Andrija Đuranović (Serbia)**
16:15-16:35	**Jerzy Beltowski (Lublin, Poland)** *Role of Leptin in The Pathogenesis of Obesity-Associated Platelet Hyperactivity & Abnormalities of Coagulation/Fibrinolysis Balance: Implications for Cardiovascular Diseases*
16:35-16:55	**Patrycja Kaczara (Krakow, Poland)** *Metabolic Control of Platelet Reactivity: Can We Improve Antiplatelet Therapy?*
16:55-17:15	**Oana Aburel (Timișoara, Romania)** *Methylene Blue as a Redox Modulator in Cardio-Metabolic Dysfunction*
17:15-17:30	**Anca Bînă (Timișoara, Romania)** *Mitochondrial Respiratory Dysfunction in Preeclampsia: Platelets Mirror When Placenta Struggles to Breathe*
17:30-17:45	**Milan Savic, Andrija Đuranović (Belgrade, Serbia)** *Comparison of Blood Biomarkers Between Professional Football Players and Recreational Athletes: Is There a Reliable Marker of Overtraining*
17:45-19:15	**POSTER SESSION – Sport Hall**
Chairs:	**Antigone Lazou (Greece), Petra Alánová (Czech Republic)**
17:45-19:15	**YOUNG INVESTIGATOR AWARD COMPETITION – Senate Hall**
Chairs:	**Ramaroson Andriantsitohaina (France), Bohuslav Ošťádal (Czech Republic)**
17:45-18:00	**Georges Madders (France)** *PEGylation Size Exclusion Technology Enables Independent Activation of Cardiac B-Adrenergic Receptors Located in Either the T-Tubule or the Outer Surface Membrane*
18:00-18:15	**Reyhaneh Nejati Bervanlou (Slovakia)**

	Greater Voluntary Exercise Does Not Rescue Hypertensive Cardiac Remodeling: Divergent Functional And BDNF–TRKB-Linked Left Ventricular Adaptation in Spontaneously Hypertensive Rats
18:15-18:30	**Ottó Tatai (Hungary)** *Tissue-Specific Autoantibody Signatures Reveal Immune Alterations Undetected by Routine Serology in Long COVID*
18:30-18:45	**Alexandra Frișan (Romania)** *A Simple Risk Score Combining Myocardial Work and Coronary Anatomy for Risk Stratification After STEMI*
18:45-19:00	**Ulrika Duľová (Slovakia)** *Beyond Antioxidants: The Role of Quercetin in Mitochondrial Energetics in the Diabetic Rat Heart*
19:00-19:15	**Răzvan Bertici (Romania)** *Sleep-Disordered Breathing in Precapillary Pulmonary Hypertension: A Case Series From Timișoara Regional Referral Center*
19:15 -	**Welcome Reception**
DAY 2 (May 28, 2026) ***Aula Magna Hall***	
09:00-10:30	**SESSION 5**
Chairs:	**Zoltán Papp (Hungary), Albano Meli (France)**
09:00-09:20	**Albano Meli (Montpellier, France)** *Integrated Functional and Genomic Profiling of LMNA-Related Dilated Cardiomyopathy*
09:20-09:40	**Zoltán Papp (Debrecen, Hungary)** *Less is More: The Paradoxical Benefit of Myosin Inhibition on Cardiac Reserve*
09:40-10:00	**Attila Tóth (Debrecen, Hungary)** *More is Less: Why Myosin Activation Fails to Improve Cardiac Performance In Vivo*
10:00-10:20	**Adina Ionac (Timișoara, Romania)** *A Comprehensive Diagnostic and Therapeutic Approach to Obstructive Hypertrophic Cardiomyopathy*
10:20-10:30	Q&A
10:30-11:00	**Coffee Break**
11:00-12:50	**SESSION 6**
Chairs:	**Bruno Podesser (Austria), Derek Hausenloy (Singapore & UK)**
11:00-11:20	**Derek Hausenloy (Singapore & London, UK)** *Target Discovery in Heart Failure from iPSC Stem Cells and Bat Biology*
11:20-11:40	**Bruno Podesser (Vienna, Austria)** *Vascular (Dys)function in the Failing Heart*
11:40-12:00	**Ludovic Gomez (Lyon, France)** *Using Ischemia-Reperfusion Model to Re-Investigate Congestive and Chronic Heart Failure Development in Mice According to Sex*

12:00-12:20	**Jaroslav Hrdlička (Prague, Czech Republic)** *Cardiac Remodelling in Wistar Rats With Early Postnatal Pressure Overload: Sex Differences and the Role of the Proliferative Phase of Cardiac Development*
12:20-12:40	**Bogdan Enache (Timișoara, Romania)** *The Non-Inferiority Trap: Lessons From Contemporary Cardiology Trials*
12:40-12:50	Q&A
12:50-14:00	**Lunch Break** *(lunch boxes provided)*
14:00-15:45	**SESSION 7**
Chairs:	**Olga Pechanova (Slovakia), Vladimir Jakovljevic (Serbia)**
14:00-14:20	**Vladimir Jakovljevic (Kragujevac, Serbia)** *Therapeutic Effects of Galium verum L.extract in an Experimental Model of Aphthous Stomatitis*
14:20-14:40	**Olga Pechanova (Bratislava, Slovakia)** *Hormetic Effects of Polyphenol-Rich Cornus mas on Redox Balance: Evidence from Animal and Human Studies*
14:40-15:00	**Monika Bartekova (Bratislava, Slovakia)** *Cardioprotection in the Diabetic Heart: Effect of Quercetin*
15:00-15:20	**Slavica Mutavdzin-Krneta (Belgrade, Serbia)** *Targeting the Homocysteine-Oxidative Stress Axis with Folate and Vitamin B6: Cardioprotection in Diabetes and Heart Failure*
15:20-15:35	**Dagmar Štěpánová Jarkovská (Prague, Czech Republic)** *Silver Nanoparticle-Potentiated Antibiotic Therapy In A Porcine Model Of Sepsis – Are the Animal Models Necessary?*
15:35-15:45	Q&A
15:45-16:15	**Coffee Break**
17:30-20:00	Social Program

20:00 GALA DINNER & AWARDS CEREMONY

DAY 3 (May 29, 2026) ***Aula Magna Hall***	
09:00-10:30	**SESSION 8**
Chairs:	**Ana Maria Gomez (France), András Varró (Hungary)**
09:00-09:20	**András Varró (Szeged, Hungary)** *The Cellular Cardiac Electrophysiological Effect of Chronic Amiodarone Treatment in End-Stage Heart Failure Patients*
09:20-09:40	**Ana Maria Gomez (Paris-Orsay, France)** *Calcium Signaling in Cardiac Arrhythmias: From Local Control to RyR2 Channelopathies*
09:40-10:00	**István Baczkó (Szeged, Hungary)** *Proarrhythmic Remodeling of Pulmonary Vein Sleeve Myocytes in a Large Animal Model of Endurance Exercise*
10:00-10:20	**Norbert Jost (Szeged, Hungary)**

	The Ultrarapid Delayed Rectifier Potassium Current Has Important Functional Role in the Repolarization Reserve of Canine and Human Ventricular Muscle
10:20-10:35	**Letiția Olteanu (Timișoara, Romania)** *Are GLP-1 Receptor Agonists Associated With Pro-Arrhythmic Signals? A Pharmacovigilance Disproportionality Analysis Using The FAERS Database*
10:35-10:45	Q&A
10:45-11:15	**Coffee Break**
11:15-13:00	**SESSION 9**
Chairs	**Viviana Ivan (Romania), Ioana Mozoș (Romania)**
11:15-11:35	**Simona Drăgan (Timișoara, Romania)** *Challenges in Diagnosing Heart Failure With Preserved Ejection Fraction*
11:35-11:55	**Viviana Ivan (Timișoara, Romania)** *Sex differences in Heart Failure: The Impact on Treatment*
11:55-12:15	**Ioana Mozoș (Timișoara, Romania)** *Decoding the Lipid–Vascular Interplay: Insights from Pulse Wave Analysis and Metabolic Biomarkers*
12:15-12:35	**Minodora Andor (Timișoara, Romania)** *Fibrosis and Associated Dysfunctions in Heart Failure: An Integrative Perspective*
12:35-12:55	**Adrian Sturza (Timișoara, Romania)** *Monoamine Oxidase-Related Oxidative Stress in Obese Patients With Heart Failure: The Beneficial Role of SGLT2i*
12:55-13:00 (Rapid Fire)	**Diana Buzzi (Timișoara, Romania)** *SGLT2 Inhibitors: Distinct Cardiac Remodeling Pattern in Heart Failure With Reduced and Preserved Ejection Fraction*
13:00	**Closing Remarks**

ABSTRACTS OF THE INVITED LECTURES & ORAL COMMUNICATIONS

PERINATAL HYPOXIA AND THE DEVELOPING HEART

B. Ošťádal

Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic

Hypoxic states of the cardiovascular system are associated with the most frequent diseases of modern times. The degree of hypoxic injury depends not only on the intensity and duration of hypoxic stimulus but also on the level of cardiac tolerance to oxygen deprivation. This variable changes significantly during ontogenetic development. Physiological hypoxia is a normal part of fetal life for all vertebrates and plays a significant role in heart formation. However, maternal chronic hypoxia „in utero" adversely affects cardiogenesis and induces a decline in cardiac performance. Furthermore, it may cause fetal reprogramming of several genes, which can change the susceptibility of the adult heart to oxygen deprivation; this effect is sex-dependent. Neonatal heart is highly resistant to hypoxia, but the tolerance decreases after birth. These age-dependent changes are, however, not linear. The tolerance of the isolated rat heart showed a triphasic pattern: significant decrease from postnatal day 1 to 7, followed by increase in the weaning period and final decline to adulthood. The mechanisms of the high resistance of the immature heart to oxygen deprivation are not satisfactorily clarified. We have observed significant changes in mitochondrial oxidative phosphorylation, mitochondrial membrane potential as well as in the role of the mitochondrial permeability transition pore in the myocardial injury. These results support the hypothesis that cardiac mitochondria are deeply involved in the regulation of cardiac tolerance to hypoxia during ontogenetic development. In addition, the altered expression pattern of different cardiac protective genes likely predisposes the developing heart to increased vulnerability to hypoxic injury later in life. In this connection question arises whether the already high tolerance of the neonatal mammalian heart can be further increased. It has been found that cardiac protective mechanisms, like ischemic preconditioning or adaptation to chronic hypoxia, failed to increase hypoxic tolerance to oxygen deprivation in the highly tolerant hearts of newborn rats. It seems, therefore, that we are dealing with a common biological phenomenon: cardiac tolerance has its ceiling. These results would have important clinical implications, since cardiac sensitivity in adult patients may be significantly affected by perinatal hypoxia in a sex dependent manner.

CARDIAC GENE THERAPY WITH PHOSPHODIESTERASES LIMITS MALADAPTIVE REMODELING IN HEART FAILURE

R. Fischmeister

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The β-adrenergic stimulation of cardiac function involves the second messenger cAMP which activates the cAMP-dependent protein kinase (PKA) to modulate key proteins of the excitation-contraction coupling (ECC) process. Intracellular cAMP levels produced upon β-stimulation are counterbalanced by the degradation of the cyclic nucleotide by enzymes called phosphodiesterases (PDEs). We have shown in the past that PDEs not only terminate the activation of cAMP effectors but also compartmentalize this second messenger in discrete subcellular domains. Clinically, PDE inhibition has been considered a promising approach to compensate for the catecholamine desensitization that accompanies heart failure (HF). In that respect, PDE3 inhibitors, such as milrinone or enoximone, have been used clinically to improve systolic function and alleviate the symptoms of acute HF. However, their chronic use has proven to be detrimental, increasing adverse remodeling and ventricular arrhythmias.

Recently, we proposed to test the opposite strategy, i.e. increasing rather than inhibiting PDE activity. We believe that this strategy, which is reminiscent of the counter-intuitive beneficial effect of beta-blockers in HF, could be therapeutically relevant in HF because it would prevent a deleterious accumulation of cAMP during catecholamines spill over. In that line, we found that constitutive overexpression of PDE4B, one of the main PDE4 isoform expressed in the cardiomyocyte to control the β-adrenergic regulation of the ECC, is cardioprotective1. We also found that gene therapy with AAV9-PDE4B exerts cardioprotective effects limiting adverse remodeling evoked by catecholamines or increased postcharge1. Similarly, we found that PDE2A constitutive overexpression exerts anti-hypertrophic effects and transgenic mice overexpressing PDE2A in the heart have preserved ejection fraction after myocardial infarction and are protected against catecholamine induced ventricular arrhythmia. Also, PDE2 gene therapy limits cardiac adverse left ventricle remodeling and dysfunction induced by sympathomimetic amines as well as ventricular arrhythmias2. Altogether, our findings suggest that increasing PDE activity, either with gene therapy or pharmacologically with PDE-specific activators yet to be discovered, could represent an interesting novel therapeutic strategy to treat heart failure.

EXTRACELLULAR VESICLES-GUIDED DELIVERY AND NLRP3 BLOCKADE: A HYPOTHALAMIC THERAPEUTIC ROADMAP FOR ATHEROSCLEROSIS AND ATRIAL FIBRILLATION

X. Vidal-Gomez[†1], L. Rauzier[†1], S. Marchal[#1], N. Suffee[#2], J. Thireau[#1], E. Milbank[3], P. Sicard[1,4], M. Decourcelle[5], E. Trenquier[2], L. Dubuquoy[6], L. Alburquerque[1], P.E. Grillet[1,7], J.P. Cristol[1,7], N. Mekrane[1], A. C. Meli[1], M.C Martinez[*1], R. Andriantsitohaina[*‡1]

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Obesity-associated inflammation contributes to atrial fibrillation (AF), but the neuroimmune mechanisms involved remain incompletely understood. Here, the ventromedial hypothalamus (VMH) is investigated as a potential regulator of metabolic and cardiac alterations. Neuron-targeted delivery of dominant-negative NLRP3 constructs reduced hypothalamic inflammatory signaling and was associated with weight reduction independent of food intake, accompanied by increased thermogenic activity in adipose tissue and reduced atherosclerotic burden. Selective inhibition of NLRP3 signaling in VMH $SF1^+$ neurons was linked to improved autonomic balance, decreased atrial fibrosis and adipose infiltration, and lower AF susceptibility in obese mice. Proteomic analysis of visceral adipose tissue indicated reduced levels of several inflammatory mediators, including S100A9. In human induced pluripotent stem cell-derived cardiomyocytes, S100A9 exposure was associated with altered electrophysiological and contractile properties. These findings support a functional connection between central inflammatory pathways, adipose tissue remodeling, and atrial dysfunction in obesity, and suggest that targeted modulation of hypothalamic signaling may represent a potential therapeutic approach.

THREE STORIES ON STRUCTURE-FUNCTION RELATIONSHIPS IN CARDIAC MYOCYTES

I. Zahradník

Department of Cellular Cardiology, Biomedical Center SAS, Bratislava, Slovak Republic

The methodology of scientific studies is often undercommunicated, although there lies the beauty and uniqueness of science. Design of a testable hypothesis, formulation of answerable questions, and validation of arguments are strongly required in grant applications, but often abbreviated to aims and methods in a typical published paper. The methodology gives to a study a firm framework including the structure, plan of research, methods, and the interpretation framework, to ensure reproducible findings.
Instead of original data I will present methodological approaches we have developed in our recent studies with the aim to better understand processes running within cardiac myocytes deep bellow the resolution of experiments. We employed 3 major approaches: 1/ Transformation of qualitative observables to quantitative data; 2/ Analysis of large datasets; and 3/ Mathematical modeling.
In general sense, the structure and function of cardiomyocytes is well known, including the excitation → contraction coupling, where the arrow represents a brief transient of calcium release. The calcium release is highly organized by components of dyadic structures, which keep together the t-tubule of sarcolemma and the terminal cisterna of sarcoplasmic reticulum carrying clusters of ryanodine receptor calcium release channels (RyR2). Under a proper experimental setup such structures produce calcium release signals upon activation.
The question we asked was: How do these structural components, individually and collectively, contribute to the rate and the intensity of calcium release? To answer it, we have developed appropriate particular methodologies. These involved collection, processing, and statistical comparison of electron microscopic images, analysis of calcium spikes recorded by laser scanning fluorescence confocal microscopy, robust simulation of RyR2 clusters in action, structural analysis of RyR2 molecules, and always the mathematical formulation of working hypothesis to validate the observed relations.
Considering the partial findings altogether we may deduce that the complex excitation - contraction coupling function emerges from the structure and the first principles governing molecular constituents under biological control.

Supported by APVV 21-0443.

UNDERSTANDING THE ROLE OF DNA DAMAGE AND DDR SIGNALING IN THE CARDIOTOXICITY AND ANTICANCER EFFICACY OF ANTHRACYCLINE CHEMOTHERAPEUTICS

M. Štěrba

Department of Pharmacology, Faculty of Medicine in Hradec Králové, Charles University, Czech Republic

Both the anticancer and cardiotoxic effects of anthracycline chemotherapeutics, such as daunorubicin and doxorubicin, appear to be linked to topoisomerase II (TOP2) poisoning and the induction of toxic DNA double-strand breaks (DSBs). Terminally differentiated cardiomyocytes express only the beta isoform of the enzyme (TOP2B), which has been proposed to play an essential role in the chronic anthracycline cardiotoxicity development. In contrast, proliferating cancer cells predominantly express the alpha isoform (TOP2A). The protective effects of dexrazoxane against chronic anthracycline cardiotoxicity have been closely associated with catalytic inhibition of TOP2B and prevention of anthracycline-induced DSB formation in the heart. We developed several new dexrazoxane derivatives with increased potency as TOP2B catalytic inhibitors and cardioprotective agents, both in vitro and in vivo. However, dexrazoxane and all its congeners bind to the same TOP2 binding pocket, which is practically identical in both TOP2 isoforms. Consequently, their effects are non-selective and may also be expected in cancer cells. These mechanistic insights further reinforced persisting concerns regarding the potential interference of dexrazoxane (and its newer derivatives) with the anticancer efficacy of anthracyclines. In our experiments using the HT1080 sarcoma cancer model, we demonstrated both in vitro and in vivo that, although dexrazoxane inhibits anthracycline-induced DSB formation, it has no significant impact on their anticancer effects. Given the biological and molecular heterogeneity of cancers, however, it may be hypothesized that the outcome of this interaction could differ depending on the specific cancer context. Therefore, we further developed first-in-class TOP2B-selective catalytic inhibitors structurally unrelated to dexrazoxane. These new drug candidates bind to a previously unidentified pocket in the TOP2 enzyme, allowing selective TOP2B targeting and preferential activity in terminally differentiated cardiomyocytes. Their cardioprotective effects have been demonstrated both in vitro and in vivo in a rabbit model of chronic anthracycline cardiotoxicity. In conclusion, non-selective TOP2 inhibition by dexrazoxane provides effective protection against anthracycline cardiotoxicity without compromising anticancer efficacy. However, selective TOP2B catalytic inhibition using novel drug candidates may open a new avenue for protecting cardiomyocytes from anthracycline toxicity without interfering with the anticancer effects of anthracyclines in tumor cells.

Supported by the OncoPharm project ID CZ.02.01.01/00/23_021/0008442.

FROM HEART FAILURE TO CORONARY ARTERY DISEASE: AN INTEGRATED INFLAMMATORY APPROACH

S. Crișan[1,2,3], R. Băghină[2,3], A. Bețiu[2,4], S. Luca[1,2,3], O. Pătru[2,3], C.T. Luca[1,2,3]

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Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide, with heart failure (HF) and coronary artery disease (CAD) representing two major and often interconnected clinical entities. Traditionally regarded as distinct conditions, growing evidence suggests that both share common inflammatory mechanisms that contribute to disease initiation, progression and adverse outcomes. Thus, inflammation is now recognized as a central pathophysiological driver across the cardiovascular continuum.

In coronary artery disease, chronic vascular inflammation promotes endothelial dysfunction, lipid accumulation, and atherosclerotic plaque formation. Activation of innate and adaptive immune pathways, along with the release of pro-inflammatory cytokines such as interleukins (IL), IL-1, IL-6, and tumor necrosis factor-alpha (TNF-α), contributes to plaque progression and destabilization, ultimately precipitating acute coronary syndromes. Numerous clinical trials have provided compelling evidence supporting the inflammatory hypothesis of atherothrombosis.

Similarly, inflammation plays a pivotal role in heart failure, irrespective of phenotype. In both heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), systemic and myocardial inflammatory activation contribute to ventricular remodelling, fibrosis, endothelial dysfunction, and impaired cardiac performance. Furthermore, ischemic injury following myocardial infarction initiates an inflammatory cascade that may accelerate maladaptive remodelling and progression to HF. We provided an integrated overview of the inflammatory pathways linking CAD and HF, highlighting the concept of an "inflammatory cardiovascular continuum ", underlying key molecular mediators, relevant biomarkers and landmark clinical trials evaluating anti-inflammatory therapies, including colchicine-based strategies and targeted cytokine inhibition. Current limitations, unresolved controversies, and future perspectives regarding personalized anti-inflammatory approaches in cardiovascular medicine have been also taken into consideration.

Understanding inflammation as a shared mechanistic and therapeutic target may reshape contemporary strategies for prevention, risk stratification, and treatment in patients with coronary artery disease and heart failure.

RESTORING MYOCARDIAL METABOLIC FLEXIBILITY IN THE DIABETIC HEART

A. Lazou

School of Biology, Aristotle University of Thessaloniki, Thessaloniki, Greece

The diabetic heart undergoes profound metabolic remodeling that compromises its ability to efficiently utilize energy substrates and adapt to changing energetic demands. Impaired glucose utilization and excessive reliance on fatty acid oxidation contribute to the development of diabetic cardiomyopathy and progressive cardiac dysfunction. Restoring myocardial metabolic flexibility has therefore emerged as an important strategy for preserving cardiac performance under diabetic conditions.
Peroxisome proliferator-activated receptor δ (PPARδ) is a major regulator of cardiac substrate metabolism, coordinating pathways involved in glucose and lipid utilization. Experimental evidence from models of type 1 diabetes demonstrates that pharmacological activation of PPARδ improves cardiac function and attenuates cardiomyocyte hypertrophy, while promoting a shift toward glucose utilization through modulation of glucose transporter expression and translocation.
Transcriptomic analysis identified coordinated regulation of pathways involved in fatty acid and branched-chain amino acid metabolism, PPAR and AMPK signaling, and cellular stress adaptation, consistent with enhanced metabolic flexibility. At the same time, pathways associated with extracellular matrix remodeling, hypertrophic growth, adrenergic signaling, and calcium handling were suppressed, suggesting improved myocardial efficiency and attenuation of maladaptive remodeling.
These findings demonstrate that metabolic modulation can profoundly influence myocardial transcriptional and signaling programs in diabetes and highlight PPARδ-driven restoration of metabolic flexibility as a promising strategy for improving cardiac adaptation and function in the diabetic heart.

PHYSICAL EXERCISE AS A NON-INVASIVE STRATEGY TO TRIGGER CELLULAR MECHANISMS OF CARDIOPROTECTION IN HEALTHY AND DISEASED HEART

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Ischemic preconditioning (PC) is the most robust adaptive phenomenon protecting the hearts of all animal species against ischemia/reperfusion (I/R) injury, but its application in humans is limited, and can be used only during elective interventions. Protection against I/R can be rendered by other forms of PC that do not require an invasive approach, such as exercise-induced PC (EPC), or "remote" PC (RPC), when brief ischemia of any organ confers protection to distant organs. Despite successful experimental studies, clinical trials did not show much benefit of RPC. The latter could be attributed to the presence of comorbidities (hypertension, diabetes, hyperglycemia), comedications or confounders, such as sex or aging.
We explored whether preventive interventions in adult male Wistar and SHR rats applied *in vivo* increase cardiac resistance to I/R *ex vivo* using voluntary exercise (2 weeks free running in the wheel-equipped cages, EPC) or RPC (3 cycles of 5min a. femoralis occlusion/5min reperfusion) using a pressure cuff on the hind limb. The efficacy of EPC and RPC was tested in isolated hearts perfused under normal or hyperglycemic (glucose 22 mmol) conditions, exposed to 30 min global ischemia/2 hrs reperfusion, focused on post-I/R recovery of function (LVDP) and extent of lethal injury (infarct size, IS). In parallel groups, heart tissue samples were processed for the investigation (WB) of the levels and activity of selected proteins involved in "pro-survival" RISK pathway and pro- and anti-apoptotic effects.
Hyperglycemia and hypertension increased the IS, reduced post-I/R LVDP in controls. Both EPC and RPC significantly reduced contractile dysfunction and IS. These effects were observed in both, normo- and hyperglycemic hearts, and in the hearts of SHR rats, but were less expressed in the pathological situations. Protective effects were associated with a significant up-regulation of selected RISK proteins, such as PKB, PKCε, eNOS, higher levels of SOD, HSP, and reduction of pro-apoptotic cascades (BAX/Bcl-2, Caspase-3) in the normal hearts, which were less expressed under pathological conditions.
Beneficial effects of non-invasive forms of PC suggest their potential in the management of IHD in clinical conditions. Potential mechanisms may involve activation of proteins of RISK cascade and indicate the need to modify the intensity or modality of adaptive interventions in patients with IHD and comorbidities.

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THE MECHANISM OF COLD-INDUCED CARDIOPROTECTION DIFFERS DEPENDING ON THE REGIMEN

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Background & Aim: Moderate cold acclimation (MCA) has emerged as a promising non-invasive strategy for increasing myocardial resistance to ischemia/reperfusion (I/R) injury without inducing adverse cardiovascular effects such as hypertension or cardiac hypertrophy. MCA consistently reduced infarct size, improved mitochondrial resistance to Ca2+-overload during both acute cold exposure and recovery periods. Cardioprotection was observed after short-term acclimation (1–10 days; StMCA), long-term acclimation (5 weeks; LtMCA), and even persisted for up to two weeks after returning to room temperature. The aim of this report is to compare the mechanisms elicited by different regimen of acclimation and to identify the mildest possible regimen that still induces cardioprotection which could be suitable for use in human medicine.
Materials & Methods: Our published experimental studies in adult male Wistar rats (350-450g) exposed to gradual or sustained cold conditions (8–9 °C) for short- and long-term periods (StMCA; LtMCA). Extent of myocardial infarction *in vivo* (open chest, ventilated animal), competitive ligand binding assays, LC chromatography, quantitative immunofluorescence microscopy and western blot analyses, multiplex cytokine analysis.
Results: The protective phenotype induced by MCA is associated with complex remodelling of β-adrenergic receptor (β-AR) signalling and immunomodulatory effect. StMCA resulted in downregulation and desensitization of β1-ARs, attenuation of β2-AR/Akt signalling and transient activation of antioxidant system, LtMCA increased membrane localization of β2- and β3-ARs without affecting β1-AR–Gsα–adenylyl cyclase signalling or PKA activation. Conversely, β2-AR/Gi/Akt signalling was specifically involved in the cardioprotection persisting after recovery from acclimation, as pharmacological inhibition of β2-ARs abolished infarct-size reduction exclusively in the recovery phase. LtMCA itself engaged non-genomic JAK2/STAT3 signalling as pharmacological inhibition of JAK2 abolished the infarct-sparing effect and mitochondrial protection induced by acclimation, demonstrating a key role of mitochondria-associated STAT3 activity. Moreover, LtMCA also reduced reperfusion-induced premature ventricular complexes and tachyarrhythmia duration and reduced the pro-arrhytmic n-6/n-3 PUFA ratio, effects that disappeared after recovery. Finally, we have identified the mildest possible regimen that still induces cardioprotection after one week and it will be also presented in this report.
Conclusion: Our data suggest the reliable potential of moderate cold acclimation in preventive medicine. A suitable regimen for humans needs to be studied.

THE ROLE OF HIF-1α AND MITOCHONDRIA IN CARDIOPROTECTION INDUCED BY CHRONIC HYPOXIA

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Adaptation to chronic hypoxia (CH) confers cardioprotection against ischemia/reperfusion (I/R) injury, yet the mechanisms linking hypoxia-inducible factor-1α (HIF-1α) to mitochondrial adaptations remain incompletely understood. In this study, we explored the hypothesis that HIF-1α regulates mitochondrial remodeling to enhance cardiomyocyte survival during I/R.
Adult male wild-type (WT) and heterozygous *Hif1a* knockout mice were exposed to CH (7000 m, 8 h/day, 4 weeks) or maintained under normoxia. Using isolated perfused hearts, we assessed infarct size following I/R insult. To uncover underlying mechanisms, we combined transcriptomic and proteomic analyses of cardiomyocytes with functional assessment of mitochondrial function, ultrastructure, and regulation of the mitochondrial permeability transition pore (mPTP). Complementary *in vitro* experiments in AC16 cardiomyocytes with modulated HIF-1α expression were performed under oxidative stress conditions.
CH markedly improved ischemic tolerance in WT mice, whereas this protection was lost in *Hif1a*$^{+/-}$ mice, identifying HIF-1α as a key upstream regulator. Omics analyses revealed a coordinated HIF-1α-dependent reprogramming of mitochondrial pathways. In WT mice, CH induced a reduction in mitochondrial content and respiration accompanied by structural remodeling, reflecting a shift toward improved mitochondrial quality rather than quantity. This adaptation was tightly linked to activation of mitophagy. Importantly, inhibition of mitochondrial fission abolished the cardioprotective effect, demonstrating that mitochondrial turnover is essential for this response. In parallel, CH reduced oxidative stress and promoted mitochondrial translocation of hexokinase-2, contributing to inhibition of mPTP opening. Pharmacological modulation of mPTP confirmed its involvement in HIF-1α-mediated protection. Consistently, HIF-1α overexpression enhanced cardiomyocyte survival under oxidative stress.
Together, these findings present a unified mechanism in which HIF-1α drives cardioprotection by reshaping mitochondrial function and quality control, integrating mitophagy, redox balance, and mPTP regulation to increase resistance to I/R injury.

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THE ROLE OF P2Y11 RECEPTOR SIGNALING IN CARDIOVASCULAR PROTECTION

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Background & Aim: Chronic inflammation is a defining feature of cardiovascular diseases, playing a crucial role in the progression of these conditions as well as the development of long-term complications. During the inflammatory response, a large amount of ATP is released, which subsequently activates various purinergic receptors, including P2Y11. This receptor is found in several cell types, such as cardiomyocytes, fibroblasts, endothelial cells, and immune cells. The aim of the studies was to evaluate the effects of purinergic modulation on: (i) human AC16 cardiomyocytes viability after hypoxia/reoxygenation (H/R); (ii) vascular function after lipopolysaccharide-induced inflammation in rats.
Material & Methods: Cultured AC16 cardiomyocytes were exposed to a 5h hypoxic episode via the hypoxic chamber or mineral oil layering. For the same duration control AC16 cells were kept in a normoxic incubator, receiving no additional intervention at reperfusion. H/R cardiomyocytes were treated with different ATP concentrations (10μM, 100μM, 1mM) in the presence vs. the absence of 100μM/300μM suramin, a broad-spectrum purinergic inhibitor. Cellular viability was assessed by MTT colorimetric assay and expressed relative to the absorbance of the non-treated cells. In parallel experiments, thoracic aortas isolated from rats acutely treated (12h) with lipopolysaccharide (LPS, 8 mg/kg, i.p) were used for the evaluation of vascular reactivity (organ bath experiments) and oxidative stress (ferrous oxidation xylenol orange/FOX assay for hydrogen peroxide) after purinergic P2Y11 receptor modulation with its specific agonist (NF546) and antagonist (NF340), respectively.
Results: In AC16 cardiomyocytes 100μM ATP improved relative cell viability in hypoxic chamber (but not mineral oil layering) experiments, while suramin mitigated this beneficial effect. In the presence of 1 mM ATP, regardless the co-administration of suramin, a significant increase of relative cell viability was recorded in H/R experiments using both methods of hypoxia induction. In vascular reactivity experiments, NF_{546} (10μmol) mitigated the LPS-induced detrimental effects, by reducing vascular H_2O_2 generation and improving aortic segments endothelial-dependent relaxation, most likely due to increased NO availability. NF_{340} (10μmol) abolished this P2Y11 receptor-dependent protection.
Conclusion: Modulation of purinergic signaling elicits cardiovascular protection, suggesting that purinergic receptors P2Y11 may be a novel therapeutic target in the setting of ischemia/reperfusion injury and inflammation.

THE ROLE OF DIMETHYL FUMARATE IN THE HEART OF FEMALE HYPERTRIGLYCERIDEMIC RATS EXPOSED TO CHRONIC PSYCHOSOCIAL STRESS

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Stress is a significant factor involved not only in the development, but also in the progression of non-communicative diseases, especially in individuals with a genetic predisposition. This study investigated the effects of chronic social stress and dimethyl fumarate (DMF), an NRF2 activator, on systolic blood pressure (BP), heart rate (HR), expression of NRF2, its target genes and activity of antioxidant enzymes in the heart of female hypertriglyceridemic (HTG) rats.

Four groups of adult female HTG rats were investigated: 1) control rats (treated with vehicle, 0.25% DMSO, p.o.), 2) stress-exposed rats (4-weeks crowding, 5 rats/cage, 182 cm^2/rat), 3) DMF-treated rats (20 mg/kg/day in the vehicle for 4 weeks, p.o.), and 4) rats exposed to 4 weeks of stress simultaneously with DMF treatment.

In contrast to male HTG rats, stress and DMF had no effect on SBP and HR measured by the tail-cuff method. QRT-PCR revealed significant upregulation of *Nfe2l2 and* its target genes *Sod1, Sod2, Fth1,Ppara* and *Gpx4* after DMF treatment. However, Western blot analysis detected no corresponding increases in protein expression of these antioxidants. In the heart, the activity of glutathione peroxidase was not affected by DMF or stress, but stress resulted in increased activity of superoxide dismutase (SOD). Notably, this elevation in SOD activity occurred independently of NRF2 activation, as stress induced no changes in expression of NRF2 or target genes at either mRNA or protein levels.

In conclusion, cardioprotective benefits of DMF in the heart may be mediated primarily through transcriptional activation of NRF2 and antioxidant genes, while the significant post-transcriptional modifications seems to be key barriers limiting NRF2 pathway efficacy.

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ROLE OF LEPTIN IN THE PATHOGENESIS OF OBESITY-ASSOCIATED PLATELET HYPERACTIVITY AND ABNORMALITIES OF COAGULATION/ FIBRINOLYSIS BALANCE: IMPLICATIONS FOR CARDIOVASCULAR DISEASES

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Background. Leptin is the adipose tissue hormone involved in the regulation of food intake and energy expenditure. Plasma leptin concentration is increased in obese individuals and hyperleptinemia is suggested to be involved in the pathogenesis of obesity-associated diseases such as atherosclerosis. Leptin has been shown to promote platelet activity, the effect important for the growth and complications of atherosclerotic plaque, but the underlying mechanism is not clear. We examined the effect of exogenous leptin on platelet activity and coagulation-fibrinolysis balance. In addition, we examined if endogenous hyperleptinemia is involved in obesity-associated abnormalities of this balance by using specific leptin receptor antagonist.
Materials & Methods. The study was performed in adult male rats divided in the following groups: (1) control, (2) leptin-treated (0.5 mg leptin/kg/day in osmotic minipumps), (3) obese, fed high-calorie diet for 1 month, (4) obese treated with PEG-ylated superactive leptin receptor antagonist (PEG-SLRA, 7 mg/kg every other day), (5) fed regular diet and treated with PEG-SLRA.
Results. Both obesity and hyperleptinemia were associated with higher plasma and urinary TXB2, the metabolite of thromboxane A2 and the marker of platelet activity *in vivo*. However, fibrinogen- or ADP-induced platelet aggregation ex vivo was not changed. Both hyperleptinemia and obesity increased plasma concentration of homocysteine thiolactone and fibrinogen N-homocysteinylation (the ratio between N-homocysteinylated and total fibrinogen). Fibrinogen isolated from hyperleptinemic or obese rats stimulated aggregation of control platelets more potently than fibrinogen isolated from control rats. In addition, fibrinogen isolated from hyperleptinemic or obese rats was more resistant to fibrinolysis. These effects were reproduced when control fibrinogen was incubated with homocysteine thiolactone in vivo. PEG-SLRA administered to obese rats did not improve the metabolic profile but reduced fibrinogen N-homocysteinylation, decreased the ability of isolated fibrinogen to stimulate platelet aggregation ex vivo and increased the sensitivity of fibrinogen to fibrinolysis. In addition, PEG-SLA reduced plasma and urinary TXB2 and serum P-selectin.
Conclusions. Obesity is associated with greater fibrinogen N-homocysteinylation and N-homocysteinylated fibrinogen is the more potent activator of platelet aggregation and is more resistant to fibrinolysis. These effects are partially accounted for by hyperleptinemia because are reproduced by exogenous leptin and attenuated by leptin receptor antagonist. The results suggest that inhibiting leptin signaling may be the novel approach to reduce atherosclerosis development as well as arterial and venous thrombosis risk associated with obesity.

METABOLIC CONTROL OF PLATELET REACTIVITY: CAN WE IMPROVE ANTIPLATELET THERAPY?

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Platelets are increasingly recognized as metabolically active cell fragments whose functional responses depend on dynamic adaptation of metabolic pathways. In resting platelets, mitochondrial oxidative phosphorylation is a major source of ATP, whereas upon activation glycolysis rapidly increases to support secretion, shape change, integrin activation, and aggregation. This metabolic flexibility is essential for normal hemostasis, but it may also contribute to platelet hyperreactivity in cardiometabolic disorders and reduced responsiveness to conventional antiplatelet therapy.

This lecture summarizes previous and recent studies examining whether mild pharmacological modulation of platelet energy metabolism can enhance the effects of established antiplatelet agents. Rather than inducing profound metabolic inhibition, these approaches focused on subtle interference with both glycolytic and mitochondrial pathways, including the use of carbon monoxide-releasing molecule A1 (CORM-A1), as well as the combination of 2-deoxyglucose with oligomycin.

Earlier studies demonstrated remarkable metabolic flexibility of platelets and showed that mild simultaneous modulation of the two major ATP-generating pathways can potentiate cangrelor-induced platelet inhibition. More recent observations indicate that similar interactions may also occur with other $P2Y_{12}$ antagonists, whereas comparable effects were not observed with antiplatelet agents acting outside the $P2Y_{12}$ pathway, suggesting pharmacological selectivity rather than nonspecific suppression of platelet function.

Available mechanistic data suggest that reduced ATP availability may contribute to these effects, although ATP depletion alone does not fully explain the magnitude of platelet inhibition. Additional metabolic and redox alterations indicate broader remodeling of platelet bioenergetics.

Together, these findings support the concept that platelet metabolic state influences responsiveness to antiplatelet therapy. Mild co-targeting of glycolysis and oxidative phosphorylation may represent a novel adjunctive strategy to improve platelet inhibition, particularly in conditions associated with residual platelet reactivity such as diabetes, obesity, and metabolic syndrome. These interactions may also be relevant in conditions associated with metabolic decline, where altered platelet sensitivity to antiplatelet therapy could influence both efficacy and safety.

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METHYLENE BLUE AS A REDOX MODULATOR IN CARDIO-METABOLIC DYSFUNCTION

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Background and objectives. Coronary heart disease, diabetes and obesity-related cardiovascular complications share common pathogenic mechanisms, including mitochondrial dysfunction, abnormal energy metabolism and oxidative stress. Epicardial adipose tissue (EAT) and perivascular adipose tissue (PVAT) are biologically active cardiovascular fat depots involved in inflammation, endothelial dysfunction and atherosclerosis. Monoamine oxidases (MAOs), mitochondrial enzymes that generate hydrogen peroxide during amine metabolism, may contribute to oxidative injury in these tissues. Methylene blue (MB), a redox-active compound with mitochondrial-modulating properties and inhibitory effects on MAO-related oxidative stress, may represent a potential therapeutic candidate. This study aimed to evaluate the effects of MB on mitochondrial bioenergetics, endothelial function and MAO-dependent oxidative stress in experimental and human cardiovascular models.
Materials and methods. Mitochondrial bioenergetics was assessed in H9c2 cardiomyoblasts and isolated rat heart mitochondria using extracellular flux analysis and high-resolution respirometry. Hydrogen peroxide production and calcium retention capacity were evaluated by spectrofluorimetry, while endothelial function was studied in isolated rat aortic rings by organ bath myography. Human EAT and PVAT samples obtained from coronary patients undergoing cardiac surgery were incubated with MB (0.1 µM, 24 h) and analyzed for ROS production, MAO expression, and immunofluorescence localization.
Results. Low-dose MB (0.1 µM) improved the bioenergetic profile of H9c2 cells by increasing oxygen consumption and extracellular acidification rates, whereas higher concentrations reduced these parameters in a dose-dependent manner. In isolated rat heart mitochondria, MB enhanced respiratory function and modulated hydrogen peroxide production in a substrate-dependent manner. MB also reduced vascular oxidative stress and partially restored endothelial-dependent relaxation in isolated aortas. In human EAT and PVAT, both MAO isoforms were detected, with predominance of MAO-A. MB reduced MAO expression and ROS generation, including serotonin-enhanced MAO-A-dependent oxidative stress.
Conclusion. Methylene blue exerts protective redox-related effects in cardio-metabolic dysfunction by improving mitochondrial bioenergetics, reducing oxidative stress, partially restoring endothelial function and limiting MAO-associated ROS production in cardiovascular adipose tissue. These findings support MB as a potential candidate for drug repurposing in coronary and metabolic cardiovascular disease.

MITOCHONDRIAL RESPIRATORY DYSFUNCTION IN PREECLAMPSIA: PLATELETS MIRROR WHEN PLACENTA STRUGGLES TO BREATHE

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Background & Aim: Preeclampsia (PE) is part of the spectrum of hypertensive diseases in pregnancy, a feature of high-risk pregnancy and a frequent complication that arises after 20 weeks of gestation. It is defined as new-onset hypertension plus one of the following organ involvements: proteinuria, low platelet count, acute kidney injury, coagulopathy, hemolysis, liver involvement, neurological complications, and fetal growth restriction (FGR). A growing body of research has unequivocally demonstrated the role of mitochondrial dysfunction and oxidative stress as central mechanisms underlying the abnormal placentation in PE. Recent advances in clinical training, prediction models, and biomarker-based screening have improved early diagnosis and reduced mortality, yet the precise etiology remains unclear. The present study was aimed at assessing the mitochondrial respiratory function in platelets and isolated placental mitochondria. A secondary objective was to evaluate the placental oxidative stress.
Materials & Methods: Fifty seven subjects were included in two groups: i) the platelet study group (n=33, with 3 subgroups: PE, healthy pregnancies & age-matched controls) and ii) the placenta study group (n=24, with 3 subgroups: PE with or without FGR & healthy pregnancies). Mitochondrial respiration of isolated platelets and placental mitochondria was assessed by means of high-resolution respirometry according to a protocol adapted to measure complex I and complex II-dependent respiration. Placental samples (central and peripheral regions) were collected and stored at -80; cryosections were incubated with dihydroethidium and analysed in confocal microscopy.
Results: Platelets isolated from preeclamptic pregnancies expressed a lower coupled and uncoupled respiration as compared to both healthy pregnancies and controls. Placental mitochondria harvested from PE associated with FGR showed a decrease in both active and maximal uncoupled respiration for both mitochondrial complexes. Contrary, placental mitochondria isolated from PE without FGR showed an increase in both active and maximal uncoupled respiration. The severe forms of preeclampsia presented increased oxidative stress in both placental regions as compared to mild preeclampsia.
Conclusion: Preeclampsia is characterized by mitochondrial dysfunction in both platelets and placentas and is associated in the severe cases with widespread placental oxidative stress.

COMPARISON OF BLOOD BIOMARKERS BETWEEN PROFESSIONAL FOOTBALL PLAYERS AND RECREATIONAL ATHLETES: IS THERE A RELIABLE MARKER OF OVERTRAINING?

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Background & Aim: Various biomarkers have been proposed to monitor training load and serve as markers of systemic fatigue and overtraining (OT). However, many parameters and suggested reference ranges have not been further validated, and discrepancies remain in the available data. Only a limited number of studies have investigated OT in elite athletes compared with non-elite athletes. Hormonal analyses, such as cortisol and testosterone, are among the most commonly studied. This study aims to examine correlations among hormonal biomarkers in elite football players across two parts of the season and to compare these parameters with those of recreational athletes.
Materials & Methods: The study included 88 healthy male professional football players with a mean age of 23.94 ± 4.5 years. The first test was conducted during the pre-season preparation period (PRE). The second was performed at the end of the first part of the season (6 months later, POST). The control group comprised 42 healthy, age-matched male recreational athletes (CONT), aged 22.84 ± 2.97 years, who reported 6.81 ± 2.64 training hours per week. The sports medical screening exam included hormonal analyses of cortisol (nmol/L), total testosterone (TT, nmol/L), and prolactin (mIU/L).
Results: Cortisol showed a statistically significant difference in PRE vs CONT (385.58 ± 82.53, 430.73 ± 101.40; $p<0.05$) and PRE vs POST (385.12 ± 87.27, 415.77 ± 75.92; $p<0.05$; change +8.86%). TT differed in POST vs CONT (25.13 ± 6.27, 20.30 ± 5.61; $p<0.001$) and PRE vs POST (22.39 ± 6.27, 25.13 ± 6.27; $p<0.01$; change +13.84%). TT/Cortisol ratio differed in PRE vs CONT (0.06 ± 0.02, 0.05 ± 0.02; $p<0.05$) and POST vs CONT (0.06 ± 0.02, 0.05 ± 0.02; $p<0.05$), but not in PRE vs POST. Difference in prolactin was observed only in PRE vs POST (358.33±145.48, 329.17±117.07; $p<0.05$; change -5.02%).
Conclusion: Biomarker results are inconsistent over time and across the investigated population. Currently, a personalized approach to systemic fatigue monitoring that combines several biomarkers, their changes over time, and internal and external training load measurements is optimal, as no biomarker is clearly associated with systemic fatigue on its own.

INTEGRATED FUNCTIONAL AND GENOMIC PROFILING OF LMNA-RELATED DILATED CARDIOMYOPATHY

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Dilated cardiomyopathy linked to *LMNA* mutations is a devastating condition characterized by dangerous arrhythmias, weakened heart muscle, and excessive fibrosis. These factors work together to drive heart failure. The underlying mechanisms are unclear while developing effective treatments has remained a significant hurdle.
To bridge this gap, we studied the functional and molecular roots of the disease using two models: human induced pluripotent stem cells (hiPSCs) collected from a patient with a specific *LMNA* mutation (c.665A>C, p.His222Pro) and a corresponding mouse model carrying the same genetic change.
Our findings revealed that heart muscle cells (cardiomyocytes) derived from the patient struggled to manage intracellular calcium properly, leading to high diastolic levels and a diminished response to calcium signals, which ultimately resulted in cardiac hypocontractility. We also observed the telltale signs of *LMNA*-related disease: abnormally shaped cell nuclei, which were linked to disorganized chromosomes and shifts in gene activity. Digging deeper into the transcriptomics, we found a clear pattern of dysregulated extracellular matrix remodeling, with a notable spike in *Loxl2* levels across both our human tissue models and the mouse model. Crucially, when we treated the mice with Simtuzumab, a LOXL2 inhibitor, we were able to effectively prevent both heart dysfunction and fibrosis.
These findings identify LOXL2 as a critical therapeutic target. Our work suggests that targeting this protein could offer a promising, practical strategy for protecting cardiac function in patients suffering from *LMNA*-associated cardiomyopathy.

LESS IS MORE: THE PARADOXICAL BENEFIT OF MYOSIN INHIBITION ON CARDIAC RESERVE

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Selective cardiac myosin inhibitors, including mavacamten and aficamten, represent a novel therapeutic approach in hypertrophic obstructive cardiomyopathy (HOCM), where hypercontractility driven by increased myofilament Ca^{2+}-sensitivity underlies left ventricular outflow tract obstruction and diastolic dysfunction. While these agents effectively reduce contractile force, a key unresolved question has been whether myosin inhibition compromises cardiac reserve - particularly in light of the obligatory monitoring of left ventricular ejection fraction (LVEF) during treatment.

To address this, we characterized the effects of aficamten across multiple levels of cardiac organization. In permeabilized cardiomyocytes from rat, dog, healthy human donor, and HCM patient myocardium, aficamten reduced maximal active force (Fmax) and myofilament Ca^{2+}-sensitivity (pCa_{50}) at concentrations approximating its IC_{50}. Critically, however, length-dependent activation (LDA) - the cellular basis of the Frank-Starling mechanism - was largely preserved at both short (1.9 µm) and long (2.3 µm) sarcomere lengths in both rat and canine preparations. In intact canine cardiomyocytes loaded with the Ca^{2+}-indicator Fura-2, aficamten shortened contraction duration and accelerated relaxation across a range of stimulation frequencies (0.25–1.25 Hz) without altering Ca^{2+} transient amplitude or duration, indicating a purely myofilament-level mechanism of action. In sedated rats administered aficamten intravenously (2 mg/bwkg), echocardiographic assessment revealed a significant reduction in LVEF across pacing frequencies of 200–400 bpm. In contrast, end-diastolic volume (EDV) increased substantially, end-systolic volume (ESV) was moderately elevated, and cardiac output (CO) remained unchanged - demonstrating that enhanced ventricular filling, mediated by improved diastolic function, recruits length-dependent activation to maintain stroke volume and CO despite reduced ejection fraction.

These findings support a mechanistic framework in which myosin inhibition, by normalizing hypercontractility and improving diastolic relaxation, paradoxically enhances cardiac reserve through Frank-Starling recruitment. The data suggest that CO or stroke volume may be more appropriate monitoring parameters than LVEF during myosin inhibitor therapy. Sarcomere length is more - even when myosin is less.

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MORE IS LESS: WHY DIRECT MYOSIN ACTIVATION FAILS TO TRANSLATE INTO IMPROVED IN VIVO CARDIAC OUTPUT

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Traditional inotropic therapies for heart failure with reduced ejection fraction (HFrEF) improve systolic performance at the expense of altered intracellular Ca^{2+} cycling, which inherently increases arrhythmia risks and myocardial oxygen demand. Direct cardiac myosin activation emerged as a revolutionary, Ca^{2+}-independent alternative designed to selectively enhance cardiomyocyte contraction without these classical drawbacks. However, despite this promising mechanism, the flagship compound omecamtiv mecarbil failed to demonstrate sufficient clinical efficacy in large-scale trials, highlighting a poorly understood translational gap.

To resolve this paradox, we evaluated the mechanical, cellular, and hemodynamic consequences of direct myosin activation across the complete cardiac cycle. At the cellular level, myosin activators successfully increased cardiomyocyte contraction and prolonged total contraction time without affecting intracellular Ca^{2+} cycling, confirming a pure myofilament-directed mechanism. However, this intervention also induced a critical on-target side effect: a significant reduction in cardiomyocyte length during the diastolic state. *In vivo,* this cellular shortening translated into a progressive reduction in ventricular diameter and a pathological shrinking of end-diastolic ventricular volumes. Consequently, while direct myosin activation significantly increased the left ventricular ejection fraction, this metric was deceptively elevated by a smaller, shrunken ventricle rather than a genuine increase in forward stroke volume. Crucially, during elevated heart rates or physiological stress, the combination of a compressed diastolic filling window and reduced ventricular volumes prevented utilization of the Frank-Starling mechanism, ultimately failing to improve total cardiac output.

These findings expose a fundamental clinical misconception in heart failure therapeutics, demonstrating that a higher ejection fraction does not equate to improved cardiac output when driven by an on-target diastolic penalty. Ultimately, this work establishes that future drug discovery must move past isolated systolic ejection metrics and focus instead on integrated measures of translational efficacy that preserve diastolic volume and relaxation

A COMPREHENSIVE DIAGNOSTIC AND THERAPEUTIC APPROACH TO OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

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Obstructive hypertrophic cardiomyopathy (OHCM) remains a complex cardiovascular disease requiring accurate diagnosis, risk stratification, and individualized therapeutic management. According to the latest European Society of Cardiology guidelines, multimodality imaging plays a central role in the diagnostic process, particularly transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (CMRI). Clinical presentation may vary widely, ranging from asymptomatic individuals to patients with severe heart failure symptoms. Physical examination findings are typically consistent with heart failure, and a systolic murmur may also be present. Multimodality imaging assessment represents the cornerstone of the diagnostic evaluation. Current guidelines recommend TTE at rest and during provocative maneuvers, while contrast-enhanced CMR is particularly valuable before invasive therapeutic procedures.
Typical ETT findings include asymmetric left ventricular (LV) hypertrophy, predominantly involving the interventricular septum, systolic anterior motion of the mitral valve, and left ventricular outflow tract (LVOT) obstruction. Doppler evaluation allows accurate assessment of LVOT gradients and mitral regurgitation severity and mechanism. Evaluation of both left and right ventricular systolic function is also essential. In patients with low resting gradients, provocative maneuvers such as the Valsalva maneuver or exercise stress testing are recommended. Transesophageal echocardiography is reserved for selected cases to further clarify the mechanism of obstruction and assess mitral regurgitation.
Therapeutic management has evolved significantly in recent years. First-line medical therapy includes beta-blockers, followed by disopyramide or the newer class of cardiac myosin inhibitors, according to current guidelines. The introduction of myosin inhibitors has led to remarkable symptomatic improvement in patients with OHCM and represents a major advancement in disease management. These agents have recently become available in our country, including in our center.
In patients with persistent symptoms and significant LVOT obstruction despite optimal medical therapy, septal reduction therapies are indicated, like alcohol septal ablation or surgical myectomy.Equally important is the evaluation of sudden cardiac death risk through ECG Holter monitoring and comprehensive clinical assessment. Genetic testing and family screening are mandatory components of patient management.
A multidisciplinary and personalized approach can significantly improve prognosis and quality of life, allowing many patients with OHCM to achieve an almost normal life expectancy and functional status.

TARGET DISCOVERY IN HEART FAILURE FROM IPSC STEM CELLS AND BAT BIOLOGY

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Heart failure (HF) is one of the leading causes of death and disability worldwide. New treatments are needed to improve cardiac function in order to improve clinical outcomes in patients with HF. We have used 2 different approaches to discover new treatment targets for preventing the onset and progression of HF. Firstly, we have generated human induced pluripotent stem cell-derived cardiomyocytes from patients with heart failure to model cardiac disease to elucidate underlying mechanistic pathways and discover new treatment targets for HF for inherited cardiomyopathies (such as hypertrophic cardiomyopathy) and more recently heart failure with preserved ejection fraction (HFpEF). Secondly and most recently, we have been investigating the cardiometabolic adaptation of the bat heart to discover novel treatment targets for HF.

VASCULAR (DYS) FUNCTION IN THE FAILING HEART

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Heart failure (HF) is not confined to contractile failure of cardiomyocytes or myocardial fibrosis. Coronary and systemic vascular dysfunction contributes to the initiation and progression of HF with or without reduced ejection fraction. Furthermore, HF compromises vascular function, creating and sustaining a vicious cycle with deranging effects on coronary blood flow, cardiac metabolism and cardiac function. In HF, systemic arterial dysfunction, characterized by increased arterial stiffness and resistance, raises cardiac afterload and impedes myocardial contractile function. Reduced coronary blood flow impairs myocardial oxygen delivery and consequently cardiomyocyte metabolism and function. Coronary microvascular dysfunction is heterogeneous in its pathogenesis and manifestations, complicating the diagnosis and management across different HF phenotypes. Understanding the alterations in function in different segments of the vasculature, from the aorta to the capillary level, offers mechanistic insights into disease drivers and therapeutic interventions. Interventional approaches can improve vascular hemodynamics, whereas established and emerging pharmacotherapies target the neurohumoral axis and reduce extravascular compression, inflammation, and oxidative stress, thereby improving vascular function and HF-related outcomes. In this presentation, I will provide a mechanistic framework of vascular dysfunction in the pathogenesis of HF with or without reduced ejection fraction, pointing towards integrated therapies that consider the vascular implications of contemporary HF management across HF phenotypes.

CARDIAC REMODELLING IN WISTAR RATS WITH EARLY POSTNATAL PRESSURE OVERLOAD: SEX DIFFERENCES AND THE ROLE OF THE PROLIFERATIVE PHASE OF CARDIAC DEVELOPMENT

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Pressure overload-induced cardiac remodelling can result in life-threatening arrhythmias or heart failure. Early postnatal abdominal aortic constriction (AAC) is a unique experimental model with the potential to mimic some congenital heart diseases and thus study the outcomes of increased pressure load in the early postnatal period on the onset of cardiac remodelling. This work aimed to determine the impact of increased pressure load applied in the early postnatal period on the development of left ventricular (LV) geometry and function in Wistar rats, emphasizing sex differences. AAC was induced by ligation of the aorta (internal diameter of the ligature 0.25 mm) in the subdiaphragmatic suprarenal region on postnatal day 2. In control groups, the aorta was exposed but not constricted. Cardiac function and geometry were assessed by echocardiography. Cardiac electrophysiology was evaluated by optical mapping, and myocardial fibrosis was assessed by immunohistochemistry.
At postnatal day 90, AAC resulted in LV dilatation and LV wall thickening in both males and females with AAC compared to controls (LVD_d: 9.26±0.23mm vs. 8.10±0.12mm and 8.15±0.27mm vs. 7.15±0.09 mm, respectively and AWT_d: 3.59 ± 0.14 mm vs. 3.10 ± 0.07 mm and 3.20 ± .011 mm vs.2.42 ± 0.11 mm, respectively). Enlargement of LV expressed as LVW/BW was similar in males and females compared to sham-operated animals (LVW/BW ratio increased by 103 ± 9 % and 99 ± 10 %, respectively). AAC also led to a decrease in systolic function in both males and females (FS: 30.3 ± 1.4 % vs. 41.6 ± 1.0 % and 33.4 ± 1.8 % vs.43.2 ± 0.9 %, respectively) and a decrease in heart rate (HR: 313 ± 7 BPM vs. 368 ± 7 BPM and 327 ± 15 BPM vs. 364 ± 5 BPM, respectively). However, cardiac output was not altered in both sexes. RVW/BW and lung/BW ratios were increased in AAC animals compared to controls and were higher in males than in females with AAC, indicating progressive cardiac dysfunction in AAC males. AAC-induced cardiac remodelling was also associated with higher levels of myocardial fibrosis in males than in females. Moreover, conduction velocity (CV) in males with AAC decreased compared to controls (CV_L 80 ± 3 vs. 92 ± 3 cm/s and CV_T 35 ± 2 vs. 54 ± 3 cm/s) but was preserved in females compared to controls (CV_L 104 ± 8 vs. 109 ± 8 cm/s and CV_T 66 ± 7 vs. 59 ± 6 cm/s).
Our data show that early postnatal exposure to pressure overload leads to similar alterations in cardiac geometry in males and females. However, AAC-induced cardiac remodelling exhibits sex-related differences resulting in pro-arrhythmogenic alterations in males but not females.

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THE NON-INFERIORITY TRAP: LESSONS FROM CONTEMPORARY CARDIOLOGY TRIALS

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Background & Aim: Non-inferiority trials are increasingly used in contemporary cardiology, particularly when new interventions offer potential advantages in safety, convenience, invasiveness, device profile, or patient preference rather than superior efficacy. However, their interpretation is frequently less intuitive than superiority trials and is vulnerable to methodological and rhetorical misuse. This talk aims to clarify the logic of non-inferiority trial design and highlight recurrent interpretive pitfalls using recent cardiology examples.
Materials & Methods: The presentation will combine methodological explanation with case-based critical appraisal. Core concepts will include the choice and justification of the non-inferiority margin, preservation of historical treatment effect, intention-to-treat versus per-protocol interpretation, event-rate assumptions, follow-up duration, composite endpoints, competing risks, and the distinction between statistical non-inferiority and clinical acceptability. These concepts will be applied to contemporary cardiovascular trials, including the PRAETORIAN trial comparing subcutaneous and transvenous implantable cardioverter-defibrillators, as well as left atrial appendage occlusion trials from early pivotal studies to more recent randomized evidence.
Results: Across these examples, several recurring problems emerge. Non-inferiority conclusions may appear persuasive despite wide confidence intervals, generous margins, low event rates, heterogeneous composite endpoints, or endpoint components that differ in clinical relevance. Apparent equivalence may conceal trade-offs between efficacy and safety, or between procedural complications and long-term protection from clinically important events. Device and procedural trials are particularly prone to these issues because comparator performance, operator learning curves, patient selection, and outcome adjudication may substantially influence results.
Conclusion: Non-inferiority trials are not "negative superiority trials" and should not be interpreted as proof that two strategies are clinically interchangeable. Their validity depends on whether the design preserves a meaningful fraction of established benefit and whether the trade-offs are acceptable to patients and clinicians. A disciplined reading of margins, endpoints, confidence intervals, and clinical context is essential to avoid the non-inferiority trap in cardiology.

THERAPEUTIC EFFECTS OF *GALIUM VERUM L.* EXTRACT IN AN EXPERIMENTAL MODEL OF APHTHOUS STOMATITIS

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Aphthous stomatitis represents the most prevalent chronic ulcerative diseaseof the oral mucosa. It can be classified into three clinical forms based on ulcer characteristics. Treatment is primarily aimed at alleviating symptoms, most commonly through the use of antiseptics. In recent years, phytotherapy has gained attention as an alternative therapeutic approach. Due to its diverse biological effects, particularly in wound healing, *Galium verum L.* has been identified as a promising agent for the management of aphthous stomatitis.

This study aimed to evaluate the therapeutic potential of *Galium verum L.* extract in the treatment of aphthous stomatitis using an experimental rat model. The study included 80 Wistar albino rats with aphthous stomatitis, which were randomly assigned to four groups. The progression and healing of lesions were monitored daily. Animals were euthanized on days 0, 3, 6, and 10, after which blood and buccal tissue samples were collected for further analyses. In addition to clinical assessment, treatment effects were evaluated through histological examination, as well as by analyzing inflammatory and oxidative stress markers using PCR and spectrophotometric methods.

Our results clearly showed that formulations containing *G. verum* extract significantly decreased ulcer size, improved histopathological scores, and reduced the level of inflammation in aphthous lesions. While no significant changes were observed in systemic redox balance, evident effects were detected locally within buccal tissue.

In conclusion, the use of *G. verum* extract in the treatment of aphthous stomatitis contributes to faster lesion healing and represents a promising therapeutic option for oral ulcerations.

HORMETIC EFFECTS OF POLYPHENOL-RICH *CORNUS MAS* ON REDOX BALANCE: EVIDENCE FROM ANIMAL AND HUMAN STUDIES

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Background & Aim: Polyphenols are widely recognized for their antioxidant and anti-inflammatory properties; however, increasing evidence suggests that their biological effects are context-dependent and may follow a hormetic dose–response relationship. This study investigated the effects of dried fruits of *Cornus mas* on nitric oxide production and redox balance in obese Zucker rats and, based on these findings, evaluated its effects in a pilot clinical study in individuals with dyslipidemia.
Materials& Methods: Male Zucker rats were divided into control and groups treated with *Cornus mas* varieties Koralovij Marka (KM) and Wild Type (WT) (5 g/kg/day, n = 6 per group) for 6 weeks. Nitric oxide synthase (NOS) activity and expression of endothelial NOS (eNOS), superoxide dismutase (SOD), and NADPH oxidase were assessed in the left ventricle (LV) and aorta. Plasma lipid profile was analyzed. The human study included 50 participants with dyslipidemia randomized to receive either 70 g of lyophilized *Cornus mas* or lyophilized apple (placebo) daily for 6 months.
Results: WT reduced total cholesterol and LDL levels. Both KM and WT increased NOS activity in the aorta, with no effect in the LV. KM increased eNOS expression without affecting oxidative parameters, whereas WT enhanced antioxidant defense by increasing SOD and reducing NADPH oxidase expression, without changes in eNOS. In the human study, no significant differences were observed between the *Cornus mas* and placebo groups overall. However, stratification by prior COVID-19 infection revealed that *Cornus mas* supplementation was associated with decreased antioxidant markers, including TAC and plasma thiol groups in individuals with previous COVID-19.
Conclusion: These findings suggest that polyphenol-rich *Cornus mas* exerts differential and context-dependent effects. The experimental data indicate predominantly vasoprotective and antioxidant actions, whereas the clinical results point to a potential hormetic response, particularly in individuals with altered redox status following COVID-19. In this subgroup, long-term supplementation with *Cornus mas* may shift its effects toward a pro-oxidative profile rather than the expected antioxidant action. Together, these observations highlight the complexity of polyphenol activity and underscore the importance of physiological context and baseline redox status in determining their biological effects.

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CARDIOPROTECTION IN THE DIABETIC HEART: EFFECT OF QUERCETIN

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Diabetic heart is characterized by several metabolically driven morphological and functional changes in comparison to the healthy non-diabetic heart, including cardiac hypertrophy and fibrosis, ventricular remodeling and microvascular dysfunction, leading to diastolic dysfunction and potentially reduced systolic function. Over time, diabetic cardiomyopathy (DCM) may develop and lead to heart failure (HF). Therefore, cardioprotective strategies are urgently needed to prevent the development of DCM and HF in the diabetic heart. Furthermore, given the changes induced by diabetes, cardioprotection in the diabetic heart, e.g., against myocardial infarction, may be influenced by diabetes as a major metabolic comorbidity.
In our previous studies, we demonstrated that the natural flavonoid quercetin (QCT) exerted robust cardioprotective effects in prevention of ischemia-reperfusion (I/R) injury in healthy non-diabetic hearts. The aim of the current study was to evaluate the cardioprotective potential of quercetin in diabetic heart, both in terms of prevention of the development of DCM and protection against I/R injury in the presence of diabetes as a comorbidity.
Zucker diabetic fatty rats (ZDF) (animal model of type 2 diabetes - T2DM) at two different age categories, 6-month-old and 1-year-old, were used in the study. QCT at a dose of 20 mg/kg/day was administered orally for 6 weeks. The effect of QCT on cardiac morphology and function *in vivo* were monitored by echocardiography. After the end of treatment, hearts were isolated and subjected to I/R *ex vivo* (30-min global ischemia/2-h reperfusion). Recovery of cardiac function and infarct size were assessed as physiological outcomes. Molecular signaling pathways involved in the effect of QCT were assessed by Western blotting.
The results showed that QCT has cardioprotective effects on the diabetic heart *in vivo* by preventing development of diastolic dysfunction and fibrosis but is ineffective in preventing I/R injury in T2DM rat hearts. In conclusion, QCT may potentially prevent the development of DCM in diabetic rats, but diabetes and aging may reduce or even abolish anti-ischemic effects of QCT.

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TARGETING THE HOMOCYSTEINE-OXIDATIVE STRESS AXIS WITH FOLATE AND VITAMIN B6: CARDIOPROTECTION IN DIABETES AND HEART FAILURE

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Diabetes mellitus (DM) and heart failure (HF) are highly prevalent and interconnected cardiovascular disorders, sharing key pathophysiological mechanisms including oxidative stress, endothelial dysfunction, and impaired homocysteine metabolism. We hypothesized that supplementation with folic acid and vitamin B6 could ameliorate cardiometabolic alterations in two well-established experimental models: streptozotocin (STZ)-induced type 1 DM and monocrotaline (MCT)-induced HF.
Homocysteine, a sulfur-containing amino acid intermediate in methionine metabolism, accumulates in the setting of B-vitamin deficiency and has been recognized as an independent risk factor for cardiovascular disease. Its prothrombotic and prooxidant properties promote reactive oxygen species (ROS) generation, endothelial dysfunction, vascular smooth muscle proliferation, and lipid peroxidation. In experimental DM, hyperhomocysteinemia amplifies oxidative stress and contributes to diabetic complications, while in MCT-induced HF, elevated homocysteine is associated with impaired cardiac function and adverse myocardial remodeling.Vitamin B6 (pyridoxal 5′-phosphate) plays a central role in homocysteine transsulfuration and exhibits antioxidant and anti-inflammatory effects, while folic acid, via its active metabolite 5-methyltetrahydrofolate, supports homocysteine remethylation, improves endothelial nitric oxide synthase (eNOS) coupling, and enhances nitric oxide bioavailability.
Our experimental data demonstrate that folic acid and vitamin B6 administration in diabetic rats attenuates cardiac oxidative stress, reflected by normalization of superoxide dismutase (SOD) and catalase activity. In monocrotaline-induced HF, combined treatment with vitamin B6 and folic acid significantly reduced elevated SOD activity and improved cardiometabolic biomarkers, although without significant effects on glutathione peroxidase activity or thiol group content. These results indicate partial restoration of redox balance and suggest a modulatory effect on myocardial adaptation.
These findings suggest that supplementation with folic acid and vitamin B6 may offer a promising adjunctive therapeutic strategy in both DM and HF by targeting the homocysteine–oxidative stress axis. Future translational research should aim to define optimal dosing strategies and evaluate long-term cardiovascular outcomes in at-risk populations.

SILVER NANOPARTICLE-POTENTIATED ANTIBIOTIC THERAPY IN A PORCINE MODEL OF SEPSIS – ARE THE ANIMAL MODELS NECESSARY?

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Background & Aim: The emergence of multidrug-resistant pathogens has renewed interest in adjunctive antimicrobial strategies. Silver nanoparticles (AgNPs) exhibit broad-spectrum antibacterial activity and *in vitro* synergy with conventional antibiotics. Yet cardiovascular stability in sepsis depends on a complex interplay of myocardial contractility, vascular tone, and neurohumoral compensation — factors rarely captured in cell-based assays. We characterized the cardiac and hemodynamic consequences of AgNP-adjuvanted antibiotic therapy in a clinically relevant porcine sepsis model.
Materials & Methods: Forty pigs (40.5 ± 4.2 kg) were randomized to six groups: control (n=6), control + AgNP (n=6), sepsis (n=7), sepsis + AgNP (n=7), sepsis + piperacillin/tazobactam (ATB; n=6), and sepsis + AgNP + ATB (n=8). Sepsis was induced by intravenous Klebsiella pneumoniae (10^7 CFU/ml). AgNPs (1 mg/kg/h) and ATB were given at protocol-defined intervals over 24 hours. Cardiac output, arterial pressure, vascular resistance, and acid-base status were monitored continuously under standardized vasopressor and volume management. Post-mortem, right ventricular trabeculae were isolated to assess contractile force and action potential duration in the presence and absence of AgNPs.
Results: All controls and sepsis + ATB animals survived 24 hours; mortality reached ~50% in untreated septic, sepsis + AgNP, and sepsis + AgNP + ATB groups. SOFA scores were significantly elevated across all septic groups relative to controls. Despite standardized vasopressor support, AgNP-treated septic animals showed lower systemic vascular resistance, more pronounced metabolic acidosis, and — unexpectedly — higher plasma lactate concentrations than untreated septic animals. Ex vivo right ventricular trabeculae showed no direct effect of AgNPs on myocardial contractility or action potential duration, dissociating the observed systemic deterioration from primary myocardial toxicity.
Conclusion: AgNP-based therapy worsened hemodynamic and metabolic outcomes relative to antibiotics alone, despite well-documented *in vitro* synergy. The absence of direct myocardial effects in isolated trabeculae indicates that deterioration reflects systemic rather than primary cardiac toxicity. These results underscore the value of large-animal cardiovascular phenotyping as an essential translational filter before candidate antimicrobial adjuvants advance toward clinical evaluation.

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THE ULTRARAPID DELAYED RECTIFIER POTASSIUM CURRENT HAS IMPORTANT FUNCTIONAL ROLE IN THE REPOLARIZATION RESERVE OF CANINE AND HUMAN VENTRICULAR MUSCLE

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The ultrarapid delayed rectifier potassium current (IKur) has long been considered an atrial-specific current with no functional role in the ventricles, despite evidence of its expression in ventricular myocytes. In the present study, we challenged this prevailing concept and investigated the potential role of IKur in ventricular repolarization. Experiments were performed on cardiac preparations obtained from Beagle dogs of both sexes. Kv1.5 protein expression was determined by immunocytochemistry in canine and undiseased human cardiac tissue samples. Action potentials were recorded using conventional microelectrode techniques in canine and human cardiac preparations, and membrane ionic currents were measured using the whole-cell configuration of the patch-clamp technique in isolated cardiomyocytes. Kv1.5 protein expression was detected in canine atrial, ventricular, and Purkinje fibre cells, as well as in undiseased human left ventricular myocardium. In canine atrial preparations, IKur inhibition shifted the plateau phase of the action potential into the positive voltage direction, and consequently shortened action potential duration. Application of 100 µM 4-AP revealed ionic currents of similar magnitude in ventricular myocytes and Purkinje fibres, which were attributed to IKur. Inhibition of IKur caused prolongation of the action potentials recorded from endocardial and midmyocardial preparations, as well as from Purkinje fibres. Under conditions of attenuated repolarization reserve, IKur inhibition induced augmented repolarization lengthening and frequent early afterdepolarizations (EADs). IKur is present and functionally active in ventricular myocardium and may represent a significant contributor to ventricular repolarization reserve.

ARE GLP-1 RECEPTOR AGONISTS ASSOCIATED WITH PRO-ARRHYTHMIC SIGNALS? A PHARMACOVIGILANCE DISPROPORTIONALITY ANALYSIS USING FAERS DATABASE

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Background & Aim: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are widely used in the management of type 2 diabetes mellitus and obesity, with increasing relevance in cardiometabolic îcare. However, their potential association with arrhythmia-related adverse events remains incompletely characterized in real-world settings. This study aimed to evaluate the disproportionality signal of arrhythmia-related adverse events associated with GLP-1 RAs using the FDA Adverse Event Reporting System (FAERS) database, with secondary comparison to dipeptidyl peptidase-4 (DPP-4) inhibitors.

Materials & Methods: We conducted a retrospective pharmacovigilance disproportionality analysis using the FAERS database accessed via the FAERS dashboard. Arrhythmia-related adverse events included atrial fibrillation, tachycardia and other arrhythmia reports. Reporting odds ratios (RORs) were calculated separately for GLP-1 RAs and DPP-4 inhibitors, each compared against all other drugs in the database. Subgroup analyses were performed at the individual GLP-1 RA level.

Results: GLP-1 RAs were associated with 2,343 arrhythmia-related reports and 396,305 non-arrhythmic reports, corresponding to a ROR of 0.65, indicating no disproportionality signal. Variability in reporting patterns was observed among individual GLP-1 receptor agonists. Semaglutide showed the highest reporting odds ratio (ROR: 1.10), followed by liraglutide (ROR: 0.99), while exenatide, tirzepatide, and dulaglutide demonstrated lower RORs (0.64, 0.47, and 0.43, respectively), suggesting overall neutral to lower reporting signals across the class.

In contrast, DPP-4 inhibitors were associated with 1,113 arrhythmia-related reports and 53,852 non-arrhythmic reports, corresponding to a ROR of 2.27, indicating a higher disproportionality signal compared to GLP-1 RAs.

Conclusion: GLP-1 RAs were not associated with an increased reporting signal for arrhythmia-related adverse events in FAERS database. In contrast, DPP-4 inhibitors demonstrated a higher disproportionality signal. These findings should be interpreted in the context of the limitations of spontaneous reporting systems. Further studies are needed to better characterize the cardiovascular safety profile of these agents.

CHALLENGES IN DIAGNOSING HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Diagnosing heart failure with preserved ejection fraction (HFpEF) is difficult due to significant overlaps with other conditions like obesity or pulmonary diseases. Incidence is increasing with aging and the prevalence of metabolic disorders like diabetes. Symptoms like dyspnea and fatigue are common in all situations and there is no biomarker or imaging technique that definitively rules out one or the other. A multi-parametric approach for diagnosis is used instead, given the interrelated pathophysiological mechanisms, which must be understood. Endothelial dysfunction and abnormal exercise-induced flow-mediated vasodilation, abnormal ventricular-vascular coupling, left atrial abnormalities, pulmonary hypertension and dysfunction of the right ventricle must be studied in individual cases. Assessment of diastolic function requires complex echocardiographic measurements, and in unclear cases, invasive techniques like right heart catheterization are required to measure filling pressures. Biomarkers may be added to exercise testing. Scoring systems like H_2FPEF and HFA-PEFF are used to help differentiate HFpEF from other causes of dyspnea. In both algorithms, score thresholds are statistically determined, above which a diagnosis of HFpEF can be made with reasonably high confidence.

SEX DIFFERENCES IN HEART FAILURE - THE IMPACT ON TREATMENT

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In recent years, an increasing body of evidence indicates that sex significantly influences the pathogenesis, clinical manifestations, and treatment outcomes of heart failure (HF). Biological sex influences cardiovascular structure and function throughout lifetime via complex interactions among genes, sex hormones, and environmental factors, which explain the distinct HF pathophysiology. While women are more likely to develop HF with preserved ejection fraction (HFpEF) and men more commonly experience HF with reduced ejection fraction (HFrEF), recent epidemiological studies show that men under 65 years represent a growing subset of HFpEF, which in these cases is driven by the rise of the cardio-reno-metabolic syndrome. HFpEF is frequently associated with hypertension, obesity, systemic inflammation, endothelial dysfunction, and microvascular disease, leading to increased ventricular stiffness and impaired diastolic function. Women present also with atypical symptoms and have specific risk factors and risk modulators, e.g., disorders of pregnancy, peripartum cardiomyopathy, early menopause. HFrEF occurs secondary to ischemic heart disease and leads to adverse ventricular remodeling and myocardial fibrosis, which contribute to systolic dysfunction. Genetic and molecular studies have revealed sex-specific patterns of abnormal signaling, mitochondrial dysfunction, impaired metabolism, defective extracellular matrix regulation and immune response underlying cardiac fibrosis, all influencing the disease progression.

Although guideline-directed medical therapy (GDMT) remains the cornerstone of HF management, women have historically been underrepresented in clinical trials, limiting the evidence base for sex-specific recommendations. Emerging evidence suggest that women may derive benefit from certain pharmacological therapies at lower doses and are less likely to receive advanced therapies, such as cardiac resynchronization therapy and recent data demonstrate significant benefits for suitably selected females *vs* males.

In conclusion, recognition of sex-related differences is essential for developing more effective and personalized therapeutic strategies. Greater inclusion of women in cardiovascular trials and the adoption of precision medicine are critical to improving outcomes for both sexes and reducing the global burden of heart failure.

DECODING THE LIPID-VASCULAR INTERPLAY: INSIGHTS FROM PULSE WAVE ANALYSIS AND METABOLIC BIOMARKERS

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Pulse wave analysis (PWA) offers detailed insight into arterial stiffness—a central indicator of vascular aging and cardiovascular risk—as well as central and peripheral blood pressure parameters. Blood lipid abnormalities are established cardiovascular risk factors, and the cardiovascular disease burden associated with dyslipidemia will continue to increase. The presentation is aimed to review standard blood lipids, non-conventional lipid markers, including lipid index and lipid balance index, and lipid ratios associated with PWA variables in clinical studies, emphasizing mechanisms, methods, and age-dependent interplay.

The interplay between serum lipids and PWA-derived parameters is mediated primarily by endothelial dysfunction, inflammation, oxidative stress, extracellular matrix remodeling, and vascular smooth muscle cell phenotypes. Both traditional and advanced lipid biomarkers showed significant associations with PWA variables. Triglyceride-rich metabolic profiles emerged as key determinants of arterial stiffness and early vascular aging, and triglyceride-rich lipoproteins are now seen as active drivers of vascular injury. Composite lipid indices demonstrated superior integrative capacity compared with isolated lipid fractions. There is a clinically relevant metabolic–hemodynamic coupling in hypertensive and high cardiovascular risk patients, linking insulin resistance, triglyceride-rich dyslipidemia, and arterial stiffness within an age-stratified framework.

The bidirectional interaction between serum lipids and PWA-derived variables forms a vicious cycle in which lipid abnormalities promote arterial stiffening and, in turn, stiffer arteries further heighten cardiovascular risk. Integrating data on lipid metabolism, insulin resistance, metabolic dysfunction–associated steatotic liver disease, and pulse wave–based vascular indices suggests that arterial stiffening represents the cumulative biological imprint of metabolic injury. The combination of metabolic profiling and PWA provides a practical framework for precision cardiometabolic medicine that emphasizes biological vascular age over isolated risk factor thresholds.

FIBROSIS AND ASSOCIATED DYSFUNCTIONS IN HEART FAILURE: AN INTEGRATIVE PERSPECTIVE

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Heart failure is increasingly recognized as a systemic syndrome in which myocardial fibrosis represents a central mechanism linking oxidative stress, inflammation, endothelial dysfunction, and metabolic impairment to progressive cardiac remodeling. Persistent redox imbalance promotes fibroblast activation, extracellular matrix accumulation, mitochondrial dysfunction, apoptosis, and ferroptosis, leading to ventricular stiffening, impaired systolic and diastolic function, arrhythmogenesis, and progression of coronary atherosclerosis. Thus, fibrosis should be regarded not merely as a structural consequence of cardiovascular disease, but as an active biological process driving disease progression across multiple cardiovascular phenotypes.

Our research activity has focused on investigating these interconnected mechanisms from an integrative perspective, exploring how fibrotic remodeling interacts with oxidative imbalance, metabolic dysfunction, and vascular injury. Particular attention has been directed toward oxidative stress biomarkers and myocardial remodeling, highlighting the role of galectin-3 as a potential mediator connecting inflammation, fibrosis, and ventricular dysfunction. The observed associations between oxidative biomarkers and remodeling severity support the concept that fibrotic progression is closely linked to chronic inflammatory and redox activation. These findings open the perspective for multifactorial approaches integrating oxidative, inflammatory, and profibrotic pathways in cardiovascular risk stratification.

In parallel, the structural and metabolic effects of SGLT2 inhibitors have been explored beyond their conventional hemodynamic benefits. The available results suggest that these therapies may attenuate maladaptive atrial and ventricular remodeling through antifibrotic, anti-inflammatory, and metabolic mechanisms, particularly in patients with severe hypertrophic phenotypes. Such findings raise important questions regarding phenotype-dependent therapeutic responses and individualized treatment strategies based on the fibrotic substrate.

Additionally, hematological indices such as RDW and MPV have shown associations with coronary lesion burden and diastolic dysfunction, suggesting that subtle hematologic alterations may reflect underlying oxidative stress, endothelial dysfunction, platelet activation, and profibrotic cardiovascular remodeling.

Taken together, these findings support the concept of fibrosis as a unifying biological substrate across cardiovascular disease and emphasize the need for integrative, mechanism-oriented approaches for improved phenotypic characterization and personalized therapeutic strategies in heart failure.

MONOAMINE OXIDASE-RELATED OXIDATIVE STRESS IN OBESE PATIENTS WITH HEART FAILURE: THE BENEFICIAL ROLE OF SGLT2 INHIBITORS

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Heart failure (HF) remains a major clinical challenge, particularly in the setting of obesity and metabolic dysfunction, which accelerate disease progression across the spectrum of HF phenotypes, including HF with preserved (HFpEF), mildly reduced (HFmrEF), and reduced ejection fraction (HFrEF). Oxidative stress and mitochondrial dysfunction are central mechanisms in HF pathophysiology. Monoamine oxidases (MAO-A and MAO-B), located on the outer mitochondrial membrane, represent relevant sources of reactive oxygen species (ROS), linking neurohormonal activation to myocardial injury.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i), such as empagliflozin and dapagliflozin, are established therapies in HF, although their underlying cardioprotective mechanisms are not fully elucidated.

Previously published studies from our group in human cardiovascular tissues including both vascular and atrial samples from overweight patients across all HF phenotypes demonstrated that exposure to angiotensin II and high glucose increased MAO-A/B expression and ROS production. Ex vivo incubation with empagliflozin and dapagliflozin in doses relevant for the clinical scenario consistently reduced MAO expression and mitigated oxidative stress in both mammary artery and atrial appendage samples.

Importantly, MAO-derived oxidative stress was observed under basal conditions and further amplified by neurohormonal and metabolic stress. Oxidative stress levels correlated positively with cardiac chamber remodelling and inversely with left ventricular ejection fraction.

These findings identify MAO-driven oxidative stress as a shared and clinically relevant pathophysiological mechanism in overweight patients with HF, prior to the occurrence of obesity and diabetes. MAO modulation by SGLT2i in the cardiovascular system is a novel off-target effect adding to their pleiotropic benefits throughout the HF spectrum.

SGLT2 INHIBITORS: DISTINCT CARDIAC REMODELING PATTERN IN HEART FAILURE WITH REDUCED AND PRESERVED EJECTION FRACTION

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Background & Aim: Sodium–glucose cotransporter 2 inhibitors (SGLT2i) improve clinical outcomes across the heart failure (HF) spectrum, yet the mechanisms underlying cardiac remodeling remain incompletely understood. We aimed to systematically evaluate imaging-derived and hemodynamic effects of SGLT2i and compare phenotype-specific remodeling patterns in HF with reduced ejection fraction (HFrEF) versus HF with preserved ejection fraction (HFpEF).
Materials & Methods: A systematic search of PubMed/MEDLINE, Scopus, and EMBASE (January 2016–March 2026) identified randomized controlled trials assessing the effect of SGLT2i in chronic HF patients on guideline directed treatment with imaging (echocardiography, speckle-tracking echocardiography, or cardiac magnetic resonance CMR) or invasive hemodynamic endpoints. Eligible studies had ≥3 months follow-up and reported remodeling parameters, including left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), LV mass indexed (LVMi), global longitudinal strain (GLS), E/e′ ratio, left atrial volume index (LAVI), pulmonary capillary wedge pressure (PCWP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Risk of bias was assessed using Cochrane RoB 2 and certainty of evidence using GRADE. Due to heterogeneity, a structured narrative synthesis (SWiM) was performed.
Results: Fifteen publications from 13 randomized controlled trials (n=1,291) were included. In HFrEF, SGLT2i consistently induced reverse remodeling, with reductions in LVEDV (7/9 studies) and LVESV (7/8), improvement in GLS (5/5), and reduction in NT-proBNP (71%). The largest volumetric effects were observed in CMR-based studies. Improvements in LVEF were variable despite consistent volume reduction. In HFpEF, no significant changes in LV volumes or LVEF were observed. However, SGLT2i significantly reduced PCWP at rest and during exercise, improved diastolic function (E/e′, LAVI), and enhanced cardiac functional reserve. NT-proBNP decreased in 50–80% of studies across phenotypes.
Conclusion: SGLT2i exert phenotype-specific remodeling effects in HF. In HFrEF, they promote volumetric reverse remodeling and improved systolic mechanics, whereas in HFpEF, benefits are primarily mediated through hemodynamic unloading and improved diastolic function without significant structural changes. These findings support phenotype-guided monitoring strategies and highlight subgroup-specific responses, including left ventricular mass index (LVMi) reduction in elderly HFpEF patients and greater NT-proBNP reductions in those with higher baseline levels.

PEGYLATION SIZE EXCLUSION TECHNOLOGY ENABLES INDEPENDENT ACTIVATION OF CARDIAC B-ADRENERGIC RECEPTORS LOCATED IN EITHER THE T-TUBULE OR THE OUTER SURFACE MEMBRANE

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Background & Aim: The adult cardiac myocyte is characterised by an outer surface membrane (OSM) and deep network of membrane invaginations called transverse-tubules (TTs). The TTM is rich in receptors, which are also present in the OSM, including β-adrenergic receptors (β-ARs) which regulate the sympathetic cardiac response through highly compartmentalised cAMP signalling pathways. Determining how location of a β-AR effects cellular function requires to being able individually activate either OSM or TTM β-ARs. We have sought to answer this fundamental question through a novel size-exclusion technology.
Materials & Methods: We covalently linked a 5 kDa PolyEthylene-Glycol (PEG) chain to both an agonist; isoprenaline (Iso) and an antagonist, alprenolol (Alp), preventing access to the TTs, and limiting binding to only the cell surface β-ARs for these PEGylated ligands (confirmed by confocal microscopy using free and PEGylated fluorescent ligands). This enabled us to independently activate three distinct populations of β-ARs based upon cellular location: 1. Free Iso binds and activates all β-ARs. 2. PEG-Iso is limited to the cell surface and activates only OSM β-ARs, whilst 3. PEG-Alp antagonizes binding to the OSM β-ARs only, so when used in conjunction with free Iso activates just TTM β-ARs. We have used these in a series of functional experiments using adult rat ventricular cardiomyocytes (ARVMs).
Results: No differences were seen in excitation-contraction coupling responses with identical $I_{Ca\text{-}L}$ and Ca^{2+} responses to Iso and PEG-Iso stimulation. However, spatial cAMP and PKA differences were observed. The maximal cytosolic cAMP response to PEG-Iso, determined with FRET sensors, is ≈30% lower than with Iso alone. At equivalent levels of cAMP, PEG-Iso stimulates cytosolic PKA with a greater efficacy than free Iso but stimulates nuclear PKA with a ≈50% lower efficacy reflected in a ≈50% reduction of PKA mediated phosphorylation of target substrates, quantified by western blot. By chemically removing the TT network with 300 µM imipramine the differences between PEG-Iso and free Iso were abolished.
Conclusion: Only activation of OSM β-ARs is required to activate cytosolic PKA and the main mechanistic pathways of excitation-contraction coupling. However, activation of TTM β-ARs is needed for nuclear PKA stimulation or nuclear protein phosphorylation.

GREATER VOLUNTARY EXERCISE DOES NOT RESCUE HYPERTENSIVE CARDIAC REMODELING: DIVERGENT FUNCTIONAL AND BDNF–TRKB-LINKED LEFT VENTRICULAR ADAPTATION IN SPONTANEOUSLY HYPERTENSIVE RATS

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Background & Aim: Hypertension drives left ventricular remodeling and may restrict the myocardium's adaptive response to exercise. Brain-derived neurotrophic factor (BDNF) and its receptor TrkB have emerged as candidate regulators of myocardial contractility and remodeling, but their role in exercise adaptation of the hypertensive heart remains unclear. We tested whether voluntary wheel running (VWR) induces comparable functional and molecular cardiac adaptation in normotensive Wistar rats and spontaneously hypertensive rats (SHR), hypothesizing that hypertensive myocardium would show a constrained response despite higher running activity.
Materials & Methods: Adult male Wistar rats and SHR were assigned to sedentary control or VWR groups (n=8/group) for 5 weeks. Echocardiography was performed at baseline and week 5 in the running groups. Left ventricular tissue was analyzed by RT-qPCR and Western blotting to evaluate BDNF-TrkB signaling and markers of inflammation, fibrosis, apoptosis/stress regulation, wall stress, and transcriptional remodeling.
Results: SHR ran significantly farther than Wistar rats throughout the intervention, yet this greater exercise volume did not translate into superior cardiac adaptation. In Wistar rats, VWR increased cardiac output and reduced heart rate. In contrast, SHR showed no significant improvement in either parameter, while relative wall thickness remained elevated, indicating persistence of concentric remodeling. Fractional shortening and ejection fraction remained lower in SHR, and E/A ratio was unchanged. At the molecular level, SHR displayed an altered left ventricular profile, including lower TrkB, IL-10, CREB, VGF, Glt-1, and CB2 expression. VWR induced selective transcriptional remodeling in Wistar, notably increased FGF21 and reduced Bicc1, whereas SHR showed limited adaptation. Protein analysis revealed stronger BDNF induction in SHR but reduced TrkB in both strains. Although IL-10 increased and caspase-3 decreased overall, TNF-α and PDCD4 shifted unfavorably in SHR runners, and BNP remained elevated in SHR.
Conclusion: Low-stress voluntary exercise elicited favorable molecular adaptation in normotensive myocardium but was insufficient to overcome hypertensive remodeling. These findings indicate that exercise dose alone does not predict myocardial benefit in hypertension and support the concept that the hypertensive heart exhibits a restricted BDNF-TrkB-linked remodeling response to exercise.

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TISSUE-SPECIFIC AUTOANTIBODY SIGNATURES REVEAL IMMUNE ALTERATIONS UNDETECTED BY ROUTINE SEROLOGY IN LONG COVID

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Background & Aim: Long COVID affects a substantial proportion of COVID-19 survivors, with autoimmunity increasingly implicated in its pathogenesis. While systemic immune alterations have been investigated, the landscape of structural, tissue-specific autoreactivity remains poorly understood. This study aimed to investigate the role of targeted autoimmunity in Long COVID by mapping autoantibody signatures against cardiac, vascular, and pulmonary antigens, and to assess their clinical relevance alongside standard serological screening.
Materials & Methods: Sera from 114 Long COVID patients (evaluated ≥30 days post-infection) and 36 pre-pandemic controls were analyzed using a specialized tissue-based Western blot assay incorporating human cardiac, pulmonary, and vascular tissue homogenates. Autoreactivity profiles were compared against standard clinical ANA HEp-2 immunofluorescence. Additionally, longitudinal follow-up samples (n=30, mean 141 days) were evaluated to track temporal autoantibody dynamics.
Results: Tissue-specific autoantibodies were highly prevalent in Long COVID compared to controls (83% vs. 53%; $p<0.05$), demonstrating a dominant cardiovascular pattern. Vascular autoreactivity was significantly elevated in patients (34% vs. 8%; $p<0.05$). Responses exhibited broad polyreactivity and a distinct IgM predominance. Longitudinal tracking revealed an atypical persistence of IgM reactivity and frequent *de novo* emergence of new isotypes. Clinically, cardiac autoreactivity correlated with neurovascular manifestations, including hypertension and headache,

while combined tissue positivity correlated with persistent anosmia, ageusia, and subclinical C-reactive protein elevations. In contrast, standard ANA HEp-2 testing showed no discriminatory diagnostic value or specific clinical associations between the cohorts.

Conclusion: Long COVID is characterized by a significant burden of tissue-specific, IgM-skewed autoantibodies, particularly targeting the cardiovascular system. This persistent autoreactive profile indicates ongoing immune dysregulation following acute infection. The strong clinical correlations between structural autoantibodies and neurovascular symptoms support an emerging microvascular model of Long COVID, suggesting sustained immune-vascular crosstalk. Importantly, these specific immune alterations are missed by routine ANA screening, highlighting the need for targeted immunodiagnostic approaches to accurately phenotype the syndrome's chronic pathophysiology.

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BEYOND ANTIOXIDANTS: THE ROLE OF QUERCETIN IN MITOCHONDRIAL ENERGETICS IN DIABETIC RAT HEART

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Background & Aim: Cardiovascular complications are strongly associated with metabolic disorders, especially type 2 diabetes mellitus (T2DM), which disrupts the energy balance of the heart muscle. Quercetin (QCT), a naturally occurring dietary polyphenol, has attracted attention due to its antioxidant properties and potential cardioprotective effects. This study investigated whether QCT supplementation can improve mitochondrial function in the diabetic heart, focusing on bioenergetic performance.
Materials & Methods: Experiments were performed in six-month-old male Zucker Diabetic Fatty rats, a well-established animal model of T2DM. The rats were administered with QCT orally at a dose of 20 mg/kg/day for six weeks. After treatment, the animals were anesthetized and left ventricular heart tissue was collected. Mitochondria were isolated by differential centrifugation, and mitochondrial oxygen consumption was determined using high-resolution respirometry with a Clark electrode under defined metabolic conditions.
Results: Mitochondria obtained from diabetic animals showed a 23% decrease in basal respiration (state 1) compared to non-diabetic controls, confirming a reduced oxidative capacity. However, QCT treatment did not significantly alter basal respiration or oxygen consumption after substrate delivery (state 2) or adenosine diphosphate (ADP)-induced activation (state 3) compared to untreated diabetic counterparts.
Conclusion: Our results suggest that QCT does not restore mitochondrial respiratory function in diabetic heart tissue under the conditions tested. Nevertheless, the absence of detectable changes in oxygen consumption does not rule out potential benefits mediated by alternative mechanisms. Given the multifaceted nature of mitochondrial regulation in T2DM, future studies should address effects on mitochondrial dynamics, redox balance, and signaling pathways involved in energy metabolism. A broader understanding of these processes may help clarify the therapeutic significance of QCT in the treatment of diabetic cardiovascular disease.

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A SIMPLE RISK SCORE COMBINING MYOCARDIAL WORK AND CORONARY ANATOMY FOR RISK STRATIFICATION AFTER STEMI

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Background & Aim: Risk stratification after ST-segment elevation myocardial infarction (STEMI) remains suboptimal despite timely reperfusion. Conventional echocardiographic parameters provide important prognostic information but are influenced by loading conditions. Global Work Efficiency (GWE), derived from myocardial work analysis, integrates myocardial deformation with afterload and may offer a more robust assessment of left ventricular function. This study aimed to evaluate the prognostic value of GWE and to develop a simple, clinically applicable risk score combining myocardial functional impairment and coronary anatomical severity in STEMI patients undergoing primary PCI.
Materials & Methods: We prospectively enrolled 215 consecutive patients with acute STEMI (mean age 61±10 years; 78.1% male) treated with primary PCI within 12 hours of symptom onset. Early transthoracic echocardiography was performed in all patients. Patients were followed for major adverse events (MAE), defined as a composite of all-cause mortality, unplanned rehospitalization, ventricular arrhythmia, and ischemic stroke. GWE was dichotomized using the median value (88%), given the absence of a validated clinical threshold. A simple risk score was constructed by assigning 1 point for reduced GWE (≤88%) and 1 point for the presence of three-vessel coronary artery disease. Patients were stratified into three categories (0, 1, or 2 points). Survival analyses were performed using Kaplan–Meier curves and Cox proportional hazards models.
Results: During a median follow-up of 7 months (IQR 5–15), 40 patients experienced MAE. The proposed risk score was significantly associated with outcomes. Event rates differed across risk categories ($\chi^2 = 10.7$, $p = 0.005$), with the highest incidence in patients with a score of 2 (28.6%). In Cox regression analysis, the score remained an independent predictor of adverse events, with a hazard ratio of 2.17 per one-point increase (95% CI 1.36–3.84; $p = 0.001$). Kaplan–Meier analysis showed significant differences in event-free survival (log-rank $p = 0.03$), with patients scoring 2 having an approximately 4.7-fold higher risk of MAE compared with those scoring 0.
Conclusion: A simple risk score combining GWE and coronary artery disease severity provides effective and clinically applicable risk stratification in STEMI patients, enabling early identification of high-risk individuals and potentially improving post-infarction management.

SLEEP-DISORDERED BREATHING IN PRECAPILLARY PULMONARY HYPERTENSION: A CASE SERIES FROM TIMIȘOARA REGIONAL REFERRAL CENTER

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Background & Aim: Sleep-disordered breathing (SDB), particularly obstructive sleep apnea (OSA), is a well-recognized contributor to pulmonary hypertension (PH), with a high prevalence (up to 80%) reported in ESC/ERS Group 2 (postcapillary) and Group 3 PH associated with lung disease and/or hypoxia. In contrast, the burden and clinical characteristics of SDB in precapillary PH remain insufficiently defined. This study aimed to describe the clinical and paraclinical profile of patients with precapillary PH and coexisting SDB/OSA.
Materials & Methods: We conducted a retrospective observational case series including all patients with precapillary PH managed within the national program at our center in 2025 and diagnosed SDB/OSA. PH was confirmed by right heart catheterization, and all patients were receiving PAH targeted therapy. OSA was diagnosed using sleep studies, and severity was classified according to the apnea–hypopnea index (AHI). Demographic, clinical, and paraclinical data, including functional status, exercise capacity (6-minute walk test), and biomarkers (NT-proBNP), were collected and descriptively analyzed.
Results: Out of 67 patients with precapillary PH, 7.46% (n=5) had coexisting SDB. The mean age was 46.6 ± 8.08 years, with a predominance of male patients (60%). A heterogeneous clinical profile was observed: two patients were obese, two presented craniofacial abnormalities, and one had mild OSA associated with hypoventilation following pulmonary thromboendarterectomy. Respiratory parameters showed variability, with a mean AHI of 36.5 ± 23.55 events/hour, indicating predominantly moderate-to-severe OSA, and a high hypoxic burden (mean T90 69.3%). Functional and biological parameters also varied (mean 6MWT 438 ± 106 m; mean NT-proBNP 783 ± 1295 pg/mL). The temporal relationship between conditions was bidirectional: OSA preceded PH in three patients, while PH was diagnosed first in two. Initiation of continuous positive airway pressure (CPAP) therapy was associated with improvements in clinical status (functional class and symptoms) as well as hemodynamic parameters.
Conclusion: SDB is a clinically relevant comorbidity in precapillary PH, characterized by marked heterogeneity. These findings support systematic screening for SDB in this population and suggest that conventional risk profiles derived from other PH groups may not be fully applicable.

ABSTRACTS OF THE POSTERS

MONITORING AND OPTIMIZING DIRECT FXa INHIBITOR THERAPY

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Background & Aim: Factor X (FX) plays a central role in blood coagulation, and its direct inhibition is essential in thrombosis prevention. However, conventional coagulation assays cannot accurately quantify FX activity or the level of FXa inhibition, limiting safe decision-making in thrombolytic therapy where bleeding risk must be carefully assessed. This study aimed to develop and validate a direct enzyme activity–based assay for measuring FX activity and to evaluate its ability to detect and quantify the effects of FXa inhibitor therapy, distinguish treated and untreated patients, and support clinical decision-making and therapy monitoring.
Materials & Methods: A colorimetric assay was established to directly measure FX activity, including endogenous and drug-induced inhibition. A total of 188 cardiology patients were included: 112 in a retrospective cohort (52 controls, 60 FX inhibitor-treated) and 76 in a prospective cohort (22 treated, 54 untreated, based on self-report). FX was activated using Russell's viper venom, and enzyme activity was assessed via a chromogenic substrate. Measurements were performed in serum across 4–1024-fold dilutions using a COBAS Integra 400 analyzer.
Results: In the retrospective cohort (12-minute incubation), ROC analysis demonstrated that treated and untreated patients could be distinguished with 92.6% sensitivity and 82.7% specificity (AUC: 0.89). In the prospective cohort (3-minute incubation), sensitivity reached 95.45% and specificity 92.59% (AUC: 0.977). Furthermore, we identified 14 patients in the retrospective cohort whose FXa inhibitor therapy could potentially be optimized, presumably reducing their risk of bleeding.
Conclusion: Direct FX activity measurement effectively identifies patients receiving FX inhibitor therapy. This method may support safer thrombolytic therapy decisions and improve monitoring of patient adherence.

APPLICATION OF ACE ACTIVITY MEASUREMENT FOR ASSESSING MEDICATION ADHERENCE AND THE EFFECTIVENESS OF ACE INHIBITOR THERAPY IN HYPERTENSIVE PATIENTS

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Background & Aim: Angiotensin-converting enzyme (ACE) inhibitors are a cornerstone in the treatment of hypertension and heart failure. Despite this, more than half of patients don't take their prescribed ACE inhibitor regularly or at all. Poor adherence reduces treatment efficacy, while excessive ACE inhibition may also lead to unfavorable clinical consequences. Therefore, objective monitoring of patient adherence and optimal dose adjustment are of particular importance. The aim of our study was to determine the extent of endogenous and exogenous inhibition by measuring ACE activity, which may be suitable for distinguishing between hypertensive patients receiving ACE inhibitor therapy.
Materials & Methods: ACE activity was determined by monitoring the change in fluorescence intensity resulting from the cleavage of a quenched fluorescent substrate. Patient sera (n=129) were measured at 4x, 35x, and 400x dilutions, in some cases with additional serial dilutions. We investigated two patient populations: in newly diagnosed hypertensive patients, samples were collected before and after initiation of ACE inhibitor therapy, and the developed method was then prospectively tested among consecutive patients attending the cardiology outpatient clinic.
Results: ACE activity decreased significantly after medication intake *(*all data are presented as median±IQR): 16048 (11949–20148) before and 1393 (676–3605) during treatment (n=40, $p<0.0001$). The degree of endogenous ACE inhibition mediated by albumin was 53% (45–62), while the inhibition measured in medicated patients was 96% (90–98) (n=40, $p<0.0001$). According to ROC analysis, discrimination of patients receiving ACE inhibitor therapy was achieved above 84.5% inhibition with 85% sensitivity and 90% specificity (AUC= 0.89). In parallel, both systolic and diastolic blood pressure decreased by 10.5 and 7 mmHg, respectively, after treatment ($p\leq0.0001$). The degree of ACE inhibition in the prospective study was 59% (52–64) in control patients (n=62), which increased to 94% (90–97) in patients taking the medication (n=27).
Conclusion: These results confirm that fluorescence-based ACE activity measurement is suitable for objective monitoring of adherence in hypertensive patients, and estimating the concentration of ACE inhibitors present in serum, thereby supporting personalized optimization of therapy.

INFLAMMATORY BIOMARKERS AS PREDICTORS OF IN-HOSPITAL OUTCOMES IN ACUTE CORONARY SYNDROMES

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Background & Aim: Inflammation plays a key role in the pathophysiology of acute coronary syndromes (ACS), contributing to plaque instability, myocardial injury, and adverse cardiovascular outcomes. Inflammatory biomarkers, including C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and the systemic immune-inflammation index (SII), have been proposed as potential tools for risk stratification in ACS. This prospective observational study aimed to evaluate the association between inflammatory biomarkers, N-terminal pro–B-type natriuretic peptide (NT-proBNP), and the occurrence of major adverse cardiovascular events (MACE) in patients presenting with ACS.
Materials & Methods: One hundred consecutive patients with ACS and elevated inflammatory biomarkers hospitalized in 2024-2025 at a tertiary cardiovascular center were enrolled. Inflammatory status was assessed by using CRP, NLR and SII. The primary endpoint was in-hospital MACE defined as: cardiovascular death, recurrent myocardial infarction, stroke, urgent coronary revascularization, or acute heart failure requiring escalation of therapy. Multivariable logistic regression and receiver operating characteristic studies were conducted.
Results: Among the 100 ACS patients, half experienced in-hospital MACE.Patients with MACE were older ($p = 0.003$) and exhibited elevated inflammatory biomarkers CRP ($p < 0.001$; strongest association), NLR ($p = 0.030$), and SII ($p = 0.042$)—as well as higher NT-proBNP ($p = 0.002$) as compared to those without episodes. Patients with MACE also had diminished renal function ($p < 0.001$) and decreased left ventricular systolic function, as demonstrated by a lower LVEF ($p = 0.001$), pointing to concurrent renal impairment and ventricular dysfunction. Both hypertension and new-onset atrial fibrillation were more frequent in the MACE group. In multivariable analysis, LVEF was identified as an independent predictor of short-term outcomes (OR 0.934 per 1% increase; $p = 0.047$).
Conclusion: The occurrence of in-hospital adverse events in patients hospitalized with acute coronary syndromes is closely linked to the activation of inflammation. While left ventricular ejection fraction remains an independent determinant of short-term outcomes, inflammatory biomarkers may offer additional insights into the ACS-driven inflammatory burden.

THE ADDITIONAL VALUE OF SGLT2 INHIBITOR THERAPY IN LV-ONLY FUSION PACING CARDIAC RESYNCHRONIZATION THERAPY

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Background & Aim: Cardiac resynchronization therapy (CRT) improves outcomes in patients with heart failure (HF) and reduced ejection fraction. However, response remains heterogeneous and may depend on pacing strategy. Sodium–glucose cotransporter-2 (SGLT2) inhibitors have demonstrated beneficial effects on cardiac remodeling, but their impact on CRT response across different pacing modalities is not well established. This study aims to evaluate the association between SGLT2 inhibitor therapy and left ventricular (LV) remodeling, functional improvement, and CRT response in patients undergoing LV only fusion CRT pacing (fCRTp).
Materials & Methods: We conducted a retrospective cohort study including 88 patients undergoing CRT implantation between 2011 and 2025. Patients were stratified according to SGLT2 inhibitor use. Echocardiographic parameters, including left ventricular ejection fraction (LVEF), end-diastolic volume (LVEDV), and end-systolic volume (LVESV), were assessed at baseline and follow-up. CRT response was defined as ≥ 5% absolute increase in LVEF or ≥ 15% reduction in LVESV. Super-response was defined as ≥ 10% increase in LVEF or ≥ 30% reduction in LVESV or ≥ 20% reduction in LVEDV. Median follow-up was 12.5 months (IQR 5.0–27.7).
Results: SGLT2 inhibitor therapy was associated with a significantly greater improvement in LVEF compared with controls (ΔLVEF: 11.9% vs. 7.4%, p = 0.006), which remained significant after multivariable adjustment (β = +4.3%, p = 0.008). This effect was consistent across both pacing groups, without a significant interaction between pacing modality and SGLT2 therapy. Reductions in LV volumes were numerically greater in the SGLT2 group, suggesting enhanced reverse remodeling, although differences were not consistently statistically significant. The proportion of CRT responders was high in both groups, while super-response was more frequent among SGLT2-treated patients (81% vs. 60%), showing a strong trend toward significance (OR 2.86, 95% CI 0.94–9.90, p = 0.057). No significant differences were observed in NYHA class improvement or tricuspid regurgitation reduction between groups.
Conclusion: In patients undergoing fCRTp, SGLT2 inhibitor therapy was associated with greater improvement in LV systolic function and a consistent trend toward enhanced reverse remodeling and super-response. These findings suggest a potential additive benefit of SGLT2 inhibitors irrespective of pacing modality, although larger studies are needed to confirm these results.

PLASMA H_2O_2 STRATIFICATION IDENTIFIES HEART FAILURE PATIENTS WITH HIGHER NT-PROBNP LEVELS

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Background & Aim: Heart failure (HF) is characterized by chronic neurohormonal activation and a sustained increase in reactive oxygen species (ROS), which contribute to cardiomyocyte injury and adverse remodeling. Plasma hydrogen peroxide (H_2O_2) is a stable, diffusible ROS species reflecting systemic oxidative burden, while NT-proBNP, released in response to ventricular wall stress, is the cornerstone biomarker for HF diagnosis and prognosis. The direct relationship between systemic oxidative stress and NT-proBNP burden in HF patients remains incompletely characterized. The present study was aimed to evaluate whether stratification of HF patients by plasma H_2O_2 levels is associated with NT-proBNP burden.
Materials & Methods: Cross-sectional study including 45 patients with chronic HF recruited at the Cardiology Clinic, ASCAR Timișoara. Plasma H_2O_2 was quantified by the ferrous oxidation–xylenol orange (FOX) spectrophotometric assay; NT-proBNP was measured by standard chemiluminescent immunoassay. Patients were stratified by median H_2O_2 value into LOW ROS (n = 23) and HIGH ROS (n = 22) groups. Between-group comparisons were performed using the Mann–Whitney U test (significance $p < 0.05$).
Results: The HIGH ROS group exhibited markedly elevated plasma H_2O_2 compared with LOW ROS (≈ 4.3 vs ≈ 1.6 nM/mL; $p < 0.0001$), validating biochemical stratification. NT-proBNP was significantly higher in the HIGH ROS group (≈ 4 000 vs ≈ 1 000 pg/mL; $p < 0.05$), with substantially greater inter-individual variability and several values exceeding 15 000 pg/mL.
Conclusion: Plasma H_2O_2 stratification distinguishes HF patients with significantly higher NT-proBNP burden, supporting a direct association between systemic oxidative stress and ventricular wall stress in heart failure. Plasma H_2O_2 may serve as a complementary biomarker reflecting the redox-related contribution to ventricular stress.

TISSUE DOPPLER-DERIVED MITRAL ANNULAR VELOCITIES FOR DETECTING CORONARY ARTERY DISEASE IN PATIENTS WITH PRESERVED EJECTION FRACTION AND NO RESTING WALL MOTION ABNORMALITIES

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Background & Aim: Resting echocardiographic assessment of chronic coronary artery disease (CAD) is mainly based on regional wall motion abnormalities, which may be subjective and absent in many patients. Tissue Doppler imaging (TDI) may provide additional quantitative markers of myocardial dysfunction. This study aimed to determine optimal cut-off values for mitral annular S′, E′, and E/E′ ratio for predicting CAD in patients with preserved ejection fraction and no regional wall motion abnormalities.
Materials & Methods: We conducted a cross-sectional observational study including 92 patients hospitalized between January 2025 and February 2026 for typical angina and elective coronary angiography. Patients with previous acute coronary syndrome, myocardial revascularization, significant valvular disease, cardiomyopathies, arrhythmias, conduction abnormalities, reduced ejection fraction, or pericardial disease were excluded. CAD was defined as at least one coronary stenosis ≥50%. Standard transthoracic echocardiography and TDI were performed, measuring S′, E′, A′, and E/E′. Diagnostic performance was assessed using ROC analysis, Youden-derived cut-offs, DeLong comparisons, and logistic regression.
Results: CAD was present in 62 patients (67%), while 30 patients had no significant coronary disease. Patients with CAD had significantly lower S′ average values compared with non-CAD patients [7.0 (6.0–7.5) vs. 9.0 (8.1–10.0) cm/s, p<0.001], lower E′ average values, and higher E/E′ ratios. Among evaluated parameters, S′ average showed the highest diagnostic accuracy for CAD, with an AUC of 0.899 (95% CI: 0.819–0.952, p<0.0001). The optimal S′ cut-off was ≤7.5 cm/s, with 77.42% sensitivity and 93.33% specificity. S′ significantly outperformed E′ average, E/E′ ratio, and A-wave velocity in pairwise ROC comparisons. In logistic regression, S′ ≤7.5 cm/s was strongly associated with CAD both before adjustment (OR=48.00, 95% CI: 10.16–226.88, p<0.0001) and after adjustment for clinical covariates (OR=57.85, 95% CI: 10.26–326.12, p<0.0001).
Conclusion: Mitral annular S′ measured by TDI is a strong independent predictor of angiographic CAD in patients with preserved ejection fraction and no resting regional wall motion abnormalities. An S′ cut-off ≤7.5 cm/s may represent a useful resting echocardiographic marker for identifying patients with significant CAD.

EFFECT OF WESTERN DIET AND DIMETHYL FUMARATE ON BLOOD PRESSURE AND LIVER IN BORDERLINE-HYPERTENSIVE RATS

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Background & Aim: This study investigated the effects of the Western diet and nuclear factor erythroid 2-related factor 2 (NRF2) function activator dimethyl fumarate (DMF) on lipid metabolism and liver function in borderline-hypertensive rats (BHR, offspring of spontaneously hypertensive dams and Wistar-Kyoto sires).
Materials & Methods: BHR were fed on a Western diet (WD; 43% energy from fat, Na 4.04g/kg, Altromin, Germany), control diet (C) (diet C-1090, w/10% energy from fat, Na 1.89g/kg, Altromin, Germany) and treated with dimethyl fumarate (DMF, 20 mg/kg in 0.25% dimethyl sulphoxide with control diet), or simultaneously with WD+DMF for 9 weeks (n=8/group).
Results: WD did not increase BW; however, it significantly increased blood pressure (BP), relative liver and kidney weights, and hepatic damage markers (ALT, ALP). WD also elevated oxidative damage to the liver, determined as elevated TBARS. WD did not alter the expression of NRF2 gene (*Nfe2l2*) but elevated the expression of peroxisome proliferator-activated receptors (PPAR γ and α) genes (*Pparg, Ppara*) and carboxylesterase 1 (*Ces1*) and reduced genes of antioxidant enzymes (*Hmox1*, *Sod1*). Interestingly, bimodal effects of WD on lipid metabolism (plasma triacylglycerols (TAG), cholesterol, and bilirubin) were found in WD-fed BHR; these markers were significantly increased (in 4 rats) or unchanged (in 4 rats) vs. control. DMF prevented alterations in BP, bilirubin, TAG, and liver weight, without the effect on expression of the above-mentioned genes.
Conclusion: The Western diet elevated BP and induced liver injury and oxidative stress in BHR independently of BW. DMF partially protected against the diet-induced hypertension and metabolic alterations despite failing to improve *Nfe2l2* and NRF2-target gene expression. The bimodal effect of WD on lipid metabolism indicates interindividual variability in susceptibility to Western diet-induced metabolic stress which needs further investigation.

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EFFECTS OF SHORT-TERM LOW-INTENSITY TRAINING ON EXCITATION–CONTRACTION COUPLING IN EARLY OBESITY

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Background & Aim: Obesity is a major risk factor for cardiovascular disease and a growing global health burden. Even at early stages, it leads to subtle alterations in cardiac function, potentially involving changes in cardiomyocyte calcium signaling. However, it remains unclear how early obesity affects calcium transients, caffeine-induced calcium release, and contractility. The aim of this study was to investigate the effects of early obesity on cardiomyocyte function and to determine whether exercise modulates calcium transients, caffeine-induced calcium release, and contractility.
Materials & Methods: Female Zucker Diabetic Fatty (ZDF) rats, including lean (fa/+) and obese (fa/fa) animals, were studied between 12 and 18 weeks of age and divided into four groups: lean sedentary, lean exercised, obese sedentary, and obese exercised. Exercise training consisted of short-term low-intensity treadmill running performed 5 days per week. At the end of the training period, ventricular cardiomyocytes were isolated for functional analysis. Cells were loaded with fluo-3 AM, and calcium transients and sarcomere shortening were recorded simultaneously using confocal line-scan imaging during electrical stimulation (1 Hz). Caffeine (20 mM) was applied at the end of the protocol to assess sarcoplasmic reticulum calcium content.Line-scan recordings were processed using TransientVisualizer (https://github.com/IuliiaBaglaeva/TransientVisualizer). Parameters of calcium transients, sarcomere shortening, and caffeine-induced responses were approximated using TransientAnalyzer (https://github.com/IuliiaBaglaeva/TransientAnalyzer). Statistical analysis was performed using linear mixed-effects models, with fixed effects evaluated by Wald χ^2 tests followed by Tukey's post hoc comparisons ($p < 0.05$).
Results: Multiple parameters of calcium transients, sarcomere shortening, and caffeine-induced calcium release were analyzed. Early obesity significantly reduced calcium transient amplitude, while kinetic parameters and sarcomere shortening remained unchanged. Caffeine-induced calcium transients were also unchanged, indicating preserved sarcoplasmic reticulum calcium content. Exercise exerted modest and differential effects on calcium transient amplitude, decreasing it in lean animals but increasing it in obese animals. A significant interaction effect was observed for the delay between calcium transients and sarcomere shortening.
Conclusion: These findings indicate that early obesity reduces cardiomyocyte calcium transient amplitude, while exercise has different effects, decreasing amplitude in lean animals but increasing it in obese animals. This suggests early changes in calcium regulation, while sarcoplasmic reticulum function and contractility remain unchanged.

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CHANGES IN DYADIC MICRODOMAIN SYSTEM IN A MODEL OF OBESITY AND EXERCISE

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Background & Aim: Obesity is a major global health problem and a key risk factor for the development of cardiovascular diseases. In obesity, cardiomyocytes undergo pathological remodeling that negatively affects their structure and function. These alterations are evident not only at the level of organelle organization but also within specialized structures known as dyadic microdomains. Dyads play a crucial role in excitation–contraction coupling, ensuring efficient communication between the transverse t-tubules and the sarcoplasmic reticulum.The aim of this study was to quantify morphological changes in the dyadic microdomain system during obesity and to evaluate the impact of aerobic training on these alterations.
Materials & Methods: The experimental model consisted of female Zucker Diabetic Fatty (ZDF) rats, including lean (fa/+) and obese (fa/fa) phenotypes. Animals were divided into sedentary and trained groups. The training group underwent a 6-week treadmill running protocol with progressively increasing intensity.
Morphometrical analysis of the dyadic microdomain system was performed using transmission electron microscopy. Dyads were classified into two categories: compact and loose, based on the spatial relationship between the sarcoplasmic reticulum cisternae and t-tubules. Compact dyads represent a structurally intact configuration, whereas loose dyads reflect disrupted coupling. Quantitative parameters included the density of compact, loose, and total dyads, as well as the fraction of compact dyads. In addition, immunofluorescence analysis was conducted to assess the distribution and spatial colocalization of key dyadic proteins, including junctophilin 2, the ryanodine receptor (RyR2), and the dihydropyridine receptor (DHPR). These proteins are essential for proper excitation–contraction coupling in cardiomyocytes.
Results: Our results indicate that obesity is associated with a shift in dyadic organization, characterized by a decreased fraction of compact dyads and an increased prevalence of loose dyads. Importantly, aerobic training exerted a protective effect by partially preserving dyadic structure, maintaining a higher proportion of compact dyads.
Conclusion: Obesity induces significant ultrastructural alterations in cardiomyocyte dyadic microdomains, while aerobic training mitigates these detrimental changes.

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GENOTYPE-SPECIFIC EFFECTS OF DIMETHYL FUMARATE ON BLOOD PRESSURE, VASCULAR REACTIVITY AND LIPID PROFILE IN WISTAR-KYOTO, BORDERLINE HYPERTENSIVE & HYPERTRIGLYCERIDEMIC RATS

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Background & Aim: This study investigated the effects of the NRF2 activator dimethyl fumarate (DMF) on blood pressure (BP), lipid profile, and vascular reactivity in normotensive Wistar-Kyoto (WKY), borderline hypertensive (BHR), and hypertriglyceridemic (HTG) rats.
Materials: Rats received DMF (20 mg/kg/day in 0.25% DMSO, p.o.) in drinking water for 4 weeks while maintained on a regular diet.
Results: Basal BP, measured by tail-cuff plethysmography, was significantly higher in BHR (~138 mmHg) and HTG (~141 mmHg) rats than in WKY rats (~125 mmHg). DMF increased BP in WKY rats when its main effect was considered, but had no effect on BP in BHR or HTG rats. Plasma TAG levels were approximately 1.15, 1.01, and 5.12 mmol/l in WKY, BHR, and HTG rats, respectively, and DMF significantly reduced TAG only in HTG rats. The atherogenic index of plasma, calculated as log(TAG/high-density lipoprotein cholesterol), was elevated in HTG compared with WKY and BHR rats and was improved by DMF only in HTG. Vascular reactivity was assessed in isolated femoral (FA) and mesenteric (MA) arteries using wire myography. Acetylcholine-induced relaxation was reduced in FA and MA of HTG rats compared with WKY and BHR, and DMF did not modify it in any genotype. Sodium nitroprusside-induced relaxation was reduced in FA and MA of BHR and HTG rats compared with WKY, while DMF improved it only in MA of HTG rats. Noradrenaline-induced contractions were lowest in WKY and highest in HTG rats; DMF increased contraction in FA of WKY rats and reduced it in MA of HTG rats.
Conclusion: DMF exerted genotype-specific cardiovascular effects, with the most pronounced benefits in HTG rats, where it improved TAG, atherogenic index, mesenteric contractility, and endothelium-independent relaxation; however, it did not reduce BP.

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EFFECTS OF TIRZEPATIDE ON ISCHEMIA-REPERFUSION INJURY OF THE HEART IN DIABETIC OBESE ZDF RATS – A PILOT STUDY

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Background & Aim: Tirzepatide, a dual agonist of GLP-1 and GIP receptors, exerts favourable metabolic and cardiovascular effects; however, its direct action on the myocardium in the context of ischemia-reperfusion (I/R) injury remains insufficiently investigated. The aim of this pilot study was to examine the effects of tirzepatide on cardiac function, structure, and molecular mechanisms of I/R injury in obese diabetic and lean non-diabetic ZDF rats.
Materials & Methods: Six-month-old obese diabetic ZDF male rats (fa/fa) and lean non-diabetic controls (fa/+) were subcutaneously administered tirzepatide for 2 weeks (0.44 mg/kg/day in the first week; 0.22 mg/kg every other day in the second week) or vehicle (PBS). Prior to sacrifice, left ventricular (LV) structure and function were assessed in vivo by transthoracic echocardiography. Isolated hearts were perfused on a Langendorff apparatus and subjected to 30-min global ischemia followed by 2-h reperfusion; recovery of hemodynamic parameters (LVDP, ±dP/dt) and infarct size were evaluated. At the molecular level, expression of proteins involved in anti-apoptotic (Bcl-2, Bax) and cardioprotective signalling (p-eNOS/eNOS, PKC-ε) was analysed in LV myocardium by Western blotting.
Results: Tirzepatide did not affect the recovery of myocardial hemodynamic parameters (LVDP, ±dP/dt) following I/R injury. Infarct size was significantly influenced by both phenotype ($p = 0.0439$) and tirzepatide treatment ($p = 0.0466$), without phenotype specificity of the treatment effect (interaction: $p = 0.7939$). At the molecular level, tirzepatide selectively increased the Bcl-2/Bax ratio in the obese phenotype (phenotype × treatment interaction: $p = 0.0109$), while expression of p-eNOS/eNOS and PKC-ε was determined primarily by phenotype and was not significantly affected by treatment. Tirzepatide significantly reduced infarct size in both phenotypes, while its cardioprotective effect at the molecular level was phenotype-dependent — selective activation of anti-apoptotic mechanisms (increased Bcl-2/Bax) was observed exclusively in the obese phenotype, independently of classical RISK signalling.
Conclusion: These findings suggest that the cardioprotective action of tirzepatide depends on the metabolic context and involves mechanisms distinct from traditional myocardial survival signalling pathways.

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DOSE OPTIMISATION OF TIRZEPATIDE AND SEMAGLUTIDE IN DIABETIC OBESE ZDF RATS: A PILOT STUDY

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Background & Aim: Cardiovascular diseases remain a leading cause of morbidity and mortality worldwide, highlighting the need for effective strategies to protect cardiac function and improve clinical outcomes. Despite advances in pharmacotherapy, no universally effective cardioprotective drug exists, and novel approaches are still being explored. Recently, increasing attention has been directed toward drugs originally developed for metabolic disorders, particularly antidiabetic agents, due to their potential cardioprotective properties. Among these, newer-generation compounds such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide and tirzepatide, have demonstrated beneficial effects on cardiovascular health in clinical and preclinical studies. However, their direct cardioprotective potential and the relationship between dose, efficacy, and safety remain insufficiently characterised, particularly in preclinical models of advanced metabolic disease. Therefore, the aim of our pilot study was to investigate the cardioprotective effects of semaglutide and tirzepatide, with particular emphasis on dose optimisation to determine an effective and safe therapeutic range.
Materials & Methods: In this experiment, two phenotypic groups of 10–12 month old male ZDF (fa/fa) rats were studied: obese non-diabetic (FAT, compensated insulin resistance) and obese diabetic (DIA, overt type 2 diabetes mellitus). Animals received subcutaneous administration of either semaglutide or tirzepatide over a 3-week period. Semaglutide was administered across dose levels ranging from 2.4µg to 90µg per rat, while tirzepatide doses ranged from 110.4µg to 664.8µg per rat. The dose was escalated every three days across five titration steps, resulting in a total of six distinct dose levels for each compound throughout the treatment period. Cardiac function was assessed using electrocardiography before and after treatment. In parallel, physiological and metabolic parameters were monitored regularly. Left ventricular tissue was collected for protein expression analysis. Cardiac signalling pathways were examined using Western blot analysis.
Results: The results indicated that the dose demonstrating a consistent effect on body weight reduction was 10.8 µg per rat for semaglutide and 332.4 µg per rat for tirzepatide. Both compounds exerted measurable effects on selected physiological and metabolic parameters in a dose-dependent manner.
Conclusions: These findings further highlight the importance of phenotypic stratification in aged ZDF rats, as age-dependent metabolic divergence may influence treatment response and contribute to variability in observed outcomes.

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DEXRAZOXANE PROVIDES CARDIOPROTECTION AGAINST ANTHRACYCLINE CARDIOTOXICITY WITHOUT COMPROMISING THE ANTITUMOR EFFICACY

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Background & Aim: Dexrazoxane is the only clinically approved agent used to prevent anthracycline-induced cardiotoxicity. Its cardioprotective mechanism of action is mainly attributed to catalytic inhibition of topoisomerase IIβ (TOP2β) and to prevention of anthracycline-induced DNA damage in cardiomyocytes. However, as a non-selective TOP2 inhibitor, dexrazoxane also targets topoisomerase IIα (TOP2α) in tumor cells, raising concerns about a potential attenuation of anticancer efficacy. This study aimed to evaluate the effects of dexrazoxane on anthracycline-induced DNA damage and DNA damage response (DDR) in both the heart and tumors, and to assess its impact on cardiotoxicity and antitumor efficacy.
Materials & Methods: The effects of dexrazoxane on daunorubicin-induced DNA damage (γH2AX) and DDR activation in the heart were investigated in rabbits, along with its efficacy against chronic anthracycline cardiotoxicity (daunorubicin, 3 mg/kg weekly for 10 weeks). In athymic mice, doxorubicin-induced DNA damage and DDR activation were assessed in the heart and subcutaneous HT1080 sarcoma xenografts. Tumor response was evaluated after repeated doxorubicin administration.
Results: Dexrazoxane effectively prevented daunorubicin-induced DNA damage in rabbit myocardium (reduced γH2AX levels assessed by western blotting and immunohistochemistry), and attenuated p53-dependent DDR activation. The TOP2β-dependency of this effect was confirmed using a dexrazoxane derivative lacking inhibitory activity against this enzyme. Repeated co-administration of dexrazoxane with daunorubicin prevented chronic cardiotoxicity in rabbits, as evidenced by preserved left ventricular systolic function assessed by echocardiography and catheterization ($p < 0.001$) and by markedly improved histopathological findings. In mice, dexrazoxane similarly reduced doxorubicin-induced DNA damage and DDR activation in the heart and HT1080 sarcoma xenografts. Nevertheless, dexrazoxane had no significant effect on doxorubicin antitumor efficacy, as assessed by tumor volume ($p > 0.994$) and weight ($p > 0.976$), with near-complete tumor regression observed in both groups. Similar results were confirmed in vitro using HT1080 cells.
Conclusion: Although dexrazoxane similarly inhibits anthracycline-induced DNA damage and DDR activation in both cardiac and tumor tissues, it leads to strikingly divergent outcomes - prevention of anthracycline cardiotoxicity while preservation of anticancer efficacy. These findings align with clinical observations in soft-tissue sarcoma patients, where dexrazoxane provided cardioprotection without compromising antitumor efficacy.

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STUDY OF SEX DIFFERENCES IN ANTHRACYCLINE CARDIOTOXICITY DEVELOPMENT IN RABBIT AND MOUSE EXPERIMENTAL MODELS

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Background & Aim: Anthracyclines (daunorubicin or doxorubicin) are essential anticancer agents, but their clinical use is limited by dose-dependent cardiotoxicity, which may progress to cardiomyopathy and chronic heart failure. Previous studies suggest that susceptibility to anthracycline-induced cardiotoxicity may differ between sexes, but the extent and mechanisms of these differences remain unclear. This study aimed to evaluate sex-related differences in chronic anthracycline cardiotoxicity using rabbit and mouse experimental models.
Materials & Methods: Chronic cardiotoxicity was induced in adult male and female New Zealand rabbits by intravenous daunorubicin (DAU, 3 mg/kg) once weekly for 10 weeks. Adult male and female BALB/c mice received intravenous doxorubicin (DOX, 5 mg/kg) once weekly for four weeks, followed by a six-week post-treatment observation period. Control groups received saline according to the same schedule. Acute myocardial responses to a single anthracycline dose were evaluated in both models, focusing on topoisomerase IIβ–dependent DNA damage (γH2AX) and activation of the p53-dependent DNA damage response pathway.
Results: In rabbits, a single DAU dose significantly increased myocardial DNA double-strand breaks (γH2AX; $p < 0.001$) 1.5 hours after administration. Expression of p53 and its downstream target genes (e.g., p21, Ddb2, Xpc and Bbc3) was significantly elevated 6 hours post-treatment ($p < 0.001$). No significant sex-related differences were observed in these effects. In the chronic rabbit model, DAU treatment caused significant left ventricular (LV) systolic dysfunction, assessed by echocardiography ($p < 0.001$), with no differences between males and females. Similarly, markers of myocardial dysfunction (ANP), injury (cTnT), and fibrosis (COL1A1, FN1) showed no sex-dependent variation. However, different results were obtained in the mouse model. While chronic DOX treatment led to significant impairment of LV systolic function in both sexes ($p < 0.001$), female mice developed significantly less severe cardiac dysfunction than males ($p < 0.001$).
Conclusion: No sex-related differences in anthracycline cardiotoxicity were observed in rabbits, whereas significant sexual dimorphism was identified in mice, suggesting species-specific variability. Further studies are needed to elucidate the molecular mechanisms underlying these differences.

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MIRO1 SHAPES HEART RESPONSE TO I/R INJURY AND FIBROSIS

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Background & Aim: Miro1 is a GTPase located at the outer mitochondrial membrane. It is responsible for binding mitochondria to cell motors and thus functions in mitochondrial dynamics. Miro1 also plays a role in energy metabolism by facilitating the formation of functional cristae, which is necessary for efficient oxidative phosphorylation. Furthermore, it has been demonstrated that Miro1 regulates mitophagy. In tumour cell lines, Miro1 is involved in the horizontal transfer of mitochondria between tumour cells. The role of Miro1 in the heart has not yet been studied; the present study aims to analyse its role in cardiac ischemic tolerance and fibrosis.
Materials & Methods: C57BL/6Gt mice with Miro-1 knockout (KO) and their wild-type (WT) controls (4–5 months old; 12-15 weeks after tamoxifen induction) were used. The sensitivity of male hearts to global ischemia was assessed ex vivo using Langendorff apparatus, the extent of fibrosis was quantified based on histological Sirius Red staining, mitochondrial respiration was measured via oxygraphy (Oroboros O2K), and protein analyses was done using Western blot.
Results: The analyses showed significantly increased extent of myocardial infarction in Miro-1 KO hearts after ischemia/reperfusion injury *ex vivo* and exhibited a significantly higher degree of fibrosis. Mitochondrial respiration analyses revealed significant increase in complex I respiration in the male KO group. Surprisingly, there was no effect of Miro-1 deletion on HK1 and GLUT4 expression, but female exhibited a significantly higher expression of GLUT4 transporter than males.
Conclusion: Our data suggest that Miro-1 deletion reduces the heart's resistance to ischemia and increasing cardiac fibrosis. There are also expressed differences in oxidative and glycolytic metabolism between male and female hearts.

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MONOAMINE OXIDASE-RELATED OXIDATIVE STRESS IN HUMAN PERITUMORAL VISCERAL ADIPOSE TISSUE IS REDUCED BY METFORMIN AND SGLT2 INHIBITORS

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Background & Aim: Peritumoral visceral adipose tissue contributes to oxidative stress and inflammation within the tumor microenvironment. Monoamine oxidases (MAO), mitochondrial enzymes with two isoforms, MAO-A and MAO-B recognized as relevant sources of reactive oxygen species (ROS) in the cardiovascular system have been recently implicated in cancer progression and tumor-associated metabolic remodelling. Although metformin and SGLT2 inhibitors have been shown to modulate MAO-related oxidative stress in cardiovascular tissues, their effects on MAO expression and redox balance in human peritumoral adipose tissue remain unknown. The present study was double-aimed: i) to assess the oxidative stress and expression of MAO isoforms in human peritumoral vs non-tumoral visceral adipose tissue, and ii) to investigate the *ex vivo* effects of metformin, empagliflozin and dapagliflozin.
Materials & Methods: Paired peritumoral and non-tumoral visceral adipose tissue samples were collected from a pilot group of patients undergoing abdominal surgery for malignant pathologies of the digestive system. Tissue fragments were incubated overnight with metformin (10 μM), empagliflozin (1 μM), or dapagliflozin (1 μM). ROS levels were assessed using the FOX (ferrous oxidation xylenol) spectrophotometric assay and DHE (dihydroethidium) staining in confocal microscopy. MAO expression was evaluated by qPCR.
Results: Peritumoral visceral adipose tissue showed increased ROS levels and higher MAO expression compared with paired non-tumoral tissue. Metformin, empagliflozin, and dapagliflozin reduced ROS levels and MAO expression in both tissue types.
Conclusion: Human peritumoral visceral adipose tissue exhibits a pro-oxidative phenotype and increased MAO expression that were attenuated *ex vivo* by both metformin and SGLT2 inhibitors. These findings suggest that oxidative stress in tumor-associated adipose tissue may represent a pharmacologically targetable component of the tumor microenvironment.

EMPAGLIFLOZIN MITIGATES ANGIOTENSIN-INDUCED MONOAMINE OXIDASE UPREGULATION AND OXIDATIVE STRESS IN HUMAN ADIPOSE TISSUE

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Background & Aim: Accumulating evidence suggests that oxidative stress is a major mediator of visceral adipose tissue dysfunction, driving inflammatory signaling and metabolic abnormalities associated with obesity-related cardiometabolic diseases. Angiotensin II (Ang II) and monoamine oxidases (MAO) are important mediators of pro-oxidative signalling, whereas SGLT2i, such as empagliflozin exert pleiotropic protective effects beyond glucose lowering.
Materials & Methods: Human visceral and subcutaneous adipose tissue samples obtained from a pilot group of non-diabetic overweight/obese patients with indication of elective abdominal surgery were incubated overnight with Ang II (100 nM) in the presence or absence of empagliflozin (1 µM). The following parameters were evaluated *ex vivo*: oxidative stress markers, hydrogen peroxide (assessed by FOX spectrophotometric assay), superoxide (assessed by DHE staining) and MAO gene and protein expressions (assessed by qPCR and immune-fluorescence).
Results: Baseline ROS levels and MAO expression were higher in visceral as compared with subcutaneous adipose tissue. Ang II significantly increased ROS production and MAO expression in both types of adipose tissue, with the visceral fat exhibiting a significantly higher pro-oxidant response. Acute co-treatment with empagliflozin in a concentration relevant for the clinical setting partially blunted the Ang II-induced effects in both visceral and subcutaneous adipose tissue samples.
Conclusion: Ang II promotes oxidative stress and MAO upregulation in human adipose tissue, particularly in visceral fat, which exhibits an enhanced basal and Ang II-induced oxidative profile. Empagliflozin partially attenuated these deleterious effects, suggesting a potential acute protective role against adipose tissue oxidative-mediated dysfunction.

SEMAGLUTIDE REDUCES OXIDATIVE STRESS IN HUMAN EPICARDIAL ADIPOSE TISSUE FROM PATIENTS UNDERGOING CORONARY ARTERY BY-PASS SURGERY

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Background & Aim: Epicardial adipose tissues has been widely acknowledged as an active contributor to coronary inflammation, oxidative stress, and cardiovascular disease progression. Glucagon-like peptide-1 receptor agonists (GLP-1RA), mainly semaglutide, have demonstrated important cardiovascular benefits, yet their direct effects on human cardiac adipose tissue remain insufficiently characterized. The present study was aimed to evaluate the effects of semaglutide on oxidative stress in human pericardial adipose tissue obtained from patients with coronary artery disease undergoing coronary artery bypass grafting (CABG).
Materials & Methods: Epicardial adipose tissue samples were collected from patients undergoing CABG surgery. Tissue fragments were incubated with semaglutide (100 nM, 12 h). Oxidative stress was assessed using the FOX (ferrous oxidation xylenol) spectrophotometric assay for hydrogen peroxide (H_2O_2) and dihydroethidium (DHE) staining by confocal microscopy for superoxide anion.
Results: Semaglutide treatment reduced oxidative stress in human epicardial adipose tissue demonstrated by decreased H_2O_2 production detected by FOX assay and reduced DHE fluorescence, respectively. These findings suggest a direct antioxidant effect of semaglutide on cardiac adipose tissue from patients with coronary artery disease.
Conclusion: Semaglutide exerts *ex vivo* protective antioxidant effects in human epicardial adipose tissue samples. Mitigation of oxidative stress within cardiac adipose depots contributes to the cardiovascular protection associated with the class of GLP-1 receptor agonists. Further studies are required to assess the sources of local oxidative stress.

SGLT2 INHIBITORS ATTENUATE ANGIOTENSIN II–INDUCED OXIDATIVE STRESS AND MONOAMINE OXIDASE ACTIVATION IN HUMAN SAPHENOUS VEINS USED FOR CORONARY ARTERY BYPASS GRAFTING

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Background & Aim: Saphenous vein graft dysfunction remains a major limitation after coronary artery bypass grafting (CABG) and oxidative stress plays a central role in vascular injury and remodelling. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) exert pleiotropic cardiovascular protective effects beyond glycemic control; however, their direct vascular actions on human graft vessels are incompletely understood. We have previously demonstrated that monoamine oxidases (MAOs), mitochondrial enzymes with 2 isoforms, MAO-A and B that constantly generate reactive oxygen species (ROS) in cardiovascular system, are also upregulated in the human varicose veins harvested from patients with chronic venous disease, and were further induced by angiotensin II (Ang II). The present pilot study was double-aimed: i) to assess the expression of MAOs in saphenous vein samples and ii) to investigate whether empagliflozin and dapagliflozin protect human saphenous veins against angiotensin II (Ang II)-induced oxidative stress and MAO upregulation.
Materials & Methods: Human saphenous vein segments were obtained from a pilot group of patients with coronary artery disease undergoing CABG surgery. Vascular samples were incubated overnight with Ang II (100 nM) in the presence or absence of empagliflozin (1 μM) or dapagliflozin (1 μM). Reactive oxygen species (ROS) generation was evaluated using a spectrophotometric (FOX – ferrous iron xylenol orange) assay for hydrogen peroxide (H_2O_2) and confocal microscopy with the dihydroethidium (DHE) probe for superoxide anion, respectively. Expression of MAO-A and MAO-B isoforms was assessed by means of qPCR.
Results: Ang II markedly increased oxidative stress in human saphenous veins, as demonstrated by significantly elevated ROS production detected by both FOX assay and DHE staining. Ang II exposure was also associated with increased MAO-A and MAO-B levels. Co-incubation with either empagliflozin or dapagliflozin significantly attenuated Ang II-induced ROS generation and prevented the increase in MAO-A and MAO-B expression.
Conclusion: Empagliflozin and dapagliflozin exert direct vasculo-protective effects on human saphenous veins by reducing Ang II-induced oxidative stress and MAO activation. These findings suggest that acute exposure to SGLT2 inhibitors might improve the biological integrity of venous grafts used for CABG and could contribute to better vascular outcomes after bypass surgery.

LIPID-RELATED DETERMINANTS OF PULSE WAVE ANALYSIS VARIABLES IN OVERWEIGHT AND OBESE CARDIAC PATIENTS

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Background & Aim: Pulse wave analysis provides information about future cardiovascular events. The study aimed to investigate the relationship between lipid profiles and pulse wave analysis variables in obese and overweight patients.
Materials & Methods: Sixty-three overweight or obese patients with high cardiovascular risk underwent pulse wave analysis. Fasting lipid biomarkers were measured, including triglycerides (TG), total cholesterol (TC), LDL- and HDL-cholesterol. The triglyceride–glucose (TyG) index and Systematic Coronary Risk Evaluation 2 (SCORE2) were calculated.
Results. Body mass index, pulse wave velocity (PWV), diastolic blood pressure (DBP), TG, TC, TyG, and HDL-cholesterol were, as follows: 31.34±4.07 kg/m^2, 9.23± 1.51 m/s, 85±11 mmHg, 193.4±192.22 mg/dl, 203.16±54.41 mg/dl, 4.89±0.37, and 47.44±12.46 mg/dl. Significant correlations were obtained between DBP and TG (r=0.32, p=0.01) and TyG (r=0.31, p=0.015), respectively. In multiple regression models, SCORE2 and TG emerged as independent predictors of PWV (MR=0.85, p<0.001), while triglycerides independently predicted DBP (MR=0.32, p=0.0096). In turn, PWV, total cholesterol, and HDL-cholesterol were independent determinants of SCORE2 (MR=0.86, p<0.0001).
Conclusion: In this cohort of overweight and obese patients at high cardiovascular risk, DBP was closely linked to TG and TyG index, suggesting a key role of insulin resistance–related lipid disturbances in blood pressure elevation. Traditional risk burden and lipid-related metabolic risk both contribute to arterial stiffness. The independent relationships between TG, PWV, and SCORE2 indicate a bidirectional interaction between arterial stiffness, global cardiovascular risk, and lipid-related metabolic dysfunction. Interventions aimed at reducing triglyceride-rich lipoproteins and improving arterial stiffness may offer complementary strategies to lower blood pressure and overall cardiovascular risk in this population. The combined assessment of pulse wave analysis parameters with lipid and metabolic indices, particularly the TyG index, may therefore provide complementary and clinically relevant information for cardiovascular risk stratification.

SYNERGISTIC EFFECTS OF SGLT2 INHIBITORS AND ARNI IN PREVENTING ATRIAL FIBRILLATION: INSIGHTS FROM CLINICAL DATA

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Background & Aim: Atrial fibrillation (AF) is a leading arrhythmia that frequently complicates heart failure (HF), significantly increasing morbidity and mortality. Delaying AF onset is a critical therapeutic goal. This study evaluates the influence of sodium–glucose cotransporter 2 inhibitors (SGLT2i) and Angiotensin Receptor-Neprilysin Inhibitors (ARNI) on AF prevention.
Materials & Methods: This retrospective observational study analyzed 260 patients hospitalized at the Cardiology Department of the "Pius Brînzeu" Emergency County Hospital (2022–2024). The cohort included 144 patients treated with SGLT2i and 116 controls without SGLT2i therapy. A subgroup analysis was performed within the SGLT2i cohort to compare SGLT2i monotherapy against combined SGLT2i and ARNI therapy.
Results: Overall, SGLT2i treatment was associated with a lower prevalence of AF compared to the control group, 6.25% in the treatment group versus 24.14% in the control group. In the subgroup analysis, the combined SGLT2i + ARNI regimen demonstrated a superior protective effect. AF occurred in 12.5% of the SGLT2i monotherapy group, while 0% of patients in the SGLT2i + ARNI group developed the arrhythmia.
Conclusions: The findings reinforce the cardiovascular benefits of SGLT2i in HF and suggest a potent synergistic effect when combined with ARNI. This combination significantly reduces the risk of AF onset, highlighting the importance of optimized quadruple therapy in preventing secondary rhythmic complications in heart failure patients.

COMORBIDITY DETERMINANTS OF ARRHYTHMIC VULNERABILITY AND CLINICAL OUTCOMES IN SEPTIC PATIENTS

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Background & Aim: Sepsis induced systemic inflammation serves as a potent catalyst for myocardial electrophysiological remodeling, significantly increasing the risk of cardiac arrhythmias. The pathogenesis involves a complex interplay between cytokine mediated oxidative stress, autonomic dysregulation, and microcirculatory dysfunction. Identifying how pre-existing clinical substrates exacerbate this proarrhythmic environment is paramount for effective risk stratification and reduction of major adverse cardiovascular events.
Materials & Methods: This clinical evaluation included a cohort of 64 patients diagnosed with sepsis. The analysis focused on the prognostic weight of specific baseline comorbidities: diabetes mellitus, a history of cerebrovascular accidents, and chronic coronary artery disease. Sepsis severity was quantified through serial measurements of inflammatory markers (procalcitonin, erythrocyte sedimentation rate, and fibrinogen). Cardiac rhythm dynamics were documented using continuous 24-hour Holter monitoring and standard 12-lead ECGs. Echocardiography was systematically performed to assess ventricular function and structural integrity, correlating these findings with serum electrolyte levels and biomarkers of myocardial injury to identify the mechanisms of rhythm instability.
Results: The data demonstrated a high incidence of diverse tachyarrhythmias, with a notable progression from supraventricular disturbances to complex ventricular instability in high-risk subgroups. Diabetes mellitus was identified as the most significant independent predictor of mortality, correlated with heightened metabolic fragility and an exaggerated inflammatory response. Coronary artery disease significantly lowered the threshold for reentry-mediated arrhythmias, while a history of stroke was associated with increased heart rate variability disturbances due to impaired autonomic tone.
Conclusion: The clinical evolution of patients in sepsis is decisively shaped by their pre-existing pathophysiological substrate. Our findings highlight that diabetes mellitus serves as the most significant determinant of an unfavorable prognosis, necessitating a proactive and individualized management plan. Consequently, the early integration of echocardiographic assessment into the standard monitoring protocol is vital for the timely identification of myocardial compromise, enabling targeted interventions to mitigate arrhythmic risk and enhance overall survival.

ASSOCIATION BETWEEN BIOIMPEDANCE-DERIVED BODY COMPOSITION AND METABOLIC-INFLAMATORY BIOMARKERS IN PATIENTS WITH HFPEF AND HFMREF

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Background & Aim: Heart failure with preserved (HFpEF) and mildly reduced ejection fraction (HFmrEF) have been shown to be strongly correlated with metabolic dysfunction, obesity, and systemic inflammation. Traditional tools for evaluating obesity, such as body mass index (BMI), fail to adequately characterize body composition. Previous research has recommended evaluating body composition in order to asses the presence of sarcopenic obesity, characterized by increased fat mass and low muscle mass, considered to lead to poorer long term outcomes in patients with heart failure. Bioimpedance analysis (BIA) offers a non-invasive method to assess fat mass, skeletal muscle mass, and fluid distribution. The main objective of this pilot study was to evaluate the relationship between body composition parameters assessed by bioimpedance and metabolic-inflammatory biomarkers in patients with HFpEF and HFmrEF.
Materials & Methods: Thirty clinically stable patients diagnosed with HFpEF (left ventricular ejection fraction ≥50%) or HFmrEF (41–49%), admitted between 2025-2026 in the Cardiology Clinic of the Timișoara County Emergency Clinical Hospital. Participants were investigated for the presence of diastolic disfunction and ejection fraction by echocardiography and NTproBNP was determined. All participants underwent bioimpedance analysis to determine fat mass percentage, visceral fat level, skeletal muscle mass, and extracellular water/total body water ratio. Laboratory assessment included high-sensitivity C-reactive protein (hs-CRP), fasting glucose, and lipid profile (total cholesterol, LDL-C, HDL-C, triglycerides).
Results: Higher fat mass percentage was positively correlated with hs-CRP and fasting glucose, suggesting an association between adiposity and systemic inflammation, as well as impaired glucose metabolism. Skeletal muscle mass showed an inverse correlation with hs-CRP and triglyceride levels. No significant correlations were observed between BMI and inflammatory markers, but BMI tends to be higher in patients with metabolic dysfunction.
Conclusion: Bioimpedance-derived body composition parameters are associated with inflammatory and metabolic biomarkers in HFpEF and HFmrEF patients. These findings suggest that BIA may provide additional clinical value beyond BMI in identifying high-risk phenotypes characterized by adiposity, sarcopenia, and low-grade inflammation.

SUDOMOTOR DYSFUNCTION AS AN INDICATOR OF EARLY CARDIAC AUTONOMIC IMPAIRMENT IN TYPE 2 DIABETES

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Background & Aim: Cardiac autonomic neuropathy (CAN) is a frequent but underdiagnosed complication of diabetes mellitus (DM) associated with increased cardiovascular morbidity and mortality. Sudomotor dysfunction reflects impairment of small sympathetic C-fibers involved in autonomic regulation and may represent an early marker of autonomic dysfunction. The aim of this study was to evaluate the relationship between sudomotor dysfunction and markers of cardiac autonomic impairment in patients with type 2 diabetes mellitus (T2DM).
Materials & Methods: Patients with T2DM underwent assessment of sudomotor function using SUDOSCAN by measuring electrochemical skin conductance (ESC). Cardiac autonomic involvement was evaluated using heart rate variability during deep breathing (RR ratio), and orthostatic blood pressure response. Orthostatic hypotension was defined as a decrease in systolic blood pressure ≥20 mmHg or diastolic blood pressure ≥10 mmHg after standing. Statistical analysis included correlation and ROC analysis.
Results: Sudomotor dysfunction was identified in approximately 60% of patients. Lower ESC values were associated with reduced RR ratio and impaired orthostatic blood pressure response, suggesting autonomic cardiovascular involvement. A significant association was observed between sudomotor dysfunction and pathological RR ratio ($p = 0.0107$). ROC analysis demonstrated moderate diagnostic performance of ESC values for autonomic dysfunction (AUC = 0.689), with high specificity and moderate sensitivity.
Conclusion: Sudomotor dysfunction is associated with markers of cardiac autonomic impairment and may serve as an early, non-invasive indicator of autonomic dysfunction in patients with T2DM. Assessment of sudomotor function could contribute to earlier identification of patients at risk for developing cardiac autonomic neuropathy.

EARLY VASCULAR AGING AND THE HEMATOLOGIC–VASCULAR AXIS IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES: INSIGHTS FROM PULSE WAVE ANALYSIS AND ESTIMATED PULSE WAVE VELOCITY

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Background & Aim: Cardiovascular diseases may contribute to excess mortality among long-term survivors of hematologic malignancies. This study aimed (1) to compare directly measured pulse wave velocity (PWV) with estimated PWV (ePWV) (2) to examine the relationships between pulse wave analysis (PWA) parameters and ePWV, and (3) to explore associations between PWA indices and complete blood count (CBC) in patients with hematologic malignancies.
Materials and methods: A total of 29 patients, aged 64±13years, with hematologic cancers (multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myelodysplastic syndrome and chronic myeloid leukemia) underwent pulse wave analysis (PWA) using the Mobil-O-Graph. Pulse wave velocity (PWV), vascular age, augmentation index (AI), augmentation pressure (AP), central and peripheral blood pressure variables were assessed. Estimated pulse wave velocity (ePWV) was calculated using the mean arterial blood pressure (MAP). Complete blood count was available for each patient from the medical records.
Results: PWV, ePWV, AI, MBP, Hb, and neutrophil count (N) were, as follows: 9.59±2.25 m/s, 10.92±2.57 m/s, 34±15%, 104±15 mmHg, 11.46±2.21 g/dl, and 10±2.74 x109/l, respectively. Early vascular aging (EVA) was detected in 19 patients (66%). Significant correlations were obtained for ePWV and PWV ($r=0.98$, $p<0.001$), AP, EVA, central systolic, diastolic, and pulse pressure. Bland–Altman analysis demonstrated a mean difference of −1.327 m/s, indicating that ePWV tends to overestimate PWV, with acceptable overall agreement that deteriorates at higher stiffness values. CBC parameters were significantly correlated with both PWA indices and ePWV.
Conclusion: In patients with hematologic malignancies, EVA is frequent and indicates marked arterial stiffening. ePWV closely parallels directly measured PWV, with slight overestimation at higher values, while maintaining clinically acceptable agreement. The observed links between CBC, PWA measures, and ePWV support a hematologic–vascular axis, in which blood abnormalities and vascular aging are closely interrelated, suggesting a cancer-associated vascular aging phenotype. CBC provides useful complementary information for interpreting pulse wave analysis in this population.

AMIODARONE-INDUCED MITOCHONDRIAL TOXICITY IN HUMAN PERIPHERAL BLOOD: A COMPARATIVE STUDY OF ISOLATED PLATELETS *VS* BUFFY COAT-DERIVED CELLS

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Background & Aim: Platelets have emerged as a useful tool to assess mitochondrial bioenergetics, providing a minimally invasive alternative to tissue biopsies. Buffy-coat-derived platelets from healthy donors represent a convenient source of viable mitochondria for studies of drug toxicity, yet no comparison with the effects on isolated platelets has been done. Amiodarone, a potent antiarrhythmic agent, known to elicit potentially life-threatening side effects, has mitochondrial respiratory dysfunction as one of the underlying pathomechanisms. The present study aimed to investigate the acute, concentration-dependent effects of amiodarone on mitochondrial respiration of isolated platelets harvested form healthy donors and compare them with the drug effects on the respiration of the buffy coat-derived platelets.
Materials & Methods: Peripheral blood platelets were isolated by differential centrifugation from a pilot group of healthy donors and from buffy coat bags provided by the Regional Blood Transfusion Centre. Two experimental series were performed, in which cells were acutely incubated with increasing concentrations of amiodarone followed by assessment of mitochondrial respiratory capacities, in intact and digitonin-permeabilized platelets, using the high-resolution respirometry technique (Oxygraph-2k, Oroboros Instruments).
Results: Amiodarone induced a comparable dose-dependent inhibition of mitochondrial respiration in donor-derived and buffy coat platelets, pointing to a reproducible mechanism of respiratory dysfunction across models. The overall inhibitory pattern was similar: in both models, complex II-supported respiration was more affected as compared to complex I-dependent one. However, buffy coat-derived platelets required higher concentrations of the drug to achieve the same effects, showing a right-shift in the dose–response curve and lower apparent sensitivity.
Conclusion: Buffy coat-derived platelets represent a useful model for studying drug-induced mitochondrial respiratory dysfunction, recapitulating the main effects seen in platelets isolated from healthy donors.

BEYOND THE ATHLETE'S HEART: NEXT-GENERATION SEQUENCING UNMASKS DIVERGENT GENETIC OUTCOMES IN TWO YOUNG PATIENTS WITH SUSPECTED HEREDITARY CARDIOMYOPATHY

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Distinguishing hereditary cardiomyopathy from athlete's heart represents a persistent diagnostic challenge in young, physically active individuals. Next-generation sequencing (NGS) has become essential for clarifying etiology, guiding management, and enabling family screening.

Patient 1 was a 22-year-old asymptomatic male with a history of intense gym training and substance use (cannabis, alcohol, anabolic steroids), incidentally found to have cardiac enlargement during a pre-employment examination. ECG revealed ventricular extrasystoles; echocardiography demonstrated interventricular septal hypertrophy (EF=60%) without outflow tract obstruction. Patient 2 was a 26-year-old professional rugby player of Tongan origin, referred after identification of markedly prolonged QT intervals (599ms on Holter monitoring), with echocardiography consistent with athlete's heart morphology.

Both patients underwent pre- and post-test genetic counseling at the Medical Genetics Office Dr. Gug, Timișoara, where comprehensive NGS-based cardiac genetic testing was indicated. Testing was performed at Invitae Laboratory (USA) using the Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel (280 genes, Illumina NGS), covering sequence analysis and deletion/duplication testing of coding regions and relevant genomic areas. Clinically significant variants were confirmed by Sanger sequencing and MLPA.

Patient 1 carried a pathogenic *TNNT2* variant (c.833G>C, p.Arg278Pro), establishing a definitive molecular diagnosis of HCM. Patient 2 showed no pathogenic HCM variant; 13 variants of uncertain significance were identified, including a *CACNA1C* variant potentially contributing to the prolonged QT phenotype.

These contrasting outcomes illustrate the dual role of genetic testing: confirming a molecular diagnosis where one exists, and excluding a genetic etiology when phenotype may reflect athletic remodelling or lifestyle factors. Comprehensive NGS-based evaluation is essential in the workup of young patients with ambiguous cardiac phenotypes.

INCIDENTAL PRE-EXCITATION IN A YOUNG ADULT: HIGH-RISK WOLFF-PARKINSON-WHITE PATHWAY SUCCESSFULLY ABLATED

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Wolff–Parkinson–White (WPW) syndrome is associated with a small but non-negligible risk of life-threatening arrhythmias, even in asymptomatic individuals. The current guidelines of the European Society of Cardiology recommend risk stratification in patients with incidental pre-excitation, particularly in young individuals. However, management remains debated when accessory pathways are located in high-risk regions such as the parahisian area. We aimed to present a high-risk asymptomatic WPW case and emphasize the role of invasive risk stratification and tailored ablation.
A 24-year-old male with no prior cardiovascular history was referred after the incidental detection of ventricular pre-excitation on a routine ECG. The patient was entirely asymptomatic, with no history of palpitations, syncope, or documented arrhythmias. ECG demonstrated a short PR interval and delta waves consistent with a WPW pattern. Transthoracic echocardiography revealed no structural abnormalities. Given the patient's age and potential arrhythmic risk, an electrophysiological study was performed for risk stratification. Mapping identified a parahisian accessory pathway with high-risk features. A cautious ablation strategy was adopted: i)high-resolution electroanatomical mapping, ii) stepwise, low radiofrequency delivery, and iii) continuous atrioventricular conduction monitoring.
Radiofrequency ablation resulted in the successful elimination of the accessory pathway with immediate loss of pre-excitation, no atrioventricular block or complications, no arrhythmia recurrence at follow-up, and preservation of normal conduction.
This case underscores that asymptomatic Wolff–Parkinson–White syndrome is not universally benign. In selected young patients, especially with high-risk pathway characteristics, invasive evaluation and ablation may be justified. Early, strategy-guided ablation in experienced centers can safely eliminate high-risk substrates, potentially preventing future malignant arrhythmic events.

SYNCOPE AS AN ATYPICAL MANIFESTATION OF PRIMARY HYPERPARATHYROIDISM

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Primary hyperparathyroidism is associated with hypercalcemia and can lead to multisystemic manifestations, including cardiovascular ones. Excess serum calcium affects myocardial excitability, cardiac conduction, and autonomic tone, and is associated with bradyarrhythmias, conduction disturbances, or changes in the sensitivity of the carotid sinus baroreceptors. In this context, syncopal episodes may occur, sometimes through reflex mechanisms or through amplification of the cardioinhibitory response.

We present the case of a 76-year-old patient with a history of hypertension, heart failure with preserved ejection fraction, and stage G3b chronic kidney disease (surgically single kidney), who presented with a syncopal episode occurring at rest.

Following carotid sinus compression, a sinus pause of 5.6 seconds is observed, suggestive of carotid sinus hypersensitivity. Laboratory tests reveal moderate azotemia (creatinine 1.5 mg/dL, urea 83 mg/dL) and abnormalities in calcium-phosphorus metabolism: hypercalcemia (total calcium 11.4 mg/dL; ionized calcium 5.58 mg/dL), phosphorus at the lower limit, and elevated parathyroid hormone levels (391.8 pg/mL), raising suspicion of primary hyperparathyroidism.

Endocrinological and ultrasound evaluation revealed a retrothyroid nodular mass suggestive of a parathyroid adenoma, and the patient was referred for surgical management.

Following parathyroidectomy, a 3-month follow-up revealed remission of carotid sinus hypersensitivity, with no recurrence of syncopal episodes. This case underscores the importance of evaluating calcium-phosphorus metabolism in the diagnostic algorithm for syncope in the elderly and highlights the benefit of etiological treatment on cardiovascular manifestations.

WHEN THE MELANOCYTE DOES NOT MAKE A GOOD TEAM WITH THE MYOCYTE – CARDIAC METASTASES IN A MELANOMA PATIENT

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Malignant melanoma represents one of the most aggressive neoplasms, characterized by an unpredictable metastatic pattern and a marked propensity for hematogenous dissemination. Although cardiac involvement is relatively uncommon in clinical practice, autopsy studies suggest a significantly higher incidence, underscoring its frequently subclinical evolution and diagnostic elusiveness. The present report aims to emphasize the diagnostic complexity and clinical relevance of cardiac metastases as an inaugural manifestation of disseminated melanoma, presenting atypically as acute decompensated heart failure.

We report the case of a hypertensive and dyslipidemic 50-year-old patient, who presented to the emergency department with progressive dyspnea, orthopnea, and pronounced fatigability, as acute decompensated heart failure. Urgent transthoracic echocardiographic evaluation reveals two well-defined hyperechogenic intracardiac masses at the level of the interventricular septum (1/1.1 cm) and the apical segment of the left ventricle (0.5/1 cm). The left ventricle had normal morphologic parameters, preserved systolic function, without overt segmental wall motion abnormalities, and moderate mitral regurgitation. Subsequent contrast-enhanced computed tomography of the thorax, abdomen, and pelvis delineated extensive metastatic dissemination, with involvement of liver, lungs, and myocardium. The identification of the primary neoplastic source was particularly challenging, ultimately revealing a pigmented nevus with malignant transformation into melanoma, located on the dorsal aspect of the left foot.

The case illustrates a highly atypical debut, wherein intracardiac metastatic involvement precipitated acute heart failure in the absence of prior oncologic history. At 6-month follow-up, imaging reassessment demonstrated a reduction of approximately 50% in the dimensions of the intracardiac masses, suggesting a favorable oncologic response, but with paradoxical progression of heart failure symptomatology, necessitating optimization of cardiologic therapy with partial clinical improvement.

Cardiac metastases secondary to malignant melanoma remain an underdiagnosed entity frequently masquerading as non-specific cardiovascular pathology. Echocardiography is an indispensable first-line diagnostic in emergency.

OBESITY-ASSOCIATED HYPERTENSION IN AN ADOLESCENT WITH EARLY CARDIOVASCULAR INVOLVEMENT

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Severe hypertension in children requires systematic evaluation for secondary causes, particularly endocrine disorders. However, the rising prevalence of severe pediatric obesity has led to increasingly complex cardiovascular phenotypes, where obesity-related mechanisms may mimic endocrine hypertension. We present here the case of a 13-year-old boy with class III obesity (BMI 41 kg/m², Z-score +3.43) admitted for evaluation of severe arterial hypertension. His history included metabolic dysfunction–associated steatotic liver disease (F2/F3), severe obstructive sleep apnea with poor CPAP adherence, and concentric left ventricular hypertrophy, indicating early target-organ damage. Ambulatory blood pressure monitoring confirmed severe non-dipping hypertension (mean 170/97 mmHg; peak 234/138 mmHg).. Extensive evaluation excluded renal, endocrine, and vascular secondary causes. Metabolic workup revealed insulin resistance (HOMA-IR 5.3) and mild albuminuria.
The patient presented a high-resistance hemodynamic profile, with elevated central systolic pressures (>150 mmHg), increased augmentation index (40%), and moderately elevated pulse wave velocity (~5 m/s), reflecting predominantly functional arterial alterations. Systemic vascular resistance was significantly increased (>2200 dyn·s/cm⁵), with a relatively reduced cardiac index, consistent with a low-output, high-resistance state driven by obesity, insulin resistance, and sympathetic overactivity, the latter being also responsible for the reported sleep-disordered breathing.
Treatment with enalapril (20 mg/day) resulted in normalization of blood pressure and improvement in vascular parameters (PWV 3.9 m/s, AIx 28%). Adjunctive measures included omega-3 fatty acids, vitamin D supplementation, and lifestyle interventions, although adherence remained suboptimal.
This case highlights the cardiovascular burden of severe pediatric obesity, where hypertension is largely driven by the extreme neuro-humoral activation. Despite a phenotype suggestive for endocrine hypertension, the comprehensive evaluation of the patient excluded secondary causes.
Obesity-related hypertension remains the most plausible etiology, which may by also contributed by the untreated obstructive sleep apnea. Early, multidisciplinary intervention is essential to prevent long-term cardiovascular complications.

GIANT CONGENITAL LYMPHATICO-VENOUS MALFORMATION WITH MEDIASTINAL EXTENSION AND TRACHEAL COMPRESSION IN A TODDLER: A CASE REPORT OF PROS CONFIRMED BY SOMATIC *PIK3CA* MUTATION

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PIK3CA-related overgrowth spectrum (PROS) is a group of congenital disorders driven by somatic gain-of-function mutations in the *PIK3CA* gene, resulting in vascular and lymphatic malformations that can be extensive, multifocal, and sometimes, when involving the mediastinum, even life-threatening. The diagnosis can be missed at the beginning. The molecular etiology is discovered after a prolonged and complicated clinical course, by tissue-level testing. Our case report aims to highlight the diagnostic pitfalls and the critical role of somatic genetic mutation analysis in guiding management. We report the case of a male child, born in 2022 via caesarean section, with a suspected right thoracic mass detected on fetal ultrasound at 18 weeks. At birth, the examination revealed a 12/10 cm soft, fluid-filled right antero-thoracic and axillary formation, and also macrodactyly of the 2nd and 3rd fingers of the right hand. Imagistic examinations over the following months included serial MRI, CT angiography, and Doppler ultrasound. Three bleomycin embolizations were performed at one month of age. Oral sirolimus was started at 13 months but remained underdosed.

At 22 months, the child developed acute respiratory failure initially attributed to bronchiolitis and COVID-19. CT revealed a voluminous multispatial cystic mass compressing the trachea, in contact with the ascending aorta, pulmonary artery, superior vena cava, and brachiocephalic vessels, with abdominal extension to the splenic hilum.

After 6 weeks, the child developed a massive pneumomediastinum and pneumothorax that required non-invasive ventilation, chest drainage, and, ultimately, urgent surgical resection performed by a multidisciplinary team in a cardiac surgery setting. Surgical resection was complete, though the postoperative course required tracheostomy for right phrenic and recurrent laryngeal nerve palsy. Postoperative tissue DNA analysis and peripheral blood genetic testing were both performed. Histopathology confirmed a predominantly lymphatic malformation with a partially thrombosed venous component. The PROS diagnosis was established by tissue DNA analysis (somatic mosaic PIK3CA mutation, totally absent from peripheral blood). Three-month follow-up MRI showed a slight increase in residual axillary-mediastinal cystic tissue.

In conclusion, in complex congenital vascular malformations, peripheral blood genetic testing has to be doubled by tissue DNA analysis. The multidisciplinary team, the surgical decision, and the molecular diagnosis have to work together.

POPLITEAL ARTERY SUBOCCLUSION: HEMODYNAMIC AND THERAPEUTIC IMPLICATIONS

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Peripheral arterial disease in diabetic patients frequently presents with complex limb-threatening complications, particularly when infection and neuropathy coexist, masking the underlying vascular etiology. Timely recognition of reversible arterial lesions is essential to prevent unnecessary amputations and improve long-term outcomes through appropriate revascularization strategies.
We report the case of a 43-year-old female patient with type 1 insulin-dependent diabetes mellitus, chronic hepatitis C, dyslipidemia under statin treatment, distal sensory diabetic neuropathy and prior ocular trauma with traumatic cataract. The patient presented with an ulcerated and infected plantar wound of the left lower limb after previously receiving an indication for forefoot amputation. Clinical examination revealed altered general condition, plantar tissue loss, blood pressure of 100/60 mmHg, heart rate of 78 bpm and oxygen saturation of 91%. Laboratory investigations demonstrated leukocytosis (13,190/uL), erythrocyte sedimentation rate of 80 mm/h, C-reactive protein of 54.4 mg/L and blood glucose of 153 mg/dL.
Echocardiography demonstrated preserved left ventricular systolic function (LVEF 63%), normal wall kinetics and mild degenerative mitral regurgitation. Vascular Doppler ultrasonography revealed preserved flow in the left common femoral and superficial femoral arteries, mild atheromatous infiltration of the profunda femoris artery, and proximal subocclusive stenosis of the left popliteal artery caused by a soft plaque, with peak systolic velocities of 417 cm/s. Wound cultures were collected, while angiographic evaluation confirmed the proximal popliteal lesion with preserved distal runoff.
Following infectious disease consultation, empiric intravenous antibiotic therapy with meropenem (1 g three times daily) and levofloxacin (750 mg), vasodilator therapy with alprostadil and local surgical debridement were initiated. Endovascular revascularization was successfully performed through percutaneous balloon angioplasty of the left popliteal artery, resulting in approximately 25% residual stenosis and restoration of distal perfusion to the plantar arch. Microbiological cultures identified methicillin-sensitive Staphylococcus aureus. The patient demonstrated marked clinical and biological improvement with leukocyte count decreasing to 8,240/uL, erythrocyte sedimentation rate to 15 mm/h, and favourable wound healing without persistent infection at discharge.
This case highlights the importance of comprehensive vascular assessment in diabetic patients presenting with severe lower limb wounds, particularly when major amputation is being considered. Identification of a reversible proximal arterial obstruction enabled successful limb salvage through endovascular intervention and significantly improved prognosis

SILENT BUT DEADLY: A CASE SUPPORTING EARLIER ULTRASOUND SCREENING FOR ABDOMINAL AORTIC ANEURYSM

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Abdominal aortic aneurysm (AAA) remains an important cause of cardiovascular mortality, mainly because the disease may remain asymptomatic for many years before rupture. Current screening recommendations are primarily focused on men over the age of 65. However, significant aneurysms may also occur earlier. The aim of this paper is to present the imagistic evolution of an infrarenal AAA diagnosed at the age of 54 and to emphasize the possible benefits of earlier ultrasound screening in selected patients.

We present the case of a 54-year-old male patient diagnosed with infrarenal abdominal aortic aneurysm. Successive CT angiography examinations performed between 2023 and 2026 were reviewed in order to evaluate aneurysm progression, morphological changes, and associated risk features. A brief review of the literature regarding AAA screening programs was also performed.

Initial CT angiography performed in 2023 revealed an infrarenal abdominal aortic aneurysm measuring approximately 40 mm in maximal diameter. Earlier that same year, an abdominal ultrasound demonstrated a similar finding, showing an abdominal aortic aneurysm measuring approximately 42 mm in maximal diameter. Follow-up examinations performed in September 2025 demonstrated an increase in aneurysm diameter from 40 mm to 49 mm, confirming progressive enlargement of the aneurysm. On January 30, 2026, the patient underwent another CT angiography, which showed a stable diameter of 49 mm compared to the previous examination performed several months earlier. However, the last CT angiography, performed immediately prior to the planned operation in April 2026, revealed further enlargement of the aneurysm from 49 mm to 53 mm. Overall, a rapid growth rate of approximately 4–5 mm over a six-month interval was documented, with a total aneurysm enlargement of 13 mm over a three-year period. Imaging also revealed partial mural thrombosis, circumferential wall thickening with an inflammatory appearance, later confirmed by PET scan, irregular ulcerated internal contours, and focal peri-aortic fat infiltration. Serial CT examinations highlighted the silent evolution of the disease, occurring before the age currently targeted by most national screening programs.

PROGNOSTIC VALUE OF PERIPHERAL BLOOD INFLAMMATORY BIOMARKERS IN OVARIAN MALIGNANCY BASED ON A RETROSPECTIVE ANALYSIS

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Background & Aim: Ovarian cancer remains the most lethal gynecologic malignancy due to its nonspecific clinical presentation and frequent diagnosis in advanced stages. Increasing evidence suggests that systemic inflammation plays an important role in tumor progression and may provide valuable prognostic information. This study aimed to evaluate the prognostic significance of peripheral blood inflammatory biomarkers in ovarian malignancy and to analyze their association with clinico-pathological characteristics and diagnostic performance.
Materials & Methods: A retrospective single-center observational study was conducted in the Gynecology Department of the Timișoara County Emergency Clinical Hospital between January 2020 and December 2025. A total of 780 patients diagnosed with ovarian tumors were included. Baseline hematological parameters obtained prior to treatment were analyzed, including neutrophil, lymphocyte, monocyte, and platelet counts. Inflammatory indices were calculated, namely neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR). Statistical analyses included comparative tests, multivariate logistic regression, and receiver operating characteristic (ROC) curve analysis.
Results: Patients with malignant ovarian tumors demonstrated significantly higher inflammatory marker values compared to benign and borderline tumors. Median NLR increased from 2.12 in benign tumors to 3.01 in malignant tumors ($p < 0.001$), while PLR increased from 128.5 to 172.9 ($p < 0.001$). Conversely, LMR showed a significant decrease in malignant cases (4.72 vs. 6.48, $p < 0.001$). Multivariate logistic regression identified NLR (OR = 1.74, 99% CI: 1.32–2.28, $p < 0.001$) and PLR (OR = 1.39, 99% CI: 1.10–1.77, $p = 0.004$) as independent predictors of malignancy, whereas LMR demonstrated a protective effect (OR = 0.68, 99% CI: 0.52–0.89, $p = 0.002$). ROC analysis showed moderate predictive performance for NLR and PLR (AUC ≈ 0.72), while a combined model integrating age, NLR, and PLR achieved improved diagnostic accuracy (AUC = 0.85).
Conclusion: Peripheral blood inflammatory biomarkers, particularly NLR and PLR, are significantly associated with ovarian malignancy and may serve as accessible and cost-effective prognostic tools. The integration of inflammatory markers with clinical parameters such as age may improve risk stratification and support individualized management strategies in patients with ovarian tumors.